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

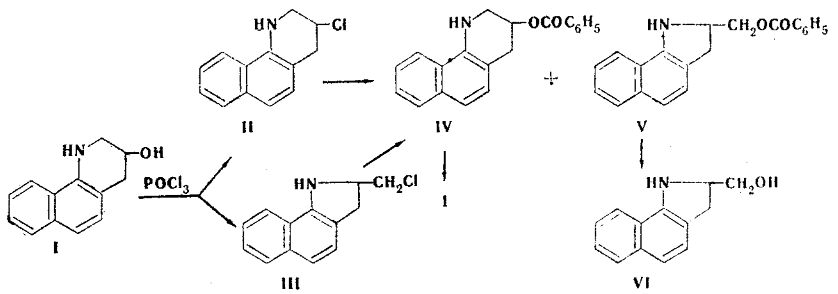
X.* ISOMERIZATION OF 3-SUBSTITUTED DERIVATIVES OF 1,2,3,4-TETRAHYDROBENZO[h]QUINOLINE

S. I. Kutkevichus and K. S. Sherenas

UDC 547.832'759:542.95

Heating 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline with phosphorus oxychloride gave a mixture of isomeric 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline and 2-(chloromethyl)-benz[g]indoline, which are converted to a mixture of 3-benzoyloxy-1,2,3,4-tetrahydrobenzo-[h]quinoline and 2-(benzoyloxymethyl)benz[g]indoline on reaction with potassium benzoate. Saponification of 2-(benzoyloxymethyl)benz[g]indoline gave 2-(hydroxymethyl)benz[g]indoline. The reaction of the isomeric chloro derivatives with potassium cyanide gave 2-(benz[g]-indolinyl)acetonitrile.

We previously reported [2] that 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (II) is obtained by the action of phosphorus oxychloride on 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I) [3]. Subsequent investigations have demonstrated that this reaction gives two products: the isomeric 2-(chloromethyl)benz-[g]indoline (III) was isolated along with the previously described II. Compounds II and III form two O-benzoyl derivatives with potassium benzoate. One, with mp 124.8-125.6°, is identical to the previously described [3] 3-benzoyloxy-1,2,3,4-tetrahydrobenzo[h]quinoline (IV), while the second, with mp 107.2-108.5° is 2-benzoyloxymethyl)benz[g]indoline (V). Saponification of ester V gave 2-(hydroxymethyl)benz[g]indoline (VI).



To confirm the structures of the synthesized 2-substituted benz[g]indolines, we prepared 1-benzoyl-2-(chloromethyl)benz[g]indoline, 2-(benzoyloxymethyl)- and 2-(hydroxymethyl)benz[g]indoline hydrochlorides, and 1-benzoyl-2-(benzoyloxymethyl)benz[g]indoline. The structures of 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinolines and 2-substituted benz[g]indolines were confirmed by the PMR spectra, IR spectra, and ionization constants (pK_a).

As compared with the PMR spectrum of 3-hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline (I), the signal of the 3-H proton in the PMR spectrum (see Fig. 1) of 3-benzoyloxy-1,2,3-4-tetrahydrobenzo[h]quinoline

---

[*] See [1] for communication IX.

Kaunas Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 362-366, March, 1972. Original article submitted December 30, 1970.

TABLE 1. Frequencies of the ν_{NH} Stretching Vibrations (in solution) and Ionization Constants (pK_a) of 3-Substituted 1,2,3,4-Tetrahydrobenzo[h]quinolines and 2-Substituted Benz[g]indolines

Compound	Name	ν_{NH}, cm^{-1}	pK_a
I	3-Hydroxy-1,2,3,4-tetrahydrobenzo[h]quinoline	3472	3,41±0,05
VI	2-(Hydroxymethyl)benz[g]indoline	3388	4,05±0,06
II	3-Chloro-1,2,3,4-tetrahydrobenzo[h]quinoline	3452	2,59±0,06
III	2-(Chloromethyl)benz[g]indoline	3403	3,08±0,07
IV	3-Benzoyloxy-1,2,3,4-tetrahydrobenzo[h]quinoline	3452	~2,92
V	2-(Benzoyloxymethyl)benz[g]indoline	3401	3,54±0,06

