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

XIII.* 6-SUBSTITUTED BENZO[h]QUINOLINES

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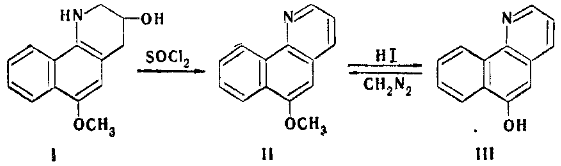
Aromatization of the tetrahydropyridine ring occurs when 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrobenzo[h]quinoline is heated with thionyl chloride. Some transformations of 6-amino- and 6-chlorobenzo[h] quinolines were studied.

In developing our previously published investigations [1-4], we have studied the action of thionyl chloride on 3-hydroxy-6-methoxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I), which was obtained by heating 4-methoxy-1-naphthylamine with epichlorohydrin. Base II, which does not contain chlorine or a hydroxyl group, was isolated after I was heated with thionyl chloride. The action of hydriodic acid on II gave III, which is quite soluble in dilute alkali solutions and is isolated on acidification with acetic acid, which indicates the presence of a hydroxyl group in III. Methylation of III with diazomethane converts it to II. Consequently, 6-methoxybenzo[h]quinoline (II) is formed when I is heated with thionyl chloride. The previously described [5] 6-hydroxybenzo[h]quinoline structure corresponds to substance III.



I II III

Compound III was also synthesized by the action of aqueous sodium hydroxide solution on 6-chlorobenzo[h]quinoline (IV) at 250-260°, as well as by fusing 3-hydroxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (V) with sodium hydroxide.

Reduction of III with tin in hydrochloric acid converts it to 6-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VI). The action of ammonia on III or IV at 250-270° gives 6-aminobenzo[h]quinoline (VII). Benzoylation of VII gives 6-benzamidobenzo[h]quinoline (VIII), while 6-(dibenzamido)benzo[h]quinoline (IX) is obtained when excess benzoyl chloride is present. The reaction of VII with epichlorohydrin gives 6-(γ-chloro-β-hydroxypropylamino)benzo[h]quinoline (X), which reacts with sodium cyanide to give γ-(benzo[h]-6-quinolinyl)amino-β-hydroxybutyronitrile (XI), and the latter gives amide XII in alkaline solution in the presence of hydrogen peroxide.

By heating X in chlorobenzene at 145°, we obtained 3-hydroxy-1,2,3,4-tetrahydro-1,8-diazatriphenylene (XIII), which forms N,O-dibenzoyl derivative XIV on benzoylation in pyridine.

The reaction of thionyl chloride with XIII gives 1,8-diazatriphenylene (XV), the structure of which was proved by alternative synthesis via the Skraup reaction. In both this case and in the case of I, only the tetrahydropyridine ring is aromatized by the action of thionyl chloride.

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*See [1] for communication XII.

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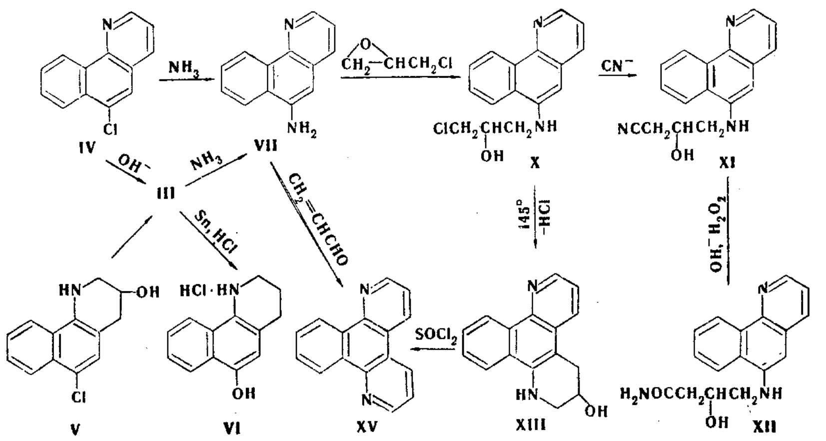

EXPERIMENTAL

3-Hydroxy-6-methoxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I). A mixture of 9.3 g (53 mmole) of 4-methoxy-1-naphthylamine and 4.9 g (53 mmole) of epichlorohydrin was held at room temperature for 3 days, after which the mass was dissolved in 10 ml of chlorobenzene and heated at 140-145° for 8 h. The hydrochloride was removed by filtration, washed with alcohol, treated with ammonia, and extracted with ether to give 4.2 g (34%) of colorless crystals with mp 128.0-128.5° (from alcohol). Found: N 6.1, 6.3%. $C_{14}H_{15}NO_2$. Calculated: N 6.1%.

