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

XII.* 3-SUBSTITUTED 1,2,3,4-TETRAHYDROBENZO[h]QUINOLINES AND 2-SUBSTITUTED BENZ[g]INDOLINES

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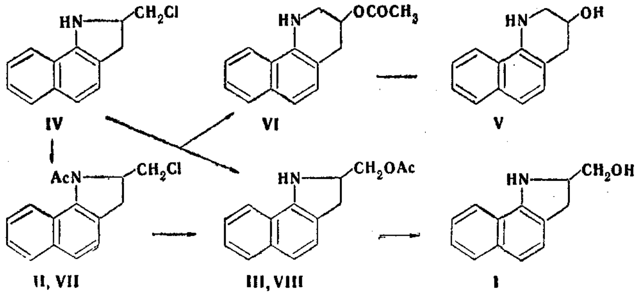
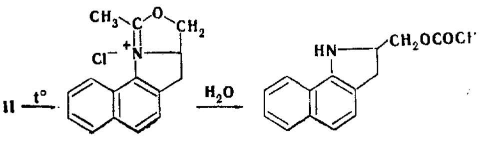
The synthesis of 2-(hydroxymethyl)benz[g]indoline derivatives by heating N-acyl derivatives of 2-(chloromethyl)benz[g]indoline in dimethyl sulfoxide is described. 3,6-Dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline, 5-chloroazirido[1,2-*a*]benz[g]indoline, and derivatives of 2-substituted 5-chlorobenz[g]indoline were synthesized.

The synthesis of 2-(hydroxymethyl)benz[g]indoline (I) from 2-(chloromethyl)benz[g]indoline or 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline is described in [2]. However, it is more convenient to obtain I by heating N-acetyl-2-(chloromethyl)benz[g]indoline (II) in dimethyl sulfoxide in the presence of alkali metal salts and weak acids. The resulting 2-(acetoxymethyl)benz[g]indoline (III) is readily converted to I. For the synthesis of II, one can use not only pure 2-(chloromethyl)benz[g]indoline (IV) but also a mixture of IV and 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline, which is obtained by the reaction of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (V) with phosphorus oxychloride [2].



II Ac=COCH$_3$; VII Ac=COC$_6$H$_5$; III Ac=COCH$_3$; VIII Ac=COC$_6$H$_5$

It would seem that the first step in this reaction is saponification of II to form IV, which then is converted to III by nucleophilic substitution. However, a mixture of III and 3-acetoxy-1,2,3,4-tetrahydrobenzo[h]quinoline (VI) is formed in the reaction of IV with potassium acetate under the same conditions. The formation of only III is observed when II is heated in dimethyl sulfoxide or in ethanol. Thus the presence of an alkali metal salt and a weak acid proves to be optional.



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*See [1] for communication XI.

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The conversion of II to III apparently proceeds in analogy with β-haloalkyl benzamides [3-6], with the intermediate formation of an oxazoline derivative, which is hydrolyzed under the reaction conditions.

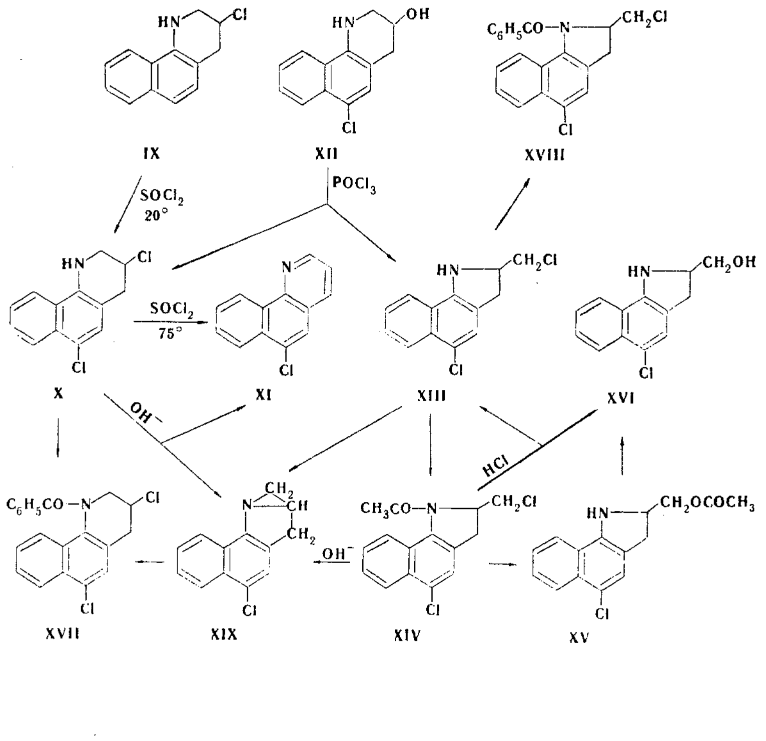
Similar transformations are observed when N-benzoyl-2-(chloromethyl)benz[g]indoline (VII) or N-acetyl-2-chloromethyl-5-chlorobenz[g]indoline are heated. In the first case, 2-(benzoxymethyl)benz[g]-indoline (VIII) is obtained, while 2-acetoxymethyl-5-chlorobenz[g]indoline is obtained in the second case. Thus this reaction is a general one for the preparation of 2-(hydroxymethyl)benz[g]indoline derivatives.

