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

VII.* 1,2,3,4-TETRAHYDRO-3-HYDROXYBENZO[f]QUINOLINE

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Benzo[f]quinoline and its 1,2,3,4-tetrahydro derivative are obtained in almost equal quantities by heating 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline with polyphosphoric or phosphoric acids at 200-205°; at 270-280° only benzo[f]quinoline is obtained. 6-Chlorobenzo[f]quinoline is obtained by the action of thionyl chloride on 1,2,3,4-tetrahydro-3-chlorobenzo[f]quinoline, while reaction of the latter with potassium cyanide gives the nitrile of 1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxylic acid. The latter is converted to 1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxamide and to 1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxylic acid.

As noted in [1], a mixture of benzo[f]quinoline (II) and its 1,2,3,4-tetrahydro derivative is obtained by heating 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline (I) with concentrated hydrochloric acid. A more convenient method for obtaining benzo[f]quinoline and 1,2,3,4-tetrahydrobenzo[f]quinoline (III) was heating of I with polyphosphoric acid (PPA) [2,3], but the process for the formation of II and III was elucidated incorrectly. In a study of this reaction it was revealed that a complex or a mixture of II and III [which gives a melting-point depression with II and III (see Fig. 1), and is readily formed by mixing II with III in solvents] rather than dihydrobenzo[f]quinoline is isolated from the reaction mass on heating of I with PPA. The substance obtained is only separated into II and III by the action of hydrochloric acid. The corresponding derivative of III and benzo[f]quinoline are obtained by the reaction of this substance with benzoyl chloride, epichlorohydrin, and ethylene oxide.

In order to simplify the process for preparing II and III, we heated 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline hydrochloride [which is obtained by heating 1-naphthylamine with epichlorohydrin [4]] rather than the free base with PPA. A more convenient and more economical method for obtaining II and III was heating of 1,2,3,4-tetrahydro-3-hydroxybenzo[f]quinoline hydrochloride with orthophosphoric acid since PPA is obtained from orthophosphoric acid and phosphorus pentoxide. In addition, it was found that II and III can be obtained by heating I not only in the presence of acidic reagents but also with powdered sodium hydroxide. In this process, the yields of II and III are somewhat lower than those obtained by heating I with polyphosphoric or orthophosphoric acids.

Only benzo[f]quinoline is obtained in 85% yield by heating the hydrochloride of I with orthophosphoric acid at higher temperatures (270-280°). Compound II can also be obtained from III by heating it with orthophosphoric acid under the same conditions, but the yield of II is somewhat lower.

The mechanism for the formation of II and III by heating I with sodium hydroxide can apparently be explained by the fact that a dihydrobenzo[f]quinoline derivative is initially formed and then disproportionates into II and III. In the case of the preparation of II by heating I with orthophosphoric acid at 270-280°, the formation of II is apparently explained by dehydrogenation of the dihydro derivative as well as of III, which can partially form by heating I with orthophosphoric acid at lower transition temperatures.

For the synthesis of a number of other derivatives of 1,2,3,4-tetrahydrobenzo[f]quinoline we thought it would be interesting to replace the hydroxyl group in I with a chlorine atom and carry out several trans-

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*See [8] for Communication VI.

