Monatshefte für Chemie 128, 681–685 (1997)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Synthesis of 2*H*-Benzo[2,3-*g*]pyridazino-[4,5-*d*,*e*]quinolin-3-one Derivatives

L. Chaker, F. Pautet, and **H. Fillion***

Laboratoire de Chimie Organique, Institut des Sciences Pharmaceutiques et Biologiques, Université Claude Bernard Lyon I, F-69373 Lyon, France

Summary. Condensation-cyclization of hydrazine with 4-methoxycarbonylbenzo[*g*]quinolinequinone or its corresponding carboxylic acid afforded 7-hydrazino-2*H*-benzo[2,3-*g*]pyridazino[4,5-*d*,*e*]-quinolin-3-one. Starting with the 9-hydroxy derivative, a similar double condensation of the nucleophile was observed, whereas its 6-hydroxylated regioisomer gave 2*H*-benzo[2,3-*g*]pyridazino-[4,5-*d*,*e*]quinolin-3,7-dione.

Keywords. Hydrazonobenzopyridazinoquinoline-3-one; Benzopyridazinoquinoline-3,7-dione; Phenylhydrazonobenzoquinolinequinone.

Synthese von 2*H*-Benzo[2,3-*g*]pyridazino[4,5-*d*,*e*]chinolin-3-on-Derivaten

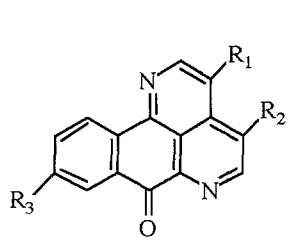
Zusammenfassung. Die Kondensation/Zyklisierung von Hydrazin mit 4-Methoxycarbonylbenzo-[*g*]chinolinchinon bzw. mit der entsprechenden Carbonsäure ergab 7-Hydrazino-2*H*-benzo[2,3-*g*]-pyridazino[4,5-*d*,*e*]chinolin-3-on. Ausgehend vom 9-Hydroxy-Derivat, wurde in analoger Weise doppelte Kondensation des Nucleophils beobachtet, wohingegen das 6-Hydroxy-Regioisomer zu 2*H*-Benzo[2,3-*g*]pyridazino[4,5-*d*,*e*]chinolin-3,7-dion reagierte.

Introduction

The naphthonaphthyridin-7-one skeleton is present in a series of copyrine alkaloids such as sampangines (**I**, [1–4]) which possess significant antifungal or antimycobacterial properties [5]. Syntheses of analogs have been performed in order to ameliorate these biological activities [6]. On the other hand, some potential new pharmacophores containing a pyridazone ring annelated to anthrone [7], benzocycloalcanes [8, 9], or tetrahydroquinoline [10] have been synthesized. Continued interest in the preparation of these compounds prompted us to synthesize 2*H*-benzo[2,3-*g*]pyridazino[4,5-*d*,*e*]quinolin-3-ones (**II**, Scheme 1).

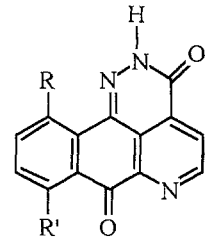
Results and Discussion

The synthesis of compounds **II** seems easily accessible through a condensation-cyclization of hydrazine with the 4-methoxycarbonyl-5,10-benzo[*g*]quinolinequinone derivatives **1** [11] or their corresponding carboxylic acid **2**. The latter were



I

I : R_1, R_2, R_3 = H or OCH_3

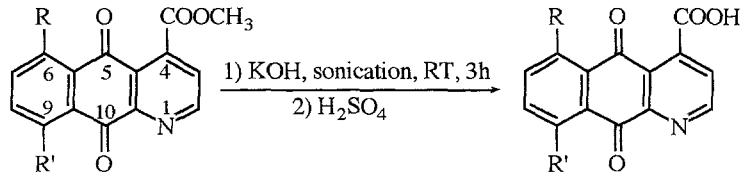


II

II : R, R' = H or OH

Scheme 1

efficiently obtained by an alkaline hydrolysis of the methyl esters **1** with potassium hydroxide under sonication and at room temperature. After acidification, compounds **2** were isolated in 80–90% yields (Scheme 2).