In order to obtain 5-chloro derivatives of benz[g]indoline, we subjected I to the action of thionyl chloride. However, the substance undergoes charring at both room temperature and −10°C, and individual compounds cannot be isolated. Thionyl chloride has a similar effect on IV and VIII. However, when 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (IX) is used at room temperature, one obtains good yields of 3,6-dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline (X), which is converted to 6-chlorobenzo[h]quinoline (XI) on refluxing with thionyl chloride. Thus chlorination in the aromatic ring on reaction with thionyl chloride occurs smoothly in the case of 1,2,3,4-tetrahydrobenzo[h]quinoline derivatives. In the case of 2-substituted benz[g]indolines, the electron density in the 5 position is apparently reduced as compared with the 6 position in 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinoline, which decreases the lability of H_5, and the increased basicity facilitates the reaction of thionyl chloride with the NH group.

A mixture of X and 2-chloromethyl-5-chlorobenz[g]indoline (XIII) is formed in the reaction of 3-hydroxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XII) with phosphorus oxychloride. Acylation, which proceeds at different rates for benz[g]indoline and 1,2,3,4-tetrahydrobenzo[h]quinoline derivatives (which is apparently associated with the difference in the basicities), was used to separate them. Chiefly XIII enters into the reaction when an ether solution of the mixture of X and XIII is treated with acetic anhydride at room temperature. The N-acetyl-2-chloromethyl-5-chlorobenz[g]indoline (XIV) formed is readily separated from X. Heating of XIV in dimethyl sulfoxide in the presence of potassium bicarbonate gives 2-acetoxymethyl-5-chlorobenz[g]indoline (XV), which is readily saponified to 2-hydroxymethyl-5-chlorobenz[g]indoline (XVI). Compound XVI is formed along with XIII by saponification of XIV with hydrochloric acid.

The formation of XVI apparently occurs with intermediate formation of XV, since the formation of XVI is not observed in the reaction of XIII with hydrochloric acid under the same conditions. Consequently, when XIV is heated with hydrochloric acid, two reactions proceed simultaneously – saponification to XIII and intramolecular cyclization to an oxazoline derivative to form XVI.

The hydrochlorides of X, XIII, and XVI, N-benzoyl-3,6-dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XVII), N-benzoyl-2-chloromethyl-5-chlorobenz[g]indoline (XVIII), and N-benzoyl-2-benzoyloxymethyl-5-chlorobenz[g]indoline were also synthesized.



The absorption band of the NH group in the IR spectra of 2-substituted benz[g]indolines is found at 3380-3400 cm^{-1}, while that of 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinolines is at 3450-3470 cm^{-1}. A similar regularity is also observed in the IR spectra of 2-substituted 5-chlorobenz[g]indolines and 3-substituted 6-chloro-1,2,3,4-tetrahydrobenzo[h]quinolines.

It has been reported [7] that azirido[1,2-*a*]benz[g]indoline is formed by the action of alcoholic alkali on 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline or 2-chloromethylbenz[g]indoline. 5-Chloroazirido[1,2-*a*]-benz[g]indoline (XIX) is obtained when N-acetyl-2-chloromethyl-5-chlorobenz[g]indoline is heated in alcoholic alkali. The structure of XIX was proved by the IR and PMR spectra and by the capacity of the aziridine ring to readily undergo opening by polar reagents [7]. Thus N-benzoyl-3,6-dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline is readily formed by the reaction of XIX with benzoyl chloride, while 3-hydroxy-6-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline is readily formed by the action of water in acid media.

The formation of XIX is also observed during chromatography of XIII (but not of X) on aluminum oxide. The increased lability of the chlorine atom in the β position in benz[g]indoline derivatives as compared with 1,2,3,4-tetrahydrobenzo[h]quinoline derivatives has also been previously noted [2]. 6-Chlorobenzo[h]quinoline is formed along with XIX in the reaction of X with alcoholic potassium hydroxide.

