2-Amination of Quinizarin via Michael Addition of Hydrazines or Amines

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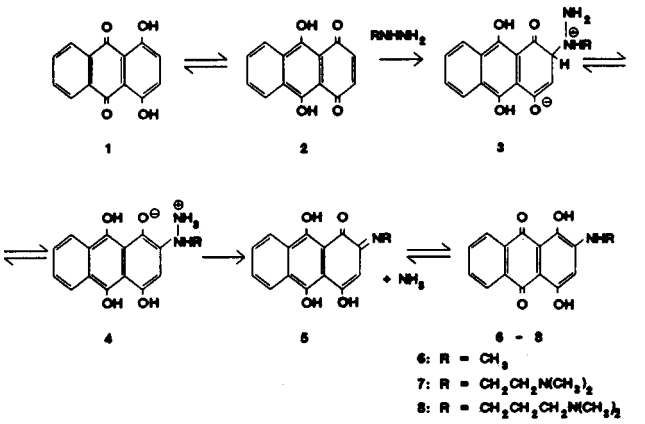
Received April 3, 1992 (Revised Manuscript Received November 30, 1992)

As a part of our antitumor drug development program[1] we have been interested in the synthesis of anthracene mono- and/or bis-9,10-hydrazones. The literature data on the reactions of anthraquinones with hydrazines are rather scarce. In one example, the treatment of leucoquinizarin with hydrazines or N-substituted hydrazines[2] led not to anthracene 9,10-hydrazones but to unstable 2,3-dihydro-9,10-dihydroxy-1,4-anthracenedione bis-hydrazones. In another paper that mentions hydrazone synthesis from quinizarin and hydrazines, the reaction conditions are not described, and no evidence for the structure of the obtained compounds is presented.[3]

In our experiments, the reactions of quinizarin and hydrazines, performed in various conditions, did not give the desired anthracene mono- or bis-9,10-hydrazones, but other products, identified as 1,4-dihydroxy-2-(aminoalkyl)-9,10-anthracenediones, were obtained. The probable mechanism of the reaction of quinizarin (1) with an excess of *N*-alkyl- or *N*-[(alkylamino)alkyl]hydrazines in DME or DMA at 80 °C is outlined in Scheme I. Michael addition of the secondary nitrogen of hydrazines to the 1,4-keto isomer of quinizarin (2) affords 3. Intramolecular proton transfer leads to intermediate 4, N–N bond cleavage, and ammonia elimination provide intermediate 5 and subsequently 2-(aminoalkyl)-substituted products 6–8. When we treated 1,4-dimethoxy-9,10-anthracene[4] with hydrazines, we were never able to obtain 1,4-dimethoxy-2-(aminoalkyl) derivatives. These results supported the mechanism for quinizarin 2-amination proposed in Scheme I.

When (2-hydroxyethyl)hydrazine was used in the reaction with quinizarin, addition of the primary nitrogen atom of hydrazine occurred, and, after ethanolamine elimination, 1,4-dihydroxy-2-amino-9,10-anthracenedione (9) was formed. A similar observation has been made by Showalter et al.;[5] 2-amino derivatives of anthraquinones were formed in poor yield, as byproducts, during anthrapyrazole synthesis.

Scheme I



The observed course of the reaction of quinizarin with hydrazines prompted us to examine whether treatment of quinizarin with amines would also lead to 2-amination. The reaction of quinizarin with various diamines, performed at elevated temperatures, is commonly utilized for the preparation of 1-[(aminoalkyl)amino]-4-hydroxy- or 1,4-bis[(aminoalkyl)amino]-substituted 9,10-anthracenediones.[6] However, we found that when quinizarin was gently heated (35–50 °C) with an excess of alkyl- or *N*[(alkylamino)alkyl]amines in DMA as a solvent, 1,4-dihydroxy-2-[(aminoalkyl)amino]-9,10-anthracenediones (**6–8, 10,** and **11**, Table I) were obtained as the main products in good yields. Under these conditions, 1-[(aminoalkyl)amino]-4-hydroxy-9,10-anthracenediones were obtained only in poor yields.

According to the literature,[7] the reaction of quinizarin with butylamine, performed in the presence of metal salts, also affords the 2-amino derivative of quinizarin.

The antileucemic activity of compounds **7** and **10** was examined against murine L1210 leukemia cells and P388 leukemia on mice. The results will be reported elsewhere.

