INVESTIGATION OF THE PRODUCTS OF THE REACTION OF EPICHLOROHYDRIN WITH AROMATIC AMINES

XIV.* SYNTHESIS OF BENZO[h]QUINOLINE AND 1,2,3,4-TETRAHYDROBENZO[h]QUINOLINE

S. I. Kutkevichus and K. S. Sherenas

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1,2,3,4-Tetrahydrobenzo[h]quinoline is obtained along with benzo[h]quinoline when benzo[h]-quinoline is synthesized via the Skraup method from 1-naphthylamine without an oxidizing agent. It is demonstrated that the dehydration of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]-quinoline by acids proceeds with the intermediate formation of esters. N-Acyl-1,2(or 1,4)-dihydrobenzo[h]quinolines are obtained by the action of alkali on N-acyl-3-chloro-1,2,3,4-tetrahydrobenzo[h]quinolines.

For a long time the only method for the preparation of benzo[h]quinoline (I) was the Skraup synthesis [2]. A substantial disadvantage in the synthesis of I via the Skraup method is the low yield of product and its inconvenient isolation from the reaction mixture. Attempts by others [3-7] to raise the yield of I by changing the ratio of starting materials, oxidizing agent, and reaction temperature did not result in a substantial increase in the yield of I. The highest yield of benzo[h]quinoline via the Skraup method did not exceed 45% [8, 9].

The most probable scheme for the formation of benzo[h]quinoline under the conditions of the Skraup synthesis includes dihydrobenzo[h]quinoline, which is oxidized to benzo[h]quinoline, as an intermediate. However, in later studies it was indicated that dihydrobenzo[h]quinoline readily disproportionates to benzo-[h]quinoline and 1,2,3,4-tetrahydrobenzo[h]quinoline (II), not only in acid media but also in alkaline or neutral media and at comparatively low temperatures. However, the formation of II via the Skraup method has not been noted.

In order to clear up this contradiction, we made attempts to observe whether II is formed in the Skraup synthesis.

The presence of II in the reaction mixture is detected in those cases when the synthesis is carried out in the absence of oxidizing agents. Thus the following yields were obtained from 1-naphthylamine (III), glycerol, and sulfuric acid in a ratio of 1:1:1.5; 15% I, 7% II, and 12% starting III. The reaction was carried out at 165-170°C with removal of the water formed in the process. The yield of II decreases as the amount of glycerol is increased. The formation of II can apparently be explained by disproportionation of dihydrobenzo[h]quinoline, the formation of which is specified in the Skraup synthesis. In addition, the isolation of II confirms that dihydro derivatives of quinoline are formed during the action of acrolein on the amine. In the preparation of quinoline, the dihydro derivative is aromatized, thereby increasing the yield of quinoline, while in the preparation of benzo[h]quinoline the dihydro derivative disproportionates to benzo[h]quinoline and its 1,2,3,4-tetrahydro derivative. Under the conditions of the Skraup synthesis, the II formed is lost in side reactions with both the oxidizing agent and acrolein. This apparently may also explain the fact that the yield of I does not exceed 50%.

The high tendency for oxidation and the absence of disproportionation of dihydroquinoline were noted in [13].

*See [1] for communication XIII.

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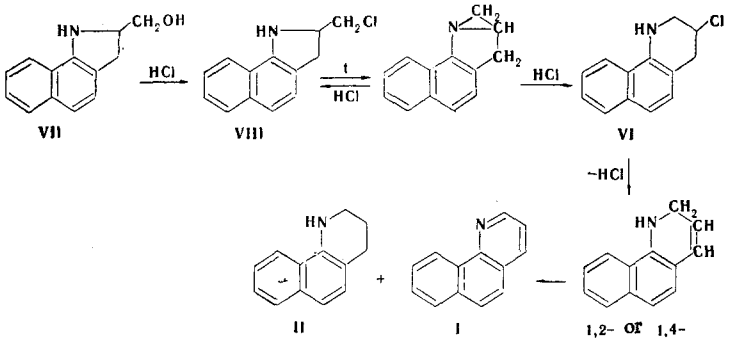
As pointed out in [11], I and II are formed from 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (IV) through disproportionation of dihydrobenzo[h]quinoline. In a further study of the dehydration of IV by polyphosphoric acid (PPA) it was observed that an ester of phosphoric acid and 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (V), which is converted to I and II on heating to 200° in PPA, is formed at 160°. Consequently, the dehydration of IV by PPA proceeds with the intermediate formation of ester V, from which phosphoric acid is split out, and the resulting dihydrobenzo[h]quinoline disproportionates to I and II.

