SYNTHESIS OF BENZO[g]QUINOLINE DERIVATIVES

II. 4-Aminobenzo[g]quinoline*

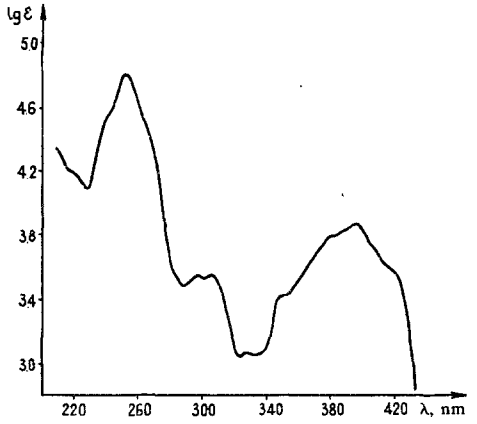
A. F. Bekhli and N. P. Kozyreva

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 2, pp. 304–306, 1968

UDC 547.832.5.07:543.422.4

The synthesis of 4-aminobenzo[g]quinoline has been effected by the following three methods: 1) replacement of the halogen in 4-chlorobenzo[g]quinoline by an amino group; 2) dehydrogenation of the oxime of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline; 3) direct condensation of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline with ammonia.

4-Aminobenzo[g]quinoline (IV), the structure of which is close to that of other groups of therapeutically valuable heterocycles, has remained a compound extremely difficult to obtain up to the present time.



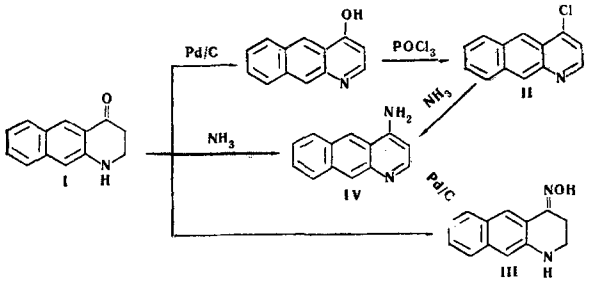
UV spectrum of 4-aminobenzo[g]quinoline

The complexity of the methods for the synthesis of IV that have been proposed can be seen from a paper [1] the authors of which, after a number of unsuccessful attempts, managed to synthesize IV by a multistage series of reactions.

We have found new methods for synthesizing 4-aminobenzo[g]quinoline which are based on the use as a starting material of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline (I), which can be easily synthesized from 2,3-aminonaphthoic acid, as we have described previously [2]. When I was dehydrogenated with palladium on carbon, 4-hydroxybenzo[g]quinoline was obtained [2]. The latter, on being heated with phosphorus oxychloride was converted into 4-chlorobenzo[g]-quinoline (II). The chlorine in this compound is highly mobile and II has a tendency to hydrolyze in an acid medium with the formation of I. It is apparently for this reason that the constants of II are not given in the literature. Then, by heating the 4-chlorobenzo[g]quinoline in phenol in a current of ammonia, 4-aminobenzo[g]quinoline was obtained with a yield of 90.3%.

We have previously established that under dehydrogenating conditions, on being heated with palladium on carbon [3], the oxime of I (III) dehydrogenates at the ring with the simultaneous reduction of the oxime group and the formation of IV with a yield of 56%.

In addition, in a study of the reaction of I with ammonia, IV was obtained (yield 24.4%), together with benzo[g]quinoline, formed as a by-product. Questions relating to the mechanism of this reaction will be discussed later.



The samples of IV that we obtained by all three routes have the same high melting point (241–242° C) as compared with the material obtained previously [1] (mp 233° C). We have succeeded in isolating the hydrochloride of IV with mp 274–275° C, which has not been reported in the literature hitherto. It was found that the latter is not stable and on drying it undergoes a partial loss of hydrogen chloride and gives a low chlorine content of analysis.