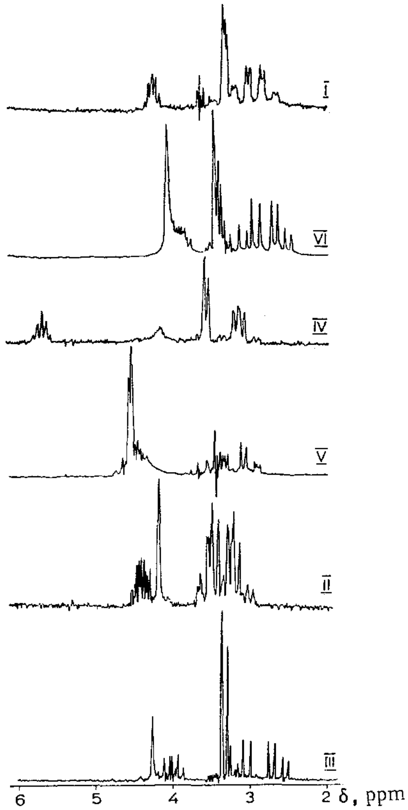


Fig. 1. PMR spectra of 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinolines (I, II, IV) and 2-substituted benz[g]indolines (III, V, VI).

(IV) is shifted to weak field by 1.4 ppm (there is a multiplet at 4.05 ppm in the case of I, while the multiplet is at 5.45 ppm in the case of IV), while the signals of the methylene protons in the 2 position are shifted by only 0.2 ppm (3.3 ppm in the case of I and 3.5 ppm in the case of IV). This corresponds to the presence of a hydroxyl group in the 3 position.

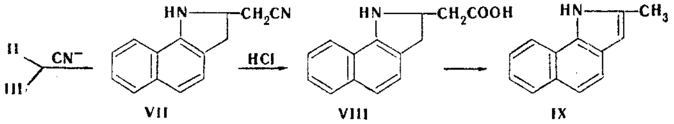
In comparing the spectra of 2-(hydroxymethyl)benz[g]indoline (VI) with its benzoate (V), it is seen that, in this case, the signals of the methylene protons of the methylol group (3.3 ppm in the case of VI and 4.45 ppm in the case of V) are shifted by 1.15 ppm to weak field when the hydroxyl group is replaced by a benzoyloxy group. The multiplet of the 2-H proton is shifted by only 0.3 ppm (3.8 ppm in the case of VI and 4.1 ppm in the case of V). This indicates the presence of a methylol group.

The band of the in-plane vibrations of the aromatic ring at 1600 cm^{-1} in the IR spectra of the investigated compounds is generally more intense for the 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinolines than for the 2-substituted benz[g]indolines. This indicates that, in the first case, the nonbonding pair of electrons of the nitrogen atom is conjugated with the π electrons of the aromatic ring to a greater degree than in the case of benz[g]indoline derivatives. This may apparently explain the fact that the ionization constants of benz[g]indoline derivatives are higher than those of the corresponding 1,2,3,4-tetrahydrobenzo[h]quinoline derivatives (see Table 1). The change in the frequency of the ν_{NH} stretching vibrations (3452-3472 cm^{-1} for 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinolines and 3388-3403 cm^{-1} for 2-substituted benz[g]indolines) is also apparently explained by the different degree of conjugation of the nonbonding pair of electrons of the nitrogen atom with the π electrons of the aromatic ring.

A change in the position of the halogen atom and a change in the basicity affect the lability of the chlorine atom in the isomeric chloro derivatives. While 60.5% of the chlorine is ionized in 240 min in II via the method in [4], all of the chlorine atoms in III are converted to the ionic form in 30 min. The indicated data on the lability of the chlorine atom are in agreement with the assumed structures of the isolated isomers.

