# SYNTHESIS OF BENZO[g]QUINOLINE DERIVATIVES. XI.*

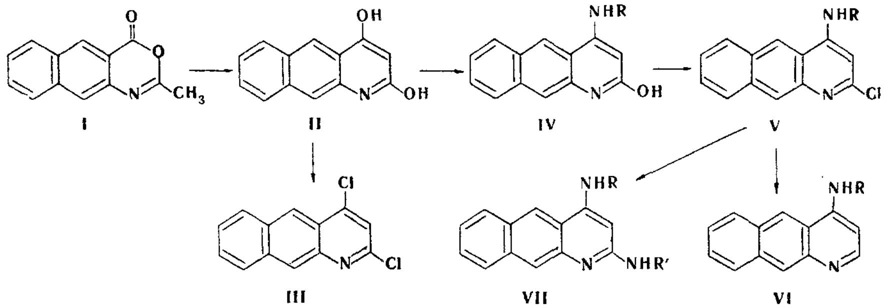
## 2,4-DIAMINO-SUBSTITUTED BENZO[g]QUINOLINES.†

N. P. Kozyreva and A. F. Bekhli

UDC 547.832.5.07

Previously unknown 2,4-diamino-substituted benzo[g]quinolines were synthesized from 2,4-dihydroxybenzo[g]quinoline.

Compounds having pronounced antimalarial activity have been found among the 4-aminobenzo[g]quinolines synthesized by us [2]. The preparation of 2,4-diaminobenzo[g]quinolines seems of interest for the search for new active compounds, particularly because substances that have demonstrated antimalarial activity are found among structurally similar heterocyclic analogs [3, 4]. The synthesis of 2,4-diamino-substituted benzo[g]quinolines was accomplished via the following scheme:



IV a $R=(CH_2)_3N(C_2H_5)_2$; b $R=CH(CH_3)(CH_2)_3N(C_2H_5)_2$; c $R=p\text{-}CH_3OC_6H_4$; d $R=p\text{-}ClC_6H_4$; V a $R=(CH_2)_3N(C_2H_5)_2$; b $R=CH(CH_3)(CH_2)_3N(C_2H_5)_2$; c $R=p\text{-}CH_3OC_6H_4$; VI a $R=(CH_2)_3N(C_2H_5)_2$; c $R=p\text{-}CH_3OC_6H_4$; VII a $R=(CH_2)_3N(C_2H_5)_2$, $R'=p\text{-}ClC_6H_4$; b $R=CH(CH_3)(CH_2)_3N(C_2H_5)_2$, $R'=p\text{-}ClC_6H_4$; c $R=p\text{-}CH_3OC_6H_4$, $R'=CH(CH_3)(CH_2)_3N(C_2H_5)_2$

2,4-Dihydroxybenzo[g]quinoline was obtained by the action of sodium methoxide on benzo[g]acetanthranil (I) [5]. 2,4-Dichlorobenzo[g]quinoline (III) was obtained by heating II with a mixture of phosphorus oxychloride and phosphorus pentoxide.

An attempt to obtain III by reaction of β-naphthylamine with malonic acid is known [6]. The 2,4-dihydroxy derivative obtained was converted to the 2,4-dichloro derivative, but the structure of the product was not proved. It may be supposed that the compound obtained is 2,4-dichlorobenzo[g]quinoline or 2,4-dichlorobenzo[f]quinoline. We have established that the substance isolated in [6] is apparently 2,4-dichlorobenzo[f]quinoline rather than 2,4-dichlorobenzo[g]quinoline. This should have been expected considering the corresponding

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*See [1] for communication X.

†This research was accomplished under agreement with the World Health Organization.

E. I. Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 517-519, April, 1975. Original article submitted April 4, 1974; revision submitted August 27, 1974.

specificity of electrophilic substitution in the naphthalene series, inasmuch as this cyclization is a reaction of this type.

We have found that 2,4-dihydroxybenzo[g]quinoline (II) reacts with aliphatic and aromatic amines on heating to give the corresponding 4-amino-substituted 2-hydroxybenzo[g]quinolines (IVa-d). The reaction of II with aromatic amines is catalyzed by their hydrochlorides.

