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INVESTIGATION OF THE PRODUCTS OF REACTION OF EPICHLOROHYDRIN WITH AROMATIC AMINES

III. Action of Thionyl Chloride on 1, 2, 3, 4-Tetrahydro-3-Hydroxy-7-Bromo[h]-Benzoquinoline and 1, 2, 3, 4-Tetrahydro-3-Hydroxy-6-Methyl[h]Benzoquinoline*

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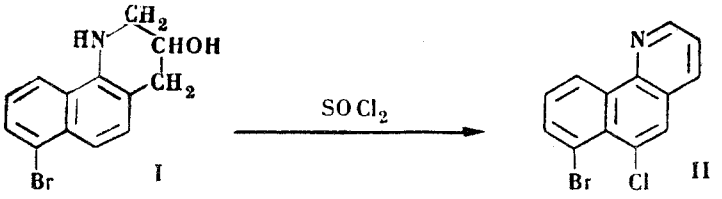
It is shown that the reaction of thionyl chloride with 1, 2, 3, 4-tetrahydro-3-hydroxy-6-methyl[h]benzoquinoline leads not only to aromatization of the tetrahydroquinoline ring, but also to chlorination of the methyl group.

As a continuation of previously published work [1], a study has now been made of the action of $SOCl_2$ on 1, 2, 3, 4-tetrahydro-3-hydroxy-7-bromo[h]benzoquinoline (I). The reaction product is 6-chloro-7-bromo[h]benzoquinoline (II), apparently formed via the 1, 2- or 1, 4-dihydro derivative



The products obtained by heating 1, 2, 3, 4-tetrahydro-3-hydroxy-6-methyl[h]benzoquinoline (III) with thionyl chloride yield a free base containing an atom of chlorine. Since it has been found [1] that under similar conditions 1, 2, 3, 4-tetrahydro-3-hydroxy[h]benzoquinoline gives the 6-chloro[h]benzoquinoline, it was of interest to ascertain where the chlorine atom entered when III was treated with thionyl chloride, position 6 in III being occupied by a methyl group.

Saponification of the chloro compound with dilute methanolic or ethanolic sodium hydroxide converts it to a compound which does not contain chlorine or free hydroxyl. Treatment of the chloro compound with sodium acetate gives an acetyl derivative, converted by alkali to a free base containing a hydroxyl group, but not corresponding to III. Oxidation of this hydroxy compound gives a crystalline substance which is readily soluble in dilute alkalies, and which is regenerated on acidification with acetic acid.

Thus from what is stated above it is evident that heating of thionyl chloride with 1, 2, 3, 4-tetrahydro-3-hydroxy-6-methyl[h]benzoquinoline leads to aromatization of the tetrahydropyridine ring, and chlorination of the methyl group. The compound isolated is 6-chloromethyl[h]benzoquinoline (IV), from which the following were obtained: methyl (V) and ethyl (VI) ethers of 6-methylol[h]benzoquinoline, 6-methylyl[h]benzoquinoline acetate (VII), and 6-methylol[h]-benzoquinoline (VIII). VIII is oxidized to [h]benzoquinoline-6-carboxylic acid (IX), whose structure is established by its also being prepared by treating 6-chloro[h]benzoquinoline (X) with cuprous cyanide followed by saponification of [h]benzoquinoline-6-nitrile or -6-carboxamide (XI, XII).