Heating of IV with concentrated hydrochloric acid [10] gives I and II, the formation of which is explained by disproportionation of the dihydro derivative obtained by splitting out of water from IV. Since the formation of I and II by the action of PPA on IV proceeds through ester V, it seemed of interest to follow the dehydration of IV with hydrochloric acid, namely, to ascertain whether a water molecule is split out directly from IV or whether the hydroxyl group is replaced by a chlorine atom with subsequent splitting out of hydrogen chloride from 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline. A mixture of I and II is formed when 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (VI) is heated with hydrochloric acid at 190°.

Compound VI and 2-(chloromethyl)benz[g]indoline (VIII) were isolated along with the starting material and slight amounts of I and II as a result of heating 2-(hydroxymethyl)benz[g]indoline (VII) with hydrochloric acid at 180°. When VIII is heated with hydrochloric acid at 190° it is smoothly converted to a mixture of I and II. Under these conditions, the reaction apparently proceeds via the scheme



The transformations of IV are similar.

Azirido[1,2-*a*]benz[g]indoline was obtained in an attempt to obtain dihydrobenzo[h]quinoline by the action of alkali on VI [14]. In a study of the reaction of N-acyl-3-chloro-1,2,3,4-tetrahydrobenzo[h]quinolines with alkalis it was established that it gives compounds that do not contain halogen, but the acyl group attached to the nitrogen is retained. In this case, the splitting out of hydrogen chloride apparently proceeds with elimination of hydrogen from C_2 or C_4. Thus N-benzoyl-1,2-(or 1,4)-dihydrobenzo[h]quinoline (X) is obtained from N-benzoyl-3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (IX), while N-acetyl-1,2-(or 1,4)-dihydrobenzo[h]quinoline (XII) is obtained from N-acetyl-3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline. The structures of X and XII were confirmed by the IR and PMR spectra. A mixture of I, II, and a dimeric compound similar to that described in [12] is obtained when XII is heated under pressure with hydrochloric acid at 140°. Consequently, in the action of alkalis on N-acyl-2-(chloromethyl)benz[g]indolines, the reaction proceeds with the formation of an aziridine ring [14], while dihydrobenzo[h]quinoline derivatives are formed in the case of N-acyl-3-chloro-1,2,3,4-tetrahydrobenzo[h]quinolines.

EXPERIMENTAL

The PMR spectra were recorded with a Varian A56/60A spectrometer (60 MHz). The IR spectra were recorded with a UR-20 spectrophotometer.

Benzo[h]quinoline (I) and 1,2,3,4-Tetrahydrobenzo[h]quinoline (II). A. The calculated amount of glycerol was added dropwise with stirring at 165-170° in the course of 40-50 min to a mixture of 43.0 g (0.3 mole) of III and 45 ml of concentrated sulfuric acid. The mixture was then diluted with water to 1000 ml, and the aqueous solution and viscous precipitate were treated with alkali and extracted with ether. The ether was removed, and the residue was vacuum-distilled (2-3 mm) under nitrogen. Two fractions were obtained – one with bp 135-140°, consisting primarily of III, and the other with bp 155-160°, consisting of I and II. Compounds I and II were separated by a known method by treatment with hydrochloric acid [11]. The results of the experiments are presented in Table 1.

TABLE 1. Experimental Results

No.	Ratio of III and glycerol	Reaction time, h	Isolated, %		
			I	II	III
1	1 : 0,75	1	10	5,5	36
2	1 : 1	1	15	7	12
3	1 : 1,5	1	31	5,5	5
4	1 : 1,5	7	33	traces	—

B. Two ampules were each charged with 1.2 g (5 mmole) of VIII and 20 ml of concentrated hydrochloric acid and heated at 190° for 4 h. The contents were made alkaline with sodium hydroxide and extracted with ether. The ether was removed, and the residue was purified by extraction with petroleum ether and treated with 5 ml of 15% hydrochloric acid. The subsequent separation of I and II was accomplished as in experiment A to give 0.7 g (39%) of I. The yield of the hydrochloride of II was 0.6 g (27%).

