A STUDY OF THE PRODUCTS OF THE REACTION OF EPICHLOROHYDRIN WITH AROMATIC AMINES

V.* HALOGENATION OF 1,2,3,4-TETRAHYDROBENZO[h]QUINOLINE AND ITS DERIVATIVES

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The halogenation of 1,2,3,4-tetrahydrobenzo[h]quinoline and of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline and its O-benzoyl and N,O-dibenzoyl derivatives has been studied. The action of thionyl chloride or bromide on 1,2,3,4-tetrahydrobenzo[h]quinoline at room temperature gives 6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline and 6-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline. When 6-chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline is heated with thionyl chloride, aromatization of the tetrahydropyridine ring takes place, and when 6-bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline is heated with thionyl chloride, in addition to the aromatization of the tetrahydropyridine ring the bromine atom is replaced by a chlorine atom with the formation of 6-chlorobenzo[h]quinoline. 6-Bromobenzo[h]quinoline has been obtained by heating 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline with thionyl bromide.

As reported [1], the corresponding 6-halogeno-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinolines could not be obtained by heating 4-halogeno-1-naphthylamines with epichlorohydrin. 6-Chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline in the form of a mixture with 3,6-dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline has been obtained by the action of thionyl chloride on 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I) [2]. Consequently, to obtain 6-halogeno derivatives of benzo[h]quinoline, benzoyl derivatives of 3-hydroxy-1,2,3,4-benzo[h]quinoline were first subjected to halogenation. The action of thionyl chloride on 3-benzoyloxy-1,2,3,4-tetrahydrobenzo[h]quinoline (II) at room temperature gave 3-benzoyloxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (III) which, on saponification in an aqueous ethanolic solution of caustic potash, was converted into 6-chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (IV). It was impossible to isolate 3-benzoyloxy-6-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline (V) by the action of thionyl bromide on II. In order to obtain 6-bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VI), 1-benzoyl-3-benzoyloxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VII) was subjected to the action of thionyl chloride, but no VIII could be isolated from the reaction mixture. Thionyl chloride does not chlorinate VII under similar conditions.

The action of bromosuccinimide on VII gave 1-benzoyl-3-benzoyloxy-5-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline (VIII), and the action of sodium hypochlorite on VII in a mixture of hydrochloric and acetic acids gave 1-benzoyl-3-benzoyloxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (IX), identical with the product obtained by the benzoylation of IV. The saponification of VII, VIII, and IX in an aqueous ethanolic solution of caustic soda yielded 1-benzoyl-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (X), N-benzoyl-6-chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (XI), and N-benzoyl-6-bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (XII). The saponification of X, XI, and XII gave, respectively, I, IV, and VI. In the benzoylation of I with benzoyl chloride in pyridine, the O-benzoyl derivative is first formed [3] and in the saponification of the O,N-dibenzoyl derivative (VII), as our investigations have shown, the N-benzoyl derivative is first formed. Consequently, not only is the hydroxy group in I benzoylated more readily, but

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*For Communication IV, see [6].