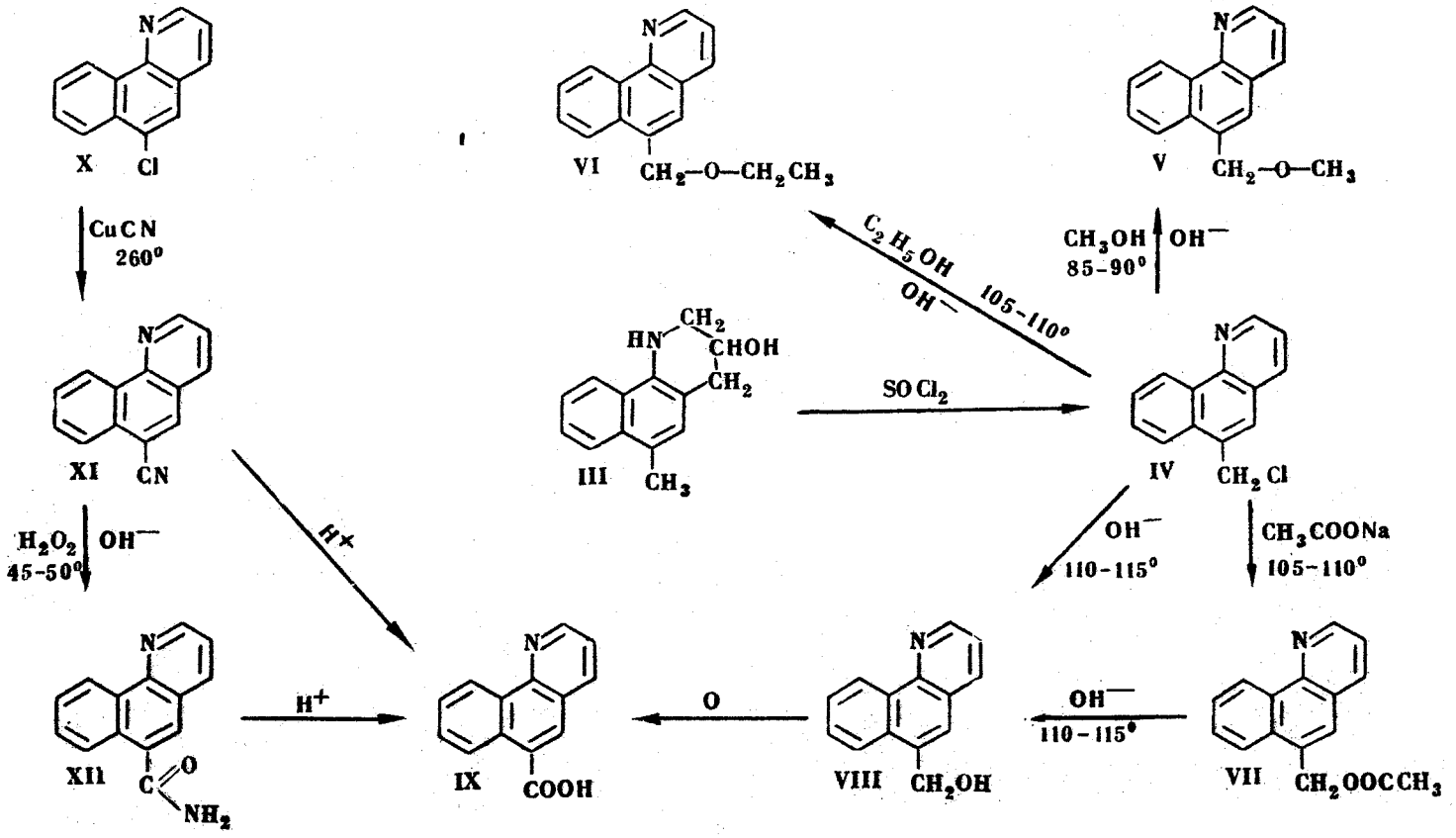
Experimental

1, 2, 3, 4-Tetrahydro-3-hydroxy-7-bromo[h]benzoquinoline (I) and 1, 2, 3, 4-tetrahydro-3-hydroxy-6-methyl[h]-benzoquinoline (III). These were prepared from the N-γ-chloro-β-hydroxypropyl derivatives of the appropriate amines [2].

6-Chloro-7-bromo-[h]benzoquinoline (II). 1.6 g (0.006 mole) 1, 2, 3, 4-tetrahydro-3-hydroxy-7-bromo[h]benzoquinoline and 15 ml thionyl chloride were heated together at 80-85° for 3 hr. After cooling the reaction products to room temperature, the precipitate was filtered off, dissolved in alcohol (20 ml), the solution made alkaline with 20% sodium hydroxide solution, and then diluted with water (60 ml). The precipitate formed was filtered off and recrystallized from alcohol. Colorless needles of II, yield 0.8 g (47%), mp 131.5-132.0°. Found: N 4.8, 4.9; Halogen; 39.9, 40.0%. Calculated for $C_{13}H_7BrClN$: N 4.8; Halogen; 39.9%.

6-Chloro-7-bromo[h]benzoquinoline picrate was prepared, mp 202.0-202.5° (from alcohol). Found: N 10.7, 10.9; Halogen 22.6, 22.7%. Calculated for $C_{19}H_{10}BrClN_4O_7$: N 10.7; Halogen 22.3%.

*For Part II see [3].


X Cl
CuCN 260°
XI CN
H_2O_2 OH⁻ 45-50°
XII C(=O)NH2
H+
IX COOH
O
VIII CH2OH
OH⁻ 110-115°
VII CH2OOCCH3
CH3COONa 105-110°
IV CH2Cl
SOCl2
III
HN CH2 CHOH CH2 CH3
C2H5OH OH⁻ 105-110°
VI CH2—O—CH2CH3
CH3OH OH⁻ 85-90°
V CH2—O—CH3
H+

6-Chloromethyl[h]benzoquinoline (IV). 3.5 g (0.0164 mole) 1, 2, 3, 4-tetrahydro-3-hydroxy-6-methyl[h]benzoquinoline was heated with 9 ml thionyl chloride for 2 hr at 80-85°. The precipitate formed was filtered off, washed with thionyl chloride (3 ml), and dried over sodium hydroxide. It was then dissolved in alcohol (35 ml), treated with aqueous 20% sodium hydroxide solution, and diluted with water (150 ml). After recrystallizing from alcohol it formed colorless needles IV mp 136.0-136.5°, yield 2.8 g (75%). Found: N 6.4, 6.2; Cl 15.6, 15.7%. Calculated for $C_{14}H_{10}ClN$: N 6.2; Cl 15.6%.