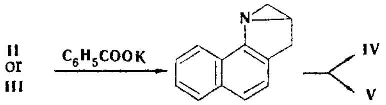
On comparing the IR spectra of the previously described [2] nitrile obtained by the action of potassium cyanide on II, of the amide, and of the carboxylic acid, to which the 1,2,3,4-tetrahydrobenzo[h]quinoline-3-carboxylic acid structure was ascribed, with the spectra of 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinoline and 2-substituted benz[g]indolines, it is apparent that the nitrile (3380 cm^{-1}), amide (3400 cm^{-1}), and carboxylic acid (3390 cm^{-1}) are more in accord with the 2-substituted benz[g]indoline structure with respect to the frequency of the ν_{NH} stretching vibrations.

In order to confirm the indicated assumption, 2-(chloromethyl)benz[g]indoline was used for the synthesis of (2-benz[g]indolinyl)acetonitrile (VII). The compound obtained proved to be identical to the previously described [2] nitrile, which was obtained using 3-chloro-1,2,3,4-tetrahydrobenzo[h]quinoline. The (2-benz[g]indolinyl)acetonitrile derivative structure was also confirmed by dehydrogenation and decarboxylation of (2-benz[g]indolinyl)acetic acid (VIII) to 2-methylbenz[g]indole (IX).



The nitrile of 1,2,3,4-tetrahydrobenzo[h]quinoline-3-carboxylic acid could not be detected in the case of the reaction of potassium cyanide with both II and III. If it is formed, it is apparently formed in very small amounts, since the yield of VII in each case exceeds 70%.

The formation of two isomeric compounds in the reaction of II or III with potassium benzoate and also in the reaction of I with phosphorus oxychloride can apparently be explained by the fact that, in each case, there is intermediate formation of azirido[1,2-a]benz[g]indoline, which is subsequently converted to a mixture of 3-substituted 1,2,3,4-tetrahydrobenzo[h]quinolines and 2-substituted benz[g]indolines as a result of opening of the aziridine ring at the 2-C—N and 3-C—N bonds.



In the reaction of potassium cyanide with II, the aziridine ring in the intermediately formed compound is apparently opened primarily at the 3-C—N bond, which increases the yield of VII.

EXPERIMENTAL

The PMR spectra of $CDCl_3$ solutions of the compounds were obtained with Varian A56/60A and Varian HA-100 spectrometers with operating frequencies of 60 and 100 MHz, respectively, with hexamethyldisiloxane as the internal standard.* The IR spectra of 5% solutions in $CHCl_3$ and of potassium bromide pellets were recorded with UR-20 and IKS-14 spectrophotometers. The ionization constants were determined spectrophotometrically from $1 \cdot 10^{-5}$ M aqueous alcohol (95 : 5) solutions at 18-23°. The optical density was measured with an SF-4 spectrophotometer, while the pH values were measured with a Radelkis pH meter.

3-Chloro-1,2,3,4-tetrahydrobenzo[h]quinoline (II) and 2-(Chloromethyl)benz[g]indoline (III). A mixture of 400 g (1.7 mole) of the hydrochloride of I and 400 ml (4.37 mole) of freshly distilled phosphorus oxychloride was heated with stirring at 75-80° for 2 h and then at 105-110° for 3 h. The hot reaction mass was poured into a beaker containing 3 kg of ice, and the mixture was allowed to stand overnight. The precipitate was removed by filtration and washed with water to give a mixture of the hydrochlorides of II and III. The yield was 90%.

A 51.0-g (0.2 mole) sample of the mixture of the hydrochlorides was pulverized and shaken with aqueous sodium carbonate in the presence of ether. The ether solution was washed with water, dried with magnesium sulfate, and filtered. The filtrate was cooled to 0-2°, and the precipitate that formed after several days was removed by filtration was washed with ether to give 18.7 g (39%) of II with mp 92.7-94.0° (from ether). PMR spectrum: δ 2.9-2.7 (multiplet 2- and 4-H), 4.1 (NH), 4.2-4.45 ppm (multiplet, 3-H). Found: C 71.6, 71.4; H 5.5, 5.4; Cl 16.5, 16.3; N 6.5, 6.3%. $C_{13}H_{12}ClN$. Calculated: C 71.7; H 5.6; Cl 16.3; N 6.4%.