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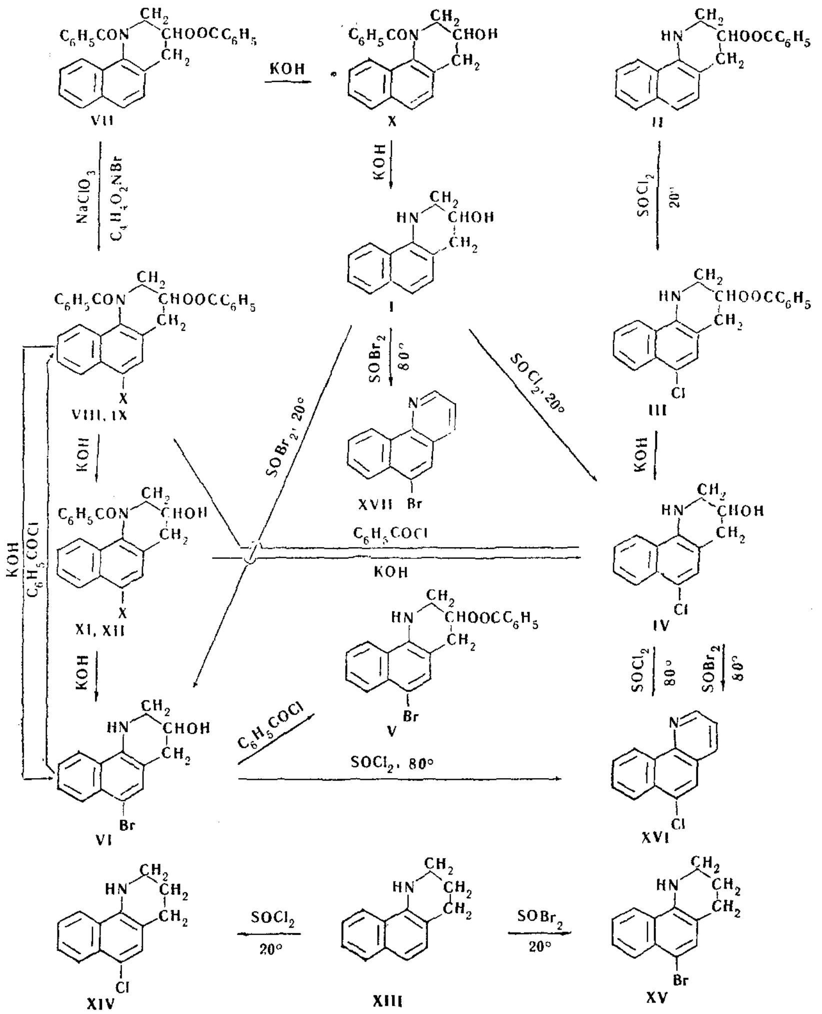
a benzoyl group substituted in it is more readily split out than from the secondary amino group connected with the aromatic ring.



VIII, XII X = Br; IX, XI X = Cl

A study of the reaction of thionyl chloride with 1,2,3,4-tetrahydrobenzo[h]quinoline (XIII) has shown that at room temperature a good yield of 6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (IV) is obtained in an hour. When the reaction is prolonged or the temperature is raised, the yield of IV decreases, and when XIII is boiled with thionyl chloride there is no XIV in the reaction mixture. The action of thionyl bromide on XIII has given 6-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline (XV).

As mentioned previously [4], the action of thionyl chloride on I at room temperature for 10 h forms a mixture of IV and 3,6-dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline, i.e., chlorine atoms replace not only the hydroxy group but also the hydrogen atom in position 6. The maximum yield of IV (about 60%) is obtained when the time of action of the thionyl chloride on I is reduced from 10 h to 20 min. When I is kept with thionyl chloride for 10 min or when the temperature is raised to 40-43°C or is lowered to 10-13°C, the yield of IV decreases.

The action of thionyl bromide on I at room temperature gave 6-bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VI), and the benzoylation of this compound gave 3-benzoyloxy-6-bromo-1,2,3,4-tetrahydrobenzo[h]quinoline (V), which preserves the basic properties of the N–H group of the heterocyclic ring. Thus it has been established that the halogenation of I can be carried out with both thionyl chloride and thionyl bromide, but the yield of halogen derivative is higher in chlorination.

It has been reported previously [4,5,6] that when 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I) and its derivatives are heated with thionyl chloride, chlorination in position 6 and also the aromatization of the tetrahydropyridine ring take place. Our work has shown that when 6-chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (IV) or 6-bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VI) is heated with thionyl chloride, the same product – 6-chlorobenzo[h]quinoline (XVI) – is obtained, i.e., when IV is heated with thionyl chloride the tetrahydropyridine ring undergoes aromatization while in the case of VI not only does the tetrahydropyridine ring aromatize but the bromine atom in position 6 is replaced by a chlorine atom. The action of thionyl bromide on I on heating is similar to the action of thionyl chloride – 6-bromobenzo[h]quinoline (XVII) is formed. It follows from this that when I is heated with thionyl bromide not only bromination but also the aromatization of the tetrahydropyridine ring takes place. At the same time, when IV is heated with thionyl bromide, as was to be expected, only the aromatization of the tetrahydropyridine ring (XVI) takes place.

