Univerzita Tomáše Bati ve Zlíně
Fakulta technologická

Disertační práce

Syntéza heterocyklů na bázi chinolin-2,4-dionů a studium jejich vlastností a následných přeměn

Synthesis of heterocycles based on quinoline-2,4-diones scaffold and the study of their properties and subsequent transformations

ÚSTAV CHEMIE

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Klíčová slova: *chinolin-2,4-dion, Riemschneiderova reakce, Pummererův přesmyk, kyselina isothiokyanatá, fosforylchlorid, thionylchlorid, dealkylace, C-debenzylace, pinakolinový přesmyk.*

Key words: *quinoline-2,4-dione, Riemschneider reaction, Pummerer rearrangement, isothiocyanic acid, phosphoryl chloride, thionyl chloride, dealkylation, C-debenzylation, pinacol rearrangement.*

Abstrakt

Předkládaná disertační práce se v první části zabývá krátkým literárním přehledem metod přípravy 4-hydroxychinolonů a chinolin-2,4-dionů. Druhá část obsahuje souhrn vlastních experimentů rozdělených do oddílů odpovídajících svým obsahem zadání práce.

Uvedené výsledky byly úspěšně publikovány v impaktovaných časopisech a proto jsou jednotlivá díla pouze stručně komentovány. Samotné publikace jsou součástí dizertace. V nedávné době byla zaslána do redakce prestižního periodika další práce s názvem: *„Reaction of 3-hydroxyquinoline-2,4-diones with inorganic thiocyanates in the presence of ammonium or alkylammonium ions: the unexpected substitution of a hydroxyl group with an amino group”*. Jelikož se nám do dnešního data nedostalo z redakce kladné nebo záporné odpovědi není tato práce uvedena ani blíže komentována.

Abstract

Presented dissertation thesis deals with a short literary summary about preparative methods of 4-hydroxyquinolones and quinolone-2,4-diones in the first part. The second part contains an extension of own experiments divided into several sections corresponding with the thesis assignment.

Introduced results were successfully published in impact journals therefore particular articles are only briefly commented. The publications form supplement part of this thesis. Recently further publication called “*Reaction of 3-hydroxyquinoline-2,4-diones with inorganic thiocyanates in the presence of ammonium or alkylammonium ions: the unexpected substitution of a hydroxyl group with an amino group”* was sent into an editorial office of prestigious journal. Because we do not have any positive or negative answer from this editorial office up to now, the article is not shown and discussed in detail.

Děkuji svému školiteli prof. Ing. Antonínu Kláskovi, DrSc. za množství rad, trpělivosti a pomoci během mého doktorského studia a při přípravě této práce.

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Díky patří i celému Ústavu chemie za nesměnitelné vědecké a profesionální zázemí a atmosféru.

V neposlední řadě, děkuji celé mé nenahraditelné rodině, Janince, Megí, Jean Bartovi, Ludvíčkovi, myšicám a všem dalším lidem co stáli za mnou.

„Kdo má z nepřítele strach je pes… kdo jím ale pohrdá je hlupák.“

Franz Moritz hrabě Lacy
(1725–1801)

„Do boje jdi vesele, neboť mrtví, kteří se nesmějí, jsou ošklivý.“

Jack London
(1876–1916)

OBSAH

1. ÚVOD

Chemie nás obklopuje celý život a jsme její součástí, i když se to nemusí na první pohled zdát. Organická chemie a její odnož heterocyklická chemie se ustavičně rozvíjejí, rozšiřují svůj záběr a prohlubují naše znalosti o světě.

Chinolinový skelet představuje zajímavý badatelský objekt velkého počtu odborných prací v oblasti chemie organické, heterocyklické, medicinální i dalších. Všeobecně je známo, že se chinoliny, chinolin-2-ony a chinolin-2,4-diony vyskytují přirozeně v životním prostředí (jako alkaloidy), vykazují zajímavé farmakologické vlastnosti (léčiva – antibiotika, chemoterapeutika), a z toho důvodu jsou na jejich základě postaveny některé oblasti chemie syntetických léčiv.

Chinolin-2,4-diony, hlavně jejich 3,3-disubstituovaná analoga jsou v popředí zájmu bádání na Ústavu chemie FT UTB ve Zlíně již dvě desítky let. Za tuto dobu výzkumné skupiny Ústavu chemie publikovaly nepřeberné množství informací a i nadále objevují na tomto poli vědy nové skutečnosti.

Prezentovaná práce přispívá k dalšímu rozšíření vědomostí o chování a reakčních možnostech chinolin-2,4-dionů.

2. TEORETICKÉ POZADÍ

2.1 Chinolin-2-ony

Známým a historickým postupem k přípravě chninolin-2-onů je metoda termické kondenzace podle Ludwiga Knorra, která vychází z β-ketoesterů a anilinů. Je-li tato směs zahřívána v úvodním kroku nad 100 °C a v následném se přidá *konc.* H_2SO_4, nebo se teplota zvýší až ke 250 °C, vzniká chinolin-2-on. Pokud složky směsi reagují nějakou dobu za laboratorní teploty a teprve poté je směs intenzivně zahřívána při 250 °C, pak výsledným produktem této reakce je chinolin-4-on. Tento postup je pojmenován po chemicích Maxi Conradovi a Leonhardu Limpachovi (Schéma 1). [1–3]

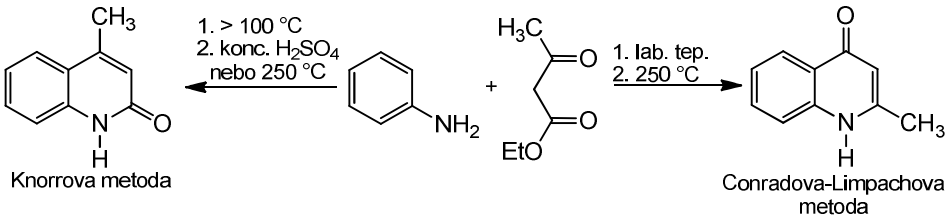


Schéma 1. Reakce podle Conradova-Limpacha a Knorra.

Moderní cestu vedoucí k přípravě chinolin-2-onů publikovala výzkumná skupina z Kanady. [4] K syntéze využila asistence Grubbsova katalyzátoru druhé generace. Během reakce dochází k cyklizaci *N*-akryloyl-2-vinylanilinů principem metathese spojené s uzavíráním kruhu „ring-closing methathesis“ za vzniku nesubstiuovaných nebo až 1,3,4-trisubstituovaných chinolin-2-onů ve výtěžku až 99 procent (Schéma 2).

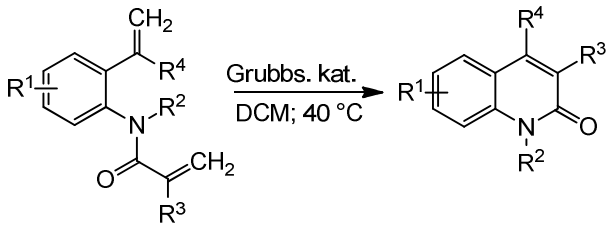


Schéma 2. Příprava chinolin-2-onů intramolekulární metathesí.

Další studie [5] popisuje cyklizaci *N*-monosubstituovaných-2-vinylanilinů katalyzovanou solemi palladia a mědi za přítomnosti plynného oxidu uhelnatého v acetonitrilu. Vznikaly tak 1,4-disubstiuované chinolin-2-ony v rozdílných výtěžcích od 15 do 92 procent (Schéma 3).

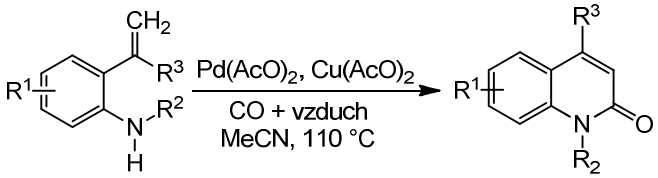


Schéma 3. Cyklizace *N*-monosubstituovaných-2-vinylanilinů.

Vědecká sekce firmy Hoffmann-La Roch zveřejnila v roce 2008 nenáročnou přípravu 3,4-disubstituovaných chinolin-2-onů modifikací reakce podle Hornera, Wadswortha a Emmonse (Schéma 4). [6] *o*-Aminofenylketony jsou v prvním kroku acylovány fosfoalkanoylchloridy a následnou intramolekulární cyklizací vznikají příslušné chinolin-2-ony.

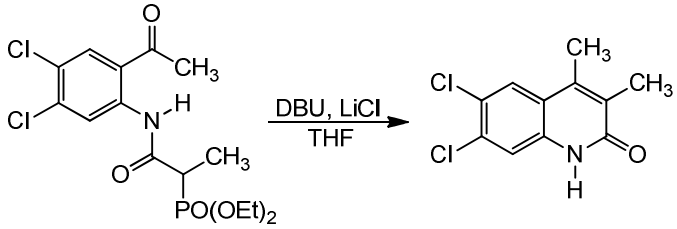


Schéma 4. Modifikace reakce podle Hornera, Wadswortha a Emmonse.

Cykloadicí substituovaného 2-allenyl-*N*-kyanoformylanilidu v xylenu za přítomnosti palladiového katalyzátoru byl získán za eliminace kyanovodíku 1,3,4-trisubstituovaný chinolin-2-on jako hlavní produkt, i když původním záměrem autorů bylo získat derivát indolin-2-onu. Stejné podmínky použili k cykloadici jednoduchého 2-vinyl-*N*-kyanoformylanilinu a získali chinolin-2-on ve výtěžku 96 procent (Schéma 5). [7]

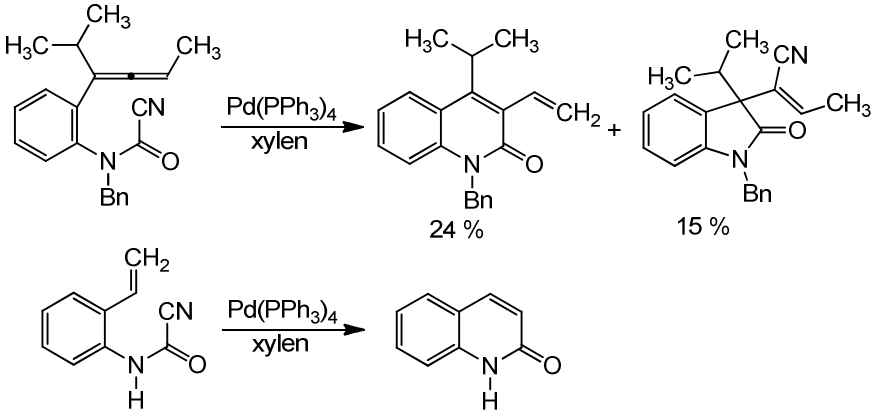


Schéma 5. Cykloadice allenyl a vinylanilinů za katalýzy $Pd(PPh_3)_4$.

N-Methylchinolin-2-on byl získán dvěma jednoduchými postupy podle autorů Junga a Chena [8, 9]. V jednom případě byl k cyklizaci *N*-(2-formylfenyl)-

N-methylacetamidu použit uhličitan cesný a ve druhém případě prostředí octanu sodného a acetanhydridu (Schéma 6).

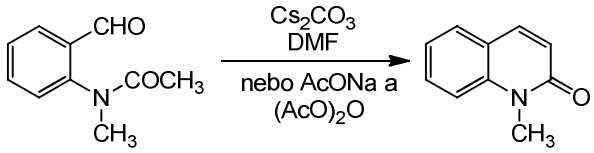


Schéma 6: Syntéza *N*-methylchinolin-2-onu v přítomnosti Cs_2CO_3 nebo AcONa

V periodiku *Molecules* byla roku 2011 uveřejněna práce [10] popisující syntézu 4-arylchinolin-2-onů. Výchozí látka 4-chloranilin byla postupně ochráněním aminoskupiny, aryoylací a kondenzací s ethyl-acetátem převedena na požadovaný produkt ve výtěžcích 70 až 80 procent (Schéma 7).

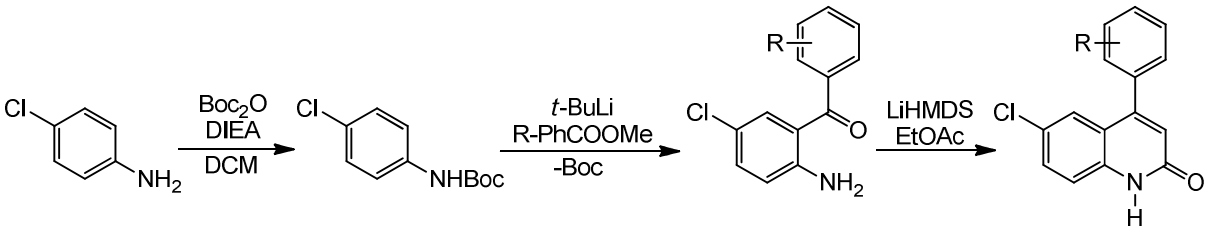


Schéma 7. Příprava 4-arylchinolin-2-onu podle Chenga [10]

Přípravu 2-arylchinolin-4-onů syntézou s mikrovlnným ohřevem v bazickém prostředí popsali vědci z Šanghaje [11]. Analýzou výsledků dospěli k závěru, že kombinací *terc*-butylalkoholátu draselného a hydroxidu sodného lze dosáhnout podle LC-MS stoprocentní konverze výchozí látky na žádaný produkt. Izolovaný výtěžek produktu byl 95 procent (Schéma 8).

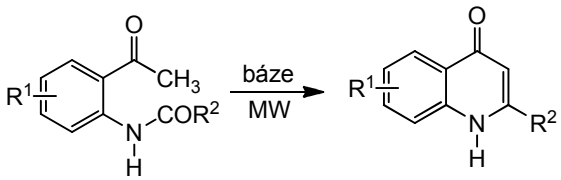


Schéma 8: Příprava 2-arylchinolin-4-onů v přítomnosti báze a mikrovln.

2.2 Chinolin-2,4-diony a 4-hydroxychinolin-2-ony

Chinolin-2,4-diony, případně 4-hydroxychinolin-2-ony, představují oproti předcházejícím chinolin-2-onům vděčnější téma výzkumných záměrů a prací. S největší pravděpodobností se tento trend dá vysvětlit nepřeberným množstvím „*anti*-vlastností“ (antifungální, antivirotické, antibakteriální), které jsou zhusta citovány v úvodech chemických článků z původní literatury zabývající se přírodními produkty a medicinálním užitím chinolonů.

Nejčastěji užívaným postupem pro přípravu chinolin-2,4-dionů resp. 4-hydroxychinolin-2-onů je reakce anilinů se substituovanou kyselinou malonovou. Výběrem typu anilinu můžeme získat pestrou škálu substitucí na benzenovém kruhu chinolonu nebo na heterocyklickém atomu dusíku. Kyselinu malonovou její α-substituovaný derivát lze eventuálně nahradit jejím diethylesterem nebo dichloridem.

Podle výchozích surovin a struktury zamýšleného produktu se volí rozlišné způsoby ohřevu a reakční prostředí. Podmínky uváděné v přístupné literatuře jsou velmi rozmanité. Z kyselin lze uvést např. kyselinu sírovou, kyselinu polyfosforečnou (PPA), z bází: hydrid sodný (NaH), alkoholáty, 3-aminopropylamid draselný (KAPA), 3-aminopropylamid sodný (NAPA), a z dehydratačních činidel např.: $ZnCl_2$ $AlCl_3$. Často užívaným reakčním činidlem je fosforylchlorid (Schéma 9). [10, 12–20]

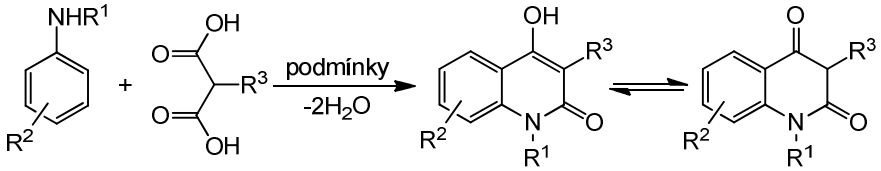


Schéma 9. Základní schéma přípravy chinolin-2,4-dionů.

Ze syntéz bazicky katalyzovaných můžeme zmínit např. práci Junga a kolektivu [21], v níž hledali vhodný typ báze a „acylačního“ činidla vedoucího k 4-hydroxykumarinu, 4-hydroxythiokumarinu a 4-hydroxychinolin-2-onu. Nejlepšího výsledku bylo dosaženo s hydridem sodným jako bází a diethylkarbonátem jako acylačním činidlem v suchém toluenu (Schéma 10).

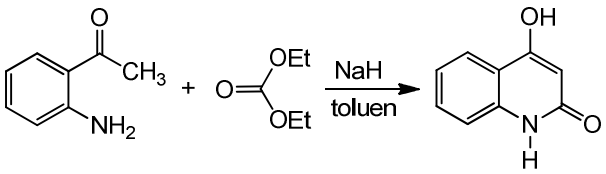


Schéma 10. Bazická syntéza podle Junga. [21]

Se zajímavou výchozí látkou k přípravě 4-hydroxychinolin-2-onu pracovaly skupiny Leeho a Tanga, [16, 17] a to s tzv. Meldrumovu kyselinou. Jedná se o 2,2-dimethyl-1,3-dioxan-4,6-dion, vykazující pozoruhodné vlastnosti, např. kyselé protony v poloze 5 [22, 23]. Lee a Tang také použili k cyklizaci intermediárního anilidu atypické Eatonovo činidlo, což je směs oxidu fosforečného a kyseliny methansulfonové, která se chová po praktické stránce jako PPA. [24, 25] Výtěžky dosahovaly až 75 procent s tím, že stejnou metodu lze aplikovat při syntéze 4-hydroxykumarinů a nebo 4-hydroxythiokumarinů, avšak s nižší efektivitou (Schéma 11).

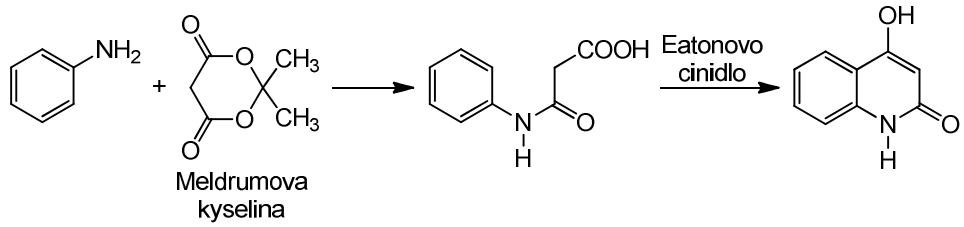


Schéma 11. Syntéza 4-hydroxychinolin-2-onu z anilinu, Meldrumovy kyseliny v přítomnosti Eatonova činidla.

3-Substituované 4-hydroxychinolin-2-ony jsou základní a výchozí látky pro experimentální část předkládané práce a lze je získat několika následujícími cestami.

Dittmer, Li a Avilov ze Syracuse University použili jako katalyzátor pro cyklizační reakce substituované anthranilové kyseliny tellurid sodný v THF. Výtěžky byly poměrně dobré a při porovnání s přípravou podobně substituovaných kumarinů dokonce o mnoho lepší. Tuto skutečnost autoři vysvětlují nižší elektronegativitou atomu dusíku oproti atomu kyslíku a snadnějšímu vzniku intermediátu – ketenu (Schéma 12). [26]

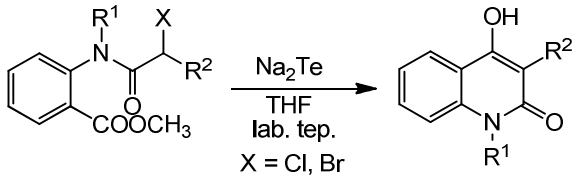


Schéma 12. Cyklizace vedoucí k 3-substituovaným 4-hydroxychinolin-2-onům.

1-Methyl-4-hydroxychinolin-2-on připravili Razzaq a Kappe [27] z *N*-methylanilinu a diethylmalonátu přes pyrano[3,2-*c*]-2,5-dion a jeho dvojnásobnou hydrolýzou, vše v prostředí mikrovln (Schéma 13). Samotná syntéza je dobře zdokumentována, např. Kappe *Il Farmaco* [28], ale úmyslem vedoucím k této práci bylo demonstrovat možnost kontinuálního odebírání nízkomolekulárního vedlejšího produktu reakce (ethanolu) destilací přímo z mikrovlnné aparatury.

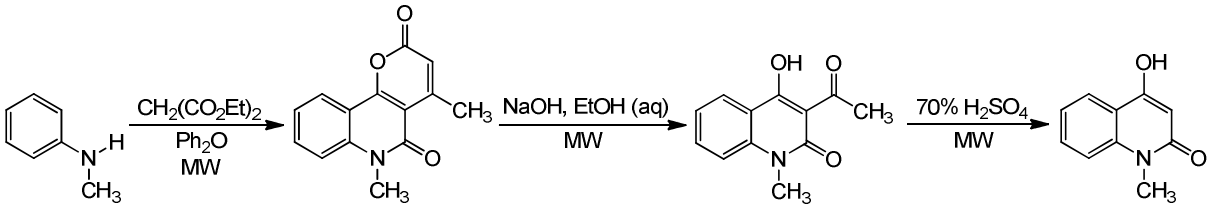


Schéma 13. Syntéza 1-methyl-4-hydroxy-chinolin-2-onu podle Razzaqa a Kappeho. [27, 28]

Další z možných reakcí vedoucích k 3-substituovaným 4-hydroxychinolonům byla uveřejněna v časopise *Bioorganic & Medicinal Chemistry* roku 2010. [29] V první fázi se mikrovlnným ohřevem ze směsi anilinu a diethylmalonátu s malým přídavkem DMF připraví nesubstituovaný 4-hydroxychinolon, který se následně alkyluje primárními alkyljodidy v prostředí hydroxidu lithného za vzniku 3-alkyl-4-hydroxychinolonu (Schéma 14).

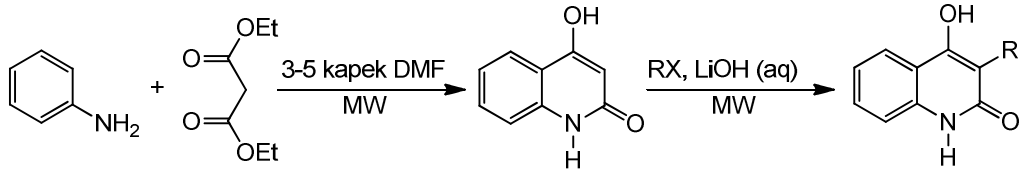


Schéma 14. Příprava 3-alkyl-4-hydroxychinolonu podle Ahmeda. [29]

V článku [30] velká skupina autorů pracovala na přípravě a testování nenukleosidových inhibitorů reverzní HIV-1 transkriptásy. Základem těchto látek byla chinolonová kostra. V první syntéze vycházeli z anilinu substituovaného na jádře (Cl^-, NO_2^-, CH_3O^-) a α-alkylovaného malonátu (Schéma 15). Drželi se standardního schématu, kdy reakce prováděli varem komponent přes noc v difenyletheru. V druhém případě jde o reakci isatoového anhydridu s ethylkyanoacetátem za varu v DMF s přídavkem TEA za vzniku 3-karbonitrilu-4-hydroxychinolin-2-onu.

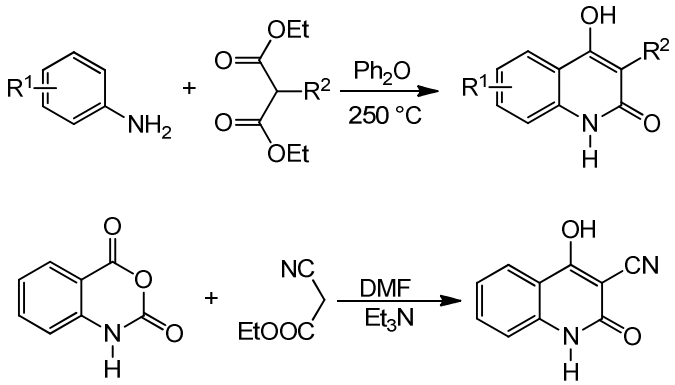


Schéma 15. Syntéza 4-hydroxychinolin-2-onů podle Freemana. [30]

Obdobnou sérii reakcí znázorněných ve Schématu 16 provedli Lange a kolektiv ze *Solvay Pharmaceuticals*, [31] s tím rozdílem, že nepoužili žádné rozpouštědlo a podle typu substituce eduktů získali výtěžky přesahující v průměru 60 procent.

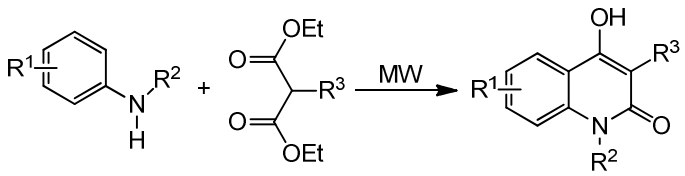


Schéma 16. Syntéza podle *Solvay Pharmaceuticals.*

Reakce na Wangově nebo TentaGel pryskyřici za produkce 3-karbonitrilu 4-hydroxychinolin-2-onu je popisována v časopisu *Tetrahedron Letters*. [32] Po zahřívání na 50–80 °C a následném přidání kyseliny trifuoroctové TFA dochází k tvorbě nitrilu hydroxychinolinonu. Podle typu pryskyřice lze izolovat až 43 procent produktu (Schéma 17). Při pokračujícím zkoumání autoři dokázali na Wangově pryskyřici syntetizovat patnáct zástupců 3-karbonitrilů hydroxychinolinonu ve výtěžcích podle typu substituce až 96 procent.

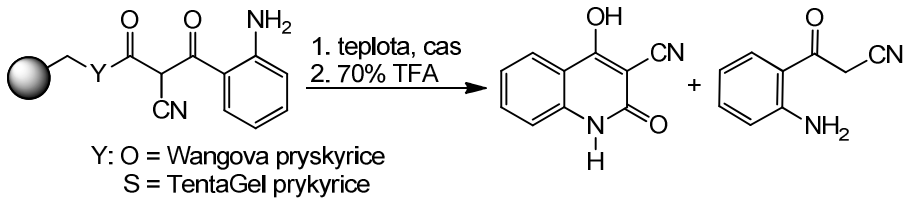


Schéma 17. Syntéza 3-karbonitrilu 4-hydroxychinolin-2-onu na Wangově nebo TentaGel pryskyřici.

Jednokrokovou přípravou 3-oxyfenyl-4-hydroxychinolin-2-onů z esterů anthranilových kyselin v přítomnosti báze popsali Toum a kol. v přítomnosti báze. [33] Pro prvotní ověřování vybrali následující báze – *terc*-butylalkoholát draselný, Cs_2CO_3, NaH, lithium diisopropylamid (LDA), bis(trimethylsilyl)amid lithný (LiHMDS) a bis(trimethylsilyl)amid draselný (KHMDS), v rozdílných rozpouštědlech. Podle analýzy reakční směsi pomocí HPLC byla dosažena stoprocentní konverze u všech činidel a rozpouštědel, ale izolovatelný výtěžek byl nejlepší pro kombinaci KHMDS v THF. V tomto systému byly provedeny další reakce různě substituovaných výchozích látek (Schéma 18).

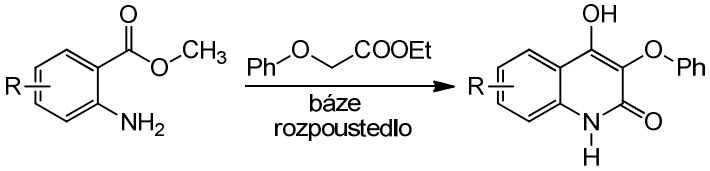


Schéma 18. Příprava 3-oxyfenyl-4-hydroxychinolin-2-onů v přítomnosti báze.

Zajímavá syntéza z oblasti biochemie byla zveřejněna v roce 2006 [34], v níž jako výchozí látky byly zvoleny deriváty koenzymu A s kyselinou anthranilovou a malonovou a produkty těchto reakcí byly jednoduché 4-hydroxychinolin-2-ony (Schéma 19). Přeměnu obstaral enzym benzalacetonsyntáza (BSA) patřící do skupiny rostlinných polyketidových syntáz třetího typu. Například procentuální přeměna eduktů na 4-hydroxy-1,3-dimethylchinolin-2-on byla 86 procent.

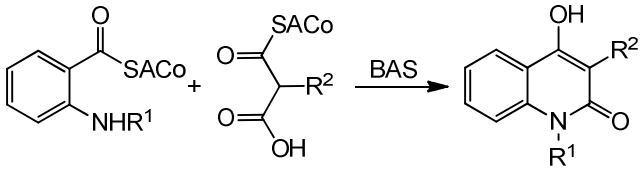
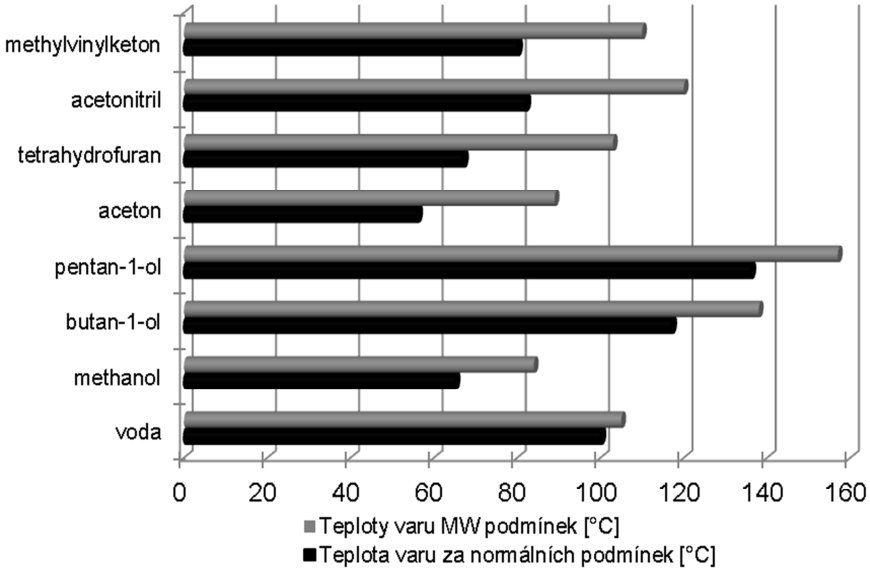


Schéma 19. Biochemická syntéza vedoucí k 4-hydroxychinolin-2-onům.

2.3 Mikrovlnný ohřev v organické syntéze

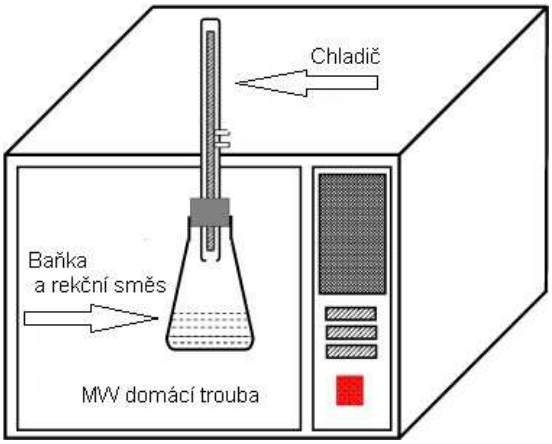
V tomto úseku teoretické části disertační práce by bylo ku prospěchu věci se krátce zmínit o kladech využití mikrovlnného záření k ohřevu reakčních směsí při organické syntéze. Trend využívání MW k ohřevu se dostal do popředí zájmu organických chemiků v poměrně nedávné době, přestože MW ohřev se začal používat již o 30 let dříve v potravinářství a v anorganické technologii, tedy v sedmdesátých letech minulého století. Prvotní práce započal R. Gedey v roce 1986 hydrolýzou benzamidu na kyselinu benzoovou v 20% H_2SO_4. „Boom“ v této oblasti organické syntézy nastal až v druhé polovině 90. let minulého století.

Neoddiskutovatelnou výhodou MW ohřevu je, že zajišťuje mnohem efektivnější využití dodávané energie matricí reakční směsi, nežli při přestupu tepla z olejové, pískové nebo vodní lázně přes stěny nádoby. Fenoménů, které mají hlavní vliv na vysokou konverzi výchozích látek je několik. Např. dipolární, polarizační a kondukční mechanismus, ztrátový úhel a tzv. *superheating effect*. *Superheating effect* je stav, kdy se dosahuje vyšší teploty varu kapalin, rozpouštědel, než během konvenčního ohřevu. Dochází k němu především vlivem mikrovlnného efektu – ohřev kapaliny probíhá přímo v celém objemu vsázky a ne prostupem přes stěny nádoby. Na Obr. 1 je uveden graf, ze kterého je jasně patrné, o kolik stupňů Celsia dochází k přehřátí u vybraných rozpouštědel během mikrovlnného a konvenčního ohřevu. Celý proces může být umocněn tlakovým provedením reakce.

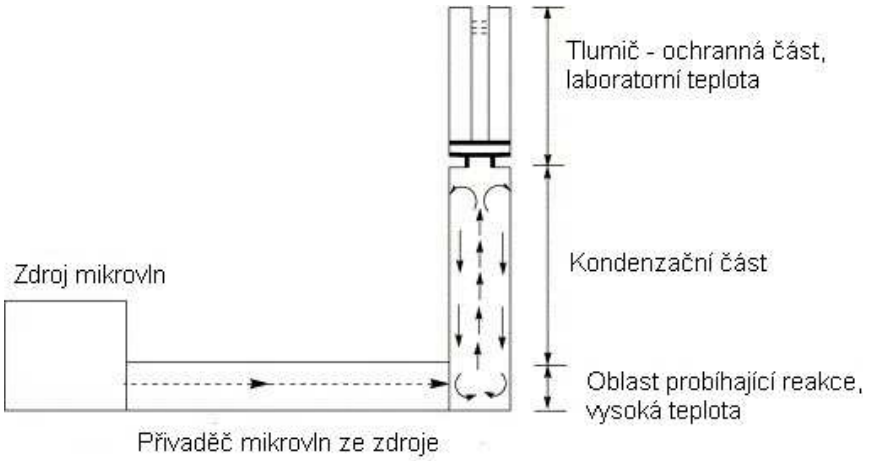


Obr. 1. Graf porovnání teplot varu rozpouštědel za normálních a podmínek MW ohřevu. Data podle Bourgina. [35]

MW reaktory můžeme principiálně rozdělit do dvou tříd. Do třídy podobné mikrovlnným troubám, *domestic oven*, Obr. 2, které jsou však spíše nouzovým a historickým řešením neumožňujícím přesné ovládání procesů a míchání reakční směsi. Anebo na zařízení s cíleným navedením svazku mikrovln do směsi reaktantů, s řízeným nastavením parametrů frekvence, teploty, tlaku atd. (Obr. 3).



Obr. 2. Domácí MW trouba upravená k syntéze, převzato. Upraveno podle Kality.[36]



Obr. 3: Schéma specializovaného MW reaktoru
s cílenými vlnami, upraveno podle Bourgina. [35]

Rozhodnutí jaké rozpouštědlo použít pro reakci, je odvislé od velikosti dielektrické konstanty. Z toho důvodu jsou upřednostňována polární rozpouštědla jako voda, DMF, DMSO, acetonitril nebo ethanol. Byl ale také pozorován efekt přídavku malého množství polárního rozpouštědla do nepolárního s nízkou dielektrickou konstantou, což ve výsledku vedlo k navýšení teploty v celém objemu reakčního roztoku. Další z možností MW ohřevu jsou metody vedené bez rozpouštědla, popřípadě v přítomnosti iontových kapalin, které velmi dobře absorbují mikrovlnné záření a lze je jednoduše recyklovat. [35, 37, 38]

K rozšíření obzorů v této oblasti lze doporučit dvě knihy od profesora C. Olivera Kappeho a spoluautorů: *Practical Microwave Synthesis for Organic Chemist* z roku 2009 [39] nebo *Microwaves in Organic and Medicinal Chemistry* z roku 2005 [40] anebo review z *Angewandte Chemie*. [41]

3. CÍLE DISERTAČNÍ PRÁCE

Cíle disertační práce navazují na Individuální studijní plán studenta, schválený v roce 2009. Základní motivy práce byly navrženy takto:

1. Provést reakce 3-aminochinolindionů s thiomočovinou a thiokyanatanem draselným.
2. Provést reakce chinolinových derivátů s fosforylchloridem.
3. Provést přeměny stericky bráněných chinolindionů.
4. Provést deacetylace 3-thiokyanatanchinolinů.

Při postupném plnění zadaných úkolů se původní okruhy zadání upravily podle schůdnosti řešení a jejich relevantnosti následovně:

1. Dokončit problematiku v oblasti reakcí 1-nesubstituovaných 3-alkyl/aryl-3-aminochinolin-2,4-dionů s kyselinou isothiokyanatou a thiomočovinou.
2. V návaznosti na předchozí téma provést reakce 1,3-disubstituovaných 3-aminochinolin-2,4-dionů s kyselinou isothiokyanatou nebo thiomočovinou.
3. Provést reakce 1,3-disubstituovaných 3-thiokyanatochinolin-2,4-dionů v prostředí silných minerálních nebo Lewisových kyselin.
4. Provést reakce nesubstituovaných 4-hydroxychinolin-2-onů s thionylchloridem.
5. Dokončit problematiku reakcí 3-chlor-1,3-disubstituovaných chinolin-2,4-dionů a 4-hydroxy-1,3-disubstituovaných chinolin-2-onů s fosforylchloridem.
6. Prozkoumat možnost redukce 3-hydroxychinolin-2,4-dionů na 3,4-dihydroxychinolin-2-ony a ověřit možnost jejich přesmyku.
7. Prozkoumat možnost redukce 3-aminochinolin-2,4-dionů na 3-amino-4-hydroxychinolin-2-ony a ověřit možnost jejich přesmyku.
8. Ověřit možnost reakce 3-hydroxychinolin-2,4-dionů s kyselinou thiokyanatou.

4. PŘEHLED PUBLIKOVANÝCH VÝSLEDKŮ A ŘEŠENÍ OKRUHŮ ZADÁNÍ

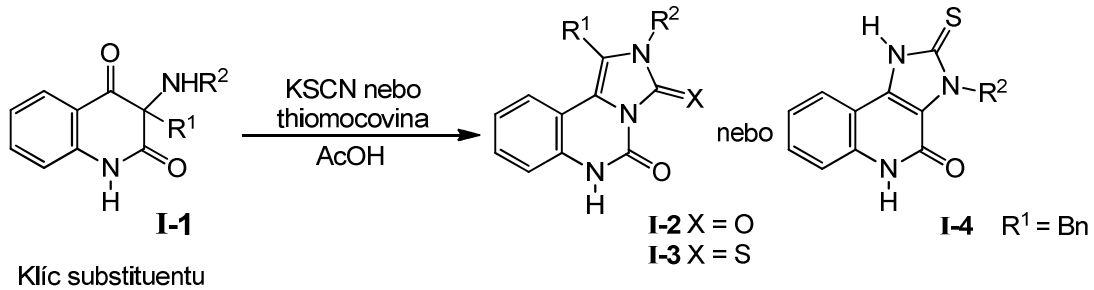
Reakce 3-aminochinolin-2,4-dionů s kyselinou isothiokyanatou – Řešení okruhu zadání 1.

Mrkvička V.; Lyčka A.; Rudolf O.; Klásek A.: Reaction of 3-aminoquinoline-2,4-diones with isothiocyanic acid – an easy pathway to thioxo derivatives of imidazo[1,5-c]quinazolin-5-ones and imidazo[4,5-c]quinolin-4-ones. *Tetrahedron*, **2010**, *66*, 8441–8445.

DOI: 10.1016/j.tet.2010.08.056

Komentář k PUBLIKACI I*

1-Nesubstituované 3-aminochinolin-2,4-diony reagují s *in situ* generovanou kyselinou isothiokyanatou. Výslednými produkty těchto reakcí jsou dva typy látek, 3-thioxoimidazo[1,5-*c*]chinazolin-5-ony nebo 2-thioxoimidazo[4,5-*c*] chinolin-4-ony (Schéma 20).



Klíč substituentu

	a	b	c	d	e	f	g	h	i
R^1	Bu	Bn	Ph	Ph	Bu	Bu	Bn	Bn	Ph
R^2	H	H	H	Bu	Bu	Bn	Bu	Bn	Bn

Schéma 20.

Z dříve uveřejněné práce [42] je známo, že močovina se ve vroucí kyselině octové rozkládá na kyselinu isokyanatou HNCO, která ochotně reaguje

* Číslování látek v této části je provedeno ve formátu pořadové číslo článku (tučné a římské číslo) a číslo látky, pod kterým je daná látka uvedena v publikaci (tučné a bezpatkové Arial) navzájem spojeny spojovníkem.

s 1-nesubstituovanými 3-aminochinolin-2,4-diony **I-1** za vzniku imidazo[1,5-*c*] chinazolin-5-onů **I-2**.

Jednou z možností, jak zavést do výsledných produktů atom síry bylo zaměnit močovinu za thiomočovinu. Výsledky dosažené s tímto činidlem byly však neuspokojivé. Množství získaných 3-thioxoimidazo[1,5-*c*]chinazolin-5-onů **I-3** bylo velmi nízké, proto byl pro další reakce vybrán thiokyanatan draselný. Ten reaguje s 3-aminochinolin-2,4-diony **I-1** mnohem ochotněji za obstojných výtěžků. Oproti močovině dává dvě skupiny produktů. V první řadě očekávaná sirná analoga látek získaných reakcí s močovinou. Jsou to 3-thioxoimidazo[1,5-*c*]chinazolin-5-ony **I-3**. V druhé řadě se jedná o produkty připravené z výchozích látek nesoucích v poloze 3 benzyl **I-1b**, **g** a **h**. Tyto izolované látky byly popsány jako 2-thioxoimidazo[4,5-*c*]chinolin-4-ony **I-4**, přičemž během reakce došlo k debenzylaci výchozích látek **I-1**.

Detailní popis reakcí, produktů a návrh reakčního mechanismu jsou uvedeny v Příloze I.

Jako spoluautor jsem se podílel na: Přípravě výchozích látek 3-alkyl/aryl-4_hydroxychinolin-2-onů, 3-alkyl/aryl-3-chlorchinolin-2,4-dionů, 3-alkyl/aryl-3-aminochinolin-2,4-dionů, na provedení reakcí 3-alkyl/aryl-3-aminochinolin-2,4-dionů s KSCN a thiomočovinou, na izolaci a purifikaci produktů, a dále na pomoci při identifikaci látek a sestavování rukopisu.

Některé z výsledků uvedených v tomto článku jsem použil v diplomové práci roku 2009.

Reakce1-substituovaných 3-aminochinolindionů s kyselinou isokyanatou a isothiokyanatou – Řešení okruhu zadání 2.

Mrkvička V.; Rudolf O.; Lyčka A.; Klásek A.: Reaction of 1-substituted 3-aminoquinolinediones with isocyanic and isothiocyanic acid. *Tetrahedron*, **2011**, *67*, 2407–2413.

DOI: 10.1016/j.tet.2011.02.002

Komentář k PUBLIKACI II

Tato práce úzce navazuje na předchozí Publikaci I. Výchozí látky substituované 1-alkyl/aryl-3-aminochinolin-2,4-diony reagují s kyselinou isokyanatou nebo isothiokyanatou. Produkty těchto reakcí jsou různé heterocyklické sloučeniny, např. ureido- nebo thioureidooxindoly, spirooxindoly anebo imidazochinolony, viz uvedené (Schéma 21).

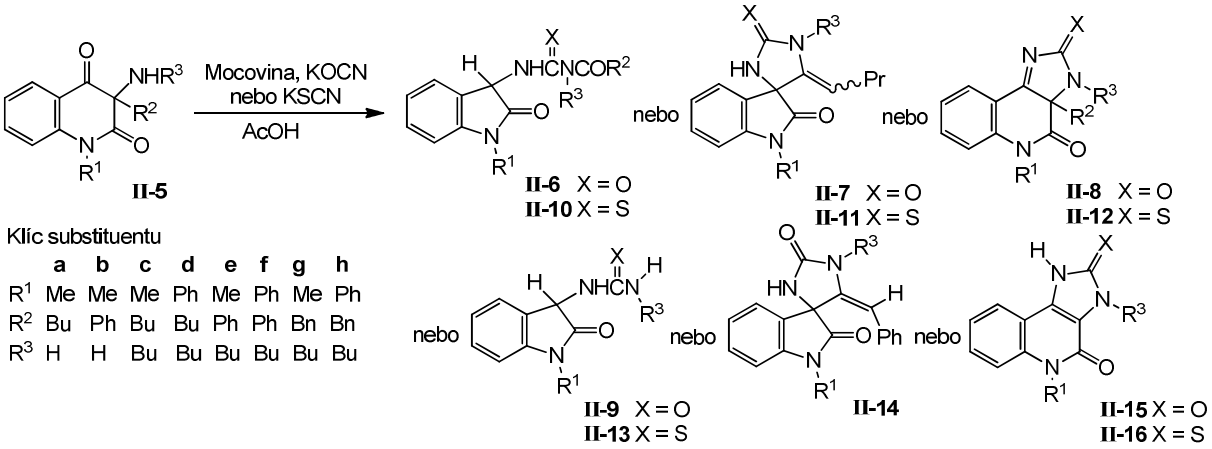


Schéma 21.

Z předchozí práce, Publikace I, a článku [42] je známo, že 1-nesubstituované 3-aminochinolin-2,4-diony reagují s kyselinou isokyanatou nebo isothiokyanatou za vzniku imidazochinazolindionů, 3-thioxoimidazo-chinazolinonů nebo 2-thioxoimidazochinolinů. U reakcí kyselin isokyanaté nebo isothiokyanaté s 1-alkyl/aryl substituovanými 3-aminochinolin-2,4-diony **II-5** se očekávalo, že produkty budou strukturně odpovídat obdobným látkám popsaných v publikacích [43, 44].

Reakce kyanatanu draselného s výchozími látkami **II-5a–f** vedly ke stejným produktům jako při reakci s močovinou [43]. Při reakci s thiokyanatem draselným se podařilo izolovat látky strukturně shodné s článkem [43], pouze s tím rozdílem, že šlo o sirná analoga. Avšak u látek s benzylem v poloze 3 **II-5g**, **II-5h** byly získány produkty debenzylované **II-16g**, **II-16h**. Je zajímavé, že i v prostředí kyseliny isokyanaté došlo k tomuto jevu za vzniku imidazo[4,5-*c*]chinolin-2,4-dionů **II-15** vedle 4-benzylidenspiro[imidazolidin-5, 3´-indol]-2,2´-dionů **II-14**.

Podrobnější vysvětlení přeměn výchozích látek na produkty včetně jejich charakterizace a návrhu reakčního mechanismu je uvedeno v Příloze II.

Jako spoluautor jsem se podílel na: Přípravě výchozích látek 3-alkyl/aryl4-hydroxychinolin-2-onů, 3-alkyl/aryl-3-chlorchinolin-2,4-dionů a 3-alkyl/aryl-3-aminochinolin-2,4-dionů; na provedení reakcí 3-aminochinolin-2,4-dionů s KSCN; následné na izolaci a purifikaci produktů; spolupracoval jsem při identifikaci látek a sestavování rukopisu.

Modifikovaná *Riemschneiderova* reakce 3-thiokyanatochinolin-dionů – Řešení okruhu zadání 3.

Rudolf O.; Mrkvička V.; Lyčka A.; Rouchal M.; Klásek A.: Modified Riemschneider reaction of 3-thiocyanatoquinolinediones. *Helvetica Chimica Acta*, **2012**, *95*, 1352–1372.

DOI: 10.1002/hlca.201200049

Komentář k PUBLIKACI III

V tomto článku byly 3-thiokyanatochinolin-2,4-diony podrobeny podmínkám *Riemschneiderovy* reakce (Schéma 22). Produkty představují rozsáhlý soubor heterocyklických sloučenin, kde se předně jednalo o 2,4-dioxochinolin-3-ylkarbamatothioáty, thiazolo[5,4-*c*]chinolin-2,4-diony v hydratované, anebo dehydratované, ale zároveň i dealkylované formě a také o 2-oxochinolin-4-ylmočoviny (Schéma 23).

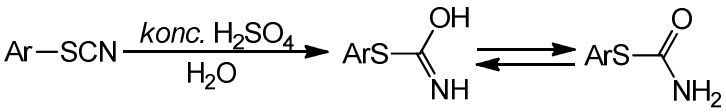


Schéma 22. Riemschneiderova reakce.

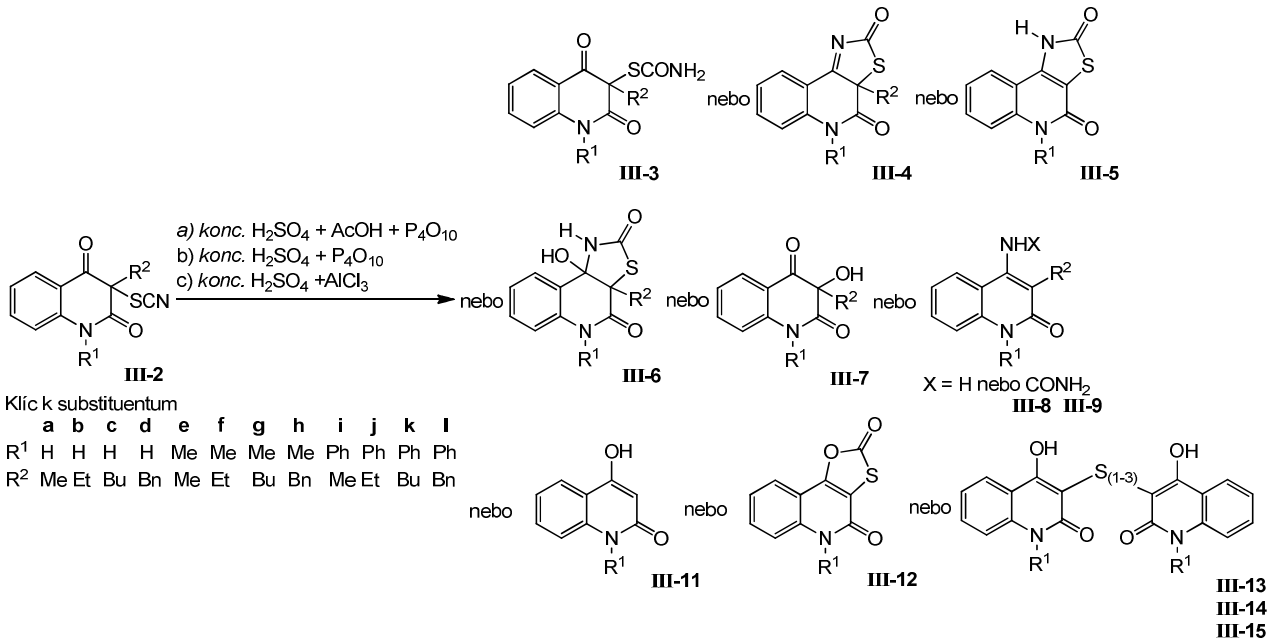


Schéma 23.

3-Thiokyanatochinolin-2,4-diony **III-2** jsou stabilní v krystalické formě. V roztocích protických rozpouštědel se snadno hydrolyticky rozkládají na

4-hydroxychinolin-2-ony. Thiokyanatochinolindiony **III-2** působením *konc.* kyseliny sírové nebo její směsi s kyselinou octovou vytvářejí thiokarbamáty **III-3** a cyklické dehydratované thiazolochinolindiony **III-4**. Pokud se během reakce přidá k roztoku výchozí látky **III-2** v *konc.* kyselině sírové oxid fosforečný, dochází k tvorbě cyklodehydratovaného a dealkylovaného thiazolo[5,4-*c*]chinolin-2,4-dionu **III-5**. [45]

Proto bylo rozhodnuto podrobit řadu 3-thiokyanatochinolin-2,4-dionů **III-2**, s rozdílnými alkylovými skupinami R^2, *Riemschneiderově* reakci za upravených podmínek.

Karbamatothioáty chinolin-2,4-dionů **III-3** byly izolovány pouze v několika případech (reakcí výchozích látek **III-2a**, **b**, **c** a **k**). [1,3]Thiazolo-[5,4-*c*]chinolin-2,4-diony **III-4** vznikají ze všech výchozích látek. Hydratovanou formu thiazolochinolindionů, 9-hydroxy[1,3]thiazolo[5,4-*c*]- chinolin-2,4-diony **III-6** bylo možné získat tehdy, jestliže edukt nesl v poloze 3 methyl nebo ethyl. 3a-Dealkylované [1,3]thiazolo[5,4-*c*]chinolin-2,4-diony **III-5** vznikaly z látek **III-2c**, **d**, a **k**.

Po přidání vodného roztoku amoniaku ke zpracovávané reakční směsi byly izolovány dvě skupiny látek lišící se od předchozích thiazolo[5,4-*c*] chinolin-2,4-dionů **III-4**. Výsledné struktury byly identifikovány jako 1,3-disubstituované 2-oxochinolin-4-yl močoviny **III-8** a 1,3-disubstituované 4-aminochinolin-2,4-diony **III-9**.

Výchozí látky **III-2d**, **h** a **l** nesoucí jako substituent R^2 benzyl se za daných podmínek chovaly odlišně. Jako první byl izolován [1,3]oxathiolo[4,5-*c*] chinolin-2,4-dion **III-12** společně s malým množstvím dealkylovaného 4-hydroxychinolin-2-onu **III-11**. Avšak hlavními produkty byly velmi špatně rozpustné látky **III-13**–**III-15**. Podle strukturní analýzy se podařilo dokázat, že benzylová skupina není přítomna a během reakce došlo k debenzylaci. Nejlepší metodou při analýze těchto látek byla vedle NMR metoda ESI-MS. Ta odhalila, že produktem reakce je směs mono **III-13**, di **III-14** a trisulfidů **III-15**.

Přeměny výchozích látek **III-2** a vznik produktů jsou blíže popsány v Příloze III.

Jako spoluautor jsem se podílel na: Přípravě výchozích látek 3-alkyl/ aryl-4-hydroxychinolin-2-onů, 3-alkyl/aryl-3-thiokyanatochinolin-2,4-dionů; provedení reakcí thiokyanatochinolindionů v prostředí *konc.* H_2SO_4 nebo směsi H_2SO_4 s AcOH, za přídavku oxidu fosforečného nebo chloridu hlinitého; následné izolaci a purifikaci produktů; spolupracoval jsem při identifikaci látek a sestavování rukopisu.

Reakce 4-hydroxychinolin-2-onů s thionylchloridem – Řešení okruhu zadání 4.

Klásek A.; Rudolf O.; Rouchal M.; Lyčka A.; Růžička A.: Reaction of 4-hydroxy-2-quinolones with thionyl chloride – preparation of new spiro-benzo[1,3]oxathioles and their transformations. *Tetrahedron*, **2012**, *69*, 492–499.

DOI: 10.1016/j.tet.2012

Komentář k PUBLIKACI IV

Tato práce byla motivována snahou najít syntetickou cestu vedoucí k získání čistých 3-monosulfidů bis-(4-hydroxychinolin-2-onů) z 3-nesubstituovaných 4-hydroxychinolin-2-onů (Schéma 24).

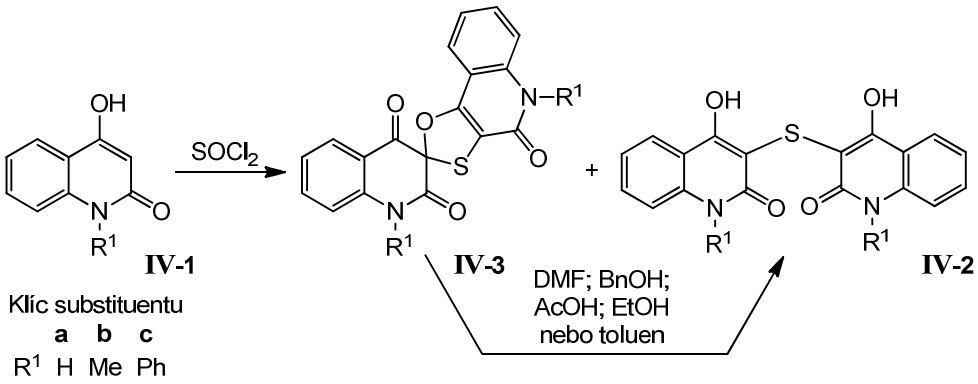


Schéma 24.

Postup podle Zieglera a Kappeho [46] má vést reakcí 3-nesubstiuovaného 4-hydroxychinolin-2-onu **IV-1** ve vroucím thionylchloridu k monosulfidu **IV-2**. Ovšem výsledky této reakce jsou v dané publikaci popsány velmi povrchně a nedostatečně. Bylo proto rozhodnuto porovnat připravené produkty debenzylace s produkty získanými metodou Zieglera a Kappeho.

Námi získané produkty byly podrobeny metodám strukturní analýzy a vykazovaly rozdílné hodnoty než u očekávaných monosulfidů **IV-2**. Sumární vzorec po elementární analýze byl jiný a stejně tak molekulová hmotnost po MS analýze. Při měření ^{13}C NMR byly pak získány signály, které odpovídaly dvěma neekvivalentním chinolonovým jádrům, a ani následné pokročilé experimenty NMR nedokázaly v plné míře odhalit strukturu produktů. Nicméně vypěstováním monokrystalu a po X-ray difrakční analýze se podařilo strukturu jednoho z produktů určit a to jako spiro[1,3-oxathiolo[4,5-*c*] chinolin-2,3´-chinolin]-2´,4,4´-trion **IV-3**.

Vedle těchto spiro-sloučenin **3** vznikaly také původně požadované monosulfidy **IV-2**. Předpokládá se, že monosulfidy vznikají až následnou transformací ze spiro-sloučenin **IV-3**. Důkazem této myšlenky je, že varem ve vybraných rozpouštědlech (BnOH, DMF) se podařilo převést spiro-benzo[1,3]thioly **IV-3** na **IV-2**. Činidlem, které s velkou pravděpodobností způsobuje zmíněnou přeměnu, je voda přítomná v nevysušených rozpouštědlech.

Přeměny výchozích látek **IV-1** a vznik produktů jsou blíže popsány v Příloze IV.

Jako spoluautor jsem se podílel na: Přípravě výchozích látek 3-nesubstiuovaných-4-hydroxychinolin-2-onů, na provedení reakcí s thionylchloridem a na reakcích ve vybraných rozpouštědlech; na následné izolaci a purifikaci produktů; na identifikaci látek a sestavování rukopisu.

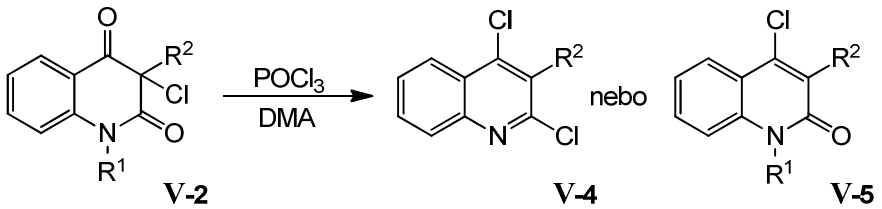
Reakce některých derivátů chinolin-2-onů s fosforylchloridem – Řešení okruhu zadání 5.

Rudolf O.; Mrkvička V.; Lyčka A.; Rouchal M.; Klásek A.: Reactions of some 2-quinolone derivatives with phosphoryl chloride: Synthesis of novel phosphoric acid esters of 4-hydroxy-2-quinolone. *Journal of Heterocyclic Chemistry*, **2013**, *50*, E100–E110.

DOI: 10.1002/jhet.1082

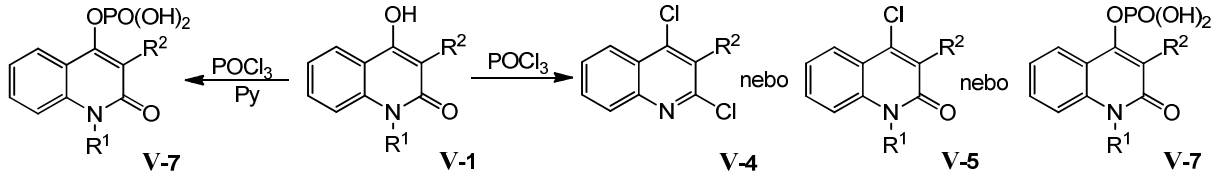
Komentář k PUBLIKACI V

3-Chlorchinolin-2,4-diony nebo 4-hydroxychinolin-2-ony reagují s fosforylchloridem, v přítomnosti nebo bez přítomnosti báze, za vzniku 4-chlorchinolin-2-onů nebo 2,4-dichorchinolinů (Schéma 25 a 26).



V-2 **V-4** **V-5**

Schéma 25.



Klic substituentu

	a	b	c	d	e	f	g	h	i	j	k	l	m
R^1	H	H	H	Me	Me	Me	Et	Bn	Bn	Ph	Ph	Ph	Ph
R^2	Bu	Bn	Ph	Bu	Bn	Ph	Ph	Bu	Ph	Me	Bu	Bn	Ph

Schéma 26.

3-Chlorchinolin-2,4-diony **V-2** jsou využívány jako jedny ze základních látek pro další syntézy, vedoucích zejména k 3-aminochinolin-2,4-dionům. Zámyslem bylo připravit jednoduchou cestou 2,3-dichlorchinolin-4-ony, které mohly sloužit pro přípravu 2,3-diaminochinolin-4-onů.

Úvodní reakce byly provedeny s vybranými 3-alkyl/aryl-3-chlorchinolin-2,4-diony **V-2** ve vroucím fosforylchloridu. I přes zahřívání směsi po dobu až pěti dní byly nazpět získány pouze nezměněné 3-chlorchinolin-2,4-diony **V-2**. 2,4-Dichlorchinoliny **V-4** byly izolovány v tom případě, že výchozí látky **V-2** nesly v pozici 3 fenyl.

Přídavkem báze, *N*,*N*-dimethylanilinu DMA, do reakční směsi byly izolovány jako hlavní produkty této reakce 2,4-dichlorchinoliny **V-4**. Ze získaných výsledků bylo vypozorováno, že *N*-alkylované chinolindiony **V-2** podléhají ochotně dealkylaci, u *N*-benzylovaných látek dochází v malé míře k debenzylaci a u *N*-fenylových látek k odtržení fenylu nedochází vůbec a produktem reakce jsou pouze 4-chlorchinolin-2-ony **V-5**.

2,4-Dichlorchinoliny **V-4** poskytovala také reakce 4-hydroxychinolin-2-onů **V-1** s fosforylchloridem, při které *N*-nesubstiuované látky **V-1** přecházely na produkty **V-4**. Pro *N*-alkylované/benzylované látky **V-1** byly hlavním produktem 4-chlorchinolin-2-ony **V-5** a malý podíl **V-4**, který se s prodlužující dobou reakce zvyšoval.

Během reakcí 3-chlorchinolindionů **V-2** ve fosforylchloridu a DMA se reakční roztok velmi intenzivně barvil do sytě modro-fialové barvy. Sloupcovou chromatografií se podařilo izolovat čistou látku posléze identifikovanou jako krystalovou či genciánovou violeť.