EXPERIMENTAL

2-(Hydroxymethyl)benz[g]indoline (I). A mixture of 2.6 g (0.01 mole) of N-acetyl-2-(chloromethyl)-benz[g]indoline, 20 ml of dimethyl sulfoxide, 8 ml of water, and 3.0 g of potassium bicarbonate was stirred at 105° for 40 min, and the mixture was diluted with water and extracted with ether. The ether was removed, and the residue was refluxed for 1 h with 20% hydrochloric acid (25 ml). The precipitate that formed on cooling was removed by filtration and washed with water to give 2.0 g (85%) of the hydrochloride of I. The product did not depress the melting point of a known sample [2].

Similar results were obtained by using sodium acetate or potassium cyanide in place of potassium bicarbonate. The yield of II decreased when the indicated salts were replaced by potassium chloride or calcium chloride. The yield was 25% when salts were not added.

N-Acetyl-2-(chloromethyl)benz[g]indoline (II). A mixture of 6.5 g (0.03 mole) of IV and 10 ml of acetic anhydride was held at room temperature for 6 h. The resulting precipitate (a) was removed by filtration and washed with acetic anhydride. The filtrate was diluted with water, and the solid remaining after decantation was washed with water and ethanol. The crystals were removed by filtration and added to precipitate a to give 6.4 g (82%) of II with mp 144.5-146.0° (from absolute ethanol). Found: Cl 14.0; N 5.4%. $C_{15}H_{14}ClNO$. Calculated: Cl 13.7; N 5.4%.

2-(Acetoxymethyl)benz[g]indoline (III). A mixture of 1.3 g (5 mmole) of II, 10 ml of dimethyl sulfoxide, 4 ml of water, and 1.5 g of potassium bicarbonate was stirred at 105° for 40 min. After extraction with ether, the substance was chromatographed on aluminum oxide to remove admixed I with elution by acetone–petroleum ether (1 : 4). The oily substance obtained was III. Found: N 5.4%. $C_{15}H_{15}NO_2$. Calculated 5.8%. IR spectrum (in CCl_4), ν, cm^{-1}: 3395 (N–H), 1740, 1226, 1036 (O–C=O).

Reaction of 2-(Chloromethyl)benz[g]indoline (IV) with Potassium Acetate. A mixture of 11.0 g (0.05 mole) of IV, 15.0 g (0.15 mole) of potassium acetate, and 70 ml of dimethyl sulfoxide was heated at 105° for 1 h. The mixture was diluted with water and extracted with ether (50 ml). The ether solution was washed with water, dried with magnesium sulfate, and cooled to −10°. The crystals that formed in the course of several days were removed by filtration and washed with ether to give 3.6 g (30%) of VI with mp 96.5-98.0° (from absolute ethanol). Found: N 6.1%. $C_{15}H_{15}NO_2$. Calculated: N 5.8%. Saponification of the latter gave V, which did not depress the melting point of a known sample [8].

The ether was removed after VI was separated from the filtrate. The oily residue was saponified to give I mixed with V. The isomers were identified by chromatography on a thin, loose layer of aluminum oxide with elution by chloroform–ethanol (66 : 1). The R_f values for I and V were 0.41 and 0.44, respectively. Compound I took on a blue color on development with iodine, while V was green in the presence of iodine.

2-(Benzoxymethyl)benz[g]indoline (VIII). A mixture of 3.2 g (0.01 mole) of VII, 30 ml of dimethyl sulfoxide, and 2.5 g of potassium bicarbonate was heated at 110° for 1 h. The mixture was diluted with water and extracted with ether. The ether was removed, and the residue was recrystallized from methanol to give 2.4 g (80%) of VIII with mp 107.0-108.5°, the melting point of which was not depressed by a known [2] sample.

3,6-Dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline (X). An 11.0-g (0.05 mole) sample of IX was added gradually with cooling to −5° to 35 ml of thionyl chloride. The mixture was then allowed to stand at room temperature for 8 h. The resulting precipitate was removed by filtration and washed with thionyl chloride. Recrystallization from methanol (with activated charcoal) gave 10.7 g (74%) of the hydrochloride of X with mp 198° (dec.). Found: Cl 36.9; N 5.0%. $C_{13}H_{11}Cl_2N \cdot HCl$. Calculated: Cl 36.9; N 4.9%.

