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

IX.* ALKYL DERIVATIVES OF 3-HYDROXY-1,2,3,4-TETRAHYDROBENZO[h]QUINOLINE

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The ethyl group of 3-hydroxy-6-ethyl-1,2,3,4-tetrahydrobenzo[h]quinoline is chlorinated and the tetrahydropyridine ring is aromatized under the influence of thionyl chloride. The corresponding 6-alkylbenzo[h]quinolines and 6-alkyl-1,2,3,4-tetrahydrobenzo[h]quinolines are formed when 3-hydroxy-6-alkyl-1,2,3,4-tetrahydrobenzo[h]quinolines are heated with polyphosphoric acid at 200-205°C, but only 6-alkylbenzo[h]quinolines are formed at up to 270°.

When 3-hydroxy-6-methyl-1,2,3,4-tetrahydrobenzo[h]quinoline is heated with thionyl chloride, the methyl group is chlorinated and the tetrahydropyridine ring is aromatized [2]. If the methyl group is in another position, chlorination proceeds at the 6 position [3]. It seemed of interest to us to investigate the action of thionyl chloride on the 6-ethyl derivative of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline.

To obtain 3-hydroxy-6-ethyl-1,2,3,4-tetrahydrobenzo[h]quinoline (II), we synthesized (from 4-ethyl-1-naphthylamine and epichlorohydrin) N-(γ-chloro-β-hydroxypropyl)-4-ethyl-1-naphthylamine (I), which was converted by the action of potassium cyanide to γ-[N-(4-ethyl-1-naphthylamino)]-β-hydroxybutyronitrile (III) and to II by heating in chlorobenzene. Ester IV was obtained by acylation of II with benzoyl chloride in pyridine.

A basic substance that contained chlorine was isolated by heating II with thionyl chloride after removal of the excess thionyl chloride and chromatography of the residue on aluminum oxide. The doublet at 2.3 ppm (J 8 Hz) in its PMR spectrum corresponds to the terminal methyl group of the side chain, and the quartet at 5.8 ppm (J 6 Hz) corresponds to the methylidyne proton attached to the carbon atom bonded in chlorine. Thus, when II is heated with thionyl chloride, the ethyl group attached to the secondary carbon atom is chlorinated, and the tetrahydropyridine ring is aromatized to form 6-(1-chloroethyl)benzo[h]quinoline (V).

As noted in [4], chlorination at the 6 position and aromatization of the tetrahydropyridine ring in 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline occur not only on heating the latter with thionyl chloride, but also on standing at room temperature for 20 days. If the action of thionyl chloride on 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline is shortened from 20 days to 20 min, 3-hydroxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline [5] is formed as the chief product (60% yield). However, we could not detect the formation of 3-hydroxy-6-chloromethyl-1,2,3,4-tetrahydrobenzo[h]quinoline in the reaction of thionyl chloride with 3-hydroxy-6-methyl-1,2,3,4-tetrahydrobenzo[h]quinoline (VI) at room temperature. The starting VI was isolated from the reaction mass when it was allowed to stand for 1 h, and traces of 6-chloromethylbenzo[h]quinoline (VII) were detected. The chief reaction product when the reaction mass is allowed to stand for 5-6 days is VII.

Similar results were also obtained by the action of thionyl chloride on II, and V was obtained in purer form than when II was heated with thionyl chloride.

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*See [1] for communication VIII.

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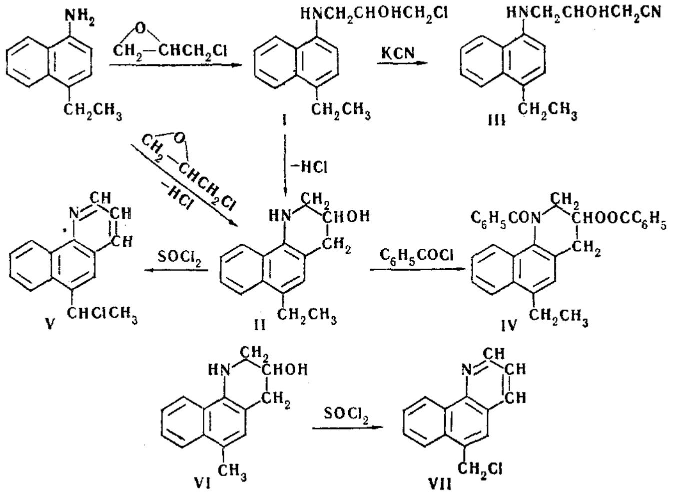
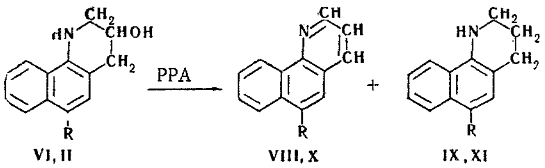


Heating of 6-methylbenzo[h]quinoline and 6-ethylbenzo[h]quinoline with thionyl chloride for 1.5 h was not accompanied by chlorination of the 6-alkyl groups. It hence follows that the chlorination of the 6-alkyl groups in 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline precedes aromatization of the ring.