U některých pokusů bylo při sloupcové chromatografii izolováno malé množství látky vykazující vysokou polaritu. Tato sloučenina byla popsána jako fosforečnanový derivát chinolonu **V-7**. Podařilo se vyvinout jednoduchou syntézní cestu, jak připravit obdobné estery kyseliny fosforečné **V-7** ve vyšších výtěžcích, při ní se vychází z hydroxychinolonu **V-1**, fosforylchloridu a pyridinu jako báze.

Přeměny výchozích látek **V-2** a **V-1** a vznik produktů jsou blíže popsány v Příloze V.

Jako spoluautor jsem se podílel na: Příprava výchozích látek 3-alkyl/aryl-4-hydroxychinolin-2-onů, 3-alkyl/aryl-3-chlorchinolin-2,4-dionů; na provedení reakcí 3-chlorchinolin-2,4-dionů respektive 4-hydroxy-chinolin-2-onů v prostředí fosforylchloridu anebo fosforylchloridu a *N*,*N*-dimethylanilinu; dále na provedení reakcí 4-hydroxychinolin-2-onů s fosforylchloridem v prostředí pyridinu; na následné izolaci a purifikaci produktů; a na identifikaci látek a sestavování rukopisu.

Některé z výsledků a závěrů v tomto článku byly použity v mé bakalářské práci z roku 2007.

Pinakolinový přesmyk 3,4-dihydro-3,4-dihydroxychinolin-2-onů – Řešení okruhu zadání 6.

Rudolf O.; Rouchal M.; Lyčka A.; Klásek A.: Pinacol rearrangement of 3,4-dihydro-3,4-dihydroxyquinolin-2(1H)-ones – an alternative pathway to viridicatin alkaloids and their analogues. *Helvetica Chimica Acta*, **2013**, *96*, 1905–1917.

DOI: 10.1002/hlca.201300074

Komentář k PUBLIKACI VI

Následující publikace je rozdělena do dvou oddílů. Prvním se zabývá redukcemi 3-hydroxychinolin-2,4-dionů a ve druhém je pak charakterizován pinakolinový přesmyk 3,4-dihydro-3,4-dihydroxychinolin-2-onů působením *konc*. kyseliny sírové (Schéma 27).

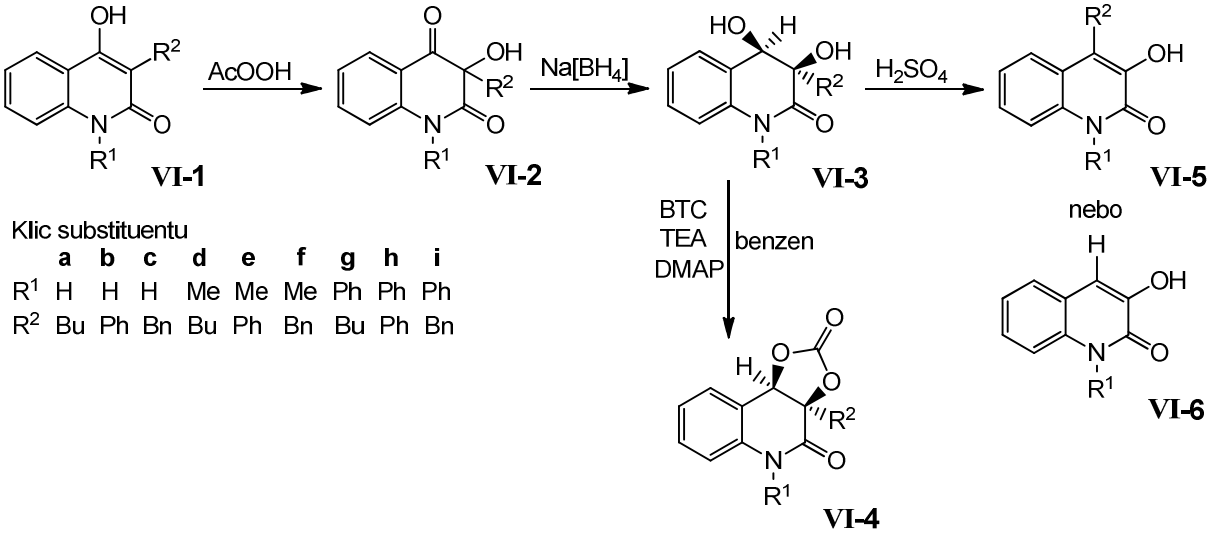


Schéma 27.

4-Hydroxychinolin-2-ony **VI-1** byly oxidovány kyselinou peroxyoctovou na 3-hydroxychinolin-2,4-diony **VI-2**. Vzniklé 3-hydroxychinolin-2,4-diony **VI-2** byly poté následně redukovány tetrahydridoboritanem sodným na 3,4-dihydroxychinolin-2-ony **VI-3** až v osmdesáti procentních výtěžcích.

Vzájemnou polohu dvou přítomných hydroxylových skupin se podařilo odvodit jak pomocí NMR experimentů, tak i reakcí 3-butyl-1-methyl-3,4_dihydroxychinolin-2-onu **VI-3d** s trifosgenem, která dávala pouze jeden typ produktu, a to cyklický karbamid **VI-4d**.

Jednou z důležitých vlastností, kterou se vicinální dioly vyznačují, je ochota podléhat pinakolinovému přesmyku, při němž podle charakteru výchozí látky, vznikají ketony nebo aldehydy. Připravené 3,4-dihydroxychinolin-2-ony **VI-3** byly podrobeny přesmyku v prostředí *konc*. kyseliny sírové. Po zpracování reakční směsi byly izolovány produkty, které oproti očekávání nevykazovaly žádné známky přítomnosti aldehydické nebo ketoskupiny. Výchozí látky **VI-3** nesoucí benzylovou skupinu poskytovaly debenzylované 3-hydroxychinolin-2-ony **VI-6**, naproti tomu ostatní výchozí látky **VI-3** dávaly 4-alkyl/aryl-3-hydroxychinolin-2-ony **VI-5**.

Přeměny výchozích látek **VI-2** a **VI-3**, a vznik produktů jsou blíže popsány v Příloze VI.

Jako spoluautor jsem se podílel na: Přípravě výchozích látek 4-hydroxychinolin-2-onů, 3-hydroxychinolin-2,4-dionů; na provedení reakcí 3-hydroxychinolin-2,4-dionů s $Na[BH_4]$; a dále na provedení přesmyku 3,4-dihydroxychinolin-2-onů v kyselém prostředí; následné izolace a čištění produktů; na identifikaci látek a sestavování rukopisu.

Redukce 3-aminochinolin-2,4-dionů a deaminace reakčních produktů – Řešení okruhu zadání 7.

Klásek A.; Lyčka A.; Rouchal M., Rudolf O.; Růžička A.: Reduction of 3-aminoquinoline-2,4-diones and deamination of the reaction products. *Helvetica Chimica Acta*, **2014**, *97*,595–612.

DOI: 10.1002/hlca.201300319

Komentář k Publikaci VII

Poslední publikace se věnuje jednak redukci 3-aminochinolin-2,4-dionů, tak deaminacím 3-amino-3,4-dihydro-4-hydroxychinolin-2-onů působením kyseliny dusité (Schéma 28).

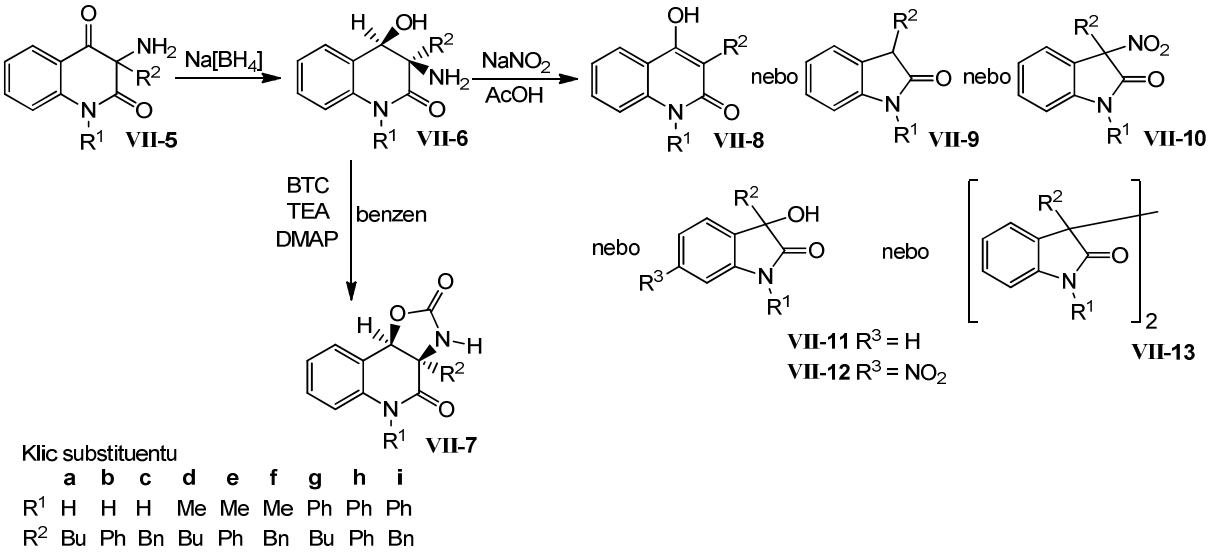


Schéma 28.

První část této práce volně navazuje na předchozí Publikaci VI. Je zaměřena na redukce tetrahydridoboritanem sodným, tentokrát ovšem 3-aminochinolin-2,4-dionů **VII-5** na výsledné 3-amino-3,4-dihydro-4-hydroxychinolin-2-ony **VII-6**.

Vzájemná poloha hydroxylové skupiny a aminoskupiny v látkách **VII-6** byla určena pomocí 2D NMR experimentů, a kontrolní reakcí látek **VII-6e** a **VII-6h** s trifosgenem. Tato reakce dávala opět pouze jeden typ produktu a to [1,3]oxazolo[4,5-*c*]chinolin-2,4-diony **VII-7e** a **VII-7h**.

Deaminací aminohydroxychinolindionů **VII-6** a následným přesmykem vzniká skupina látek se základní strukturou 3-substituovaných indolin-2-onů **VII-9**. Byly izolovány také další produkty přesmyku, např. 3-nitro- nebo 3-hydroxy-3-substiuované indolin-2-ony.

Přeměny výchozích látek **VII-5** a **VII-6** a vznik produktů jsou blíže popsány v Příloze VII.

Jako spoluautor jsem se podílel: Na přípravě výchozích látek 4-hydroxychinolin-2-onů, 3-aminochinolin-2,4-dionů; na provedení reakcí 3-aminochinolin-2,4-dionů s $Na[BH_4]$; na provedení deaminace kyselinou dusitou; a na následné izolaci a čištění produktů; na identifikaci látek a sestavování rukopisu.

5. PŘÍNOS PRO VĚDU A PRAXI

Přínos této práce pro vědu a praxi spočívá ve více bodech. Jako výhodu našich postupů lze považovat využívání jednoduchých, dostupných a levných činidel schopných transformovat výchozí látky (substituované chinolin-2,4-diony) na poměrně komplikované struktury. Pro námi provedené reakce není třeba využívat složité katalytické systémy, inertní atmosféru nebo absolutizovaná rozpouštědla.

Podařilo se obohatit heterocyklickou chemii také o vědomosti a praktické dovednosti v oblasti příprav některých výchozích substituovaných chinolin-2,4-dionů a jejich dalších přeměn v rozmanité heterosystémy.

Z konkrétních přínosů jednotlivých publikací lze uvést například tyto:

- Byla otevřena nová syntetická cesta vedoucí k novým imidazochinolinonům, imidazochinazolinonům a jejich sirným analogům na základě jednoduché reakce 3-aminochinolindionů s kyanatou nebo isothiokyanatou kyselinou.
- Bylo popsáno několik případů *C*-debenzylace při výše uvedených reakcích 3-amino-3-benzylchinolin-2,4-dionů s isothiokyanatou kyselinou.
- Dříve neznámé dealkylace výchozích 3-thiokyanátochinolindionů byly popsány také v průběhu *Riemschneiderovy* reakce.
- Podařilo se napravit mylnou literární informaci o průběhu reakce thionylchloridu s 4-hydroxychinolin-2-ony.
- Podrobné studium reakce fosforylchloridem s některými deriváty 2-chinolonu za různých reakčních podmínek umožnilo přípravu nových fosforečných esterů 4-hydroxychinolin-2-onů.
- Bylo zjištěno, že redukce 3-hydroxy- a 3-aminochinolin-2,4-dionů pomocí tetrahydridoboritanu sodného probíhá stereospecificky za vzniku *cis*-diolů resp. *cis*-aminoalkoholů. Získané produkty byly využity ke studiu molekulárních přesmyků, které poskytly jednak analoga chinolinových alkaloidů, tak nové látky na bázi indolonů.
- Bylo potvrzeno, že také redukce 3-aminochinolindionů tetrahydridoboritanem sodným probíhá stereospecificky a získané aminoalkoholy lze deaminovat kyselinou dusitou za vzniku indolonových derivátů.

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SEZNAM ZKRATEK

AcOH	kyselina octová
aq	vodný roztok
BAS	benzalaceton syntáza
Bn	benzyl
BnOH	benzylalkohol
Boc_2O	di-*t*-butyl dikarbonát
BTC	bis(trichlormethyl)karbonát – trifosgen
Bu	butyl
DBU	1,8-diazabicyklo[5.4.0]undek-7-en
DMA	*N*,*N*-dimethylanilin
DMAP	*N*,*N*-dimethylaminopyridin
DMF	*N*,*N*-dimethylformamid
ESI-MS	hmotnostní spektrometrie s elektronsprejovou ionizací
KAPA	3-aminopropylamid draselný
KHMDS	bis(trimethylsilyl)amid draselný
konc.	koncentrovaný
LDA	lithium diisopropylamid
LiHMDS	bis(trimethylsilyl)amid lithný
MS	hmotnostní spektrometrie
NAPA	3-aminopropylamid sodný
NaH	hydrid sodný
NMR	nukleární magnetická rezonance
Ph	fenyl
Ph_2O	difenylether
PPA	kyselina polyfosforečná
TEA	triethylamin
TFA	kyselina trifluoroctová
TU	thiomočovina

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Reaction of 3-aminoquinoline-2,4-diones with isothiocyanic acid—an easy pathway to thioxo derivatives of imidazo[1,5-*c*]quinazolin-5-ones and imidazo-[4,5-*c*]quinolin-4-ones

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ABSTRACT

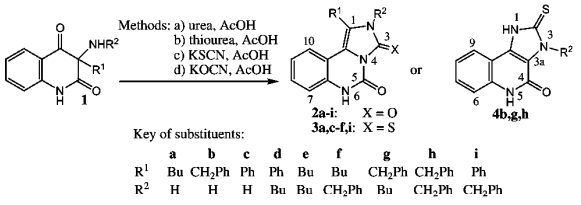
3-Amino-1*H*,3*H*-quinoline-2,4-diones react with thiourea or potassium thiocyanate in boiling acetic acid to give novel 2,3-dihydro-3-thioxoimidazo[1,5-*c*]quinazolin-5(6*H*)-ones in high yields. However, if the starting compounds are substituted with a benzyl group at position 3, a C-debenzylation proceeds to give 2,3-dihydro-2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones. According to a proposed reaction mechanism, a molecular rearrangement of the primarily formed mono-substituted thiourea takes place. All compounds were characterized by ^{1}H, ^{13}C and ^{15}N NMR and IR spectroscopy as well as by mass spectrometry.

1. Introduction

In our laboratory, much attention has been paid to the reactivity of 3-alkyl/aryl-3-amino-quinolinediones **1**. The addition products of these compounds with isocyanic acid (from the decomposition of urea or nitrourea) or isocyanates rearrange in an acidic medium to give imidazoquinazolines, oxindoles, indolylureas, bis[2-(imidazolyl)phenyl]ureas, imidazol-ones, or spiro-linked imidazolidine-oxindoles, depending on the character of the substituents. An illustrative survey of these transformations is given in our last paper on this topic.[1]

The exceptional structural diversity of the reaction products of the molecular rearrangement mentioned above gave us incentive to perform an analogous reaction of 3-aminoquinolinediones **1** with isothiocyanates. We have found that the addition products of **1** with isothiocyanates also rearrange in an acidic medium, resulting in (*E*)- and/or (*Z*)-4-butylidene-2-thioxo-1′*H*-spiro[imidazoline-5,3′-indole]-2,2′-diones,[2] 4-(2-aminophenyl)-1*H*-imid-azole-2(3*H*)-thi-ones,[3] and 1,3-bis(2-(2,3-dihydro-2-thioxo-1*H*-imidazol-5-yl)phenyl)ureas.[3] Owing to the simple reaction protocols, these transformations open an easy pathway to the preparation of new types of heterocyclic compounds.

We have described the reaction of 3-amino-1*H*,3*H*-quinoline-2,4-diones **1** with urea in boiling acetic acid, which produces novel 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones **2** (Scheme 1, method A).[4] In anticipation of the possibility that 3-aminoquinolinediones **1** could have reacted analogously with isothiocyanic acid, we carried out experiments leading to this objective. We demonstrate in this work that the reaction of 3-aminoquinolinediones **1** with potassium thiocyanate in boiling acetic acid yields two structurally diverse products **3** and **4**, whereas the reaction of **1** with urea or potassium cyanate produces only single product **2**.



Scheme 1.

2. Results and discussion

Reactions of aminoketones **1** with compounds providing isocyanic or isothiocyanic acid (potassium cyanate, urea, thiourea,

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potassium thiocyanate) were performed by boiling the reaction components in acetic acid (Table 1). The starting aminoketones **1** were obtained from the corresponding 3-chloro derivatives in accordance with procedures described earlier.[5]

Table 1
Reactions of 3-aminoquinolinediones **1** with urea (method A)[a], thiourea (method B), KSCN (method C) and KOCN (method D)

Ewntry	Starting compound			Method	Time (min)	Products (yield, %)
	1	R^1	R^2			
1	**a**	Bu	H	A	90	**2a** (73)
2				B	30	**3a** (5), **Ac-1a** (18)[b]
3				C	5	**3a** (93)
4				D	60	**2a** (62)
5	**b**	Bz	H	A	20	**2b** (71)
6				B	30	**1b** (22)[b]
7				C	5	**4b** (70)
8				D	30	**2b** (64)
9	**c**	Ph	H	A	5	**2c** (90)
10				B	30	**3c** (16)
11				C	9	**3c** (82)
12				D	50	**2c** (58)
13	**d**	Ph	Bu	A	30	**2d** (76)
14				B	30	**3d** (2), **1d** (12)[c]
15				C	30	**3d** (70)
16				D	25	**2d** (80)
17	**e**	Bu	Bu	A	30	**2e** (95)
18				B	25	**3e** (3), **1e** (45)[c]
19				C	30	**3e** (79)
20				D	40	**2e** (78)
21	**f**	Bu	Bz	A	30	**2f** (93)
22				B	65	**3f** (4), **1f** (24)[c]
23				C	30	**3f** (53)
24				D	60	**2f** (74)
25	**g**	Bz	Bu	A	120	**2g** (87)
26				B	20	**4g** (4), **1g** (57)[c]
27				C	5	**4g** (66)
28				D	120	**2g** (74)
29	**h**	Bz	Bz	A	120	**2h** (66)
30				B	30	**1h** (21)[a]
31				C	10	**4h** (71)
32				D	130	**2h** (64)
33	**i**	Ph	Bz	A	—	—
34				B	120	**3i** (33), **1i** (3)[c]
35				C	30	**3i** (78)
36				D	120	**2i** (67)

[a] Data from Ref. 4.
[b] *N*(3)-Acetylated compound **1a**, identical in all respects to the authentic compound.[6]
[c] Recovered starting material.

We have found that the reactions of **1** with thiourea (method B) are relatively unsuccessful and in many cases only the starting compound was recovered (Table 1).

In contrast to urea, thiourea decomposes to isothiocyanic acid in only small amounts under the given reaction conditions. Therefore, we focused our attention on the reaction of **1** with potassium thiocyanate (method C). This reaction affords two different sets of products (Table 1). The first group of the products has ^{1}H and ^{13}C NMR spectra that are very similar to those of compounds **2**.[4] The only exception is the presence of NMR signals in the δ 160.1–161.6 ppm region (Table 2). It is evident that these signals can be attributed to C=S carbon atoms at the position 3; therefore, compounds of the first group are 2,3-dihydro-3-thioxoimidazo[1,5-*c*]quinazolin-5(6*H*)-ones **3a**,**c**–**f**,**i**. In cases **3a** and **3c**, the NH proton signals appear at δ 12.87 and 10.98 or 13.22 and 11.11 ppm. The occurrence of ^1J (^{15}N,^{1}H) for all of these protons (Table 2) excludes the possibility of S–H tautomers.

Mass spectra of compounds in the second group exhibit a molecular peak, that is, *m*/*z* 90 less than expected. In addition, signals corresponding to the C-benzyl group were not found in ^{1}H and ^{13}C NMR spectra of the reaction products from **1b**,**g**,**h**, which shows that a C-debenzylation must occur during the reaction. We postulated that the reaction products were 2,3-dihydro-2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones **4b**,**g**,**h**. These structures were confirmed by certain assignment of all resonances using 2D NMR spectra (Table 3). In the NOESY spectrum, the H-1 protons have a cross-peak with the H-9 protons and the CONH protons have a cross-peak with the H-6 protons, which evidences their spatial vicinity. The determination of ^1J (^{15}N,^{1}H) for all NH protons (Table 3) excludes the possibility of the presence of S–H tautomers.

For comparison, we also carried out the reaction of compounds **1** with potassium cyanate in boiling acetic acid (Table 1, method D). From these experiments, only compounds **2** were obtained in yields somewhat lower than those obtained by method A.[4] A C-debenzylation was not observed in any case. This result pointed to the decisive conclusion that potassium thiocyanate is required for the debenzylation process. From potassium thiocyanate, only weak thiocyanic acid H-SCN (pK_a 5.4)[7] can be liberated with acetic acid (pK_a 4.75). However, this weak acid isomerizes promptly to the more stable isothiocyanic acid H-NCS, which is very strong acid (pK_a −1.3).[7,8] The formation of this acid causes the strong acidification of the reaction mixture, which leads to C-debenzylation. We have observed a similar reaction (C-debutylation) in the case of 3-butyl-3-thiocyanato-quinoline-2,4-diones during their reaction with concentrated sulfuric acid in the presence of phosphorus pentoxide.[9] Isocyanic acid (pK_a 3.9), arising from potassium cyanate and acetic acid through the weak isomeric cyanic acid (pK_a 6.4), is a mesoscale acid and does not induce a debenzylation of compounds **1**.

The proposed reaction mechanism (Scheme 2) supposes the addition of α-aminoketone **1** to isocyanic or isothiocyanic acid. This would create the intermediate **A**, which cyclizes to intermediate **B** and subsequently converts into intermediate **D**. In a medium-acidity environment, both of these intermediates convert to the isocyanate intermediate **C**, which provides product **2** (X=O) or **3** (X=S). The rearrangement of intermediate **B** to isocyanate intermediate **C** was observed in the reaction of compounds **1** with isocyanates.[10] On the other hand, in a strong-acidic medium, protonation of intermediate **D** proceeds and the protonated intermediate **D** stabilizes by ejecting the benzylic cation. We presumed that this cation reacts with high nucleophilic thiocyanate anion. Indeed, the presence of benzyl thiocyanate as the main component of the benzene extract of the aqueous portion after reaction of **1g** with potassium thiocyanate was evidenced by TLC analysis in three different solvent systems. This extract contains also a small quantity of benzyl alcohol; however, the presence of benzyl acetate was not observed.

3. Conclusions

In conclusion, we would like to emphasize that the described reaction of 3-aminoquinolinediones **1** with isothiocyanic acid generated from potassium thiocyanate allows the preparation, in very good yields, of 2,3-dihydro-3-thioxoimidazo[1,5-*c*]quinazolin-5(6*H*)-ones (**3**) and 2,3-dihydro-2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones (**4**). Compounds **3** have not been previously described in the literature. Since many biologically active compounds contain a sulfur atom,[11,12] compounds **3** could also be interesting structures for study.

The C-debenzylation of starting compounds **1** bearing a benzyl group at position 3 not only has theoretical significance, but enables the targeted preparation of compounds **4** through a simple procedure. To our surprise, only one compound of this type, described as tautomeric 5-butyl-2-mercapto-1-methyl-1*H*-imidazo

Table 2
^{1}H and ^{13}C chemical shifts of compounds **2i** and **3a,c–f,i** in DMSO-d_6

Position	**2i**		**3a**		**3c**		**3d**		**3e**		**3f**		**3i**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	—	117.8	—	123.9	—	122.6	—	123.8	—	125.0	—	125.2	—	123.9
3	—	148.3	—	160.7	—	161.6	—	160.2	—	160.1	—	161.4	—	161.4
5	—	145.0	—	145.1	—	145.1	—	144.8	—	144.8	—	144.8	—	144.8
6	10.81	—	10.98[a]	—	11.11[b]	—	11.17	—	11.06	—	11.13	—	11.23	—
6a	—	134.5	—	134.3	—	134.6	—	134.4	—	134.2	—	134.3	—	134.5
7	7.04	115.3	7.09	115.1	7.10	115.3	7.10	115.2	7.11	115.1	7.13	115.2	7.12	115.3
8	7.18	128.3	7.29	128.0	7.27	128.8	7.25	128.9	7.32	128.3	7.32	128.5	7.26	129.0
9	6.79	122.6	7.15	123.2	6.90	122.6	6.84	122.7	7.19	123.3	7.18	123.3	6.83	122.7
10	6.73	121.2	7.63	121.8	7.19	120.9	6.67	121.4	7.66	122.0	7.61	122.1	6.68	121.5
10a	—	112.9	—	113.4	—	112.7	—	112.2	—	112.7	—	112.6	—	112.2
10b	—	113.5	—	119.8	—	120.3	—	120.3	—	119.3	—	119.7	—	120.8
1′(R^1)	—	128.1	2.83	24.2	—	128.2	—	128.0	2.99	23.7	2.84	24.1	—	127.7
2′(R^1)	7.40	131.0	1.62	30.0	7.60	129.2	7.63	131.2	1.60	30.1	1.20	29.4	7.36	131.0
3′(R^1)	7.55	129.4	1.40	21.7	7.60	129.9	7.70	129.8	1.53	21.9	1.34	21.8	7.54	129.5
4′(R^1)	7.58	130.1	0.94	13.8	7.60	129.9	7.70	130.6	0.99	13.7	0.81	13.6	7.61	130.5
1′(R^2)	4.72	43.9	12.87[c]		13.22[d]		3.91	43.7	4.18	43.2	5.65	46.2	5.29	46.9
2′(R^2)	—	137.0	—	—	—	—	1.52	28.9	1.69	29.5	—	136.4	—	136.0
3′(R^2)	6.99	126.7	—	—	—	—	1.14	19.3	1.43	19.6	7.28	126.7	6.98	126.7
4′(R^2)	7.27	128.5	—	—	—	—	0.72	13.5	0.99	13.7	7.39	128.7	7.24	128.3
5′(R^2)	7.27	127.3	—	—	—	—	—	—	—	—	7.32	127.5	7.24	127.2

[a] ^{1}J (15N, 1H)=97.4 Hz.
[b] ^{1}J (15N, 1H)=91.5 Hz.
[c] ^{1}J (15N, 1H)=92.1 Hz.
[d] ^{1}J (15N, 1H)=97.6 Hz.

Table 3
^{1}H, ^{13}C and ^{15}N chemical shifts of compounds **4b,g,h** in DMSO-d_6

Position	**4b**		**4g**		**4h**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1 (NH)	13.57[a]	−219.4[b]	13.81	[b,c]	13.96[d]	—
2	—	167.1	—	166.2	—	167.5
3 (NR^2)	13.30[e]	−221.9[b]	—	−214.1[b]	—	—
3a	—	119.3	—	118.0	—	117.9
4	—	152.4	—	152.9	—	152.8
5 (NH)	11.90[f]	−233.9[b]	11.93[g]	−232.6[b]	11.95	—
5a	—	136.4	—	136.3	—	136.4
6	7.46	116.2	7.47	116.1	7.47	116.2
7	7.52	128.9	7.53	129.2	7.54	129.3
8	7.30	122.3	7.31	122.4	7.29	122.5
9	8.05	121.7	8.09	121.7	8.11	121.8
9a	—	109.7	—	109.5	—	109.5
9b	—	133.4	—	132.8	—	133.1
1′(R^2)	13.30[g]	−221.9[b]	4.50	44.4	5.76	47.3
2′(R^2)	—	—	1.79	30.9	—	137.3
3′(R^2)	—	—	1.38	19.4	7.43	127.7
4′(R^2)	—	—	0.96	13.8	7.32	128.3
5′(R^2	—	—	—		7.26	127.3

[a] ^{1}J (^{15}N, ^{1}H)=98.1 Hz.
[b] δ (^{15}N).
[c] Not found.
[d] Broadened signal.
[e] ^{1}J (^{15}N, ^{1}H)=99.4 Hz.
[f] ^{1}J (^{15}N, ^{1}H)=89.7 Hz.
[g] ^{1}J (^{15}N, ^{1}H)=90.0 Hz.

[4,5-*c*]quinolin-4(5*H*)-one, was found in the literature. This compound, which induces contraction in tracheal strips of passively sensitized guinea pigs, was prepared by five different multi-step reactions starting from 3-nitroquinolin-2-ones bearing a hydroxy, chloro, or methylamino substituent in position 4.[13]

4. Experimental

4.1. General

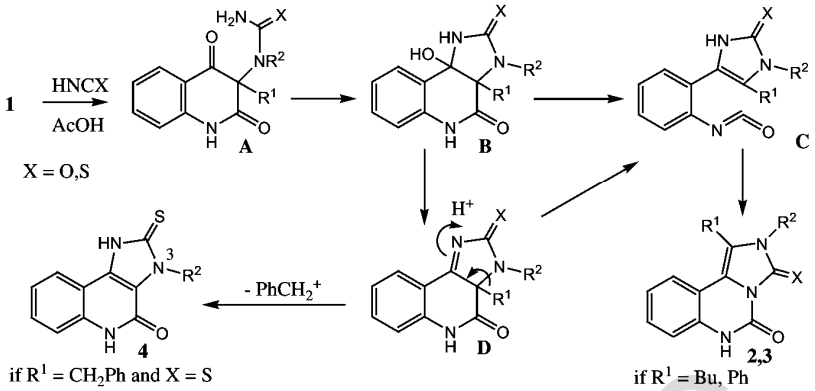
Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, 50.68 MHz for ^{15}N) in DMSO-d_6 or $CDCl_3$. ^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS. ^{15}N chemical shifts were referred to external neat nitromethane in co-axial capillary (δ=0.0). All 2D experiments (gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. Proton spectra were assigned using gs-COSY. Protonated carbons were assigned by gs-HMQC. Quaternary carbons were assigned by gs-HMBC. The positive-ion EI mass spectra were measured on a Shimadzu QP-2010 instrument within the mass range m/z=50–600 using direct inlet probe (DI). Samples were dissolved in dichloromethane (30 μg/mL) and 10 μL of the solution was evaporated in DI cuvette at 50 °C. The ion source temperature was 200 °C; the energy of the electrons was 70 eV. Only signals exceeding relative abundance of 5% are listed. Column chromatography was carried out on Silica gel (Merck, grade 60, 70–230 mesh) using chloroform and then successive mixtures of chloroform/ethanol (in rations from 99:1 to 8:2) or benzene and then successive mixtures of benzene/ethyl acetate (in rations from 99:1 to 8:2). Reactions as well as the course of separation and also the purity of substances were monitored by TLC in elution systems benzene/ethyl acetate (4:1), chloroform/ethanol (9:1 and/or 19:1) and chloroform/ethyl acetate (7:3) on Alugram® SIL G/UV_{254} foils (Macherey–Nagel). Elemental analyses (C, H, N) were performed with a EA 1108 Elemental Analyzer (Fisons Instrument) at our Institute.

4.2. Starting 3-amino-1*H*,3*H*-quinoline-2,4-diones (1)

Compounds (**1**) were prepared from corresponding 3-chloro derivatives according to the protocol described in literature.[6]

4.3. General procedure for the preparation of compounds 2, 3 and 4

A mixture of appropriate 3-amino-1*H*,3*H*-quinoline-2,4-dione (**1a–i**) (1 mmol) and appropriate reagent (see below) in acetic acid (3 mL) was heated to reflux for the time given in Table 1. The



Scheme 2.

course of reaction was monitored by TLC. After cooling, the reaction mixture was poured onto ice (50 g). The precipitated product was filtered off and triturated with a solution of sodium hydroxide (1 M, 50 mL) to remove cyanuric acid or 1,3,5-trithiocyanuric acid. The insoluble portion was filtered off with suction and recrystallized from an appropriate solvent. Using method B, the aqueous portion after filtration of the precipitated product was basified with ammonia and extracted three times with chloroform. The collected extracts were evaporated and the residue was crystallized from appropriate solvent or column chromatographed.

Method A: Urea was used as reagent; see Ref. 4.

Method B. Thiourea (457 mg, 6 mmol) was used as reagent.

Method C. Potassium thiocyanate (583 mg, 6 mmol) was used as reagent.

Method D. Potassium cyanate (487 mg, 6 mmol) was used as reagent.

In the case of **1g**, the aqueous portion after filtration of **4g** was extracted with benzene. The extract was dried with anhydrous potassium carbonate and analyzed by TLC using benzyl acetate, benzyl thiocyanate and benzyl alcohol as reference compounds.

*4.3.1. 2-Benzyl-1-phenyl-2,6-dihydroimidazo[1,5-c]quin-azoline-3,5-dione (**2i**).* Yield 246 mg (67%, method D). Colourless prisms, mp 290–296 °C (acetic acid). IR: 3295, 3250, 3065, 2931, 2865, 1763, 1751, 1679, 1635, 1614, 1589, 1495, 1483, 1445, 1376, 1365, 1347, 1326, 1315, 1266, 1174, 1071, 1030, 1011, 970, 924, 915, 884, 790, 755, 740, 697, 669, 654, 599, 583, 521 cm^{-1}. For ^{1}H and ^{13}C NMR see Table 2. EIMS *m/z* (%): 368 (21), 367 (M^+, 81), 277 (19), 276 (99), 248 (10), 235 (13), 234 (71), 206 (22), 205 (10), 161 (6), 149 (7), 133 (6), 132 (8), 118 (6), 117 (6), 106 (6), 105 (43), 104 (16), 92 (11), 91 (100), 90 (13), 77 (34), 76 (6), 72 (8), 71 (6), 65 (26), 57 (10), 55 (7), 51 (13), 41 (7). Anal. Calcd (found) for $C_{23}H_{17}N_3O_2$: C 75.19 (75.15); H 4.66 (4.67); N 11.44 (11.35).

*4.3.2. 1-Butyl-2,3-dihydro-3-thioxoimidazo[1,5-c]quin-azolin-5(6H)-one (**3a**).* Yield 14 mg (5%, method B) or 254 mg (93%, method C). Colourless needles, mp 305–313 °C dec (AcOH). IR: 3080, 2947, 2925, 2865, 2748, 1721, 1636, 1615, 1589, 1498, 1448, 1386, 1360, 1285, 1253, 1226, 1127, 1075, 826, 779, 753, 741, 527, 485 cm^{-1}. EIMS: *m/z* (%): 273 (M^+, 59), 230 (100), 201(9), 187 (5), 172 (50), 144 (10), 130 (27), 116 (15), 102 (20), 90 (9), 77 (8), 63 (6), 52 (8). Anal. Calcd (found) for $C_{14}H_{15}N_3OS$: C 61.51 (61.55); H 5.53 (5.50); N 15.37 (15.31); S 11.73 (11.71).

*4.3.3. 2,3-Dihydro-1-phenyl-3-thioxoimidazo[1,5-c]quin-azolin-5(6H)-one (**3c**).* Yield 241 mg (82%, method C). Yellowish plates, mp 356–362 °C (acetic acid). IR: 3077, 2986, 2919, 1731, 1633, 1615, 1591, 1506, 1488, 1445, 1388, 1345, 1256, 1224, 1159, 1131, 1101, 1067, 781, 754, 699, 669, 569 cm^{-1}. EIMS: *m/z* (%): 293 (M^+, 100), 260 (10), 234 (17), 206 (8), 190 (8), 117 (9), 104 (16), 89 (6), 77 (9), 51 (5). Anal. Calcd (found) for $C_{16}H_{11}N_3OS$: C 65.51 (65.30); H 3.78 (3.76); N 14.32 (14.44); S 10.93 (11.00).

*4.3.4. 2-Butyl-2,3-dihydro-1-phenyl-3-thioxoimidazo[1,5-c]quinazolin-5(6H)-one (**3d**).* Yield 7 mg (2%, method B) or 245 mg (70%, method C). Colourless needles, mp 265–267 °C (acetic acid). IR: 3226, 3163, 3098, 2955, 2932, 2871, 1727, 1654, 1615, 1592, 1484, 1394, 1375, 1330, 1292, 1266, 1229, 1183, 1134, 1076, 1061, 1025, 1000, 921, 864, 829, 790, 757, 742, 711, 696, 671, 588 cm^{-1}. EIMS *m/z* (%) 349 (M^+, 37), 316 (100), 293 (45), 260 (6), 233 (13), 206 (8), 190 (8), 149 (7), 135 (7), 111 (11), 104 (19), 97 (19), 85 (21), 71 (29), 57 (55). Anal. Calcd (found) for $C_{20}H_{19}N_3OS$: C 68.74 (68.55); H 5.48 (5.46); N 12.02 (11.98); S 9.18 (8.97).

*4.3.5. 1,2-Dibutyl-2,3-dihydro-3-thioxoimidazo[1,5-c]quinazolin-5(6H)-one (**3e**).* Yield 10 mg (3%, method C) or 260 mg (79%, method D). Colourless prisms, mp 273–274 °C (acetic acid). IR: 3239, 3190, 3130, 2956, 2930, 2871, 1727, 1629, 1612, 1590, 1490, 1467, 1377, 1342, 1291, 1261, 1231, 1154, 1134, 1080, 1052, 1016, 937, 909, 822, 741, 696, 682, 660, 574, 556, 537 cm^{-1}. EIMS: *m/z* (%): 329 (M^+, 44), 296 (100), 272 (12), 254 (7), 245 (8), 231 (31), 172 (15), 130 (10), 69 (6), 55 (16). Anal. Calcd (found) for $C_{18}H_{23}N_3OS$: C 65.62 (65.56); H 7.04 (7.03); N 12.75 (12.81); S 9.73 (9.68).

*4.3.6. 2-Benzyl-1-butyl-2,3-dihydro-3-thioxoimidazo[1,5-c]quinazolin-5(6H)-one (**3f**).* Yield 15 mg (4%, method B) or 193 mg (53%, method C). Colourless needles, mp 253–254 °C (acetic acid). IR: 3190, 2955, 2928, 2870, 1729, 1612, 1590, 1492, 1455, 1397, 1375, 1324, 1291, 1245, 1216, 1153, 1126, 1089, 1054, 1023, 967, 911, 841, 822, 754, 741, 710, 695, 585, 569, 550, 535 cm^{-1}. EIMS: *m/z* (%): 363 (M^+, 65), 330 (77), 321 (15), 288 (6), 272 (19), 230 (28), 218 (9), 172 (10), 130 (7), 97 (7), 91 (100), 85 (10), 71 (12), 65 (16), 57 (20). Anal. Calcd (found) for $C_{21}H_{21}N_3OS$: C 69.39 (69.52); H 5.82 (5.86); N 11.56 (11.58); S 8.82 (8.72).

*4.3.7. 2-Benzyl-2,3-dihydro-1-phenyl-3-thioxoimidazo [1,5-c]quinazolin-5(6H)-one (**3i**).* Yield 127 mg (33%, method B) or 299 mg (78%, method C). Colourless plates, mp 282–284 °C (acetic acid). IR: 3230, 3166, 3102, 3064, 3003, 2946, 1727, 1645, 1590, 1484, 1443, 1425, 1382, 1324, 1253, 1233, 1077, 836, 789, 758, 743, 712, 700, 670, 568 cm^{-1}. EIMS: *m/z* (%) 383 (M^+, 64), 350 (99), 234 (91), 206 (15), 149 (6), 135 (12), 111 (11), 104 (13), 97 (16), 91 (100), 85 (19), 71 (26), 65 (20), 57 (50). Anal. Calcd (found) for

$C_{23}H_{17}N_3OS$: C 72.04 (72.11); H 4.47 (4.51); N 10.96 (10.94); S 8.36 (8.16).

*4.3.8. 2,3-Dihydro-2-thioxo-1H-imidazo[4,5-c]quinolin-4(5H)-one (**4b**).* Yield 152 mg (70%, method C). Colourless needles, mp>350 °C dec (acetic acid). IR: 3071, 3009, 2928, 2844, 1709, 1655, 1619, 1573, 1500, 1481, 1450, 1426, 1384, 1340, 1257, 1200, 1164, 1154, 964, 941, 885, 769, 688, 624, 602, 516, 470 cm^{-1}. EIMS *m/z* (%): 217 (M^+, 100), 207 (9), 185 (18), 157 (7), 118 (5), 103 (23), 91 (5), 76 (14), 65 (7), 51 (9). Anal. Calcd (found) for $C_{10}H_7N_3OS$: C 55.29 (55.39); H 3.25 (3.41); N 19.34 (19.37); S 14.76 (14.64).

*4.3.9. 1-Butyl-2,3-dihydro-2-thioxo-1H-imidazo[4,5-c]quinolin-4 (5H)-one (**4g**).* Yield 11 mg (4%, method B) or 180 mg (66%, method C). Colourless needles, mp>350 °C (acetic acid). IR: 3101, 2993, 2870, 1661, 1615, 1571, 1520, 1500, 1466, 1442, 1370, 1347, 1289, 1256, 1243, 1208, 1151, 1101, 1035, 939, 853, 799, 746, 699, 679, 603, 536 cm^{-1}. EIMS: *m/z* (%): 273 (M^+, 47), 240 (62), 231 (8), 217 (100), 129 (12), 103 (11). Anal. Calcd (found) for $C_{14}H_{15}N_3OS$: C 61.51 (61.58); H 5.53 (5.53); N 15.37 (15.57); S 11.73 (11.59).

*4.3.10. 3-Benzyl-2,3-dihydro-2-thioxo-1H-imidazo[4,5-c]quinolin-4 (5H)-one (**4h**).* Yield 218 mg (71%, method C). Colourless prisms, mp>350 °C (acetic acid). IR: 3420, 3103, 3046, 2991, 2890, 2836, 1659, 1614, 1571, 1518, 1496, 1477, 1456, 1434, 1377, 1346, 1322, 1254, 1201, 1145, 1102, 1077, 1033, 993, 935, 868, 794, 751, 705, 674, 604, 585, 528 cm^{-1}. EIMS: *m/z* (%) 307 (M^+, 365), 274 (24), 137 (5), 129 (7), 97 (11), 92 (9), 91 (100), 83 (13), 71(13), 69 (15), 59 (22), 55 (33). Anal. Calcd (found) for $C_{17}H_{13}N_3OS$: C 66.43 (66.37); H 4.26 (4.27); N 13.67 (13.46); S 10.43 (10.15).

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PŘÍLOHA II

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Reaction of 1-substituted 3-aminoquinolinediones with isocyanic and isothiocyanic acid

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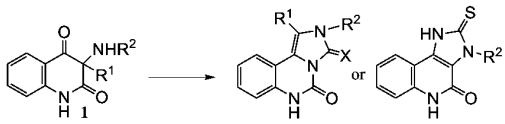
ABSTRACT

1-Substituted-3-aminoquinoline-2,4(1*H*,3*H*)-diones react with potassium cyanate or potassium thiocyanate in boiling acetic acid to give ureido- or thioureidooxindoles, spiro-oxindoles and dihydroimidazoquinolones. However, if the starting compounds are substituted with a benzyl group at position 3, a C-debenzylation proceeds to give imidazoquinolones. According to a proposed reaction mechanism, a molecular rearrangement of the primarily formed mono-substituted urea or thiourea takes place. All compounds were characterized by ^{1}H, ^{13}C and IR spectroscopy and MS data.

1. Introduction

Recently, we published the reaction of 1-unsubstituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **1** with isothiocyanic acid (prepared in situ from potassium thiocyanate) in boiling acetic acid.[1] During a rearrangement of the addition products, novel 2,3-dihydro-3-thioxoimidazo[1,5-*c*]quinazolin-5(6*H*)-ones **2** arose in high yields. However, if the starting compounds were substituted with a benzyl group at position 3, a C-debenzylation proceeded to give 2,3-dihydro-2-thioxo-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones **3**. When using thiourea as a source of thiocyanic acid, the yields of compounds **2** and **3** were substantially lower. The reaction of **1** with urea[2] or potassium cyanate[1] in boiling acetic acid resulted in no observed C-debenzylation; instead, only 2,6-dihydro-imidazo[1,5-*c*]quinazoline-3,5-diones **4** were obtained (Scheme 1).

These interesting results gave us the incentive to perform analogous reactions with 1-substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **5**. We had studied the reaction of these compounds with urea in acetic acid earlier[3] and, depending on the type of substitution at position 3 and on the nitrogen atom of the 3-amino group, four novel types of heterocyclic compounds (**6**–**9**) could be obtained (Scheme 2). All of these compounds arose due to rearrangement of the intermediate 3-ureido-1*H*,3*H*-quinoline-2,4-diones or 9b-hydroxy-



2; X = S
4; X = O

3; if $R^1 = CH_2Ph$

Scheme 1.

3,3a,5,9b-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-2,4-diones, which are obtained by the reaction of **5** with nitrourea and subsequently converted to **6**–**9** by boiling in acetic acid.[4]

In this work, we would like to describe the reaction of 1-substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **5** with potassium cyanate or potassium thiocyanate in boiling acetic acid. In the reaction of **5** with potassium cyanate, we expect the formation of the same products (**6**–**9**) as those produced in the reaction with urea.[3] The production of novel sulfur analogues of compounds **6**–**9** are expected when using potassium thiocyanate. Finally, the formation of 1-substituted analogues of compounds **3** is expected when the starting compound bears a benzyl group at position 3.

2. Results and discussion

Reactions of 3-aminoquinolinediones **5** with the appropriate reagent (Scheme 2) were performed by boiling the reaction

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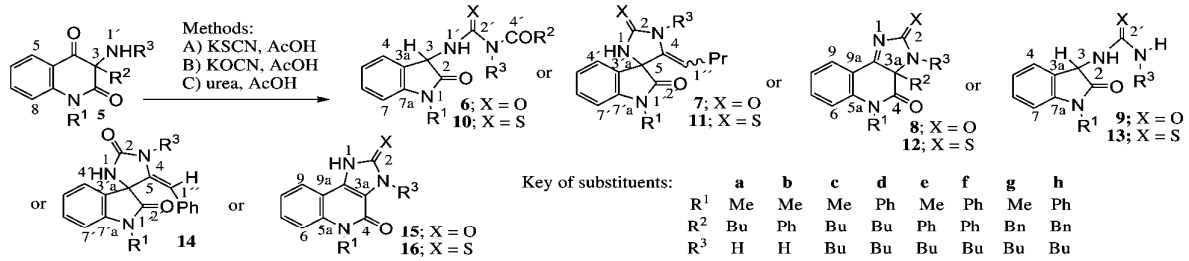


Scheme 2.

components in acetic acid. Starting aminoketones **5** were prepared from the corresponding 3-chloro derivatives in accordance with the procedure described earlier.[5] Potassium thiocyanate (method A) or potassium cyanate (method B) were used as reagents. In two cases (compounds **5g,h**), urea was also used. In preliminary experiments, reaction of thiourea with compounds **1**[1] and **5** did not give good results; accordingly, we did not use this reagent further in our work. The trituration of the crude reaction product with sodium hydroxide solution, described in our previous paper[1] to remove traces of cyanuric or 1,3,5-trithiocyanuric acid, was omitted due to the high solubility of some reaction products in an alkaline medium.

We have found that the reaction of **5a–f** with potassium cyanate (method B) proceed in the same manner as those with urea.[3] Compounds **6a,b,e,f**, **7c,d**, **8e,f** and **9e** were isolated (Table 1) in yields comparable to those obtained from the reaction of **5a–f** with urea.[3] In addition, a new compound (*Z*)-**7a** was isolated. In the presence of potassium thiocyanate (method A), the reaction of compounds **5a–f** proceed as expected affording the novel compounds **10b,f**, **11a,c,d**, **12e** and **13f**, sulfur analogues of compounds **6**, **7**, **8** and **9**; all of these compounds were obtained in good yields except for **10f** and **12e**, both having a phenyl group as substituent R^2. The NMR spectra of these new compounds are very similar to those of compounds **6–9** (Tables 2–4), with the only significant difference between them being the shift of the C=S group signals to 179–196 ppm compared to the C=O group signals.[3]

Table 1
Reaction of 3-aminoquinolinediones **5** with potassium thiocyanate (method A), potassium cyanate (method B) and urea (method C)

Entry	5	Substituents			Method	Time (min)	Product (yield, %)
		R^1	R^2	R^3			
1	**a**	Me	Bu	H	A	30	(*E*/*Z*)-**11a** (30)
2					B	60	**6a** (43)[a], (*Z*)-**7a** (11)
3	**b**	Me	Ph	H	A	35	**10b** (74)
4					B	50	**6b** (39)[b]
5	**c**	Me	Bu	Bu	A	30	(*E*)-**11c** (68)
6					B	50	(*E*)-**7c** (70)[a]
7	**d**	Ph	Bu	Bu	A	50	(*E*)-**11d** (79)
8					B	60	(*E*)-**7d** (72)[a]
9	**e**	Me	Ph	Bu	A	45	**12e** (7)
10					B	40	**8e** (47)[a], **6e** (5)[a], **9e** (4)[a]
11	**f**	Ph	Ph	Bu	A	40	**10f** (13), **13f** (8), **NPI** (6)[c]
12					B	45	**8f** (36)[a], **6f** (2)[a]
13	**g**	Me	Bn	Bu	A	30	**16g** (33)
14					B	60	**15g** (43), (*E*)-**14g** (13)
15					C	60	**15g** (38), (*E*)-**14g** (14)
16	**h**	Ph	Bn	Bu	A	50	**16h** (27)
17					B	60	**15h** (42), (*E*)-**14h** (16)
18					C	60	**15h** (42), (*E*)-**14h** (12)

[a] Identical in all respects to the authentic compound.[3]
[b] Mp 178–179 °C (benzene/hexane), identical in all respects to the authentic compound, for which incorrect mp 83–86 °C was formerly published.[3]
[c] *N*-Phenylisatin.

Compounds **5g,h**, bearing the benzyl group at position 3, react with potassium cyanate (method B) differently to give only small amounts of the expected compounds **14g,h**. In the NMR spectra of the observed products (Table 4), no signals corresponding to a benzyl group are seen. Mass spectra of these products also indicate that no benzyl group is present, leading us to identify these products as structures **15g,h**. The loss of the *C*-benzyl group is surprising, as we do not observe this phenomenon in the potassium cyanate reaction method with the analogous compounds unsubstituted at position 1.[1] This observation indicates that not only the very strong isothiocyanic acid (pK_a −1.3),[6,7] arising by isomerization of weak thiocyanic acid (pK_a 5.4),[6] but also mesoscale isocyanic acid (pK_a 3.9), arising from isomerization of weak thiocyanic acid (pK_a 5.4),[6] can eliminate the benzyl group from compounds **5g,h**. Thus, not only the acidity of the reaction medium, but also the type of substituent at position 1 of the starting compounds **5** influence the course of the reaction. In the reaction of **5g,h** with isothiocyanic acid (method A), *C*-debenzylated compounds **16g,h** were obtained in moderate yields as the only reaction products. This result is in agreement with our expectation based on the results of the same reaction using 1-unsubstituted analogues.[1] However, these reactions afforded approximately half the expected yields for **16g,h** compared to reactions of 1-unsubstituted analogues[1] indicating that other transformations are able to produce side products, which seemingly have not been isolated. The NMR spectra comparison of compounds **15** and **16** (Table 4) shows a significant difference only in the chemical shifts of the C=S and C=O groups. The same difference is seen in the comparison of NMR spectra for **11** and **14** (Table 3). However, these compounds can differ in their configuration at the butylidene or benzylidene double bonds. The stereochemistry of the individual compounds **7**, **11** and **14** was established by 2D-NOESY experiments.

In our opinion, the formation of an *E*- or *Z*-isomer is dependent on the steric conditions of intermediate **D** (Scheme 3). If **D** contains a butyl group, a strong steric interaction exists between the *N*(3)-butyl and *C*(4)-butyl or -benzyl groups, resulting unambiguously in the formation of the isomers (*E*)-**7c,d**, (*E*)-**11c,d** and (*E*)-**14g,h**. If there is a hydrogen atom at N(3), such a steric interaction does not exist, and elimination of the proton occurs preferentially to give the (*Z*)-**7a** and (*Z*)-**11a** isomers. We have observed similar behaviour in analogous compounds isolated from the reaction of 3-butylquinolinediones with isothiocyanates.[8] In the case of compound **11a**, a mixture of both stereoisomers was isolated, but with a significantly greater quantity of the *Z*-isomer (Table 3). Our proposal for the reaction mechanism of the conversion of compounds **5** to the products **6–16** (Scheme 3) is different from that described earlier.[3] In our original proposal we thought to describe the mechanism of the transformation of compounds **5** during their reaction with urea by means of two different paths, depending on whether starting compound **5** bore a primary or secondary amino group. However, afterwards we prepared[4] addition products of **5** with nitrourea, whose structures corresponded to intermediates **A** and **B** in

Table 2
^{1}H and ^{13}C chemical shifts (δ, ppm) of compounds **5**, **10** and **13** in DMSO-d_6

Position	**5g**		**5h**		**10b**		**10f**		**13f**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	—	171.8	—	172.0	—	172.3	—	173.4	—	174.1
3	—	74.4	—	74.4	6.09	56.6	5.72	58.4	5.70	58.8
3a	—	—	—	—	—	125.6	—	[b]	—	127.1
4	—	195.2	—	195.5	7.35	123.5	[a]	[b]	7.36	129.7
4a	—	121.0	—	120.7	—	—	—	—	—	—
5	7.82	126.7	7.91	126.9	7.05	122.1	[a]	[b]	7.11	123.0
6	7.18	122.9	7.16	123.2	7.35	128.8	[a]	[b]	7.11	127.7
7	7.62	136.4	7.43	136.2	7.03	108.6	[a]	[b]	7.32	121.8
7a	—	—	—	—	—	144.3	—	142.5	—	142.5
8	7.12	115.5	6.14	116.4	—	—	—	—	—	—
8a	—	142.5	—	143.4	—	—	—	—	—	—
1′(R^1)	3.33	29.6	—	137.4	3.20	26.5	—	135.7	—	144.6
2′(R^1)	—	—	7.30	129.2	—	—	[a]	[b]	6.93	116.7
			7.05	128.8						
3′(R^1)	—	—	7.64	130.5	—	—	[a]	[b]	7.25	129.2
			7.59	130.3						
4′(R^1)	—	—	7.57	128.9	—	—	[a]	[b]	6.86	119.9
1′(R^2)	3.09	47.0	3.27	46.7	—	132.2	—	132.1	—	—
			3.21							
2′(R^2)	—	133.7	—	133.8	8.01	128.7	[a]	[b]	—	—
3′(R^2)	6.89	129.8	7.04	130.2	7.59	128.5	a	[b]	—	—
4′(R^2)	7.10	127.6	7.19	128.0	7.71	133.1	[a]	[b]	—	—
5′(R^2)	7.10	127.0	7.19	127.2	—	—	—	—	—	—
1′(R^3)	2.27	44.1	2.42	44.1	11.67	—	3.75	40.3	3.73	40.2
2′(R^3)	1.38	32.2	1.39	32.2	—	—	1.62	29.4	1.57	29.4
3′(R^3)	1.31	19.8	1.30	19.8	—	—	1.33	19.5	1.29	19.5
4′(R^3)	0.86	13.9	0.87	13.9	—	—	0.94	13.7	0.90	13.7
1′(NH)	2.50	—	2.60	—	11.32	—	10.75	—	10.72[c]	—
2′(C=S)	—	—	—	—	—	181.3	—	183.7	—	182.9
4′(C=O)	—	—	—	—	—	167.9	—	170.1	—	—

[a] δ_H=7.18–7.64.
[b] δ_C=126.2–130.3.
[c] δ_H=7.51 (N***H***C_6H_5).

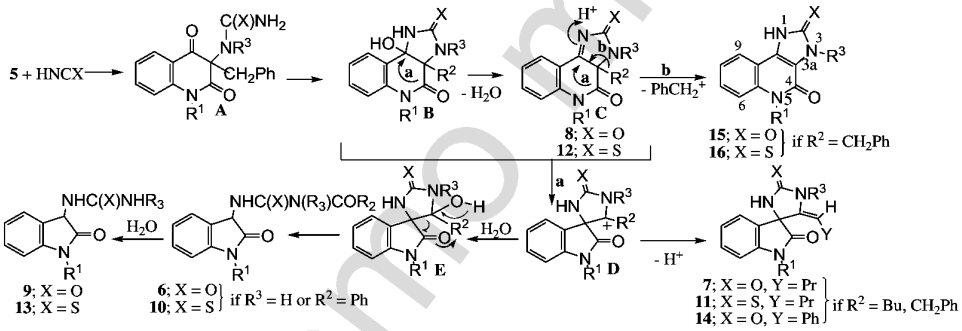
Table 3
^{1}H and ^{13}C chemical shifts (δ, ppm) of compounds **7**, **11** and **14** in DMSO-d_6

Position	(*Z*)-**7a**		(*Z*)-**11a**[a]		(*E*)-**11a**[a]		(*E*)-**11c**		(*E*)-**11d**		(*E*)-**14g**		(*E*)-**14h**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1 (NH)	7.54	—	9.22	—	9.15	—	9.45	—	9.60	—	7.94	—	8.12	—
2	—	159.8	—	181.6	—	179.6	—	179.8	—	179.6	—	157.7	—	157.5
4	—	138.2	—	139.9	—	139.6	—	139.0	—	139.1	—	140.1	—	139.5
5	—	65.9	—	69.7	—	68.6	—	66.7	—	66.9	—	63.6	—	63.7
2′	—	174.7	—	173.4	—	172.4	—	172.3	—	171.9	—	173.3	—	172.5
3a′	—	130.2	—	128.4	—	128.1	—	128.2	—	128.0	—	129.2	—	129.1
4′	7.27	124.1	7.25	124.3	7.31	124.5	7.21	124.3	7.32	124.9	7.19	123.7	7.36	124.5
5′	7.14	123.2	7.17	123.4	7.17	123.5	7.17	123.6	7.23	124.2	7.02	122.9	7.15	123.7
6′	7.41	129.8	7.43	130.3	7.46	130.4	7.47	130.5	7.41	130.5	7.23	129.8	7.27	130.0
7	7.10	109.0	7.12	109.3	7.12	109.3	7.17	109.3	6.85	109.7	6.64	108.8	6.51	109.4
7a′	—	143.9	—	143.8	—	143.4	—	143.5	—	143.3	—	143.4	—	143.3
1′(R^1)	3.17	26.5	3.18	22.3	3.22	22.4	3.24	26.6	—	133.8	2.80	26.1	—	133.7
2′(R^1)	—	—	—	—	—	—	—	—	7.43	126.3	—	—	7.05	126.1
3′(R^1)	—	—	—	—	—	—	—	—	7.68	130.1	—	—	7.57	129.5
4′(R^1)	—	—	—	—	—	—	—	—	7.58	128.7	—	—	7.47	128.2
1″	3.61	96.2	3.81	99.2	4.77 [b]	101.5	4.84[b]	102.7	4.93[b]	103.1	5.82[b]	99.4	5.94[b]	100.2
2″	1.90 [b]	27.5	2.03[b]	27.4	1.24	27.1	1.42	27.2	1.64	27.5	—	134.3	—	134.6
					1.16		1.27		1.41					
3″	1.19	22.4	1.22	22.3	1.00	22.4	1.07	22.4	1.15	22.5	6.52	129.2	6.64	129.0
					0.90		0.98		1.06					
4″	0.77	13.3	0.78	13.3	0.52	13.5	0.55	13.4	0.60	13.5	6.98	127.2	7.01	127.6
5″	—	—	—	—	—	—	—	—	—	—	6.98	125.9	7.01	126.1
1′(R^3)	9.34[b]	—	10.77[b]	—	10.71 [b]	—	3.90 [b]	42.2	3.93[b]	42.3	3.64[b]	39.3	3.67[b]	39.3
							3.78 [b]		3.81[b]		3.56[b]		3.59[b]	
2′(R^3)	—	—	—	—	—	—	1.59	27.9	1.49	27.9	1.67[b]	28.1	1.69[b]	28.1
3′(R^3)	—	—	—	—	—	—	1.40	19.4	1.40	19.4	1.45	19.3	1.47	19.5
4′(R^3)	—	—	—	—	—	—	0.98	14.0	0.99	13.9	1.01	13.9	1.02	13.9

[a] Measured as a 2.6:1 mixture of (*Z*)- and (*E*)-isomers.
[b] Through-space interaction observed in NOESY allowing geometrical isomer determination and, for (*Z*)-**7a**, also the assignment of NH protons.

Table 4
^{1}H and ^{13}C chemical shifts (δ, ppm) of compounds **12**, **15** and **16** in DMSO-d_6

Position	**12e**		**15g**		**15h**		**16g**		**16h**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1 (NH)	—	—	12.01	—	12.17	—	13.78	—	13.39	—
2	—	194.3	—	153.7	—	153.8	—	166.8	—	167.0
3a	—	83.6	—	113.1	—	113.1	—	110.1	—	110.1
4	—	165.1	—	152.8	—	152.9	—	152.4	—	152.5
5a	—	141.3	—	136.5	—	137.6	—	137.0	—	138.4
6	7.43	116.9	7.59	115.6	6.60	116.4	7.62	115.9	6.59	117.5
7	7.69	135.5	7.56	128.5	7.34	128.3	7.62	122.6	7.43	122.8
8	7.31	124.2	7.34	122.2	7.32	122.5	7.38	122.3	7.34	122.2
9	7.96	126.2	7.89	121.5	7.98	121.5	8.12	129.5	8.20	129.0
9a	—	116.9	—	110.9	—	110.8	—	117.4	—	117.5
9b	—	182.8	—	128.1	—	129.0	—	131.8	—	132.5
1′(R^1)	3.48	30.3	3.69	28.8	—	137.8	3.70	29.1	—	137.4
2′(R^1)	—	—	—	—	7.38	129.6	—	—	7.39	129.5
3′(R^1)	—	—	—	—	7.67	130.0	—	—	7.67	130.1
4′(R^1)	—	—	—	—	7.60	128.9	—	—	7.62	129.3
1′(R^2)	—	131.9	—	—	—	—	—	—	—	—
2′(R^2)	7.06	126.1	—	—	—	—	—	—	—	—
3′(R^2)	7.51	130.1	—	—	—	—	—	—	—	—
4′(R^2)	7.51	130.4	—	—	—	—	—	—	—	—
1′(R^3)	3.83 3.53	45.9	4.05	40.9	4.03	41.0	4.48	44.4	4.45	44.5
2′(R^3)	1.76 1.29	28.1	1.68	31.9	1.68	31.9	1.75	30.9	1.70	30.8
3′(R^3)	1.20	19.8	1.32	19.4	1.32	19.4	1.28	19.4	1.35	19.4
4′(R^3)	0.82	13.6	0.93	13.7	0.92	13.7	0.98	13.8	0.92	13.7



Scheme 3.