C. When VI was used under the conditions of experiment B, 0.7 g (39%) of I and 0.7 g (32%) of the hydrochloride of II were isolated.

Approximately the same yields were obtained when the reaction of VI or VIII with hydrochloric acid was carried out at 200° for 4 h.

D. An ampule was charged with 0.55 g (2.5 mmole) of XII and 10 ml of concentrated hydrochloric acid and heated at 140° for 4 h. The contents were made alkaline with sodium hydroxide and extracted with ether. Thin-layer chromatography (TLC) on aluminum oxide established the formation of I and II (R_f 0.58) and the previously described [12] dimeric compound (R_f 0.25) [ether–heptane (3 : 2)].

Action of Nitrobenzene on 1,2,3,4-Tetrahydrobenzo[h]quinoline under the Conditions of the Skraup Synthesis. A mixture of 7.3 g (0.04 mole) of II, 5.0 g (0.04 mole) of nitrobenzene, and 6.0 g (0.06 mole) of concentrated sulfuric acid was heated at 160–170° for 1 h. The mass was treated with alkali and ethanol. Thin-layer chromatography on aluminum oxide established the absence of both starting II and I.

Action of Acrolein on 1,2,3,4-Tetrahydrobenzo[h]quinoline under the Conditions of the Skraup Synthesis. A mixture of 9.1 g (0.05 mole) of II, 7.0 g (0.075 mole) of glycerol, and 8.0 g (0.075 mole) of concentrated sulfuric acid was heated at 165–170° for 1 h. Thin-layer chromatography on aluminum oxide established that starting II was absent in the reaction mixture.

Ester of Phosphoric Acid and 3-Hydroxy-1,2,3,4-Tetrahydrobenzo[h]quinoline (V). A 10.0-g (0.05 mole) sample of IV was added to polyphosphoric acid, prepared from 20 ml of orthophosphoric acid and 30 g of phosphorus pentoxide, and the mixture was stirred at 160° for 1 h. The mixture was then poured into 500 ml of water and cooled. The resulting precipitate was removed by filtration and washed with water to give 13.2 g (95%) of V with mp 182.5–184.5° (from dilute orthophosphoric acid). Found: N 4.8%. $C_{13}H_{14}NO_4P$. Calculated: N 5.0%.

3-Chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (VI) and N-Benzoyl-2-(chloromethyl)benz[g]indoline. Each of three ampules was charged with 0.6 g (2.5 mmole) of the hydrochloride of VII and 10 ml of concentrated hydrochloric acid and heated at 180° for 6 h. The contents were made alkaline with sodium carbonate and extracted with ether. The resulting mixture of VI and VIII was separated from the unchanged VII by chromatography on aluminum oxide with elution by ether–heptane (3 : 2). The mixture of VI and VIII in dry ether was treated with benzoyl chloride in the presence of potassium carbonate at room temperature, and the resulting N-benzoyl-2-(chloromethyl)benz[g]indoline was removed by filtration and washed with ether and water to give 0.2 g (8%) of a product with mp 172.0–174.0°. No melting-point depression was observed in a mixture of this product and an authentic sample [15]. The ether filtrate yielded 0.2 g (12%) of VI, which did not depress the melting point of the previously described compound [11].

The starting material was primarily isolated in the reaction of IV with hydrochloric acid under the same conditions. Thin-layer chromatography on aluminum oxide revealed only traces of the chloro derivative (R_f 0.55) [ether–heptane (3 : 2)] and traces of I and II. When the temperature was raised to 190°, thin-layer chromatography established that there was an increase in the amount of I and II in the reaction mixture and a decrease in the amount of starting IV (R_f 0.44) [chloroform–ethanol (66 : 1)], and only traces of the chloro derivative were detected.