Experimental Section

Melting points, determined on a Boetius PHMK 05 apparatus, were uncorrected. Elemental analyses were performed by the Laboratory of Elemental Microanalyses, University of Camerino. ^{1}H NMR spectra were taken on a Varian 300-MHz spectrometer in Me_2SO-d_6 with tetramethylsilane as the internal standard. Molecular weights were determined by mass spectrometry (field desorption technique) on a Varian Mat 711 instrument. The instrumental conditions were as follows: wire heating current, 5–18 mA; ion-source temperature, 70–100 °C; accelerating voltage, 4–6 kV. Column chromatography was performed on MN silica gel (35–70 mesh, Merck) and on Sephadex LH-20 (Pharmacia). The following TLC solvent systems were used: (A) $CHCl_3$–MeOH (30:1), (B) $CHCl_3$–MeOH–25% NH_4OH (5:1:0.2), and (C) toluene–acetone (10:1). The HCl salts of **7**, **8**, and **10** were prepared by the addition of HCl/ethyl ether to cold chloroform solutions of the free amines.

General Procedure. Reaction of Quinizarin with Hydrazines (Method A). A mixture of quinizarin (120 mg, 0.5

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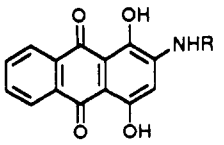
0022-3263/93/1958-1568$04.00/0

Table I. Reaction Conditions for the Syntheses of 1,4-Dihydroxy-2-[(aminoalkyl)amino]-9,10-anthracenediones



compd.	R	method[a]	reactn condns			yield (%)
			solvent	time (h)	temp (°C)	
6	CH_3	A	DME	3	80	35
		B	DMA	6	50	40
7	$CH_2CH_2N(CH_3)_2$	A	DME	1	80	25
		B	DMA	3	50	50
8	$CH_2CH_2CH_2N(CH_3)_2$	A	DME	4	80	20
		B	DMA	3.5	35	75
9	H	A[b]	DMA	2	80	10
10	$CH_2CH_2NHCH_2CH_2OH$	B	DMA	3	35	70
11	CH_2CH_2OH	B	DMA	20 min + 5 min	20	
					60	90

[a] Reagents: method A, hydrazines; method B, amines. [b] Reagent: (2-hydroxyethyl)hydrazine.

mmol), a 20-molar excess of the appropriate hydrazine, and a catalytic amount of AcOH was heated with stirring in 20 mL of DME or in 15 mL of DMA in the presence of 4A molecular sieves. The course of the reaction was monitored by TLC analysis. When the reaction was complete, the resulting red reaction mixture was diluted with $CHCl_3$ and washed with H_2O. The following compounds were obtained with method A.

1,4-Dihydroxy-2-(methylamino)-9,10-anthracenedione (6). The reaction mixture was evaporated and the residue was crystallized (toluene–acetone) to give **6** as a dark purple solid: mp 290–295 °C dec; ^1H NMR δ 2.9 (d, 3 H, CH_3), 6.15 (s, 1 H, C-3), 7.6 (m, 1 H, ArNH, exchangeable with D_2O), 7.8–8.0 (m, 2 H, C-6, C-7), 8.2–8.3 (m, 2 H, C-5, C-8), 14.6 (m, 2 H, OH exchangeable with D_2O); MS–FD *m/z* (relative intensity) 269 ([M]$^+$, 100). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 65.84; H, 3.56; N, 5.49. Found: C, 65.28; H, 3.89; N, 5.19.

1,4-Dihydroxy-2-[[2-(dimethylamino)ethyl]amino]-9,10-anthracenedione Hydrochloride (7). Crude **7** was extracted from the reaction mixture with a 0.1 N HCl solution, and the aqueous layer was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. Then, the solvent was evaporated, and the residue was chromatographed (Sephadex LH-20 column, eluent $CHCl_3$–MeOH (1:1)) to yield **7** as a dark purple solid: mp (as hydrochloride) 282–285 °C; ^1H NMR δ 2.3 (s, 6 H, CH_3), 2.7 (t, 2 H, CH_2N), 3.3 (m, 2 H, $ArNHCH_2$), 6.1 (s, 1 H, C-3), 6.2 (m, 1 H, ArNH, exchangeable with D_2O), 7.7–7.8 (m, 2 H, C-6, C-7), 8.3 (m, 2 H, C-5, C-8), 14.2 (m, 2 H, OH, exchangeable with D_2O); MS–FD *m/z* (relative intensity) 327 ([M]$^+$, 100). Anal. Calcd for $C_{18}H_{18}N_2O_4 \cdot HCl \cdot H_2O$: C, 51.9; H, 5.09; N, 6.73. Found: C, 51.5; H, 4.89; N, 6.51.