Scheme 3. Both identically substituted compounds **A**, **B** and also **8** (prepared by dehydration of **B**) were rearranged in boiling acetic acid under formation of the same reaction product. Compounds of type **8** derived from primary amines **5** (R^3=H) could not be obtained by dehydrating compounds **B** (R^3=H). Hence, it was considered that the rearrangement occurs with these compounds already in the stage of aminocarbinol **B**.

Therefore, we suppose that compounds **5** react with isocyanic or isothiocyanic acid to give intermediate **A** that cyclizes to form intermediate **B** and subsequently dehydrates to give intermediate **C**. This intermediate is one of the final products in cases where R^2=Ph (compounds **8** and **12**). The crucial step in the mechanism is the acid-catalyzed migration of the amide group in **B** or **C** to the C(9b), to form intermediate **D** (path **a**). If a hydrogen atom is present on the first carbon atom of the substituent R^2 (R^2=Bu or CH_2Ph), it is eliminated to form compounds **7**, **11** and **13**. If R^2 is a phenyl group, the addition of water to intermediate **D** leads to the formation of intermediate **E**, in which the imidazolidine ring opens to afford compounds **6** and **10**, and their hydrolytic products **9** and **13**. It is interesting to note that compounds **6** and **10** arise via intermediate **E** even in cases where R^3=H. We never observed the elimination of the hydrogen from the N(3) atom of intermediate **D** to give a C=N bond.

The alternative path **b**, which is dominant in the reactions of **5g,h** with isothiocyanic acid (method A), leads to debenzylated compounds **15g,h** and **16g,h**. It is still unclear why compounds **5g,h** are debenzylated also by the weak isocyanic acid, considering such reactions were not observed when using analogous 1-unsubstituted compounds **1**.[1]

3. Conclusions

In conclusion, we would like to emphasize that the described reaction of 3-aminoquinolinediones **5** with isocyanic or isothiocyanic acid allows the preparation of 3-ureido- or thioureidooxindoles and different types of spiro-oxindole derivatives in good yields. While many biologically active compounds contain sulfur atoms,[9,10] compounds **10**–**13** could also be interesting structures for further studies.

The C-debenzylation of starting compounds **5** bearing a benzyl group at position 3 not only has theoretical significance but also enables the targeted preparation of compounds **15** and **16** by a simple procedure. To our surprise, only one compound **15**, described as the –OH tautomer (5-butyl-2-hydroxy-1-methyl-1,5-dihydro-imidazo[4,5-*c*]quinolin-4-one), and only one compound

16, described as the –SH tautomer (5-butyl-2-mercapto-1-methyl-1,5-dihydro-imidazo[4,5-*c*]quinolin-4-one), were found in the literature.[11] Both of these compounds, which induce contraction in tracheal strips of passively sensitized guinea pigs, were prepared by five different multi-step reactions starting from 3-nitro-quinolin-2-ones bearing the hydroxy, chloro, or methylamino substituents in position 4 and also from *N*-butylisatoic anhydride.

4. Experimental

4.1. General

Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C and 50.68 MHz for ^{15}N) in DMSO-d_6. ^{1}H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS. All 2D experiments (gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. Proton spectra were assigned using gs-COSY. Protonated carbons were assigned by gs-HMQC. Quaternary carbons were assigned by gs-HMBC. The positive-ion EI mass spectra were measured on a Shimadzu QP-2010 instrument within the mass range m/z=50–600 using direct inlet probe (DI). Samples were dissolved in dichloromethane (30 μg/mL) and 10 μL of the solution was evaporated in DI cuvette at 50 °C. The ion source temperature was 200 °C; the energy of electrons was 70 eV. Only signals exceeding relative abundance of 9% are listed. Column chromatography was carried out on Silica gel (Merck, grade 60, 70–230 mesh) using chloroform and then successive mixtures of chloroform/ethanol (in rations from 99:1 to 8:2) or benzene and then successive mixtures of benzene/ethyl acetate (in rations from 99:1 to 8:2). Reactions as well as the course of separation and also the purity of substances were monitored by TLC in elution systems benzene/ethyl acetate (4:1), chloroform/ethanol (9:1 and/or 19:1) and chloroform/ethyl acetate (7:3) on Alugram® SIL G/UV$_{254}$ foils (Macherey–Nagel). Elemental analyses (C, H and N) were performed with a EA 1108 Elemental Analyzer (Fisons Instrument).

4.2. Preparation of 3-aminoquinoline-2,4(1*H*,3*H*)-diones (5)

Starting 1-substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones **5a**–**h** were prepared from corresponding 3-chloro derivatives according to the general procedure described in literature.[5] Two new derivatives (**5g**,**h**) were prepared.

*4.2.1. 3-Benzyl-3-butylamino-1-methyl-1H,3H-quinoline-2,4-dione (**5g**).* Compound was prepared from 3-benzyl-3-chloro-1-methyl-1*H*,3*H*-quinoline-2,4-dione and butyl-amine in 53% yield. Colourless crystals, mp 70–71 °C (cyclohexane); IR: 3312, 3032, 2961, 2928, 2861, 2824, 1691, 1652, 1599, 1492, 1472, 1435, 1412, 1362, 1302, 1282, 1245, 1207, 1179, 1149, 1121, 1079, 1051, 1033, 939, 917, 845, 769, 750, 735, 701, 661, 633, 587, 526 cm^{-1}. EIMS (m/z, %): 336 (M^{+}, 2), 246 (16), 245 (100), 203 (7), 191 (12), 190 (15), 189 (7), 161 (15), 146 (7), 118 (6), 104 (5), 91 (26), 77 (8), 65 (6). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{21}H_{24}N_2O_2$: C 74.97 (75.09); H 7.19 (7.23); N 8.33 (8.14).

*4.2.2. 3-Benzyl-3-butylamino-1-phenyl-1H,3H-quinoline-2,4-dione (**5h**).* Compound was prepared from 3-benzyl-3-chloro-1-phenyl-1*H*,3*H*-quinoline-2,4-dione and butyl-amine in 61% yield. Colourless crystals, mp 137–139 °C (benzene/hexane); IR: 3310, 3061, 3032, 2948, 2926, 2869, 2823, 1696, 1660, 1598, 1494, 1466, 1454, 1438, 1347, 1303, 1268, 1241, 1205, 1183, 1162, 1112, 1089, 1073, 1026, 942, 917, 843, 780, 767, 735, 701, 664, 651, 557, 542, 525 cm^{-1}. EIMS (m/z, %): 398 (M^{+}, 2), 307 (100), 252 (13), 223 (13), 196 (8), 195 (7), 167 (8), 91 (25), 77 (9), 65 (5). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{26}H_{26}N_2O_2$: C 78.36 (78.55); H 6.58 (6.65); N 7.03 (7.12).

4.3. General procedure for the preparation of compounds 6–15

A mixture of the appropriate 3-aminoquinolinedione (**5a**–**h**) (2.5 mmol) and the appropriate reagent (see below) in acetic acid (3 mL) was heated to reflux for the time given in Table 1. The course of the reaction was monitored by TLC. After cooling, the reaction mixture was poured onto ice (50 g). The precipitated product was filtered off with suction, washed with water, dried and crystallized from an appropriate solvent or column chromatographed.

Reagents: method A: potassium thiocyanate (583 mg, 6 mmol); method B: potassium cyanate (487 mg, 6 mmol); method C: urea, see Ref. 3.

*4.3.1. (Z)-4-Butylidene-1′-methyl-1′H-spiro[imidazolidine-5,3′-indole]-2,2′-indole (**7a**).* Compound was prepared besides **6a** from **5a** in 11% yield (method B). Colourless crystals, mp 236–238 °C (ethyl acetate/hexane); IR: 3254, 3104, 2950, 2929, 2869, 1724, 1713, 1694, 1617, 1496, 1472, 1450, 1391, 1370, 1355, 1314, 1239, 1192, 1161, 1130, 1106, 1060, 1022, 973, 896, 848, 801, 757, 728, 697, 679, 539 cm^{-1}. EIMS (m/z, %): 271 (M^{+}, 86), 242 (82), 228 (39), 214 (14), 200 (100), 188 (82), 171 (16), 160 (45), 146 (31), 132 (50), 117 (14), 104 (24), 84 (17), 77 (23), 54 (22), 41 (12). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{15}H_{17}N_3O_2$: C 66.40 (66.24); H 6.32 (6.32); N 15.49 (15.54).

*4.3.2. 3-(3′-Benzoylthioureido)-1-methyl-2-oxo-2,3-di-hydro-1H-indole (**10b**).* Compound was prepared from **5b** in 74% yield (method A). Yellowish crystals, mp 219–220 °C (benzene); IR: 3245, 3060, 3033, 2934, 2900, 1709, 1684, 1613, 1532, 1494, 1469, 1449, 1423, 1375, 1353, 1311, 1259, 1197, 1169, 1125, 1087, 1074, 1054, 1019, 981, 940, 932, 913, 879, 821, 786, 753, 697, 664, 643, 594, 539 cm^{-1}. EIMS (m/z, %): 325 (17), 204 (18), 188 (6), 161 (15), 146 (13), 118 (16), 105 (100), 91 (10), 77 (54), 51 (16). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{17}H_{15}N_3O_2S$: C 62.75 (62.66); H 4.65 (4.63); N 12.91 (12.93); S 9.85 (9.79).

*4.3.3. 3-(3′-Benzoyl-3′-butyl-thioureido)-1-phenyl-2-oxo-2,3-dihydro-1H-indole (**10f**).* Compound was prepared from **5f** besides **13f** and *N*-phenylisatin in 13% yield (method A). Colourless crystals, mp 173–176 °C (benzene/hexane); IR: 3187, 3061, 3050, 2957, 2930, 2870, 1749, 1629, 1592, 1576, 1506, 1492, 1447, 1436, 1405, 1353, 1313, 1288, 1232, 1223, 1181, 1161, 1123, 1079, 1027, 966, 949, 924, 855, 822, 792, 759, 729, 697, 659, 625, 550, 518 cm^{-1}. EIMS (m/z, %): 443 (M^{+}, 14), 279 (22), 180 (8), 105 (100), 77 (38). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{26}H_{25}N_3O_2S$: C 70.40 (70.36); H 5.68 (5.69); N 9.47 (9.61); S 7.23 (7.14).

*4.3.4. (E/Z)-4-Butylidene-1′-methyl-2-thioxo-1′H-spiro[imidazolidine-5,3′-indole]-2′-one (**11a**).* Compound was prepared from **5a** in 30% yield (method A). Colourless crystals, mp 182–187 °C (ethyl acetate/hexane); IR: 3241, 3156, 2957, 2928, 2867, 1731, 1709, 1612, 1518, 1470, 1416, 1366, 1349, 1302, 1205, 1158, 1125, 1102, 1006, 952, 753, 695, 593, 539 cm^{-1}. EIMS (m/z, %): 288 (19), 287 (M^{+}, 100), 258 (39), 244 (22), 216 (55), 200 (53), 184 (13), 172 (11), 146 (12), 143 (10), 118 (12), 117 (14), 116 (11), 115 (10), 102 (10), 77 (12), 41 (11). For NMR spectra of both stereoisomers see Table 3. Anal. Calcd (found) for $C_{15}H_{17}N_3OS$: C 62.69 (62.62); H 5.96 (6.04); N 14.62 (14.51); S 11.16 (10.85).

*4.3.5. (E)-3-Butyl-4-butylidene-1′-methyl-2-thioxo-1′H-spiro[imidazolidine-5,3′-indole]-2′-one (**11c**).* Compound was prepared from **5c** in 68% yield (method A). Colourless crystals, mp 152–154 °C

(benzene/hexane); IR: 3405, 3314, 3058, 2955, 2930, 2868, 1735, 1723, 1677, 1609, 1492, 1468, 1438, 1418, 1368, 1343, 1303, 1291, 1251, 1194, 1156, 1129, 1109, 1279, 1021, 985, 942, 878, 853, 760, 693, 668, 565, 539 cm^{-1}. EIMS (*m/z*, %): 343 (M^+, 100), 314 (52), 310 (36), 298 (14), 286 (51), 282 (35), 272 (23), 258 (55), 256 (20), 244 (11), 226 (14), 216 (28), 213 (24), 204 (20), 200 (29), 184 (25), 143 (14), 140 (11), 130 (11), 115 (15), 77 (10), 55 (17), 41 (40). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{19}H_{25}N_3OS$: C 66.44 (66.40); H 7.34 (7.35); N 12.23 (12.22); S 9.34 (9.13).

*4.3.6. (E)-3-Butyl-4-butylidene-1′-phenyl-2-thioxo-1′H-spiro[imidazolidine-5,3′-indole]-2′-one (**11d**).* Compound was prepared from **5d** in 79% yield (method A). Colourless crystals, mp 147–150 °C (benzene/hexane); IR: 3406, 3056, 3013, 2957, 2930, 2869, 1720, 1669, 1615, 1596, 1500, 1464, 1417, 1355, 1327, 1297, 1287, 1260, 1227, 1213, 1199, 1175, 1150, 1114, 1092, 1049, 1028, 1003, 978, 938, 820, 774, 751, 702, 666, 618, 559, 510 cm^{-1}. EIMS (*m/z*, %): 406 (29), 405 (M^+, 100), 378 (26), 377 (98), 376 (48), 373 (33), 372 (56), 360 (12), 350 (11), 349 (30), 348 (57), 345 (17), 344 (67), 335 (24), 334 (42), 321 (10), 320 (23), 318 (18), 316 (11), 289 (15), 288 (13), 279 (14), 278 (73), 276 (12), 275 (35), 274 (15), 266 (17), 262 (17), 261 (15), 247 (14), 246 (30), 219 (10), 218 (10), 217 (13), 205 (11), 204 (15), 180 (15), 140 (14), 128 (10), 115 (12), 77 (34), 55 (18), 54 (17), 51 (12), 41 (44). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{24}H_{27}N_3OS$: C 71.08 (71.00); H 6.71 (6.73); N 10.36 (10.43); S 7.91 (7.78).

*4.3.7. 3-Butyl-5-methyl-3a-phenyl-2-thioxo-3,3a-dihydro-5H-imidazo[4,5-c]quinoline-2-one (**12e**).* Compound was prepared from **5e** in 7% yield (method A). Yellow crystals, mp 175–180 °C (benzene/hexane); IR: 2957, 2936, 2894, 2873, 2855, 1689, 1609, 1589, 1469, 1448, 1399, 1356, 1324, 1283, 1270, 1253, 1219, 1165, 1126, 1064, 1043, 1013, 993, 969, 860, 776, 751, 726, 697, 659, 619, 612, 571, 529 cm^{-1}. EIMS (*m/z*, %): 363 (M^+, 29), 331 (25), 330 (100), 320 (10), 307 (31), 293 (12), 292 (24), 248 (10), 204 (19), 118 (12), 104 (48), 103 (10), 77 (16), 41 (13). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{21}H_{21}N_3OS$: C 69.39 (69.49); H 5.82 (5.85); N 11.56 (11.49); S 8.82 (8.65).

*4.3.8. 1-Butyl-3-(2-oxo-1-phenylindolin-3-yl)thiourea (**13f**).* Compound was prepared besides **10f** and *N*-phenylisatin from **5f** in 8% yield (method A). Colourless crystals, mp 111–114 °C (cyclohexane), get blue on air and light; IR: 3330, 3166, 3048, 2959, 2932, 2871, 1745, 1598, 1580, 1510, 1499, 1455, 1438, 1413, 1352, 1283, 1260, 1229, 1190, 1174, 1129, 1110, 1081, 1033, 923, 878, 826, 797, 748, 693, 649, 637, 618, 577, 540 cm^{-1}. EIMS (*m/z*, %): 340 (23), 339 (M^+, 100), 337 (12), 266 (31), 250 (10), 237 (13), 224 (29), 223 (12), 209 (13), 208 (33), 195 (29), 181 (16), 180 (92), 179 (19), 77 (18), 74 (16), 72 (16), 66 (7), 51 (7), 41 (11). For NMR spectra see Table 2. Anal. Calcd (found) for $C_{19}H_{21}N_3OS$: C 67.23 (67.37); H 6.24 (6.33); N 12.38 (12.43); S 9.45 (9.39).

*4.3.9. (E)-4-Benzylidene-3-butyl-1′-methyl-1′H-spiro-[imidazolidine-5,3′-indole]-2,2′-indole (**14g**).* Compound was prepared from **5g** besides **15g** in respective yields 13% (method B) or 14% (method C). Colourless crystals, mp 198–200 °C (benzene/hexane); IR: 3216, 3085, 3012, 2960, 2932, 2873, 1734, 1719, 1666, 1613, 1494, 1470, 1456, 1426, 1371, 1342, 1305, 1261, 1229, 1175, 1155, 1127, 1088, 1066, 1011, 945, 923, 898, 863, 824, 786, 751, 700, 674, 666, 620, 539 cm^{-1}. EIMS (*m/z*, %): 362 (25), 361 (M^+, 100), 319 (15), 276 (10), 270 (15), 256 (39), 247 (14), 228 (51), 215 (13), 200 (41), 189 (13), 188 (99), 160 (34), 132 (42), 131 (25), 118 (14), 117 (50), 116 (16), 104 (14), 91 (62), 90 (17), 89 (14), 77 (15), 41 (30). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{22}H_{23}N_3O_2$: C 73.11 (72.92); H 6.41 (6.41); N 11.63 (11.58).

*4.3.10. (E)-3-Butyl-4-benzylidene-1′-phenyl-1′H-spiro-[imidazolidine-5,3′-indole]-2,2′-dione (**14h**).* Compound was prepared besides **15h** from **5h** in respective yields 16% (method B) and 12% (method C). Colourless crystals, mp 161–165 °C (benzene/hexane); IR: 3199, 3080, 2951, 2931, 2870, 1740, 1717, 1663, 1615, 1596, 1501, 1480, 1465, 1445, 1432, 1370, 1327, 1295, 1281, 1251, 1233, 1210, 1177, 1134, 1114, 1089, 1039, 1026, 986, 940, 924, 897, 816, 786, 750, 702, 676, 628, 583, 551 cm^{-1}. EIMS (*m/z*, %): 424 (30), 423 (M^+, 100), 395 (10), 381 (12), 319 (19), 318 (80), 290 (30), 277 (13), 263 (11), 262 (56), 251 (13), 250 (75), 194 (26), 117 (34), 91 (31), 90 (10), 77 (23), 66 (10), 41 (16). For NMR spectra see Table 3. Anal. Calcd (found) for $C_{27}H_{25}N_3O_2$: C 76.57 (76.59); H 5.95 (5.95); N 9.92 (9.78).

*4.3.11. 3-Butyl-5-methyl-1H-imidazo[4,5-c]quinoline-2,4(3H,5H)-dione (**15g**).* Compound was prepared from **5g** besides (*E*)-**14g** in respective yields 43% (method B) and 38% (method C). Colourless crystals, mp 289–290 °C (chloroform/ethyl acetate); IR: 2954, 2870, 2824, 2748, 1685, 1657, 1638, 1593, 1571, 1528, 1466, 1376, 1354, 1323, 1294, 1245, 1227, 1168, 1117, 1086, 1044, 968, 940, 903, 881, 857, 826, 746, 726, 710, 665, 650, 551, 539 cm^{-1}. EIMS (*m/z*, %): 272 (10), 271 (M^+, 55), 254 (11), 229 (12), 228 (26), 216 (16), 215 (100), 200 (15). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{15}H_{17}N_3O_2$: C 66.40 (66.50); H 6.32 (6.30); N 15.49 (15.70).

*4.3.12. 3-Butyl-5-phenyl-1H-imidazo[4,5-c]quinoline-2,4(3H,5H)-dione (**15h**).* Compound was prepared from **5h** besides (*E*)-**14h** in 42% yield (method B, method C). Colourless crystals, mp 329–333 °C (acetic acid); IR: 3102, 3036, 2955, 2874, 2809, 2727, 1706, 1663, 1636, 1594, 1567, 1520, 1491, 1468, 1453, 1416, 1373, 1324, 1280, 1246, 1226, 1171, 1153, 1118, 1096, 1070, 1050, 1012, 934, 892, 824, 794, 750, 729, 702, 654, 601, 503 cm^{-1}. EIMS (*m/z*, %): 334 (15), 333 (M^+, 63), 316 (16), 304 (11), 291 (18), 290 (20), 278 (21), 277 (100), 276 (53), 262 (15), 77 (24). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{20}H_{19}N_3O_2$: C 72.05 (71.91); H 5.74 (5.75); N 12.60 (12.43).

*4.3.13. 3-Butyl-2,3-dihydro-5-methyl-2-thioxo-1H-imid-azo[4,5-c]quinolin-4(5H)-one (**16g**).* Compound was prepared from **5g** in 33% yield (method A). Colourless crystals, mp 299–303 °C (benzene); IR: 3029, 2954, 2927, 1670, 1638, 1588, 1571, 1525, 1481, 1458, 1433, 1392, 1324, 1295, 1245, 1215, 1164, 1115, 1084, 1043, 970, 844, 775, 745, 732, 679, 624, 593, 583, 521 cm^{-1}. EIMS (*m/z*, %): 287 (M^+, 60), 255 (16), 254 (84), 244 (11), 243 (10), 232 (29), 231 (100), 203 (11), 202 (36), 117 (12), 116 (13). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{15}H_{17}N_3OS$: C 62.69 (62.51); H 5.96 (5.99); N 14.62 (14.51); S 11.16 (10.85).

*4.3.14. 3-Butyl-2,3-dihydro-5-phenyl-2-thioxo-1H-imid-azo[4,5-c]quinolin-4(5H)-one (**16h**).* Compound was prepared from **5h** in 27% yield (method A). Colourless crystals, mp 349–350 °C (acetic acid); IR: 3154, 3120, 3069, 3055, 2958, 2932, 2871, 2733, 1672, 1634, 1591, 1565, 1518, 1478, 1459, 1393, 1362, 1338, 1323, 1294, 1278, 1258, 1235, 1214, 1160, 1119, 1096, 1071, 1046, 1029, 1004, 943, 852, 836, 755, 733, 699, 681, 662, 605, 561, 513 cm^{-1}. EIMS (*m/z*, %): 350(17), 349 (M^+, 71), 317 (34), 316 (100), 307 (11), 306 (10), 294 (37), 293 (97), 292 (68), 277 (11), 275 (10), 274 (10), 261 (12), 260 (20), 205 (14), 77 (32), 51 (14), 41 (14). For NMR spectra see Table 4. Anal. Calcd (found) for $C_{20}H_{19}N_3OS$: C 68.74 (68.92); H 5.48 (5.45); N 12.02 (12.21); S 9.18 (9.12).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.002.

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PŘÍLOHA III

Modified *Riemschneider* Reaction of 3-Thiocyanatoquinolinediones

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The *Riemschneider* reaction of 3-thiocyanatoquinoline-2,4(1*H*,3*H*)-diones with conc. H_2SO_4 was investigated. Using different reaction conditions, 13 types of reaction products were isolated. Compounds bearing a Me, Et, or Bu group at C(3) afforded mainly [1,3]thiazolo[5,4-*c*]quinoline-2,4-diones and 1,9b-dihydro-9b-hydroxythiazolo[5,4-*c*]quinoline-2,4-diones. In the case of the 3-Bu derivatives of the starting compounds, *C*-debutylation was also observed. If a Bn group is present at C(3), rapid *C*-debenzylation of the starting thiocyanates occurred, yielding [1,3]oxathiolo[4,5-*c*]quinoline-2,4-diones, and mixtures of mono-, di-, and trisulfides derived from 4-hydroxy-3-sulfanylquinoline-2-ones. The reaction mechanism of all of the transformations is discussed. All new compounds were characterized by IR, ^{1}H- and ^{13}C-NMR, and EI and ESI mass spectra, and in some cases, ^{15}N-NMR spectra were also used to characterize new compounds.

1. Introduction. – One of the most important families of naturally occurring sulfur compounds is the glucosinolate family, which occurs in cruciferous vegetables. By enzymatic hydrolysis, this class of compounds affords glucose, HSO_4^- ions, and aglycone derivatives, as well as isothiocyanates, thiocyanates, and nitriles [1].

Some aglycones such as thiocyanates act as chemoprotective agents against chemically induced carcinogenesis by blocking the initiation of tumors in a variety of rodent tissues [2]. Thiocyanates are also important starting compounds for the synthesis of various heterocyclic compounds that possess important biological activities [3][4].

Several methods are known for the introduction of S functionalities into molecules [5][6]. We found that 3-chloro- and 3-bromoquinoline-2,4-diones react with some S reagents (NaSH, AcSH, KSCN, thiourea) to give 4-hydroxy-1*H*-quinoline-2-ones **1** [7]. In this reaction, the 3-halogenoquinoline-2,4-diones, which bear a 'positive charged' halogen atom, exhibit a strong oxidative effect on all of the compounds that have a free SH group. Therefore, the preparation of their 3-sulfanyl or 3-thiocyanato analogs by a nucleophilic substitution route is impossible. However, we have prepared 3-thiocyanatoquinoline-2,4-diones **2** *via* the reaction of 4-hydroxy-1*H*-quinoline-2-ones **1** with an *in situ* prepared $(SCN)_2$ in AcOH [7].

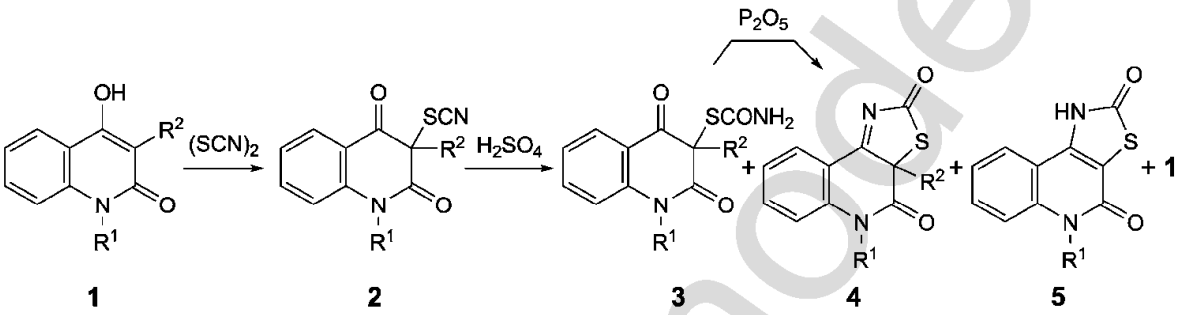
Although the non-enolizable α-thiocyanato derivatives of β-dicarbonyl compounds should be relatively stable [6], compounds **2** are only stable in the crystalline form. In protic solvents, they readily undergo nucleophilic attack by H_2O on the S-atom to form the starting 4-hydroxy-1*H*-quinoline-2-ones **1** [7]. This reaction is analogous to the reactions of α-thiocyanato β-diketones with aqueous alkali or with NH_4OH [8][9]. We

also found that the thiocyanato (SCN) group can be selectively transferred from **2** to some nucleophiles (amines, activated aromatic compounds, thioles, *Wittig* reagents) [10].

The SCN group can be transformed to the thiocarbamate group *via* the *Riemschneider* reaction by treatment with conc. H_2SO_4 [11][12]. The reaction of α-thiocyanato ketones with H_2SO_4, most frequently carried out in the presence of AcOH, usually does not stop at the formation of the carbamates but continues through a dehydration process to form thiazol-2(3*H*)-ones [13–15].

In a previous report [16], we described the reaction of 3-thiocyanatoquinoline-2,4-diones **2** in conc. H_2SO_4, or in its mixture with AcOH, to give a mixture of hydrolytically unstable thiocarbamates **3** and [1,3]thiazolo[5,4-*c*]quinoline-2,4(3a*H*,5*H*)-diones **4** (*Scheme 1*). Compounds **3** were cyclodehydrated to **4** by treatment with P_2O_5 in AcOH. In two cases, the *C*(*3*)-dealkylated products, which were identified as thiazoloquinolinediones **5**, were also isolated. The extent of this reaction substantially increases, when excess of P_2O_5 was added to the mixture.

Scheme 1



Therefore, we decided to study the modified *Riemschneider* reaction in detail under different reaction conditions and using compounds that bear varying substituents at C(3). Owing to the high reactivity of quinoline-2,4-dione derivatives and our experiences in this area, we anticipated the isolation of novel compounds in this process.

2. Results and Discussion. – To determine the influence of the R^2 substituent (*cf. Scheme 1*) on the transformation of compounds **2**, we chose the Me, Et, Bu, and Bn groups, and H, Me, and Ph were selected as R^1. The starting compounds **2** were prepared by the reaction of 4-hydroxy-1*H*-quinolin-2-ones **1** with $(SCN)_2$ according to [7][16]. By this process, seven novel compounds were prepared. Although two new methods for the α-thiocyanation of ketones and β-dicarbonyl compounds were recently described [17][18], we were unable to use them, because 4-hydroxy-1*H*-quinolin-2-ones **1** were insoluble in the procedure's requisite solvents. The starting compound **1l** was almost insoluble even in AcOH. Thus, we carried out the thiocyanation of **1l** in a DMF solution. The ^{1}H- and ^{13}C-NMR spectra of the new compounds **2** are presented in *Table 1*.

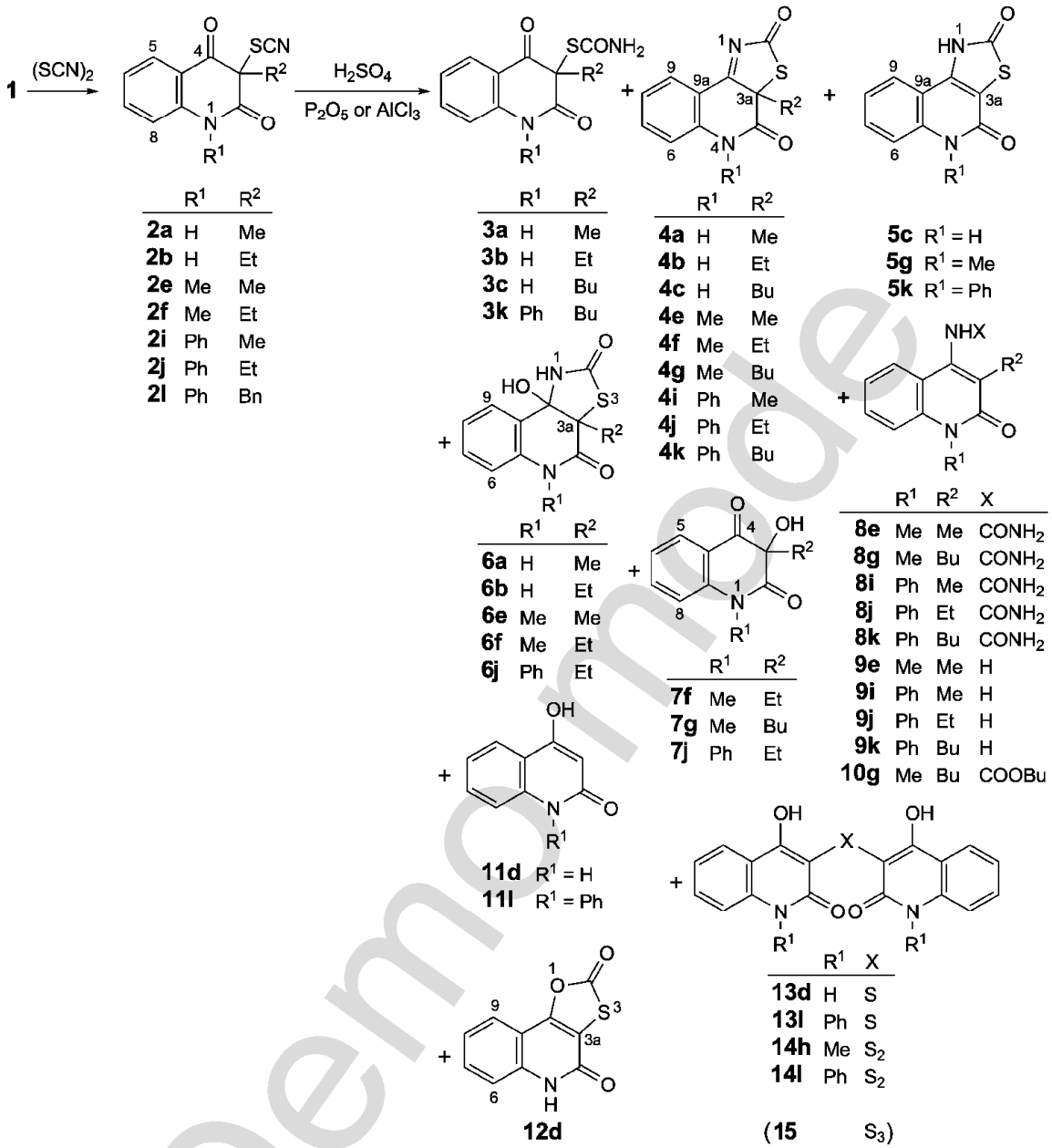
Because the composition of the mixture for the reaction of thiocyanates **2** substantially influences the ratio of the reaction products [16], we carried out the reaction under three different reaction conditions. In the first method, P_2O_5 was added

Table 1. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$) *of New Compounds* **2** (δ in ppm)

Position	**2a**		**2b**		**2e**		**2f**		**2i**		**2j**		**2l**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	168.7	–	168.5	–	166.8	–	166.2	–	166.9	–	166.7	–	166.4
3	–	59.7	–	64.8	–	59.8	–	65.6	–	59.0	–	65.1	–	63.4
4	–	188.5	–	188.7	–	188.6	–	188.8	–	188.7	–	189.1	–	189.2
4a	–	118.0	–	118.5	–	119.5	–	119.9	–	119.0	–	119.4	–	119.4
5	8.01	128.7	8.02	128.5	8.06	129.0	8.07	128.9	8.10	128.8	8.11	128.6	8.06	128.5
6	7.25	124.8	7.26	124.8	7.29	124.3	7.27	124.1	7.24	124.4	7.25	124.3	7.13	124.2
7	7.67	137.5	7.67	137.6	7.73	137.3	7.73	137.4	7.48	136.9	7.49	137.0	7.37	137.0
8	7.15	117.0	7.13	117.0	7.24	115.4	7.23	115.4	6.52	117.4	6.52	117.4	6.28	117.2
8a	–	139.9	–	139.9	–	142.3	–	142.4	–	143.5	–	143.5	–	143.3
Substituent at N(1)														
1	10.08	–	9.97	–	3.55	30.8	3.56	30.6	–	136.5	–	136.5	–	136.2
2,6	–	–	–	–	–	–	–	–	7.24, 7.62	129.0, 128.4	7.24, 7.62	129.0, 128.6	6.83, 7.53	129.0, 128.3
3,5	–	–	–	–	–	–	–	–	7.42, 7.57	130.7, 130.4	7.40, 7.59	130.7, 130.4	7.36, 7.58	130.6, 130.4
4	–	–	–	–	–	–	–	–	7.54	129.6	7.55	129.6	7.52	129.5
Substituent at C(3)														
1	2.01	20.9	2.52	30.0	1.97	21.0	2.44	30.0	2.01	20.1	2.53	29.7	3.77	42.4
			2.45				2.43				2.46			
2	–	–	1.02	9.8	–	–	0.96	9.9	–	–	1.08	10.0	–	133.1
3	–	–	–	–	–	–	–	–	–	–	–	–	7.19	128.6
4	–	–	–	–	–	–	–	–	–	–	–	–	7.19	130.7
5	–	–	–	–	–	–	–	–	–	–	–	–	7.19	129.5
SCN	–	108.3	–	108.6	–	108.3	–	108.8	–	108.3	–	108.8	–	108.6

to the solution of **2** in a 1:9 mixture AcOH conc. H_2SO_4 (*Method A*), in the second one, P_2O_5 was added to the solution of **2** in conc. H_2SO_4 (*Method B*), and in the third method (*Method C*), $AlCl_3$ was added to the solution of **2** in conc. H_2SO_4. The results of these experiments are compiled in *Scheme 2* and *Table 2*.

Scheme 2



To our surprise, thiocarbamates **3** were isolated in only four cases, *i.e.* **3a**, **3b**, **3c**, and **3g**. Thiazoloquinolinediones **4** were found as products from all of the starting

Table 2. *Results of Modified* Riemschneider *Reaction of 3-Thiocyanatoquinoline-2,4-diones* **2**

Entry	**2**	R^1	R^2	*Method*[a])	Time [min]	Product(s) (Yield [%])[b])[c])
1	**a**	H	Me	*A*	60	**6a** (46)
2				*B*	30	**3a** (35), **4a** (7)
3				*C**	50	**1a** (52)[b]), **6a** (8)
4	**b**	H	Et	*A*	180	**4b** (7), **6b** (40)
5				*B*	60	**3b** (42), **4b** (18)
6				*C*	60	**1b** (26), **4b** (18)
7	**c**	H	Bu	*A*	10	**3c** (52), **4c** (10)
8				*A*	30	**1c** (33), **4c** (14)
9				*A*	21 h	**5c** (43)
10				*B**	30	**1c** (30)
11				*B**	40	**1c** (47)
12				*C*	21 h	**5c** (34)
13	**d**	H	Bn	*A*	180	**12d** (48), **Md** (4)[d])
14				*B*	30	**11d** (6), **12d** (5), **Md**[d]) (55)
15				*B**		**Md**[d]) (22)
16				*C**	30	**Md**[d]) (35)
17	**e**	Me	Me	*A*	150	**1e** (5), **4e** (18), **6e** (63)
18				*B**	60	**1e** (27), **4e** (8), **8e** (29)
19				*C**	60	**1e** (24), **4e** (4), **6e** (3), **8e** (23)
20	**f**	Me	Et	*A*	17 h	**4f** (41), **6f** (16), **7f** (4)
21				*B**	40	**1f** (13), **4f** (53)
22				*C*	60	**1f** (5), **4f** (42)
23	**g**	Me	Bu	*A*	180	**5g** (63)
24				*B*	60	**1g** (14), **4g** (21), **5g** (1)
25				*B**	90	**1g** (10), **4g** (18), **5g** (3), **7g** (4), **8g** (18)
26				*C**	90	**1g** (38), **4g** (4), **8g** (10)
27	**h**	Me	Bn	*A*	60	**Mh**[d]) (33)
28				*B*	30	**Mh**[d]) (46)
29				*C*	60	**Mh**[d]) (33)
30	**i**	Ph	Me	*A*	120	**1i** (7), **4i** (69)
31				*B**	60	**1i** (36), **4i** (4), **8i** (25)
32				*C**	60	**1i** (59), **4i** (2), **8i** (22)
33	**j**	Ph	Et	*A*	60	**1j** (7), **4j** (61), **6j** (8)
34				*B**	40	**1j** (30), **4j** (12), **7j** (7)
35				*C**	30	**1j** (30), **4j** (35)
36	**k**	Ph	Bu	*A*	60	**1k** (22), **4k** (54)
37				*A*	21 h	**1k** (6), **4k** (15), **5k** (34)
38				*A**	45	**1k** (14), **4k** (23), **8k** (26), **9k** (4)
39				*B*	25	**3k** (40), **4k** (23)
40				*C*	45	**3k** (23), **4k** (51)
41	**l**	Ph	Bn	*A*	45	**11l** (9)[b], **12l** (7), **Ml**[d]) (30)
42				*A**	45	**Ml**[d]) (44)
43				*B*	45	**11l** (4), **12l** (26), **Ml**[d]) (25)
44				*B**	30	**11l** (3), **Ml**[d]) (32)
45				*C**	60	**11l** (5), **Ml**[d]) (42)

[a]) *Methods: A:* H_2SO_4 96%/AcOH, 9:1, P_2O_5; *B:* H_2SO_4 96%, P_2O_5; *C:* H_2SO_4 96%, $AlCl_3$. In experiments designated with asterisk, for alkalization of the crude mixture, NH_4OH was used. [b]) All isolated compounds **1** and **7** were identical to authentic samples. [c]) In most cases, elemental sulfur was also isolated. [d]) Mixtures of compounds **13**, **14**, and **15**, yields were calculated to pure compound **14**.

compounds **2** with the exception of **2d**, **2h**, and **2l**, which bear a Bn group at C(3). In the reactions in which **4a**, **4b**, **4e**, **4f**, and **4j** were formed, their hydrated analogs **6a**, **6b**, **6e**, **6f**, and **6j**, none of which has been reported previously, arose from their corresponding starting materials. The structures of studied compounds were based on standard 1D ^{1}H- and ^{13}C-NMR spectra, and on several 2D experiments (gradient-selected (gs)-COSY, gs-HMQC, gs-HMBC). The presence of one sp^3 C-atom (C(3)) and ^{13}C signals resonating at 194 ppm (C(4)) was a typical feature of compounds **3**, whereas compounds **4** showed one sp^3 C-atom resonance (C(3a)), and compounds **6** displayed two sp^3 C-atom resonances (C(3a) and C(9b); *cf. Tables 3–5*).

Table 3. *^{1}H- and ^{13}C-NMR Data* ($CDCl_3$) *of Compounds* **3** (δ in ppm)

Position	**3a**		**3b**		**3c**		**3k**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	171.7	–	171.0	–	171.1	–	170.8
3	–	61.9	–	66.3	–	65.5	–	65.8
4	–	193.8	–	193.7	–	193.7	–	193.2
4a	–	117.8	–	119.0	–	119.0	–	119.8
5	7.82	127.3	7.80	126.8	7.80	126.8	7.98	127.2
6	7.15	122.5	7.14	122.4	7.13	122.4	7.24	123.0
7	7.66	136.1	7.64	136.0	7.64	136.0	7.56	136.0
8	7.18	116.4	7.16	116.4	7.16	116.4	6.38	116.6
8a	–	141.6	–	141.6	–	141.6	–	143.5
Substituent at N(1)								
1	11.01	–	11.05	–	11.04	–	–	138.0
2,6	–	–	–	–	–	–	7.42, 7.16	130.4, 128.6
3,5	–	–	–	–	–	–	7.67, 7.42	130.3, 129.4
4	–	–	–	–	–	–	7.56	128.9
Substituent at C(3)								
1	1.46	21.7	1.92	29.8	1.86	36.0	1.99	36.2
			1.87		1.82			
2	–	–	0.83	9.0	1.22	26.2	1.39	26.3
					1.12		1.24	
3	–	–	–	–	1.19	22.1	1.24	22.1
4	–	–	–	–	0.78	13.6	1.07	13.6
$SCONH_2$	7.90, 7.41	166.4	7.86, 7.39	166.4	7.82, 7.38	166.4	7.97, 7.45	166.5

Unfortunately, we have found that the dealkylated products **5** were formed only in cases in which the starting compounds contained a Bu group at C(3) (*i.e.*, **5c**, **5g**, and **5k**), and prolonged reaction times were employed (*Table 2*). In some cases, nucleophilic substitution was found to proceed in thiocyanates **2**, and small quantities of known 3-hydroxyquinoline-2,4-diones **7f**, **7g**, and **7j** were isolated.

In several cases, conc. NH_4OH was used during the isolation of the reaction product with the aim to basify the crude extract after the reaction (*Methods A**, *B**, and *C**). Under these conditions, side-products **8i**, **8k** and **9e**, **9g**, and **9k** were isolated (*Table 2*). We propose that compounds **8** and **9** arise from the nucleophilic ring opening of the thiazolones **4** with NH_4OH and subsequent desulfuration (*Scheme 3*). The presence of the $CONH_2$ group at the N-atom in compounds **8** implies that the C(O)–S bond in

Table 4. *^{1}H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds* **4** (δ in ppm)

Position	**4a**		**4b**		**4e**		**4f**		**4g**		**4i**		**4j**		**4k**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	–	184.9	–	185.3	–	184.7	–	185.1	–	185.2	–	184.9	–	185.3	–	185.4
3a	–	72.5	–	78.2	–	72.6	–	78.3	–	77.8	–	72.9	–	78.6	–	78.1
4	–	167.9	–	167.3	–	167.2	–	166.5	–	166.5	–	167.4	–	166.7	–	166.7
5a	–	141.1	–	141.1	–	142.2	–	142.2	–	142.3	–	143.3	–	143.3	–	143.3
6	7.24	117.1	7.24	117.0	7.56	116.8	7.55	116.9	7.55	116.8	6.51	117.4	6.50	117.4	6.50	117.4
7	7.76	137.1	7.76	137.0	7.88	137.1	7.88	137.1	7.87	137.1	7.88	136.6	7.67	136.6	7.67	136.6
8	7.31	123.7	7.30	123.7	7.40	123.9	7.39	123.9	7.39	124.0	7.40	123.9	7.36	123.9	7.36	124.0
9	8.00	128.2	7.98	128.0	8.07	128.2	8.05	128.0	8.05	128.1	8.13	128.4	8.11	128.1	8.10	128.2
9a	–	114.7	–	115.0	–	116.3	–	116.5	–	116.6	–	115.9	–	116.1	–	116.2
9b	–	193.2	–	192.3	–	192.6	–	191.7	–	191.9	–	192.7	–	191.8	–	191.9
Substituent at N(1)																
1	11.30	–	11.30	–	3.44	30.4	3.45	30.4	3.44	30.5	–	137.0	–	137.0	–	137.1
2,6	–	–	–	–	–	–	–	–	–	–	7.55, 7.40	129.5, 128.9	7.54, 7.38	129.5, 128.9	7.54, 7.38	129.5, 128.9
3,5	–	–	–	–	–	–	–	–	–	–	7.67, 7.63	130.4, 130.1	7.67, 7.63	130.4, 130.1	7.65, 7.61	130.4, 130.2
4	–	–	–	–	–	–	–	–	–	–	7.40	129.3	7.56	128.9	7.55	129.3
Substituent at C(3)																
1	1.91	31.0	2.24	36.0	1.89	30.7	2.20	35.8	2.16	41.7	2.07	30.8	2.42	36.0	2.38	41.7
			1.98						1.91				2.20		2.11	
2	–	–	0.93	9.6	–	–	0.91	9.5	1.37	27.3	–	–	0.99	9.8	1.45	27.3
									1.14						1.23	
3	–	–	–	–	–	–	–	–	1.21	21.4	–	–	–	–	1.31	21.4
4	–	–	–	–	–	–	–	–	0.79	13.6	–	–	–	–	0.85	13.6
5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 5. *^{1}H- and ^{13}C-NMR Data* ((D$_6$)DMSO) *of Compounds* **6** (δ in ppm)

Position	**6a**		**6b**		**6e**		**6f**		**6j**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	9.06	–	8.91a)	–	9.08b)	–	8.95c)	–	9.13	–
2	–	170.5	–	171.1	–	170.7	–	171.2	–	171.2
3a	–	63.7	–	69.2	–	64.5	–	69.8	–	70.5
4	–	169.6	–	169.4	–	169.3	–	169.0	–	168.9
5a	–	134.9	–	134.9	–	136.8	–	136.7	–	137.9
6	6.99	115.2	6.97	115.1	7.26	114.9	7.23	114.8	6.25	115.8
7	7.37	130.1	7.35	130.0	7.50	130.4	7.50	130.3	7.30	129.9
8	7.14	122.8	7.11	122.7	7.26	123.3	7.23	123.2	7.21	123.3
9	7.71	127.8	7.69	127.0	7.82	127.7	7.81	126.9	7.86	127.5
9a	–	122.1	–	122.6	–	123.4	–	124.1	–	123.5
9b	–	87.3	–	86.7	–	86.6	–	85.6	–	86.1
Substituent at N(1)										
1	10.72	–	10.75c)		3.39	30.5	3.43	30.4	–	137.7
2,6	–	–	–	–	–	–	–	–	7.35	129.0
3,5	–	–	–	–	–	–	–	–	7.65	130.2
4	–	–	–	–	–	–	–	–	7.56	128.7
Substituent at C(3a)										
1	1.54	18.9	2.04	26.1	1.51	18.9	2.04	26.2	2.16	26.0
			1.96				1.95		2.12	
2	–	–	0.78	10.1	–	–	0.68	10.1	0.88	10.3
3	–	–	–	–	–	–	–	–	–	–
4	–	–	–	–	–	–	–	–	–	–
5	–	–	–	–	–	–	–	–	–	–
OH	7.00	–	7.08	–	7.07	–	7.22	–	7.25	–

a) ^1J (^{15}N, ^{1}H) = 90.8. b) ^1J (^{15}N, ^{1}H) = 90.9. c) ^1J (^{15}N, ^{1}H) = 90.2.

compounds **4** must be primarily attacked during the formation of intermediate **A**. We confirmed our assumption by carrying out the reactions of compounds **4e**, **4g**, **4i**, and **4j** with NH_4OH in EtOH (*Method D*), and these reactions yielded compounds **8e**, **8g**, **8j** and **9e**, **9i**, **9j**, respectively. In all cases, elemental S arises simultaneously. The analogous reaction proceeds also with **6e**, but does not occur with compounds **5**. The most characteristic ^{13}C resonance in compounds **9** was that of C(3), which reflected the strong donor effect of the amino group at C(4) (*Table 6*). The presence of the

Scheme 3

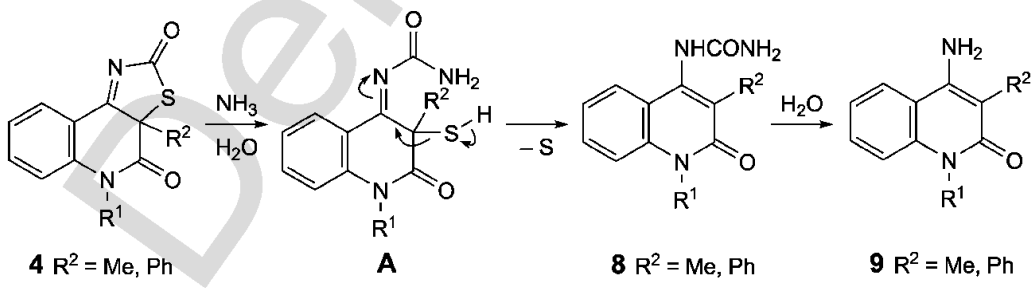


Table 6. *^1H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds* **8**, **9**, *and* **10** (δ in ppm)

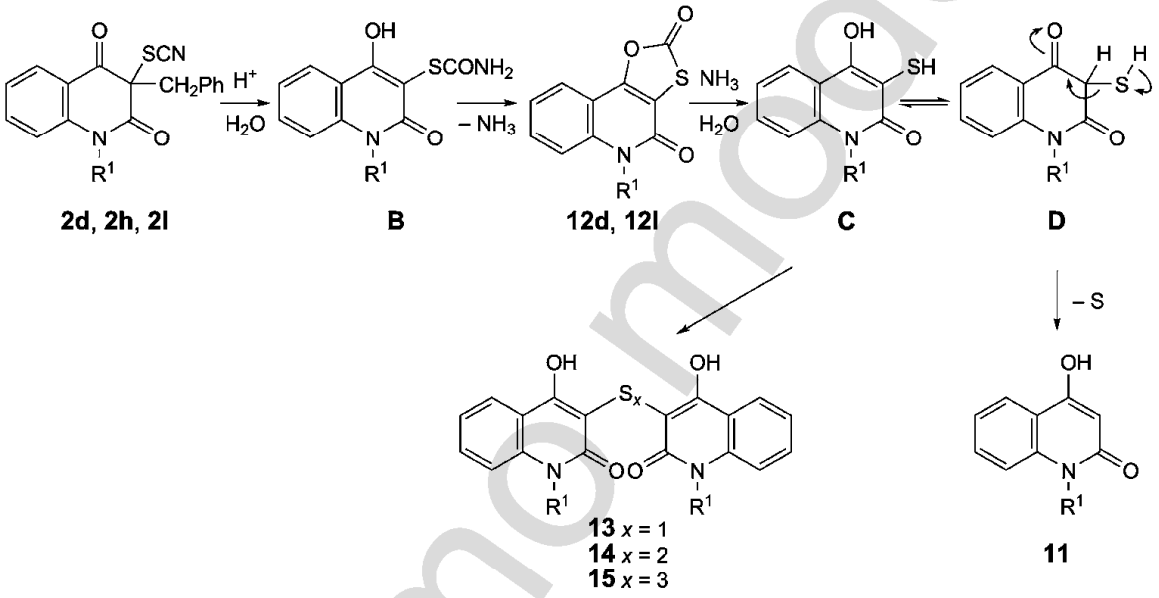
Position	**8e**		**8g**		**8i**		**8j**		**8k**		**9e**		**9i**		**9j**		**10g**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	163.2	–	161.9	–	163.2	–	161.9	–	162.0	–	162.1	–	162.2	–	161.8	–	161.7
3	–	106.6	–	119.8	–	106.6	–	119.7	–	119.6	–	99.5	–	99.3	–	105.6	–	119.2
4	–	156.1	–	140.8	–	156.1	–	141.5	–	141.6	–	147.4	–	148.2	–	147.4	–	139.5
4a	–	116.4	–	129.3	–	116.2	–	130.8	–	129.7	–	114.6	–	114.4	–	114.6	–	130.4
5	8.01	123.0	7.70	125.0	8.05	123.0	7.74	125.1	7.72	125.1	8.06	122.8	8.10	122.8	8.10	123.0	7.65	124.4
6	7.28	121.4	7.30	121.6	7.26	121.6	7.28	121.9	7.26	121.9	7.22	120.6	7.20	121.0	7.19	120.9	7.32	122.0
7	7.61	130.3	7.61	129.8	7.40	129.9	7.40	128.8	7.38	128.8	7.56	129.7	7.35	129.4	7.34	129.4	7.63	130.2
8	7.50	114.4	7.55	114.4	6.51	115.1	6.54	115.2	6.53	115.1	7.43	114.4	6.46	115.4	6.46	115.3	7.58	114.7
8a	–	138.3	–	138.2	–	139.2	–	139.3	–	139.2	–	138.5	–	139.5	–	139.6	–	138.3
Substituent at N(1)																		
1	3.63	29.3	3.69	29.6	–	138.5	–	138.2	–	138.1	3.59	29.0	–	139.3	–	139.0	3.71	29.7
2,6	–	–	–	–	7.30	129.5	7.35	129.2	7.33	129.1	–	–	7.25	129.7	7.26	129.7	–	–
3,5	–	–	–	–	7.64	130.0	7.68	130.2	7.67	130.2	–	–	7.61	130.9	7.61	129.8	–	–
4	–	–	–	–	7.57	128.5	7.60	129.6	7.29	129.6	–	–	7.53	128.2	7.53	128.1	–	–
Substituent at C(3)																		
1	2.09	10.4	2.61	26.4	2.11	10.1	2.64	20.0	2.62	30.0	2.03	11.0	2.03	10.7	2.60	17.6	2.60	26.3
2	–	–	1.47	30.0	–	–	1.12	12.8	1.50	26.2	–	–	–	–	1.06	12.4	1.46	29.8
3	–	–	1.35	22.6	–	–	–	–	1.38	22.6	–	–	–	–	–	–	1.34	22.5
4	–	–	0.94	14.0	–	–	–	–	0.93	14.0	–	–	–	–	–	–	0.93	13.9
Substituent at C(4)																		
1	10.2	–	8.16[a])	–[b])	10.3	–	8.30	–	8.30	–	6.21	–	6.40	–	6.40	–	9.42	–
2	–	158.8	–	156.7	–	158.7	–	156.8	–	156.8	–	–	–	–	–	–	–	154.8
3	5.50	–	6.06[c])	–[d])	5.48[e])	–[f])	6.16	–	6.16	–	–	–	–	–	–	–	–	[g])

[a]) $^1J(^{15}N,^1H) = 88.9$. [b]) $\delta(^{15}N) = -243.7$. [c]) $^1J(^{15}N,^1H) = 86.6$. [d]) $\delta(^{15}N) = -245.3$. [e]) $^1J(^{15}N,^1H) = 85.6$. [f]) $\delta(^{15}N) = -245.5$. [g]) 4.13/64.3 (CH_2(1)), 1.64/30.8 (CH_2(2)), 1.46 and 1.34/18.6 (CH_2(3)), 0.95/13.7 (Me(4)).

$NHCONH_2$ fragment in compounds **8g** was clearly demonstrated by using ^{15}N-NMR spectra (*Table 6*). Surprisingly, the corresponding carbamate **10g** was obtained after recrystallization of **8g** from BuOH. Compared with the NMR data of compound **8g**, a second set of Bu group signals appeared in the spectrum of compound **10g**, and the typical ^{13}C resonance of the carbamate COO group (154.8 ppm) was observed (*Table 6*).

The reaction of compounds **2** with the Bn group at C(3), *i.e.*, **2d**, **2h**, and **2l**, proceeds differently. A minute quantity of compound **11l** was obtained from the reaction of **2l**. In two cases, novel dealkylated compounds **12d** and **12l** were obtained. The presence of an oxathiolone ring in these compounds indicated a rapid debenzylation of compounds **2** under the formation of intermediate **B**, followed by closure of the oxathiolone ring to give compounds **12** (*Scheme 4*). However, compounds **12** behave unlike their aza analogs **5**. Whereas compounds **5** did not react with NH_4OH, compounds **12d** and **12l** yielded (*Method D*) 4-hydroxyquinoline-2-ones **11d** and **11l**, respectively (*Scheme 4*). Compounds **12** were possibly transformed to compounds **11** through intermediates **C** and their tautomers **D**.

Scheme 4



The main products of the reaction of **2d**, **2h**, and **2l** are poorly soluble fractions designated as **Md**, **Mh**, and **Ml** (*Table 2*). In both their ^1H- and ^{13}C-NMR spectra, the signals corresponding to the Bn group are not present, *i.e.*, the debenzylation of starting compounds **2** took place during the formation of compounds **12**. The molecular peak corresponding to sulfides **13** appears in EI-MS of fractions **M**. However, the results of elemental analyses are not in accord with those expected for structure **13**. They show considerable higher levels of S and more likely correspond to disulfides **14**. Therefore, we used ESI-MS, a process with milder conditions. The results of these recordings provided evidence that fractions **M** are mixtures of sulfides **13**, disulfides **14**, and

trisulfides **15**. However, the dominant compound in mixtures **M** was always disulfide **14**. The origin of this compound can be explained by the dehydrogenation of intermediate **C** (*Scheme 4*). The formation of compounds **13** and **15** can be rationalized by the disproportionation of disulfide **14**. Another possibility is the formation of **15** by the reaction of **14** with elemental S, which was isolated in most cases from the mixture, and the formation of **13** by the reaction of disulfide **14** with **11**, similar to that which was described for the reaction of **11** with disulfides [19].

All of our attempts to isolate pure individual compounds from the mixtures **M** by column chromatography failed. In particular, this failure was due to their poor solubility and very similar chromatographic characteristics. Therefore, we tried to separate the mixtures **M** by repeated fractional crystallization. By this method, albeit in poor yields, pure compounds **13d**, **13l**, **14h**, and **14l** were obtained (see *Table 7*, *Exper. Part*, for NMR data for these compounds).

3. Conclusions. – The the *Riemschneider* reaction of thiocyanates **2** under classical conditions in H_2SO_4 or its mixture with AcOH provide only compounds **3** and **4** [16]. In conclusion, we would like to emphasize that the addition of P_2O_5 or $AlCl_3$ to the mixture leads, according to presumption, to the formation of other new compounds, mainly **6** (*Table 2*). In addition, compounds **8** and **9** can be obtained by modifying the procedure treating the crude reaction product with NH_4OH. The best results for these experiments were obtained by *Method A*, where the smallest quantities of **1** as degradation products were produced. *Method C* was found to be inconvenient in the majority of cases. The exceptionally easy *C*-debenzylation of compounds **2** enabled the desired preparation of novel [1,3]oxathiolo[4,5-*c*]quinoline-2,4-diones **12** by a simple procedure. Because many biologically active compounds contain a S-atom [20][21], compounds **12** could also be interesting structures to be studied in further investigations.

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Experimental Part

1. *General.* TLC: *Alugram®-SIL-G/UV$_{254}$* foils (*Macherey-Nagel*); elution with benzene/AcOEt 4:1, $CHCl_3$/EtOH 9:1 and/or 19:1, $CHCl_3$/AcOEt 7:3, and $CHCl_3$/AcOH 9:1. Column chromatography (CC): silica gel (SiO_2; *Merck*, grade *60*, 70–230 mesh); elution with $CHCl_3$, then $CHCl_3$/EtOH 99:1 → 8:2, or benzene, and then benzene/AcOEt 99:1 → 8:2. M.p.: *Kofler* block or *Gallencamp* apparatus. IR Spectra: *Nicolet iS10* spectrophotometer; KBr pellets; ν in cm^{-1}. NMR Spectra: *Bruker Avance* spectrometer at 500.13 (^1H) and 125.76 MHz (^{13}C), and *Bruker Avance II 400* spectrometer at 400.13 (^1H), 100.56 (^{13}C), and 40.55 MHz (^{15}N); (D_6)DMSO soln.; δ in ppm rel. to Me_4Si as internal or ^{15}N-enriched $MeNO_2$ as external (in a co-axial capillary) standard; J in Hz; manufacturer's software for all 2D experiments (gradient-selected (gs)-COSY, gs-NOESY, gs-HMQC, and gs-HMBC). EI-MS (pos.): *Shimadzu QP-2010* instrument within m/z 50–600 using direct inlet probe (DI); analysis of samples in CH_2Cl_2 (30 µg/ml), 10 µl of the soln. was evaporated in DI cuvette at 50°; ion-source temp., 200°; the energy of electrons, 70 eV; only signals exceeding rel. abundance of 5% are listed. ESI-MS (pos. as well as neg.): *amaZon X* ion-trap mass spectrometer (*Bruker Daltonics*, D-Bremen) equipped with an ESI source; individual samples infused into the ion source as MeOH/H_2O 1:1 (*v*/*v*) solns. *via* a syringe pump

at a constant flow rate of 4 µl/min; other instrumental conditions: *m/z* range 50–1500; electrospray voltage, ±4.2 kV; drying gas temp., 220 , drying gas flow, 6.0 dm^3/min; nebulizer pressure, 55.16 kPa; cap. exit ±140 V; N_2 used as nebulizing as well as drying gas. Elemental analysis (C, H, N, S): *Flash EA 1112* elemental analyzer (*Thermo Fisher Scientific*).

2. *Starting 3-Thiocyanatoquinoline-2,4-(1*H,3H*)-diones (=1,2,3,4-Tetrahydro-2,4-dioxoquinolin-3-yl Thiocyanates*; **2**). Compounds **2** were prepared according to the procedure described in [7][16]. Seven new derivatives, **2a**, **2b**, **2e**, **2f**, **2i**, **2j**, **2l**, were prepared. Compound **2l** was also prepared by a modification of this method, using DMF as solvent instead of AcOH.