6-Methylol[h]benzoquinoline methyl ether (V). 0.8 g (0.0035 mole) 6-chloromethyl[h]benzoquinoline, 20 ml methanol, 3 ml water, and 0.8 g potassium hydroxide were heated together at 85-90° for 8 hr. After evaporating off the methanol, the residue was washed with water, and recrystallized from alcohol to give colorless crystals of V, mass 0.6 g, mp 26-27°. Found: N 6.3, 6.5%. Calculated for $C_{15}H_{13}NO$: N 6.4%.

6-Methylol[h]benzoquinoline ethyl ether (VI). 0.8 g (0.0035 mole) 6-chloromethyl[h]benzoquinoline, 20 ml alcohol, 5 ml water, and 0.7 g potassium hydroxide were heated for 6 hr at 105-110°. After distilling off the solvent, the residue crystallized. Recrystallization from methanol gave colorless crystals of VI, mp 46.5-47.0°, mass 0.5 g. Found: N 5.9, 5.9%. Calculated for $C_{16}H_{15}NO$: N 5.9%.

6-Methylol[h]benzoquinoline acetate (VII). 0.55 g (0.0025 mole) 6-chloromethyl[h]benzoquinoline, 0.7 g (0.005 mole) sodium acetate, and 15 ml alcohol were heated for 12 hr at 105-110°. The alcohol was evaporated off, and the residue treated with water (10 ml). It was then recrystallized from dilute methanol, when it formed colorless crystals of VII, mass 0.48 g, mp 66-67°. Found: N 5.6, 5.6%. Calculated for $C_{16}H_{13}NO_2$: N 5.6%.

6-Methylol[h]benzoquinoline (VIII).

a) 0.3 g (0.001 mole) 6-methylol[h]benzoquinoline acetate 5 ml alcohol, 5 ml water, and 0.8 g potassium hydroxide were heated for 12 hr at 110-115°. The precipitate which separated on cooling (5-10°) was recrystallized from methanol, to give colorless needles, mass 0.2 g, mp 115-116°. Found: N 6.4, 6.6%. Calculated for $C_{14}H_{11}NO$: N 6.7%.

b) 0.66 g (0.003 mole) 6-chloromethyl[h]benzoquinoline, 10 ml alcohol, 20 ml water and 1.0 g potassium acetate were heated for 2 hr 30 min at 110-115°. The solvent was evaporated off, and the precipitate recrystallized from methanol, mass 0.35 g, mp 115-116°. Mixed mp with the crystals obtained in Expt. a) undepressed.

[h]Benzoquinoline-6-carboxylic acid (IX).

a) 0.7 g (0.0035 mole) 6-methylol[h]benzoquinoline was dissolved in 2 ml 70% sulfuric acid, the solution heated to 80-85°, and a solution of potassium dichromate (2.9 g $K_2Cr_2O_7$ in 10 ml water) added dropwise during 30 min, after which the temperature was held for 2 hr. The products were then cooled, the precipitate filtered off and recrystallized from alcohol, to give colorless needles, mass 0.5 g, mp 259-260°. Found: N 6.4, 6.4%. Calculated for $C_{14}H_9NO_2$: N 6.3%.

b) 2.5 g (0.012 mole) [h]benzoquinoline-6-nitrile and 60 ml 75% sulfuric acid was heated for 2 hr at 155-160°, and 1 hr 30 min at 185-190°. The solution was then poured into 200 ml cold water, and the crystals formed were filtered off, mass 2.3 g, mp 259-260° (from alcohol). Mixed mp with crystals obtained in Expt. a), undepressed.

c) 0.2 g (0.001 mole) [h]benzoquinoline-6-carboxamide and 4 ml hydrochloric acid (d 1.19) was heated for 1 hr at 120-125°, the hydrochloric acid evaporated off, when there was obtained 0.12 g of IX, mp 259-260° (from alcohol.)

[h]Benzoquinoline-6-nitrile (XI). 16.8 g (0.08 mole) 6-chloro[h]benzoquinoline and 15.0 g (0.09 mole) cuprous cyanide were stirred for 3 hr at 260-265°, the products cooled, powdered, treated with 10% aqueous sodium hydroxide solution, and extracted with toluene (250 ml). After evaporating off the solvent the residue was recrystallized from alcohol, to give colorless needles of XI, mass 10.6 g, mp 164.0-165.5°. Found: C 82.3, 82.1; H 4.4, 4.2%. Calculated for $C_{14}H_8N_2$: C 82.4; H 4.0%.

[h]Benzoquinoline-6-carboxamide (XII). 0.7 g (0.0035 mole) [h]benzoquinoline-6-nitrile, 20 ml methanol, 10 ml water, 0.6 g potassium hydroxide, and 5 ml 20% hydrogen peroxide were kept at 45-50° for 1 hr, then cooled to 2-5°, and the crystals of XII which separated, recrystallized from alcohol, mass 0.5 g, mp 240-241°. Found: N 12.7, 12.7%. Calculated for $C_{14}H_{10}N_2O$: N 12.6%.

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