On heating with phosphorus oxychloride, 2-hydroxy-4-amino-substituted benzo[g]quinolines (IVa-c) are converted to the corresponding 2-chloro derivatives (Va-c) in good yields (74-89%). The reductive dehalogenation of Va,c over Pd/C gives 4-amino-substituted benzo[g]quinolines (VIa, c), which are completely identical to the compounds obtained by the reaction of 4-chlorobenzo[g]quinoline and 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline ring with the appropriate amines [7].

Thus the nucleophilic substitution of the hydroxyl group by amines in 2,4-dihydroxybenzo[g]quinolines occurs preferably at the 4 position.

By reaction of 2-chloro-4-amino-substituted benzo[g]quinolines (Va-c) with amines we were able for the first time to obtain 2,4-diamino-substituted benzo[g]quinolines (VIIa-c). The antimalarial activity of VIIa-c is lower than that of the corresponding 4-amino-substituted analogs [2].

## EXPERIMENTAL METHOD

The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-20 spectrometer.

2,4-Dihydroxybenzo[g]quinoline (II). A 6.3-g (0.03 mole) sample of benzo[g]acetanthranil was heated in 50 ml of dry xylene at 110-120° for 15 min until all of it had dissolved, after which 3 g of sodium methoxide was added, and the mixture was refluxed for 45 min. It was then cooled, and the precipitated sodium salt was removed by filtration and washed with xylene. The dry solid was dissolved in water, the solution was acidified to pH 4, and the precipitated II was removed by filtration to give 4.8 g (74%) of a cream-colored powder with mp > 360° [from dimethylformamide (DMFA)]. IR spectrum, $cm^{-1}$: 1687 (CO); 2737, 2632 (OH); 3052 (NH). Found %: C 73.5; H 4.7; N 6.8. $C_{13}H_9NO_2$. Calculated %: C 73.9; H 4.3; N 6.6.

2,4-Dichlorobenzo[g]quinoline (III). A mixture of 4.2 g (0.02 mole) of II, 20 g (0.04 mole) of $PCl_5$, and 16 ml of $POCl_3$ was heated at 100° for 2 h, after which the excess $POCl_3$ was removed by vacuum distillaton, and 100 g of ice was added to the residue. The aqueous mixture was neutralized with $Na_2CO_3$, and the resulting precipitate was removed by filtration and washed with water to give 4.1 g (83%) of III as a lemon-yellow powder with mp 192-193° (from chloroform). Found %: Cl 28.9; N 5.4. $C_{13}H_7Cl_2N$. Calculated %: Cl 28.6; N 5.6.

2-Hydroxy-4-(dialkylaminoalkylamino)benzo[g]quinolines (IVa, b). A mixture of 0.05 mole of II and 0.1 mole of dialkylaminoalkylamine was refluxed for 18 h, after which it was poured into water, and the resulting oily product was reprecipitated from 50% acetic acid to give IVa as a cream-colored powder with mp 196-197° (from benzene) in 39% yield. Found %: N 13.5. $C_{20}H_{25}N_3O$. Calculated %: N 13.0. Compound IVb was similarly obtained as a cream-colored powder with mp 178-179° (from benzene) in 23% yield. Found %: N 12.4. $C_{22}H_{29}N_3O$. Calculated %: N 12.0.

2-Hydroxy-4-arylaminobenzo[g]quinolines (IVc, d). A mixture of 0.025 mole of II, 0.125 mole of arylamine, and 0.025 mole of arylamine hydrochloride was heated at 180-190° for 4 h, after which it was cooled and treated with 50 ml of methanol The resulting precipitate was removed by filtration to give IVc as a gray powder with mp 348-349° (from DMFA) in 73% yield. Found %: N 9.1. $C_{20}H_{16}N_2O_2$. Calculated %: N 8.8. Compound IVd was similarly obtained as a gray powder with mp 346-347° (from DMFA) in 52% yield. Found %: Cl 10.7; N 8.1. $C_{19}H_{13}ClN_2O$. Calculated %: Cl 11.0; N 8.7.