1,2,3,4-Tetrahydro-3-methyl-2,4-dioxoquinolin-3-yl Thiocyanate (**2a**). Prepared from **1a** in 46% yield. Yellowish oil. IR 3084, 2989, 1920, 2156, 1709, 1674, 1612, 1597, 1500, 1485, 1441, 1377, 1350, 1321, 1277, 1232, 1159, 1101, 1057, 1009, 964, 908, 872, 760, 665, 579, 525. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 232 (35, M^+), 204 (20), 176 (7), 175 (64), 174 (11), 147 (11), 146 (65), 128 (22), 120 (58), 119 (100), 118 (11), 117 (16), 93 (12), 92 (44), 91 (20), 90 (16), 77 (22), 76 (12), 65 (24), 64 (20), 63 (18), 59 (28), 55 (21), 51 (12). ESI-MS (pos.): 486.9 (37, $[2\,M + Na]^+$), 430.0 (25, $[2\,M + Na - SCN + H]^+$), 368.0 (33, $[3\,M + Ca]^{2+}$), 270.9 (44, $[M + K]^+$), 255.0 (100, $[M + Na]^+$), 250.0 (14, $[M + NH_4]^+$), 233.0 (5, $[M + H]^+$), 198.0 (5, $[M + Na - SCN + H]^+$), 176.0 (25, $[M + H - SCN + H]^+$). ESI-MS (neg.): 230.9 (100, $[M - H]^-$), 173.9 (17, $[M - SCN]^-$).

3-Ethyl-1,2,3,4-tetrahydro-2,4-dioxoquinolin-3-yl Thiocyanate (**2b**). Prepared from **1b** in 68% yield. Yellow crystals. M.p. 103–107° (benzene/hexane). IR: 3217, 3141, 3085, 2987, 2933, 2874, 2738, 2156, 1709, 1659, 1614, 1597, 1506, 1485, 1458, 1434, 1374, 1318, 1299, 1252, 1232, 1156, 1060, 1000, 959, 909, 870, 842, 807, 773, 745, 684, 663, 617, 528, 516. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 246 (4, M^+), 190 (10), 189 (76), 188 (33), 187 (5), 186 (9), 175 (13), 174 (100), 161 (15), 156 (5), 146 (14), 128 (8), 127 (5), 120 (27), 119 (11), 115 (9), 113 (7), 99 (7), 93 (6), 92 (26), 91 (7), 90 (8), 87 (12), 85 (12), 77 (15), 71 (24), 69 (13), 65 (18), 64 (11), 63 (9), 59 (29), 58 (6), 57 (39), 56 (5), 55 (26), 43 (21), 41 (19). Anal. calc. for $C_{12}H_{10}N_2O_2S$ (246.29): C 58.52, H 4.09, N 11.37, S 13.02; found: C 58.34, H 4.11, N 11.27, S 12.92.

1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxoquinolin-3-yl Thiocyanate (**2e**). Prepared from **1e** in 90% yield. Yellow oil. IR: 3087, 2988, 2944, 2893, 2360, 2342, 2155, 1704, 1667, 1603, 1493, 1473, 1419, 1373, 1357, 1301, 1258, 1177, 1120, 1092, 1046, 969, 903, 761, 664, 613, 584, 530. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 246 (11, M^+), 190 (12), 189 (100), 188 (7), 161 (8), 160 (44), 147 (8), 146 (52), 144 (7), 134 (24), 133 (23), 132 (20), 130 (8), 118 (6), 117 (12), 116 (9), 106 (9), 105 (27), 104 (24), 103 (5), 95 (6), 92 (5), 91 (12), 90 (7), 79 (8), 78 (12), 77 (37), 76 (7), 65 (8), 64 (7), 63 (9), 59 (15), 51 (12). ESI-MS (pos.): 515.1 (14, $[2\,M + Na]^+$), 458.2 (9, $[2\,M + Na - SCN + H]^+$), 389.2 (15, $[3\,M + Ca]^{2+}$), 285.1 (20, $[M + K]^+$), 269.2 (100, $[M + Na]^+$), 265.2 (17, $[M + NH_4]^+$), 247.2 (32, $[M + H]^+$), 228.2 (13, $[M + K - SCN + H]^+$), 212.2 (5, $[M + Na - SCN + H]^+$), 190.3 (30, $[M + H - SCN + H]^+$), 188.3 (21, $[M - SCN]^+$). ESI-MS (neg.): 188.1 (100),$[M - SCN]^-$).

3-Ethyl-1,2,3,4-tetrahydro-1-methyl-2,4-dioxoquinolin-3-yl Thiocyanate (**2f**). Prepared from **1f** in 67% yield. Yellowish crystals. M.p. 62–65° (benzene/cyclohexane). IR: 2992, 2971, 2936, 2155, 1698, 1668, 1603, 1473, 1355, 1242, 1159, 1186, 1031, 818, 778, 755, 660, 462. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 219 (13), 204 (11), 203 (81), 202 (13), 189 (13), 188 (100), 175 (9), 163 (29), 162 (54), 160 (13), 149 (14), 147 (6), 146 (9), 135 (6), 134 (47), 132 (13), 130 (11), 117 (9), 116 (11), 115 (7), 106 (16), 105 (13), 104 (18), 103 (6), 102 (7), 97 (9), 95 (6), 94 (7), 92 (9), 91 (14), 90 (8), 89 (7), 85 (10), 83 (10), 81 (8), 79 (12), 78 (15), 77 (43), 76 (9), 71 (18), 69 (23), 67 (6), 65 (10), 64 (8), 63 (10), 57 (41). ESI-MS (pos.): 543.1 (14, $[2\,M + Na]^+$), 486.2 (5, $[2\,M + Na - SCN + H]^+$), 410.2 (10, $[3\,M + Ca]^{2+}$), 299.2 (23, $[M + K]^+$), 283.2 (100, $[M + Na]^+$), 278.2 (7, $[M + NH_4]^+$), 261.2 (16, $[M + H]^+$), 242.2 (5, $[M + K - SCN + H]^+$), 226.2 (5, $[M + Na - SCN + H]^+$), 204.3 (9, $[M + H - SCN + H]^+$), 202.3 (8, $[M - SCN]^+$). ESI-MS (neg.): 202.1 (100, $[M - SCN]^-$). Anal. calc. for $C_{13}H_{12}N_2O_2S$ (260.31): C 59.98, H 4.65, N 10.76, S 12.32; found: C 60.25, H 4.72, N 10.60, S 12.12.

1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-phenylquinolin-3-yl Thiocyanate (**2i**). Prepared from **1i** in 71% yield. Yellow crystals. M.p. 132–135° (benzene/hexane). IR: 3065, 3015, 2363, 2154, 1701, 1667, 1601, 1583, 1491, 1464, 1370, 1340, 1304, 1256, 1132, 1166, 1157, 1103, 1071, 1055, 1026, 961, 895, 843, 795, 769, 759, 744, 703, 657, 602, 554, 537. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 308 (9, M^+), 251 (19), 250 (20), 222 (11), 195 (11), 167 (10), 126 (10), 114 (24), 112 (9), 104 (17), 98 (7), 97 (6), 95 (7), 86 (9), 83 (11), 81 (6), 77 (8), 74 (100), 72 (47), 69 (16), 67 (8), 62 (7), 60 (15), 59 (82), 57 (10), 56 (7), 55 (34), 44

(15), 43 (24), 41 (17). Anal. calc. for $C_{17}H_{12}N_2O_2S$ (308.35): C 66.22, H 3.92, N 9.08, S 10.40; found: C 66.19, H 3.88, N 9.08, S 10.28.

3-Ethyl-1,2,3,4-tetrahydro-2,4-dioxo-1-phenylquinolin-3-yl Thiocyanate (**2j**). Prepared from **1j** in 67% yield. Yellowish crystals. M.p. 110–113° (benzene). IR: 3067, 2977, 2934, 2162, 1708, 1673, 1599, 1491, 1464, 1346, 1397, 1249, 1100, 1013, 813, 777, 767, 751, 704, 660, 603, 512. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 281 (6), 266 (19), 265 (100), 264 (51), 251 (17), 250 (89), 237 (11), 225 (12), 224 (9), 196 (28), 195 (19), 168 (9), 167 (29), 166 (11), 149 (20), 140 (7), 139 (9), 127 (10), 124 (11), 115 (8), 114 (6), 111 (10), 99 (6), 98 (9), 97 (16), 95 (8), 85 (11), 84 (7), 83 (19), 81 (8), 77 (25), 74 (10), 72 (9), 71 (22), 70 (11), 69 (29), 67 (8), 59 (17), 57 (36). ESI-MS (pos.): 667.1 (6, $[2M+Na]^+$), 610.2 (5, $[2M+Na-SCN+H]^+$), 553.3 (5, $[2M+Na-2\cdot SCN+2\cdot H]^+$), 503.2 (6, $[3M+Ca]^{2+}$), 361.2 (26, $[M+K]^+$), 345.2 (100, $[M+Na]^+$), 340.3 (6, $[M+NH_4]^+$), 323.2 (19, $[M+H]^+$), 304.2 (7, $[M+K-SCN+H]^+$), 288.3 (18, $[M+Na-SCN+H]^+$), 266.3 (22, $[M+H-SCN+H]^+$). ESI-MS (neg.): 264.1 (100, $[M-SCN]^-$). Anal. calc. for $C_{18}H_{14}N_2O_2S$ (322.38): C 67.06, H 4.38, N 8.69, S 9.95; found: C 66.91, H 4.39, N 8.60, S 9.74.

3-Benzyl-1,2,3,4-tetrahydro-2,4-dioxo-1-phenylquinolin-3-yl Thiocyanate (**2l**). *a*) Prepared from **1l** in 7% yield according to the procedure described in [7]. Yellowish crystals. M.p. 141–144° (benzene/hexane). IR: 3080, 3028, 2958, 2924, 2859, 2157, 1708, 1677, 1598, 1492, 1461, 1331, 1298, 1245, 1213, 1183, 1160, 1086, 1071, 1045, 1030, 1002, 957, 944, 923, 806, 765, 750, 703, 661, 611, 581, 502. ^{1}H- and ^{13}C-NMR: see *Table 1*. EI-MS: 384 (7, M^+), 328 (12), 327 (49), 326 (18), 256 (6), 222 (8), 196 (10), 167 (10), 140 (7), 127 (9), 126 (19), 125 (11), 124 (6), 114 (21), 113 (11), 112 (17), 111 (18), 110 (8), 109 (10), 97 (29), 91 (31), 85 (21), 83 (30), 74 (100), 69 (31), 59 (92), 57 (45), 55 (51), 43 (56). Anal. calc. for $C_{23}H_{16}N_2O_2S$ (384.45): C 71.85, H 4.19, N 7.29, S 8.34; found: C 71.70, H 4.24, N 7.11, S 8.18.

b) A soln. of **1l** (2.45 g, 7.5 mmol) in DMF (37.5 ml) was added in one portion to the stirred soln. of $(SCN)_2$, prepared by adding Br_2 (0.42 ml, 8.25 mmol) to the soln. of KSCN (1.75 g, 18 mmol) in DMF (38 ml). The stirring was continued for 5 min, and then the mixture was poured into a well-stirred mixture of H_2O (260 ml) and benzene (110 ml). The benzene layer was separated, and the aq. layer was extracted with benzene (6 × 50 ml). The collected extracts were washed with H_2O (3 × 40 ml), dried (anh. Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was separated by CC (SiO_2; benzene) and crystallized from benzene/hexane. Yield of **2l**: 50%.

3. *Modified* Riemschneider *Reaction of Compounds* **2**. *General Methods. Method A*. Compound **2** (2 mmol) was added under vigorous stirring at 0° to a mixture of 96% H_2SO_4 and AcOH (40 ml, 9:1 (*v*/*v*)). After dissolution of the starting compounds, P_2O_5 (4 g, 28 mmol) was added in two portions, and the mixture was stirred at r.t. The course of the reaction was monitored with TLC. After disappearance of the spot corresponding to **2** (for reaction time, see *Table 2*), the mixture was poured onto crushed ice (400 ml). Deposited precipitate was filtered with suction and washed with H_2O. The filtrate was extracted several times with AcOEt; the soln. was dried (anh. Na_2SO_4) and evaporated to dryness. The residue was dissolved in EtOH and filtered. The filtrate was evaporated to dryness, and the residue was crystallized from the appropriate solvent or separated by CC (SiO_2). In some cases, designated with asterisk in *Table 2*, the EtOH soln. was alkalized with NH_4OH (25%) before filtration.

Method B. The reaction was carried out as in *Method A*, but 96% H_2SO_4 (36 ml) was used instead of its mixture with AcOH.

Method C. The reaction was carried out as in *Method B*, anh. $AlCl_3$ (3.7 g, 14 mmol) was added instead of P_2O_5.

S-*(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxoquinolin-3-yl) Carbamothioate* (**3a**). Prepared from **2a** in 35% yield (*Method B*). Colorless crystals. M.p. 172–174° and then 266–272° (AcOEt). IR: 3400, 3227, 3174, 3067, 2927, 2867, 1698, 1662, 1610, 1597, 1486, 1446, 1380, 1354, 1324, 1230, 1103, 969, 806, 786, 751, 676, 623, 529. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 176 (11), 175 (100, $[M-SCONH]^+$), 174 (11), 147 (9), 146 (32), 129 (5), 128 (5), 120 (70), 119 (38), 118 (8), 117 (6), 104 (9), 93 (17), 92 (34), 91 (10), 90 (6), 88 (6), 77 (15), 76 (6), 74 (14), 65 (24), 64 (5), 63 (10), 59 (7), 55 (14), 51 (10). ESI-MS (pos.): 373.2 (100, $[2M+Na-2\cdot SCONH]^+$), 198.2 (46, $[M+Na-SCONH]^+$), 176.2 (46, $[M+H-SCONH]^+$). ESI-MS (neg.): 174.1 (100, $[M-H-SCONH]^-$). Anal. calc. for $C_{11}H_{10}N_2O_3S$ (250.27): C 52.79, H 4.03, N 11.19, S 12.81; found: C 52.88, H 4.03, N 11.17, S 12.65.

S-*(3-Ethyl-1,2,3,4-tetrahydro-2,4-dioxoquinolin-3-yl) Carbamothioate* (**3b**). Prepared from **2b** in 42% yield (*Method B*). Colorless crystals. M.p. 173–179° (AcOEt). IR: 3407, 3382, 3302, 3254, 3184,

2974, 1678, 1667, 1653, 1612, 1598, 1488, 1362, 1296, 1160, 848, 776, 753, 678, 667, 622, 594, 528. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 221 (30, [M – CONH]$^+$), 206 (15), 193 (24), 190 (9), 189 (76, [M – SCONH]$^+$), 188 (38), 175 (11), 174 (100), 170 (6), 161 (15), 149 (6), 148 (10), 146 (19), 132 (6), 130 (10), 128 (9), 120 (47), 119 (17), 117 (7), 116 (5), 115 (11), 93 (6), 92 (34), 91 (9), 90 (13), 89 (6), 87 (12), 77 (18), 76 (7), 74 (15), 73 (20), 69 (14), 66 (7), 65 (21), 64 (42), 63 (12), 59 (6), 55 (18), 50 (5). ESI-MS (pos.): 551.1 (5, [2 M + Na]$^+$), 476.2 (25, [2 M + Na – SCONH]$^+$), 401.2 (91, [2 M + Na – 2 · SCONH]$^+$), 303.2 (20, [M + K]$^+$), 287.2 (100, [M + Na]$^+$), 212.2 (56, [M + Na – SCONH]$^+$), 190.2 (56, [M + H – SCONH]$^+$). ESI-MS (neg.): 188.1 (100, [M – H – SCONH]$^-$). Anal. calc. for $C_{12}H_{12}N_2O_3S$ (264.30): C 54.53, H 4.58, N 10.60, S 12.13; found: C 54.48, H 4.56, N 10.53, S 11.86.

S-*(3-Butyl-1,2,3,4-tetrahydro-2,4-dioxoquinolin-3-yl) Carbamothioate* (**3c**). Prepared from **2c** by *Method A* in 52% yield. Colorless crystals. M.p. 163–165° (AcOEt/benzene). Identical in all respects to an authentic sample [16]. ^{1}H- and ^{13}C-NMR: see *Table 3*.

S-*(3-Butyl-1,2,3,4-tetrahydro-2,4-dioxo-1-phenylquinolin-3-yl) Carbamothioate* (**3k**). Prepared from **2k** in 40 (*Method B*) and 23% yield (*Method C*), resp. Yellowish crystals. M.p. 177–182° (benzene/hexane). IR: 3395, 3202, 2955, 2872, 1684, 1667, 1655, 1601, 1491, 1464, 1346, 1303, 761, 749, 701, 687, 662. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 368 (1, M^+), 293 (18, [M – SCONH]$^+$), 264 (33), 252 (18), 251 (100), 250 (53), 237 (9), 196 (16), 195 (11), 168 (8), 167 (12), 166 (5), 77 (14), 51 (7). Anal. calc. for $C_{20}H_{20}N_2O_3S$ (368.45): C 65.20, H 5.47, N 7.60, S 8.70; found: C 65.38, H 5.48, N 7.51, S 8.57.

*3a-Methyl[1,3]thiazolo[5,4-c]quinoline-2,4(3a*H,5H*)-dione* (**4a**). Prepared from **2a** in 7% yield (*Method B*). Yellow crystals. M.p. 187–189° and then 274–280° (benzene/hexane). IR: 3215, 3164, 3111, 3060, 2993, 2921, 2856, 1724, 1700, 1610, 1589, 1574, 1503, 1475, 1379, 1344, 1275, 1239, 1155, 1132, 1106, 1077, 1028, 972, 960, 780, 755, 674, 643, 288, 526. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 234 (6), 233 (13), 232 (100, M^+), 204 (7), 203 (31), 175 (30), 174 (7), 171 (11), 160 (6), 146 (15), 145 (23), 144 (7), 120 (25), 119 (13), 118 (15), 117 (14), 116 (8), 102 (15), 93 (6), 92 (12), 91 (7), 90 (13), 89 (7), 77 (7), 76 (7), 75 (7), 65 (9), 64 (9), 63 (10), 60 (13), 59 (52), 58 (6), 51 (9). Anal. calc. for $C_{11}H_8N_2O_2S$ (232.26): C 56.88, H 3.47, N 12.06, S 13.81; found: C 56.81, H 3.31, N 12.03, S 13.65.

*3a-Ethyl[1,3]thiazolo[5,4-c]quinoline-2,4(3a*H,5H*)-dione* (**4b**). Prepared from **2b** in 7 (*Method A*), 18 (*Method B*), and 18% yield (*Method C*), resp. Yellow crystals. M.p. 186–198° (AcOEt). IR: 3209, 3152, 3056, 2978, 2965, 2927, 2857, 1721, 1698, 1609, 1567, 1505, 1476, 1435, 1360, 1336, 1266, 1242, 1155, 1137, 1081, 1035, 1011, 978, 960, 926, 873, 804, 772, 745, 694, 674, 642, 590, 526. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 247 (14), 246 (100, M^+), 232 (7), 231 (44), 217 (8), 204 (5), 203 (47), 185 (12), 184 (6), 175 (9), 171 (11), 145 (8), 129 (8), 128 (6), 127 (7), 126 (6), 125 (7), 123 (7), 118 (6), 117 (11), 116 (10), 115 (6), 114 (5), 113 (6), 112 (5), 111 (10), 110 (6), 109 (8), 102 (12), 101 (7), 100 (24), 99 (7), 98 (8), 97 (14), 96 (7), 95 (11), 87 (7), 86 (7), 85 (14), 84 (10), 83 (20), 82 (8), 81 (12), 79 (9), 74 (21), 73 (24), 72 (20), 71 (29), 70 (12), 69 (26), 67 (9), 60 (6), 59 (23), 58 (16), 57 (34), 56 (9), 55 (28). Anal. calc. for $C_{12}H_{10}N_2O_2S$ (246.29): C 58.52, H 4.09, N 11.37, S 13.02; found: C 58.20, H 4.12, N 11.21, S 12.86.

*3a-Butyl[1,3]thiazolo[5,4-c]quinoline-2,4(3a*H,5H*)-dione* (**4c**). Prepared from **2c** in 10 and 14% yield (*Method A*), resp. Yellow crystals. M.p. 180–185° (AcOEt/benzene). Identical in all respects to the authentic sample [16].

*3a,5-Dimethyl[1,3]thiazolo[5,4-c]quinoline-2,4(3a*H,5H*)-dione* (**4e**). Prepared from **2e** in 18 (*Method A*), 8 (*Method B**), and 4% yield (*Method C**), resp. Yellow crystals. M.p. 147–149° (benzene/hexane). IR: 3083, 2985, 2929, 1724, 1685, 1592, 1571, 1470, 1420, 1382, 1351, 1292, 1176, 1133, 1095, 1061, 1042, 970, 933, 867, 774, 755, 690, 663, 643, 601, 549, 525. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 247 (15), 246 (100, M^+), 214 (15), 189 (8), 188 (24), 187 (6), 186 (6), 185 (10), 160 (14), 143 (7), 132 (9), 131 (6), 116 (7), 109 (6), 102 (11), 89 (5), 77 (10), 76 (6), 75 (6), 63 (5), 59 (53), 51 (6). Anal. calc. for $C_{12}H_{10}N_2O_2S$ (246.29): C 58.52, H 4.09, N 11.37, S 13.02; found: C 58.37, H 4.06, N 11.29, S 12.82.

*3a-Ethyl-5-methyl[1,3]thiazolo[5,4-c]quinoline-2,4(3a*H,5H*)-dione* (**4f**). Prepared from **2f** in 41 (*Method A*), 53 (*Method B**), and 42% yield (*Method C*), resp. Yellow crystals. M.p. 111–113° (benzene/hexane). IR: 2973, 1717, 1679, 1601, 1583, 1472, 1356, 1291, 1128, 1094, 1068, 1038, 1009, 953, 784, 768,748, 694, 683. ^{1}H and ^{13}C-NMR: see *Table 4*. EI-MS: 261 (12), 260 (70, M^+), 245 (16), 232 (42), 231 (9), 228 (24), 227 (19), 217 (12), 213 (17), 200 (20), 199 (20), 189 (6), 188 (27), 187 (26), 185 (12), 173 (7), 167 (33), 163 (8), 162 (6), 160 (10), 159 (7), 155 (6), 150 (12), 149 (100), 145 (6), 142 (8), 141 (9), 131 (6), 127 (12), 125 (11), 116 (11), 113 (18), 111 (16), 109 (10), 105 (13), 104 (11), 102 (12), 100

(80), 97 (19), 95 (11), 85 (16), 83 (29), 81 (18), 77 (16), 76 (12), 73 (12), 72 (33), 71 (66), 70 (26), 69 (38), 59 (37), 57 (70). Anal. calc. for $C_{13}H_{12}N_2O_2S$ (260.31): C 59.98, H 4.65, N 10.76, S 12.32; found: C 60.18, H 4.64, N 10.75, S 12.04.

3a-Butyl-5-methyl[1,3]thiazolo[5,4-c]quinoline-2,4(3aH,5H)-dione (**4g**). Prepared from **2g** in 21 (*Method B*), 18 (*Method B**), and 4% yield (*Method C**), resp. Yellow crystals. M.p. 109–110° (benzene/hexane). ^{1}H- and ^{13}C-NMR: see *Table 4*. Identical in all respects to an authentic sample [16].

3a-Methyl-5-phenyl[1,3]thiazolo[5,4-c]quinoline-2,4(3aH,5H)-dione (**4i**). Prepared from **2i** in 69 (*Method A*), 4 (*Method B*), and 2% yield (*Method C**), resp. Yellow crystals. M.p. 206–209° (benzene/hexane). IR: 3383, 3088, 3049, 3036, 2998, 2938, 1712, 1698, 1603, 1587, 1491, 1465, 1381, 1340, 1296, 1273, 1252, 1161, 1122, 1079, 1041, 1009, 966, 931, 868, 852, 768, 755, 745,723, 703, 691, 644, 616, 512. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 309 (19), 308 (92, M^+), 307 (14), 278 (6), 277 (35), 276 (86), 275 (100), 251 (7), 250 (31), 249 (23), 248 (8), 247 (12), 221 (6), 219 (11), 205 (11), 204 (12), 194 (10), 193 (5), 192 (6), 167 (10), 151 (5), 150 (6), 149 (49), 140 (10), 139 (6), 138 (5), 128 (11), 127 (5), 125 (8), 111 (12), 109 (11), 103 (11), 102 (19), 97 (17), 95 (11), 85 (15), 83 (22), 81 (11), 77 (42), 71 (35), 70 (14), 69 (26), 60 (15), 59 (42), 57 (46), 56 (13), 55 (22), 51 (20), 45 (29), 43 (61), 41 (32). Anal. calc. for $C_{17}H_{12}N_2O_2S$ (308.35): C 66.22, H 3.92, N 9.08, S 10.40; found: C 65.97, H 3.86, N 8.99, S 10.23.

3a-Ethyl-5-phenyl[1,3]thiazolo[5,4-c]quinoline-2,4(3aH,5H)-dione (**4j**). Prepared from **2j** in 61 (*Method A*), 12 (*Method B**), and 35% yield (*Method C**), resp. Yellow crystals. M.p. 191–193° (benzene/AcOEt). IR: 3079, 3051, 2979, 2966, 2932, 2874, 1719, 1688, 1603, 1584, 1491, 1462, 1380, 1349, 1328, 1299, 1283, 1266, 1246, 1162, 1153, 1098, 1076, 1038, 1027, 993, 955, 919, 805, 782, 764, 754, 732, 704, 682, 644, 619, 534, 516. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 324 (7), 323 (22), 322 (100, M^+), 307 (22), 294 (21), 293 (10), 289 (11), 279 (11), 262 (8), 261 (8), 250 (25), 249 (10), 203 (6), 194 (8), 188 (9), 109 (5), 102 (6), 77 (35), 73 (39), 71 (7), 57 (8), 51 (17). Anal. calc. for $C_{18}H_{14}N_2O_2S$ (322.38): C 67.06, H 4.38, N 8.69, S 9.95; found: C 67.11, H 4.34, N 8.63, S 9.75.

3a-Butyl-5-phenyl[1,3]thiazolo[5,4-c]quinoline-2,4(3aH,5H)-dione (**4k**). Prepared from **2k** in 15 and 54 (*Method A*), 23 (*Method A**), 23 (*Method B*), and 51% yield (*Method C*), resp. Yellow crystals. M.p. 158–160° (benzene/hexane). ^{1}H- and ^{13}C-NMR: see *Table 4*. Identical in all respects to an authentic sample [16].

[1,3]Thiazolo[5,4-c]quinoline-2,4(1H,5H)-dione (**5c**). Prepared from **2c** in 43 (*Method A*) and 34% yield (*Method C*), resp., using prolonged reaction times. Beige crystals. M.p. >320° (DMF). IR: 3150, 3111, 3000, 2970, 2883, 2850, 2693, 1665, 1646, 1600, 1543, 1424, 1387, 1277, 1175, 1138, 917, 859, 755, 727, 680, 622, 506. ^{1}H- and ^{13}C-NMR: see *Table 7*. EI-MS: 219 (13), 218 (100, M^+), 162 (23), 157 (14), 146 (6), 145 (6), 129 (20), 118 (11), 109 (9), 103 (7), 102 (9), 91 (7), 81 (8), 76 (9). Anal. calc. for $C_{10}H_6N_2O_2S$ (218.23): C 55.04, H 2.77, N 12.84, S 14.69; found: C 55.07, H 2.75, N 12.69, S 14.51.

5-Methyl[1,3]thiazolo[5,4-c]quinoline-2,4(1H,5H)-dione (**5g**). Prepared from **2g** in 63 (*Method A*), 1 (*Method B*), and 3% yield (*Method B**), resp. Colorless crystals. M.p. >330° (DMF). IR: 3113, 3050, 2986, 2893, 2819, 1712, 1627, 1617, 1585, 1564, 1528, 1464, 1451, 1429, 1374, 1347, 1216, 1187, 1156, 1118, 1079, 1047, 978, 946, 846, 751, 726, 691, 664, 653, 622, 556, 542. ^{1}H- and ^{13}C-NMR: see *Table 7*. EI-MS: 233 (14), 232 (100, M^+), 189 (6), 176 (12), 175 (6), 171 (8), 161 (7), 132 (9), 131 (9), 117 (6), 115 (11), 104 (6), 102 (12), 77 (7), 76 (7). Anal. calc. for $C_{11}H_8N_2O_2S$ (232.26): C 56.88, H 3.47, N 12.06, S 13.81; found: C 56.86, H 3.57, N 11.87, S 13.57.

5-Phenyl[1,3]thiazolo[5,4-c]quinoline-2,4(1H,5H)-dione (**5k**). Prepared from **2k** in 34% yield (*Method A*; prolonged reaction time). Colorless crystals. M.p. 329–331° (AcOEt). ^{1}H- and ^{13}C-NMR: see *Table 7*. Identical in all respects to an authentic sample [16].

5,9b-Dihydro-9b-hydroxy-3a-methyl[1,3]thiazolo[5,4-c]quinoline-2,4(1H,3aH)-dione (**6a**). Prepared from **2a** in 46 (*Method A*) and 8% yield (*Method C**), resp. Colorless crystals. M.p. 179–183° and then 227–236° (THF/hexane). IR: 3297, 3238, 3064, 2984, 2929, 1677, 1667, 1600, 1497, 1439, 1393, 1378, 1352, 1258, 1197, 1161, 1140, 1122, 1098, 1072, 1053, 1039, 951, 926, 828, 776, 757, 717, 704, 680, 643, 608, 567, 535, 501. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 250 (5, M^+), 207 (21), 176 (10), 175 (92), 174 (13), 159 (19), 157 (9), 149 (11), 148 (9), 147 (9), 146 (33), 142 (11), 141 (100), 140 (11), 139 (7), 130 (6), 129 (7), 128 (11), 123 (7), 121 (6), 120 (71), 119 (42), 118 (8), 104 (6), 98 (8), 97 (95), 95 (6), 93 (18), 92 (35), 91 (10), 90 (7), 85 (7), 84 (6), 81 (7), 77 (14), 76 (5), 70 (12), 69 (10), 66 (6), 65 (20), 64 (36), 63

Table 7. *^{1}H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds* **5** *and* **12** (δ in ppm)

Position	**5c**		**5g**		**5k**		**12d**		**12l**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	13.0	–	13.01	–	13.12	–	–	–	–	–
2	–	156.3	–	155.7	–	155.7	–	156.1	–	155.6
3a	–	108.7	–	108.6	–	108.6	–	110.4	–	110.4
4	–	171.8	–	171.1	–	171.7	–	168.5	–	168.4
5a	–	137.8	–	138.6	–	139.8	–	137.7	–	139.8
6	7.45	116.4	7.72	116.1	6.66	116.7	7.51	116.4	6.73	116.7
7	7.60	130.5	7.72	131.0	7.52	130.7	7.69	131.6	7.62	131.4
8	7.32	122.3	7.45	122.6	7.37	122.8	7.38	123.1	7.46	123.6
9	8.03	122.7	8.11	123.3	8.14	123.2	7.80	121.8	7.96	122.5
9a	–	110.2	–	111.1	–	110.9	–	109.2	–	110.1
9b	–	140.3	–	139.3	–	140.0	–	150.6	–	150.4
Substituent at N(1)										
1	12.05	–	3.73	29.5	–	137.2	12.46	–	–	136.7
2	–	–	–	–	7.41	129.4	–	–	7.44	129.2
3	–	–	–	–	7.68	130.2	–	–	7.71	130.4
4	–	–	–	–	7.63	129.1	–	–	7.66	129.5

(8), 59 (10), 55 (12), 51 (9), 44 (8), 43 (43), 42 (22), 41 (11). Anal. calc. for $C_{11}H_{10}N_2O_3S$ (250.27): C 52.79, H 4.03, N 11.19, S 12.81; found: C 52.81, H 4.21, N 11.03, S 12.65.

*3a-Ethyl-5,9b-dihydro-9b-hydroxy[1,3]thiazolo[5,4-c]quinoline-2,4(1*H*,3a*H*)-dione* (**6b**). Prepared from **1b** in 40% yield (*Method A*). Colorless crystals. M.p. 175–179° (AcOEt). IR: 3481, 3193, 3075, 2981, 2933, 1689, 1667, 1599, 1497, 1440, 1376, 1315, 1291, 1251, 1212, 1132, 1108, 1076, 1046, 998, 947, 893, 849, 755, 680, 655, 630, 609, 567, 542. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 264 (1, M^+), 246 (1), 221 (17), 206 (10), 193 (15), 189 (76), 188 (36), 175 (12), 174 (100), 170 (6), 161 (15), 149 (11), 148 (6), 146 (17), 132 (5), 130 (9), 128 (8), 120 (39), 119 (14), 117 (6), 115 (10), 100 (7), 93 (6), 92 (29), 91 (8), 90 (10), 89 (6), 87 (7), 86 (6), 77 (18), 76 (7), 73 (7), 71 (6), 69 (14), 65 (19), 64 (37), 63 (10), 55 (21), 51 (8). Anal. calc. for $C_{12}H_{12}N_2O_3S$ (264.30): C 54.53, H 4.58, N 10.60, S 12.13; found: C 54.67, H 4.61, N 10.55, S 12.05.

*5,9b-Dihydro-9b-hydroxy-3a,5-dimethyl[1,3]thiazolo[5,4-c]quinoline-2,4(1*H*,3a*H*)-dione* (**6e**). Prepared from **2e** in 63 (*Method A*) and 3% yield (*Method C**), resp. Colorless crystals. M.p. 172–176° (AcOEt). IR: 3318, 3216, 3079, 2996, 2924, 2830, 1680, 1640, 1605, 1597, 1504, 1471, 1445, 1414, 1382, 1367, 1298, 1258, 1206, 1185, 1135, 1103, 1090, 1070, 1054, 948, 919, 870, 841, 770, 759, 727, 690, 650, 589, 553, 511. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 264 (18, M^+), 246 (5), 222 (6), 221 (46), 190 (12), 189 (89), 188 (10), 177 (6), 165 (6), 164 (27), 163 (53), 162 (58), 161 (21), 160 (50), 147 (10), 146 (45), 145 (6), 144 (8), 134 (37), 133 (28), 132 (27), 131 (8), 130 (12), 127 (5), 125 (5), 123 (7), 117 (19), 105 (35), 104 (34), 97 (15), 91 (17), 85 (20), 83 (18), 78 (19), 77 (56), 71 (33), 64 (22), 57 (38), 55 (28), 43 (100). Anal. calc. for $C_{12}H_{12}N_2O_3S$ (264.30): C 54.53, H 4.58, N 10.60, S 12.13; found: C 54.35, H 4.61, N 10.49, S 11.93.

*3a-Ethyl-5,9b-dihydro-9b-hydroxy-5-methyl[1,3]thiazolo[5,4-c]quinoline-2,4(1*H*,3a*H*)-dione* (**6f**). Prepared from **2f** in 16% yield (*Method A*). Colorless crystals. M.p. 104–106° and then 118–123° ($CHCl_3$). IR: 3293, 3179, 1680, 1647, 1604, 1478, 1372, 1251, 1209, 1181, 1164, 1116, 1078, 1056, 977, 861, 817, 766, 687, 622, 471, 459. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 279 (5), 278 (33, M^+), 235 (17), 208 (8), 207 (61), 204 (11), 203 (80), 202 (44), 189 (13), 188 (100), 178 (15), 175 (11), 174 (6), 163 (32), 162 (30), 161 (8), 160 (16), 147 (7), 146 (16), 135 (7), 134 (64), 133 (10), 132 (17), 131 (7), 130 (14), 117 (11), 116 (13), 115 (8), 106 (14), 105 (18), 104 (25), 103 (7), 102 (9), 94 (8), 92 (8), 91 (13), 90 (9), 89 (7), 79 (12), 78 (18), 77 (49), 76 (10), 75 (6), 73 (19), 69 (20), 66 (5), 65 (9), 64 (17), 55 (7), 51 (15). Anal. calc. for $C_{13}H_{14}N_2O_3S$ (278.33): C 56.10, H 5.07, N 10.06, S 11.52; found: C 55.81, H 5.07, N 9.82, S 11.29.

3a-Ethyl-5,9b-dihydro-9b-hydroxy-5-phenyl[1,3]thiazolo[5,4-c]quinoline-2,4(1H,3aH)-dione (**6j**). Prepared from **2j** in 8% yield by *Method A*. Colorless crystals. M.p. 250–256° (AcOEt). IR: 3369, 3187, 3073, 2976, 2876, 1682, 1657, 1602, 1497, 1466, 1456, 1354, 1328, 1305, 1262, 1206, 1131, 1073, 1049, 1004, 978, 927, 852, 805, 767, 753, 724, 701, 636, 621, 574, 516. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 340 (1, M^+), 322 (5), 269 (10), 266 (18), 265 (100), 264 (50), 251 (16), 250 (88), 237 (11), 196 (25), 195 (22), 167 (27), 166 (12), 92 (8), 77 (31), 69 (12), 64 (20), 51 (16). Anal. calc. for $C_{18}H_{16}N_2O_3S$ (340.40): C 63.51, H 4.74, N 8.23, S 9.42; found: C 63.42, H 4.74, N 8.19, S 9.21.

3-Ethyl-3-hydroxy-1-methylquinoline-2,4(1H,3H)-dione (**7f**). Prepared from **2f** in 4% yield (*Method A*). M.p. 145–146° (AcOEt/benzene). Identical in all respects to the authentic sample, prepared according to [22].

3-Butyl-3-hydroxy-1-methylquinoline-2,4(1H,3H)-dione (**7g**). Prepared from **2g** in 4% yield (*Method B**). Colorless crystals. M.p. 123–125° (hexane). Identical in all respects to an authentic sample [23].

3-Ethyl-3-hydroxy-1-phenylquinoline-2,4(1H,3H)-dione (**7j**). Prepared from **2j** in 7% yield (*Method B**). Colorless crystals. M.p. 196–201° (EtOH/AcOEt). Identical in all respects to an authentic sample [23].

1-(1,2-Dihydro-1,3-dimethyl-2-oxoquinolin-4-yl)urea (**8e**). Prepared from **2e** in 29% yield (*Method B**) and 23% yield (*Method C**), resp., from **4e** in 20% yield (*Method D*), and from **6e** (*Method D*) in 79% yield (*Method D*), resp. Colorless crystals. M.p. 197–200° (AcOEt). IR: 3398, 3190, 2943, 1673, 1642, 1607, 1577, 1506, 1462, 1420, 1401, 1372, 1343, 1290, 1216, 1183, 1165, 1120, 1096, 1045, 982, 945, 902, 832, 817, 753, 678, 655, 621, 605, 562, 460. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 232 (10), 231 (73, M^+), 230 (9), 216 (32), 215 (29), 214 (100), 189 (7), 188 (43), 187 (23), 186 (12), 185 (33), 173 (16), 172 (8), 161 (9), 160 (20), 159 (48), 158 (12), 156 (10), 145 (20), 144 (16), 143 (20), 132 (10), 131 (13), 130 (17), 129 (12), 128 (12), 117 (17), 116 (13), 115 (14), 103 (14), 102 (17), 89 (12), 77 (27), 76 (11), 63 (10), 51 (14), 44 (14), 43 (12). ESI-MS (pos.): 463.2 (13, $[2\,M+H]^+$), 401.2 (100, $[2\,M+Na-2\cdot NCO]^+$), 212.2 (41, $[M+Na-NCO]^+$), 190.2 (41, $[M+H-NCO]^+$). ESI-MS (neg.): 188.1 (100, $[M-H-NCO]^-$). Anal. calc. for $C_{12}H_{13}N_3O_2$ (231.25): C 62.33, H 5.67, N 18.17; found: C 62.39, H 5.81, N 18.19.

1-(3-Butyl-1,2-dihydro-1-methyl-2-oxoquinolin-4-yl)urea (**8g**). Prepared from **2g** in 18 (*Method B**) and 10% yield (*Method C**), resp., and from **4g** in 50% yield (*Method D*). Colorless crystals. M.p. 250–258° (EtOH). IR: 3418*s*, 3293, 3246, 2956, 2934, 2869, 1665, 1633, 1593, 1573, 1528, 1499, 1463, 1413, 1386, 1354, 1295, 1227, 1164, 1123, 1098, 753, 672, 634, 597, 572, 541. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 273 (24, M^+), 256 (18), 244 (19), 241 (8), 232 (10), 231 (71), 230 (28), 227 (27), 216 (31), 215 (29), 214 (100), 213 (53), 201 (52), 199 (16), 188 (71), 187 (79), 185 (16), 184 (11), 159 (20), 144 (12), 143 (10), 132 (9), 131(11), 130 (15), 117 (14), 116 (11), 115 (14), 103 (10), 77 (20), 44 (14), 43 (14). ESI-MS (pos.): 569.3 (37, $[2\,M+Na]^+$), 429.8 (10, $[3\,M+Ca]^{2+}$), 312.2 (29, $[M+K]^+$), 296.3 (100, $[M+Na]^+$), 293.3 (12, $[2\,M+Ca]^{2+}$), 274.3 (53, $[M+H]^+$). ESI-MS (neg.): 581.0 (5, $[2\,M+Cl]^-$), 545.2 (21, $[2\,M-H]^-$), 308.2 (26, $[M+Cl]^-$), 272.2 (100, $[M-H]^-$), 229.2 (35, $[M-NH_2CO]^-$). Anal. calc. for $C_{15}H_{19}N_3O_2$ (273.33): C 65.91, H 7.01, N 15.37; found: C 65.80, H 7.06, N 15.52.

1-(1,2-Dihydro-3-methyl-2-oxo-1-phenylquinolin-4-yl)urea (**8i**). Prepared from **2i** in 25 (*Method B**) and 22% yield (*Method C**), resp. Colorless crystals. M.p. 275–278° (AcOEt). IR: 3489, 3454, 3325, 3199, 3055, 1678, 1628, 1601, 1587, 1562, 1496, 1452, 1377, 1356, 1334, 1304, 1288, 1228, 1182, 1135, 1113, 1043, 1003, 964, 901, 754, 696, 661, 651, 617, 546, 515. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 252 (17), 251 (100, $[M-NCO]^+$), 250 (90), 222 (8), 196 (9), 195 (31), 194 (8), 167 (23), 166 (9), 146 (9), 126 (8), 92 (6), 84 (11), 77 (20), 51 (11). ESI-MS (pos.): 525.2 (56, $[2\,M+Na-2\cdot NCO]^+$), 396.7 (18, $[3\,M+Ca-3\cdot NCO]^{2+}$), 290.2 (10, $[M+K-NCO]^+$), 274.2 (65, $[M+Na-NCO]^+$), 252.3 (100, $[M+H-NCO]^+$). ESI-MS (neg.): 250.1 (100, $[M-H-NCO]^-$). Anal. calc. for $C_{17}H_{15}N_3O_2$ (293.32): C 69.61, H 5.15, N 14.33; found: C 69.55, H 4.86, N 14.12.

1-(3-Butyl-1,2-dihydro-2-oxo-1-phenylquinolin-4-yl)urea (**8k**). Prepared from **2k** in 26% yield (*Method A**). Colorless needles. M.p. 228–230° (EtOH). IR: 3436, 3214, 2954, 2924, 2857, 1670, 1630, 1601, 1570, 1521, 1492, 1454, 1359, 1228, 1174, 1115, 748, 698, 648, 592, 526. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 335 (1, M^+), 318 (8), 303 (6), 290 (10), 289 (21), 277 (21), 276 (100), 275 (51), 263 (6), 262 (5), 261 (23), 204 (9), 77 (15), 51 (7). Anal. calc. for $C_{20}H_{21}N_3O_2$ (335.40): C 71.62, H 6.31, N 12.53; found: C 71.37, H 6.34, N 12.49.

4-Amino-3-butyl-1-phenylquinolin-2(1H)-one (**9k**). Prepared from **2k** in 4% yield (*Method A**). Colorless crystals. M.p. 263–270° (AcOEt). Identical in all respects to an authentic compound [24].

Butyl (3-Butyl-1,2-dihydro-1-methyl-2-oxoquinolin-4-yl)carbamate (**10g**). Prepared in 75% yield by boiling a soln. of **8g** in BuOH for 2 h. Colorless crystals. M.p. 108–112° (cyclohexane). IR: 3265, 2958, 2931, 2871, 1716, 1695, 1637, 1591, 1572, 1508, 1498, 1460, 1414, 1381, 1315, 1277, 1244, 1167, 1101, 1086, 1063, 1037, 1007, 943, 906, 874, 775, 754, 746, 683, 658, 638, 567, 544. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 331 (7), 330 (32, M^+), 313 (14), 301 (10), 289 (19), 288 (100), 259 (6), 257 (7), 246 (19), 245 (35), 232 (13), 231 (20), 229 (8), 227 (7), 215 (17), 214 (49), 213 (58), 201 (20), 199 (11), 189 (9), 188 (61), 187 (28), 185 (8), 130 (7), 159 (11), 149 (18), 145 (6), 144 (7), 131 (7), 130 (8), 77 (9), 57 (24), 55 (12). Anal. calc. for $C_{19}H_{26}N_2O_3$ (330.42): C 69.06, H 7.93, N 8.48; found: C 68.83, H 7.83, N 8.45.

4-Hydroxyquinolin-2(1H)-one (**11d**). Prepared from **2d** (*Method B*) in 6 and from **12d** (*Method D*) in 50% yield. Colorless crystals. M.p. >350°. Identical in all respects to an authentic compound (*Aldrich 86-59-9*).

4-Hydroxy-1-phenylquinolin-2(1H)-one (**11l**). Prepared from **2l** in 9 (*Method A*), 4 (*Method B*), 3 (*Method B**), and 5% yield (*Method C**), and from **12l** in 61% yield (*Method D*), resp. Colorless crystals. M.p. >350°. Identical in all respects to an authentic compound prepared in 51% yield from Ph_2NH and malonic acid according to [25].

[1,3]Oxathiolo[4,5-c]quinoline-2,4(5H)-dione (**12d**). Prepared from **2d** in 48 (*Method A*) and 5% yield (*Method B*), resp. Beige crystals. M.p. 344–348° (AcOH). IR: 3001, 2956, 2925, 2843, 1762, 1735, 1650, 1622, 1602, 1567, 1501, 1477, 1442, 1386, 1332, 1271, 1165, 1149, 1128, 1095, 992, 912, 896, 869, 757, 729, 676, 657, 635, 603, 536. ^{1}H- and ^{13}C-NMR: see *Table 7*. EI-MS: 220 (12), 219 (100, M^+), 192 (5), 191 (47), 163 (22), 146 (33), 141 (8), 136 (6), 135 (60), 130 (6), 120 (7), 119 (18), 109 (9), 108 (15), 104 (9), 97 (15), 92 (21), 91 (8), 90 (12), 85 (9), 83 (7), 76 (17), 75 (5), 74 (10), 71 (31), 70 (11), 69 (15), 64 (20), 63 (16), 57 (17), 55 (9), 50 (10), 43 (18). Anal. calc. for $C_{10}H_5NO_3S$ (219.22): C 54.79, H 2.30, N 6.39, S 14.63; found: C 54.75, H 2.38, N 6.22, S 14.52.

5-Phenyl[1,3]oxathiolo[4,5-c]quinoline-2,4(5H)-dione (**12l**). Prepared from **2l** in 7 (*Method A*) and 26% yield (*Method B*), resp. Colorless needles. M.p. 243–247° (benzene). IR: 3058, 1780, 1757, 1662, 1595, 1558, 1496, 1489, 1446, 1388, 1329, 1296, 1259, 1219, 1153, 1105, 1088, 1036, 997, 949, 883, 810, 769, 754, 744, 731, 702, 656, 627, 611, 548, 511. ^{1}H- and ^{13}C-NMR: see *Table 7*. EI-MS: 297 (7), 296 (19), 295 (100, M^+), 267 (12), 240 (11), 239 (64), 238 (25), 211 (12), 210 (14), 195 (10), 167 (21), 166 (12), 146 (17), 140 (8), 139 (9), 121 (17), 92 (9), 84 (27), 77 (32), 76 (16), 75 (5), 71 (6), 63 (8), 51 (25), 50 (10). Anal. calc. for $C_{16}H_9NO_3S$ (295.31): C 65.07, H 3.07, N 4.74, S 10.86; found: C 64.88, H 2.95, N 4.75, S 10.65.

4. *Purification of the Crude Mixtures* **Md**, **Mh**, *and* **Ml**. Mixtures of compounds **13**, **14**, and **15** were obtained from compounds **2d**, **2h**, and **2l** in yields given in *Table 2*. After separation by fractional crystallization, the following pure compounds were isolated.

3,3'-Sulfanediylbis(4-hydroxyquinolin-2(1H)-one) (**13d**). Isolated from **Md**. Yellowish crystals. M.p. >320° (DMF). For **13d**, a m.p. of 370° (dec.) was reported in [26]. IR: 3138, 3072, 2949, 2860, 2742, 1649, 1604, 1541, 1494, 1477, 1421, 1367, 1350, 1313, 1263, 1163, 1147, 1109, 1080, 1028, 947, 870, 785, 750, 717, 671, 644, 542, 468. ^{1}H- and ^{13}C-NMR: see *Table 8*. EI-MS: 353 (11), 352 (51, M^+), 335 (6), 334 (28, $[M-H_2O]^+$), 319 (11), 162 (34), 161 (100), 146 (10), 133 (16), 120 (52), 119 (49), 105 (11), 104 (12), 92 (45), 77 (19), 76 (9), 65 (22), 64 (19), 63 (12), 51 (11). ESI-MS (pos.): 391.0 (27, $[M+K]^+$), 375.0 (100, $[M+Na]^+$), 353.1 (40, $[M+H]^+$). ESI-MS (neg.): 351.0 (100, $[M-H]^-$). Anal. calc. for $C_{18}H_{12}N_2O_4S$ (352.36): C 61.35, H 3.43, N 7.95, S 9.10; found: C 61.12, H 3.23, N 8.15, S 8.84.

3,3'-Sulfanediylbis(4-hydroxy-1-phenylquinolin-2(1H)-one) (**13l**). Isolated from **Ml**. Beige crystals. M.p. 325–326° (benzene/hexane). IR: 3034, 2925, 2848, 2713, 2578, 1620, 1568, 1552, 1491, 1454, 1442, 1350, 1321, 1284, 1248, 1213, 1171, 1103, 1072, 1036, 1003, 955, 910, 860, 802, 756, 698, 677, 631, 567, 550, 513, 469. ^{1}H- and ^{13}C-NMR: see *Table 8*. EI-MS: 487 (19), 486 (57, $[M-H_2O]^+$), 322 (6), 281 (9), 267 (5), 242 (12), 238 (16), 237 (100), 236 (82), 208 (13), 207 (55), 196 (15), 195 (61), 180 (9), 168 (8), 167 (17), 166 (15), 140 (8), 98 (19), 92 (13), 77 (23), 73 (13), 64 (18), 63 (7), 54 (9), 51 (21). ESI-MS (pos.): 543.1 (28, $[M+K]^+$), 527.1 (81, $[M+Na]^+$), 505.1 (100, $[M+H]^+$). ESI-MS (neg.): 1029.2 (17, $[2M-2\cdot H+Na]^-$), 503.1 (100, $[M-H]^-$). Anal. calc. for $C_{30}H_{20}N_2O_4S$ (504.56): C 71.41, H 4.00, N 5.55, S 6.36; found: C 71.67, H 4.26, N 5.37, S 6.20.

Table 8. *^{1}H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds* **13** *and* **14** (δ in ppm)

Position	**13d**		**13l**		**14h**		**14l**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	165.3	–	165.0	–	162.6	–	162.8
3	–	103.0	–	103.7	–	100.3	–	100.1
4	–	172.5[a])	–	166.7	–	168.3	–	169.4
4a	–	118.2	–	115.3	–	119.7	–	119.5
5	7.96	124.6	8.07	124.2	8.16	124.6	8.17	125.3
6	7.14	120.9	7.39	123.2	7.24	120.8	7.18	121.1
7	7.48	130.8	7.60	133.0	7.60	131.0	7.36	130.7
8	7.26	115.0	6.67	116.3	7.41	114.1	6.40	115.1
8a	–	138.5	–	140.4	–	139.7	–	140.9
OH	n.o.		11.87	–	n.o.	–	n.o.	–
Substituent at N(1)								
1	11.06		–	137.4	3.58	29.3	–	139.3
2,6	–		7.44	129.1	–	–	7.29	129.8
3,5	–		7.69	130.3	–	–	7.62	130.0
4	–		7.62	129.2	–	–	7.53	128.2

*3,3′-Disulfanediylbis(4-hydroxy-1-methylquinolin-2(1*H*)-one)* (**14h**). Isolated from **Mh**. Yellowish crystals. M.p. 261–263° (AcOEt). IR: 3094, 2945, 2904, 1617, 1607, 1574, 1540, 1504, 1446, 1419, 1401, 1337, 1316, 1269, 1248, 1208, 1170, 1118, 1077, 1041, 971, 944, 860, 834, 755, 686, 662, 618, 587, 537. ^{1}H- and ^{13}C-NMR: see *Table 8*. EI-MS: 381 (15), 380 (65, $[M-S]^+$), 207 (23), 176 (18), 175 (100), 174 (8), 162 (12), 147 (14), 146 (30), 134 (37), 133 (12), 132 (23), 116 (10), 105 (17), 104 (18), 91 (11), 78 (10), 77 (29), 64 (16), 51 (8). ESI-MS (pos.): 847.0 (21, $[2M+Na]^+$), 451.1 (18, $[M+K]^+$), 435.1 (100, $[M+Na]^+$), 413.1 (24, $[M+H]^+$). ESI-MS (neg.): 411.0 (100, $[M-H]^-$). Anal. calc. for $C_{20}H_{16}N_2O_4S_2$ (412.48): C 58.24, H 3.91, N 6.79, S 15.55; found: C 58.04, H 3.93, N 6.95, S 15.27.

*3,3′-Disulfanediylbis(4-hydroxy-1-phenylquinolin-2(1*H*)-one)* (**14l**). Isolated from **Ml**. Yellow crystals. M.p. 241–246° and then 320–328° (benzene). IR: 3140, 3010, 2814, 1597, 1587, 1560, 1498, 1452, 1414, 1377, 1319, 1257, 1218, 1174, 1109, 1070, 1038, 910, 860, 835, 798, 766, 754, 700, 690, 671, 627, 580, 546. ^{1}H- and ^{13}C-NMR: see *Table 8*. EI-MS: 505 (22), 504 (62, $[M-S]^+$), 385 (6), 269 (22), 238 (25), 237 (100), 236 (68), 209 (7), 208 (10), 197 (10), 196 (84), 195 (37), 180 (11), 168 (7), 167 (32), 166 (9), 139 (6), 102 (6), 77 (30), 73 (15), 64 (66), 61 (11), 60 (18), 51 (16), 45 (15), 44 (38), 43 (26). ESI-MS (pos.): 575.1 (28, $[M+K]^+$), 559.1 (100, $[M+Na]^+$), 537.1 (81, $[M+H]^+$). ESI-MS (neg.): 1093.1 (5, $[2M-2\cdot H+Na]^-$), 535.1 (100, $[M-H]^-$). Anal. calc. for $C_{30}H_{20}N_2O_4S_2$ (536.62): C 67.15, H 3.76, N 5.22, S 11.95; found: C 67.26, H 3.68, N 5.31, S 11.63.

5. *General Procedure for the Reaction of Compounds* **4**, **6**, *and* **12** *with NH$_4$OH* (*Method D*). To a soln. of compound **4**, **6**, or **12** (50 mg) in EtOH (5 ml), 0.3 ml of NH_4OH (35%) was added, and the mixture was heated to 70° for 1 h. The solvent was evaporated, and the residue was crystallized from an appropriate solvent or separated by CC. The following compounds were obtained: *a*) from **4e**, compounds **8e** and **9e** were obtained in yields of 20 and 31%, resp.; *b*) from **4g**, compound **8g** was obtained in 50% yield; *c*) from **4i**, compound **9i** was obtained in 27% yield; *d*) from **4j**, compounds **8j** and **9j** were obtained in yields 28 and 23%, resp.; *e*) from **6e**, compound **8e** was obtained in 79% yield; *f*) from **12d**, compound **11d** was prepared in 50% yield; *g*) from **12l**, compound **11l** was prepared in 61% yield. Compounds **8j**, **9e**, **9i**, and **9j** were prepared merely by *Method D*. Compounds **8e**, **8g**, **9e**, **11d**, and **11l** were prepared also by *Methods A*, *B*, *C*, and are described in *Sect. 3* of the *Exper. Part*.

1-(3-Ethyl-1,2-dihydro-2-oxo-1-phenylquinolin-4-yl)urea (**8j**). Prepared from **4j** by *Method D* in 28% yield. Colorless crystals. M.p. 222–225° and then 294–297° (EtOH). IR: 3431, 3292, 3246, 2962, 2931, 2871, 1668, 1637, 1601, 1568, 1529, 1493, 1450, 1387, 1358, 1323, 1299, 1279, 1250, 1215, 1171, 1138, 1113, 1047, 881, 752, 700, 673, 642, 517. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 307 (5, M^+), 291 (20), 290

(95), 289 (41), 275 (23), 264 (17), 263 (29), 262 (96), 261 (100), 249 (18), 247 (12), 236 (7), 235 (32), 234 (7), 218 (6), 217 /5), 205 (9), 204 (17), 167 (9), 140 (7), 137 (10), 131 (7), 116 (9), 115 (10), 109 (9), 103 (7), 102 (16), 96 (6), 91 (7), 77 (35), 65 (6), 58 (6), 51 (25). Anal. calc. for $C_{18}H_{17}N_3O_2$ (307.35): C 70.34, H 5.58, N 13.67; found: C 70.23, H 5.74, N 13.51.

*4-Amino-1,3-dimethylquinolin-2(1*H*)-one* (**9e**). Prepared from **4e** by *Method D* in 31% yield. Colorless crystals. M.p. 168–179° (AcOEt). For **9e**, an m.p. of 185° was reported in [27]. IR: 3413, 3363, 3244, 1655, 1624, 1599, 1564, 1421, 1342, 1228, 1132, 1095, 1049, 1034, 980, 939, 752, 746, 677, 625, 536, 459. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 189 (17), 188 (100, M^+), 173 (19), 161 (10), 160 (17), 159 (51), 146 (9), 145 (22), 144 (8), 132 (8), 131 (9), 130 (10), 118 (8), 117 (9), 115 (6), 104 (7), 103 (6), 80 (15), 77 (16), 51 (8). Anal. calc. for $C_{11}H_{12}N_2O$ (188.23): C 70.19, H 6.43, N 14.88; found: C 69.95, H 6.40, N 14.71.

*4-Amino-3-methyl-1-phenylquinolin-2(1*H*)-one* (**9i**). Prepared from **4i** by *Method D* in 27% yield. Colorless crystals. M.p. 254–255° (AcOEt). IR: 3469, 3332, 3224, 3070, 2912, 2854, 1655, 1603, 1577, 1558, 1504, 1491, 1448, 1421, 1358, 1333, 1319, 1307, 1286, 1234, 1198, 1167, 1124, 1111, 1074, 1003, 951, 918, 841, 796, 758, 702, 673, 652, 623, 592, 546, 515. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 251 (13), 250 (81, M^+), 249 (100), 221 (11), 125 (8), 103 (5), 77 (12), 51 (7). Anal. calc. for $C_{16}H_{14}N_2O$ (250.30): C 76.78, H 5.64, N 11.19; found: C 76.83, H 5.44, N 11.29.

*4-Amino-3-ethyl-1-phenylquinolin-2(1*H*)-one* (**9j**). Prepared from **4j** by *Method D* in 23% yield. Colorless crystals. M.p. 297–299° (AcOEt). IR: 3463, 3329, 3222, 3062, 2960, 2949, 2924, 2864, 1655, 1620, 1603, 1577, 1558, 1504, 1444, 1419, 1360, 1340, 1323, 1284, 1261, 1230, 1155, 1117, 1074, 1063, 1022, 1003, 943, 858, 821, 781, 764, 752, 700, 677, 654, 619, 552, 517. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 265 (18), 264 (92, M^+), 263 (50), 250 (19), 149 (100), 235 (9), 221 (10), 219 (6), 204 (6), 132 (8), 124 (12), 116 (5), 110 (11), 103 (5), 77 (13), 51 (7). Anal. calc. for $C_{17}H_{16}N_2O$ (264.32): C 77.25, H 6.10, N 10.60; found: C 76.98, H 6.10, N 10.51.

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Reaction of 4-hydroxy-2-quinolones with thionyl chloride—preparation of new spiro-benzo[1,3]oxathioles and their transformations

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ABSTRACT

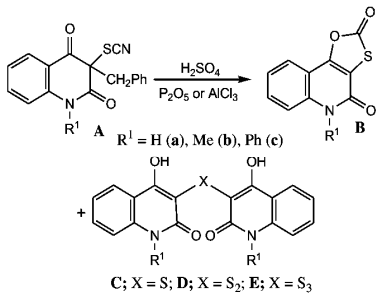
4-Hydroxy-2-quinolones (**1**) react with thionyl chloride to give new spiro-benzo[1,3]oxathioles (**3**) and bis(4-hydroxy-2-quinolone-3-yl)sulfides (**2**) and small quantities of 3-chloro-4-hydroxyquinolin-2-ones (**4**). Compounds **3** afford sulfides **2** by heating in different solvents and [1,4]oxathiino[3,2-*c*:5,6-*c*′]diquinoline-6,8(5*H*,9*H*)-diones (**6**) by reaction with triphenylphosphine. The reconversion of compounds **2** to **3** was achieved using bromine. The reaction mechanisms are discussed for all transformations. All compounds were characterized by IR, ^{1}H, and ^{13}C NMR (in some cases also ^{15}N NMR) spectroscopy, and EI and/or ESI mass spectrometry. The X-ray structure was determined for compound **3b**.

1. Introduction

In our preceding paper,[1] we described the modified Riemschneider reaction of 3-thiocyanatoquinoline-2,4-diones (**A**). When a benzyl group was present at the 3 position of the starting compounds, rapid C-debenzylation was observed, yielding [1,3]oxathiolo[4,5-*c*]quinoline-2,4-diones (**B**) and mixtures of primarily mono- (**C**), di- (**D**), and trisulfides (**E**) from 4-hydroxy-3-sulfanylquinolin-2-ones (Scheme 1). The results of ESI-MS measurements provided evidence that the dominant compound in these mixtures was disulfide **D**. Repeated fraction crystallization produced the pure compounds **Ca** (R^1=H), **Cc** (R^1=Ph), **Db** (R^1=Me), and **Dc** (R^1=Ph), albeit in poor yields.

In the literature, only seven symmetric sulfides derived from 4-hydroxy-3-sulfanylquinoline-2-ones are described: **Ca**,[2] **Cb**,[3] **Cc**,[1] and four derivatives of **Ca** substituted with chlorine in the benzene nucleus.[4] A more extensive group of sulfides based on 4-hydroxy-3-sulfanylquinoline-2-one scaffold consists of unsymmetrical sulfides, which arise from the reaction of 4-hydroxy-2-quinolones with aromatic disulfides.[5]

To the best of our knowledge, the corresponding disulfides (**D**) and trisulfides (**E**) have not yet been described in the literature.



Scheme 1.