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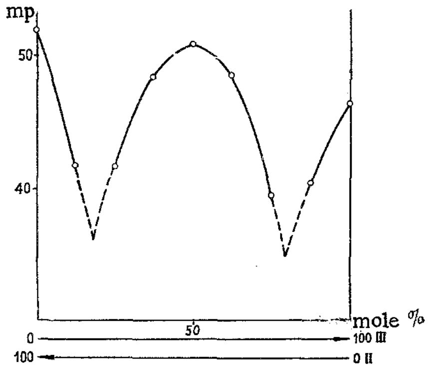
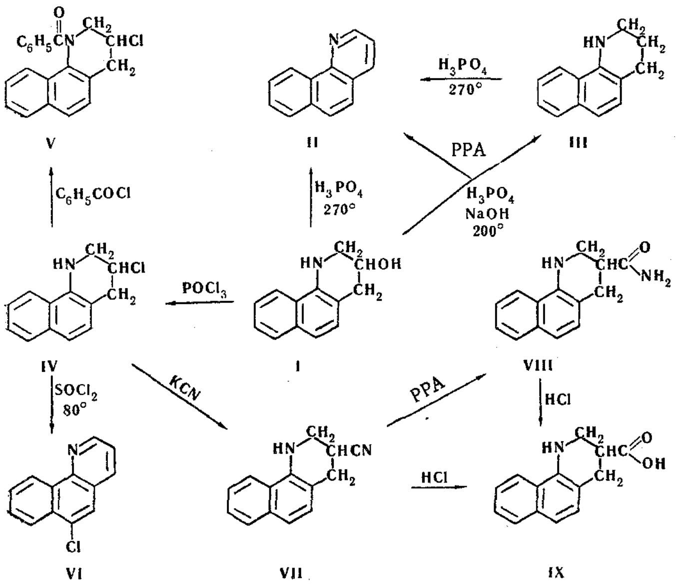


Fig. 1. Phase diagram of a binary mixture of benzo[f]quinoline (II) and 1,2,3,4-tetrahydrobenzo[f]quinoline (III).

formations of the chloro derivative. Heating of the hydrochloride of I with phosphorus oxychloride gave 1,2,3,4-tetrahydro-3-chlorobenzo[f]quinoline (IV), which on benzoylation is converted to N-benzoyl-1,2,3,4-tetrahydro-3-chlorobenzo[f]quinoline (V) and to 6-chlorobenzo[f]quinoline (VI) by heating with thionyl chloride.

Consequently, both the tetrahydro-3-hydroxy- and tetrahydro-3-chloropyridine rings undergo aromatization under the influence of thionyl chloride.

Reaction of IV with potassium cyanide in dimethyl sulfoxide gives the nitrile of 1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxylic acid (VII), which is converted to 1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxamide (VIII) by heating with polyphosphoric acid.



1,2,3,4-Tetrahydrobenzo[f]quinoline-3-carboxylic acid (IX) is obtained by heating VII or VIII with hydrochloric acid. The N-benzoyl derivative of the nitrile of 1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxylic acid is obtained by acylation of VII.

EXPERIMENTAL

Benzo[f]quinoline (II) and 1,2,3,4-Tetrahydrobenzo[f]quinoline (III). A. The hydrochloride of I [470.0 g (2.0 mole)] was added gradually with stirring to 1665 g of polyphosphoric acid heated to 170-180°. The hydrogen chloride evolved was evacuated with a water aspirator. The reaction mixture was stirred for 2 h at 200-205° and poured into 8000 ml of water cooled to 3°. The resulting mixture was neutralized with 50% aqueous sodium hydroxide or 25% ammonium hydroxide. The resulting oil was separated, the aqueous layer was extracted with ether, the oil was dissolved in the extract, and the solution was washed three times with water. The solution was dried with magnesium sulfate, the ether was removed, and the residue was vacuum distilled under nitrogen. The major portion distilled at 146.0-147.0° (3-4 mm) and had mp 49.5-51.0° (from ethanol or petroleum ether). The distillate obtained was poured with stirring into 2000 ml of 10% hydrochloric acid. The resulting crystals of III hydrochloride were filtered and washed with 5% hydrochloric acid in water to give 180.5 g (41.2%) of a product with mp 259.0° (decomp.). Recrystallization from ethanol gave crystals with mp 262.0° (decomp.) [1].

The free base (III) was obtained by reaction of the hydrochloride with aqueous sodium hydroxide in the presence of ether. The product (147.4 g) had mp 45.6-46.3° (from ethanol) [6]. N-Benzoyl-1,2,3,4-tetrahydrobenzo[f]quinoline had mp 195.0-195.5° (from ethanol) (mp 191.5-192.0° [1]).