The filtrate remaining after separation of II was diluted with n-hexane until it became turbid. It was then filtered and cooled to 0-2°. The rhombic crystals of III that formed after several days were removed by filtration and recrystallized from ether—n-hexane (1 : 9) to give 14.8 g (31%) of a product with mp 48.0-49.0°. PMR spectrum: 2.5-2.75 (quartet, $j_{gem} = 16$ Hz, $J_{2,3} = 7$ Hz) and 3.0-3.25 (quartet, $J_{gem} = 16$ Hz, $J_{2,3} = 9$ Hz), methylene protons in the 3 position; 3.35 (doublet, J = 8 Hz), methylene proton of the chloro-

---

*We sincerely thank N. N. Vorozhtsov, Jr., and V. A. Koptyug for making it possible for us to use the spectroscopic laboratory of the Novosibirsk Institute of Organic Chemistry, and I. K. Korobeinicheva and A. I. Rezvukhin for recording the spectra and for their valuable consultations.

methyl group; 3.85-4.15 (multiplet), proton in the 2 position; 4.3 ppm, signal of the NH group. Found: C 71.9, 71.1; H 5.3, 5.5; Cl 16.4, 16.3; N 6.5, 6.7%. $C_{13}H_{12}ClN$. Calculated: C 71.7; H 5.6; Cl 16.3; N 6.4%.

1-Benzoyl-2-(chloromethyl)benz[g]indoline. A mixture of 1.1 g (5 mmole) of III, 1.0 g (7 mmole) of benzoyl chloride, 1.0 g of potassium carbonate, and 10 ml of dry ether was refluxed for 2 h. The solid material was removed by filtration, washed with ether and water, and recrystallized from methanol to give 1.4 g (87%) of a product with mp 173.0-174.5°. Found: Cl 11.1, 11.1; N 4.8, 4.7%. $C_{20}H_{16}ClNO$. Calculated: Cl 11.0; N 4.4%.

3-Benzoyloxy-1,2,3,4-tetrahydrobenzo[h]quinoline (IV) and 2-(Benzoyloxymethyl)benz[g]indoline (V). A mixture of 87.0 g (0.4 mole) of II, 96.0 g (0.6 mole) of potassium benzoate, and 300 ml of dimethyl sulfoxide was heated with stirring at 120° for 3 h. The reaction mass was poured into 1.5 liter of water, 100 ml of ether was added, and the mixture was shaken. The resulting crystals were removed by suction filtration and washed with water and ether to give 80.4 g of a mixture of isomers IV and V with mp 88.0-93.0°. Fractional crystallization from methanol or ethanol gave 23.5 g of V with mp 107.2-108.5° (from methanol). Found: N 4.9, 4.7%. $C_{20}H_{17}NO_2$. Calculated: N 4.6%. The hydrochloride was prepared as follows. A solution of 0.6 g (2 mmole) of V in 10 ml of absolute ethanol was saturated with hydrogen chloride at room temperature. The resulting precipitate was removed by suction filtration and recrystallized from methanol to give 0.65 g (96%) of a product with mp 228° (dec.). Found: Cl 10.3, 10.3; N 4.5, 4.4%. $C_{20}H_{17}NO_2 \cdot HCl$. Calculated: Cl 10.4; N 4.1%.

In addition to V, 27.4 g of IV with mp 124.8-125.6° was isolated. This product did not depress the melting point of 3-benzoyloxy-1,2,3,4-tetrahydrobenzo[h]quinoline [3]. Similar results were obtained when III or a mixture of II and III were used as the starting material.