Compound **Cb** was prepared in 87% yield by refluxing of ethyl 2-cyano-2(1′-methyl-2′,4′-dioxo-2′,4′-dihydro-1*H*′spiro[[1,3]dithiethane-2,3′-quinoline]-4-ylidene)acetate in DMSO.[3] Ziegler and Kappe[2] reported the preparation of compound **Ca** by the reaction of 4-hydroxyquinoline-2-one with thionyl chloride in 60–68% yield but failed to adequately describe the characterization of the product: the only information given was **Ca** is a colorless compound of mp 370 °C (dec), insoluble in all common solvents. Therefore, we decided to prepare **Ca** (hereafter **2a**) using the published[2] procedure and compare the reaction product with what we[1] prepared from 3-thiocyanatoquinoline-2,4-dione **Aa**.

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This manuscript reports that the reaction of 4-hydroxy-2-quinolones **1** with thionyl chloride does not proceeds as unambiguously as previously described.[2,4] The main reaction products **3** arise from a Pummerer-like rearrangement of the reaction intermediates, and compounds **2** are products of their subsequent transformation.

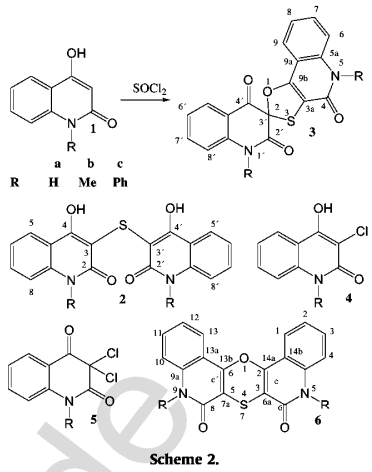
2. Results and discussion

We repeated the previously published reaction of **1a** with thionyl chloride, which was reported to produce compound **2a**.[2] The ratio of reactants, reaction time, and treatment of the crude product were identical to those in the original study. In the original procedure,[2] the crude product was boiled in DMF after washing with water and ethanol. Given that the reaction time was not reported, we used 15 min of boiling. However, we obtained a yellow compound of mp >325 °C exhibiting two characteristic IR absorption bands at 1722 and 1693 cm^{-1} rather than a colorless compound. Similar results were obtained starting from compounds **1b** and **1c** (Table 1).

Table 1
Results of the reaction of compounds **1** with thionyl chloride (*Method A*)

Entry	Starting compound	R	Products (yields,[a] %)
1	**1a**	H	**3a** (83)
2			**3a** (88), **4a** (7)
3			**3a** (85), **4a** (6)
4			**3a** (85), **4a** (3)
5	**1b**	Me	**3b** (51), **6b** (8)
6			**2b** (43), **3b** (25), **4b** (3), **5b** (2), **6b** (3)
7			**2b** (23), **3b** (38), **4b** (3), **6b** (4)
8	**1c**	Ph	**2c** (11), **3c** (41)
9			**2c** (32), **3c** (25)
10			**2c** (39), **3c** (20), **4c** (6), **6c** (2)

[a] For NMR spectra of compounds **2**, **4** and **5** see Table 4, for those of compounds **6** see Table 5.



Scheme 2.

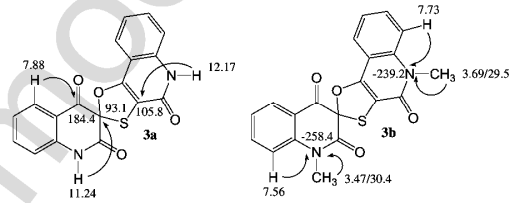


Fig. 1. Correlations of N–H and C(5′)–H protons with C(2) and C(3a) in gs-HMBC spectrum of **3a** and *peri* and CH_3 protons with nitrogen atoms in gs-H–^{15}N–HMBC spectrum of **3b**.

In both cases, the main product was a yellow or orange compound exhibiting the two above-mentioned characteristic IR absorption bands. Based on elemental analysis, the yellow compound prepared from **1a** has the composition $C_{18}H_{10}N_2O_4S$ (350.35), which differs from the composition of **2a**, $C_{18}H_{12}N_2O_4S$ (352.36). The molecular weight of 350 was subsequently confirmed using ESI-MS analysis. In the ^{13}C NMR spectrum, the yellow product obtained from **1a** exhibits signals corresponding to two non-equivalently substituted quinoline moieties as well as two NH groups, eight –CH= atoms for the benzene nucleus, and ten quaternary carbon atoms. The signal at 184.4 ppm suggests that one keto group is present in the molecule. Based on these results, we proposed the structure **3a** (Scheme 2) for the product of the reaction **1a** with thionyl chloride. The analogous NMR results for the compounds prepared from **1b** and **1c** were used to propose the structures **3b** and **3c** as the base scaffold is undoubtedly identical for each isolated compounds. The complete assignment of the carbon atoms using NMR spectra was rather difficult because the most important parts of the molecules **3**, which involve atoms other then carbon, do not contain the hydrogen atoms necessary to obtain correlated HMBC spectra. Moreover, the proton resonances of the 1,2-disubstituted benzene rings overlapped. Thus, gs-TOCSY and gs-HMQC–RELAY experiments were performed in addition to the classical (gs)-COSY, gs-HMQC, and gs-HMBC measurements. The resonance of the carbonyl group at 184 ppm was key in differentiating the 1,2-disubstituted benzene rings using gs-HMBC correlations in all compounds **3**. Moreover, NH protons were used for correlation with C(2) and C(3a) in the gs-HMBC spectrum of compound **3a** (Fig. 1, left formula). Independently, the correlation of the *peri* protons and methyl group protons with the corresponding nitrogen atoms was observed in the gs-^{1}H–^{15}N–HMBC spectrum of compound **3b** (Fig. 1, right formula). The 2,6- and 3,5-carbons of the phenyl ring(s) were non-equivalent due to a hindered rotation in compound **3c**. The NMR data are collected in Table 2.

Until recently, we were unable to prepare single crystals of compounds **3a–c**. We have now obtained a single crystal of **3b** using the liquid diffusion method[6] with dichloromethane and benzene as the solvent-precipitant pair. The molecular structure of compound **3b**, confirmed by single-crystal X-ray diffraction, is illustrated in Fig. 2.

Although 46 examples of oxathia spiro compounds structures are available in the Cambridge Structural Data Base, there is no structural match to the structure of **3**. The structure of **3b** is composed of two nearly perpendicular planes defined by both aromatic systems with an interplanar angle of 76.64 (5)°. The primary deviation from these planes occurs for carbon atom C10 (spiro one, for numbering see Fig. 2), which lies 0.266 (3) Å above the plane containing the oxathia cycle and 0.488 (3) Å above the second plane. Three additional atoms or groups deviate from their parent rings: two methyl groups (0.526 (3) and 0.601 (3) Å) and the oxygen atom O4 of one of the carbonyl groups. All the other interatomic distances and angles are in line with previous findings in the literature.[7] The molecular system does not contain any H-bonding.

The ESI-MS measurements of compounds **3** were performed in both the positive- and the negative-ion polarity modes. In the positive-ion first-order mass spectra, three signals at *m*/*z* corresponding to the protonated molecular ion $[M+H]^+$ and its sodium $[M+Na]^+$ and potassium $[M+K]^+$ adducts were determined for each structure. Moreover, these ions were accompanied by several types of higher associates: the protonated dimer $[2M+H]^+$ (**3b**) and

Table 2
^{1}H and ^{13}C chemical shifts of compounds **3** in DMSO-d_6

Position	**3a**		**3b**		**3c**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2≅3′	—	93.1	—	93.2	—	93.6
3a	—	105.8	—	105.6	—	105.9
4	—	157.3	—	156.6	—	156.6
5	—	—	—	−239.2[a]	—	—
5a	—	138.7	—	139.4	—	140.6
6	7.49	116.1	7.73	115.9	6.69	116.4
7	7.67	131.3	7.81	131.7	7.60	131.4
8	7.38	122.8	7.48	122.9	7.48	123.1
9	7.75	122.0	7.83	122.5	7.90	122.3
9a	—	110.1	—	110.7	—	110.7
9b	—	157.3	—	156.0	—	156.6
1′	—	—	—	−258.4[a]	—	—
2′	—	166.1	—	165.9	—	165.9
4′	—	184.4	—	184.0	—	183.9
4a′	—	117.0	—	118.6	—	118.5
5′	7.88	128.0	7.97	128.1	8.05	128.1
6′	7.25	123.5	7.36	123.9	7.33	123.9
7′	7.72	136.7	7.83	136.9	7.60	136.4
8′	7.19	117.3	7.50	116.6	6.49	117.2
8a′	—	141.0	—	142.1	—	143.1
1 (N-5)	12.17	—	3.69	29.5	—	136.8
2 (N-5)	—	—	—	—	[b]	[c]
3 (N-5)	—	—	—	—	[b]	[c]
4 (N-5	—	—	—	—	[b]	[c]
1 (N-1′)	11.24	—	3.47	30.4	—	136.8
2 (N-1′)	—	—	—	—	[b]	[c]
3 (N-1′)	—	—	—	—	[b]	[c]
4 (N-1′)	—	—	—	—	[b]	[c]

[a] $\delta(^{15}N)$.
[b] Strongly overlapped and broadened signals at 7.59–7.76 and 7.41–7.52 ppm.
[c] 130.4, 130.1, 129.3, 129.2, 129.1, 128.9, 128.3, 128.1 (2,6- and 3,5-carbons of phenyl ring(s) are non-equivalent due to a hindered rotation).

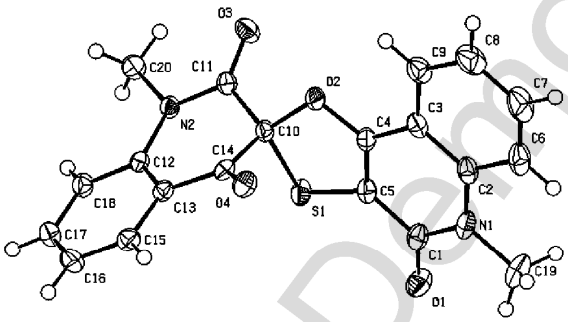


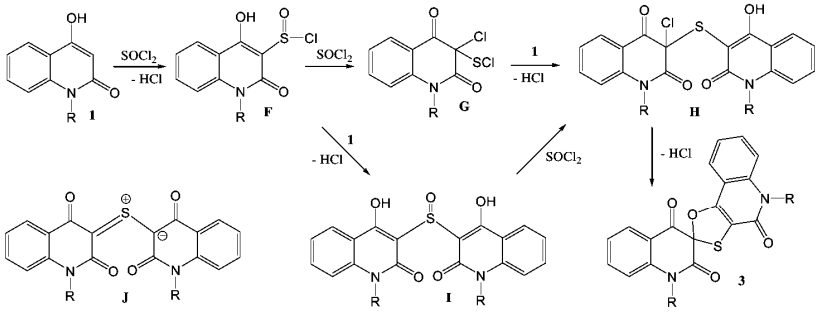
Fig. 2. Molecular structure (ORTEP 50% probability level) of **3b** C_6H_6. Selected interatomic distances [Å] and angles [°]: S1 C5 1.7543 (17), S1 C10 1.8665 (17), O2 C4 1.364 (2), O2 C10 1.4161 (19), O4 C14 1.212 (2), O3 C11 1.211 (2), N2 C11 1.372 (2), N2 C12 1.421 (2), N2 C20 1.465 (2), O1 C1 1.235 (2), C5 C4 1.344 (2), C5 C1 1.434 (2), N1 C1 1.391 (2), N1 C2 1.396 (2), N1 C19 1.465 (2), C5 S1 C10 86.09 (8), C4 O2 C10 109.06 (12), C11 N2 C12 122.78 (14), C11 N2 C20 117.49 (14), C12 N2 C20 118.74 (13).

its sodium adduct $[2M+Na]^+$ (**3a** and **3c**) and doubly charged calcium adduct $[2M+Ca]^{2+}$ observed in the ESI mass spectra of all of the analyzed compounds. Unsurprisingly, only compound **3a** also provided signals in the negative-ion polarity mode: the deprotonated molecular ion $[M-H]^-$ and a signal with twice the intensity of $[M-H]^-$ (i.e., $[2M-2H+Na]^-$). More detailed structural information for compounds **3** was obtained from the tandem mass spectra of the $[M+H]^+$ ion. In the ESI-MS/MS spectra of compounds **3**, two fragmentation pathways were observed: the cleavage of the [1,3]oxathiole core and the neutral loss of carbon monoxide (28 *m/z*) from the $[M+H]^+$ ion. The further fragmentation (MS^3) of the $[M+H-CO]^+$ product ion (323 *m/z* for **3a**, 351 *m/z* for **3b** and 475 *m/z* for **3c**) led to the neutral loss of the second carbon monoxide molecule and the formation of the corresponding protonated benzo[*b*]azet-2(1*H*)-one and [1,3]oxathiolo[4,5-*b*]indol-2-ylium. Compounds **3b** and **3c** were also analyzed using electron impact ionization mass spectrometry (EI-MS). Contrary to the ESI-MS experiments, the direct loss of two carbon monoxide molecules (56 *m/z*) is the typical fragmentation pathway observed in the EI-MS spectra of compounds **3b** and **3c**.

Only a few compounds based on the 2,2-dicarbonyl-2*H*-[1,3]-oxathiole structural motif are described in the literature, four of which are spirocyclic compounds conformable to that of structure **3**. From dimedone, 4′,4′,6,6-tetramethyl-6,7-dihydro-2′*H*,6′*H*-spiro[1,3-benz-oxathio-2,1′-cyclohexane]-2′,4,6′(5*H*)-trione has been prepared in several different ways.[8–16] One approach was the reaction of dimedone with thionyl chloride in benzene.[9,10,15] The formation of [1,3]oxathioles was also described in the reaction of dibenzoylmethane with thionyl chloride.[17,18] Compounds analogous to **3** were also prepared by the reaction of 4-hydroxy-1-propyl-1,8-naphtyridin-2(1*H*)-one and 4-hydroxy-1-propylquinolin-2(1*H*)-one with thionyl chloride and the oxidation of primarily formed sulfides with manganese dioxide.[19] Unfortunately, the corresponding sulfides are insufficiently described. Because the yellow coloring of first such compound and its melting point are almost identical to those of the final [1,3]oxathiole, it is unclear whether the primary product was sulfide or [1,3]oxathiole, or perhaps even a mixture of both compounds.

These examples show a strong tendency of β-dicarbonyl compounds to form a [1,3]oxathiole ring it their reactions with thionyl chloride and suggest that the analogous reaction, giving products **3**, also proceeds with 4-hydroxyquinolin-2-ones **1**. The mechanism of the reaction of **1** with thionyl chloride can be explained by the initial formation of intermediate **F**, which can be further transformed by two ways (Scheme 3): the Pummerer-like rearrangement of **F** to **G**, which reacts with compound **1** to give the intermediate **H**, cyclizing to the final compound **3**, and the reaction of the intermediate **F** with the starting compound **1** to give the intermediate **I**, liable to Pummerer-like rearrangement to the intermediate **H**. The formation of the intermediate thiocarbonyl ylide **J** during the transformation of the intermediate **H** to the final compound **3** is not possible under the given reaction conditions. The formation of intermediate **J** analog was described by Oka et al.,[17] but the reaction was carried out in the presence of triethylamine.

In addition to 4′,4′,6,6-tetramethyl-6,7-dihydro-2′*H*,6′*H*-spiro[1,3-benzoxathio-2,1′-cyclohexane]-2′,4,6′(5*H*)-trione, the only reaction product in the presence of pyridine, 2-(4,4-dimethyl-2,6-dioxocyclohexylthio)-5,5-dimethylcyclohexane-1,3-dione is also formed in the reaction of dimedone with thionyl chloride in the absence of pyridine.[10,15] We found that, in addition to compounds **3b** and **3c**, compounds **2b** and **2c** arise through the reaction of 4-hydroxyquinolin-2-ones **1b** and **1c** with thionyl chloride (Table 1, Scheme 2). Unfortunately, we were unable to isolate compound **2a**, which is reportedly one of the main products of the reaction of **1a** with thionyl chloride.[2,4] From the reaction of compounds **1** with thionyl chloride, four minority compounds (**4a**, **4b**, **4c**, **5b**) were also isolated (Table 1). According to the literature, compound **4a** arises from the reaction of 4-hydroxy-3-phenyliodonium-2-quinolone methanesulfonate with hydrogen chloride[20,21] or the reduction of 3,3-dichloroquinoline-2,4-dione with zinc.[22–24] Its *N*-methyl derivative **4b** arises from the reaction of 4-hydroxy-1-methyl-3-phenyliodoniumquinolin-2-one methanesulfonate with hydrogen chloride,[20] the chlorination of 4-hydroxy-1-methylquinolin-2-one with *N*-chloro-succinimide,[25,26] the reaction of 4-hydroxy-1-methyl-3-nitroquinolin-2-one with phosphorus oxychloride,[27] and the reduction of 3,3-dichloro-1-methylquinoline-2,4-dione.[28] Compound **5b** was prepared by the reaction of 4-hydroxy-1-methyl-3-nitroquinolin-2-one with thionyl chloride[27] and the chlorination of



Scheme 3.

4-hydroxy-1-methylquinolin-2-one with sulfuryl chloride[29,30] or nascent chlorine.[29] Thus, the literature indicates that the formation of compounds **4a**, **4b**, **4c**, and **5b** during the reaction of **1a** or **1b** with thionyl chloride is not surprising and can be readily explained.

However, it is much more difficult to explain the formation of compounds **2**. We found that these compounds not only arise during the reaction of compounds **1** with thionyl chloride, but also via the long-term boiling of compounds **3** in different solvents (Table 3). The question is whether compounds **2** arise directly from the reaction of **1** with thionyl chloride or after the further transformation of compounds **3**, the primary products. We believe that the second possibility is more likely because we were unsuccessful in isolation of compounds **2** from the reaction mixture after the reaction of **1** with thionyl chloride in several cases (Table 1). The subsequent transformation of the primarily generated **3** to sulfide **2** can also explain the finding that the yellow crude reaction product of **1a** discolors after heating in dimethylformamide to give sulfide **2a**.[2,4] However, the main issue is that the conversion of **3** to **2** is a reduction process. Despite significant effort, we were unable to find an analogous reaction in the literature. We performed several experiments to convert compounds **3** to **2**, using dimethylformamide, acetic acid, or alcohols (Table 3). The conversion occurs very quickly in benzyl alcohol and even more so in dimethylformamide, but slowly in acetic acid and ethanol. The long-term boiling of **3c** in *p*-xylene (Table 3, entry 8) only results in the isolation of starting material, insofar that the conversion of **3** to **2** is not thermal process. Because there was no reducing agent in the reaction mixture during conversion of **3** to **2** and the reaction must proceed through C(2)–O bond fission, we suggest the nucleophilic attack of compound **3** by water (from non-dried solvents) under the formation of the thioketal **K** (Scheme 4). This compound could reduce to compound **2** by a second nucleophilic attack by water, yielding compound **2** and hydrogen peroxide, which is decomposed thermally or by the reaction with the solvent. The possibility of the nucleophilic attack of **3** or **K** with the solvent bearing the exchangeable hydrogen atom cannot be also excluded. Based on our experience, the 'positively charged' heteroatoms in position 3 of the quinoline-2,4-diones are very easily attacked by nucleophiles.[31]

Table 3
Results of the transformations of compounds **2** and **3**

Entry	Starting compound	R	*Method*	Time (h)	Solvent	Products (yields, %)
1	**3a**	H	*B*	3	DMF	**2a** (55), **3a** (21)
2			*B*	0.25	BnOH	**2a** (67)
3	**3b**	Me	*B*	5	AcOH	**2b** (24), **3b** (68)
4			*B*	5	DMF	**2b** (50)
5			*B*	20	EtOH	**2b** (27), **3b** (54)
6	**3c**	Ph	*B*	20	EtOH	**2c** (38), **3c** (42)
7			*B*	15	DMF	**2c** (47)
8			*B*	3.5	*p*-xylene	**3c** (67)
9	**2a**	H	*C*	0.5	CH_2Cl_2	**2a** (94)
10	**2b**	Me	*C*	0.5	CH_2Cl_2	**3b** (75)
11	**2c**	Ph	*C*	0.5	CH_2Cl_2	**3c** (72)
12			*C*	0.25	PhH	**2c** (31), **3c** (26)
13	**3a**	H	*D*	1	PhMe	**2a** (53)
14	**3b**	Me	*D*	1	PhMe	**2b** (27), **6b** (61)
15	**3c**	Ph	*D*	1	PhMe	**2c** (18), **6c** (37)

An alternative but similar reaction mechanism for the reaction of **3b** and **3c** with triphenylphosphine, providing 1,4-oxathiines **6a,b**, is as follows. Because the sulfur atom in **3** remains part of the product **6**, the fission of the C(2)–O bond must be the first reaction step. The nucleophilic attack of triphenylphosphine affords the intermediate **L**, which cyclizes to betaine **M** (Scheme 4, path **a**). The final oxathiines **6** arise from the elimination of triphenylphospine oxide in a way typified by the final step of the Mitsunobu reaction.[32]

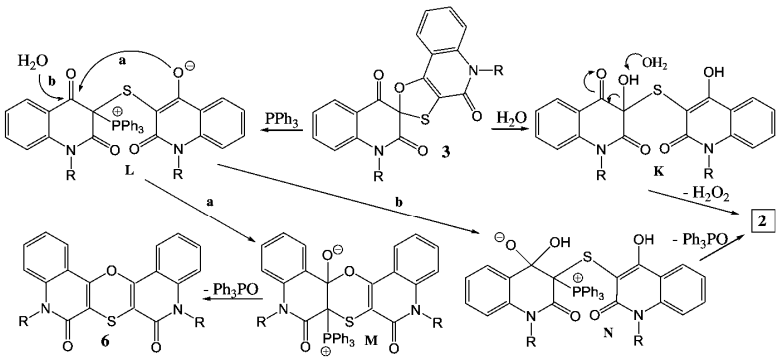
In addition to **6b** and **6c**, sulfides **2b** and **2c** were also isolated from the reaction of **3b** and **3c** with triphenylphosphine. These compounds most likely arise from the addition of water to the carbonyl group at C(4) of intermediate **L** (Scheme 4, path **b**) and following the elimination of triphenylphosphine oxide from the produced intermediate **N**. In the case of **3a**, which is barely soluble in the reaction medium, only sulfide **2a** was isolated (Table 3). Although the conversion of oxathioles based on a dimedone scaffold to the corresponding thiiranes by reaction with triphenylphosphine has been described,[10] no reaction mechanism has been proposed.

In agreement with the results described in Ref. 10 for dimedone-derived analogs of **2**, we found that compounds **2** can easily be converted to compounds **3** by their reaction with bromine (Table 3). The fruitfulness of the reaction depends on the solvent used. In benzene, in which compound **2c** is poorly soluble, the yield was low and a large quantity of the starting compound **2c** was isolated. In dichloromethane, the yields of **3b** and **3c** were very good (Table 3, entries 10 and 11). The attempt to prepare **3a** from **2a** failed due to the negligible solubility of **2a** in all common solvents.

3. Conclusions

In conclusion, the described reaction of 4-hydroxyquinolin-2-ones **1** with thionyl chloride allows the preparation, in very good yields, of spiro-compounds **3**, which have not been previously described in the literature. The results of our experiments also bear evidence that compounds **3** and not[2,4,19] sulfides **2** are the primary products of this reaction.

Since many biologically active compounds contain a sulfur atom[33,34] and two spiro-compounds analogous to **3** exhibit cysteine protease inhibition activity,[19] compounds **3** could also be interesting structures for further study.



Scheme 4.

4. Experimental

4.1. General

Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. The ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker Avance 500 spectrometer (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C, and 50.68 MHz for ^{15}N) in DMSO-d_6. ^{1}H and ^{13}C chemical shifts are given on the δ scale (parts per million) and are referenced to internal TMS (δ=0.0). ^{15}N chemical shifts were referred to external neat CH_3NO_2 in a co-axial capillary (δ=0.0). All 2D experiments (gradient-selected (gs)-COSY, gs-TOCSY, gs-HMQC, gs-HMQC-RELAY, gs-HMBC) were performed using manufacturer's software. The positive-ion EI mass spectra were measured on a Shimadzu QP-2010 instrument within the mass range m/z=50–600 using direct inlet probe (DI). Samples were dissolved in dichloromethane (30 μg mL^{-1}) and 10 μL of the solution was evaporated in DI cuvette at 50 °C. The ion source temperature was 200 °C; the energy of electrons was 70 eV. Only signals exceeding relative abundance of 5% are listed. The electrospray mass spectra (ESI-MS) were recorded using an amaZon X ion-trap mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an electrospray ion source. All experiments were conducted in the positive as well as negative-ion polarity mode. Individual samples (with a concentration of 500 ng mL^{-1}) were infused into the ESI source as methanol or methanol/water (1:1, v:v) solutions via a syringe pump with a constant flow rate of 4 μL min^{-1}. The other instrumental conditions were as follows: electrospray voltage of ±4.2 kV, capillary exit voltage of ±140 V, drying gas temperature of 220 °C, drying gas flow of 6.0 dm^3 min^{-1}, nebulizer pressure of 8.0 psi. Nitrogen was used as the nebulizing and drying gases for all experiments. Tandem mass spectra were collected using collision-induced dissociation (CID) with He as the collision gas after isolating of the required ions. Column chromatography was carried out on silica gel (Merck, grade 60, 70–230 mesh) using chloroform/ethanol (in ratios from 99:1 to 8:2) (S1), successive mixtures of benzene/ethyl acetate (in ratios from 99:1 to 8:2) (S2) and isopropylalcohol/acetic acid (9:1) (S3). Reactions as well as the course of separation and also the purity of substances were monitored by TLC (elution systems benzene/ethyl acetate) (4:1) (S4), chloroform/ethanol (9:1 and 1:1) (S5 and S6), chloroform/ethyl acetate (7:3) (S7), and tetrahydrofuran/acetic acid (4:1) (S8) on Alugram® SIL G/UV_{254} foils (Macherey–Nagel). Elemental analyses (C, H, N) were performed with a EA Flash EA 1112 Elemental Analyzer (Thermo Fisher Scientific).

X-ray analysis. The X-ray data for colorless crystals of **3b** C_6H_6, (prepared by liquid diffusion method[6] using dichloromethane and benzene as solvent-precipitant pair) were obtained at 150 K using Oxford Cryostream low-temperature device on a Nonius KappaCCD diffractometer with MoKα radiation (λ=0.71073 Å), a graphite monochromator, and the ϕ and χ scan mode. Data reductions were performed with DENZO-SMN.[35] The absorption was corrected by integration methods.[36] Structures were solved by direct methods (Sir92)[37] and refined by full matrix least-square based on F^2 (SHELXL97).[38] Hydrogen atoms were mostly localized on a difference Fourier map, however to ensure uniformity of the treatment of the crystal, all hydrogen atoms were recalculated into idealized positions (riding model) and assigned temperature factors H_{iso}(H)=1.2 U_{eq} (pivot atom) or of 1.5 U_{eq} for the methyl moiety with C–H=0.96 and 0.93 Å for methyl and hydrogen atoms on sp^2 carbon atoms, respectively.

There is disordered solvent (benzene) in the structure of **3b**. Attempts were made to model this disorder or split it into two positions, but were unsuccessful. PLATON/SQUEZZE[39] was used to correct the data for the presence of disordered solvent. A potential solvent volume of 258 $Å^3$ was found, 89 electrons per unit cell worth of scattering were located in the void. The calculated stoichiometry of solvent was calculated to be two molecules of benzene per unit cell resulting in 84 electrons.

Crystallographic data for **3b** C_6H_6: $C_{26}H_{20}N_2O_4S$, M=456.50, triclinic, $P\bar{1}$, a=9.2091 (5), b=9.9390 (3), c=12.2420 (4), α=101.774 (4), β=105.928 (3), γ=94.182 (3), Z=2, V=1044.86 (7) $Å^3$, D_{calcd}=1.451 g cm^{-3}, μ=0.194 mm^{-1}; 21,453 reflections measured (θ_{max}=27.5°), 4721 independent (R_{int}=0.0339), 3851 with $I>2\sigma(I)$, 244 parameters, S=1.038, $R1$ (obs. data)=0.0453, $wR2$ (all data)=0.1100; max, min electron density=0.290, −0.244 e $Å^{-3}$.

CCDC 890932 for **3b** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

4.2. General method for the reaction of compounds 1 with thionyl chloride (*Method A*)

The solution of 4-hydroxyquinolin-2-one (**1**) (6 mmol) in dioxane (3.5 mL) and thionyl chloride (10 mL) was refluxed for 90 min. The mixture was evaporated to dryness in vacuo and the residue was treated with water (30 mL). The precipitate was filtered with suction and washed with water to the neutral reaction. Then the precipitate was rinsed with hot ethanol (20 mL). The insoluble and soluble portions were worked up separately by repeated

crystallization or column chromatography. The results are given in Table 1.

4.3. General method for transformation of spiro-compounds 3 to sulfides 2 (*Method B*)

A yellow colored mixture of compound **3** (0.25 mmol) and appropriate solvent (6 mL) was heated to reflux and the reaction was monitored by TLC. After time stated in Table 3, the mixture was evaporated to dryness and the residue was crystallized. In the case of **3a** (Table 3, entry 2), the reaction mixture was cooled and deposited **2a** was obtained by filtration.

4.4. General method for transformation of sulfides 2 to spiro-compounds 3 (*Method C*)

To the solution of compound **2** (0.5 mmol) in the mixture of dichloromethane (10 mL) and triethylamine (0.30 mL, 2.18 mmol), a 0.195 M solution of bromine in dichloromethane (2.56 mL) was added in one portion. The solution was stirred at room temperature and the course of the reaction was monitored by TLC. After 30 min, the spot corresponding to **2** disappeared and only that corresponding to compound **3** was observed. The solution was evaporated to dryness in vacuo, the residue was triturated with water and filtered with suction. The filter cake was recrystallized from ethyl acetate or benzene. The yields are given in Table 3. In the case of **2a**, only starting compound was isolated. In one case (Table 3, entry 11) the reaction was performed in benzene.

4.5. General method for the reaction of spiro-compounds 3 with triphenylphosphine (*Method D*)

A suspension of compound **3** (0.3 mmol) and triphenylphosphine (0.091 g, 0.346 mmol) in toluene (6.6 mL) was heated to reflux. The suspension comes to solution and after ca. 5 min the new deposition of crystals started. After 1 h, the reaction mixture was cooled and filtered with suction to give yellow compound **6**. In the case of **3a**, only **2a** was isolated (Table 3).

4.6. Isolated compounds

*4.6.1. 3-(1,2-Dihydro-4-hydroxy-2-oxoquinolin-3-ylthio)-4-hydroxyquinolin-2(1H)-one (**2a**).* Compound was prepared from **3a** in respective yields 67 and 55% by *Method B* and from **3a** in 53% yield by *Method D* (Table 3). Colorless crystals, mp >330 °C, For IR, NMR and ESI-MS spectra see Ref. 1.

*4.6.2. 3-(1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinolin-3-ylthio)-4-hydroxy-1-methylquinolin-2(1H)-one (**2b**).* Compound was prepared from **1b** in respective yields 43% and 23% (Table 1, *Method A*) and from **3b** in respective yields 24%, 50% and 27% (Table 3, *Method B*), and 27% (Table 3, *Method D*). Colorless crystals, mp 302–310 °C (ethanol). For **2b**, mp >300 °C was reported.[3] IR: 3089, 2945, 1635, 1577, 1502, 1468, 1329, 1294, 1174, 1163, 1113, 1074, 1043, 752, 673, 451 cm^{-1}. For NMR spectra see Table 4. ESI-MS (pos.) *m/z* (%): 419.1 $[M+K]^+$ (13), 403.2 $[M+Na]^+$ (80), 381.2 $[M+H]^+$ (100). Anal. Calcd (found) for $C_{20}H_{16}N_2O_4S$: C 63.14 (63.07); H 4.24 (4.05); N 7.36 (7.33), S 8.43 (8.31).

*4.6.3. 3-(1,2-Dihydro-4-hydroxy-1-phenyl-2-oxoquinolin-3-ylthio)-4-hydroxy-1-phenylquinolin-2(1H)-one (**2c**).* Compound was prepared from **1c** in respective yields 11%, 32%, and 39% (Table 1, *Method A*) and from **3c** in respective yields 38% and 47% (Table 3, *Method B*), and 18% (Table 3, *Method D*). Colorless crystals, mp 339–340 °C (benzene). For **2c**, mp 325–326 °C was reported.[1] For NMR and ESI-MS spectra see Ref. 1.

Table 4
^1H and ^{13}C chemical shifts of compounds **2**,[a] **4** and **5** in DMSO-d_6

Position	**2b**		**4a**		**4b**		**4c**		**5b**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	—	164.8	—	159.1	—	158.7	—	158.6	—	162.9
3	—	104.0	—	105.1	—	105.0	—	104.9	—	80.2
4	—	165.8	—	157.4	—	156.3	—	157.0	—	180.9
4a	—	115.3	—	115.4	—	115.5	—	115.5	—	118.4
5	8.09	124.2	7.93	122.9	8.03	123.4	8.08	123.4	8.03	128.7
6	7.43	123.0	7.26	121.8	7.35	122.1	7.33	122.3	7.36	123.9
7	7.80	133.2	7.58	131.1	7.70	131.5	7.49	131.1	7.85	137.0
8	7.69	115.8	7.36	114.8	7.58	114.9	6.55	115.4	7.51	116.5
8a	—	139.4	—	136.9	—	137.9	—	138.9	—	141.5
OH	11.99	—	11.40	—	11.45	—	11.63	—	—	—
1′ (N-1)	3.75	30.8	11.86[b]	—	3.68	30.1	—	137.7	—	—
2′ (N-1)	—	—	—	—	—	—	7.38	129.3	—	—
3′ (N-1)	—	—	—	—	—	—	7.66	130.1	—	—
4′ (N-1)	—	—	—	—	—	—	7.58	128.9	—	—

[a] For NMR data of compounds **2a** and **2c** see Ref. 1.
[b] $^1J(^{15}N)$=90.6 Hz.

*4.6.4. 2′H-Spiro[1,3-oxathiolo[4,5-c]quinoline-2,3′-quinoline]-2′,4,4′(1′H,5H)trione (**3a**).* Compound was prepared from **1a** by *Method A* in respective yields 83%, 88%, and 85% (Table 1). Yellow crystals, mp >325 °C. IR: 3203, 3134, 3072, 2908, 2862, 1722, 1693, 1646, 1604, 1540, 1500, 1479, 1429, 1369, 1149, 1122, 947, 914, 785, 769, 750, 671, 611, 538 cm^{-1}. For NMR spectra see Table 2. ESI-MS (pos.) *m/z* (%): 723.1 $[2M+Na]^+$ (7), 389.1 $[M+K]^+$ (24), 373.1 $[M+Na]^+$ (100), 370.1 $[2M+Ca]^+$ (40), 351.1 $[M+H]^+$ (45). ESI-MS (neg.) *m/z* (%): 721.1 $[2M-2H+Na]^-$ (5), 349.1 $[M-H]^-$ (100). Anal. Calcd (found) for $C_{18}H_{10}N_2O_4S$: C 61.71 (61.89); H 2.88 (3.15); N 8.00 (7.92), S 9.15 (9.28).

*4.6.5. 1′,5-Dimethyl-2′H-spiro[1,3-oxathiolo[4,5-c]quinoline-2,3′-quinoline]-2′,4,4′(1′H,5H)trione (**3b**).* Compound was prepared from **1b** by *Method A* in respective yields 51%, 25%, and 38% (Table 1) and from **2b** by *Method C* in 75% yield (Table 3). Yellow crystals, mp 278–281 °C (ethyl acetate). IR: 3078, 2945, 2891, 1724, 1685, 1643, 1593, 1502, 1471, 1419, 1383, 1358, 1329, 1298, 1205, 1109, 1068, 999, 947, 773, 762, 748, 731, 642, 534 cm^{-1}. For NMR spectra see Table 2. EI-MS *m/z* (%): 380 (16), 379 (23), 378 (M^+, 100), 363 (22), 322 (6), 321 (9), 189 (11), 175 (13), 146 (31), 132 (14), 117 (48), 105 (11), 104 (20), 102 (11), 91 (12), 90 (15), 78 (12), 77 (21), 76 (9). ESI-MS (pos.) *m/z* (%): 757.0 $[2M+H]^+$ (7), 417.0 $[M+K]^+$ (20), 401.0 $[M+Na]^+$ (42), 398.0 $[2M+Ca]^{2+}$ (8), 379.1 $[M+H]^+$ (100). Anal. Calcd (found) for $C_{20}H_{14}N_2O_4S$: C 63.48 (63.37); H 3.73 (3.74); N 7.40 (7.33), S 8.47 (8.31). For crystallographic data of **3b** see paragraph 4.1.

*4.6.6. 1′,5-Diphenyl-2′H-spiro[1,3-oxathiolo[4,5-c]quinoline-2,3′-quinoline]-2′,4,4′(1′H,5H)trione (**3c**).* Compound was prepared from **1c** in respective yields 41%, 20%, and 25% (Table 1, *Method A*) and from **2c** in respective yields 72% and 26% (Table 3, *Method C*). Orange crystals, mp 288–292 °C (ethyl acetate). IR: 3066, 3033, 3014, 1720, 1693, 1655, 1597, 1493, 1460, 1383, 1338, 1248, 1149, 1107, 1043, 970, 764, 754, 694, 623 cm^{-1}. For NMR spectra see Table 2. EI-MS *m/z* (%): 504 (15), 503 (34), 502 (M^+, 100), 446 (5), 445 (14), 413 (10), 251 (10), 195 (11), 179 (10), 167 (13), 166 (11), 77 (18). ESI-MS (pos.) *m/z* (%): 1027.2 $[2M+Na]^+$ (5), 541.2 $[M+K]^+$ (29), 525.2 $[M+Na]^+$ (92), 522.2 $[2M+Ca]^{2+}$ (21), 503.2 $[M+H]^+$ (100). Anal. Calcd (found) for $C_{30}H_{18}N_2O_4S$: C 71.70 (71.65); H 3.61 (3.85); N 5.57 (5.49), S 6.38 (6.17).

*4.6.7. 3-Chloro-4-hydroxyquinolin-2-one (**4a**).* Compound was prepared from **1a** besides **3a** in respective yields 7%, 6%, and 3% (Table 1, *Method A*). Colorless crystals, mp 269–274 °C. For **4a**, mp 276 °C was reported.[22] IR: 3137, 3005, 2900, 1643, 1606, 1549, 1460, 1361, 1280, 1265, 1236, 1159, 1086, 860, 748, 673, 532, 469 cm^{-1}. For

NMR spectra see Table 4. EI-MS *m/z* (%): 197 (17), 196 (6), 195 (M^+(^{35}Cl), 52), 132 (11), 121 (9), 120 (100), 102 (11), 100 (16), 92 (27), 77 (15), 76 (13), 75 (10), 65 (15), 51 (14), 45 (12), 44 (34), 43 (16). ESI-MS (pos.) *m/z* (%): 413.1 [2M(^{35}Cl)+Na]$^+$ (59), 312.6 [3M(^{35}Cl)+Ca]$^{2+}$ (77), 234.1 [M(^{35}Cl)+K]$^+$ (30), 218.1 [M(^{35}Cl)+Na]$^+$ (75), 196.1 [M(^{35}Cl)+H]$^+$ (100). ESI-MS (neg.) *m/z* (%): 411.0 [2M(^{35}Cl)−2H+Na]$^-$ (7), 194.1 [M(^{35}Cl)−H]$^-$ (100). Anal. Calcd (found) for $C_9H_6ClNO_2$: C 55.26, H 3.09, N 7.16; C 55.22, H 3.04, N 7.14.

*4.6.8. 3-Chloro-4-hydroxy-1-methylquinolin-2-one (**4b**).* Compound was prepared from **1b** in 3% yield (Table 1, *Method A*). Yellowish crystals, mp 226–231 °C (chloroform/hexane). For **4b**, mp 229–231 °C was published.[40] IR: 3050, 1628, 1608, 1587, 1566, 1271, 1221, 1161, 1078, 866, 741, 646, 582 cm^{-1}. For NMR spectra see Table 4. ESI-MS (pos.) *m/z* (%): 441.1 [2M(^{35}Cl)+Na]$^+$ (27), 333.6 [3M(^{35}Cl)+Ca]$^{2+}$ (27), 248.1 [M(^{35}Cl)+K]$^+$ (15), 232.1 [M(^{35}Cl)+Na]$^+$ (63), 210.2 [M(^{35}Cl)+H]$^+$ (100). ESI-MS (neg.) *m/z* (%): 208.1 [M(^{35}Cl)−H]$^-$ (100). Anal. Calcd (found) for $C_{10}H_8ClNO_2$: C 57.30 (57.05); H 3.85 (3.74); N 6.68 (6.51).

*4.6.9. 3-Chloro-4-hydroxy-1-phenylquinolin-2-one (**4c**).* Compound was prepared from **1c** in 6% yield (Table 1, *Method A*). Colorless crystals, mp 263–272 °C (ethanol). For **4c**, mp 264 °C was reported.[23] IR: 3062, 1631, 1591, 1550, 1496, 1334, 1294, 1184, 1155, 1080, 858, 752, 698, 658, 625, 467 cm^{-1}. For NMR spectra see Table 4. EI-MS *m/z* (%): 273 (22), 272 (44), 271 (M^+(^{35}Cl), 71), 270 (100), 196 (11), 195 (10), 167 (25), 166 (11), 77 (34), 76 (16), 75 (11), 51 (27). ESI-MS (pos.) *m/z* (%): 565.1 [2M(^{35}Cl)+Na]$^+$ (26), 426.6 [3M(^{35}Cl)+Ca]$^{2+}$ (11), 310.1 [M(^{35}Cl)+K]$^+$ (18), 294.1 [M(^{35}Cl)+Na]$^+$ (100), 272.1 [M(^{35}Cl)+H]$^+$ (56). ESI-MS (neg.) *m/z* (%): 270.1 [M(^{35}Cl)−H]$^-$ (100). Anal. Calcd (found) for $C_{15}H_{10}ClNO_2$: C 66.31 (66.61); H 3.71 (3.74); N 5.16 (5.18).

*4.6.10. 3,3-Dichloro-1-methylquinoline-2,4(1H,3H)-dione (**5b**).* Compound was prepared from **1b** in 2% yield (Table 1, *Method A*). Yellow crystals, mp 144–148 °C (cyclohexane). For **5b**, mp 147 °C was reported.[29] IR: 3118, 3093, 1705, 1678, 1601, 1469, 1360, 1296, 1145, 845, 781, 746, 646, 573, 528 cm^{-1}. For NMR spectra see Table 4. ESI-MS (pos.) *m/z* (%): 509.0 [2M(^{35}Cl$_2$)+Na]$^+$ (8), 384.5 [3M(^{35}Cl$_2$)+Ca]$^{2+}$ (12), 266.1 [M(^{35}Cl$_2$)+Na]$^+$ (64), 244.1 [M(^{35}Cl$_2$)+H]$^+$ (45), 180.1 [M(^{35}Cl$_2$)+H−HCOCl]$^+$ (100). Anal. Calcd (found) for $C_{10}H_7Cl_2NO_2$: C 49.21, H 2.89, N 5.74; found C 49.32, H 2.86, N 5.66.

*4.6.11. 5,9-Dimethyl-[1,4]oxathiino[3,2-c:5,6-c′]diquinoline-6,8(5H,9H)-dione (**6b**).* Compound was prepared from **1b** in respective yields 8%, 3%, and 4% (Table 1, *Method A*), and from **3b** in 61% yield (Table 3, *Method D*). Yellow crystals, mp >335 °C. IR: 3077, 1655, 1624, 1597, 1460, 1417, 1336, 1305, 1151, 1113, 1045, 748, 667, 629, 503 cm^{-1}. For NMR spectra see Table 5. EI-MS *m/z* (%): 363 (24), 362 (M^+, 100), 333 (9), 301 (8), 181 (9), 128 (12), 102 (10), 77 (12). ESI-MS (pos.) *m/z* (%): 747.2 [2M+Na]$^+$ (5), 401.1 [M+K]$^+$ (5), 385.2 [M+Na]$^+$ (44), 363.2 [M+H]$^+$ (100). Anal. Calcd (found) for $C_{20}H_{14}N_2O_3S$ (362.40): C 66.28 (65.97); H 3.89 (3.87); N 7.73 (7.57), S 8.85 (8.64).

Table 5
^{1}H and ^{13}C chemical shifts of compounds **6**

Position	**6b**[a]		**6c**[b]	
	δ_H	δ_C	δ_H	δ_C
1, 13	8.24	123.8	8.26	121.8
2, 12	7.62	127.2	7.47	123.3
3, 11	7.86	134.9	7.59	131.5
4, 10	7.67	117.4	6.87	115.9
4a, 9a	—	139.5	—	138.7
6, 8	—	162.8	—	158.2
6a, 7a	—	107.8	—	106.1
13a, 14b	—	116.5	—	113.0
13b, 14a	—	154.1	—	149.5
1′ (N-5, 9)	3.93	32.8	—	136.8
2′ (N-5, 9)	—	—	7.45	129.1
3′ (N-5, 9)	—	—	7.70	130.3
4′ (N-5, 9)	—	—	7.65	129.4

[a] Measured in CF_3COOD.
[b] Measured in DMSO-d_6.

*4.6.12. 5,9-Diphenyl-[1,4]oxathiino[3,2-c:5,6-c′]diquinoline-6,8(5H,9H)-dione (**6c**).* Compound was prepared from **1c** (Table 1, *Method A*) in 2% yield and from **3c** (Table 3, *Method D*) in 37% yield. Yellow crystals, mp >335 °C. IR: 3037, 1651, 1602, 1491, 1448, 1321, 1209, 1109, 766, 702, 623, 511 cm^{-1}. For NMR spectra see Table 5. EI-MS *m/z* (%) 488 (11), 487 (33), 486 (M^+, 100), 243 (13), 242 (20), 77 (15), 44 (19). ESI-MS (pos.) *m/z* (%): 995.2 [2M+Na]$^+$ (3), 525.2 [M+K]$^+$ (16), 509.2 [M+Na]$^+$ (40), 506.2 [2M+Ca]$^{2+}$ (6), 487.2 [M+H]$^+$ (100). Anal. Calcd (found) for $C_{30}H_{18}N_2O_3S$: C 74.06 (73.91); H 3.73 (3.95); N 5.76 (5.72), S 6.59 (6.34).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.11.034. These data include MOL files and InChiKeys of the most important compounds described in this article.

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PŘÍLOHA V

Reaction of Some 2-Quinolone Derivatives with Phosphoryl Chloride: Synthesis of Novel Phosphoric Acid Esters of 4-Hydroxy-2-quinolone

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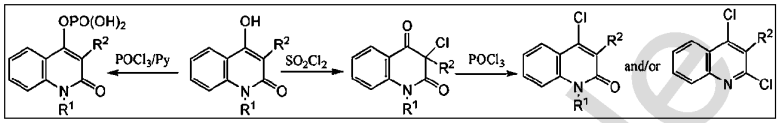

3-Chloroquinoline-2,4-diones do not react with phosphoryl chloride, however, 2,4-dichloroquinolines and/or 4-chloroquinolin-2-ones are formed in the presence of *N,N*-dimethylaniline. Along with these compounds, small quantities of novel dihydrogen phosphates of 4-hydroxyquinolin-2-ones were isolated. We outline a simple procedure that allows for the preparation of these compounds in moderate to good yields. All compounds were characterized by ^{1}H and ^{13}C NMR, IR, EI-MS, and ESI-MS spectroscopy, and in select cases by ^{31}P NMR spectroscopy.

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INTRODUCTION

Phosphoryl chloride (phosphoryl trichloride, phosphorus oxychloride) is a popular reagent for the conversion of —CO—NH— groups to —C(Cl)=N— groups. Therefore, it is not surprising that more than 600 reactions that describe the conversion of quinoline-2-ones to 2-chloroquinolines have been reported in the literature. 1-Unsubstituted 4-hydroxyquinoline-2-ones react with phosphoryl chloride or a mixture of phosphoryl chloride and phosphorus pentachloride to give 2,4-dichloroquinolines [1–4]. To date, more than 230 2,4-dichloroquinolines are known, and some of them exhibit interesting biological activity. For example, the 7-dimethylamino-3-methyl derivative exhibits antiviral activity [5], the 3-butyl-6-(3,5-dimethyl-pyrazol-1-yl) derivative is mildly active against *Staphyllococcus aureus* and *Saccharomyces cerevisiae* [6], the 3-(2-chloroethyl)-8-methyl derivative has the ability to inhibit (H+/K+)-ATPase affinity in lyophilized gastric vesicles [7], and the 3,7-dichloro and 3-chloro-6,7-difluoro derivatives exhibit affinity for pentacyclidine and glycine binding sites on NMDA receptors [8].

The dealkylation during the formation of 2-chloroquinolines occurs when 1-substituted quinoline-2-ones react with phosphoryl chloride. This happens most frequently in the presence of phosphorus pentachloride. This class of reactions was studied extensively in the mid-twentieth century [9–14]. A series of studies since 1982 have found that reactions of 1-substituted 4-hydroxyquinoline-2-ones with phosphoryl chloride produce high yields of the corresponding 1-substituted 4-chloroquinoline-2-ones [15, 16].

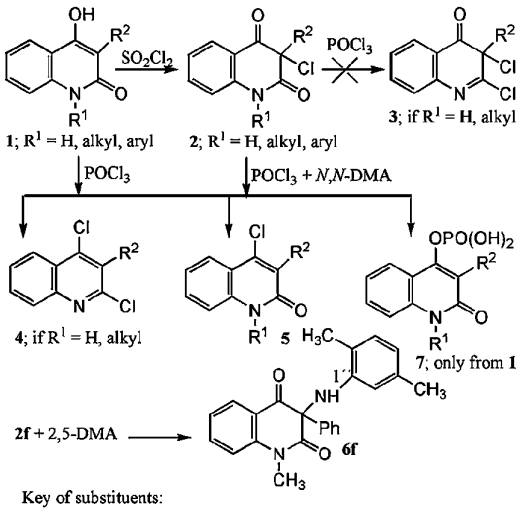
In 1991, Stadlbauer *et al.* [17] reported that the reaction of some 1-alkyl-3-aryl-7-methoxy-4-hydroxyquinoline-2-ones with phosphoryl chloride leads, without any catalyst, not only to the expected 1-alkyl-3-aryl-7-methoxy-4-chloroquinoline-2-ones but also to 3-aryl-2,4-dichloro-7-methoxyquinolines.

As a part of our institute's systematic research into 3,3-disubstituted 1*H*,3*H*-quinoline-2,4-diones we decided to study the previously undescribed reaction of 3-alkyl/aryl-3-chloroquinoline-2,4-diones **2** with phosphoryl chloride. We expected that 3-alkyl/aryl-2,3-dichloro-3*H*-quinolin-4-ones **3** would be formed, which subsequently could be reacted with amines to give two different types of the products suitable for biological testing.

RESULTS AND DISCUSSION

The initial 3-alkyl/aryl-3-chloroquinolin-2,4-diones **2** (Scheme 1) were prepared by reacting 3-alkyl/aryl-4-hydroxyquinolin-2-ones **1** with sulfuryl chloride [18,19]. The preliminary experiments were carried out by boiling of starting compounds **2a,c–e,g,h** in phosphoryl chloride (Table 1, Method A). In most cases, only the starting material was isolated despite an extended reaction time (Table 1, entries 1, 6, 8, and 11). Compound **4c** was isolated in addition to recovered starting material only with two starting

Scheme 1



Key of substituents:

	a	b	c	d	e	f	g	h	i	j	k	l	m
R^1	H	H	H	Me	Me	Me	Et	Bn	Bn	Ph	Ph	Ph	Ph
R^2	Bu	Bn	Ph	Bu	Bn	Ph	Ph	Bu	Ph	Me	Bu	Bz	Ph

compound (**2c** and **2i**), both of which bear a phenyl group in position 3.

Hence, we carried out further experiments in the presence of *N,N*-dimethylaniline (DMA), which is frequently used as a catalyst in the reaction of amides with phosphoryl chloride. Under these conditions (Table 1, Method B), the reactions take place. However, instead of the expected 3-alkyl/aryl-2,3-dichloro-3*H*-quinolin-4-ones **3**, only 2,4-dichloroquinolines **4a–c** were obtained from all starting compounds except those that have a phenyl group at position 1 (Table 1). These results show that the dealkylation of the N(1) atom proceeds in all compounds that have an alkyl group on the nitrogen atom in position 1, but conversion is low in the case of *N*-benzyl derivatives.

N-Phenyl substituted compounds **2j–m** react differently under of the same reaction conditions (Table 1, Method B). Mainly starting material was recovered; however, compounds **5k–m** were also isolated in small quantities (Table 1, entries 17–19).

The conversion of 3-chloro-1-phenylquinoline-2,4-diones **2k–m** to their corresponding 4-chloroquinolin-2-ones **5** is a net reduction. Therefore, we considered a cleavage of the C(3)—Cl bond as the first reaction step in the transformation of compounds **2k–m**. The transfer of a chlorine atom (or a bromine atom or a thiocyanato group) from position 3 of the corresponding quinoline-2,4-diones to a nucleophile has been observed previously [20–22]. Hydroxide ions [20], sulfide ions [21], amines [22], thioalcohols [22], or activated aromatic compounds [22] can act as nucleophile.

In the case of compounds **2k–m**, DMA can act as a nucleophile. We found that the reaction of **2c** and **2m** with DMA in chloroform, acetic acid, ethanol, or toluene solution affords compounds **1**. Unfortunately, we did not succeeded in isolating the expected 4-chloro-*N,N*-dimethylaniline from the complex reaction mixture. Conversion of **2f** to **1f** also

Table 1

Reactions of 3-chloroquinoline-2,4-diones **2** with phosphoryl chloride (Method A: in the absence of a catalyst; Method B: in the presence of DMA).

		Substituents				
Entry	2	R^1	R^2	Method	Time (h)	Product(s) (yield, %)[a]
1	**a**	H	Bu	*A*	120	**2a** (47)[b]
2	**a**			*B*	5	**4a** (83)
3	**b**	H	Bn	*B*	8	**4b** (75)
4	**c**	H	Ph	*A*	60	**2c** (32)[b], **4c** (40)
5	**c**			*B*	5	**4c** (84)
6	**d**	Me	Bu	*A*	10	**2d** (92)[b]
7	**d**			*B*	18	**4a** (65)
8	**e**	Me	Bn	*A*	23	**2e** (92)[b]
9	**e**			*B*	30	**4b** (46)
10	**f**	Me	Ph	*B*	10	**4c** (70)
11	**g**	Et	Ph	*A*	30	**2g** (92)[b]
12	**g**			*B*	30	**4c** (54)
13	**h**	Bn	Bu	*B*	8	**2h** (77)[b], **4a** (5)
14	**i**	Bn	Ph	*A*	18	**2i** (30)[b], **4c** (4)
15	**i**			*B*	16	**4c** (60)
16	**j**	Ph	Me	*B*	30	**2j** (73)[b]
17	**k**	Ph	Bu	*B*	20	**2k** (18)[b], **5k** (11)
18	**l**	Ph	Bn	*B*	20	**2l** (28)[b], **5l** (4)
19	**m**	Ph	Ph	*B*	30	**2m** (32)[b], **5m** (12)

[a]Refers to isolated percent yield of pure product.
[b]Recovered starting compound.

Table 2

Reaction of 4-hydroxyquinolin-2-ones **1** with phosphoryl chloride (*methods A and B:* see Table 1; *Method A1:* modified *Method A*).[a]

Entry	1	Substituents		Method	Time (h)	Product(s) (yield, %)[b]
		R^1	R^2			
1	**a**	H	Bu	*A1*	0.6	**4a** (79)
2	**b**	H	Bn	*A1*	0.6	**4b** (77)
3	**c**	H	Ph	*A1*	0.6	**4c** (74)
4	**c**			*B*	5	**4c** (97)
5	**d**	Me	Bu	*A*	1	**5d** (93)
6	**e**	Me	Bn	*A1*	0.5	**5e** (41), **7e** (3)
7	**f**	Me	Ph	*A1*	0.5	**4c** (2), **5f** (57), **7f** (2)
8	**f**			*A1*	6	**4c** (15), **5f** (60)
9	**g**	Et	Ph	*A1*	0.5	**4c** (1), **5g** (60), **7g** (3)
10	**h**	Bn	Bu	*A1*	0.5	**4a** (7), **5h** (19), **7h** (28)
11	**h**			*A1*	6	**4a** (19), **5h** (25), **7h** (24)
12	**i**	Bn	Ph	*A1*	0.5	**4c** (1), **5i** (30), **7i** (4)
13	**i**			*A1*	6	**4c** (31), **5i** (39), **7i** (15)
14	**j**	Ph	Me	*A1*	0.5	**5j** (59), **7j** (5)
15	**k**	Ph	Bu	*A*	0.7	**5k** (39), **7k** (22)
16	**k**	Ph	Bu	*A1*	0.7	**5k** (65)
17	**l**	Ph	Bn	*A*	1	**5l** (33), **7l** (9)
18	**l**			*A1*	0.7	**5l** (36), **7l** (32)
19	**m**	Ph	Ph	*A*	0.7	**5m** (33)
20	**m**			*A1*	0.7	**5m** (80)
21	**m**			*B*	2	**5m** (79)

[a]See Experimental.
[b]Refers to isolated percent yield of pure product.

proceeds in the presence of *N,N*-dimethyl-*p*-toluidine. However, facile transport of a chlorine atom from **2m** was apparent in its reaction with 2-sulfanylbenzothiazole. In addition to **1m**, 2,2′-dithiobis(benzothiazole) was isolated. These results are similar to the transfer of thiocyanato groups from 3-thiocyanatoquinoline-2,4-diones to 2-sulfanylbenzo-thiazoles [22]. However, the reaction of **2f** with 2,5-dimethylaniline leads only to *N*-alkylation along with formation of compound **6f**.

To clarify the reaction mechanism, we also carried out the reaction of compounds **1** with phosphoryl chloride (Table 2). In the absence of a catalyst, compounds **4a–c** were obtained in high yields from **1a–c** (Methods A and A1). The reaction times were much shorter than those necessary for the conversion of **2a–c** to **4a–c**. However, compounds **1e–m** provide, in low yields, compounds **4**, but only if the starting compounds have a phenyl group at position 3 or a benzyl group at position 1 (**1f–i**). The yield of **4** can be increased by increasing the reaction time (cf. entries 7–8, 10–11, and 12–13 in Table 2). The main (or the only) products isolated from the reaction of **1d–m** with phosphoryl chloride were compounds **5**. As we expected, compounds **1** bearing the *N*-phenyl group afford mainly (or exclusively) compounds **5**. The NMR data of all products **4** and **5** are compiled in Table 3.

The proposed reaction mechanism of the conversion of **2** to **4** is depicted in Scheme 2. We anticipated that after transfer of the chlorine atom from **2** to a nucleophile, intermediate compound **1** would arise and react with phosphoryl chloride to give compound **5**, which is the final minor product of the reaction of compounds **2k–m**, as long as they bear a phenyl group at position 1. In the case of *N*-unsubstituted or *N*-alkyl substituted compounds **2a–i**, compound **1** is an intermediate, which is subsequently enolized to intermediate **A**. Then, the reaction of **A** with phosphoryl chloride produces intermediate **B** which dealkylates to compound **4**. The enolization of **1** in the formation of **A** is, as hypothesized by Bell *et al.* [23], facilitated by the catalytic effect of DMA. The resulting compound is converted to its hydrochloride, which protonates the carboxamide group and facilitates its enolization and subsequent dealkylation through intermediate **B**. If DMA is not present in the reaction mixture, the extent of enolization is lower, so mainly compounds **5** were obtained from **1** (Table 2).

Unfortunately, when compounds **2** and phosphoryl chloride reacted in the presence of DMA, a significant quantity of an intensely blue compound was formed. This compound was isolated and its melting point, IR, and ^{1}H and ^{13}C NMR spectra were identical to those published [24] for 4,4′,4″-tris (dimethylaminotritylium) chloride (crystal violet, gentian violet, methyl violet 6B). An EI-MS spectrum of this compound (MW 408) exhibits a peak at *m/z* 373, which is almost identical to the mass of 4,4′,4″-tris(dimethylamino)-triphenyl-methane (leuco crystal violet, MW 373.5) [24]. In the literature, we found no information about this unintended side product of the reaction of secondary amides with phosphoryl chloride in the presence of DMA, although it must have been observed. When we refluxed a solution of DMA in

Table 3

^{1}H and ^{13}C NMR data (δ, ppm) of compounds **2**, **4**, and **5** in DMSO-d_6.