EXPERIMENTAL

6-Chloro-1,2,3,4-tetrahydrobenzo[h]quinolin-3-yl Benzoate (III). A solution of 10.0 g (0.03 mole) of II in 40 ml of thionyl chloride was kept at 20-23°C for 30 min. Then, with stirring, the solution was slowly poured into methanol (150 ml) and the mixture was made alkaline with 50% caustic soda and diluted with water (300 ml). The precipitate that formed was filtered off and washed with water, giving colorless plates of III, mp 156.0-156.5°C (from ethanol). Yield 10.5 g (94%). Found %: Cl 10.4, 10.2. $C_{20}H_{16}ClNO_2$. Calculated %: Cl 10.5.

6-Chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (IV). a. A hot solution of 4.0 g of III in 140 ml of ethanol was treated with 1.5 g of caustic potash and 1.5 ml of water. The mixture was shaken at room temperature for 3 h, diluted with water (250 ml), and cooled to −2°C. The precipitate formed was recrystallized from ethanol, mp 131.5-132.0°C, yield 2.5 g (91%). Found %: N 6.0, 6.0; Cl 15.4, 15.1. $C_{13}H_{12}ClNO$. Calculated %: N 6.0; Cl 15.1.

b. A mixture of 4.0 g (0.01 mole) of IX, 60 ml of ethanol, 1.12 g (0.02 mole) of caustic potash, and 1 ml of water was kept at room temperature for 12 h and was then diluted with water (70 ml). This gave crystals of IV in the form of colorless needles, mp 131.0-132.0°C (from ethanol). Yield 1.6 g (73.9%). Found %: N 5.9, 5.8; Cl 14.9, 15.0. $C_{13}H_{12}ClNO$. Calculated %: N 6.0; Cl 15.1.

c. A mixture of 10.0 g (0.05 mole) of I and 40 ml of thionyl chloride was kept at 20-23°C for 20 min. The precipitate of hydrochloride that formed was filtered off, washed with thionyl chloride, and dried. Then it was dissolved in ethanol (75 ml) and the solution was made alkaline with 50% caustic soda solution and diluted with water to 250 ml. The crystals were filtered off, mp 130.5-131.5°C, yield 7.1 g (60.2%). After recrystallization from dilute ethanol, mp 131.0-132.0°C. A mixture with the crystals of 6-chloro-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline obtained in experiment a melted without depression. In the chlorination of I at the same temperature for 5, 10, 30, 40, and 60 min, the yields of IV were, respectively, 26, 57.8, 53.2, 39.6, and 35.7%. At a temperature of 40-43°C and a time of 10 min, the yield of IV was 40.7%. At a temperature of 10-13°C and a time of 30 min, 31.0% of IV was obtained.

When compound I was chlorinated with thionyl chloride for 10 h at room temperature, after the mixture had been made alkaline and diluted with water as described in experiment a, a mixture of bases I and IV with mp 118.0-120.5°C was obtained. Purification on alumina with elution by acetone yielded crystals of IV with mp 129.5-130.0°C. Yield 3.2 g (35%).

N-Benzoyl-6-bromo-1,2,3,4-tetrahydrobenzo[h]quinolin-3-yl Benzoate (VIII). a. A solution of 20.0 g (0.05 mole) of VII in 150 ml of carbon tetrachloride was treated with 8.9 g (0.05 mole) of bromosuccinimide and heated in the boiling water bath for 2 h. After cooling, the precipitate that had deposited was filtered off, washed with water, and recrystallized from ethanol. This gave colorless crystals of VIII, with mp 161.0-162.5°C, yield 13.3 g (55.7%). Found %: N 2.9, 3.0; Br 16.1, 16.2. $C_{27}H_{20}BrNO_3$. Calculated %: N 2.9; Br 16.4.

b. Compound VIII was obtained by the action of benzoyl chloride on VI in a similar manner to the preparation of IX from IV (see following experiment, paragraph b), mp 161.0-162.0°C.

1-Benzoyl-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinolin-3-yl Benzoate (IX). With stirring, 0.6 g of sodium hypochlorite in 2.5 ml of water was added to a solution of 4.1 g (0.01 mole) of VII in a mixture (1 : 3) of hydrochloric and acetic acids, the temperature being kept below 50°C. After the decantation of the aqueous layer and washing with water, the viscous product that separated out was dried and was treated with methanol. This gave colorless plates of IX, mp 161.0-162.5°C (from methanol). Yield 3.5 g (75%). Found %: C 73.4, 73.2; H 4.8, 4.6; Cl 7.9, 8.3. $C_{27}H_{20}ClNO_3$. Calculated %: C 73.4; H 4.6; Cl 8.0.

b. A solution of 0.7 g (0.003 mole) of IV in 8 ml of pyridine was treated with 2.3 g of benzoyl chloride, and the reaction mixture was heated in the boiling water bath for 3 h. Then it was treated with 25 ml of 25% solution of sulfuric acid and diluted with water. After the decantation of the aqueous layer, the viscous product that had separated out was treated with 15 ml of methanol, and the precipitate was filtered off and recrystallized from methanol, mp 161.5-162.5°C, weight 1.3 g. A mixture with the crystals obtained in experiment a melted without depression.