2-(Hydroxymethyl)benz[g]indoline (VI). A mixture of 9.1 g (0.03 mole) of V and a solution of 1.7 g of potassium hydroxide in 50 ml of alcohol was shaken for 30 min. The reaction mixture was diluted with water and extracted with 40 ml of ether. The ether solution was washed with water and dried with magnesium sulfate. Ethanol (10 ml) was added, and the mixture was acidified with respect to litmus with a mixture of concentrated sulfuric acid and ethanol (1 : 1). The precipitate was removed by filtration and washed with ethanol–ether (2 : 1) to give 5.3 g (75%) of the hydrochloride of VI with mp 245.0° (dec., from absolute ethanol). Found: Cl 15.0, 14.9; N 6.2, N 6.0%. $C_{13}H_{13}NO \cdot HCl$. Calculated: Cl 15.0; N 5.9%. A mixture of 2.4 g (0.01 mole) of the hydrochloride of VI and an aqueous solution of sodium carbonate was shaken in the presence of ether. The ether solution was treated with activated charcoal, the ether was removed, and the residue was vacuum-dried over calcium chloride. The resulting oily substance was base VI. The yield was almost quantitative. Found: N 7.0, 6.9%. $C_{13}H_{13}NO$. Calculated: N 7.0%. PMR spectrum: 2.4-2.65 (quartet, $J_{gem}=16$ Hz, $J_{2,3}=9$ Hz), methylene protons in the 3 position; 3.3, methylene protons of the methylol group; 3.6-3.9 (multiplet), proton in the 2 position; 3.9, signal of the NH and OH groups.

1-Benzoyl-2-(benzoyloxymethyl)benz[g]indoline. A mixture of 1.5 g (5 mmole) of V, 1.0 g (7 mmole) of benzoyl chloride, and 10 ml of pyridine was heated at 100° for 1.5 h. The usual workup gave 1.9 g (93%) of the dibenzoyl derivative with mp 136.0-137.3° (from absolute ethanol). Found: N 3.6, 3.5%. $C_{27}H_{21}NO_3$. Calculated: N 3.4%.

(2-Benz[g]indolinyl)acetonitrile (VII). A solution of 2.2 g (0.01 mole) of III in 10 ml of dimethyl sulfoxide was added with vigorous stirring in the course of 20 min at 140° to 3.2 g (0.05 mole) of potassium cyanide in 4 ml of distilled water and 5 ml of dimethyl sulfoxide. The reaction mixture was diluted with water and extracted with ether–benzene. The extract was dried with magnesium sulfate, the solvents were removed, and the residue was dried over $CaCl_2$ and stored over n-butyl alcohol. The resulting crystals were removed by filtration and washed with ether to give 1.5 g (72%) of a product with mp 96.5-97.5° [from ethanol–ether (1 : 2)]. The product did not depress the melting point of a genuine sample [2].

2-Methylbenz[g]indole (IX). A mixture of 2.3 g (0.01 mole) of VIII and 1.0 g of Raney nickel was heated under nitrogen at 160° for 15 min. The reaction mixture was vacuum-distilled, and the fraction with bp 150-153° (2-3 mm) was collected to give 1.0 g (55%) of a product with mp 131.5-132.5° (from methanol) (mp 132° [5]). The picrate was obtained as dark-red needles with mp 162.0-164.0° (from ethanol) (mp 167° [5]).

LITERATURE CITED

1. S. I. Kutkevichus and R. I. Shablinskas, Khim. Geterotsikl. Soedin., 1403 (1971).
2. S. I. Kutkevichus and K. S. Sherenas, Khim. Geterotsikl. Soedin., 1526 (1970).
3. N. N. Vorozhtsov, Jr., and S. I. Kutkevichus, Zh. Obshch. Khim., 27, 2521 (1957).
4. Yu. A. Degutis and V. A. Beksha, Trudy Akad. Nauk Lit. SSR (Ser. B), 4(55), 105 (1968).
5. H. Schlieper, Ann., 239, 237 (1887).