	2h		**4a**		**4b**		**4c**		**5d**		**5e**		**5f**	
Position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	–	166.9	–	150.5	–	151.0	–	149.5	–	159.9	–	160.2	–	159.7
3	–	68.0	–	132.0	–	132.0	–	133.0	–	131.6	–	130.2	–	131.5
4	–	187.7	–	141.9	–	143.3	–	142.4	–	139.5	–	140.8	–	140.3
4a	–	119.2	–	125.2	–	125.2	–	125.0	–	118.2	–	118.2	–	118.3
5	8.00	128.3	8.20	124.1	8.27	124.4	8.29	124.6	7.98	125.2	8.02	125.5	8.09	126.0
6	7.30	123.9	7.80	128.8	7.86	129.0	7.88	129.0	7.40	122.7	7.42	122.9	7.46	122.9
7	7.71	137.0	7.90	131.2	7.95	131.6	8.00	131.9	7.70	131.1	7.73	131.6	7.80	132.0
8	7.28	116.6	8.01	128.4	8.07	128.5	8.13	128.5	7.60	115.0	7.64	115.2	7.70	115.2
8a	–	141.3	–	145.6	–	145.9	–	146.3	–	138.1	–	138.3	–	138.8
1′(N)	5.48 5.23[a]	46.0	–	–	–	–	–	–	3.69	30.0	3.71	30.2	3.72	30.2
2′(N)	–	136.1	–	–	–	–	–	–	–	–	–	–	–	–
3′(N)	7.36	126.3	–	–	–	–	–	–	–	–	–	–	–	–
4′(N)	7.41	128.8	–	–	–	–	–	–	–	–	–	–	–	–
5′(N)	7.33	127.4	–	–	–	–	–	–	–	–	–	–	–	–
1′(C-3)	2.39	35.6	3.03	30.9	4.52	36.4	–	135.6	2.79	28.6	4.18	34.2	–	135.1
2′(C-3)	1.33	26.8	1.62	29.9	–	137.1	7.46	129.6	1.52	29.5	–	138.5	7.38	130.0
3′(C-3)	1.33	22.3	1.48	22.3	7.22	127.0	7.60	128.6	1.39	22.3	7.34	128.4	7.50	127.9
4′(C-3)	0.89	13.7	0.98	13.7	7.34	128.7	7.54	128.8	0.95	13.9	7.29	128.4	7.46	128.0
5′(C-3)	–	–	–	–	7.26	126.6	–	–	–	–	7.21	126.3	–	–

	5g		**5h**		**5i**		**5j**		**5k**		**5l**		**5m**	
Position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	–	159.3	–	160.3	–	160.1	–	160.3	–	160.0	–	160.2	–	159.7
3	–	131.5	–	131.7	–	131.5	–	128.1	–	132.1	–	130.7	–	131.9
4	–	140.5	–	140.2	–	140.9	–	140.4	–	140.3	–	141.7	–	141.1
4a	–	118.6	–	118.6	–	118.7	–	118.2	–	118.2	–	118.2	–	118.3
5	8.11	126.4	8.03	125.5	8.13	126.3	8.05	125.1	8.06	125.2	8.08	125.5	8.16	126.0
6	7.43	122.9	7.37	122.9	7.42	123.1	7.40	123.0	7.39	123.0	7.42	123.1	7.45	123.1
7	7.78	132.2	7.60	131.1	7.70	132.0	7.51	130.8	7.52	131.0	7.55	131.3	7.60	131.9
8	7.74	115.0	7.48	115.5	7.53	115.6	6.61	115.7	6.59	115.7	6.62	115.8	6.67	115.8
8a	–	137.8	–	137.3	–	138.1	–	139.0	–	139.1	–	139.3	–	139.8
1′(N)	4.37	37.8	5.61	45.6	5.63	45.7	–	137.7	–	137.6	–	138.4	–	137.6
2′(N)	1.30	12.7	–	136.6	–	136.5	7.39	129.0	7.39	129.0	7.42	128.5	7.45	129.0
3′(N)	–	–	7.23	126.5	7.31	126.7	7.69	130.2	7.69	130.2	7.68	130.2	7.69	130.2
4′(N)	–	–	7.35	128.8	7.36	128.8	7.62	129.0	7.61	129.0	7.61	129.1	7.63	129.0
5′(N)	–	–	7.26	127.2	7.30	127.3	–	–	–	–	–	–	–	–
1′(C-3)	–	135.10	2.88	28.7	–	135.0	2.53	14.9	2.83	28.4	4.21	33.9	–	134.6
2′(C-3)	7.38	130.1	1.60	29.6	7.47	130.1	–	–	1.59	29.6	–	137.6	7.45	130.2
3′(C-3)	7.50	128.0	1.43	22.4	7.52	128.0	–	–	1.43	22.4	7.38	128.4	7.52	128.0
4′(C-3)	7.45	128.1	0.97	13.9	7.47	128.1	–	–	0.96	13.9	7.32	128.5	7.43	128.2
5′(C-3)	–	–	–	–	–	–	–	–	–	–	7.24	126.3	–	–

[a]Prochiral methylene group.

phosphoryl chloride under aerobic conditions for 20 hours, crystal violet was obtained in 40% yield. This result shows that under these reaction conditions DMA oxidizes to *N*-methylformanilide and the subsequent Vilsmeier-Haack reaction between these two compounds generates *N,N*-dimethylbenzaldehyde [25]. This compound subsequently reacts with two molecules of DMA and, under aerobic conditions, crystal violet is produced.

Highly hydrophilic products besides **4** and **5** were obtained in small quantities from the reaction of **1e–l** with phosphoryl chloride (Table 2). The IR spectra of these compounds showed two broad bands of low intensity approximately in the ranges of 2320–2360 and 2560–2800 cm^{-1}. These bands correspond to the OH stretching vibrations of phosphoric acid esters, which usually appear in the regions of 2100–2300 and 2560–2700 cm^{-1} [26]. The IR and analytical data suggest the presence of phosphoric acid fragment in the structure of the isolated compounds. Therefore, we suggest structure **7** for those compounds. In the electron impact mass spectra of compounds **7**, a higher peak appears at a *m/z* that corresponds to 4-hydroxyderivatives **1**. The course of the fragmentation is also almost identical to that of compounds **1**. It stands to reason that esters **7** decompose during EI-MS acquisition

and produces **1**. Hence, a softer ionization technique, namely electrospray, was used to obtain the proper MS data for compounds **7**. The ESI-IT-MS experiments were carried out in both positive and negative scanning mode. However, due to the acidic character of esters **7**, the negative ionization was more suitable for the MS analyses. In the first-order mass spectra, one dominant signal at *m/z* corresponding to the $[M–H]^-$ ion was accompanied by *m/z* signals about twice as high (exactly $[2M–H]^-$ and $[2M–2H+Na]^-$) for all examined structures. Moreover, the peak corresponding to the $[2M–H–H_3PO_4]^-$ ion was observed in the negative ESI mass spectra of compounds **7a–c**, **7e**, and **7j–m**.

To the best of our knowledge, compounds **7** have not been described in the literature. Only some phosphoric acid tri-esters, based on the 4-hydroxy-2-quinolone scaffold, have been reported. (3-Chloro-2-oxo-1,2-dihydroquinolin-4-yl) dimethyl and diethyl phosphates, prepared by the reaction of 3,3-dichloroquinoline-2,4(1*H*,3*H*)-dione with their corresponding trialkyl phosphites, were noted for their anticholinesterase activity [27]. Several 1,3-disubstituted (2-oxo-1,2-dihydroquinolin-4-yl) diethyl phosphates, prepared by the Perkow reaction of fluorinated 3-acyloxyquinoline-2,4-diones with triethyl phosphate, exhibit significant cytostatic activity toward leukemic K-562 cells and breast carcinoma MCF-7 cells [28].

Therefore, we decided to prepare phosphoric esters **7** through a route that would provide higher yields. We found that the reaction of **1** with phosphoryl chloride at low temperature in the presence of pyridine leads to the formation of desired compounds **7**. According to the TLC analysis, the conversion of **1** to **7** is almost quantitative. Unfortunately, isolation and especially crystallization of the product are troublesome in some cases. One contributing cause is the low hydrolytic stability of compounds **7**, which convert to **1** in alkaline media and even in an acetic acid solution at elevated temperature. Nevertheless, most of the compounds **7** were obtained in moderate to good yields (Table 4).

The ^1H, ^{13}C, and ^{31}P NMR spectra of all prepared compounds **7a–m** are in agreement with the proposed structures. Proton spectra were assigned using gs-COSY. Protonated carbons were assigned by gs-HMQC and quaternary carbons by gs-HMBC. The $^nJ(^{31}P, ^{13}C)$ coupling constants were used to assign the quaternary carbons situated near the phosphorus atom. ^{31}P NMR chemical shifts in compounds **7** are very similar, being in the range −5.1 to −5.7 ppm. All NMR data are compiled in Table 5.

Scheme 2

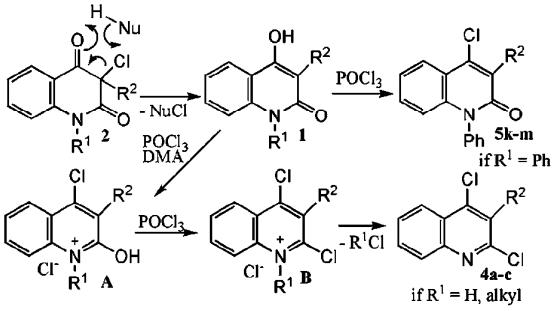


Table 4

Preparation of dihydrogen phosphates **7** from 4-hydroxy-2-quinolones **1** (*Method C*).

Entry	1	Substituents R^1	Substituents R^2	Product (yield, %)[a]
1	**a**	H	Bu	**7a** (54)
2	**b**	H	Bn	**7b** (49)
3	**c**	H	Ph	**7c** (51)
4	**d**	Me	Bu	**7d** (34)
5	**e**	Me	Bn	**7e** (39)
6	**f**	Me	Ph	**7f** (48)
7	**g**	Et	Ph	**7g** (34)
8	**h**	Bn	Bu	**7h** (37)
9	**i**	Bn	Ph	**7i** (32)
10	**j**	Ph	Me	**7j** (64)
11	**k**	Ph	Bu	**7k** (56)
12	**l**	Ph	Bn	**7l** (83)
13	**m**	Ph	Ph	**7m** (78)

[a]Refers to isolated percent yield of pure compound.

CONCLUSIONS

In conclusion, we would like to emphasize that our results reveal new information about the behavior of reactive quinoline-2,4-dione systems. We found that 3-chloroquinolinediones do not react with phosphoryl chloride. However, in the presence of DMA, the chlorine atom is split-off from these compounds and 2,4-dichloroquinolines and/or 4-chloroquinoline-2-ones are formed. We have prepared several new compounds **4** and **5** in good yield.

A significant result of our experiments is the isolation of minor compounds **7**, whose formation during the reaction of **1** with phosphoryl chloride has not been previously described. We outlined a simple procedure for the preparation of compounds **7**, which are suitable for biological testing as well as further synthetic elaboration.

EXPERIMENTAL

General. Melting points were determined on a Kofler block or Gallencamp apparatus. IR (KBr) spectra were recorded on a Mattson 3000 spectrophotometer. NMR spectra were recorded on a Bruker Avance spectrometer (500.13 MHz for ^1H, 125.76 MHz for ^{13}C), and on a Bruker Avance II 400 spectrometer (161.97 MHz for ^{31}P) in DMSO-d_6. ^1H and ^{13}C chemical shifts are given on the δ scale (ppm) and are referenced to internal TMS (δ = 0.0). ^{31}P chemical shifts were referred to external neat 85% H_3PO_4 in a co-axial capillary (δ = 0.0). All 2D

Table 5

^{1}H, ^{13}C, and ^{31}P NMR chemical shifts (δ, ppm) and $^{n}J(^{31}P, ^{13}C)$ coupling constants (Hz) of compounds **7** and **8f** in DMSO-d_6.

	7a		**7b**		**7c**		**7d**		**7e**		**7f**		**7g**	
Position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	–	163.2 (1.3)[a]	–	163.1 (1.2)[a]	–	162.5 (1.3)[a]	–	162.5 (1.2)[a]	–	162.4 (1.4)[a]	–	162.0 (1.5)[a]	–	161.4 (1.4)[a]
3	–	123.2 (4.6)[a]	–	122.0 (4.4)[a]	–	122.8 (4.7)[a]	–	122.5 (4.4)[a]	–	121.3 (4.5)[a]	–	122.3 (4.7)[a]	–	122.2 (4.6)[a]
4	–	153.1 (7.7)[a]	–	153.8 (7.6)[a]	–	153.2 (7.5)[a]	–	152.1 (7.6)[a]	–	152.7 (7.7)[a]	–	152.4 (7.3)[a]	–	152.3 (7.4)[a]
4a	–	116.7 (1.6)[a]	–	116.6 (1.4)[a]	–	116.8 (1.4)[a]	–	117.3 (1.4)[a]	–	117.2 (1.4)[a]	–	117.5 (1.5)[a]	–	117.7 (1.6)[a]
5	7.92	123.9	7.98	124.2	8.08	124.8	8.02	124.3	8.07	124.6	8.18	125.2	8.19	125.4
6	7.23	121.5	7.23	121.6	7.28	121.7	7.34	121.8	7.36	121.9	7.37	122.0	7.35	121.8
7	7.51	130.0	7.53	130.3	7.59	130.8	7.65	130.5	7.67	130.9	7.73	131.3	7.74	131.4
8	7.33	114.8	7.34	114.9	7.39	114.9	7.57	114.4	7.58	114.5	7.64	114.6	7.69	114.3
8a	–	137.2	–	137.5	–	137.9	–	138.2	–	138.4	–	138.9	–	137.8
1′(N)	11.79	–	11.86	–	11.99	–	3.68	29.6	3.68	29.8	3.71	29.9	3.37	37.4
2′(N)	–	–	–	–	–	–	–	–	–	–	–	–	1.30	12.8
3′(N)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
4′(N)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
5′(N)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
1′(C-3)	2.69	24.2	4.08	29.7	–	132.6(1.4)[a]	2.74	25.0	4.13	30.6	–	133.0 (1.2)[a]	–	132.9 (1.4)[a]
2′(C-3)	1.53	29.9	–	140.3	7.39	127.3	1.53	29.8	–	140.1	7.40	127.4	7.37	127.3
3′(C-3)	1.34	22.5	7.33	128.1	7.44	130.9	1.36	22.5	7.34	128.2	7.40	130.9	7.42	130.9
4′(C-3)	0.93	14.0	7.25	128.6	7.35	127.2	0.94	14.0	7.26	128.6	7.40	127.2	7.34	127.2
5′(C-3)	–	–	7.17	125.8	–	–	–	–	7.17	125.9	–	–	–	–
δ (^{31}P)	–	–5.4	–	–5.1	–	–5.7	–	–5.3	–	–5.3	–	–5.4	–	–5.7
	7h		**7i**		**7j**		**7k**		**7l**		**7m**		**8f**	
Position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	–	162.8	–	162.3(1.4)[a]	–	162.9(1.4)[a]	–	162.6(1.2)[a]	–	162.6(1.3)[a]	–	162.0(1.4)[a]	–	170.2
3	–	122.5(4.7)[a]	–	122.2(4.7)[a]	–	118.6(4.4)[a]	–	122.9(4.5)[a]	–	121.6(4.6)[a]	–	122.4(4.6)[a]	–	74.8
4	–	152.5(7.7)[a]	–	152.7(7.3)[a]	–	152.7(7.6)[a]	–	152.8(7.7)[a]	–	153.7(7.7)[a]	–	153.1(7.5)[a]	–	191.6
4a	–	117.7	–	117.9(1.6)[a]	–	117.2(1.6)[a]	–	117.3(1.6)[a]	–	117.3(1.4)[a]	–	117.5(1.6)[a]	–	120.4
5	8.04	124.6	8.21	125.5	8.04	124.1	8.07	124.4	8.13	124.8	8.24	125.3	7.85	127.9
6	7.30	121.9	7.33	122.1	7.31	122.0	7.31	122.0	7.32	122.1	7.33	122.1	7.27	123.6
7	7.53	130.4	7.62	131.3	7.45	130.2	7.44	130.2	7.46	130.5	7.53	130.9	7.81	136.8
8	7.43	114.8	7.51	114.9	6.56	115.1	6.55	115.0	6.56	115.2	6.60	115.1	7.55	116.3
8a	–	137.4	–	139.3	–	139.0	–	139.2	–	139.4	–	139.8	–	142.0
1′(N)	5.59	45.2	5.61	45.5	–	137.9	–	137.9	–	137.9	–	137.9	3.64	30.3
2′(N)	–	137.1	–	137.0	7.36	129.2	7.35	129.2	7.33	129.2	7.39	129.2	–	–
3′(N)	7.24	128.7	7.30	126.7	7.69	130.1	7.67	130.1	7.66	130.2	7.68	130.2	–	–
4′(N)	7.36	126.6	7.36	128.8	7.60	128.8	7.60	128.8	7.58	128.9	7.61	128.8	–	–
5′(N)	7.27	127.1	7.36	128.8	–	–	–	–	–	–	–	–	–	–
1′(C-3)	2.81	25.0	–,	132.9	2.20	11.5	2.76	24.8	4.15	30.4	–	132.6	–	134.7
2′(C-3)	1.58	29.9	7.51	131.0	–	–	1.56	29.9	–	140.2	7.49	131.0	7.46	127.0
3′(C-3)	1.39	22.5	7.42	127.3	–	–	1.38	22.5	7.39	128.2	7.38	127.2	7.39	129.3
4′(C-3)	0.96	14.0	7.28	127.2	–	–	0.94	14.0	7.27	128.7	7.34	127.3	7.39	129.4
5′(C-3)	–	–	–	–	–	–	–	–	7.18	125.9	–	–	–	–
δ (^{31}P)	–	–5.3	–	–5.7	–	–5.2	–	–5.2	–	–5.2	–	–5.3	–	–
NH[b]	–	–	–	–	–	–	–	–	–	–	–	–	5.15	–

[a] ^{n}J (^{31}P, ^{13}C) (Hz, ± 0.2 Hz).

[b] 2,5-Dimethylphenyl at NH (position: δ_H/δ_C): 1″ –/143.2; 2″: –/121.1; 3″: 6.96/130.0; 4″: 6.44/118.4; 5″: –/136.2; 6″: 5.61/114.0; CH_3(2″): 2.24/17.4; CH_3(5″): 1.97/21.3.

experiments (gradient-selected (gs)-COSY, NOESY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. The positive-ion EI mass spectra were measured on a Shimadzu QP-2010 instrument within the mass range *m/z* = 50–600 using direct inlet probe (DI). Samples were dissolved in dichloromethane (30 μg/mL), and 10 μL of the solution was evaporated in DI cuvette at 50°C. The ion source temperature was 200°C; the energy of electrons was 70 eV. Only signals exceeding relative abundance of 5% are listed. The ESI-MS spectra were recorded on an amaZon X ion-trap mass spectrometer (Bruker Daltonics, Bremen, Germany) equipped with an electrospray ion source. Individual samples were infused into the ESI source as methanol solutions *via* a syringe pump at a constant flow rate of 4 μL min^{-1}. The other instrument conditions were as follows: electrospray voltage ±4.2 kV, drying gas temperature 220°C, drying gas flow 6.0 dm^3 min^{-1}, nebulizer pressure 8.0 psi. Nitrogen was used as nebulizing as well as drying gas. Column chromatography was carried out on silica gel (Merck, grade 60, 70–230 mesh) using chloroform/ethanol (in ratios from 99:1 to 8:2) (S1), successive mixtures of benzene/ethyl acetate (in ratios from 99:1 to 8:2) (S2) and isopropylalcohol/acetic acid (9:1) (S3). Reactions as well as the course of separation and also the purity of substances were monitored by TLC (elution systems benzene/ethyl acetate (4:1) (S4), chloroform/ethanol (9:1 and 1:1) (S5 and S6), chloroform/ethyl acetate (7:3) (S7), and tetrahydrofuran/acetic acid (4:1) (S8) on Alugram® SIL G/UV_{254} foils (Macherey-Nagel). Elemental analyses (C, H, N) were performed with a EA Flash EA 1112 Elemental Analyzer (Thermo Fisher Scientific).

Preparation of 3-alkyl/aryl-3-chloroquinolin-2,4(1*H*,3*H*)-diones (2). Starting compounds **2a–m** were prepared by the reaction of 3-alkyl/aryl-4-hydroxyquinolin-2-ones **1** with sulfuryl chloride according to the procedure described in literature [18,19]. One novel derivative (**2h**) was prepared.

1-Benzyl-3-butyl-3-chloroquinoline-2,4(1H,3H)-dione (2h). Compound was prepared from **1h** and sulfuryl chloride in 63% yield. Colorless crystals, mp 69–72°C (cyclohexane); IR (KBr) v: 2953, 2930, 2969, 1706, 1678, 1599, 1488, 1467, 1360, 1304, 1207, 1167, 950, 774, 755, 731, 698, 662, 626, 526 cm^{-1}; For NMR spectra see Table 3; EI-MS (*m/z*, %) 341 (M^+, 3), 307 (8), 306 (17), 285 (8), 265 (7), 174 (9), 92 (9), 91 (100), 65 (9). Anal. Calcd. for $C_{20}H_{20}ClNO_2$: C, 70.27; H, 5.90; N, 4.10. Found: C, 70.31; H, 5.92; N, 4.10.

General procedure for the reaction of compounds 1, 2 and 6 with phosphoryl chloride. Method A. *N,N*-Dimethylaniline (DMA, 1.5 mL) was added to a solution of starting compound (3 mmol) in phosphoryl chloride (15 mL) and the reaction mixture was heated under reflux for the time given in Table 1. After cooling, the reaction mixture was poured onto crushed ice (100 g) and extracted with chloroform (3 × 50 mL). The extract was filtered through a short column of silica gel to removing of crystal violet, the filtrate was evaporated to dryness and the residue was extracted with benzene or ethyl acetate. The extract was evaporated to dryness and the residue was crystallized from an appropriate solvent or separated by column chromatography.

Method A1. Appropriate starting compound (2 mmol) was dissolved in phosphoryl chloride (10 mL) and the mixture was heated under reflux for the time given in Table 2. After cooling, phosphoryl chloride was evaporated, the residue was mixed with crushed ice (100 g) and, after 10 min of stirring, the acidity was adjusted to pH 5 by successive addition of a solution of sodium hydroxide (10%). The precipitated product was filtered off with suction, washed with water, dried, and recrystallized from an appropriate solvent. In case when the product was of pasty consistence, the mixture was extracted with chloroform (three times, 30 mL each). After evaporation, the residue was crystallized from an appropriate solvent or column chromatographed. In all cases, the mother liquors were separated by column chromatography. Compounds **7** were isolated by the extraction of the chloroform solutions of crude reaction product or mother liquors with aqueous solution (6%) of sodium hydrogen carbonate. The aqueous extract was acidified with 5% hydrochloric acid and extracted with chloroform. The chloroform solution was dried, filtered, evaporated *in vacuo*, and crystallized to give product **7.**

Method B. The reaction was carried out analogously to Method A, but the addition of DMA was omitted.

3-Butyl-2,4-dichloroquinoline (4a). Compound was prepared from **1a**, **1h** (Method A1, Table 2), **2a** and **2d** (Method B, Table 1). Colorless crystals, mp 47–49°C (hexane); IR (KBr) v: 2961, 2924, 2858, 1571, 1557, 1482, 1466, 1454, 1384, 1367, 1328, 1303, 1277, 1219, 1149, 1141, 1087, 1048, 961, 916, 802, 764, 724, 707, 699, 598 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 255 (23), 254 (M^+, 5), 253 (36), 218 (8), 214 (13), 213 (18), 212 (65), 211 (28), 210 (100), 197 (7), 176 (22), 175 (9), 174 (31), 153 (8), 152 (11), 151 (5), 141 (7), 140 (46), 139 (10), 127 (10), 126 (11), 125 (8), 114 (16), 113 (18), 101 (6), 99 (8), 89 (6), 88 (8), 87 (9), 77 (7), 76 7), 75 12), 74 (6), 73 (6), 63 (18), 62 (7), 51 (9), 43 (21), 41 (25). Anal. Calcd. for $C_{13}H_{13}Cl_2N$: C, 61.43; H, 5.16; N, 5.51. Found: C, 61.28; H, 5.15; N, 5.55.

3-Benzyl-2,4-dichloroquinoline (4b). Compound was prepared from **1b** (Method A1, Table 2), **2b**, and **2e** (Method B, Table 1). Colorless crystals, mp 71–72°C (hexane); For **4b**, mp 72–73°C (ethanol) was referred [1]; For NMR see Table 3; EI-MS (*m/z*, %): 289 (14), 288 (5), 287 (22), 254 (6), 253 (6), 252 (19), 251 (9), 250 (7), 217 (25), 216 (100), 215 (9), 214 (13), 189 (8), 126 (13), 125 (6), 113 (6), 108 (27), 95 (15), 94 (6), 89 (6), 63 (11), 51 (11). Anal. Calcd. for $C_{16}H_{11}Cl_2N$: C, 66.69; H, 3.85; N, 4.86. Found: C, 66.75; H, 3.83; N, 4.89.

2,4-Dichloro-3-phenylquinoline (4c). Compound was prepared from **1c,f,g,i**, (Method A1, Table 2), **2c,f,g**, and **2i** (Method B, Table 1). Colorless crystals, mp 85–87°C (hexane); For **4c**, mp 90°C was referred [29]; For NMR see Table 3; EI-MS (*m/z*, %): 276 (11), 275 (69), 274 (18), 273 (100), 240 (15), 239 (9), 238 (45), 204 (10), 203 (60), 202 (26), 201 (19), 177 (9), 176 (27), 175 (17), 174 (7), 151 (11), 150 (13), 149 (7), 136 (10), 126 (6), 123 (5), 120 (9), 119 (24), 105 (5), 101 (23), 99 (11), 98 (8), 88 (45), 87 (20), 86 (7), 77 (9), 76 (9), 75 (26), 74 (15), 63 (11), 62 (9), 51 (19), 50 (11). Anal. Calcd. for $C_{15}H_9Cl_2N$: C, 65.72; H, 3.31; N, 5.11. Found: C, 65.91; H, 3.32; N, 5.14.

3-Butyl-4-chloro-1-methylquinolin-2-one (5d). Compound was prepared from **1d** (Method A, Table 2) in 93% yield. Colorless crystals, mp 67–70°C (hexane); IR (KBr) v: 3079, 3029, 2956, 2929, 2859, 1633, 1592, 1573, 1497, 1461, 1412, 1351, 1316, 1299, 1280, 1253, 1216, 1167, 1107, 1087, 1047, 1019, 943, 904, 812, 777, 753, 733, 662, 609, 593, 504 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 249 (M^+, 11), 234 (8), 222 (10), 221 (5), 220 (31), 215 (8), 214 (48), 209 (33), 208 (17), 207 (100), 206 (20), 179 (7), 178 (11), 172 (7), 144 (8), 143 (9), 142 (8), 140 (6), 128 (13), 116 (6), 115 (20), 102 (6), 101 (8), 89 (5), 77 (5). Anal. Calcd. for $C_{14}H_{16}ClNO$: C, 67.33; H, 6.46; N, 5.61. Found: C, 67.44; H, 6.46; N, 5.65.

3-Benzyl-4-chloro-1-methylquinolin-2-one (5e). Compound was prepared from **1e** in 41% yield besides **7e** (Method A1, Table 2). Colorless crystals, mp 133–138°C (benzene-ethyl acetate). For **5e**, mp 122°C (ligroin) was reported [16]; IR (KBr) v: 3059, 3026, 1638, 1613, 1591, 1567, 1492, 1453, 1349, 1333, 1314, 1290, 1211, 1091, 1047, 1027, 950, 937, 880, 849, 757, 736, 695, 645, 620, 592 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 285 (34), 284 (23), 283 (M^+, 100), 282 (12), 267 (10), 266 (25), 249 (14), 248 (77), 247 (19), 233 (12), 232 (16), 231 (10), 220 (7), 218 (10), 217 (7), 216 (6), 205 (7), 204 (16), 203 (8), 189 (5), 178 (7), 177 (5), 142 (10), 128 (5), 124 (34), 116 (6), 115 (13), 108 (9), 102 (13), 101 (9), 95 (6), 91 (11), 88 (7), 77 (7), 75 (6), 65 (8), 63 (7), 51 (6). Anal. Calcd. for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found C, 72.03; H, 4.93; N, 4.81.

4-Chloro-1-methyl-3-phenylquinolin-2-one (5f). Compound was prepared from **1f** in 57% yield besides **4c** and **7f** (Method A1, Table 2). Colorless crystals, mp 121–122°C (benzene-cyclohexane); For **5f**, mp 106°C (aqueous ethanol) was reported [15]; IR (KBr) v: 1630, 1608, 1560, 1586, 1567, 1496, 1458, 1444, 1330, 1313, 1239, 1062, 965, 844, 754, 745, 697, 668, 609, 524 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 271 (21), 270 (42), 269 (64), 268 (M^+, 100), 253 (6), 205 (6), 204 (12), 190 (8), 176 (6), 117 (25), 102 (13), 89 (6), 88 (9), 76 (5). Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.38; H, 4.51; N, 5.13.

4-Chloro-1-ethyl-3-phenylquinolin-2-one (5g). Compound was prepared from **1g** in 60% yield besides **4c** and **7g** (Method A1, Table 2). Colorless crystals, mp 124–125°C (benzene-cyclohexane); IR (KBr) v: 3050, 2984, 1635, 1609, 1601, 1587, 1564, 1488, 1452, 1374, 1337, 1309, 1294, 1216, 958, 921, 844, 818, 782, 752, 695, 662, 612 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 285 (20), 284 (31), 283 (M^+, 60), 282 (66), 257 (13), 256 (36), 255 (38), 254 (100), 238 (10), 220 (7), 219 (14), 205 (5), 204 (16), 203 (7), 191 (6), 190 (15), 176 (9), 165 (9), 164 (6), 163 (6), 110 (10), 102 (13), 96 (5), 89 (9), 88 (11), 75 (5), 63 (5). Anal. Calcd. for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.95; H, 4.98; N, 4.81.

1-Benzyl-3-butyl-4-chloroquinolin-2-one (5h). Compound was prepared from **1h** in 25% yield besides **4a** and **7h** (Method A1, Table 2). Colorless crystals, mp 77–79°C (hexane-cyclohexane); IR (KBr) v: 2955, 2925, 2859, 1634, 1614, 1593, 1567, 1492, 1462, 1425, 1320, 1129, 1076, 934, 754, 703, 649, 458 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 325 (M^+, 9), 290 (13), 285 (5), 283 (16), 194 (10), 192 (30), 92 (8), 91 (100), 65 (12). Anal. Calcd. for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19; N, 4.30. Found: C, 73.85; H, 6.20; N, 4.42.

1-Benzyl-4-chloro-3-phenylquinolin-2-one (5i). Compound was prepared from **1i** in 39% yield besides **4c** and **7i** (Method A1, Table 2). Colorless crystals, mp 197–199°C (benzene-cyclohexane); IR (KBr) v: 2956, 1635, 1608, 1600, 1588, 1565, 1489, 1453, 1444, 1312, 1064, 1028, 948, 906, 781, 757, 708, 694, 671, 662, 639, 535 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 347 (15), 346 (19), 345 (M^+, 44), 344 (32), 310 (12), 204 (16), 190 (5), 92 (8), 91 (100), 65 (16), 57 (5). Anal. Calcd. for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66; N, 4.05. Found: C, 76.54; H, 4.69; N, 3.94.

4-Chloro-3-methyl-1-phenylquinolin-2-one (5j). Compound was prepared from **1j** besides **7j** in 59% yield (Method A1, Table 2). Colorless crystals, mp 223–224°C (ethyl acetate); IR: 3069, 3056, 2923, 1645, 1613, 1593, 1567, 1491, 1452, 1351, 1322, 1296, 1216, 1121, 1020, 911, 767, 753, 696, 666, 513 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 271 (26), 270 (44), 269 (M^+, 79), 268 (100), 234 (7), 233 (5), 206 (6), 205 (8), 204 (23), 140 (12), 135 (6), 128 (9), 117 (9), 103 (8), 102 (36), 101 (12), 89 (7), 88 (7), 77 (20), 76 (6), 75 (6), 63 (7), 51 (16). Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.48; H, 4.48; N, 4.97.

3-Butyl-4-chloro-1-phenylquinolin-2-one (5k). Compound was prepared from **1k** in 65% yield (Method A1, Table 2). Colorless crystals, mp 98–99°C (hexane); IR (KBr), v: 2952, 2927, 2863, 1640, 1612, 1595, 1564, 1492, 1455, 1350, 1328, 1302, 1277, 1250, 1219, 1128, 1105, 1078, 1025, 977, 925, 908, 856, 813, 778, 753, 697, 671, 658, 631, 559, 518 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 311 (M^+, 8), 296 (11), 284 (10), 283 (7), 282 (29), 277 (16), 276 (78), 271 (33), 270 (37), 269 (100), 268 (65), 240 (9), 217 (7), 205 (10), 204 (34), 203 (6), 128 (5), 102 (9), 77 (17), 51 (10). Anal. Calcd. for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.37; H, 5.86; N, 4.71.

3-Benzyl-4-chloro-1-phenylquinolin-2-one (5l). Compound was prepared from **1l** in 36% yield besides **7l** (Method A1, Table 2). Colorless crystals, mp 170–173 °C (benzene-hexane). For **5l**, mp 146–148°C was reported [16]; IR (KBr), v: 3080, 3026, 3001, 2934, 1645, 1609, 1596, 1563, 1492, 1452, 1428, 1349, 1328, 1291, 1247, 1215, 1186, 1162, 1108, 1073, 1029, 977, 942, 923, 901, 880, 827, 773, 755, 745, 735, 696, 651, 623, 511, 584, 519 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 348 (8), 347 (36), 346 (M^+, 29), 345 (100), 344 (15), 328 (12), 311 (18), 310 (76), 309 (15), 308 (12), 280 (12), 266 (11), 232 (13), 218 (6), 217 (5), 216 (14), 205 (5), 204 (23), 203 (8), 173 (6), 155 (6), 139 (8), 134 (9), 91 (9), 77 (20), 51 (13). Anal. Calcd. for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66; N, 4.05. Found: C, 76.58; H, 4.71; N, 4.08.

1,3-Diphenyl-4-chloroquinolin-2-one (5m). Compound was prepared from **1m** in respective yields 80% (Method A1) or 79% (Method B, Table 2); Colorless crystals, mp 186–188°C (benzene-hexane); For **5m**, mp 164–166°C was reported [15]; IR (KBr) v: 1652, 1605, 1589, 1560, 1489, 1451, 1349, 1310, 1292, 1261, 1224, 1177, 1151, 1056, 1017, 970, 914, 898, 837, 806, 780, 763, 745, 734, 698, 671, 634, 606, 567, 521 cm^{-1}; For NMR see Table 3; EI-MS (*m/z*, %): 333 (25), 332 (M^+, 47), 331 (73), 330 (100), 268 (5), 267 (17), 266 (14), 265 (8), 195 (5), 165 (12), 164 (5), 148 (8), 134 (20), 133 (15), 121 (8), 77 (11), 51 (9). Anal. Calcd. for $C_{21}H_{14}ClNO$: C, 76.02; H, 4.25; N, 4.22. Found: C, 76.08; H, 4.21; N, 4.28.

General procedure for the preparation of dihydrogen phosphates 7 from 4-hydroxy-2-quinolones 1 (*Method C*). A stirred suspension of compound **1** (2 mmol) in pyridine (0.485 mL, 6 mmol) and acetonitrile (5 mL) was cooled to 0°C and phosphoryl chloride (0.92 g, 0.559 mL, 6 mmol) was added in one portion. The mixture was stirred at 0°C for 1 h and then warmed slowly to the room temperature. In most cases, the suspension changed into a turbid solution. After overnight stirring, water (1 mL) was added under cooling and the mixture was evaporated to dryness *in vacuo*. The residue was crushed with water (10 mL), the precipitate was filtered off, dried, and recrystallized from an appropriated solvent. In several cases (**7b, 7g**), the precipitate was purified by trituration with the solution of sodium hydrogen carbonate (6%); the solution was filtered, the filtrate was acidified with concentrated hydrochloric acid, the precipitate was filtered off and recrystallized from appropriate solvent. If the precipitate was of gummy or pasty character (**7d**), it was decanted three times with water, dried,

and recrystallized from an appropriate solvent or column chromatographed using solvent system S1 or S3. The mother liquors were extracted with ethyl acetate, the extract was dried, evaporated to dryness and column chromatographed using solvent system S3. The results are given in Table 4.

3-Butyl-1,2-dihydro-2-oxoquinolin-4-yl dihydrogen phosphate (7a). Compound was prepared from **1a** in 54% yield (Method C, Table 4); Colorless crystals, mp 226–230°C (benzene-DMF); IR (KBr) v: 2960, 2934, 2863, 2356br, 1649, 1606, 1526, 1467, 1449, 1331, 1274, 1220, 1187, 1127, 1071, 940, 886, 794, 755, 650, 625, 557, 459 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 217 (19), 202 (8), 200 10), 188 (26), 176 (11), 175 (100), 174 (38), 161 (14), 120 (21), 119 (9), 115 (5), 92 (18), 77 (14), 65 (11), 55 (23), 44 (10). ESI-MS (*m/z*, %): 615.1 $[2M–2H+Na]^-$ (5), 593.1 $[2M–H]^-$ (83), 495.2 $[2M–H–H_3PO_4]^-$ (24), 476 (24), 296.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{13}H_{16}NO_5P$: C, 52.53; H, 5.43; N, 4.71. Found: C, 52.57; H, 5.52; N, 4.88.

3-Benzyl-1,2-dihydro-2-oxoquinolin-4-yl dihydrogen phosphate (7b). Compound was prepared from **1b** in 49% yield (Method C, Table 4). Colorless crystals, mp 246–250°C (DMF-benzene); IR (KBr) v: 3427, 3067, 3030, 2948, 2799, 2362br, 1650, 1604, 1529, 1494, 1455, 1379, 1334, 1299, 1275, 1220, 1185, 1133, 1100, 944, 895, 788, 774, 759, 735, 702, 677, 650, 625, 556, 526 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 252 (18), 251 (100), 250 (26), 235 (6), 234 (32), 222 (7), 204 (8), 174 (8), 173 (6), 172 (7), 146 (18), 131 (23), 125 (10), 124 (5), 120 (16), 103 (13), 93 (6), 92 (18), 91 (25), 90 (8), 89 (7), 77 (22), 76 (7), 65 (16), 63 (7), 51 (11); ESI-MS (*m/z*, %): 683.1 $[2M–2H+Na]^-$ (5), 661.1 $[2M–H]^-$ (8), 563.2 $[2M–H–H_3PO_4]^-$ (88), 348.0 $[2M–H+H_2O]^-$ (56), 330.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{16}H_{14}NO_5P$: C, 58.01; H, 4.26; N, 4.23. Found: C, 57.85; H, 4.40; N, 4.37.

1,2-Dihydro-2-oxo-3-phenylquinolin-4-yl dihydrogen phosphate (7c). Compound was prepared from **1c** in 51% yield (Method C, Table 4); Colorless crystals, mp 245–255°C (DMF-benzene); IR (KBr) v: 2790, 2351br, 1674, 1607, 1537, 1502, 1447, 1366, 1334, 1287, 1127, 1110, 1074, 989, 938, 886, 863, 801, 760, 680, 651, 560, 500, 458 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 238 (16), 237 (99), 236 (100), 180 (8), 121 (7), 120 (92), 119 (9), 118 (6), 92 (44), 91 (7), 90 (10), 89 (9), 77 (16), 76 (10), 65 (23), 64 (7), 63 (11), 51 (7), 44 (21); ESI-MS (*m/z*, %): 655.1 $[2M–2H+Na]^-$ (28), 633.1 $[2M–H]^-$ (49), 535.1 $[2M–H–H_3PO_4]^-$ (7), 316.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{15}H_{12}NO_5P$: C, 56.79; H, 3.81; N, 4.42. Found: C, 56.72; H, 3.85; N, 4.47.

3-Butyl-1,2-dihydro-1-methyl-2-oxoquinolin-4-yl dihydrogen phosphate (7d). Compound was prepared from **1d** in 34% yield (Method C, Table 4). Colorless crystals, mp 162–170°C (water); IR (KBr) v: 3396br, 2965, 2930, 2878, 2716br, 2359br, 2329, 2208br, 1631, 1610, 1557, 1503, 1457, 1420, 1376, 1332, 1292, 1226, 1154, 118, 1100, 1085, 1057, 958, 880, 811, 785, 755, 743, 684, 614, 547, 521 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 231 (26), 216 (7), 214 (5), 203 (12), 202 (13), 190 (22), 189 (100), 188 (28), 186 (9), 160 (17), 146 (26), 145 (6), 136 (14), 135 (12), 134 (42), 133 (15), 132 (6), 131 (7), 128 (5), 127 (11), 126 (7), 125 (5), 119 (6), 118 (6), 117 (7), 114 (26), 112 (6), 106 (6), 104 (6), 99 (7), 97 (10), 96 (7), 91 (7), 84 (11), 83 (13), 82 (5), 79 (12), 77 (32), 72 (21), 71 (6), 70 (9), 69 (27), 68 (10), 67 (14), 63 (9), 60 (13), 59 (33), 57 (18), 55 (19), 53 (9), 45 (9), 43 (19), 41 (25), 40 (7); ESI-MS (*m/z*, %): 643.2 $[2M–2H+Na]^-$ (27), 621.2 $[2M–H]^-$ (37), 310.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{14}H_{18}NO_5P$: C, 54.02; H, 5.83; N, 4.50. Found: C, 54.22; H, 5.89; N, 4.56.

3-Benzyl-1,2-dihydro-1-methyl-2-oxoquinolin-4-yl dihydrogen phosphate hydrate (7e). Compound was prepared from **1e** in respective yields 3% (Method A1, Table 2) or 39% (Method C, Table 4). Colorless crystals, mp 170–185°C (water); IR (KBr) v: 3030, 2946, 2931, 2853, 2320br, 1631, 1611, 1577, 1495, 1461, 1418, 1373, 1330, 1222, 1181, 1101, 1030, 959, 898, 867, 787, 751, 704, 627, 583, 532 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 266 (14), 265 (73), 264 (18), 248 (20), 236 (6), 160 (12), 149 (35), 134 (11), 131 (14), 128 (9), 127 (12), 126 (18), 125 (10), 124 (7), 123 (9), 115 (7), 114 (15), 113 (9), 112 (17), 111 (17), 110 (9), 109 (13), 104 (16), 103 (10), 100 (7), 99 (11), 98 (16), 97 (28), 96 (14), 95 (18), 91 (17), 86 (12), 85 (17), 84 (13), 83 (32), 82 (13), 81 (20), 77 (16), 74 (57), 73 (15), 72 (80), 71 (35), 70 (18), 69 (53), 68 (11), 67 (22), 60 (24), 59 (100), 58 (6), 57 (58), 56 (18), 55 (64), 54 (9), 45 (8), 44 (15), 43 (78), 42 (13), 41 (58); ESI-MS (*m/z*, %): 711.1 $[2M–2H+Na]^-$ (13), 689.2 $[2M–H]^-$ (29), 591.2 $[2M–H–H_3PO_4]^-$ (5), 344.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{17}H_{18}NO_6P$: C, 56.20; H, 4.99; N, 3.86. Found: C, 56.39; H, 4.89; N, 3.72.

1,2-Dihydro-1-methyl-2-oxo-3-phenylquinolin-4-yl dihydrogen phosphate hydrate (7f). Compound was prepared from **1f** in respective yields 2% (Method A1, Table 2), or 48% (Method C, Table 4). Colorless crystals, mp 212–217°C (water); IR (KBr) v: 3642, 3313, 3198, 3083, 3057, 3034, 2948, 2660br, 2178br, 1629, 1590, 1574, 1450, 1460, 1418, 1367, 1285, 1237, 1142, 1103, 960, 882, 850, 805, 774, 754, 699, 683, 629, 563, 554, 493 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 251 (34), 250 (36), 162 (7), 155 (6), 139 (9), 134 (18), 127 (12), 125 (20), 111 (28), 105 (20), 97 (40), 96 (16), 95 (23), 85 (43), 71 (62), 57 (80), 43 (100); ESI-MS (*m/z*, %): 683.1 $[2M–2H+Na]^-$ (24), 661.1 $[2M–H]^-$ (41), 330.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{16}H_{16}NO_6P$: C, 55.02; H, 4.62; N, 4.01. Found: C, 54.86; H, 4.66; N, 4.11.

1,2-Dihydro-1-ethyl-2-oxo-3-phenylquinolin-4-yl dihydrogen phosphate hydrate (7g). Compound was prepared from **1g** in respective yields 3% (Method A1, Table 2) or 34% (Method C, Table 4). Colorless crystals, mp 150–160°C (water); IR (KBr) v: 3584, 3324, 3051, 2978, 2936, 2875, 2560, 2260br, 1640, 1620, 1606, 1593, 1499, 1456, 1368, 1305, 1222, 1144, 1113, 1085, 1040, 979, 884, 847, 819, 780, 753, 702, 681, 633, 533, 505 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 266 (16), 265 (88), 264 (82), 238 (6), 237 (55), 236 (100), 180 (7), 146 (10), 132 (10), 130 (16), 120 (39), 118 (10), 92 (11), 91 (15), 90 (8), 89 (6), 77 (30), 76 (8), 65 (8), 63 (6), 44 (24); ESI-MS (*m/z*, %): 711.1 $[2M–2H+Na]^-$ (12), 689.1 $[2M–H]^-$ (67), 641.2 $[2M–H–48]^-$ (17), 344.1 $[M–H]^-$ (100), 296.1 $[M–H–48]^-$ (11). Anal. Calcd. for $C_{17}H_{18}NO_6P$: C, 56.20; H, 4.99; N, 3.86. Found: C, 56.10; H, 4.99; N, 3.85.

1-Benzyl-3-butyl-1,2-dihydro-2-oxoquinolin-4-yl dihydrogen phosphate (7h). Compound was prepared from **1h** in 28% yield besides **4a** and **5h** (Method A1, Table 2) or 37% (Method C, Table 4). Colorless crystals, mp 220–225°C (ethyl acetate); IR (KBr) v: 3450, 3064, 3030, 2964, 2928, 2861, 2679, 2321, 2190, 1625, 1607, 1526, 1499, 1455, 1444, 1383, 1334, 1259, 1229, 1207, 1181, 1145, 1114, 1044, 1019, 959, 877, 799, 763, 734, 699, 648, 577, 552, 526 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 307 (20), 278 (5), 265 (26), 264 (9), 174 (37), 132 (5), 92 (9), 91 (100), 65 (10); ESI-MS (*m/z*, %): 795.2 $[2M–2H+Na]^-$ (10), 773.2 $[2M–H]^-$ (12), 386.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{20}H_{22}NO_5P$: C, 62.01; H, 5.72; N, 3.62. Found: C, 61.88; H, 5.67; N, 3.40.

1-Benzyl-1,2-dihydro-2-oxo-3-phenylquinolin-4-yl dihydrogen phosphate (7i). Compound was prepared from **1i** in 4% yield besides **4c** and **5i** (Method A1, Table 2) or 32% (Method C, Table 4). Colorless crystals, mp 235–247 °C (water); IR (KBr) v: 3057, 3032, 2971, 2944, 2360br, 2340br, 1642, 1597, 1573, 1496, 1453, 1437, 1357, 1314, 1299, 1247, 1161, 1125, 1078, 1034, 971, 951,

880, 855, 823, 805, 766, 741, 731, 703, 644, 605, 557, 535, 516, 501 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 327 (63), 326 (52), 236 (8), 220 (18), 152 (5), 91 (100), 77 (10), 65 (14), 46 (15), 45 (14), 44 (26); ESI-MS (*m/z*, %): 835.1 $[2M–2H+Na]^-$ (8), 813.2 $[2M–H]^-$ (24), 406.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{22}H_{18}NO_5P$: C, 64.87; H, 4.45; N 3.44; Found: C, 64.81; H, 4.51; N, 3.58.

1,2-Dihydro-3-methyl-2-oxo-1-phenylquinolin-4-yl dihydrogen phosphate (7j). Compound was prepared from **1j** besides **5j** in 5% yield (Method A1, Table 2) or 64% (Method C, Table 4). Colorless crystals, mp 242–247°C (ethyl acetate); IR (KBr) v: 2956, 2927, 2361, 2332br, 1633, 1596, 1552, 1492, 1459, 1387, 1366, 1343, 1313, 1249, 1223, 1168, 1157, 1141, 1108, 1043, 957, 844, 783, 756, 695, 683, 642, 569, 520 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 252 (17), 251 (100), 250 (90), 222 (9), 196 (11), 195 (34), 194 (9), 167 (27), 166 (12), 146 (11), 140 (6), 139 (7), 92 (9), 91 (7), 83 (9), 77 (23), 51 (14); ESI-MS (*m/z*, %): 683.1 $[2M–2H+Na]^-$ (12), 661.1 $[2M–H]^-$ (7), 563.2 $[2M–H–H_3PO_4]^-$ (13), 510.1 (23), 330.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{16}H_{14}NO_5P$: C, 58.01; H, 4.26; N, 4.23. Found: C, 58.21; H, 4.33; N, 4.17.

3-Butyl-1,2-dihydro-2-oxo-1-phenylquinolin-4-yl dihydrogen phosphate hydrate (7k). Compound was prepared from **1k** in 22% yield besides **5k** (Method A, Table 2) or 56% (Method C, Table 4). Colorless crystals, mp 232–237°C (ethyl acetate); IR (KBr) v: 3426br, 3083, 3065, 2958, 2937, 2920, 2876, 2830, 2668br, 2333br, 1621, 1499, 1457, 1437, 1378, 1349, 1334, 1316, 1288, 1266, 1251, 1228, 1202, 1161, 1110, 1075, 1052, 971, 952, 852, 804, 788, 772, 762, 748, 738, 697, 685, 676, 643, 568, 558, 525 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 293 (16), 278 (10), 276 (11), 265 (7), 264 (32), 252 (17), 251 (100), 250 (60), 237 (9), 196 (16), 195 (11), 168 (7), 167 (9), 166 (6), 77 (16), 51 (6), 44 (7); ESI-MS (*m/z*, %): 767.2 $[2M–2H+Na]^-$ (13), 745.2 $[2M–H]^-$ (10), 647.3 $[2M–H–H_3PO_4]^-$ (33), 372.1 $[M–H]^-$ (100). Anal. Calcd. for $C_{19}H_{22}NO_6P$: C, 58.31; H, 5.67; N, 3.58. Found: C, 58.11; H, 5.45; N, 3.40.

3-Benzyl-1,2-dihydro-2-oxo-1-phenylquinolin-4-yl dihydrogen phosphate hydrate (7l). Compound was prepared from **1l** in 32% yield besides **5l** (Method A1, Table 2) or 83% (Method C, Table 4). Colorless crystals, mp 178–182°C (DMF-benzene); IR (KBr) v: 3430br, 3083, 3026, 2975, 2934, 2802br, 2359br, 1643, 1599, 1570, 1494, 1457, 1372, 1326, 1305, 1263, 1226, 1158, 1090, 1048, 1021, 969, 956, 931, 820, 769, 756, 743, 705, 686, 643, 598, 570, 562, 545, 521 cm^{-1}; For NMR spectra see Table 5; EI-MS (*m/z*, %): 328 (24), 327 (100), 326 (26), 310 (17), 250 (5), 248 (12), 222 (17), 196 (17), 195 (11), 167 (14), 166 (7), 131 (9), 103 (8), 92 (5), 91 (13), 77 (20), 51 (8), 44 (7); ESI-MS (*m/z*, %): 835.2 $[2M–2H+Na]^-$ (11), 813.2 $[2M–H]^-$ (8), 715.3 $[2M–H–H_3PO_4]^-$ (13), 406.2 $[M–H]^-$ (100). Anal. Calcd. for $C_{22}H_{20}NO_6P$: C, 62.12; H, 4.74; N, 3.29. Found: C, 62.11; H, 4.86; N, 3.47.

1,2-Dihydro-1,3-diphenyl-2-oxo-quinolin-4-yl dihydrogen phosphate (7m). Compound was prepared from **1m** in 78% yield (Method C, Table 4). Colorless crystals, mp 177–181°C (DMF-benzene); IR (KBr) v: 3410br, 3132, 3096, 3065, 2840br, 1636, 1596, 1568, 1526, 1494, 1454, 1363, 1316, 1268, 1230, 1194, 1166, 1143, 1099, 1073, 1023, 963, 869, 824, 802, 787, 758, 700, 682, 641, 608, 576, 554, 522 cm^{-1}; For NMR spectra see Table 5; EI-MS (*m/z*, %): 314 (19), 313 (91), 312 (100), 256 (5), 196 (35), 195 (23), 167 (27), 166 (7), 157 (6), 152 (5), 139 (6), 127 (8), 105 (9), 89 (6), 77 (18), 51 (10), 46 (11), 45 (14), 44 (15); ESI-MS (*m/z*, %): 807.2 $[2M–2H+Na]^-$ (22), 785.2 $[2M–H]^-$ (11), 687.3 $[2M–H–H_3PO_4]^-$ (74), 392.2 $[M–H]^-$ (100). Anal. Calcd. for $C_{21}H_{16}NO_5P$: C, 64.13; H, 4.10; N, 3.56. Found: C, 63.91; H, 4.25; N, 3.53.

Isolation of crystal violet.

A. Chloroform extracts obtained using the Method A were filtered through a short column of silica gel. The adsorbed blue compound was obtained by washing of the column with ethanol, evaporating the filtrate to dryness and crystallization of the residue from ethanol. In all cases, crystal violet, identical to the authentic sample, was obtained in yields of 10–20%.

B. The mixture of DMA (5 mL, 39.4 mmol) and phosphoryl chloride (50 mL) was heated to reflux for 20 h. The reaction mixture was cooled, poured onto ice (100 g) and the mixture was extracted with chloroform. After drying and evaporation of the extract, the residue was crystallized from ethanol. Blue crystals of mp 202–204°C (dec.), whose IR and ^1H NMR spectra were identical to those of crystal violet ($C_{25}H_{30}N_3Cl$, MW 407.98) [24] were obtained in 64% yield. For commercial crystal violet (Aldrich), mp 205°C (dec.) is presented; EI-MS (*m/z*, %): 374 (13), 373 (47), 372 (16), 254 (21), 253 (100), 252 (68), 238 (7), 237 (26), 208 (8), 186 (10), 126 (18), 118 (6), 18 (8).

Reactions of compounds 2 with some nucleophiles.

A. A solution of 2-sulfanylbenzothiazol (334.5 mg, 2 mmol) and **2f** (571.5 mg, 2 mmol) in chloroform (50 mL) was stirred at room temperature for 2 h and subsequently heated to reflux for 3 h. After cooling, the mixture was evaporated to dryness and the residue was column chromatographed. 4-Hydroxy-1-methyl-3-phenyl-2-quinolone (**1f**), (382 mg, 76%) of mp 223–225°C (ethanol) and 2,2′-dithiobis(benzothiazole) (256 mg, 77%) of mp 177–178°C (benzene) were obtained. Both compounds were identical in all respects to the authentic specimens [22].

B. A solution of 2,5-dimethylaniline (121 mg, 1 mmol) and **2f** (285.7 mg, 1 mmol) in chloroform (25 mL) was stirred at room temperature for 1 h and subsequently heated to reflux for 6 h. After cooling, deposited 2,5-dimethylaniline hydrochloride (31%) was filtered with suction. The filtrate was evaporated to dryness and column chromatographed on silica gel. Besides starting compound **2f** (42%), 3-(2,5-dimethylphenylamino)-1-methyl-3-phenylquinoline-2,4(1*H*,3*H*)-dione (**6f**) was obtained in 31% yield. Colorless crystals, mp 202–210°C (benzene-hexane); IR (KBr) v: 3409, 3055, 3021, 2937, 2916, 2859, 1704, 1664, 1599, 1585, 1519, 1493, 1471, 1447, 1420, 1354, 1305, 1296, 1189, 1169, 1133, 1105, 1056, 1037, 1001, 914, 792, 765, 745, 735, 717, 699, 651, 588, 545, 529 cm^{-1}; For NMR see Table 5; EI-MS (*m/z*, %): 371 (7), 370 (M^+, 24), 337 (5), 222 (13), 209 (13), 208 (73), 194 (5), 193 (7), 126 (13), 120 (14), 114 (17), 112 (11), 105 (13), 104 (11), 103 (7), 98 (11), 97 (13), 96 (7), 95 (10), 91 (6), 86 (9), 84 (5), 83 (16), 82 (6), 81 (11), 79 (12), 77 (16), 74 (29), 73 (7), 72 (64), 71 (7), 70 (7), 69 (29), 67 (14), 60 (20), 59 (100), 57 (18), 56 (10), 55 (47), 54 (8), 44 (14), 43 (35), 41 (34). Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.52; H, 6.04; N, 7.48.

C. A solution of DMA (121 mg, 1 mmol) and compound **2** (1 mmol) in corresponding solvent (25 mL) was stirred at room temperature for 1 h and subsequently heated to reflux for 4.5 h. After cooling, the solution was evaporated to dryness and column chromatographed on silica gel. In all cases, besides the starting compound, only compounds **1** were isolated from the complex reaction mixture in the following yields: (a) in chloroform: **1f** (37%); (b) in acetic acid: **1c** (81%); (c) in ethanol: **1c** (12%); d) in toluene: **1f** (6%).

Conversion of compounds 7 to 1.

A. A solution of **7m** (50 mg) in 3% solution of potassium carbonate (5 mL) was stirred at 100°C for 4.5 h. After cooling and acidification with concentrated hydrochloric acid, the precipitate was filtered off with suction, washed with water and dried. 1,3-Diphenyl-4-hydroxyquinolin-2-one (**1m**), mp 231–234°C, identical in all respect to the authentic sample, was isolated in 41% yield.
B. A solution of **7m** (101 mg) in acetic acid (10 mL) was heated to reflux for 2.5 h. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol. Colorless crystals, mp 232–234°C (ethanol), identical in all respects to **1m**, were isolated in 30% yield.

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PŘÍLOHA VI

Pinacol Rearrangement of 3,4-Dihydro-3,4-dihydroxyquinolin-2(1*H*)-ones: An Alternative Pathway to Viridicatin Alkaloids and Their Analogs

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Dedicated to Prof. *Vojeslav Štěrba* on the occasion of his 90th birthday

3-Alkyl/aryl-3-hydroxyquinoline-2,4-diones were reduced with $NaBH_4$ to give *cis*-3-alkyl/aryl-3,4-dihydro-3,4-dihydroxyquinolin-2(1*H*)-ones. These compounds were subjected to pinacol rearrangement by treatment with concentrated H_2SO_4, resulting in 4-alkyl/aryl-3-hydroxyquinolin-2(1*H*)-ones. When a benzyl (Bn) group was present in position 3 of the starting compound, its elimination occurred during the rearrangement, and the corresponding 3-hydroxyquinolin-2(1*H*)-one was formed. The reaction mechanisms are discussed for all transformations. All compounds were characterized by IR, ^{1}H- and ^{13}C-NMR spectroscopy, as well as mass spectrometry.

Introduction. – 3-Hydroxyquinoline-2,4-diones **2** are known as metabolites of some *Pseudomonas* species [1][2]. These compounds are available by several pathways: the photooxidation of 4-hydroxyquinolin-2(1*H*)-ones **1** [3], the oxidation of 4-hydroxyquinolin-2(1*H*)-ones with peroxy acids [1][4], or the reaction of the quinisatines and/or their hydrates and aminals with phenols [5][6]. We studied, the reaction of **2** with ethyl (triphenylphosphoranylidene)acetate to give (*E*)-4-[(ethoxycarbonyl)methylidene]-3-hydroxy-1,2,3,4-tetrahydroquinolin-2-ones and 2,3a,4,5-tetrahydrofuro[2,3-*c*]quinoline-2,4-diones was studied [7][8]. The same reaction with 3,5,8-trisubstituted starting compounds afforded, *via* a molecular rearrangement of **2**, 1,3-dihydro-3-phenylacetoxy-2*H*-indol-2-ones [9]. 3-Acyloxy-1,3-dihydro-2*H*-indole-2-ones and isomeric 4-acyl-1,4-dihydro-3,1-benzoxazin-2-ones were obtained by the double rearrangement of **2** in boiling xylene in the presence of 4-(dimethylamino)-pyridine (DMAP) or Ph_3P as a catalyst [10], or by the thermally induced rearrangement of **2** in boiling cyclohexylbenzene [11]. The rearrangement of compounds **2** also proceeded in aqueous KOH with the formation of 2-hydroxyindoxyls and/or dioxindoles [12].

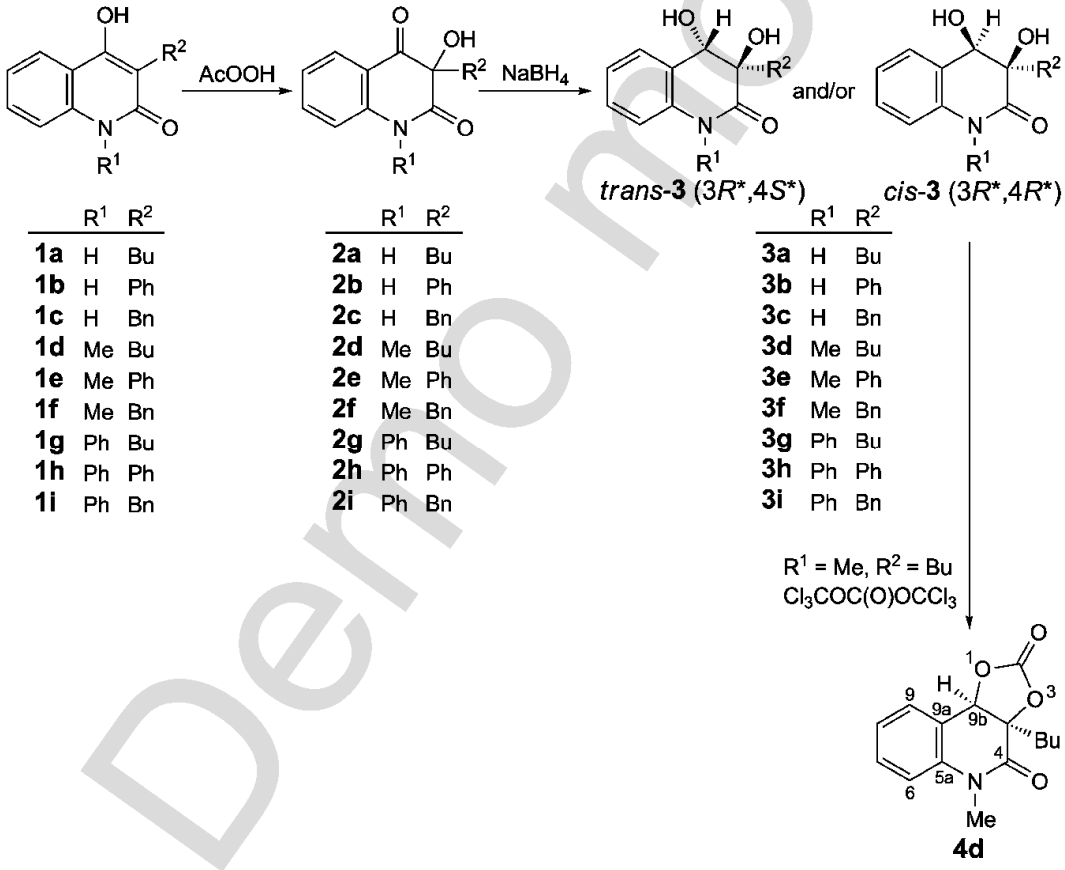
Our results revealed that 3-hydroxyquinoline-2,4-diones **2** are very reactive compounds, prone to the molecular rearrangements that result in the formation of new heterocyclic compounds. The chemistry of **2** inspired us to attempt at their reduction to the corresponding diols, which should also be suitable compounds to study molecular rearrangements. Herein, we report the validity of that presumption, and that

novel and interesting compounds, including quinoline alkaloids, can be prepared in this way.

Results and Discussion. – We have found only two examples of the reduction of 3-hydroxyquinoline-2,4-diones **2** in the literature. *Podesva et al.* [13] prepared 6-chloro-3,4-dihydro-3,4-dihydroxy-1-methyl-3-phenylquinolin-2(1*H*)-one by the reduction of the corresponding 3-hydroxyquinoline-2,4-dione with $NaBH_4$, and *Kappe et al.* [5] prepared 3,4-dihydro-3,4-dihydroxy-3-(pyridin-2-yl)methylquinolin-2(1*H*)-one by the hydrogenation of the corresponding 3-hydroxyquinoline-2,4-dione in the presence of a Pd/C catalyst. In both cases, the configuration of the product was not described. For our experiments, we chose $NaBH_4$ as the reducing agent. The starting 3-hydroxyquinoline-2,4-diones **2a**–**2i** were prepared by oxidation of the corresponding 4-hydroxyquinolin-2(1*H*)-ones **1** with AcOOH according to a well-known protocol [7]. To determine the influence of the R^2 substituent on the transformation of compounds **2**, we chose Bu, Ph, and Bn groups. The H-atom, and the Me and Ph groups were selected as the R^1 substituent.