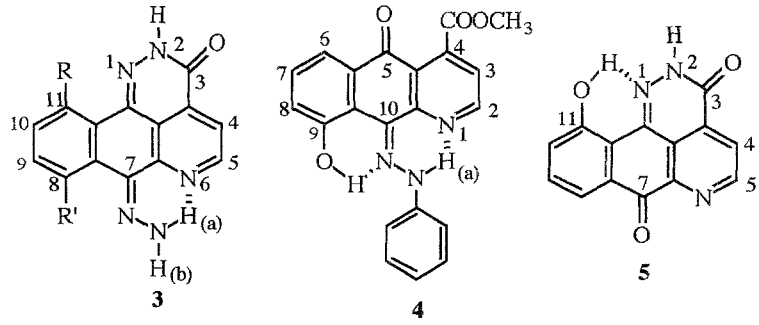
1 2

1a, **2a** : R=R'=H ; **1b**, **2b** : R=H, R'=OH ; **1c**, **2c** : R=OH, R'=H

Scheme 2

Heating of **1a** or **2a** and **1b** or **2b** with an excess of hydrazine in *DMF* afforded 7-hydrazonobenzo[2,3-*g*]pyridazino[4,5-*d*,*e*]quinolin-3-ones **3a** and **3b**, respectively (Scheme 3). Attempts to carry out a monocondensation of hydrazine with CO-5 failed. In the case of **1b** or **2b**, this result could be explained by an activation of CO-10 through an intramolecular hydrogen bond with the 9-hyroxyl substituent. Indeed, this carbonyl group is the most reactive one towards nucleophiles. This result was confirmed by treatment of **1b** with phenylhydrazine in ethanol at 80°C. Thus, the phenylhydrazone **4** crystallized from the reaction mixture. A similar behaviour had been observed in the reaction of 2-hydroxy-ethylhydrazine with 5-hydroxy-1,4-dichloroanthracene-9,10-dione [12].

In contrast, when condensation of hydrazine was carried out with **1c** following the same conditions as above, we obtained benzo[2,3-*g*]pyridazino[4,5-*d*,*e*]quinolin-3,7-dione (**5**). Its formation agrees with the increased reactivity of CO-5 due to its proximity with the 6-hydroxyl group. Further condensation of hydrazine with the second carbonyl group (CO-10) did not occur in this case, probably because of the low solubility of this product which precipitated as formed from the reaction mixture.



3 **4** **5**

3a : R=R'=H ; **3b** : R=H, R'=OH

Starting material	Compound	Yield (%)
1a	**3a**	80
2a	**3a**	66
1b	**3b**	70
2b	**3b**	64
1b	**4**	67
1c	**5**	49

Scheme 3

Table 1. ^{1}H NMR spectra (300 MHz, *DMSO*-d_6, δ (ppm))

	OH	NH_a	NH_b	^1J (Hz)	CONH
3a	–	13.06	10.08	16.3	7.55
3b	13.21	12.37	9.70	15.4	13.28
4	12.81	15.36	–	–	–

Structural assignments of compounds **3a**, **3b**, **4**, and **5** agree with their IR, ^{1}H NMR, and mass spectra. The ^{1}H NMR data for OH or NH signals of compounds **3a**, **3b**, and **4** are given in the following Table 1. The deshielded signals for the OH and NH protons in compounds **3b** and **4** agree with the existence of an intramolecular hydrogen bond with the nitrogen atom of the pyridine ring or the hydrazone function.

Experimental

IR spectra were measured on a Perkin-Elmer 1310 spectrophotometer. The ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AM 300 spectrometer. Elemental analysis was performed at the Centre de Microanalyse du CNRS at Solaize. Mass spectra were run at 70 eV on an AE 1 MS 902 spectrometer. Column chromatography was carried out with Matrex (60 Å, 35–70 μm) acidic silica gel.