Chromatography of all three samples of IV in a thin nonfixed layer of alumina in the solvent system dioxane—water (15:1) gave the same R_f value (0.675).

The UV spectrum of IV with two main absorption maxima has a curve identical in shape with that of 4-aminoquinoline [4], but shifted into the long-wave region and very close to the spectum of 9-aminoacridine [5, 6].

In the IR spectrum of IV in chloroform, the positions of the bands corresponding to antisymmetric and symmetric vibrations of the NH_2 group are in agreement with Mason's data [7]. When the IR spectra of IV in the crystalline state were recorded, these bands were shifted in the long-wave direction [8].

EXPERIMENTAL

4-Chlorobenzo[g]quinoline (II). A mixture of 1.5 g (7.7 mM) of 4-hydroxybenzo[g]quinoline and 15 ml of phosphorus oxychloride was heated at 125° C for an hour. After the phosphorus oxychloride had been distilled off in vacuum, the residue was dissolved in dichloroethane and treated with a mixture of ice and aqueous ammonia. The or-

*For communication I, see [2].

ganic layer was separated off, washed with water, and dried with sodium sulfate. After the dichloroethane had been distilled off, 4-chlorobenzo[g]quinoline was obtained in the form of green crystals, yield 1.3 g (79.2%), mp 126.5–127.5° C. Found, %: Cl 16.17, 16.14; N 6.20, 6.50. Calculated for $C_{13}H_8ClN$, %: Cl 16.60; N 6.55.

Oxime of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline (III). A saturated aqueous solution of 2.5 g (0.075 mole) of hydroxylamine hydrochloride was added to a solution of 5.0 g (0.025 mole) of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline in 100 ml of ethanol and the mixture was heated to boiling for 1 hr. After cooling, it was neturalized with aqueous alkali. The yellow crystalline oxime that deposited was filtered off and washed with aqueous ethanol; yield 4.7 g (89.0%), mp 220–221° C (from aqueous ethanol). Found, %: N 13.58, 12.99. Calculated for $C_{13}H_{12}N_2O$, %: N 13.20.

4-Aminobenzo[g]quinoline (IV). a) Ammonia was passed into a mixture of 0.8 g (3.7 mM) of 4-chlorobenzo[g]quinoline and 4 g of phenol at 170–175° C for 4 hr. The reaction mixture was poured into 10% sodium hydroxide solution and the precipitate that separated was filtered off. Yield 0.65 g (90.3%), mp 241–242° C (in a sealed capillary; from a mixture of dioxane and petroleum ether). 4-Aminobenzo[g]quinoline forms a light yellow crystalline powder readily soluble in ethanol and dioxane, soluble in benzene and ether, and insoluble in petroleum ether and water. Alcoholic solutions of IV have a blue fluorescence. Found, %: C 80.41, 80.22; H 5.33, 5.23; N 14.64, 14.46. Calculated for $C_{13}H_{10}N_2$, %: C 80.38; H 5.19; N 14.42. UV* spectrum: λ_{max} 255 nm (log ε 4.806), 398 nm (log ε 3.845). IR* spectrum in chloroform–3520, 3433 cm^{-1}; in the crystalline state (tablets with KBr)–3350, 3225 cm^{-1}.

The hydrochloride of **IV** was obtained by adding ethanolic hydrogen chloride to an ethanolic solution of the base until it was acid to Congo Red and precipitating the product with dry ether. Yellow crystalline powder, mp 274–275° C, soluble in water and ethanol, insoluble in ether; alcoholic solutions give a blue fluorescence. Found, %: Cl 14.74, 14.75. Calculated for $C_{13}H_{10}N_2 \cdot HCl$, %: Cl 15.37.