The results of the reduction of compounds **2** with $NaBH_4$ are compiled in *Table 1*. In principle, four stereoisomers, *i.e.*, two pairs of diastereoisomers, *trans*-**3** and *cis*-**3**, should form from the reduction (*Scheme 1*). However, all the reduction products **3a**–**3i**

Scheme 1



	R^1	R^2
1a	H	Bu
1b	H	Ph
1c	H	Bn
1d	Me	Bu
1e	Me	Ph
1f	Me	Bn
1g	Ph	Bu
1h	Ph	Ph
1i	Ph	Bn

	R^1	R^2
2a	H	Bu
2b	H	Ph
2c	H	Bn
2d	Me	Bu
2e	Me	Ph
2f	Me	Bn
2g	Ph	Bu
2h	Ph	Ph
2i	Ph	Bn

	R^1	R^2
3a	H	Bu
3b	H	Ph
3c	H	Bn
3d	Me	Bu
3e	Me	Ph
3f	Me	Bn
3g	Ph	Bu
3h	Ph	Ph
3i	Ph	Bn

Table 1. *The Results of the Reduction of Compounds* **2a**–**2i**

Entry	Starting compound	R^1	R^2	Product (Yield [%])[a])
1	**2a**	H	Bu	*cis*-**3a** (79)
2	**2b**	H	Ph	*cis*-**3b** (88)
3	**2c**	H	Bn	*cis*-**3c** (74)
4	**2d**	Me	Bu	*cis*-**3d** (64)
5	**2e**	Me	Ph	*cis*-**3e** (77)
6	**2f**	Me	Bn	*cis*-**3f** (75)
7	**2g**	Ph	Bu	*cis*-**3g** (83)
8	**2h**	Ph	Ph	*cis*-**3h** (93)
9	**2i**	Ph	Bn	*cis*-**3i** (83)

[a]) The yields of pure recrystallized compounds are given.

exhibited only one TLC spot in several solvent systems. In the NMR spectra of the reaction products (*Table 2*), only one set of signals was observed, indicating that the reaction proceeded with high diastereoselectivity to give only one of the possible two diastereoisomers.

The assignment of the ^{1}H- and ^{13}C-NMR chemical shifts of compounds **3** followed from the analysis of 1D- and 2D-NMR (COSY, NOESY, HMQC, and gs-HMBC) experiments. The differentiation of the resonance of the OH group was based on the presenece of a ^3J(C(4)H,C(4)OH) coupling, with a value of 4.8 ± 0.5 Hz in the ^{1}H-NMR spectra, while the OH group at C(3) appeared as a *singlet*. The NOESY spectra of compounds **3** were recorded with the aim of determining the mutual orientation of the substituents at C(3) and C(4). The results strongly supported a through-space proximity of both OH groups, as well as the proximity of H–C(4) with suitable H-atoms of the R^2 substituent due to the appearance of appropriate cross-peaks in the NOESY spectra. However, because the compounds **3** were not completely rigid, the dynamic behavior of the substituents on C(3) and C(4) (certain rotamers) resulted in some additional cross-peaks. The ^{1}H and ^{13}C chemical shifts of compounds **3** are collected in *Table 2*.

Thus, it was possible to differentiate between the possible diastereoisomers *trans* and *cis* with NMR spectra. However, we decided to prepare a cyclic carbonate of one of the reaction products by its reaction with triphosgene (= bis(trichloromethyl) carbonate). From *cis*-**3d**, carbonate **4d** was prepared, which is convincingly indicative of the *cis*-configuration of the OH groups in **3d**. In the ^{1}H-NMR spectrum of **4d**, no OH group signals appeared, while a new resonance was detected in the ^{13}C-NMR spectrum of this compound, ascribed to a C(3)–O–C(=O)–O–C(4) fragment, resonating at 153.2 ppm (*Table 2*).

The ESI-MS experiments of compounds *cis*-**3** were carried out in the positive-ion mode. Typically, signals at *m/z* corresponding to $[M+H]^+$, as well as $[M+Na]^+$ and $[M+K]^+$ were observed for all of the examined structures (except the $[M+H]^+$ ion for *cis*-**3b**). These signals were accompanied by several types of higher associates, namely the singly charged Na^+ adduct of the dimer $[2M+Na]^+$ and the doubly charged Ca^{2+} adduct of the trimer $[3M+Ca]^{2+}$. In addition, the doubly charged Ca^{2+} adduct of the dimer $[2M+Ca]^{2+}$ was determined in the first-order ESI mass spectra of *cis*-**3c**, *cis*-**3f**,

Table 2. *^{1}H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds cis-***3** *and* **4d** (δ in ppm)

Position	*cis*-**3a**		*cis*-**3b**		*cis*-**3c**		*cis*-**3d**		*cis*-**3e**		*cis*-**3f**		*cis*-**3g**		*cis*-**3h**		*cis*-**3i**		**4d**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	172.6	–	171.1	–	171.6	–	171.8	–	171.7	–	170.9	–	171.9	–	171.6	–	171.0	–	153.2
3	–	74.8	–	77.2	–	74.6	–	74.8	–	77.5	–	74.9	–	75.3	–	77.6	–	75.1	–	–
3-OH	5.59	–	6.02	–	5.30	–	5.16	–	6.10	–	5.33	–	5.36	–	6.28	–	5.62	–	–	–
3a											–	–	–	–	–	–	–	–	–	83.2
4	4.62	71.8	4.92	73.1	4.31	70.8	4.62	71.0	4.95	72.1	4.35	70.2	4.81	71.2	5.17	72.4	4.50	70.4	–	164.9
4-OH	5.09	–	5.93	–	5.69	–	5.67	–	6.07	–	5.81	–	5.81	–	6.19	–	5.96	–	–	–
4a	–	127.4	–	127.4	–	126.9	–	128.7	–	128.6	–	128.2	–	128.4	–	128.5	–	128.0	–	–
5	7.38	126.8	7.30	125.9	7.23	126.0	7.45	126.5	7.34	125.3	7.32	127.6	7.49	127.1	7.42	125.9	7.38	126.2	–	–
5a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	137.8
6	7.01	122.1	7.00	122.6	6.98	122.0	7.11	122.8	7.07	123.2	7.08	122.7	7.09	122.9	7.05	123.3	7.05	122.8	7.40	116.6
7	7.21	128.0	7.23	128.1	7.21	128.2	7.32	128.2	7.32	128.1	7.34	128.4	7.14	128.2	7.14	127.9	7.14	128.1	7.53	129.4
8	6.86	114.5	6.97	114.7	6.89	114.7	7.13	114.3	7.20	114.4	7.10	114.4	6.21	115.6	6.29	115.7	6.23	115.9	7.29	124.1
8a	–	135.9	–	138.9	–	136.5	–	138.1	–	138.7	–	138.4	–	139.1	–	138.7	–	139.5	–	–
9	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7.40	121.7
9a	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	121.9
9b	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6.19	78.4
Substituent at N(1)																				
1	10.15	–	10.59	–	10.23	–	3.32	29.6	3.46	29.9	3.31	29.6	–	138.7	–	138.7	–	138.8	3.37	29.8
2,6	–	–	–	–	–	–	–	–	–	–	–	–	7.24	129.2	7.25	129.1	7.24	129.1	–	–
3,5	–	–	–	–	–	–	–	–	–	–	–	–	7.60	130.0	7.64	130.1	7.60	129.9	–	–
4	–	–	–	–	–	–	–	–	–	–	–	–	7.50	127.9	7.55	128.5	7.50	128.0	–	–
Substituent at C(3)																				
1	1.70	30.1	–	135.6	3.05	36.6	1.68	30.4	–	137.7	3.02	37.3	1.81	30.3	–	138.4	3.13	37.2	1.52	28.5
	1.39	–	–	–	2.97	–	1.39	–	–	–	2.96	–	1.56	–	–	–	3.07	–	1.30	–
2	1.41	24.6	7.37	127.5	–	137.0	1.39	24.6	7.24	127.7	–	136.8	1.50	24.7	7.47	127.8	–	136.8	1.34	24.6
	1.18	–	–	–	–	–	1.18	–	–	–	–	–	1.26	–	–	–	–	–	1.17	–
3,7	1.22	22.9	7.21	127.2	7.27	130.9	1.21	22.8	7.17	127.1	7.18	130.8	1.26	22.9	7.40	127.3	7.31	130.9	1.17	22.0
4,6	0.86	14.2	7.21	127.2	7.27	127.6	0.84	14.1	7.17	127.3	7.25	127.5	0.89	14.2	7.25	127.4	7.61	127.7	0.78	13.7
5	–	–	–	–	7.27	127.8	–	–	–	–	7.22	127.6	–	–	–	–	7.26	127.7	–	–

and *cis*-**3i** bearing a Bn group at C(3). The fragmentation (MS/MS) of the $[M+H]^+$ ion under collision-induced dissociation (CID) conditions led in all cases to the loss of a H_2O molecule. Further fragmentation (MS^3) of the $[M+H-H_2O]^+$ ion was considerably affected by the R^2 substituent at C(3). In the MS^3 of compounds *cis*-**3a**, *cis*-**3d**, and *cis*-**3g** ($R^2=Bu$), three signals originating from consecutive losses of CO and two $CH_2{=}CH_2$ molecules were observed. When a Ph group was present at C(3) (*cis*-**3b**, *cis*-**3e**, and *cis*-**3h**), only the loss of CO (*m/z* 28) occurred. Finally, in the MS^3 of compounds *cis*-**3c**, *cis*-**3f**, and *cis*-**3i** ($R^2=Bn$), two signals, assigned to $[M+H-H_2O-CO]^+$ and Bn^+ (*m/z* 91), were observed.

Only two compounds **3** were reported in the literature [5][13], but neither their configuration nor biological activity were. However, from *Penicilium janczewskii*, two diastereoisomeric alkaloids were isolated, differing from *cis*-**3b** only by the presence of the 4-methoxyphenyl group at C(4) and the H-atom at C(3). These alkaloids showed low-to-moderate cytotoxic activities against various human tumor cell lines, but significantly stronger cytotoxicities against SKOV-3 cells (human ovary adenocarcinoma) [14].

Compounds *cis*-**3** are vicinal diols that are easily liable to the pinacol rearrangement [15–17] under acid catalysis. To perform the rearrangement of compounds *cis*-**3**, we used concentrated H_2SO_4.

The rearrangement of diols *cis*-**3a**, *cis*-**3b**, *cis*-**3d**, *cis*-**3e**, *cis*-**3g**, and *cis*-**3h** took place quickly and, with the exception of *cis*-**3g**, only a single product was obtained (*Table 3*). The IR spectrum of the products exhibited strong absorption bands characteristic of a OH group in the region of 3251–3436 cm^{-1}, and an amide group in the region of 1643–1685 cm^{-1}, but it did not exhibit any absorption bands in the aldehyde or ketone region.

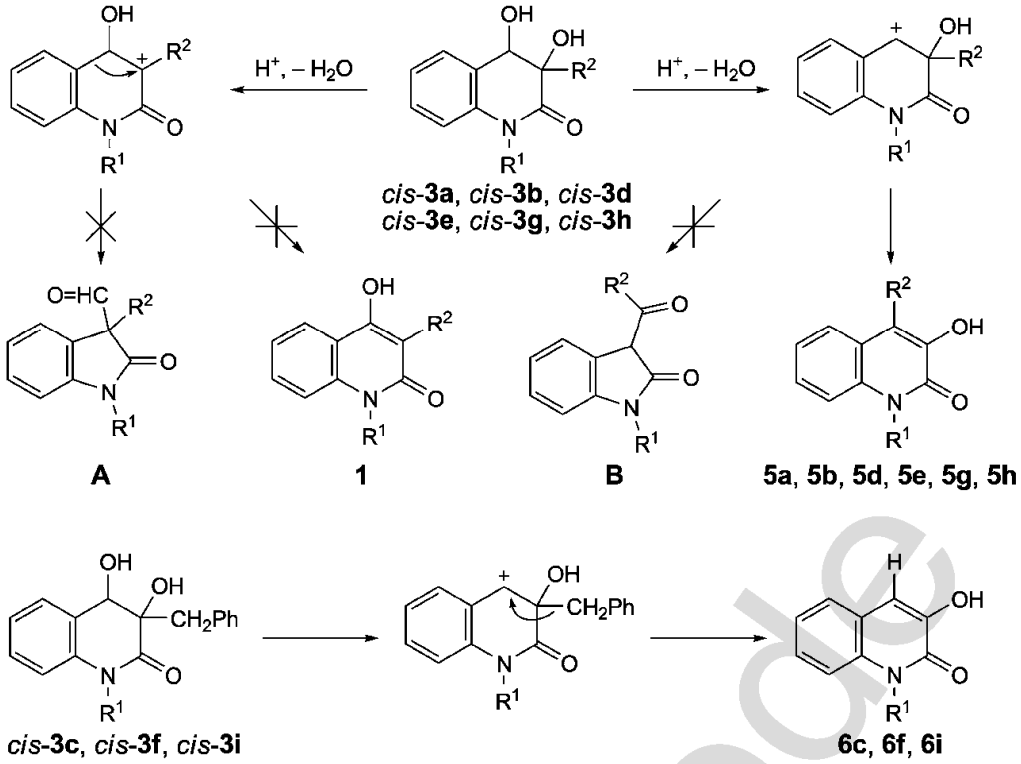
Table 3. *The Results of the Rearrangement of Compounds cis*-**3**

Entry	Starting compound	R^1	R^2	Product (Yield [%])[a])
1	*cis*-**3a**	H	Bu	**5a** (71)
2	*cis*-**3b**	H	Ph	**5b** (85)
3	*cis*-**3c**	H	Bn	**6c** (59)
4	*cis*-**3d**	Me	Bu	**5d** (72)
5	*cis*-**3e**	Me	Ph	**5e** (93)
6	*cis*-**3f**	Me	Bn	**6f** (63)
7	*cis*-**3g**	Ph	Bu	**5g** (61), **1g** (9)[b])
8	*cis*-**3h**	Ph	Ph	**5h** (65)
9	*cis*-**3i**	Ph	Bn	**6i** (58)

[a]) The yields of pure recrystallized compounds. [b]) Identical in all respects to the authentic sample.

Four compounds may be produced during the rearrangement of compounds *cis*-**3** (*Scheme 2*). The structures **A**, **B**, and **1** can be excluded, because they are not in accordance with the IR spectra of the products. The remaining structure **5** is, therefore, plausible as the structure of the products of the pinacol rearrangement of compounds *cis*-**3**. This result indicates that the elimination of H_2O from C(4) of the protonated *cis*-**3** results in the formation of a secondary carbocation securing the aromatic ring, which

Scheme 2



contributes to the delocalization of the positive charge (benzylic cation). The following 1,2-shift of the alkyl or aryl group from C(3) provides a tertiary carbocation which, after the deprotonation, gives compound **5**. It is interesting that also compounds *cis*-**3b**, **3e**, and **3h** with Ph substituents at C(3), which should be able to create a carbocation at C(3), also react to give products **5**. From this viewpoint, it is surprising that the isomeric side product **1g** was isolated in addition to **5g** from the reaction of *cis*-**3g** with H_2SO_4. The NMR data of compounds **5** are compiled in *Table 4*. In the case of compounds *cis*-**3c**, *cis*-**3f**, and *cis*-**3i**, the products of molecular rearrangement did not exhibit the Bn signals in their NMR spectra and were identified as debenzylated compounds **6**. The formation of **6** can be explained as the result of the stabilization of the intermediate carbocation by removal of the Bn group (*Scheme 2*). The NMR data of compounds **6** are given in *Table 4*.

In the positive-ion-mode first-order ESI-MS of compounds **5**, we observed five significant peaks for each structure. These peaks were assigned to the $[M+H]^+$ ion, Na^+ and K^+ adducts of the molecular ion, Na^+ adduct of the dimer, and doubly charged Ca^{2+} adduct of the trimer $[3M+Ca]^{2+}$. In the first-order ESI-MS of compounds **6**, the peaks mentioned above were accompanied by those of two additional ions, namely of the K^+ adduct of the dimer $[2M+K]^+$ and a peak at *m/z* corresponding to the doubly charged Ca^{2+} adduct of the tetramer $[4M+Ca]^{2+}$. Moreover, in the case of compounds **6c** and **6f**, the $[3M+K]^+$ ion peak was also detected. It should be noted that the peak at *m/z* 91 (Bn^+), which was formed during the fragmentation (MS^3) of compounds *cis*-**3c**, *cis*-**3f**, and *cis*-**3i**, and was also observed at low intensity in the first-order MS of these

Table 4. *^{1}H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds* **5** *and* **6** (δ in ppm)

Position	**5a**		**5b**		**5d**		**5e**		**5g**		**5h**		**6c**		**6f**		**6i**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(H)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	158.0	–	158.4	–	157.7	–	158.2	–	157.7	–	158.2	–	158.7	–	158.4	–	158.4
3	–	133.4	–	133.3	–	134.5	–	134.4	–	135.7	–	133.8	–	146.3	–	145.3	–	145.7
3-OH	9.08	–	9.25	–	9.10	–	9.25	–	9.24	–	9.38	–	9.48	–	9.30	–	9.20	–
4	–	124.0	–	124.1	–	122.8	–	123.1	–	123.8	–	123.9	7.14	112.6	7.16	111.8	7.29	112.7
4a	–	120.6	–	121.0	–	121.0	–	121.5	–	121.0	–	121.5	–	120.8	–	121.2	–	121.1
5	7.66	123.1	7.12	124.4	7.74	123.5	7.17	125.0	7.79	123.6	7.20	125.0	7.53	125.9	7.60	126.7	7.64	126.6
6	7.24	122.3	7.12	122.3	7.33	122.7	7.22	122.6	7.30	122.8	7.18	122.7	7.17	122.2	7.26	122.6	7.23	122.7
7	7.34	126.3	7.38	126.6	7.48	126.8	7.49	127.0	7.27	126.7	7.28	126.7	7.32	126.4	7.46	126.8	7.26	126.5
8	7.34	115.5	7.38	115.4	7.53	114.9	7.61	114.9	6.54	115.6	6.61	115.6	7.32	114.8	7.50	114.5	6.49	115.1
8a	–	142.7	–	142.6	–	141.9	–	141.7	–	142.2	–	142.1	–	133.6	–	134.8	–	136.1
Substituent at N(1)																		
1	12.03	–	12.28	–	3.75	30.1	3.83	30.1	–	137.7	–	135.7	12.04	–	3.74	29.9	–	137.7
2,6	–	–	–	–	–	–	–	–	7.39	129.1	7.46	130.0	–	–	–	–	7.39	129.0
3,5	–	–	–	–	–	–	–	–	7.68	130.2	7.62	128.6	–	–	–	–	7.68	130.2
4	–	–	–	–	–	–	–	–	7.61	128.9	7.53	127.9	–	–	–	–	7.60	129.0
Substituent at C(3)																		
1	2.84	24.1	–	133.8	2.86	24.1	–	133.8	2.94	24.3	–	137.6	–	–	–	–	–	–
2,6	1.55	30.5	7.38	130.0	1.55	30.6	7.37	130.0	1.60	30.6	7.49	128.6	–	–	–	–	–	–
3,5	1.39	22.4	7.56	128.5	1.42	22.4	7.56	128.5	1.48	22.5	7.73	130.7	–	–	–	–	–	–
4	0.96	14.0	7.49	128.4	0.95	14.0	7.49	127.8	0.99	14.0	7.66	129.1	–	–	–	–	–	–

structures (see *Exper. Part*), was completely absent in the ESI-MS of compounds **6**. These results were in accordance with other structural analyses, indicating that structures **6c**, **6f**, and **6i** are debenzylated products due to the rearrangement of corresponding compounds *cis*-**3**.

In nature, compounds **5** bearing a Ph group at C(4) occur frequently as secondary metabolites of fungi belonging to the genus *Penicillium* [18]. Two of the well-known quinolin-2-ones of fungal origin are viridicatin (**5b**) and viridicatol (viridicatin bearing a OH group at C(3) of the Ph substituent). These compounds showed significant biological activities [19], *e.g.*, inhibition of the glycine binding site associated with the NMDA receptor [20], inhibition of human immunodeficiency virus (HIV) induced by tumor necrosis factor (TNF-α) [21], and antibacterial activities owing to their action as maxi-K channel openers [22]. Additionally, compounds **6** exhibit biological activities, *e.g.*, **6c** causes reduction of lymphocyte MT-4 cells, and inhibits activity of reverse transcriptase ribonuclease H of HIV-1 and D-amino acid oxidase [23], and **6f** inhibits activity of D-amino acid oxidase [23]. 3-Butyl derivatives **5a**, **5d**, and **5g** have not been described in the literature yet, but a 4-Me analog of **5a** exhibited biological effects similar to those of compounds **6c** and **6f** [23].

4-Alkyl/aryl-3-hydroxyquinolin-2(1*H*)-ones or their 4-unsubstituted analogs were most frequently prepared by the reaction of isatins with aryldiazomethanes or diazoalkanes [24–26], or by *Friedländer*-type condensations [27]. The best hitherto known method for the preparation of 4-arylquinolin-2(1*H*)-one derivatives appears to be the *Knoevenagel* condensation of cyanoacetanilides with aromatic aldehydes, followed by oxidative cyclization [19].

Conclusions. – In summary, we have demonstrated an efficient approach to the synthesis of 4-alkyl/aryl-3-hydroxyquinolin-2(1*H*)-ones **5** or **6**, starting from the easily accessible 3-hydroxyquinoline-2,4-diones **2**. The $NaBH_4$ reduction of **2** proceeds with high diastereoselectivity to give *cis*-3,4-dihydro-3,4-dihydroxyquinolin-2(1*H*)-ones, *cis*-**3**, as the sole products. The subsequent pinacol rearrangement of *cis*-**3** to **5** or **6** opens the way to prepare a broad-spectrum of both 4-alkyl- or 4-aryl substituted compounds **5** and 4-unsubstituted compounds **6**. The described transformations are very interesting from the viewpoint of theory and, owing to the simple reaction protocol, open a path to the synthesis of new compounds of types **3**, **5**, and **6**. Because compounds **3**, **5**, and **6** exhibit significant biological activities, the new compounds described in this article could also be interesting structures for studies in this direction.

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Experimental Part

1. *General.* TLC: *Alugram®-SIL-G/UV$_{254}$* foils (*Macherey–Nagel*); elution with benzene/AcOEt 4 : 1, $CHCl_3$/EtOH 9 : 1 and/or 19 : 1, $CHCl_3$/AcOEt 7 : 3, and THF/AcOH 4 : 1. Column chromatography (CC): silica gel (SiO_2; *Merck*, grade *60*, 70–230 mesh); elution with $CHCl_3$, then $CHCl_3$/EtOH 99 : 1 → 8 : 2 or benzene, and then benzene/AcOEt 99 : 1 → 8 : 2. M.p.: *Kofler* block or *Gallencamp* apparatus. IR Spectra: *Nicolet iS10* spectrophotometer; KBr; in cm^{-1}. NMR Spectra: *Bruker Avance* spectrometer at 500.13

structures (see *Exper. Part*), was completely absent in the ESI-MS of compounds **6**. These results were in accordance with other structural analyses, indicating that structures **6c**, **6f**, and **6i** are debenzylated products due to the rearrangement of corresponding compounds *cis*-**3**.

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Experimental Part

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$[3M + Ca]^{2+}$), 308.2 (17, $[M + K]^+$), 292.2 (100, $[M + Na]^+$), 270.2 (5, $[M + H]^+$), 252.2 (24, $[M + H - H_2O]^+$), 224.2 (23, $[252 - CO]^+$). Anal. calc. for $C_{16}H_{15}NO_3$ (269.29): C 71.36, H 5.61, N 5.20; found: C 71.50, H 5.59, N 5.18).

cis-*3-Benzyl-3,4-dihydro-3,4-dihydroxy-1-methylquinolin-2(1*H*)-one* (*cis*-**3f**). Prepared from **2f** in 75% yield. White solid. M.p. 144–147° (benzene). IR: 3396, 3021, 1643, 1604, 1473, 1415, 1380, 1305, 1213, 1157, 1122, 1066, 1045, 1006, 916, 873, 786, 754, 732, 698, 673, 646, 584. EI-MS: 283 (21, M^+), 265 (9), 236 (17), 192 (39), 191 (5), 175 (9), 174 (45), 164 (15), 147 (14), 146 (100), 136 (17), 135 (7), 118 (30), 106 (18), 91 (63), 78 (7), 77 (22), 65 (16), 51 (9). ESI-MS (pos.): 589.2 (7, $[2M + Na]^+$), 444.7 (20, $[3M + Ca]^{2+}$), 322.2 (30, $[M + K]^+$), 306.2 (100, $[M + Na]^+$), 303.2 (58, $[2M + Ca]^{2+}$), 284.2 (23, $[M + H]^+$), 91.3 (4, $[Bn]^+$). Anal. calc. for $C_{17}H_{17}NO_3$ (283.32): C 72.07, H 6.05, N 4.94; found: C 72.03, H 6.05), N 4.98.

cis-*3-Butyl-3,4-dihydro-3,4-dihydroxy-1-phenylquinolin-2(1*H*)-one* (*cis*-**3g**). Prepared from **2g** in 83% yield. White solid. M.p. 165–169° (benzene/hexane). IR: 3475, 3440, 3062, 2954, 1677, 1604, 1492, 1459, 1346, 1299, 1282, 1265, 1186, 1147, 1079, 1058, 1004, 944, 871, 856, 763, 696, 646, 559. EI-MS: 311 (16, M^+), 238 (9), 237 (7), 227 (6), 226 (42), 209 (17), 208 (100), 198 (24), 197 (18), 196 (11), 181 (12), 180 (80), 168 (25), 167 (14), 93 (6), 77 (22), 65 (6), 57 (16), 51 (9), 43 (11), 41 (17). ESI-MS (pos.): 645.3 (12, $[2M + Na]^+$), 627.3 (9, $[2M + Na - H_2O]^+$), 486.8 (40, $[3M + Ca]^{2+}$), 677.8 (16, $[2M + Ca - H_2O]^{2+}$), 350.2 (19, $[M + K]^+$), 234.3 (100, $[M + Na]^+$), 216.2 (32, $[M + Na - H_2O]^+$), 312.3 (19, $[M + H]^+$), 294.3 (77, $[M + H - H_2O]^+$), 266.3 (4, $[294 - CO]^+$). Anal. calc. for $C_{19}H_{21}NO_3$ (311.38): C 73.29, H 6.80, N 4.50; found: C 73.35, H 6.79, N 4.30.

cis-*3,4-Dihydro-3,4-dihydroxy-1,3-diphenylquinolin-2(1*H*)-one* (*cis*-**3h**). Prepared from **2h** in 93% yield. White solid. M.p. 197–200° (benzene/hexane). IR: 3469, 3311, 2852, 1675, 1606, 1494, 1459, 1347, 1267, 1184, 1120, 1074, 1027, 1000, 944, 854, 761, 725, 700, 688, 649, 588. EI-MS: 331 (13, M^+), 303 (5), 227 (7), 226 (43), 209 (11), 208 (66), 199 (8), 198 (56), 197 (30), 196 (17), 181 (15), 180 (100), 169 (7), 168 (44), 167 (19), 152 (8), 106 (9), 105 (45), 93 (9), 78 (9), 77 (78), 65 (10), 51 (23). ESI-MS (pos.): 685.3 (7, $[2M + Na]^+$), 516.8 (6, $[3M + Ca]^{2+}$), 370.2 (33, $[M + K]^+$), 354.2 (100, $[M + Na]^+$), 332.3 (3, $[M + H]^+$), 314.3 (6, $[M + H - H_2O]^+$), 286.3 (5, $[314 - CO]^+$). Anal. calc. for $C_{21}H_{17}NO_3$ (331.36): C 76.12, H 5.17, N 4.23; found: C 76.26, H 5.28), N 3.95.

cis-*3-Benzyl-3,4-dihydro-3,4-dihydroxy-1-phenylquinolin-2(1*H*)-one* (*cis*-**3i**). Prepared from **2i** in 83% yield. White solid. M.p. 148–152° (benzene/hexane). IR: 3461, 3062, 1687, 1602, 1494, 1459, 1351, 1299, 1236, 1199, 1128, 1108, 1022, 960, 875, 862, 761, 730, 696, 647, 599. EI-MS: 346 (8), 345 (32, M^+), 327 (7), 298 (20), 255 (8), 254 (49), 237 (10), 236 (48), 226 (29), 209 (18), 208 (100), 198 (15), 197 (16), 196 (13), 181 (13), 180 (97), 179 (8), 168 (31), 167 (19), 152 (10), 105 (15), 92 (12), 91 (55), 78 (7), 77 (38), 66 (6), 65 (21), 51 (16). ESI-MS (pos.): 713.2 (5, $[2M + Na]^+$), 537.8 (7, $[3M + Ca]^{2+}$), 384.2 (43, $[M + K]^+$), 368.2 (100, $[M + Na]^+$), 365.2 (41, $[2M + Ca]^{2+}$), 346.3 (10, $[M + H]^+$), 328.3 (5, $[M + H - H_2O]^+$), 91.3 (3, $[Bn]^+$). Anal. calc. for $C_{22}H_{19}NO_3$ (345.39): C 76.50, H 5.54, N 4.06; found: C 76.54, H 5.55, N 3.88.

3. *Synthesis of 3a-Butyl-5,9b-dihydro-5-methyl[1,3]dioxolo[4,5-*c*]quinoline-2,4(3a*H*)-dione* (**4d**). Triphosgene (= bis(trichloromethyl) carbonate; 43 mg, 0.073 mmol) was added at r.t. in several portions during 1 h to the well-stirred soln. of *cis*-**3d** (99 mg, 0.4 mmol), Et_3N (0.138 ml, 0.1 mmol), and DMAP (= 4-(dimethylamino)pyridine; 20 mg, 0.18 mmol) in benzene (10 ml). The soln was stirred at r.t. for 1 h and then heated at reflux for 4 h. After cooling, the soln was filtered, and the filtrate was evaporated to dryness. H_2O (15 ml) was added to the residue, and the suspension was extracted with benzene (3 × 20 ml). Collected extracts were dried (Na_2SO_4), evaporated, and the residue was separated by CC (SiO_2). Compound **4d** was obtained in 34% yield. White solid. M.p. 150–151° (benzene/hexane). IR: 2956, 2871, 1818, 1700, 1616, 1585, 1496, 1465, 1379, 1344, 1232, 1188, 1165, 1109, 1070, 1008, 979, 935, 918, 777, 763, 679, 638, 532. NMR Spectra: see *Table 2*. EI-MS: 276 (10), 275 (60, M^+), 247 (11), 205 (15), 203 (11), 189 (8), 188 (15), 175 (33), 174 (19), 161 (10), 160 (43), 149 (23), 148 (10), 147 (51), 135 (15), 134 (16), 133 (8), 132 (23), 130 (13), 125 (10), 120 (13), 119 (31), 118 (100), 117 (27), 113 (10), 111 (12), 107 (9), 106 (9), 104 (10), 99 (11), 97 (17), 95 (9), 91 (55),90 (13), 89 12), 85 (32), 83 (26), 81 (13), 78 (11), 77 (40), 76 (10), 71 (40), 70 (16), 69 (25), 65 (16), 57 (81), 56 (13), 55 (41), 51 (19), 44 (42), 43 71), 42 (23), 41 (77). ESI-MS (pos.): 573.2 (25, $[2M + Na]^+$), 314.2 (33, $[M + K]^+$), 298.2 (100, $[M + Na]^+$), 276.2 (12, $[M + H]^+$), 254.2 (6, $[M + Na - CO_2]^+$), 232.2 (5, $[M + H - CO_2]^+$). Anal. calc. for $C_{15}H_{17}NO_4$ (275.30): C 65.44, H 6.22, N 5.09; found: C 65.58, H 6.28, N 5.09.

4. *General Procedure for the Rearrangement of Compounds cis-***3**. Under intensive stirring, the starting compound *cis*-**3** (0.75 mmol) was dissolved at 0° in conc. H_2SO_4 (2 ml), and stirring was continued for 1 h at r.t. The mixture was blended with crushed ice (15 g), the deposited precipitate was filtered with suction, washed with H_2O (10 ml), then with a 3% soln. of $NaHCO_3$ (4 ml) and H_2O, and recrystallized from an appropriate solvent. In the case of *cis*-**3i**, the crude mixture after blending with crushed ice was extracted with $CHCl_3$. The dried (Na_2SO_4) extract was evaporated to dryness and worked-up by CC (SiO_2). The yields are given in *Table 3*, for NMR spectra of compounds **5** and **6**, see *Table 4*.

*4-Butyl-3-hydroxyquinolin-2(1*H*)-one* (**5a**). Prepared from *cis*-**3a** in 71% yield. White solid. M.p. 179–188° (benzene). IR: 3436, 3291, 2956, 2871, 1646, 1625, 1569, 1506, 1405, 1288, 1259, 1218, 1114, 952, 904, 755, 715, 682, 626, 565. EI-MS: 217 (M^+, 20), 188 (13), 176 (11), 175 (100), 174 (14), 146 (19), 129 (8), 128 (22), 117 (10), 115 (8), 91 (7), 90 (7), 77 (13), 43 (7), 41 (9). ESI-MS (pos.): 457.3 (19, $[2M + Na]^+$), 345.8 (45, $[3M + Ca]^{2+}$), 256.2 (21, $[M + K]^+$), 240.2 (81, $[M + Na]^+$), 218.2 (100, $[M + H]^+$). Anal. calc. for $C_{13}H_{15}NO_2$ (217.26): C 71.87, H 6.96, N 6.45; found: C 72.12, H 6.94, N 6.51.

*3-Hydroxy-4-phenylquinolin-2(1*H*)-one* (**5b**). Prepared from *cis*-**3b** in 85% yield. White solid. M.p. 270–271° (benzene). For **5b** (*viridicatin*), m.p. of 266–269° was reported [19]. IR: 3357, 3058, 2994, 2869, 1658, 1635, 1575, 1506, 1409, 1351, 1309, 1292, 1226, 1157, 952, 883, 759, 717, 698, 673, 611, 595. EI-MS: 238 (14), 237 (91, M^+), 236 (100), 191 (6), 190 (22), 180 (23), 165 (7), 152 (14), 118 (10), 95 (8), 90 (8), 77 (18), 76 (16), 57 (11), 43 (12). ESI-MS (pos.): 497.2 (25, $[2M + Na]^+$), 375.7 (56, $[3M + Ca]^{2+}$), 276.2 (36, $[M + K]^+$), 260.2 (100, $[M + Na]^+$), 238.2 (40, $[M + H]^+$). Anal. calc. for $C_{15}H_{11}NO_2$ (237.25): C 75.94, H 4.67, N 5.90; found: C 76.02, H 4.71, N 5.83.

*4-Butyl-3-hydroxy-1-methylquinolin-2(1*H*)-one* (**5d**). Prepared from *cis*-**3d** in 72% yield. White solid. M.p. 118–121° (benzene/hexane). IR: 3284, 2958, 2925, 2852, 1644, 1616, 1600, 1506, 1467, 1459, 1415, 1400, 1328, 1249, 1168, 1120, 1049, 954, 848, 781, 744, 682, 646, 599. EI-MS: 231 (22, M^+), 202 (11), 190 (13), 189 (100), 188 (12), 161 (10), 160 (39), 149 (38), 132 (12), 131 (7), 130 (15), 117 (20), 115 (12), 113 (13), 111 (16), 109 (10), 99 (16), 98 (11), 97 (27), 95 (16), 91 (12), 71 (54), 69 (52), 67 (18), 57 (91), 55 (45), 43 (92), 41 (69). ESI-MS (pos.): 485.2 (18, $[2M + Na]^+$), 366.8 (78, $[3M + Ca]^{2+}$), 270.2 (10, $[M + K]^+$), 254.2 (100, $[M + Na]^+$), 232.3 (55, $[M + H]^+$). Anal. calc. for $C_{14}H_{17}NO_2$ (231.29): C 72.70, H 7.41, N 6.06; found: C 72.62, H 7.44, N 6.05.

*3-Hydroxy-1-methyl-4-phenylquinolin-2(1*H*)-one* (**5e**). Prepared from *cis*-**3e** in 93% yield. White solid. M.p. 212–215° (benzene: [19]: 190–191°). IR: 3262, 3064, 2940, 1642, 1623, 1600, 1498, 1463, 1417, 1394, 1346, 1328, 1272, 1162, 1118, 948, 912, 782, 754, 742, 700, 673, 644, 559. EI-MS: 252 (15), 251 (91, M^+), *250* (100), 194 (18), 165 (13), 152 (11), 126 (6), 89 (6), 77 (12), 76 (9), 51 (5). ESI-MS (pos.): 525.2 (21, $[2M + Na]^+$), 396.8 (51, $[3M + Ca]^{2+}$), 290.2 (28, $[M + K]^+$), 274.2 (100, $[M + Na]^+$), 252.2 (53, $[M + H]^+$). Anal. calc. for $C_{16}H_{13}NO_2$ (251.28): C 76.48, H 5.21, N 5.57; found: C 76.45, H 5.21, N 5.74.

*4-Butyl-3-hydroxy-1-phenylquinolin-2(1*H*)-one* (**5g**). Prepared from *cis*-**3g** in 61% yield besides **1g**. White solid. M.p. 167–170° (benzene). IR: 3311, 2960, 2854, 1643, 1622, 1599, 1591, 1562, 1500, 1489, 1458, 1396, 1323, 1302, 1232, 1199, 1176, 1162, 1112, 1068, 1047, 978, 962, 901, 827, 781, 733, 752, 694, 661, 631, 511. EI-MS: 293 (17, M^+), 278 (8), 264 (22), 252 (17), 251 (100), 250 (47), 222 (9), 196 (10), 195 (7), 168 (6), 167 (13), 77 (18), 69 (5), 55 (7), 51 (7), 43 (10), 41 (12). ESI-MS (pos.): 609.3 (18, $[2M + Na]^+$), 459.8 (13, $[3M + Ca]^{2+}$), 332.2 (29, $[M + K]^+$), 316.3 (81, $[M + Na]^+$), 294.3 (100, $[M + H]^+$). Anal. calc. for $C_{19}H_{19}NO_2$ (293.36): C 77.79, H 6.53, N 4.77; found: C 77.64, H 6.53, N 4.40.

*3-Hydroxy-1,4-diphenylquinolin-2(1*H*)-one* (**5h**). Prepared from *cis*-**3h** in 65% yield. White solid. M.p. 254–257° (benzene). IR: 3291, 3062, 1637, 1623, 1602, 1592, 1492, 1455, 1392, 1322, 1272, 1191, 1126, 1068, 985, 954, 823, 755, 744, 694, 659, 615, 516. EI-MS: 314 (21), 313 (100, M^+), 312 (98), 256 (16), 254 (15), 179 (9), 178 (6), 152 (9), 151 (5), 127 (10), 77 (19), 51 (11). ESI-MS (pos.): 649.2 (10, $[2M + Na]^+$), 489.7 (10, $[3M + Ca]^{2+}$), 352.2 (14, $[M + K]^+$), 336.2 (100, $[M + Na]^+$), 314.2 (25, $[M + H]^+$). Anal. calc. for $C_{21}H_{15}NO_2$ (313.35): C 80.49, H 4.82, N 4.47; found: C 80.35m, H 4.80, N 4.42.

*3-Hydroxyquinolin-2(1*H*)-one* (**6c**). Prepared from *cis*-**3c** in 59% yield. White solid. M.p. 263–270° (benzene). For **6c**, m.p. 261–263° was reported [28]. IR: 3276, 3166, 3056, 3000, 1654, 1625, 1612, 1575, 1504, 1400, 1349, 1290, 1274, 1249, 1184, 1126, 939, 906, 862, 755, 736, 701, 603, 551. ESI-MS (pos.): 522.2 (8, $[3M + K]^+$), 361.2 (10, $[2M + K]^+$), 345.1 (48, $[2M + Na]^+$), 342.2 (35, $[4M + Ca]^{2+}$), 261.7 (80, $[3M +$

Ca]$^{2+}$), 200.1 (6, [M + K]$^+$), 184.1 (100, [M + Na]$^+$), 162.2 (33, [M + H]$^+$). Anal. calc. for $C_9H_7NO_2$ (161.16): C 67.07, H 4.38, N 8.69; found: C 66.88, H 4.55, N 8.62.

*3-Hydroxy-1-methylquinolin-2(1*H*)-one* (**6f**). Prepared from *cis*-**3f** in 63% yield. White solid. M.p. 168–179°, then 187–189° (benzene/cyclohexane: [29]: 186°). IR: 3251, 3037, 1654, 1617, 1600, 1504, 1465, 1421, 1334, 1299, 1245, 1182, 1116, 1041, 933, 883, 777, 752, 738, 727, 682, 532. EI-MS: 175 (65, M^+), 167 (10), 155 (7), 149 (22), 147 (36), 146 (12), 141 (10), 127 (15), 125 (18), 123 (14), 122 (9), 118 (22), 113 (32), 111 (29), 109 (16), 99 (22), 97 (35), 95 (21), 91 (11), 90 (6), 85 (52), 83 (43), 81 (25), 77 (15), 71 (87), 70 (19), 69 (43), 67 (12), 57 (100), 56 (29), 55 (34), 43 (51), 41 (19). ESI-MS (pos.): 564.2 (27, [3M + K]$^+$), 389.2 (74, [2M + K]$^+$), 373.2 (38, [2M + Na]$^+$), 370.1 (13, [4M + Ca]$^{2+}$), 282.7 (90, [3M + Ca]$^{2+}$), 214.1 (14, [M + K]$^+$), 198.2 (69, [M + Na]$^+$), 176.2 (100, [M + H]$^+$). Anal. calc. for $C_{10}H_9NO_2$ (175.18): C 68.56, H 5.18, N 8.00; found: C 68.36, H 5.23, N 7.89.

*3-Hydroxy-1-phenylquinolin-2(1*H*)-one* (**6i**). Prepared from *cis*-**3i** in 58% yield. White solid. M.p. 184–185° (benzene/hexane). IR: 3255, 3029, 1650, 1631, 1600, 1488, 1459, 1411, 1317, 1290, 1234, 1184, 1124, 1074, 944, 904, 881, 777, 761, 752, 696, 667, 613. ESI-MS (pos.): 513.2 (5, [2M + K]$^+$), 497.2 (40, [2M + Na]$^+$), 494.1 (6, [4M + Ca]$^{2+}$), 375.7 (19, [3M + Ca]$^{2+}$), 276.2 (7, [M + K]$^+$), 260.2 (100, [M + Na]$^+$), 238.2 (36, [M + H]$^+$). Anal. calc. for $C_{15}H_{11}NO_2$ (237.25): C 75.94, H 4.67, N 5.90; found: C 75.80, H 4.70, N 5.71.

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PŘÍLOHA VII

Reduction of 3-Aminoquinoline-2,4(1*H*,3*H*)-diones and Deamination of the Reaction Products

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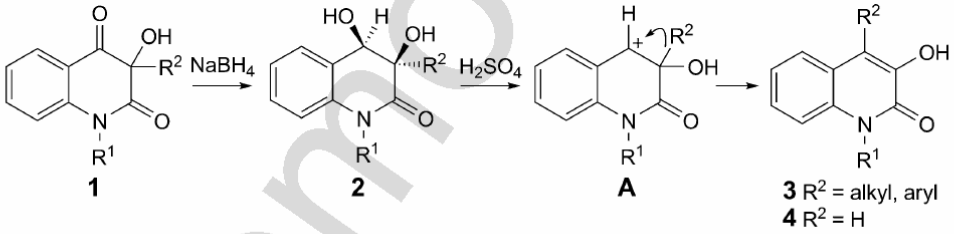
3-Aminoquinoline-2,4-diones were stereoselectively reduced with $NaBH_4$ to give *cis*-3-amino-3,4-dihydro-4-hydroxyquinolin-2(1*H*)-ones. Using triphosgene (= bis(trichloromethyl) carbonate), these compounds were converted to 3,3a-dihydrooxazolo[4,5-*c*]quinoline-2,4(5*H*,9b*H*)-diones. The deamination of the reduction products using HNO_2 afforded mixtures of several compounds, from which 3-alkyl/aryl-2,3-dihydro-1*H*-indol-2-ones and their 3-hydroxy and 3-nitro derivatives were isolated as the products of the molecular rearrangement.

Introduction. – Recently, we reported that the reduction of 3-hydroxyquinoline-2,4-diones **1** with $NaBH_4$ proceeds in a highly stereoselective manner to give *cis*-diols **2**. These compounds undergo rearrangement through the action of H_2SO_4 *via* an intermediate carbocation **A** to 4-alkyl/aryl-3-hydroxy-1*H*-quinolin-2-ones **3**. Starting with the 3-benzyl derivatives of **1**, 4-unsubstituted 3-hydroxy-1*H*-quinolin-2-ones **4** can be obtained (*Scheme 1*) [1].

Scheme 1

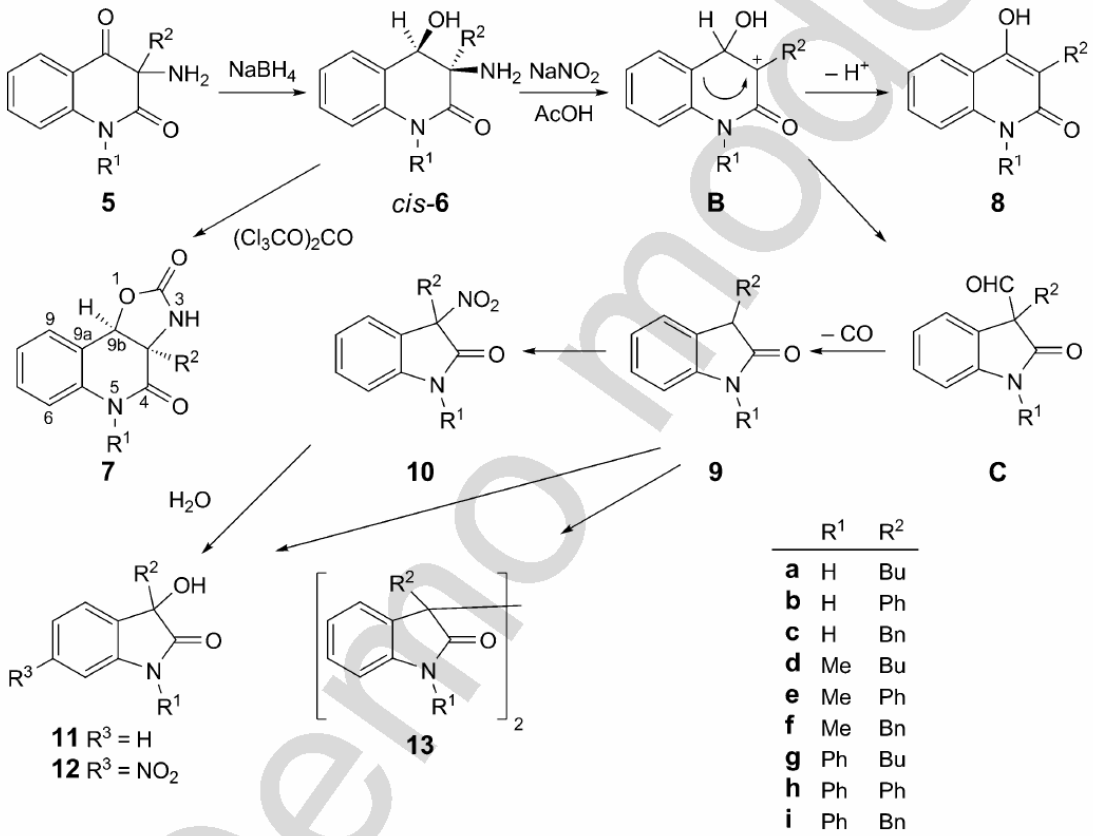


The ease and high stereoselectivity of the reduction of diones **1** to diols **2**, and their facile pinacol-pinacoline-type rearrangement to compounds **3** or **4**, which pertains to the synthesis of biologically active viridicatin alkaloids [2–6] (if R^2 = aryl), prompted us to study the analogous reactions of 3-aminoquinoline-2,4(1*H*,3*H*)-diones **5** (*cf. Scheme 2*). We found that the reduction of **5** with $NaBH_4$ also proceeds with high stereoselectivity and in high yields, but the subsequent deamination of **6** with HNO_2 is a complex reaction leading to a mixture of several products.

Results and Discussion. – For our experiments, we selected $NaBH_4$ as the reduction agent. The starting 3-aminoquinoline-2,4(1*H*,3*H*)-diones **5a**–**5i** were prepared by the reaction of the corresponding 3-chloroquinoline-2,4(1*H*,3*H*)-diones with NH_3 generated *in situ* according to a well-tested protocol [7]. In addition to the seven known compounds **5**, two novel amines **5f** and **5i** were prepared. Notably, the yields of these amines with a Bn group at C(3) were much lower than those of the amines with a Ph or Bu group at C(3) [7], and a considerable quantity of 3-hydroxy derivatives **1** was simultaneously obtained from this reaction.

Although many 3-aminoquinoline-2,4(1*H*,3*H*)-diones **5** are known, their reduction to the corresponding amino alcohols **6** (*cf. Scheme 2*) had not been described in the literature until recently. According to the literature, 25 reductions of α-amino ketones bearing a NH_2 group at a tertiary C-atom to the corresponding 2-amino alcohols were accomplished using different reagents; however, primarily the reactions with $NaBH_4$ [8–13] were successful. To determine the influence of the R^2 substituent on the transformation of diones **5**, we selected compounds with the Ph, Bu, and Bn groups in this position. The H, Me, and Ph groups were selected as the R^1 substituents.

Scheme 2



The results of the reduction of compounds **5** with $NaBH_4$ are compiled in *Table 1*. All of the reductions exhibited only one spot in TLC in several solvent systems. In the NMR spectra of the reaction products, only one set of signals was observed, indicating that the reaction proceeded with high stereoselectivity to give only one of the two

Table 1. *Reduction of Compounds* **5a**–**5i**.

Entry	Starting compound	R^1	R^2	Product (yield [%])[a])
1	**5a**	H	Bu	**6a** (75)
2	**5b**	H	Ph	**6b** (80)
3	**5c**	H	Bn	**6c** (75)
4	**5d**	Me	Bu	**6d** (73)
5	**5e**	Me	Ph	**6e** (90)
6	**5f**	Me	Bn	**6f** (75)
7	**5g**	Ph	Bu	**6g** (69)
8	**5h**	Ph	Ph	**6h** (78)
9	**5i**	Ph	Bn	**6i** (80)

[a]) The yields of pure recrystallized compounds.

possible diastereoisomers. This situation was completely analogous to that reported in our previous publication [1] for the derivatives with OH instead of NH_2 at C(3) (compare *Schemes 1* and *2*). The NOESY spectra of compounds **6** were recorded to determine the mutual orientation of the substituents at C(3) and C(4). The results strongly supported the through-space proximity of the H-atom at C(4) with the H-atoms of the R^2 substituent, evidenced by the appropriate cross-peaks in the NOESY spectra. However, additional cross-peaks were also observed, because compounds **6** are not completely rigid, and the dynamic behavior of the substituents at C(3) and C(4) (rotamers) give rise to additional cross-peaks. The reactions of compounds **6** with triphosgene (= bis(trichloromethyl) carbonate) afford compounds **7**, confirming the *cis*-configuration of the NH_2 and OH groups in **6**.

Compounds **6** were analyzed by two MS methods with differing ionization techniques, electron impact (EI) and electrospray ionization (ESI). In the first-order EI-mass spectra of compounds **6a**, **6d**, and **6g** (R^2 = Bu), and **6b**, **6e**, and **6h** (R^2 = Ph), the peak of the molecular radical cation, $M^{+\bullet}$, was unambiguously detected. On the other hand, in the EI-mass spectra of compounds with a Bn group at C(3), *i.e.*, **6c**, **6f**, and **6i**, the peak of the molecular ion, $M^{+\bullet}$, was not observed, and the most abundant peak was at the *m*/*z* corresponding to the $[M - Bn]^{+\bullet}$ fragment. The ESI-MS experiments of compounds **6** were performed in the positive-ion mode. In the first-order mass spectra, one dominant signal at *m*/*z* corresponding to the $[M + H]^+$ ion was observed for all of the examined compounds. In most of the cases, this signal was accompanied by that for the Na^+ adduct $[M + Na]^+$ and signals approximately twice as high for $[2M + H]^+$ and/or $[2M + Na]^+$. Moreover, in the first-order mass spectra of compounds **6a**, **6d**, and **6g** (R^2 = Bu), and **6b**, **6e**, and **6h** (R^2 = Ph), additional signals were detected. Using tandem mass spectrometry (under collision-induced dissociation conditions) of the $[M + H]^+$ ion, these signals were attributed to the singly charged fragments of the precursor ion originating from consecutive neutral losses of NH_3 ($[M + H - NH_3]^+$) and CO ($[M + H - NH_3 - CO]^+$). While the latter product ion peak was observed in the ESI-mass spectra of compounds bearing both Bu and Ph substituents at C(3), the $[M + H - NH_3]^+$ ion peak was detected only in the spectra of compounds **6b**, **6e** and **6h** (R^2 = Ph). These signals were completely absent in the first-order mass spectra of compounds with a Bn group at C(3) (**6c**, **6f** and **6i**).

When a substituted α-amino alcohol is treated with HNO_2, its deamination is accompanied by rearrangement to form a ketone or an aldehyde; in some cases, the glycol corresponding to the amino alcohol is produced in varying yields [14]. The deamination of α-amino alcohols bearing a primary NH_2 group at the secondary C-atom to provide an intermediate carbocation is called the 'semipinacolinic' deamination [15]. The deamination of these types of α-amino alcohols with HNO_2 was studied in detail from 1923 to 1960, and this topic has been well-reviewed [16]. However, we were not able to find any analogous reaction involving the deamination of a compound with a OH group at the secondary C-atom and an NH_2 group at the tertiary C-atom. In this sense, the rearrangement of compounds **6** is exceptional.

In contrast to diols **2**, for which two different carbocations can form in the reaction with H_2SO_4 [1], the deamination of amino alcohols **6** with HNO_2 can result in only one carbocation **B** (*Scheme 2*). This carbocation can react with a nucleophile (possibly H_2O, or AcO^- or NO_2^- ions) to generate the corresponding 3,4-dihydro-4-hydroxyquinolin-2(1*H*)-ones substituted with OH, AcO, or NO_2 group at C(3). A further possibility is its deprotonation to yield 4-hydroxy-1*H*-quinolin-2-ones **8**. The molecular rearrangement of **B** can proceed through the migration of the aryl group in **B** (C(4a)) to C(3) to form aldehyde **C**. However, preliminary analyses of the products of the molecular rearrangement of **6** indicated that none of the molecules contain an aldehyde function.

Unfortunately, the deamination of compounds **6** yielded complex mixtures of several compounds according to TLC, and their separation was very difficult. This result is the main reason for the relatively low yields of isolated compounds (*Table 2*). The main reaction products were identified as 3-alkyl/aryl-2,3-dihydro-1*H*-indol-2-ones **9**, indicating that decarbonylation of the primarily formed intermediate **C** occured during the rearrangement. All of the isolated compounds **9** are known, but some of them have been insufficiently described. Therefore, we determined their spectroscopic characteristics (*Exper. Part*). In only one case, **6h**, the rearranged product **9h** was not isolated.

In addition to compounds **9** and starting compounds **6**, 4-hydroxy-1*H*-quinolin-2-ones **8** were obtained (*Table 2*). In *Scheme 2*, it is shown that the reaction pathway also proceeds through deprotonation of intermediate **B**. Compounds **8** do not form when the substituent R^2 in **6** is a Ph group. Through deamination of these compounds (*i.e.*, **6b**, **6e**, and **6h**), additional compounds were isolated (*Table 2*). According to elemental analysis, compounds containing an ONO or NO_2 group are present. Differentiation between these two possibilities was accomplished by studying the chemical shifts of C(3) in their ^{13}C-NMR spectra. In the literature, the signal of an sp^3-C-atom bearing both a C=O and a ONO group appears in the region of 82–84 ppm [17]. In analogous compounds, bearing a NO_2 group instead of a ONO group, the chemical shift of the sp^3-C-atom is detected in the region of 92–96 ppm [18][19]. The compounds that we isolated exhibit signals in the region from 94.4–94.9 ppm, which is consistent with structure **10**. Only two compounds of this type are known in the literature [20]. These compounds were prepared by oxidation of the corresponding 3-alkylindoles with thallium(III) trinitrate, but their NMR spectra were not reported. Structure **10** was finally confirmed through X-ray diffraction analysis of compound **10h**; the ORTEP view of this compound shows a NO_2 group at C(3) (*Fig.*). Compound **10h** crystallizes as

Table 2. *Rearrangement of Compounds* **6**

Entry	Starting compound	R^1	R^2	*Method*[a])	Products (yield [%])[b])
1	**6a**	H	Bu	*A*	**8a** (11)[c]), **9a** (24)
2				*B*	**8a** (13)[c]), **9a** (23)
3	**6b**	H	Ph	*A*	**9b** (3), **10b** (31), **13b** (4)
4				*B*	**6b** (21)[d]), **9b** (9), **10b** (7), **11b** (8)
5	**6c**	H	Bn	*A*	**8c** (11)[c]), **9c** (28)
6				*B*	**8c** (15)[c]), **9c** (35)
7	**6d**	Me	Bu	*A*	**6d** (10)[d]), **9d** (51)
8				*B*	**6d** (13)[d]), **9d** (42)
9	**6e**	Me	Ph	*A*	**2e** (1)[c]), **9e** (5), **10e** (28), **13e** (2)
10				*B*	**2e** (2)[c]), **9e** (11), **10e** (12), **13e** (2)
11	**6f**	Me	Bn	*A*	**8f** (4)[c]), **9f** (40)
12				*B*	**6f** (7)[d]), **8f** (7)[c]), **9f** (28)
13	**6g**	Ph	Bu	*A*	**6g** (28)[d]), **9g** (46)
14				*B*	**2g** (3)[c]), **6g** (27)[d]), **9g** (39)
15	**6h**	Ph	Ph	*A*	**10h** (4), **11h** (13), **12h** (3), **13h** (6)
16				*B*	**2h** (3)[c]), **6h** (5)[d]), **10h** (16), **11h** (9), **12h** (8), **13h** (3)
17	**6i**	Ph	Bn	*A*	**6i** (21)[d]), **8i** (16)[c]), **9i** (23)
18				*B*	**6i** (13)[d]) **8i** (9)[c]), **9i** (26)

[a]) *Method A:* $NaNO_2$ in AcOH, urea was added at the end of the reaction; *Method B:* as *Method A*, but without urea addition. [b]) The yields of pure recrystallized or distilled compounds. [c]) Identical in all respects to the authentic sample. [d]) Recovered starting material.

a racemic mixture in the triclinic space group $P\bar{1}$ with two molecules within the unit cell. From the selected bond distances and angles, the typical features of the aromatic C(3)–C(4) bond, as well those showing the peptidic character of N–C(=O) moiety and NO_2 group were deduced. Unfortunately, the only slightly similar but comparable molecules are two 7-nitro-6-oxo-3,4,6,7,8,9-hexahydroimidazo[4,5-*f*]indolizin-8a-carboxylates [21], in which the same arrangement of the NO_2 group at the aliphatic stereogenic center of a five-membered ring is present.

In the first-order positive-ion-mode ESI-MS spectra of compounds **10**, the most abundant peak was attributed to the $[M + H - NO_2]^{+\bullet}$ ion originating from in-source fragmentation of the $[M + H]^+$ ion, of which the peak was not observed in the mass spectra. On the other hand, other even-electron ions such as $[M + Na]^+$ and $[M + K]^+$ were formed under ESI conditions. Additionally, the last two ions undergo in-source fragmentation to give the $[M + Na - NO_2]^{+\bullet}$ and $[M + K - NO_2]^{+\bullet}$ ions.

Further isolated compounds, indicating the presence of a OH group in their IR spectra, were identified as **11**, mainly from the chemical shifts of C(3) at 77.2 and 77.4 ppm. In the ESI-mass spectra of compounds **11**, five significant signals were observed. The base peak, which we assigned to the $[M + H - H_2O]^+$ ion, was accompanied by those of the $[M + Na]^+$ and $[M + K]^+$ ions. Moreover, peaks of two types of singly charged dimeric $[2M + Na]^+$ and doubly charged trimeric $[3M + Ca]^{2+}$ ions were also detected.

These results indicate that the primary products of the rearrangement of compound **6** are most likely compounds **9**, which result from decarbonylation of intermediate **C**

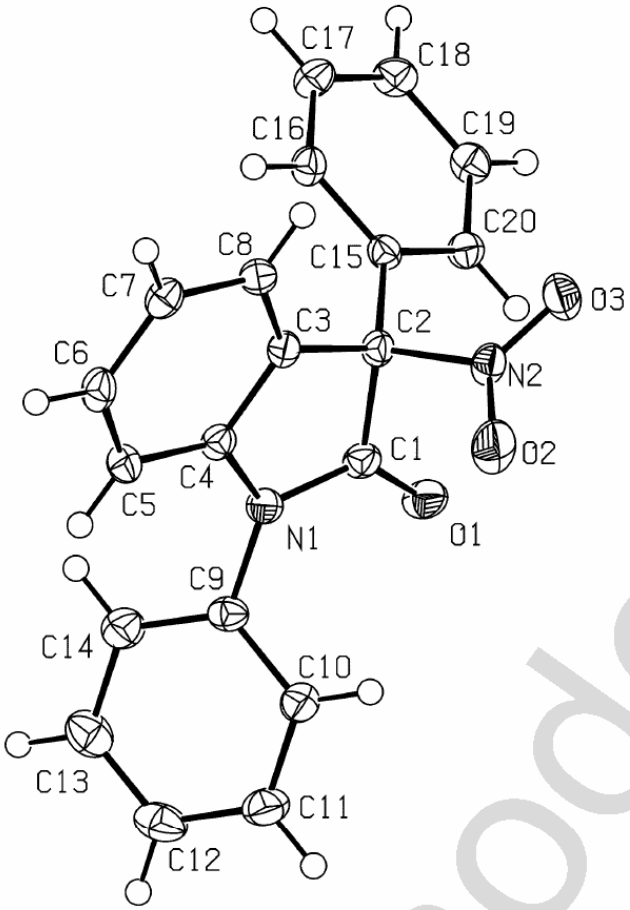


Figure. *The molecular structure of compound* **10h**, *ORTEP view* (50% probability level). Selected interatomic distances [Å] and angles [°]: O1–C1, 1.2063(16); C1–C2, 1.5588(18); C2–C3, 1.5047(16); C3–C4, 1.3935(17); N1–C4, 1.4162(16); N1–C1, 1.3697(17); N2–C2, 1.5510(16); N2–O2, 1.2220(15); N2–O3, 1.2112(15); O1–C1–N1, 127.06(12); C1–N1–C4, 110.89(11); O2–N2–O3, 124.66(12).

(*Scheme 2*). Independent of the method, compounds **10** are formed from nitration of **9** with HNO_3, which is the product of the decomposition of HNO_2 with H_2O [22][23]. However, these compounds originate only from **9b**, **9e**, and **9h**, which have a Ph group at C(3), which facilitates the replacement of an H-atom with the NO_2 group. Compounds **11** are hydrolytic products of **10**. Nucleophilic replacement of the aliphatic tertiary NO_2 group in α-position to the C=O group with a OH moiety proceeds easily not only under alkaline conditions [24], but also by heating in AcOH [25][26]. However, we cannot exclude that at least a portion of **11** is formed by direct oxidation of **9**.