A 5.8-g (0.02 mole) sample of the hydrochloride of X was shaken with aqueous sodium carbonate in the presence of benzene. The benzene was removed, and the solid was crystallized from methanol to give 4.8 g (95%) of X with mp 85.5-87.0°. Found: Cl 28.3; N 5.8%. $C_{13}H_{11}Cl_2N$. Calculated: Cl 28.1; N 5.6%. IR spectrum, ν, cm^{-1}: 3432 (NH). See also the experimental method for the preparation of XIV.

6-Chlorobenzo[h]quinoline (XI). A mixture of 2.5 g of X and 6 ml of thionyl chloride was refluxed for 1 h. The precipitate was removed by filtration and washed with thionyl chloride. Treatment with sodium carbonate and recrystallization from methanol gave 1.0 g (48%) of XI with mp 99.5-100.5°. The melting point of the product was not depressed by an authentic sample [9]. See also method B for the preparation of XVII.

2-Chloromethyl-5-chlorobenz[g]indoline (XIII). A mixture of 2.9 g (0.01 mole) of XIV, 15 ml of ethanol, and 20 ml of concentrated hydrochloric acid was heated at 65-70° for 8 h. The mixture was cooled, and the resulting crystals were removed by filtration and washed with water. The yield of a mixture of the hydrochlorides of XIII and XVI was 2.7 g. The mixture was chromatographed on aluminum oxide with elution with ether−n-heptane (3 : 2). The eluent was removed, and the oily residue was stored in a desiccator over calcium chloride. The resulting crystals were removed by filtration and washed with absolute ethanol to give 0.9 g (36%) of a product with mp 48.5-50.0°. Found: Cl 28.3; N 5.7%. $C_{13}H_{11}Cl_2N$. Calculated: Cl 28.1; N 5.6%. IR spectrum (in $CHCl_3$), ν, cm^{-1}: 3387 (N−H). When the aluminum oxide used for the purification of XIII was extracted with ether, 0.4 g of XVI with mp 87.0-88.0° was obtained. The hydrochloride of XIII had mp 208° (dec., from absolute ethanol). Found: Cl 36.7; N 5.1%. $C_{13}H_{11}Cl_2N \cdot HCl$. Calculated: Cl 36.9; N 4.9%.

N-Acetyl-2-chloromethyl-5-chlorobenz[g]indoline (XIV) and 3,6-Dichloro-1,2,3,4-Tetrahydrobenzo[h]quinoline (X). A mixture of 27.0 g (0.1 mole) of the hydrochloride of XII and 46 ml of freshly distilled phosphorus oxychloride was refluxed for 1.5 h. The mixture was then poured over ice, and the resulting crystals of the hydrochlorides of X and XIII were removed by filtration and washed with water. The mixture of hydrochlorides was shaken with aqueous sodium carbonate in the presence of ether. The ether solution was dried with magnesium sulfate and treated with activated charcoal. Acetic anhydride (14 ml) was added, and the mixture was held at 28-30° for 24 h. It was then treated with activated charcoal. The filtrate was washed with sodium carbonate solution and water, and the resulting crystals were removed by filtration and washed with ether to give 8.8 g (30%) of XIV with mp 119.5-120.5° (from methanol). Found: Cl 24.0; N 4.9%. $C_{15}H_{13}Cl_2NO$. Calculated: Cl 24.1; N 4.8%.

The ether was removed from the filtrate after separation of XIV, and the residue was treated with concentrated hydrochloric acid. The resulting hydrochloride of X was washed with methanol and acetone and recrystallized from methanol. Treatment of the hydrochloride with sodium carbonate gave 8.4 g (33.4%) of X with mp 84.0-86.0°, the melting point of which was not depressed by the product obtained via the method described above.

2-Acetoxymethyl-5-chlorobenz[g]indoline (XV). A mixture of 2.9 g (0.01 mole) of XIV, 25 ml of dimethyl sulfoxide, 9 ml of water, and 3.1 g of potassium bicarbonate was stirred at 120° for 2 h. The mixture was diluted with water and extracted with ether. The ether was removed, and the oily residue was chromatographed on aluminum oxide with elution by ether−n-heptane (4 : 1) to give 0.9 g (33%) of a product with mp 76.5-77.5° (from n-hexane). Found: Cl 12.8; N 5.1%. $C_{15}H_{14}ClNO_2$. Calculated: Cl 12.9; N 5.1%. IR spectrum (in $CHCl_3$), ν, cm^{-1}: 3392 (N−H). In addition, ether extraction of the aluminum oxide used to purify XIV yielded 0.5 g (21%) of XVI.