b) A mixture of 0.5 g (2.4 mM) of the oxime of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline and 0.5 g of 20% palladium on carbon was heated in a thick-walled glass tube in a vacuum of 25 mm for 30 min in a metal bath, the temperature slowly being raised to 240–250° C and kept there for 15 min. Then, after the vacuum had been increased to 3 mm, the mixture was heated for another 15 min. Under these conditions, the 4-aminobenzo[g]quinoline sublimed onto the cold walls of the tube. After crystallization from a mixture of dioxane and petroleum ether, a yellow crystalline powder was obtained in a yield of 0.25 g (54.6%), mp 241–242° C (in a sealed capillary); a mixture with a sample of the 4-aminobenzo[g]quinoline obtained by method (a) gave no depression.

c) A mixture of 5.0 g (0.025 mole) of 1,2,3,4-tetrahydro-4-oxobenzo[g]quinoline, 8.5 g of phenol, and 1.0 g (0.007 mole) of o-nitrophenol was stirred at 120–130° C (bath temperature) with the passage of a current of ammonia for 25 min. Then the reaction mixture was poured into 10% aqueous sodium hydroxide, and the precipitate that deposited was filtered off and washed to neutrality. The reaction product (5 g) was extracted with boiling benzene. The insoluble residue was filtered off and treated with concentrated hydrochloric acid. The acid solution was separated from the resin formed and was made alkaline. This gave **IV** in the form of a light yellow precipitate; after crystallization from a mixture of dioxane and petroleum ether, mp 241–242° C, yield 1.2 g (24.4%); the melting point of a mixture with the samples obtained by methods (a) and (b) gave no depression. The benzene was distilled off from the benzene filtrate and the residue was extracted with ether, and the ethereal solution was washed with water and dried with potassium carbonate. After the ether had been driven off, the residue was distilled in vacuum to give a yellowish transparent oil [bp 150–155° C (1 mm)], which crystallized on cooling. It was purified by fractional precipitation from acid solution; at pH 4 a small amount of resin deposited and at pH 8 benzo[g]quinoline in the form of light-colored crystals, mp 116–117° C (according to the literature [9], mp 116–117° C). Found, %: N 7.66, 7.94. Calculated for $C_{13}H_9N$, %: N 7.82. Benzo[g]quinoline is readily soluble in ether and ethanol, and almost insoluble in water. Concentrated aqueous solutions give a green fluorescence and dilute solutions a blue-violet fluorescence.

Benzo[g]quinoline hydrochloride was obtained by adding an ethanolic solution of hydrochloric acid to an ethereal solution of the base. It formed a yellow crystalline powder, mp 198–199° C (according to the literature [10], mp 196–197° C); benzo[g]quinoline picrate forms a yellow crystalline powder with mp 256–257° C (according to the literature [10], mp 258° C).

REFERENCES

1. A. Albert, D. J. Browns, and H. Duewell, J. Chem. Soc., 1284, 1948.

2. A. F. Bekhli and N. P. Kozyreva, KhGS, collection: 1, p. 296, 1967.

3. W. S. Johnson, E. I. Woroch, and B. G. Buell, J. Am. Chem. Soc., 71, 1901, 1949.

4. E. A. Steck and G. W. Ewing, J. Am. Chem. Soc., 70, 3397, 1948.

5. D. P. Graig and L. N. Short, J. Chem. Soc., 419, 1945.

6. A. K. Sukhomlinov, ZhOKh, 28, 1038, 1958.

7. S. F. Mason, J. Chem. Soc., 1281, 1959.

8. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], Moscow, p. 356, 1963.

9. A. Etienne and A. Stachelin, Bull. Soc. Chem. France, 748, 1954.

10. J. von. Braun and H. Gruber, Ber., **55**, 1710, 1922.

22 April 1966

Martsinovskii Institute of Medicinal Parasitology and Tropical Medicine, Moscow

*The UV spectrum was taken in alcohol on an EPS-3 instrument and the IR spectrum on a UR-10 instrument. The authors express their thanks to E. M. Peresleni for recording the spectra.