3-Benzoxy-6-methoxy-1-benzoyl-1,2,3,4-tetrahydrobenzo[h]quinoline. A 0.62-g (4 mmole) sample of benzoyl chloride was added to a solution of 0.5 g (2 mmole) of I in 5 ml of pyridine, and the mixture was held at 80° for 1 h. It was then treated with 25% sulfuric acid and water. Methanol was added to the viscous reaction product, and the precipitate was removed by filtration to give 0.75 g (79%) of colorless crystals with mp 207.5-208° (from alcohol). Found: N 3.1, 3.4%. $C_{28}H_{23}NO_4$. Calculated: N 3.2%.

6-Methoxybenzo[h]quinoline (II). A. A mixture of 4.0 g (18 mmole) of I and 12 ml of thionyl chloride was heated at 80-85° for 1 h. The resulting precipitate was removed by filtration, treated with ammonia, and extracted with ether. The solvent was removed, and 2 ml of methanol was added to the residue to give 0.9 g (24%) of II with mp 61.5-62.5° (from hexane). Found: N 6.6, 6.6%. $C_{14}H_{11}NO$. Calculated: N 6.7%.

B. A 3.5-g (18 mmole) sample of III was dissolved in 200 ml of a mixture (1 : 1) of methanol and ether. A solution of 4 g of diazomethane in 200 ml of ether was then added slowly with stirring at 0 to −5°, and the mixture was allowed to stand at room temperature for 12 h. The solvent was removed, and the residue was dissolved in hexane, from which 2.8 g (75%) of crystals with mp 59.5-60.0° was obtained. These products did not depress the melting point of an authentic sample.

6-Hydroxybenzo[h]quinoline (III). A. A mixture of 0.4 g (0.002 mole) of II and 15 ml of hydriodic acid (sp. gr. 1.7) was heated at 65° for 4 h and at 130-140° for 2.5 h. The resulting precipitate was removed by filtration, treated with 50% sodium hydroxide solution (30 ml), and acidified with glacial acetic acid. The precipitate was removed by filtration, washed with water, and recrystallized from epichlorohydrin to give 0.33 g (89%) of product. Found: N 6.9, 7.1%. $C_{13}H_9NO$. Calculated: N 7.2%.

B. A mixture of 5.0 g (0.02 mole) of IV, 6.4 g (0.16 mole) of sodium hydroxide, and 60 ml of water was heated at 250-260° in an autoclave for 12 h. The mass was acidified with glacial acetic acid, and the resulting precipitate was removed by filtration, washed with water, and recrystallized from epichlorohydrin to give 4.2 g (91%) of product.

C. A 4.3-g (18 mmole) sample of V was fused with 2.4 g (60 mmole) of powdered sodium hydroxide at 200-210° for 1.5 h. The mass was cooled, treated with water, and extracted with ether. The aqueous layer was acidified with glacial acetic acid, and the resulting precipitate (2.1 g) was recrystallized from epichlorohydrin.

6-Hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline Hydrochloride (VI). A mixture of 4.0 g (0.02 mole) of III, 80 ml of concentrated hydrochloric acid, and 20.0 g of tin was heated at 140° for 25 h. The precipitate was removed by filtration and recrystallized from absolute alcohol to give 4.1 g (85%) of a product with mp 260° (dec.). Found: N 6.3, 6.2; Cl 15.3, 15.3%. $C_{13}H_{13}NO \cdot HCl$. Calculated: N 5.9; Cl 15.0%. The base darkened in air.

6-Aminobenzo[h]quinoline (VII). A. A mixture of 5.0 g (0.02 mole) of IV, 30 ml of ammonia, 2.0 g of ammonium sulfate, and 2.4 g of cuprous oxide was fused in an autoclave at 260-270° for 10 h. The reaction mass was thendiluted with water and extracted with ether. The solid was recrystallized from petroleum ether to give 0.05 g (1.1%) of a product with mp 111.5-112.0° (mp 117.0-118.0° [6]). Found: N 14.3, 14.2%. $C_{13}H_{10}N_2$. Calculated: N 14.4%.

B. A mixture of 4.3 g (0.02 mole) of III, 30 ml of ammonia, and 5.3 g (0.04 mole) of ammonium sulfate was heated in an autoclave at 260-270° for 12 h. The solid was removed by filtration, washed with water, and recrystallized from petroleum ether to give 3.5 g (82%) of a product with mp 111-112°. A mixture of this product with a sample of the compound obtained in experiment A melted without a depression.