General procedure for the hydrolysis of 4-methoxycarbonylbenzo[g]quinolinequinones **1**

An aqueous solution of potassium hydroxide (3*N*, 20 ml) was added to 0.100 g of the ester **1**. The mixture was sonicated for 3 h in an ultrasonic cleaning bath thermostatted at 20°C. Then, the solution was poured into 20 ml of cold water and acidified dropwise with conc. H_2SO_4. The precipitate of the corresponding carboxylic acid **2** was isolated and recrystallized from glacial acetic acid.

5,10-Benzo[g]quinolinequinone-4-carboxylic acid (**2a**)

Compound **2a** was obtained as a beige solid in 90% yield. M. p.: > 300°C IR (KBr): $\nu = 1715, 1690, 1670\,cm^{-1}$; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 13.82$ (broad signal, 1H, COOH), 9.13 (d, 1H, $J = 4.7$ Hz, H-2), 8.23 (m, 1H, H-6 or H-9), 8.14 (m, 1H, H-6 or H-9), 7.96 (m, 2H, H-7 and H-8), 7.86 (d, 1H, $J = 4.7$ Hz, H-3) ppm; $C_{14}H_7NO_4 \cdot 0.25\ H_2O$ (257.5); calc.: C 65.24, H 2.93, N 5.43; found: C 65.23, H 3.01, N 5.34.

9-Hydroxy-5,10-benzo[g]quinolinequinone-4-carboxylic acid (**2b**)

Compound **2b** was obtained as an orange solid in 80% yield. M.p.: > 300°C; IR (KBr): $\nu = 1720, 1680, 1640\ cm^{-1}$; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 13.81$ (broad signal, 1H, COOH), 12.27 (s, 1H, OH), 9.14 (d, 1H, $J = 4.7$ Hz, H-2), 7.87 (d, 1H, $J = 4.7$ Hz, H-3), 7.84 (m, 1H, H-7), 7.70 (dd, 1H, $J = 7.5$ and 1 Hz, H-6), 7.45 (dd, 1H, $J = 8.4$ and 1 Hz, H-8) ppm; $C_{14}H_7NO_5 \cdot 0.5\ H_2O$ (278); calc.: C 60.43, H 2.89, N 5.03; found: C 60.63, H 2.97, N 4.87.

6-Hydroxy-5,10-benzo[g]quinolinequinone-4-carboxylic acid (**2c**)

Compound **2c** was obtained as a yellow solid in 85% yield. M.p.: > 300°C; IR (KBr): $\nu = 1715, 1690, 1640\ cm^{-1}$; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 11.82$ (s, 1H, OH), 9.13 (d, 1H, $J = 4.6$ Hz, H-2), 7.87 (d, 1H, $J = 4.6$ Hz, H-3), 7.84 (m, 1H, H-8), 7.77 (dd, 1H, $J = 7.4$ and 1 Hz, H-9), 7.43 (dd, 1H, $J = 8.1$ and 1 Hz, H-7) ppm; $C_{14}H_7NO_5 \cdot 0.25\ H_2O$ (273.5); calc.: C 61.43, H 2.76, N 5.11; found: C 61.45, H 2.66, N 5.13.

General procedure for condensations of hydrazines with esters **1** *or carboxylic acids* **2**

A stirred solution or suspension of the corresponding ester **1** or carboxylic acid **2** (0.100 g) in *DMF* (10 ml) was heated at 100°C. Then, 0.5 ml of hydrazine hydrate were added. Stirring and heating were continued for 3 h. The insoluble compounds **3b** or **5** crystallized from the warm solution. The more soluble derivative **3a** was precipitated by addition of water (10 ml) to the cooled reaction mixture. Each solid was isolated by filtration and washed with ethanol and then with ether.
Phenylhydrazone **4** was prepared from **1b**. Ethanol was used instead of *DMF*, and the solution was heated to reflux for 3 h. The product crystallized from the warm solution and was isolated as above.