2-Hydroxymethyl-5-chlorobenz[g]indoline (XVI). A 2.9-g (0.01 mole) sample of XIV was treated as in the preceding experiment. The resulting oily substance was refluxed with 10 ml of 20% hydrochloric acid for 1 h. The mixture was cooled, and the resulting crystals were removed by filtration, washed with water and methanol, and recrystallized from methanol (with activated charcoal) to give 2.2 g (82%) of the hydrochloride of XVI with mp 225° (dec.). Found: Cl 26.2; N 5.3%. $C_{13}H_{12}ClNO \cdot HCl$. Calculated: Cl 26.2; N 5.2%.

A 1.4-g (5 mmole) sample of the hydrochloride of XVI was shaken with aqueous sodium carbonate solution in the presence of ether. The ether was removed to give an almost quantitative yield of XVI with mp 87.0-88.0° (from chlorobenzene). Found: Cl 15.1; N 6.1%. $C_{13}H_{12}ClNO$. Calculated: Cl 15.2; N 6.0%. IR spectrum (in $CHCl_3$), ν, cm^{-1}: 3372 (NH). See also the experiments for the preparation of XIII and XV.

N-Benzoyl-2-benzoxymethyl-5-chlorobenz[g]indoline. A mixture of 0.5 g (2 mmole) of XVI, 0.8 g (6 mmole) of benzoyl chloride, and 4 ml of pyridine was heated at 100° for 1 h. Workup gave 0.8 g (90%) of the N,O-dibenzoyl derivative of 2-hydroxymethyl-5-chlorobenz[g]indoline with mp 138.5-139.5° (from methanol). Found: Cl 8.1; N 3.4%. $C_{27}H_{20}ClNO_3$. Calculated: Cl 8.0; N 3.2%.

N-Benzoyl-3,6-dichloro-1,2,3,4-tetrahydrobenzo[h]quinoline (XVII). A. A mixture of 0.5 g (2 mmole) of X, 0.4 g (3 mmole) of benzoyl chloride, and 4 ml of pyridine was heated at 100° for 1 h. Workup of the reaction mixture gave 0.7 g (98%) of XVII with mp 179.5-180.5° (from methanol). Found: Cl 19.8; N 3.9%. $C_{20}H_{15}Cl_2NO$. Calculated: Cl 19.9; N 3.9%.

B. A mixture of 5.0 g (0.02 mole) of X, 3.4 g (0.06 mole) of potassium hydroxide, and 15 ml of absolute ethanol was refluxed for 50 min. As in the preparation of XIX, 4.0 g of an oily substance, in which 6-chlorobenzo[h]quinoline (XI) was chromatographically detected along with XIX, was obtained. The mixture was dissolved in 30 ml of dry ether, 1.8 g of benzoyl chloride was added, and the mixture was held at room temperature for 2 h. The resulting precipitate was removed by filtration, washed with ether, and recrystallized from ethanol to give 3.4 g (54%) of a product with mp 179.0-180.5°. The melting point was not depressed by the product obtained in experiment A. In addition, 1.1 g (29%) of XI was isolated from the ether filtrate.

N-Benzoyl-2-chloromethyl-5-chlorobenz[g]indoline (XVIII). A mixture of 0.5 g (2 mmole) of XIII, 0.4 g (3 mmole) of benzoyl chloride, 0.4 g of potassium carbonate, and 10 ml of dry ether was refluxed for 6 h and worked up to give 0.7 g (98%) of XVIII with mp 173.5-175° (from absolute ethanol). Found: Cl 20.1; N 4.3%. $C_{20}H_{15}Cl_2NO$. Calculated: Cl 19.9; N 3.9%.

5-Chloroazirido[1,2-*a*]benz[g]indoline (XIX). A mixture of 5.9 g (0.02 mole) of XIV, 4.5 g (0.08 mole) of potassium hydroxide, and 20 ml of absolute ethanol was refluxed for 20 min. The mixture was filtered, and the solution was evaporated. The residue was extracted with petroleum ether. The petroleum ether was removed, and the residue was allowed to stand over calcium chloride. The resulting crystals were removed by filtration and washed with pentane to give 3.2 g (74%) of XIX with mp 41.5-43.0° (from pentane). Found: Cl 16.4; N 6.5%. $C_{13}H_{10}ClN$. Calculated: Cl 16.4; N 6.5%.

Thin-layer chromatography established the formation of XII [R_f 0.37, elution by chloroform–ethanol (66:1)] after treatment of 0.1 g of XIX with 3 ml of 20% sulfuric acid.

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