In developing our previously published studies [6], we also studied the action of polyphosphoric acid (PPA) on 6-alkyl derivatives of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline. 6-Methylbenzo[h]quinoline (VIII) and 6-methyl-1,2,3,4-tetrahydrobenzo[h]quinoline (IX) were isolated from the reaction mass when 6-methyl derivative VI was heated with PPA at 200-205°, while only VIII is formed on heating to 270-275°.



VI, VIII, IX R=CH_3; II, X, XI R=C_2H_5

6-Ethylbenzo[h]quinoline (X) and 6-ethyl-1,2,3,4-tetrahydrobenzo[h]quinoline (XI) or only X are obtained when II is heated with PPA under the conditions indicated above. The mixtures of VIII and IX and X and XI obtained as a result of the reaction were separated by benzoylation with subsequent saponification of the N-benzoyl derivatives.

The mechanism of the formation of VIII and X when VI and II are heated with PPA to 270-275° is apparently similar to that proposed for the reaction of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline with orthophosphoric acid at 270-280° [6].

EXPERIMENTAL

N-(γ-Chloro-β-hydroxypropyl)-4-ethyl-1-naphthylamine (I). A mixture of 10.3 g (0.06 mole) of 4-ethyl-1-naphthylamine and 5.5 g (0.06 mole) of epichlorohydrin was held at 30-35° in a thermostat for 3 days. The mass was treated with 20 ml of chlorobenzene, and the precipitate that formed on cooling was removed by filtration and recrystallized from chlorobenzene to give 8.5 g (53.8%) of colorless needles with mp 83.5-84.5°. Found: Cl 13.6; N 5.6%. $C_{15}H_{18}ClNO$. Calculated: Cl 13.4; N 5.3%.

3-Hydroxy-6-ethyl-1,2,3,4-tetrahydrobenzo[h]quinoline (II). A) A mixture of 7.9 g (0.029 mole) of I and 8 ml of chlorobenzene was heated at 150-155° for 4 h. The crystals that formed were removed by filtration, washed with chlorobenzene, and dissolved in 40 ml of methanol. The methanol solution was treated with 25% NaOH and diluted with water. The resulting precipitate was recrystallized from dilute methanol (1 : 1) to give colorless needles of II with mp 106.0-107.0°. The yield was 3.3 g (50.0%). Found: N 6.3%. $C_{15}H_{17}NO$. Calculated: N 6.2%.

B) A mixture of 3.3 g (0.019 mole) of 4-ethyl-1-naphthylamine, 1.8 g (0.019 mole) of epichlorohydrin, and 6 ml of chlorobenzene was heated at 150-155° for 7 h. Workup as in method A gave 1.0 g (23.2%) of II with mp 106.0-107.0°.

γ-[N-(4-Ethyl-1-naphthylamino)]-β-hydroxybutyronitrile (III). A mixture of 1.1 g (0.004 mole) of I, 10 ml of methanol, and 0.26 g (0.004 mole) of potassium cyanide was heated at 70-75° for 1 h. The solvent was removed by distillation, and the residue was washed with water and alcohol. Recrystallization from alcohol gave 0.6 g (60.0%) of colorless crystals of III with mp 95.0-96.5°. Found: N 10.8%. $C_{16}H_{18}N_2O$. Calculated: N 11.1%.

N-Benzoyl-3-benzoyloxy-6-ethyl-1,2,3,4-tetrahydrobenzo[h]quinoline (IV). A 0.45-g (0.002 mole) sample of II was dissolved in 4 ml of pyridine, 0.7 g (0.005 mole) of benzoyl chloride was added, and the mixture was heated on a boiling-water bath for 1 h. The mixture was cooled, treated with 15 ml of 25% H_2SO_4, and diluted with water. The viscous oil remaining after the aqueous layer was decanted was treated with 10 ml of methanol, and the resulting precipitate was removed by filtration and recrystallized from methanol to give 0.5 g (57.5%) of colorless needles of IV with mp 180.0-181.0°. Found: N 3.3%. $C_{23}H_{25}NO_3$. Calculated: N 3.2%.