1-Benzoyl-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (X). A mixture of 12.0 g (0.03 mole) of VII, 180 ml of ethanol, and 1.7 g (0.03 mole) of caustic potash was shaken at room temperature for 1 h 30 min. Then it was diluted with water (400 ml) and cooled to −3°C. The precipitate formed (6.8 g) was recrystallized from ethanol. This gave colorless crystals of X with mp 174.0-175.0°C, yield 3.3 g (37.3%). Found %: N 4.8, 4.8. $C_{20}H_{17}NO_2$. Calculated %: N 4.6.

1-Benzoyl-3-hydroxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline and the Corresponding 6-Bromo Derivative (XI and XII). A mixture of 2.0 g (0.005 mole) of IX, 30 ml of ethanol, 0.28 g (0.005 mole) of caustic potash, and 1 ml of water was shaken at room temperature for 5 h. After the solvent had been distilled off in vacuum, the residue was washed with water and extracted with ether. This gave colorless plates of XI, mp 179.5-180.5°C (from methanol), yield 0.12 g (7.6%). Found %: N 4.3, 4.3; Cl 10.6, 10.3. $C_{20}H_{16}ClNO_2$. Calculated %: N 4.2; Cl 10.5.

Compound XII was obtained similarly from 3.0 g (0.006 mole) of VIII, 0.28 g (0.005 mole) of caustic potash, 30 ml of ethanol, and 1 ml of water, mp 177.0-178.0°C (from methanol), yield 0.25 g (10.6%). Found %: N 3.6, 3.6; Br 20.3, 20.4. $C_{20}H_{16}BrNO_2$. Calculated %: N 3.7; Br 20.9.

6-Bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VI). a. A mixture of 2.0 g (0.004 mole) of VIII, 40 ml of ethanol, 0.46 g (0.008 mole) of caustic potash, and 0.5 ml of water was heated at 115°C for 15 min. Then it was diluted with water (80 ml) and the crystalline precipitate then formed on cooling to 0°C was filtered off and washed with water. Recrystallization from ethanol gave colorless needles of VI, mp 115°C (decomp., rate of heating 12°C/min), yield 0.86 g (75.5%). The substance is readily soluble in ether, acetone, ethanol, and benzene and sparingly soluble in petroleum ether. Found %: N 5.2, 5.2; Br 29.0, 29.1. $C_{13}H_{12}BrNO$. Calculated %: N 5.0; Br 28.7.

b. A mixture of 4.0 g (0.02 mole) of I and 16 ml of thionyl bromide was kept at 20-23°C for 15 min. The precipitate formed was filtered off, treated with 20% ammonia solution, and extracted with ether. The ether was driven off, the residual mass was dissolved in ethanol (8 ml), and the solution was diluted with water (20 ml). The precipitate (1.8 g) was subjected to chromatographic purification on alumina. Elution with acetone and then with methanol yielded 0.5 g (8.9%) of substance with mp 115°C (decomp.). A mixture with crystals of authentic 6-bromo-3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline melted without depression.

3-Hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I). A mixture of 1.0 g (0.003 mole) of X, 15 ml of ethanol, and 0.2 g (0.003 mole) of caustic potash was shaken at room temperature for 6 h. Then it was diluted with water (20 ml) and cooled to −3°C. The precipitate formed was recrystallized from chlorobenzene, mp 150.0-151.0°C, yield 0.4 g (60.6%).

Similarly, the saponification of XI and XII gave IV and VI, respectively.