Interestingly, compounds **12h** and **13h** were also obtained in low yields from the rearrangement of **6h**. The occurrence of compound **12h** evidences that nitration of the aromatic nucleus can proceed under the given reaction conditions not only at C(3), but also at C(6). In the literature, only one compound of this type, namely 1,3-dimethyl-3-[β-(dimethylamino)ethyl]-6-nitroindolinone, has been described as the product from nitration of the corresponding indolinone [27].

Dimeric compounds **13b**, **13e**, and **13h** resulted from dehydrogenation of the corresponding compounds **9**. The spontaneous dimerization of crude 3-substituted 2,3-dihydro-1*H*-indol-2-ones to produce a 3,3′-leucoisoindigo such as **13** has been described [17]. Several compounds **13**, including **13b** and **13e**, were prepared, in addition to dioxindoles **11**, by oxidation of the corresponding oxindoles **9** with O_2 in the presence of Co^{II} *Schiff*'s base complexes [28]. A dimer similar to **13** was also prepared by the reaction of 3-[(ethoxycarbonyl)methyl]indolin-2-one enolate with CI_4 and was used as a starting material for the synthesis of the alkaloid (±)-folicanthine [29]. Both the ^{1}H- and ^{13}C-NMR spectra of dimeric compounds **13b**, **13e**, and **13h** were very complex. They consisted of very broad signals that became narrower when the spectra were recorded at 360 K, and the original shape was observed again after cooling to 300 K. Hindered rotation due to the presence of bulky substituents is most likely responsible for this behavior.

Two methods were applied for the deamination of compounds **6** (*Table 2*). These methods differ only in that the addition of urea, which was used in *Method A* ($NaNO_2$ in AcOH) to quench the excess HNO_2, was omitted in *Method B*. However, as shown in *Table 2*, there are no substantial differences between the methods in most cases. Our presumption about the potential reduction of **10** with urea proved to be groundless.

To establish the origin of compounds **10** and **11**, we performed additional experiments. Compound **9h**, which we prepared as described in [30], was reacted with HNO_2 under the conditions of *Method C* (procedure as in *Method A*, but the charge of $NaNO_2$ was doubled, and the reaction time was prolonged). After separation of the crude reaction product by column chromatography (CC; SiO_2), the starting compound **9h** and three additional compounds, identified as **10h**, **12h**, and **13h**, were obtained. This result confirmed our assumption that compounds **10** result from **9** *via* nitration with HNO_3 produced from HNO_2 decomposition. Interesting results were obtained when the reaction of **9h** was performed in the presence of HNO_3 (*Method D*, procedure as in *Method A*, but concentrated HNO_3 was added instead of H_2O, and the reaction time was prolonged). Starting compound **9h** was not isolated, and, in addition to compound **11h**, which was the main reaction product, compound **10h** and a considerable quantity of 6-NO_2 derivative **12h** were obtained. The formation of compounds **11** from **10** was established by hydrolyzing **10h** with aqueous AcOH in the presence of urea. In addition to **11h**, a small quantity of **9h** was obtained, evidencing that the reduction of **10h** with urea also occurs, but only to a small extent at an elevated temperature.

Conclusions. – The described diastereoselective reduction of 3-aminoquinoline-2,4(1*H*,3*H*)-diones **5** represents an straightforward access to the previously unknown *cis*-amino alcohols **6**. The molecular rearrangement during their deamination with HNO_2 offered an alternative pathway to not only 3-alkyl/aryl-2,3-dihydro-1*H*-indol-2-ones **9**, but also 3-OH and 3-NO_2 derivatives **11** and **10**, respectively. Because many biologically active compounds and natural products possess a 3-hydroxy-oxindole framework with a tetrasubstituted stereogenic center C(3) [31][32], 3-NO_2 derivatives **10** are interesting structures for further study. In addition, compounds **10** are potential precursors for the synthesis of their 3-NH_2 analogs.

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Experimental Part

1. *General.* TLC: *Alugram® -SIL-G/UV$_{254}$* foils (*Macherey-Nagel*); elution with benzene/AcOEt 4 : 1, $CHCl_3$/EtOH 9 : 1 and/or 19 : 1, and $CHCl_3$/AcOEt 7 : 3. Column chromatography (CC): silica gel (SiO_2; *Merck*, grade *60*, 70 – 230 mesh); elution with $CHCl_3$, then $CHCl_3$/EtOH 99 : 1 → 8 : 2 or benzene, and then benzene/AcOEt 99 : 1 → 8 : 2. M.p.: *Kofler* block or *Gallencamp* apparatus. IR Spectra: *Smart OMNI-Transmission Nicolet iS10* spectrophotometer; KBr; in cm^{-1}. NMR Spectra: *Bruker Avance* spectrometer operating at 500.13 (^1H), 125.76 (^{13}C), and 50.68 MHz (^{15}N), and *Bruker Avance II 400* spectrometer operating at 400.13 (^1H), 100.56 (^{13}C), and 40.55 MHz (^{15}N); in (D_6)DMSO; δ in ppm rel. to TMS as an internal standard or to $MeNO_2$ as an external standard in a co-axial capillary; J in Hz; manufacturer's software for all 2D experiments (gradient-selected gs-COSY, gs-NOESY, gs-HMQC, and gs-HMBC). EI-MS (pos.): *Shimadzu QP-2010* instrument within m/z 50 – 600 using direct inlet probe (DI); analysis of samples in CH_2Cl_2 (30 μg/ml), 10 μl of the soln. evaporated in DI cuvette at 50°; ion-source temp., 200°; the energy of electrons, 70 eV; only signals exceeding rel. abundance of 5% are listed. ESI-MS (pos.): *amaZon X* ion-trap mass spectrometer (*Bruker Daltonics,* DE-Bremen) equipped with an ESI source; individual samples infused into the ion source as MeOH/H_2O 1 : 1 (*v*/*v*) soln. *via* a syringe pump at a constant flow rate of 4 μl/min; other instrumental conditions: m/z range 50 – 1500, electrospray voltage, – 4.2 kV; drying gas temp., 220°; drying gas flow, 6.0 dm^3/min, nebulizer pressure, 55.16 kPa, cap. exit, 140 V; N_2 used as nebulizing as well as drying gas. Elemental analysis (C, H, N): *Flash EA 1112* elemental analyzer (*Thermo Fisher Scientific*).

Crystallography. Single crystals of **10h** were prepared by liquid diffusion method [33] with AcOEt/hexane as solvent/precipitant pair. The X-ray data were obtained at 150 K using *Oxford Cryostream* low-temperature device on a *Nonius KappaCCD diffractometer* with MoK_α radiation ($\lambda = 0.71073$ Å), a graphite monochromator, and the ϕ and χ scan mode. Data reductions were performed with DENZO-SMN [34]. The absorption was corrected by integration methods [35]. Structures were solved by direct methods (SIR92) [36] and refined by full matrix least-square based on F^2 (SHELXL97) [37]. The H-atoms were mostly localized on a difference *Fourier* map; however, to ensure uniformity of treatment of crystal, all H-atoms were recalculated into idealized positions (riding model) and assigned temp. factors $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) with C–H = 0.93 Å for H-atoms in aromatic rings. $R_{int} = \Sigma\,|F_o^2 - F_{o,mean}^2|\,/\,\Sigma F_o^2$, GOF = $[\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{1/2}$ for all data, $R(F) = \Sigma\,||F_o| - |F_c||\,/\Sigma\,|F_o|$ for observed data, $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{1/2}$ for all data. All X-ray diffraction experiments, refinement, and analysis of the obtained XRD data were carried out by *A. R.*

Crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre*, No. CCDC-944756 for **10h**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB21EY, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

2. *General Procedure for the Preparation of 3-Aminoquinoline-2,4(1*H*,3*H*)-diones* **5f** *and* **5i**. Compounds were prepared by modifying the procedure described in [7]. The soln. of appropriate 3-chloroquinoline-2,4(1*H*,3*H*)-dione (40 mmol) in DMF (120 ml) was added during 15 min to the stirred and cooled (0°) suspension of NH_4Cl (4.27 g, 80 mmol) and K_2CO_3 (22.11 g, 160 mmol) in DMF (100 ml). The mixture was stirred for 48 h and then poured onto crushed ice (800 ml). In the case of **5f**, an oily product was obtained, which was extracted with $CHCl_3$ (3 × 30 ml), and the dried extract was separated by CC (SiO_2) to give **5f**. In the case of **5i**, the deposited precipitate was filtered with suction and suspended in HCl (10%, 160 ml). After 2 h intensive stirring, the soluble portion was extracted with benzene (3 × 15 ml), alkalized with aq. NH_3, and the precipitate of **5i** was filtered with suction and crystallized from benzene. The insoluble portion was filtered off, collected with the evaporation residue of benzene extract, and crystallized from AcOEt to give compound **5i**.

2.1. *3-Amino-3-benzyl-1-methylquinoline-2,4(1*H,*3*H*)-dione* (**5f**). Prepared from 3-benzyl-3-chloro-1-methylquinoline-2,4(1*H*,3*H*)-dione besides 2.36 g (21%) of *3-benzyl-3-hydroxy-1-methylquinoline-2,4(1*H,*3*H*)-dione* (**1f**). Yield: 3.584 g (32%). White solid. M.p. 101–104° (benzene/hexane). IR: 3392, 3319, 3059, 3025, 2917, 1697, 1654, 1601, 1546, 1473, 1373, 1298, 1242, 1109, 1016, 943, 899, 852, 771, 735, 698, 663, 624, 582, 513. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 281 (8), 280 (43, M^+), 190 (11), 189 (90), 162 (13), 161 (92), 133 (5), 118 (18), 116 (10), 106 (12), 105(5), 104 (10), 91 (11), 90 (7), 79 (6), 78 (9), 77 (23), 65 (20), 63 (6), 51 (10). ESI-MS (pos.): 561.2 (23, $[2M+H]^+$), 303.2 (4, $[M+Na]^+$), 281.2 (100, $[M+H]^+$), 264.2 (4, $[M+H-NH_3]^+$). Anal. calc. for $C_{17}H_{16}N_2O_2$ (280.32): C 72.84, H 5.75, N 9.99; found: C 72.86, H 5.75, N 9.63.

2.2. *3-Amino-3-benzyl-1-phenylquinoline-2,4(1*H,*3*H*)-dione* (**5i**). Prepared from 3-benzyl-3-chloro-1-phenylquinoline-2,4(1*H*,3*H*)-dione besides 4.94 g (36%) of *3-benzyl-3-hydroxy-1-phenylquinoline-2,4(1*H,*3*H*)-dione* (**1i**). Yield: 4.241 g (31%). White solid. M.p. 174–178° (benzene). IR: 3394, 3321, 3062, 3027, 2925, 1708, 1673, 1598, 1494, 1463, 1344, 1300, 1288, 1245, 1209, 1136, 1105, 1072, 980, 933, 831, 798, 758, 712, 702, 667, 646, 592, 521, 501. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 343 (11), 342 (45, M^+), 252 (16), 251 (94), 224 (17), 223 (100), 196 (18), 195 (13), 167 (24), 166 (8), 143 (9), 139 (6), 92 (9), 91 (56), 77 (24), 65 (7), 51 (13). ESI-MS (pos.): 685.2 (25, $[2M+H]^+$), 343.2 (100, $[M+H]^+$). Anal. calc. for $C_{22}H_{18}N_2O_2$ (342.39) : C 77.17, H 5.30, N 8.18; found: C 77.06, H 5.31, N 7.96.

Table 3. *^{1}H- and ^{13}C-NMR Data* ((D$_6$)DMSO) *of Compounds* **5** *and* **7** (δ in ppm)

Position	**5f**		**5i**		**7e**		**7h**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	171.9	–	176.1	–	158.5	–	158.3
3	–	69.7	–	69.9	9.26	–	9.34	–
3a	–	–	–	–	–	66.0	–	66.3
3-NH$_2$	2.25	–	2.24	–	–	–	–	–
4	–	194.8	–	194.8	–	167.2	–	167.1
4a	–	120.3	–	120.1	–	–	–	–
5	7.83	127.0	7.90	127.1	–	–	–	–
5a	–	–	–	–	–	137.6	–	137.7
6	7.25	123.0	7.22	123.2	7.17	116.2	6.23	117.4
7	7.71	136.2	7.51	135.7	7.15	123.6	7.14	123.9
8	7.28	115.6	6.31	116.5	7.30	128.4	7.09	128.2
8a	–	142.6	–	143.6	–	–	–	–
9	–	–	–	–	7.41	121.5	7.52	121.9
9a	–	–	–	–	–	124.5	–	124.5
9b	–	–	–	–	6.01	7.82	6.39	78.2
Substituent at N(1)								
1	3.38	29.7	–	137.7	3.40	29.9	–	–
2,6	–	–	7.38	129.3	–	–	7.34	129.0
			7.31	129.1				
3,5	–	–	7.82	130.1	–	–	7.63	130.1
			7.28	130.4				
4	–	–	7.57	129.0	–	–	7.55	128.9
Substituent at C(3)								
1	2.98	40.3	3.17	48.6	–	135.5	–	135.4
2	–	134.1	–	134.2	7.18	126.7	7.40	126.8
3,7	6.95	130.0	7.10	130.3	7.24	128.8	7.34	128.8
4,6	7.18	127.7	7.24	127.8	7.24	128.8	7.34	128.9
5	7.18	126.9	7.24	127.0	–	–	–	–

3. *General Procedure for the Reduction of Compounds* **5**. $NaBH_4$ (85 mg, 2.5 mmol) was added in four portions during 5 min to the stirred soln. of compound **5** (2 mmol) in MeOH (10 ml). After 20 min, crushed ice (up to 20 g), conc. HCl (0.25 ml), and H_2O (4 ml) were added in successive steps under cooling with crushed ice. The soln. was filtered, and the filtrate was alkalized with 6% $NaHCO_3$. Precipitated product was filtered off, washed with H_2O, and recrystallized from an appropriate solvent. The filtrate was extracted with $CHCl_3$ (3 × 20 ml). The dried extract was evaporated to dryness, and the residue was recrystallized from appropriate solvent. The yields are compiled in *Table 1*.

3.1. cis-*3-Amino-3-butyl-3,4-dihydro-4-hydroxyquinolin-2(1*H*)-one* (**6a**). Prepared from **5a**. Yield: 351 mg (75%). White solid. M.p. 175–177° (AcOEt). IR: 3365, 3073, 2958, 1681, 1596, 1565, 1486, 1390, 1307, 1251, 1201, 1072, 1033, 1004, 941, 840, 752, 698, 669, 520. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 234 (24, M^+), 160 (5), 132 (15), 122 (28), 121 (6), 113 (58), 105 (9), 104 (8), 94 (12), 93 (13), 85 (27), 77 (18), 71 (10), 57 (21), 56 (100), 55 (9), 43 (44). ESI-MS (pos.): 491.3 (5, $[2M + Na]^+$), 462.2 (4, $[2M + H]^+$), 257.2 (4, $[M + Na]^+$), 235.2 (100, $[M + H]^+$), 190.2 (15, $[M + H - NH_3 - CO]^+$). Anal. calc. for $C_{13}H_{18}N_2O_2$ (234.29): C 66.64, H 7.74, N 11.96; found: C 66.42, H 7.72, N 11.86.

3.2. cis-*3-Amino-3,4-dihydro-4-hydroxy-3-phenylquinolin-2(1*H*)-one* (**6b**). Prepared from **5b**. Yield: 406 mg (80%). White solid. M.p. 248–254° (EtOH). IR: 3361, 3197, 3079, 2908, 1673, 1596, 1550, 1483, 1382, 1184, 1130, 1079, 1018, 975, 939, 817, 752, 694, 663, 568, 538. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 254 (24, M^+), 133 (31), 122 (15), 106 (13), 105 (100), 104 (48), 94 (8), 93 (8), 77 (28), 51 (8). ESI-MS (pos.): 277.2 (5, $[M + Na]^+$), 255.2 (100, $[M + H]^+$), 238.2 (29, $[M + H - NH_3]^+$), 210.2 (9, $[M + H - NH_3 - CO]^+$). Anal. calc. for $C_{15}H_{14}N_2O_2$ (254.28): C 70.85, H 5.55, N 11.02; found: C 70.70, H 5.47, N 10.79.

3.3. cis-*3-Amino-3-benzyl-3,4-dihydro-4-hydroxyquinolin-2(1*H*)-one* (**6c**). Prepared from **5c**. Yield: 402 mg (75%). White solid. M.p. 184–194° and then 234–235° (AcOEt). IR: 3347, 3207, 3153, 3095, 2958, 2896, 2726, 1689, 1614, 1596, 1556, 1494, 1479, 1454, 1392, 1357, 1324, 1272, 1243, 1203, 1128, 1072, 1004, 935, 908, 755, 721, 700, 659, 592, 491. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 178 (11), 177 (100, $[M - Bn]^+$), 176 (43), 175 (6), 160 (40), 159 (13), 149 (10), 147 (13), 132 (75), 131 (14), 122 (13), 120 (15), 119 (42), 118 (11), 117 (9), 105 (9), 104 (36), 94 (8), 93 (16), 92 (17), 91 (58), 77 (33), 65 (23), 51 (11). ESI-MS (pos.): 307.2 (4, $[M + K]^+$), 291.2 (10, $[M + Na]^+$), 269.2 (100, $[M + H]^+$). Anal. calc. for $C_{16}H_{16}N_2O_2$ (268.31): C 71.62, H 6.01, N 10.44; found: C 71.73, H 6.04, N 10.39.

3.4. cis-*3-Amino-3-butyl-3,4-dihydro-4-hydroxy-1-methylquinolin-2(1*H*)-one* (**6d**). Prepared from **5d**. Yield: 362 mg (73%). White solid. M.p. 117–120° (benzene/hexane). IR: 3357, 3297, 2954, 2869, 1672, 1604, 1575, 1457, 1363, 1309, 1232, 1122, 1081, 1006, 950, 759, 673, 607. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 248 (10, M^+), 220 (11), 191 (12), 189 (9), 174 (14), 163 (9), 160 (7), 147 (7), 146 (31), 137 (11), 136 (100), 135 (19), 119 (8), 118 (51), 117 (8), 113 (69), 106 (20), 93 (8), 91 (22), 86 (13), 85 (20), 78 (7), 77 (20), 57 (11), 56 (88), 43 (34). ESI-MS (pos.): 491.3 (4, $[2M + Na]^+$), 271.3 (4, $[M + Na]^+$), 249.3 (100, $[M + H]^+$), 204.3 (11, $[M + H - NH_3 - CO]^+$). Anal. calc. for $C_{14}H_{20}N_2O_2$ (248.32): C 67.71, H 8.12, N 11.28; found: C 67.94, H 8.14, N 11.31.

3.5. cis-*3-Amino-3,4-dihydro-4-hydroxy-1-methyl-3-phenylquinolin-2(1*H*)-one* (**6e**). Prepared from **5e**. Yield: 482 mg (90%). White solid. M.p. 199–203° (benzene). IR: 3353, 3288, 3066, 2881, 2817, 1668, 1604, 1548, 1473, 1365, 1259, 1201, 1124, 1076, 1039, 987, 848, 757, 703, 684, 615, 568, 545. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 268 (30, M^+), 136 (37), 135 (10), 134 (6), 133 (31), 118 (28), 106 (29), 105 (100), 104 (44), 91 (12), 77 (30), 51 (9). ESI-MS (pos.): 291.2 (5, $[M + Na]^+$), 269.3 (100, $[M + H]^+$), 252.2 (20, $[M + H - NH_3]^+$), 224.3 (8, $[M + H - NH_3 - CO]^+$). Anal. calc. for $C_{16}H_{16}N_2O_2$ (268.31): C 71.62, H 6.01, N 10.44; found: C 71.78, H 6.11, N 10.45.

3.6. cis-*3-Amino-3-benzyl-3,4-dihydro-4-hydroxy-1-methylquinolin-2(1*H*)-one* (**6f**). Prepared from **5f**. Yield: 423 mg (75%). White solid. M.p. 137–140° (AcOEt). IR: 3350, 3281, 3059, 3028, 2884, 2816, 2718, 1665, 1604, 1591, 1495, 1472, 1415, 1371, 1207, 1117, 1071, 1048, 971, 871, 761, 730, 701, 643, 587, 508. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 192 (12), 191 (100, $[M - Bn]^+$), 190 (33), 174 (70), 173 (9), 147 (15), 146 (83), 145 (13), 136 (13), 119 (24), 118 (36), 117 (14), 106 (15), 104 (23), 92 (11), 91 (72), 77 (25), 65 (22), 51 (10). ESI-MS (pos.): 321.2 (4, $[M + K]^+$), 305.2 (5, $[M + Na]^+$), 283.3 (100, $[M + H]^+$). Anal. calc. for $C_{17}H_{18}N_2O_2$ (282.34): C 72.32, H 6.43, N 9.92; found: C 72.26, H 6.42, N 9.78.

3.7. cis-*3-Amino-3-butyl-3,4-dihydro-4-hydroxy-1-phenylquinolin-2(1*H*)-one* (**6g**). Prepared from **5g**. Yield: 428 mg (69%). White solid. M.p. 192–195° (AcOEt). IR: 3376, 3342, 3288, 2954, 2929, 2859, 1674,

Table 4. *^{1}H- and ^{13}C-NMR Data* ((D_6)DMSO) *of Compounds* **6** (δ in ppm)

Position	**6a**		**6b**		**6c**		**6d**		**6e**		**6f**		**6g**		**6h**		**6i**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
2	–	173.2	–	172.8	–	172.1	–	172.4	–	172.4	–	171.4	–	172.7	–	172.7	–	171.6
3	–	59.4	–	63.2	–	60.3	–	59.6	–	63.6	–	60.6	–	60.0	–	60.0	–	60.8
3-NH_2	1.84	–	2.46	–	1.75	–	1.85	–	2.48	–	1.79	–	1.95	–	1.95	–	1.90	–
4	4.62	72.9	4.93	73.4	4.54	72.3	4.62	72.1	4.95	72.4	4.56	71.5	4.83	72.2	4.83	72.2	4.73	71.7
4-OH	5.61	–	5.94	–	5.83	–	5.67	–	6.06	–	5.89	–	5.79	–	5.79	–	6.01	–
4a	–	127.3	–	127.8	–	127.0	–	128.8	–	129.3	–	128.4	–	128.4	–	128.4	–	128.1
5	7.39	126.0	7.34	125.2	7.38	126.0	7.46	125.8	7.37	124.7	7.46	126.1	7.52	126.3	7.52	126.3	7.50	126.3
6	7.01	122.1	6.98	122.5	7.03	122.1	7.13	122.8	7.06	123.1	7.14	122.8	7.10	122.9	7.10	122.9	7.11	123.0
7	7.21	127.9	7.19	127.8	7.22	128.1	7.34	128.1	7.29	127.9	7.37	128.3	7.14	127.7	7.14	127.8	7.18	128.1
8	6.86	114.4	6.93	114.6	6.93	114.5	7.11	114.1	7.15	114.3	7.16	114.3	6.20	115.4	6.20	115.4	6.27	115.9
8a	–	135.7	–	135.3	–	136.0	–	137.9	–	137.5	–	138.0	–	138.8	–	138.8	–	139.1
Substituent at N(1)																		
1	10.12	–	10.53	–	10.26	–	3.31	29.6	3.44	29.9	3.31	29.6	–	138.7	–	138.7	–	138.8
2,6	–	–	–	–	–	–	–	–	–	–	–	–	7.22	129.9	7.22	129.2	7.28	129.2
3,5	–	–	–	–	–	–	–	–	–	–	–	–	7.59	129.2	7.59	129.9	7.59	129.8
4	–	–	–	–	–	–	–	–	–	–	–	–	7.49	128.1	7.50	128.2	7.50	128.1
Substituent at C(3)																		
1	1.59, 1.27	31.0	–	140.4	2.86, 2.69	37.3	1.50, 1.22	31.1	–	140.4	2.80, 2.68	37.7	1.62, 1.44	31.0	1.64, 1.45	31.0	2.96, 2.84	37.5
2	1.35, 1.10	24.9	7.44	127.7	–	137.0	1.34, 1.08	24.9	7.26	127.7	–	136.8	1.44, 1.23	25.0	1.47, 1.23	25.0	–	136.8
3,7	1.17	22.8	7.17	127.4	7.18	130.6	1.16	22.8	7.13	127.4	7.07	130.5	1.23	22.8	1.23	22.8	7.26	130.8
4,6	0.83	14.1	7.17	126.9	7.26	127.6	0.81	14.1	7.13	126.9	7.26	127.7	0.88	14.1	0.86	14.1	7.31	127.8
5	–	–	–	–	7.21	126.1	–	–	–	–	7.22	126.3	–	–	–	–	7.26	126.8

1604, 1591, 1575, 1492, 1456, 1377, 1346, 1257, 1199, 1170, 1155, 1070, 1012, 989, 837, 756, 700, 646, 532, 501. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 310 (21, M^+), 236 (6), 235 (7), 223 (6), 208 (12), 198 (21), 197 (64), 196 (21), 181 (14), 180 (61), 169 (7), 168 (31), 167 (17), 152 (6), 150 (7), 149 (69), 113 (54), 105 (10), 104 (11), 97 (14), 93 (15), 86 (33), 85 (27), 84 (9), 83 (14), 81 (9), 77 (25), 71 (20), 70 (12), 69 (24), 67 (12), 65 (13), 57 (54), 56 (100), 55 (31), 51 (12), 43 (65), 42 (25), 41 (52). ESI-MS (pos.): 621.3 (5, $[2M+H]^+$), 311.3 (100, $[M+H]^+$), 266.3 (7, $[M+H-NH_3-CO]^+$). Anal. calc. for $C_{19}H_{22}N_2O_2$ (310.39): C 73.52, H 7.14, N 9.03; found: C 73.54, H 7.11, N 8.80.

3.8. cis-*3-Amino-3,4-dihydro-1,3-diphenyl-4-hydroxyquinolin-2(1*H*)-one* (**6h**). Prepared from **5h**. Yield: 515 mg (78%). White solid. M.p. 197–199° (AcOEt). IR: 3357, 3303, 3224, 3058, 1685, 1589, 1493, 1459, 1446, 1349, 1297, 1261, 1197, 1122, 1072, 1035, 947, 893, 852, 762, 721, 698, 679, 650, 555, 509. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 331 (5), 330 (20, M^+), 198 (13), 197 (53), 196 (18), 181 (9), 180 (41), 169 (6), 168 (28), 167 (12), 133 (26), 106 (32), 105 (100), 104 (51), 93 (8), 77 (32), 65 (6), 57 (6), 51 (13). ESI-MS (pos.): 683.3 (7, $[2M+Na]^+$), 661.2 (10, $[2M+H]^+$), 369.2 (5, $[M+K]^+$), 353.2 (10, $[M+Na]^+$), 331.2 (100, $[M+H]^+$), 314.2 (31, $[M+H-NH_3]^+$), 286.2 (24, $[M+H-NH_3-CO]^+$). Anal. calc. for $C_{21}H_{18}N_2O_2$ (330.38): C 76.34, H 5.49, N 8.48; found: C 76.44, H 5.52, N 8.51.

3.9. cis-*3-Amino-3-benzyl-3,4-dihydro-4-hydroxy-1-phenylquinolin-2(1*H*)-one* (**6i**). Prepared from **5i**. Yield: 550 mg (80%). White solid. M.p. 200–201° (AcOEt). IR: 3355, 3278, 3060, 2917, 2724, 1676, 1585, 1489, 1454, 1358, 1346, 1292, 1255, 1201, 1128, 1072, 975, 955, 877, 856, 759, 729, 698, 640, 598, 503. ^{1}H- and ^{13}C-NMR: see *Table 4*. EI-MS: 254 (17), 253 (100, $[M-Bn]^+$), 252 (24), 236 (45), 235 (16), 208 (42), 197 (13), 196 (9), 180 (43), 168 (19), 167 (14), 120 (9), 119 (28), 118 (9), 104 (22), 92 (11), 91 (41), 77 (27), 65 (18), 51 (13). ESI-MS (pos.): 689.3 (11, $[2M+H]^+$), 345.3 (100, $[M+H]^+$). Anal. calc. for $C_{22}H_{20}N_2O_2$ (344.41): C 76.72, H 5.85, N 8.13; found: C 76.83, H 5.90, N 8.13.

4. *Reaction of Compounds* **6** *with Triphosgene.* Triphosgene (= bis(trichloromethyl) carbonate; 43 mg, 0.145 mmol) was added in several portions during 1 h to the well-stirred soln. of **6** (0.4 mmol), Et_3N (0.121 ml, 0.87 mmol), and 4-(dimethylamino)pyridine (DMAP; 20 mg, 0.18 mmol) in benzene (10 ml). The soln. was stirred at r.t. for 1 h, and the reaction was monitored by TLC. The suspension was filtered, and the filtrate was evaporated to dryness. H_2O (15 ml) was added to the residue, and the suspension was extracted with benzene (3 × 20 ml). Collected extracts were dried, evaporated, and the residue was crystallized from appropriate solvent or subjected to CC (SiO_2).

4.1. *3,3a,5,9b-Tetrahydro-5-methyl-3a-phenyl[1,3]oxazolo[4,5-*c*]quinoline-2,4-dione* (**7e**). Prepared from **6e**. Yield: 82 mg (70%). White solid. M.p. 267–273° (EtOH). IR: 3232, 3123, 2971, 1754, 1690, 1614, 1584, 1492, 1465, 1448, 1395, 1346, 1304, 1265, 1209, 1191, 1160, 1131, 1092, 1021, 976, 949, 939, 896, 768, 722, 700, 679, 639, 581, 548. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 295 (19), 294 (100, M^+), 266 (18), 250 (13), 221 (15), 207 (12), 206 (11), 205 (7), 194 (16), 165 (11), 163 (18), 152 (10), 147 (21), 146 (13), 135 (61), 134 (58), 118 (64), 117 (16), 107 (33), 106 (89), 105 (36), 104 (82), 103 (34), 91 (30), 90 (13), 89 (22), 78 (21), 77 (96), 76 (18), 65 (14), 63 (17), 51 (43). ESI-MS (pos.): 333.2 (27, $[M+K]^+$), 317.2 (84, $[M+Na]^+$), 295.3 (51, $[M+H]^+$), 251.3 (100, $[M+H-CO_2]^+$). Anal. calc. for $C_{17}H_{14}N_2O_3$ (294.30): C 69.38, H 4.79, N 9.52; found: C 69.43, H 4.91, N 9.37.

4.2. *3,3a,5,9b-Tetrahydro-3a,5-diphenyl[1,3]oxazolo[4,5-*c*]quinoline-2,4-dione* (**7h**). Prepared from **6h**. Yield: 92 mg (65%). White solid. M.p. 260–270° (EtOH). IR: 3292, 3062, 2972, 1778, 1702, 1612, 1492, 1459, 1324, 1257, 1200, 1132, 1095, 1025, 948, 935, 896, 765, 752, 723, 696, 638, 596, 582. ^{1}H- and ^{13}C-NMR: see *Table 3*. EI-MS: 357 (22), 356 (89, M^+), 328 (23), 285 (9), 284 (36), 283 (28), 256 (18), 208 (7), 207 (21), 205 (7), 197 (29), 196 (44), 181 (17), 180 (100), 179 (10), 168 (36), 152 (15), 127 (14), 104 (34), 103 (21), 89 (14), 77 (72), 63 (10), 51 (39). ESI-MS (pos.): 735.2 (5, $[2M+Na]^+$), 395.2 (7, $[M+K]^+$), 379.3 (28, $[M+Na]^+$), 357.3 (31, $[M+H]^+$), 313.3 (100, $[M+H-CO_2]^+$). Anal. calc. for $C_{22}H_{16}N_2O_3$ (356.37): C 74.15, H 4.53, N 7.86; found: C 74.22, H 4.75, N 7.76.

5. Rearrangement of Compounds **6**. *Method A.* Under intensive stirring, compound **6** (0.75 mmol) was dissolved in AcOH (4.5 ml). After cooling to 0°, H_2O (0.45 ml) and then solid $NaNO_2$ (103 mg, 1.5 mmol) were added during 5 min, and stirring was continued for 2 h at r.t. Solid urea (45 mg, 0.75 mmol) was added to quench redundant HNO_2, and after 15 min the mixture was blended with crushed ice (15 g). The deposited precipitate was filtered with suction and washed with H_2O (10 ml). The filtrate was extracted with $CHCl_3$ (3 × 20 ml). The extract was dried and evaporated *in vacuo* to dryness. Both portions were collected and subjected to CC (SiO_2). In the cases when the crude product was pasty,

the reaction mixture was extracted with $CHCl_3$ (3×20 ml), the collected extracts were evaporated to dryness and purified by CC (SiO_2). *Method B:* The reaction was carried out in the same way as *Method A*, merely the addition of urea was omitted. The yields are collected in *Table 2*.

5.1. *3-Butyl-1,3-dihydro-2*H-*indol-2-one* (**9a**). Prepared from **6a.** Yields: 34 (24%, *Method A*) and 33 mg (23%; *Method B*). White solid. M.p. 62–64° ([38]: 62–63° (hexane)). IR: 2956, 2931, 2867, 1705, 1618, 1469, 1411, 1376, 1340, 1317, 1228, 1172, 1153, 1101, 1020, 1002, 941, 929, 868, 831, 795, 748, 727, 704, 667, 580, 557, 492. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 189 (21, M^+) , 146 (49), 133 (100), 132 (29), 128 (7), 119 (7), 118 (8), 117 (10), 105 (7), 104 (19), 91 (6), 90 (5), 78 (7), 77 (21), 51 (9). ESI-MS (pos.): 401.2 (8, $[2M + Na]^+$), 379.3 (23, $[2M + H]^+$), 228.1 (5, $[M + K]^+$), 212.2 (19, $[M + Na]^+$), 190.2 (100, $[M + H]^+$). Anal. calc. for $C_{12}H_{15}NO$ (189.25): C 76.16, H 7.99, N 7.40; found: C 76.22, H 8.05, N 7.49.

5.2. *1,3-Dihydro-3-phenyl-2*H-*indol-2-one* (**9b**). Prepared from **6b**. Yields: 5 (3%; *Method A*) and 14 mg (9%; *Method B*). White solid. M.p. 190–195° ([39]: 190–192° (benzene/hexane)). IR: 3185, 3085, 3031, 1704, 1616, 1469, 1322, 1224, 1182, 1097, 1074, 1035, 939, 871, 836, 752, 709, 684, 663, 593. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 210 (14), 209 (87, M^+), 181 (15), 180 (100), 179 (6), 165 (8), 152 (15), 96 (16), 90 (15), 89 (6), 77 (14), 76 (12), 63 (6), 51 (9). ESI-MS (pos.): 441.2 (14, $[2M + Na]^+$), 438.2 (5, $[4M + Ca]^{2+}$), 419.2 (25, $[2M + H]^+$), 333.7 (13, $[3M + Ca]^{2+}$), 232.2 (17, $[M + Na]^+$), 229.2 (8, $[2M + Ca]^{2+}$), 210.2 (100, $[M + H]^+$), 132.2 (38, $[M + H - C_6H_6]^+$). Anal. calc. for $C_{14}H_{11}NO$ (209.24): C 80.36, H 5.30, N 6.69; found C 80.20, H 5.12, N 6.45.

5.3. *3-Benzyl-1,3-dihydro-2*H-*indol-2-one* (**9c**). Prepared from **6c**. Yields: 47 (28%; *Method A*) and 58 mg (35%; *Method B*). White solid. M.p. 129–131° ([40]: 129–130° (AcOEt/hexane)). IR: 3033, 2920, 2895, 2850, 1708, 1622, 1496, 1471, 1340, 1311, 1236, 1151, 1078, 1016, 962, 937, 854, 808, 748, 694, 665, 613, 588, 550. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 223 (19, M^+), 132 (17), 104 (6), 92 (8), 91 (100), 77 (10), 65 (10), 51 (6). ESI-MS (pos.): 485.2 (6, $[2M + K]^+$), 469.2 (12, $[2M + Na]^+$), 466.2 (6, $[4M + Ca]^{2+}$), 447.2 (5, $[2M + H]^+$), 354.7 (9, $[3M + Ca]^{2+}$), 262.1 (6, $[M + K]^+$), 246.2 (32, $[M + Na]^+$), 243.2 (17, $[2M + Ca]^+$), 224.2 (100, $[M + H]^+$), 196.2 (19, $[M + H - CO]^+$). Anal. calc. for $C_{15}H_{13}NO$ (223.27): C 80.69, H 5.87, N 6.27; found: C 80.25, H 5.95, N 6.52.

5.4. *3-Butyl-1,3-dihydro-1-methyl-2*H-*indol-2-one* (**9d**). Prepared from **6d**. Yields: 78 (51%; *Method A*) and 64 mg (42%; *Method B*). Yellowish oil, b.p. 110–120°/0.5 Torr ([41]: 120–122°/0.6 Torr). IR: 3055, 2956, 2931, 1712, 1614, 1494, 1469, 1376, 1346, 1259, 1130, 1085, 1020, 925, 750, 701, 611, 541. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 203 (58, M^+), 202 (54), 174 (11), 161 (16), 160 (100), 148 (10), 147 (50), 132 (15), 131 (11), 130 19), 104 (8). ESI-MS (pos.): 429.3 (19, $[2M + Na]^+$), 426.3 (7, $[4M + Ca]^{2+}$), 407.3 (5, $[2M + H]^+$), 242.2 (13, $[M + K]^+$), 226.2 (44, $[M + Na]^+$), 204.2 (100, $[M + H]^+$). Anal. calc. for $C_{13}H_{17}NO$ (203.28): C 76.81, H 8.43, N 6.89; found: C 76.65, H 8.41, N 6.79.

5.5. *1,3-Dihydro-1-methyl-3-phenyl-2*H-*indol-2-one* (**9e**). Prepared from **6e**. Yields: 8 (5%; *Method A*) and 18 mg (11%; *Method B*). White solid. M.p. 117–120° ([42]: 117–119° (cyclohexane)). IR: 3052, 3023, 2933, 2908, 1693, 1610, 1496, 1465, 1374, 1346, 1263, 1170, 1124, 1085, 1020, 931, 877, 752, 730, 703, 642, 543. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 224 (18), 223 (100, M^+), 195 (13), 194 (73), 180 (6), 179 (10), 167 (11), 165 (15), 153 (7), 152 (12), 150 (7), 149 (52), 139 (8), 127 (11), 125 (11), 118 (13), 113 (14), 111 (19), 109 (9), 99 (13), 97 (26), 95 (13), 85 (31), 84 (10), 83 (32), 82 (13), 81 (16), 77 (11), 76 (11), 71 (53), 70 (20), 69 (32), 57 (69), 56 (14), 55 (33), 43 (51). ESI-MS (pos.): 469.2 (36, $[2M + Na]^+$), 447.2 (5, $[2M + H]^+$), 354.7 (9, $[3M + Ca]^{2+}$), 262.1 (36, $[M + K]^+$), 246.2 (100, $[M + Na]^+$), 243.2 (30, $[2M + Ca]^+$), 224.2 (78, $[M + H]^+$). Anal. calc. for $C_{15}H_{13}NO$ (223.27): C 80.69, H 5.87, N 6.27; found: C 80.27, H 5.82, N 6.14.

5.6. *3-Benzyl-1,3-dihydro-1-methyl-2*H-*indol-2-one* (**9f**). Prepared from **6f**. Yields: 71 (40%; *Method A*) and 50 mg (28%; *Method B*). White solid. M.p. 65–68° ([43]: 67–68° (hexane)). IR: 3055, 3027, 2917, 1700, 1610, 1492, 1469, 1454, 1371, 1355, 1338, 1265, 1232, 1157, 1120, 1087, 991, 894, 850, 792, 755, 750, 725, 703, 622, 584, 539. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 238 (7), 237 (39, M^+), 160 (8), 147 (8), 146 (75), 118 (8), 117 (7), 92 (8), 91 (100), 77 (5), 65 (13). ESI-MS (pos.): 497.2 (26, $[2M + Na]^+$), 494.3 (9, $[4M + Ca]^{2+}$), 375.8 (18, $[3M + Ca]^{2+}$), 276.2 (13, $[M + K]^+$), 260.2 (82, $[M + Na]^+$), 257.2 (35, $[2M + Ca]^+$), 238.3 (100, $[M + H]^+$), 210.3 (5, $[M + H - CO]^+$). Anal. calc. for $C_{16}H_{15}NO$ (237.30): C 80.98, H 6.37, N 5.90; found: C 80.68, H 6.34, N 5.84.

5.7. *3-Butyl-1,3-dihydro-1-phenyl-2*H-*indol-2-one* (**9g**). Prepared from **6g**. Yields: 91 (46%; *Method A*) and 78 mg (39%; *Method B*). Yellowish oil. B.p. 165–185°/0.5 Torr ([30]: 170–190°/0.5 Torr). IR:

Table 5. *^{1}H- and ^{13}C-NMR Data* ($(D_6)DMSO$) *of Rearrangement Products of* **6***: Compounds* **9** (δ in ppm)

	9b		**9c**		**9d**		**9e**		**9f**		**9g**		**9h**		**9i**	
δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
179.0	–	176.9		178.2	–	177.0	–	175.4	–	176.2	–	176.6	–	175.0	–	175.9
45.1	4.77	51.7	3.84	46.5	3.53	44.6	4.87	51.2	3.91	46.0	3.78	44.8	5.11	51.5	4.14	46.2
129.9	–	129.9	–	129.0	–	129.0	–	129.2	–	128.1	–	128.9	–	129.3	–	129.7
124.0	7.08	124.6	6.90	124.4	7.33	123.7	7.13	124.5	6.91	124.0	7.44	124.3	7.22	125.1	7.16	124.7
121.3	6.99	121.4	6.87	121.0	7.07	122.0	7.07	122.4	6.95	121.7	7.14	122.6	7.13	123.0	7.04	122.3
127.6	7.27	127.9	7.14	127.7	7.32	127.7	7.38	128.3	7.25	127.0	7.26	127.8	7.31	128.2	7.17	128.0
109.2	6.97	109.3	6.77	109.2	7.02	108.2	7.13	108.7	6.92	108.2	6.76	108.7	6.84	109.1	6.60	108.6
142.9	–	142.7	–	142.7	–	144.3	–	144.3	–	144.1	–	144.0	–	144.0	–	144.0
–	10.43	–	10.36	–	3.16	25.9	3.23	26.2	3.10	25.9	–	134.6	–	134.5	–	134.5
–	–	–	–	–	–	–	–	–	–	–	7.44	126.7	7.53	127.0	7.25	126.7
–	–	–	–	–	–	–	–	–	–	–	7.62	129.7	7.64	129.7	7.58	129.7
–	–	–	–	–	–	–	–	–	–	–	7.49	128.0	7.51	128.3	7.48	127.9
29.6	–	137.6	3.36, 2.99	35.3	1.92, 1.82	29.6	–	144.3	3.38, 2.97	35.5	2.02, 1.97	29.8	–	137.6	3.46, 3.21	35.8
27.4	7.20	128.1	–	138.2	1.22	27.4	7.18	128.5	–	138.0	1.34	27.3	7.33	128.6	–	137.5
22.3	7.39	128.5	7.18	129.4	1.29	22.2	7.38	128.8	7.18	129.3	1.34	22.2	7.43	128.9	7.17	129.4
13.9	7.32	126.9	7.25	128.1	0.86	13.8	7.33	127.3	7.27	128.1	0.88	13.8	7.37	127.4	7.23	128.1
–	–	–	7.21	126.4	–	–	–	–	7.20	126.4	–	–	–	–	7.21	126.6

2956, 2929, 2857, 1720, 1612, 1502, 1481, 1463, 1373, 1326, 1220, 1170, 1101, 1025, 752, 700, 644, 626, 590, 566. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 266 (9), 265 (44, M^+), 223 (12), 222 (67, 210 (16), 209 (100), 196 (14), 181 (8), 180 (47), 167 (12), 152 (12), 115 8), 91 (14), 77 (28), 51 (19). ESI-MS (pos.): 553.3 (6, $[2M+Na]^+$), 531.2 (6, $[2M+H]^+$), 304.2 (7, $[M+K]^+$), 288.3 (19, $[M+Na]^+$), 266.3 (100, $[M+H]^+$). Anal. calc. for $C_{18}H_{19}NO$ (265.35): C 81.47, H 7.22, N 5.28; found: C 81.21, H 7.13, N 5.13.

5.8. *1,3-Dihydro-1,3-diphenyl-2*H-*indol-2-one* (**9h**). Prepared according to [30]. White solid. M.p. 110–112° ([30]: 111–113° (hexane)). IR: 3068, 3028, 2998, 1713, 1610, 1594, 1501, 1467, 1454, 1366, 1325, 1298, 1251, 1215, 1178, 1168, 1099, 1074, 1026, 980, 883, 868, 795, 756, 739, 697, 659, 638, 619, 601, 505. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 286 (13), 285 (59, M^+), 257 (21), 256 (100), 254 (16), 180 (13), 152 (8), 128 (7), 127 (13), 77 (10), 51 (8). ESI-MS (pos.): 593.2 (14, $[2M+Na]^+$), 571.2 (4, $[2M+H]^+$), 324.2 (20, $[M+K]^+$), 308.2 (58, $[M+Na]^+$), 286.2 (100, $[M+H]^+$). Anal. calc. for $C_{20}H_{15}NO$ (285.34): C 84.19, H 5.30, N 4.91; found: C 84.29, H 5.30, N 4.76.

5.9. *3-Benzyl-1,3-dihydro-1-phenyl-2*H-*indol-2-one* (**9i**). Prepared from **6i**. Yields: 52 (23%; *Method A*) and 58 mg (26%; *Method B*). White solid. M.p. 90–94° ([30]: 90–94° (i-PrOH)). IR: 3060, 3035, 2917, 2865, 1722, 1608, 1592, 1496, 1479, 1463, 1452, 1371, 1327, 1275, 1225, 1171, 1101, 1078, 1024, 914, 845, 752, 733, 700, 645, 633, 594, 561. ^{1}H- and ^{13}C-NMR: see *Table 5*. EI-MS: 300 (13), 299 (54, M^+), 222 (10), 209 (13), 208 (81), 181 (7), 180 (49), 179 (12), 178 (8), 152 (19), 92 (8), 91 (100), 77 (22), 65 (13), 51 (19). ESI-MS (pos.): 621.2 (11, $[2M+Na]^+$), 599.2 (7, $[2M+H]^+$), 338.2 (10, $[M+K]^+$), 322.2 (24, $[M+Na]^+$), 300.2 (100, $[M+H]^+$). Anal. calc. for $C_{21}H_{17}NO$ (299.37): C 84.25, H 5.72, N 4.68; found: C 84.02, H 5.71, N 4.50.

5.10. *1,3-Dihydro-3-nitro-3-phenyl-2*H-*indol-2-one* (**10b**). Prepared from **6b**. Yields: 59 (31%; *Method A*) and 13 mg (7%; *Method B*). Yellowish solid. M.p 140–142° (benzene/hexane). IR: 3208, 3178, 3108, 1727, 1617, 1552, 1471, 1448, 1411, 1340, 1328, 1295, 1218, 1101, 1083, 1002, 948, 821, 748, 698, 674, 644, 620, 611, 485. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 210 (14), 209 (93), 208 (32), 181 (17), 180 (100), 179 (11), 178 (6), 152 (17), 90 (17), 89 (7), 77 (12), 76 (12), 63 (5), 51 (6). ESI-MS (pos.): 531.1 (5, $[2M+Na]^+$), 293.1 (20, $[M+K]^+$), 277.2 (16, $[M+Na]^+$), 247.1 (17, $[M+K-NO_2]^+$), 231.2 (24, $[M+Na-NO_2]^+$), 208.2 (100, $[M+H-NO_2]^+$), 180.2 (8, $[M+H-NO_2-CO]^+$). Anal calc. for $C_{14}H_{10}N_2O_3$ (254.24): C 66.14, H 3.96, N 11.02; found: C 66.08, H 3.80, N 10.93.

5.11. *3,4-Dihydro-1-methyl-3-nitro-3-phenylquinolin-2(1*H*)-one* (**10e**). Prepared from **6e**. Yields: 56 (28%; *Method A*) and 24 mg (12%; *Method B*). Yellow solid, m.p. 123–128° (cyclohexane). IR: 3060, 2975, 2937, 1727, 1610, 1558, 1492, 1469, 1336, 1245, 1128, 1089, 952, 806, 752, 738, 696, 684, 538. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 224 (15), 223 (100), 222 (68), 208 (8), 207 (14), 195 (11), 194 (69), 193 (11), 179 (10), 178 (6), 166 (7), 165 (26), 153 (6), 152 (17), 151 (8), 118 (12), 116 (7), 89 (8), 76 (7). ESI-MS (pos.): 559.2 (5, $[2M+Na]^+$), 307.1 (45, $[M+K]^+$), 291.2 (62, $[M+Na]^+$), 261.1 (37, $[M+K-NO_2]^+$), 245.2 (98, $[M+Na-NO_2]^+$), 222.2 (100, $[M+H-NO_2]^+$), 194.2 (4, $[M+H-NO_2-CO]^+$). Anal. calc. for $C_{15}H_{12}N_2O_3$ (268.27): C 67.16, H 4.51, N 10.44; found: C 66.99, H 4.47, N 10.45.

5.12. *1,3-Dihydro-3-nitro-1,3-diphenyl-2*H-*indol-2-one* (**10h**). Prepared from **6b**. Yields: 10 (4%; *Method A*) and 40 mg (16%; *Method B*). Yellowish solid, M.p. 133–138° (benzene/hexane). IR: 3066, 3043, 2924, 1739, 1610, 1594, 1556, 1498, 1465, 1446, 1371, 1340, 1324, 1309, 1213, 1180, 1099, 1076, 1025, 962, 948, 835, 808, 757, 732, 694, 651, 622, 588. ^{1}H- and ^{13}C-NMR: see *Table 6*. EI-MS: 286 (11), 285 (50), 284 (8), 257 (21), 256 (100), 254 (20), 180 (16), 179 (6), 178 (6), 152 (11), 151 (6), 128 (8), 127 (15), 51 (9), 44 (7). ESI-MS (pos.): 683.1 (3, $[2M+Na]^+$), 369.1 (16, $[M+K]^+$), 353.2 (24, $[M+Na]^+$), 323.2 (30, $[M+K-NO_2]^+$), 307.2 (66, $[M+Na-NO_2]^+$), 285.2 (100, $[M+H-NO_2]^+$). Anal. calc. for $C_{20}H_{14}N_2O_3$ (330.34): C 72.72, H 4.27, N 8.48; found: C 72.29, H 4.26, N 8.26.

Crystallographic Data for **10h**. $C_{20}H_{14}N_2O_3$, M_r 330.33, triclinic, $P\bar{1}$, $a = 8.7901(5)$, $b = 9.5950(4)$, $c = 9.9790(3)$ Å, $\alpha = 91.935(4)$, $\beta = 101.309(6)$, $\gamma = 106.188(5)°$, $Z = 2$, $V = 789.07(7)$ Å^3, $D_c = 1.390$ g cm^{-3}, $\mu = 0.095$ mm^{-1}, $T_{min}/T_{max} = 0.973/0.982$; $-11 \le h \le 11$, $-12 \le k \le 12$, $-12 \le l \le 12$; 14684 reflections measured ($\theta_{max} = 27.5°$), 14644 independent ($R_{int} = 0.0229$), 3073 with $I > 2\sigma(I)$, 226 parameters, $S = 1.077$, R_1 (obs. data) = 0.0388, wR_2 (all data) = 0.0971; max., min. residual electron density = 0.303, −0.227 eÅ^{-3}.

5.13. *1,3-Dihydro-3-hydroxy-3-phenyl-2*H-*indol-2-one* (**11b**). Prepared from **6b**. Yield: 14 mg (8%, *Method B*). White solid. M.p. 211–216° ([44]: 211–214° (benzene)). IR: 3415, 3214, 3072, 1708, 1617, 1469, 1340, 1303, 1184, 1120, 1066, 939, 900, 781, 755, 738, 690, 665, 609, 497. ^{1}H- and ^{13}C-NMR: see

Table 6. *^{1}H-, ^{13}C-, and ^{15}N-NMR Data* ((D$_6$)DMSO) *of Rearrangement Products of* **6***: Compounds* **10**, **11**, *and* **12** (δ in ppm)

Position	**10b**		**10e**		**10h**		**11b**		**11h**		**12h**	
	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)	δ(H)	δ(C)
1	–	246.0[a])	–	–	–	–	–	–	–	–	–	–
2	–	168.8	–	167.4	–	166.9	–	178.6	–	176.4	–	176.0
3	–	94.9	–	94.4	–	94.6	–	77.4	–	77.2	–	76.8
3-OH	–	–	–	–	–	–	6.67	–	6.99	–	7.33	–
3a	–	124.9	–	123.4	–	123.2	–	133.8	–	133.1	–	133.5
4	7.63	126.1	7.69	125.9	7.81	126.5	7.15	124.9	7.30	125.1	7.57	126.0
5	7.24	123.2	7.32	123.8	7.38	124.4	7.01	122.1	7.16	123.5	8.06	119.2
6	7.55	132.4	7.66	132.5	7.59	132.6	7.29	129.3	7.35	129.5	–	148.4
7	7.11	111.4	7.33	110.6	6.97	110.9	6.95	109.9	6.68	109.4	7.47	103.9
7a	–	143.0	–	144.3	–	144.2	–	142.0	–	143.2	–	144.3
Substituent at N(1)												
1	11.38[b])	–	3.30	27.0	–	133.0	10.45	–	–	134.3	–	139.9
2, 6	–	–	–	–	7.55	126.9	–	–	7.51	126.8	7.59	126.8
3, 5	–	–	–	–	7.66	130.1	–	–	7.64	129.8	7.68	130.2
4	–	–	–	–	[c])	129.2	–	–	7.53	128.3	7.59	129.0
Substituent at C(3)												
1	–	131.8	–	131.6	–	131.6	–	141.6	–	141.3	–	139.9
2	7.53	129.0	7.52	129.0	[c])	129.1	7.33	125.5	7.43	125.5	7.53	125.5
3, 7	7.51	128.3	7.52	128.4	[c])	128.4	7.36	128.2	7.44	128.4	7.50	128.7
4, 6	7.55	130.2	7.55	130.3	[c])	130.5	7.31	127.5	7.35	127.8	7.50	128.3

[a]) δ(^{15}N). [b]) ^1J(^{15}N,^{1}H) = 95.1 Hz. [c]) 7.57 – 7.64.

Table 6. EI-MS: 225 (38, M^+), 198 (8), 197 (61), 196 (100, $[M-29]^+$), 180 (13), 167 (8), 120 (29), 105 (15), 98 (12), 92 (18), 77 (31), 76 (11), 65 (12), 51 (12), identical to that of (*R*)-**11b** [45]. ESI-MS (pos.): 489.1 (5, $[2M+K]^+$), 473.1 (43, $[2M+Na]^+$), 470.2 (10, $[4M+Ca]^{2+}$), 357.7 (64, $[3M+Ca]^{2+}$), 264.1 (53, $[M+K]^+$), 248.2 (100, $[M+Na]^+$), 208.2 (98, $[M+H-H_2O]^+$), 180.2 (10, $[M+H-H_2O-CO]^+$). Anal. calc. for $C_{14}H_{11}NO_2$ (225.24): C 74.65, H 4.92, N 6.22; found C 74.50, H 4.97, N 5.95.

5.14. *1,3-Dihydro-3-hydroxy-1,3-diphenyl-2*H*-indol-2-one* (**11h**). Prepared from **6h**. Yields: 29 (13%; *Method A*) and 20 mg (9%; *Method B*). Colorless solid. M.p. 170 – 175° ([46]: 172 – 173° (benzene/cyclohexane)). IR: 3419, 3027, 1708, 1612, 1594, 1498, 1465, 1454, 1374, 1355, 1282, 1172, 1112, 1068, 1025, 989, 927, 902, 827, 779, 755, 725, 700, 647, 611, 576, 489 cm^{-1}. ^{1}H- and ^{13}C-NMR: see *Table 6.* EI-MS: 302 (7), 301 (31, M^+), 274 (6), 273 (35), 272 (100), 256 (8), 196 (9), 191 (13), 167 (18), 166 (6), 105 (17), 77 (43), 57 (26), 51 (15). ESI-MS (pos.): 625.1 (22, $[2M+Na]^+$), 471.7 (14, $[3M+Ca]^{2+}$), 340.2 (12, $[M+K]^+$), 324.2 (33, $[M+Na]^+$), 302.2 (5, $[M+H]^+$), 284.2 (100, $[M+H-H_2O]^+$). Anal. calc. for $C_{20}H_{15}NO_2$ (301.34): C 79.72, H 5.02, N 4.65; found: C 79.59, H 4.94), N 4.63.

5.15. *1,3-Dihydro-3-hydroxy-6-nitro-1,3-diphenyl-2*H*-indol-2-one* (**12h**). Prepared from **6h**. Yields: 8 (3%; *Method A*) and 21 mg (8%; *Method B*). Colorless solid. M.p. 301 – 305° (AcOEt). IR: 3335, 3092, 1705, 1609, 1527, 1453, 1434, 1376, 1345, 1260, 1210, 1177, 1119, 1060, 1032, 958, 918, 870, 858, 837, 779, 731, 714, 697, 656, 643, 505. EI-MS: 347 (7), 346 (31, M^+), 319 (7), 318 (37), 317 (57), 301 (11), 285 (12), 273 (7), 272 (20), 271 (17), 256 (21), 167 (10), 166 (6), 135 (11), 105 (37), 77 (49), 51 (11), 45 (13), 44 (100). ESI-MS (pos.): 385.1 (10, $[M+K]^+$), 369.2 (100, $[M+Na]^+$), 347.2 (25, $[M+H]^+$), 329.2 (75, $[M+H-H_2O]^+$). Anal. calc. for $C_{20}H_{14}N_2O_4$ (346.34): C 69.36, H 4.07, N 8.09; found: C 69.45, H 4.19, N 7.94.

5.16. *1,1′,3,3′-Tetrahydro-3,3′-diphenyl-2*H,*2′*H*-3,3′-biindole-2,2′-dione* (**13b**). Prepared from **6b**. Yield: 12.5 mg (4%; *Method A*). White solid. M.p. 187 – 206° ([47]: 188 – 192°, [28]: 234 – 236°

(AcOEt/hexane). IR: 3416, 3203, 3057, 1705, 1673, 1618, 1595, 1472, 1448, 1374, 1326, 1296, 1239, 1201, 1104, 1067, 1026, 1002, 926, 873, 846, 758, 750, 696, 658, 608, 589, 570, 537. ESI-MS (pos.): 455.1 (12, $[M+K]^+$), 439.2 (37, $[M+Na]^+$), 417.2 (100, $[M+H]^+$), 208.2 (100, $[M+H-209]^+$). Anal. calc. for $C_{28}H_{20}N_2O_2$ (416.67): C 80.75, H 4.84, N 6.73; found C 80.50, H 4.97, N 6.95.

5.17. *1,1′,3,3′-Tetrahydro-1,1′-dimethyl-3,3′-diphenyl-2*H,*2′*H-*3,3′-biindole-2,2′-dione* (**13e**). Prepared from **6e**. Yields: 7 (2%; *Method A*) and 7 mg (2%; *Method B*). White solid. M.p. 212–220° ([28]: 215–217° (benzene/cyclohexane)). IR: 3048, 2962, 2929, 2881, 1708, 1608, 1492, 1471, 1373, 1347, 1259, 1133, 1081, 1027, 973, 757, 736, 701, 646, 603, 541, 526. EI-MS: 223 (81), 222 (100), 208 (8), 207 (26), 195 (12), 194 (68), 193 (16), 192 (9), 181 (11), 179 (11), 166 (11), 165 (37), 153 (11), 152 (26), 151 (13), 127 (11), 126 (10), 118 (9), 116 (12), 113 (10), 111 (24), 99 (12), 98 (9), 97 (22), 96 (10), 95 (8), 91 (12), 89 (11), 85 (23), 84 (12), 83 (24), 82 (14), 77 (12), 76 (14), 71 (39), 70 (16), 69 (24), 57 (46), 55 (20), 43 (40), 41 (15). ESI-MS (pos.): 911.3 (26, $[2M+H]^+$), 483.2 (4, $[M+K]^+$), 467.2 (100, $[M+Na]^+$), 445.3 (7, $[M+H]^+$). Anal. calc. for $C_{30}H_{24}N_2O_2$ (444.52): C 81.06, H 5.44, N 6.30; found: C 80.98, H 5.43, N 6.21.

5.18. *1,1′,3,3′-Tetrahydro-1,1′,3,3′-tetraphenyl-2*H,*2′*H-*3,3′-biindole-2,2′-dione* (**13h**). Prepared from **6h**. Yields: 26 (6%; *Method A*) and 13 mg (3%; *Method B*). White solid. M.p. 220–223°(EtOH). IR: 3059, 2922, 1720, 1607, 1589, 1498, 1464, 1372, 1324, 1297, 1239, 1203, 1179, 1105, 1073, 1033, 1011, 912, 879, 758, 732, 698, 654, 633, 612, 597, 521. EI-MS: 286 (10), 285 (50), 284 (36), 257 (21), 256 (100), 255 (10), 254 (35), 181 (7), 180 (14), 179 (8), 178 (10), 152 (16), 151 (11), 128 (9), 127 (23), 126 (10), 77 (23), 51 (23). ESI-MS (pos.): 607.2 (8, $[M+K]^+$), 591.2 (16, $[M+Na]^+$), 569.2 (55, $[M+H]^+$), 324.2 (12, $[M+K-283]^+$), 308.2 (33, $[M+Na-283]^+$), 286.3 (100, $[M+H-283]^+$). Anal. calc. for $C_{40}H_{28}N_2O_2$ (568.66): C 84.48, H 4.96, N 5.63; found: C 84.68, H 5.06, N 5.63.

6. *Transformations of Compounds* **9** *and* **10**. 6.1. *Reaction of* **9h** *with* HNO_2. *Method C.* The reaction was carried out in the same way as described for *Method A*, merely the charge of $NaNO_2$ was doubled, and the reaction time was prolonged to 3 h. CC (SiO_2) of the crude reaction product provided compounds **9h** (66 mg, 31%), **10h** (37 mg, 15%), **12h** (16 mg, 6%) and **13h** (30 mg, 7%).

6.2. *Reaction of* **9h** *with* $NaNO_2$ *and* HNO_3. *Method D.* The reaction was carried out in the same way as described for *Method A*, merely the addition of H_2O was omitted, conc. HNO_3 (0.2 ml) was added, and the reaction time was prolonged to 3 h. CC (SiO_2) of the crude reaction product furnished compounds **10h** (37 mg, 15%), **11h** (59 mg, 26%), and **12h** (41 mg, 16%).

6.3. *Reaction of* **10h** *with Urea.* The soln. of **10h** (42 mg, 0.126 mmol) and urea (11 mg, 0.18 mmol) in AcOH (2 ml) and H_2O (0.1 ml) was heated to 50° for 3 h. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. After evaporation, the residue was purified by CC (SiO_2), to yield **10h** (19 mg, 62%), **11h** (7 mg, 24%) and **9h** (0.3 mg, 1%).

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Syntéza heterocyklů na bázi chinolin-2,4-dionů a studium jejich vlastností a následných přeměn

Synthesis of heterocycles based on quinoline-2,4-diones scaffold and the study of their properties and subsequent transformations

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