1,4-Dihydroxy-2-[[3-(dimethylamino)propyl]amino]-9,10-anthracenedione Hydrochloride (8). Crude **8** was purified in the manner described for **7**: mp (as hydrochloride) 295–300 °C; ^1H NMR δ 2.0 (m, 2 H, CH_2), 2.3 (s, 6 H, CH_3), 2.7 (t, 2 H, CH_2N), 3.25 (m, 2 H, $ArNHCH_2$), 6.1 (s, 1 H, C-3), 6.2 (m, 1 H, ArNH, exchangeable with D_2O), 7.7–7.8 (m, 2 H, C-6, C-7), 8.25 (m, 2 H, C-5, C-8), 14.2 (m, 2 H, OH, exchangeable with D_2O); MS–FD *m/z* (relative intensity) 340 ([M]$^+$, 100). Anal. Calcd for $C_{19}H_{20}N_2O_4 \cdot HCl$: C, 55.32; H, 5.14; N, 6.80. Found: C, 54.98; H, 4.92; N, 6.51.

1,4-Dihydroxy-2-amino-9,10-anthracenedione (9). Crude **9** was crystallized from DME: mp 320–325 °C; ^1H NMR δ 6.3 (s, 1 H, C-3), 7.1–7.2 (m, 2 H, NH_2, exchangeable with D_2O), 7.8–7.9 (m, 2 H, C-6, C-7), 8.2 (m, 2 H, C-5, C-8), 13.5–13.7 (br s, 1 H, OH, exchangeable with D_2O), 14.1 (s, 1 H, OH, exchangeable with D_2O); MS–FD *m/z* (relative intensity) 255 ([M]$^+$, 100). Anal. Calcd for $C_{14}H_9NO_4$: C, 65.84; H, 3.56; N, 5.49. Found: C, 65.28; H, 3.89; N, 5.19.

Reaction of Quinizarin with Amines (Method B). A sample of quinizarin (120 mg, 0.5 mmol) and a 20-molar excess of the appropriate amine were heated with stirring in 5 mL of DMA; for the preparation of **6**, methylamine hydrochloride and NEt_3 were used. The progress of the reaction was monitored by TLC. Crude **6**, **7**, **8**, and **10** were isolated and purified as described in method A.

1,4-Dihydroxy-2-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione hydrochloride (10): mp 285–290 dec; ^1H NMR δ 2.9–3.1 (m, 4 H, CH_2NHCH_2), 3.5 (m, 4 H, CH_2O, $ArNCH_2$), 6.2 (s, 1 H, C-3), 6.3 (m, 1 H, ArNh, exchangeable with D_2O), 7.6–7.7 (m, 2 H, C-6, C-7), 8.25 (m, 2 H, C-5, C-8), 14.3 (m, 2 H, ArOH, exchangeable with D_2O); MS–FD *m/z* (relative intensity) 342 ([M]$^+$, 100). Anal. Calcd for $C_{18}H_{18}N_2O_5 \cdot HCl$: C, 52.19; H, 4.63; N, 6.77. Found: C, 52.58; H, 4.99; N, 7.10.

1,4-Dihydroxy-2-[(2-hydroxyethyl)amino]-9,10-anthracenedione (11). Crude **11** was dissolved in $CHCl_3$, and the solution was washed with an HCl solution and then with H_2O; after evaporation of the solvent, the residue was chromatographed (Sephadex LH-20, eluent CH_3Cl–MeOH (1:1)) to afford **11** as a dark purple solid: mp 245–251 °C dec; ^1H NMR δ 3.3 (m, 2 H, $ArNHCH_2$), 3.6 (m, 2 H, CH_2O), 5.0 (t, 1 H, OH, exchangeable with D_2O), 6.2 (s, 1 H, C-3), 7.2 (t, 1 H, ArNH), 7.7–7.9 (m, 2 H, C-6, C-7), 8.2 (m, 2 H, C-5, C-8), 13.9 (s, 1 H, ArOH, exchangeable with D_2O), 14.3 (s, 1 H, ArOH, exchangeable with D_2O); MS–FD *m/z* (relative intensity) 299 ([M]$^+$, 100). Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.20; H, 4.38; N, 4.68. Found: C, 64.29; H, 4.43; N, 4.60.

Acknowledgment. Financial support from the State Committee for Scientific Research, Warsaw (Grant No. 406329101) and from Italian Ministero della Publica Instruzione (Fonde 60%) is gratefully acknowledged.