The filtrate after separation of III hydrochloride was treated with sodium nitrite to remove traces of III, made alkaline with sodium hydroxide, and extracted with ether. After removal of the ether, the residue was vacuum distilled under nitrogen. The major fraction had bp 158.0-160.0 (2-3 mm). The yield of II was 146.2 g (40.8%), and it had mp 49.0-50.0°. After recrystallization from ethanol, the product had mp 51.5-52.0° [7].

B. Compound III hydrochloride [19.0 g (43.5%)] and 15.1 g (42.1%) of II were similarly isolated from 47.0 g (0.2 mole) of I hydrochloride after stirring for 2 h with 150 ml of 85% H_3PO_4 at 200-205°.

C. A flask with a fractionating column was charged with 20.0 g (0.1 mole) of I and 10.0 g (0.25 mole) of powdered sodium hydroxide and placed in a bath heated to 120-130°. The mass was rapidly distilled in vacuo (3-4 mm) under nitrogen. The distillate was treated with dilute hydrochloric acid (5%) and the resulting precipitate was filtered. After recrystallization from ethanol 2.6 g (11.8%) of III hydrochloride with mp 261.5° (decomp.) was obtained. Benzo[f]quinoline was isolated from the filtrate after removal of III hydrochloride, as indicated in experiment A. The yield was 2.7 g (14.8%), and the product had mp 51.5-52.0° (from ethanol).

Benzo[f]quinoline (II). A. A mixture of 23.6 g (0.1 mole) of I hydrochloride and 75 ml of 85% H_3PO_4 was stirred for 3 h at 270-280°. The reaction mass was poured into 400 ml of water and neutralized (to litmus) with sodium hydroxide. The resulting base (II) was purified by extraction with ether and vacuum distillation. The fraction [15.0 g (83.8%)] boiling at 158.0-160.0° (2-3 mm) was collected and had mp 51.5-52.0° (from ethanol).

B. A mixture of 9.2 g (0.05 mole) of III and 37 ml of 85% H_3PO_4 was stirred for 3 h at 270-280° to give 6.0 g (67.0%) of II.

1,2,3,4-Tetrahydro-3-chlorobenzo[f]quinoline (IV). A mixture of 100.0 g (0.425 mole) of I hydrochloride and 100 ml (1.09 mole) of phosphorus oxychloride was heated for 2 h with stirring at 70-75° and then for 3 h at 105-110°. The reaction mass was transferred to a separatory funnel, the excess phosphorus oxychloride was cautiously decomposed with 1500 g of ice, 400 ml of ether was added, and the mixture was shaken. After 2 h, the resulting crystals of 1,2,3,4-tetrahydro-3-chlorobenzo[f]quinoline hydrochloride were filtered, washed with water, acetone, and ethanol, and recrystallized from ethanol to give a product with mp 181.0° (decomp. from ethanol). Found %: N 5.6, 5.5; Cl 28.2, 28.1. $C_{13}H_{12}ClN \cdot HCl$. Calculated %: N 5.5; Cl 27.9.

The hydrochloride of IV was treated with 20% aqueous potassium carbonate, and the free base (IV) was extracted with ether. The ether solution was washed with water, dried, and the ether was removed to give 52.8 g (57.2%) of colorless plates of IV with mp 92.7-94° (from ether). Found %: N 6.8, 6.7; Cl 16.4, 16.3. $C_{13}H_{12}ClN$. Calculated %: N 6.5; Cl 16.3.

N-Benzoyl-1,2,3,4-tetrahydro-3-chlorobenzo[f]quinoline (V). A mixture of 2.0 g (9.2 mmole) of IV, 9 ml of pyridine, and 1.6 g (11.0 mmole) of benzoyl chloride was heated for 2.5 h at 80°. After cooling, the reaction mass was treated with 30 ml of 25% aqueous H_2SO_4 and diluted with 60 ml of water. The resulting oil was washed with water and dissolved in 20 ml of methanol. The resulting colorless crystals were filtered and washed with methanol to give 2.0 g (66.2%) of a product with mp 172.0-173.0 (from methanol). Found %: N 4.7, 4.6; Cl 11.1, 11.1. $C_{20}H_{16}ClNO$. Calculated %: N 4.4; Cl 11.0.