6-(1-Chloroethyl)benzo[h]quinoline (V). A) A mixture of 3.4 g (0.015 mole) of II and 15 ml of thionyl chloride was heated at 70-75° for 2 h. The thionyl chloride was removed by vacuum distillation, and the residue was dissolved in alcohol and subjected to chromatographic separation on aluminum oxide with elution by benzene to give 1.2 g (33.3%) of light-yellow needles with mp 101.0-102.0° (from absolute alcohol). Found: N 5.8; Cl 14.4%. $C_{15}H_{12}ClN$. Calculated: N 5.8; Cl 14.7%.

B) A mixture of 1.1 g (0.005 mole) of II and 10 ml of thionyl chloride was held at room temperature for 6 days. The mixture was then worked up as in method A to give 0.4 g (33.3%) of V with mp 101.0-102.0°. This product did not depress the melting point of the crystals obtained in method A.

6-Chloromethylbenzo[h]quinoline (VII). A mixture of 2.1 g (0.01 mole) of 3-hydroxy-6-methyl-1,2,3,4-tetrahydrobenzo[h]quinoline (VI) and 14 ml of thionyl chloride was held at room temperature for 6 days. The thionyl chloride was removed by distillation, and the residue was dissolved in 25 ml of alcohol. The solution was treated with 25 ml of 25% Na_2CO_3 and diluted with 30 ml of water to yield 1.3 g (55.1%) of a product with mp 136.0-136.5° (from alcohol) (mp 136.0-136.5° [2]).

6-Methylbenzo[h]quinoline (VIII) and 6-Methyl-1,2,3,4-tetrahydrobenzo[h]quinoline (IX). A) A mixture of 9.2 g (0.037 mole) of the hydrochloride of VI and 50 ml of PPA was heated at 200-205° for 2 h. The mass was poured into 200 ml of water, and the mixture was made alkaline with 25% NaOH and extracted with ether. The solvent was removed by distillation, and the residue was dissolved in 50 ml of absolute ether. Benzoyl chloride [3.4 g (0.024 mole)] and 4.0 g of anhydrous potassium carbonate were added to the solution, and the mixture was heated at 40-45° for 4 h. The precipitate was removed by filtration and washed with water. Alcohol (40 ml), 4.0 g of potassium hydroxide, and 12 ml of water were added to it, and the mixture was heated for 12 h. The solvent was removed by distillation, and the residue was extracted with ether to give 1.2 g (33.3%) of colorless plates of IX with mp 52.0-53.0° (from petroleum ether) (mp 52.0-53.0° [7]). The ether filtrate that remained after benzoylation was washed with water and aqueous sodium carbonate, dried with magnesium sulfate, and subjected to chromatographic separation on aluminum oxide with elution by benzene to give 1.3 g (36.1%) of colorless crystals of VIII with mp 56.0-57.0° (from petroleum ether) (mp 57.0-58.0° [7]).

B) A mixture of 1.7 g (0.007 mole) of the hydrochloride of VI and 15 ml of PPA was heated at 270-275° for 4 h. The mass was poured into 75 ml of water, and the mixture was made alkaline with 25% NaOH and extracted with ether. The solvent was removed by distillation, and the residue was recrystallized from petroleum ether to give 0.9 g (70.0%) of VIII.

6-Ethylbenzo[h]quinoline (X) and 6-Ethyl-1,2,3,4-tetrahydrobenzo[h]quinoline (XI). A) A mixture of 6.8 g (0.026 mole) of the hydrochloride of II and 60 ml of PPA was heated at 200-205° for 1.5 h. Compounds X and XI were isolated in the same way as VIII and IX. Compound X melted at 40.5-42.0° (from petroleum ether) and was obtained in a yield of 1.2 g (34.3%). Found: N 6.8%. $C_{15}H_{13}N$. Calculated: N 6.8%. Compound XI melted at 74.0-75.5° and was obtained in a yield of 1.2 g (32.2%). Found: N 6.7%. Calculated: N 6.6%.

B) A mixture of 1.3 g (0.005 mole) of the hydrochloride of II and 10 ml of PPA was heated at 270-275° for 4 h. Compound X was isolated in the same way as VIII (method B). Crystallization from petroleum ether gave 0.7 g (67.3%) of colorless plates of X with mp 40.5-42.0°.

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