6-Chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XIV). A mixture of 4.0 g (0.02 mole) of XIII and 16 ml of thionyl chloride was kept at 20-23°C for 1 h. The precipitate that had formed was filtered off, treated with 25% ammonia solution, and extracted with ether. After the elimination of the solvent, recrystallization from petroleum ether yielded colorless crystals of XIV with mp 67.5-68.5°C, yield 2.44 g (51.4%). Found %: N 6.4, 6.5; Cl 16.1, 16.4. $C_{13}H_{12}ClN$. Calculated %: N 6.4; Cl 16.3.

6-Bromo-1,2,3,4-tetrahydrobenzo[h]quinoline (XV). This was obtained in a similar manner to XIV from 2.0 g (0.01 mole) of XIII and 8 ml of thionyl bromide in the form of light yellow crystals with mp 69.0-70.0°C. Yield 0.55 g (19.2%). Found %: Br 30.4, 30.8; N 5.30, 5.32. $C_{13}H_{12}BrN$. Calculated %: Br 30.5; N 5.3.

6-Bromo-1,2,3,4-tetrahydrobenzo[h]quinolin-3-yl Benzoate (V). A solution of 1.1 g (0.004 mole) of VI in 5 ml of pyridine was treated with 0.6 g (0.004 mole) of benzoyl chloride and the mixture was heated at 85-90°C for 30 min. Then it was diluted with 25% sulfuric acid (5 ml). After decantation of the aqueous layer, the viscous oil that had separated out was washed with water and treated with methanol (5 ml), and the resulting crystals were filtered off and recrystallized from ethanol, giving colorless needles with mp 131.0-132.5°C. Yield 0.8 g (54.4%). Found %: N 3.5, 3.6; Br 20.4. $C_{20}H_{16}BrNO_2$. Calculated %: N 3.7; Br 20.9.

The action of hydrogen chloride on an ethereal solution of V gave the hydrochloride of 6-bromo-1,2,3,4-tetrahydrobenzo[h]quinolin-3-yl benzoate, mp 170.0°C (decomp.). Found %: ionic chlorine 6.8, 5.8. $C_{20}H_{16}BrNO_2 \cdot HCl$. Calculated %: ionic chlorine 8.5.

6-Chlorobenzo[h]quinoline (XVI). a. A mixture of 2.0 g (0.009 mole) of IV and 10 ml of thionyl chloride was heated at 80-85°C for 2 h. Then it was cooled to room temperature and the precipitate was filtered off and dissolved in ethanol (25 ml), and the solution was made alkaline with 50% caustic soda solution and diluted with water (70 ml). The crystals that formed were filtered off, mp 99.0-100.0°C. Yield 1.23 g (47.7%). Recrystallization from ethanol gave colorless needles of XVI, mp 100.5-101.0°C. A mixture with the 6-chlorobenzo[h]quinoline obtained by the method used by Polish workers [7] melted without depression. Found %: N 6.8, 6.6; Cl 16.7, 16.4. $C_{13}H_8ClN$. Calculated %: N 6.6; Cl 16.6.

b. A mixture of 2.0 g (0.009 mole) of IV and 10 ml of thionyl bromide was heated at 80-85°C for 2 h. The further treatment of the reaction mixture was similar to that described above. This gave 0.74 g (41%) of XVI with mp 100.5-101.5°C (from ethanol). A mixture with authentic 6-chlorobenzo[h]quinoline melted without depression.

c. A mixture of 2.0 g (0.007 mole) of VI and 10 ml of thionyl chloride was heated at 75-80°C for 2 h. After cooling, the reaction mixture was poured onto ice. After the decantation of the aqueous layer and washing with water, the viscous product that had separated was treated by the method described above, and the crystals were filtered off and recrystallized from methanol, giving colorless needles with mp 100.5-101.5°C, yield 0.66 g (44%). A mixture with the crystals of XVI obtained in experiment a melted without depression.

6-Bromobenzo[h]quinoline (XVII). A mixture of 2.0 g (0.01 mole) of I and 9.5 ml of thionyl bromide was heated at 80-85°C for 2 h. Then it was cooled to −2°C and treated by the method described above, giving crystals with mp 109.0-111.5°C, yield 0.73 g (28.2%). Recrystallization from methanol gave colorless needles with mp 115.0-116.0°C. A mixture with the 6-bromobenzo[h]quinoline obtained by the Skraup method melted without depression. Found %: N 5.4, 5.4; Br 31.6, 31.5. $C_{13}H_8BrN$. Calculated %: N 5.4; Br 31.0.

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