7-Hydrazino-2H-benzo[2,3-g]pyridazino[4,5-d,e]quinoline-3-one (**3a**)

Compound **3a** was obtained as a brown solid in 80% yield. M.p.: > 300°C; IR (KBr): $\nu = 1665, 1615, 1600\ cm^{-1}$; ^1H NMR (*DMSO*-d_6, 300 MHz): $\delta = 13.06$, (d, 1H, $J = 16.3$ Hz, NH), 10.08 (d, 1H, $J = 16.3$ Hz, NH), 8.85 (d, 1H, $J = 5$ Hz, H-5), 8.29 (d, 1H, $J = 8.1$ Hz, H-8 or H-11), 8.09 (d, 1H, $J = 8.1$ Hz, H-8 or H-11), 7.7 (m, 1H, H-9 or H-10), 7.55 (broad signal, CONH), 7.45 (m, 1H, H-9 or H-10), 7.28 (d, 1H, $J = 5$ Hz, H-4) ppm; MS: m/z (%) = 263 (M^+, 32), 249 (100), 235 (18), 221 (5) 206 (2.4); HRMS: calcd. for $C_{14}H_9N_5O$ 263.08072, found 263.08071.

8-Hydroxy-7-hydrazino-2H-benzo[2,3-g]pyridazino[4,5-d,e]quinoline-3-one (**3b**)

Compound **3b** was obtained as a yellow-brown solid in 80% yield. M.p.: > 300°C; IR (KBr): ν = 1670, 1600 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): δ = 13.28 (broad signal, CONH), 13.21 (s, 1H, OH), 12.37 (broad d, J = 15.4 Hz, NH), 9.70 (broad d, 1H, J = 15.4 Hz, NH) 9.11 (d, 1H, J = 5.3 Hz, H-5), 8.09 (d, 1H, J = 5.3 Hz, H-4), 7.84 (d, 1H, J = 6.9 Hz, H-11), 7.31 (dd, 1H, J = 7.9 Hz, H-10), 6.97 (d, 1H, J = 7.9 Hz, H-9) ppm; MS: m/z (%) = 279 (M^+, 100), 262 (90), 251 (68), 237 (10), 222 (17); HRMS: calcd. for $C_{14}H_9N_5O_2$ 279.07564, found 279.07562.

9-Hydroxy-4-methoxycarbonyl-10-N-phenylhydrazonobenzo[g]quinoline-5-one (**4**)

Compound **4** was obtained as a red solid in 67% yield. M.p.: > 300°C; IR (KBr): ν = 1740, 1650, 1610, 1600 cm^{-1}; ^1H NMR (*DMSO*-d_6, 300 MHz): δ = 15.36 (s, 1H, NH), 12.81 (s, 1H, OH), 9.01 (d, 1H, J = 4.9 Hz, H-2), 7.89 (m, 1H, H aromat.), 7.49 (d, 1H, J = 4.9 Hz, H-3), 7.44 (m, 3H, H aromat.), 7.32 (m, 3H, H aromat.), 7.13 (m, 1H, H aromat.), 4.09 (s, 3 H, CH_3) ppm; $C_{21}H_{15}N_3O_4$ (373.0): calc.: C 67.54, H 4.05, N 11.25; found: C 67.41, H 4.07, N 11.12.

11-Hydroxy-2H-benzo[2,3-g]pyridazino[4,5-d,e]quinoline-3,7-dione (**5**)

Compound **5** was obtained as a yellow solid in 49% yield. M.p.: > 300°C; IR (KBr): ν = 1680, 1600 cm^{-1}; ^1H NMR (CF_3COOD, 300 MHz): δ = 9.61 (d, 1H, J = 5.7 Hz, H-5), 9.36 (d, 1H, J = 5.7 Hz, H-4), 8.25 (d, 1H, J = 7.2 Hz, H-8 or H-10), 7.83 (dd, 1H, J = 7.2 and 8.3 Hz, H-9) 7.71 (d, 1H, J = 8.3 Hz, H-8 or H-10) ppm; MS: m/z (%) = 265 (M^+ , 100), 237 (10), 209 (9); HRMS: calcd. for $C_{14}H_7N_3O_3$ 265.04875, found 265.04874.

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Received January 21, 1997. Accepted January 29, 1997