N-Benzoyl-1,2(or 1,4)-dihydrobenzo[h]quinoline (X). A mixture of 6.4 g (0.02 mole) of IX, 100 ml of ethanol, 15 ml of pyridine, and 1.2 g (0.02 mole) of potassium hydroxide was refluxed for 2 h. The mixture was cooled, and the crystals were removed by filtration and washed with water to give 5.0 g (88%) of X with mp 198.0-199.0° (from absolute ethanol). Found: N 4.9%. $C_{20}H_{15}NO$. Calculated: N 4.9%. IR spectrum (KBr pellet), ν, cm^{-1}: 2900, 2860 (CH_2), 1655 (amide CO). PMR spectrum (in $CClF_2COOH$), δ, ppm: 3.6-4.2 (multiplet, 2H, CH_2), 6.3-7.5 (group of signals, 13H).

N-Acetyl-3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XI). A mixture of 4.4 g (0.02 mole) of VIII and 15 ml of acetic anhydride was heated at 70° for 6 h. The mixture was diluted with water, made alkaline with sodium carbonate, and extracted with benzene. The benzene solution was washed with water, the benzene was removed, and the crystals were washed with ethanol to give 4.8 g (92%) of a product with mp 90.5-91.5° (from ethanol). Found: Cl 13.8; N 5.4%. $C_{15}H_{14}ClNO$. Calculated: Cl 13.7; N 5.4%.

N-Acetyl-1,2(or 1,4)-dihydrobenzo[h]quinoline (XII). A mixture of 2.6 g (0.01 mole) of XI, 0.6 g (0.01 mole) of potassium hydroxide, and 30 ml of absolute ethanol was refluxed for 20 min. The precipitated potassium chloride was removed by filtration, and the ethanol was removed. The residue was washed with water and ether to give 1.8 g (81%) of XII with mp 101.5-102.5° (from dilute ethanol). Found: N 6.4%. $C_{15}H_{13}NO$. Calculated: N 6.3%. PMR spectrum (in CCl_4), δ, ppm: 1.64 (singlet, 3H) (methyl protons of the acetyl group), 3.3-3.6 (multiplet, 1H) and 5.25-5.6 (multiplet, 1H) (apparently methylene protons), 6.03-6.24 (multiplet, 1H) and 6.43-6.6 (doublet of doublets, 1H, $J_1 = 10$ Hz, $J_2 = 2$ Hz) (protons attached to the double bond), 7.0-7.8 (group of signals, 6H) (aromatic protons).

LITERATURE CITED

1. S. I. Kutkevichus and R. I. Valite, Khim. Geterotsikl. Soedin., 1117 (1972).
2. Z. Skraup, Monatsh., 2, 162 (1881).
3. Z. Skraup and A. Cobenzyl, Monatsh., 4, 459 (1883).
4. E. Bamberger and L. Stettenheimer, Ber., 24, 2472 (1891).
5. A. Claus and P. Imhoff, J. Pr. Chem., 57, 68 (1898).
6. R. Haid, Monatsh., 27, 318 (1906).
7. J. Baltrop and K. MacPhee, J. Chem. Soc., 638 (1952).
8. Masao Yokete, Yasuo Hakamada, and Tomiyora Kimura, J. Chem. Soc. Japan, 56, 962 (1953).
9. A. Purenas and I. Zdanavichyus, First Republic Conference of Chemists of the Lithuanian SSR, Vilnius [in Russian] (1959), p. 175.
10. N. N. Vorozhtsov, Jr., and S. I. Kutkevichus, Zh. Obshch. Khim., 28, 2682 (1958).
11. S. I. Kutkevichus and K. S. Sherenas, Khim. Geterotsikl. Soedin., 1526 (1970).
12. S. I. Kutkevichus and V. A. Darashkaite, Khim. Geterotsikl. Soedin., 548 (1972).
13. W. S. Johnson and B. G. Buell, J. Am. Chem. Soc., 74, 4517 (1952).
14. S. I. Kutkevichus and K. S. Sherenas, Nauchnye Trudy Vuzov Lit. SSR, Khim. i Khim. Tekhnol., 13, 157 (1971).
15. S. I. Kutkevichus and K. S. Sherenas, Khim. Geterotsikl. Soedin., 362 (1972).