2-Chloro-4-amino-Substituted Benzo[g]quinolines (Va-c). A mixture of 0.01 mole of IVa, b and 6 ml of $POCl_3$, was refluxed for 20 h, after which the excess $POCl_3$ was removed by distillation, and the residue was neutralized and extracted with ether. The ether extract was evaporated, and the residue solidified to give Va as a yellow powder with mp 144-145° (from ethyl acetate) in 89% yield. Found %: Cl 10.3; N 12.7. $C_{20}H_{24}ClN_3$. Calculated %: Cl 10.4; N 12.3. Compound Vb was similarly obtained as a cream-colored powder with mp 192-193° (from ethyl acetate) in 74% yield. Found %: Cl 10.2; N 11.8. $C_{22}H_{28}ClN_3$. Calculated %: Cl 9.6; N 11.4.

A mixture of 0.02 mole of IVc and 10 ml of $POCl_3$ was heated at 110-120° for 1.25 h, after which the excess $POCl_3$ was removed by vacuum distillation, and the residue was treated with water and neutralized. The resulting precipitate was removed by filtration to give IVc as a dark-gray powder with mp 223-224° (from methanol) in 87% yield. Found %: Cl 10.1; N 8.1. $C_{20}H_{15}ClN_2O$. Calculated %: Cl 10.6; N 8.4.

*4-(p-Methoxyphenyl)aminobenzo[g]quinoline (VIc).* A 0.84-g (0.025 mole) sample of Vc was dissolved in 130 ml of 1 N alcoholic KOH, 1 g of 10% Pd/C was added, and hydrogen was bubbled through the mixture until the theoretical amount of hydrogen had been absorbed. The catalyst was then removed by filtration, the solution was poured into 250 ml of cold water, and the resulting precipitate was removed by filtration to give 0.6 g (80%) of VIc with mp 205-206° (from aqueous alcohol) as a lemon-yellow powder. No melting-point depression was observed for a mixture of this product with an authentic sample [7].

4-(γ-Diethylaminopropyl)aminobenzo[g]quinoline (VIa). This compound was similarly obtained from Va as yellow crystals with mp 97-98° (from hexane). No melting-point depression was observed for a mixture of this product with an authentic sample [7].

*2,4-Diamino-Substituted Benzo[g]quinolines (VIIa-c).* A mixture of 0.015 mole of Va, b, 0.04 mole of p-chloroaniline, and 0.05 mole of potassium iodide was heated at 200° for 6 h, and the resulting oily product was reprecipitated from hot 10% hydrochloric acid. The product was removed by filtration and dissolved in chloroform, and the solution was disbributed between 5% acetic acid and ether. The acidic aqueous layer was separated and made alkaline to pH 8, and the resulting product was removed by filtration to give VIIa as a light-yellow powder with mp 182-183° (from benzene—ether) in 56% yield. Found %: Cl 7.9; N 13.1. $C_{26}H_{29}ClN_4$. Calculated %: Cl 8.2; N 12.9. Compound VIIb was similarly obtained as an amorphous yellow powder with mp 91-92° (from benzene—ether) in 62% yield. Found %: Cl 6.9; N 12.0. $C_{28}H_{33}ClN_4$. Calculated %: Cl 7.7; N 12.1. The diphosphate of VIIb was obtained as a dark-cream-colored powder with mp 187-188°. Found %: Cl 4.8; N 8.3. $C_{28}H_{33}ClN_4 \cdot H_6P_2O_8$. Calculated %: Cl 5.4; N 8.5.

A mixture of 0.01 mole of Vc and 0.015 mole of δ-diethylamino-α-methylbutylamine was heated at 130-140° for 14 h, and the resulting oily product was reprecipitated from 10% hydrochloric acid to give VIIc as an amorphous dark-yellow powder with mp 92-93° (from benzene—ether) in 44% yield. Found %: N 12.2. $C_{29}H_{36}N_4O$. Calculated %: N 12.3.

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