6-Chlorobenzo[f]quinoline (VI). A mixture of 2.2 g (0.01 mole) of IV and 8 ml of thionyl chloride was heated for 1.5 h at 80°. The cooled mass was poured over 100 g of ice, and the resulting mixture was made alkaline with sodium hydroxide and extracted with ether. After removal of the ether and recrystallization from petroleum ether, 0.9 g (42.2%) of 6-chlorobenzo[f]quinoline with mp 99.5-100.5° (from ethanol) [5] was obtained.

Nitrile of 1,2,3,4-Tetrahydrobenzo[f]quinoline-3-carboxylic Acid (VII). A mixture of 18.5 g (0.0845 mole) of IV, 11.0 g (0.169 mole) of potassium cyanide, and 70 ml of dimethyl sulfoxide was heated with stirring for 1.5-2 h at 150°. The reaction mass was diluted with 800 ml of water and extracted with ether. The ether solution was washed with water, dried, and the ether was removed to give 14.0 g (79.7%) of a product with mp 96.5-97.5° [from ethanol–ether (1:2)]. Found %: N 13.4, 13.2. $C_{14}H_{12}N_2$. Calculated %: N 13.4.

The nitrile of N-benzoyl-1,2,3,4-tetrahydrobenzo[f]quinoline-3-carboxylic acid melts at 170.2-171.2° (from methanol). Found %: N 9.0, 9.1. $C_{21}H_{16}N_2O$. Calculated %: N 9.0.

1,2,3,4-Tetrahydrobenzo[f]quinoline-3-carboxamide (VIII). A mixture of 4.0 g (19.2 mmole) of VII and 22.5 g of polyphosphoric acid was heated for 1 h at 110°. The reaction mass was poured into 200 ml of water, and the mixture was filtered. The filtrate was made alkaline with sodium hydroxide and extracted with ether. After removal of the ether, 2.7 g (62.3%) of VIII with mp 124.0-125.0° (from absolute ethanol) was obtained. Found %: N 12.2, 12.4. $C_{14}H_{14}N_2O$. Calculated %: N 12.4.

1,2,3,4-Tetrahydrobenzo[f]quinoline-3-carboxylic Acid (IX). A. A mixture of 2.1 g (0.01 mole) of VII and 20 ml of hydrochloric acid (sp. gr. 1.17) was refluxed for 1 h. The reaction mass was cooled to −5 to −10°, and the resulting hydrochloride of IX was filtered and washed with water to give 2.4 g (91.0%) of a product with mp 238.0° (decomp., from ethanol). Found %: N 5.4, 5.3; Cl 13.2, 13.4. $C_{14}H_{13}NO_2 \cdot HCl$. Calculated %: N 5.3; Cl 13.5.

The hydrochloride of IX [0.9 g (3.4 mmole)] was dissolved in water and 0.4 g (5.1 mmole) of sodium acetate was added. The resulting viscous oil was washed with water. The mass began to crystallize after three days in a desiccator over n-butanol to give 0.7 g (91.0%) of a product with mp 108.0-109.3° [from ethanol−n-hexane (1 : 9)]. Found %: N 6.3, 6.4. $C_{14}H_{13}NO_2$. Calculated %: N 6.2.

B. Compound VIII [0.5 g (2.2 mmole)] was refluxed with 4 ml of hydrochloric acid (sp. gr. 1.17) for 1 h. After evaporation of the hydrochloric acid, 0.58 g (100%) of IX hydrochloride was obtained. After recrystallization from ethanol the hydrochloride had mp 238.0° (decomp.).

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