6-Benzamidobenzo[h]quinoline (VIII). A 1.4-g (0.01 mole) sample of benzoyl chloride was added to a solution of 1.9 g (0.01 mole) of VII in 20 ml of pyridine, and the mixture was held at room temperature for 2 h. It was then treated with 20 ml of 25% sulfuric acid and diluted with water. The resulting viscous oil was treated with 10 ml of methanol to give a precipitate with mp 195°. Two recrystallizations from alcohol gave colorless needles with mp 211.5-212.0°. Found: N 9.5, 9.6%. $C_{20}H_{14}N_2O$. Calculated: N 9.4%.

6-(Dibenzamido)benzo[h]quinoline (IX). A 0.84-g (6 mmole) sample of benzoyl chloride was added to a solution of 0.5 g (3 mmole) of VII in 6 ml of pyridine, and the mixture was held at room temperature for 2 h. It was then treated with 5 ml of 25% sulfuric acid and diluted with water. The resulting viscous product was treated with 1 ml of methanol, and the resulting precipitate was removed by filtration and recrystallized from alcohol to give 0.5 g (48%) of a product with mp 216.5-218.5°. Found: N 6.9, 7.2%. $C_{27}H_{18}N_2O_2$. Calculated: N 7.0%.

6-(γ-Chloro-β-hydroxypropylamino)benzo[h]quinoline (X). A 10.0-g (52 mmole) sample of VII was dissolved in 15 ml of glacial acetic acid, and 4.77 g (52 mmole) of epichlorohydrin was added. The mass was held at room temperature for 48 h and at 40° for 8 h. It was then diluted with water and extracted with ether. The resulting viscous product was treated with isobutyl alcohol to give 6.64 g (45%) of a product with mp 125.5-126.5° (from isobutyl alcohol). Found: Cl 11.9, 12.1; N 9.7, 9.8%. $C_{16}H_{15}ClN_2O$. Calculated: Cl 12.4; N 9.8%.

γ-(Benzo[h]-6-quinolinyl)amino-β-hydroxybutyronitrile (XI). A 0.96-g (19 mmole) sample of sodium cyanide was added to a solution of 3.75 g (13 mmole) of X in 35 ml of methanol, and the mixture was heated at 70-75° for 1 h. The solvent was removed, and the residue was washed with water and extracted with ether. The solid was recrystallized from dilute alcohol to give 0.52 g (14%) of a product with mp 151.5-152.5°. Found: N 15.0, 15.2%. $C_{17}H_{15}N_3O$. Calculated: N 15.2%.

γ-(Benzo[h]-6-quinolinyl)amino-β-hydroxybutyramide (XII). A 2.0-g (7 mmole) sample of XI was dissolved in 20 ml of methanol, and 0.5 g of sodium hydroxide, 5 ml of water, and 7 ml of 25% H_2O_2 were added. The reaction proceeded in 3 min at the boiling point. The reaction mass was then diluted with water and extracted with ether. The solid was recrystallized from alcohol to give 0.59 g (28%) of a product with mp 178-180°. Found: N 14.0, 14.1%. $C_{17}H_{17}N_3O_2$. Calculated: N 14.2%.

3-Hydroxy-1,2,3,4-tetrahydro-1,8-diazatriphenylene (XIII). A mixture of 1.07 g (4 mmole) of X and 1.5 ml of chlorobenzene was heated at 145-150° for 8 h. It was then cooled to 30-40°, and the hydrochloride (0.67 g) was removed by filtration and treated with 50% sodium hydroxide solution. The alkaline mixture was extracted with ether. Recrystallization from benzene gave 0.1 g (11%) of yellow crystals of XIII with mp 170-172°. Found: N 10.5, 10.6%. $C_{16}H_{14}N_2O$. Calculated: N 11.2%.

3-Benzoxy-1-benzoyl-1,2,3,4-tetrahydro-1,8-diazatriphenylene (XIV). A 3-ml sample of benzoyl chloride was added to a solution of 2.0 g (8 mmole) of XIII in 10 ml of pyridine, and the mixture was held at room temperature for 5 h. It was then treated with 25% sulfuric acid and diluted with water. Methanol (15 ml) was added to the viscous reaction product, and the resulting precipitate was removed by filtration and recrystallized from alcohol to give 0.74 g (20%) of a product with mp 218-219°. Found: N 6.1, 6.2%. $C_{30}H_{22}N_2O_3$. Calculated: N 6.1%.

1,8-Diazatriphenylene (XV). A mixture of 1.0 g (4 mmole) of XIII and 5 ml of thionyl chloride was heated at 80° for 2 h, and the resulting precipitate was removed by filtration and treated with sodium hydroxide solution. The alkaline mixture was extracted with ether. Recrystallization from petroleum ether gave 0.29 g (31%) of crystals of XV with mp 151.0-151.6°. Found: N 11.8, 11.9%. $C_{16}H_{10}N_2$. Calculated: N 12.2%.

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