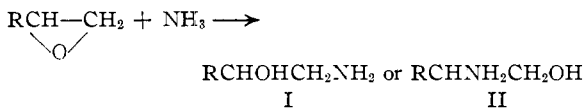


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Constitution of the Product of the Reaction of Benzylethylene Oxide with Ammonia

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In connection with an investigation of their pharmacological properties, a number of amino alcohols have been prepared by the reaction of safrole oxide or methyleugenol oxide with various amines.^{1a} When ammonia or amines react with unsymmetrically substituted ethylene oxides, it is possible for two isomers to be formed depending on which oxide bond is opened.

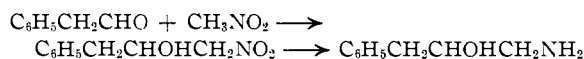


Where the substituent in the ethylene oxide ring is an aliphatic radical, it seems certain that the product is a secondary alcohol (type I).² Where the substituent is a benzyl group, it has been assumed, presumably by analogy, that a secondary alcohol is formed.³ In the reaction of safrole oxide with dimethylamine or with piperidine, both isomers were considered as possible products.⁴ Hence it seemed desirable to establish definitely the course of the reaction in a typical case as a basis for predicting the structure of the products. For this purpose the simplest example was chosen, namely, the reaction of benzylethylene oxide and ammonia. As was to be expected, the products of reaction of more than one mole of oxide with ammonia were obtained but, in contrast to previous work,³ the desired reaction product of one mole of oxide and one mole of ammonia also was isolated. The amino alcohol, C₉H₁₃NO, was a solid which could be purified by crystallization; m. p. 71.7–72.3°. It was converted to its hydrochloride, m. p. 174–176°, to the monobenzoate, m. p. 141.7–142.4°, by the Schotten-Baumann procedure, and to the O,N-dibenzoate, m. p. 103.2–103.7°, and O,N,N-tribenzoate, m. p. 89.5–90°, by reaction with benzoyl chloride in pyridine.

The preparation of 3-phenyl-2-aminopropanol-1 by the sodium and alcohol reduction of inactive ethyl 3-phenyl-2-aminopropionate has been described.⁵ It apparently is a liquid, the melting point of the hydrochloride being reported as 128°. Oeda,⁶ however, reduced ethyl 3-phenyl-2-aminopropionate from "natural phenylalanine" and obtained dibenzylpiperazine and two amino

alcohols, C₉H₁₃NO, one of which was optically active and the other inactive. The latter melted at 71–73° and gave a monobenzoate, m. p. 148–149°.

In order to obtain material for direct comparison, ethyl 3-phenyl-2-acetylaminopropionate was reduced with sodium and butyl alcohol.⁷ An oil was obtained which could not be converted into a crystalline hydrochloride. Benzoylation by the Schotten-Baumann procedure gave only a dibenzoate, m. p. 150.8–151.4°. Hence the indication is that the product of the reaction of one mole of benzylethylene oxide with ammonia is not 3-phenyl-2-aminopropanol-1 but probably is 3-phenyl-1-aminopropanol-2. In order to test this assumption, the last compound was synthesized by the following series of reactions



The amino alcohol was isolated as the hydrochloride, m. p. 176–177°, and converted to the monobenzoate, m. p. 142.1–142.6°. No depression in melting point was observed on mixing these derivatives with the corresponding compounds obtained from the reaction of benzylethylene oxide and ammonia.

Experimental

Condensation of Benzylethylene Oxide and Ammonia.—To a mixture of 65 cc. of ethyl alcohol and 52 cc. of aqueous ammonia (sp. gr. 0.90) was added, with shaking and cooling, 9.8 g. of benzylethylene oxide, b. p. 86–88° at 9–10 mm.,⁸ prepared by the reaction of allylbenzene with perbenzoic acid.^{1a} After standing at room temperature twenty-four hours, the water and alcohol were removed and the residue distilled. Three main fractions were obtained: (a) 5.5 g., b. p. 138–164° (10–12 mm.), (b) 1.6 g., b. p. 196–197° (12 mm.), and (c) 1.7 g., b. p. 274–276° (9 mm.). Titration of samples of the three fractions with standard acid, using methyl red as an indicator, gave values for the equivalent weights of 157, 241 and 430. The equivalent weights of the primary, secondary and tertiary amines resulting from the condensation of one, two and three moles of benzylethylene oxide with one of ammonia are 151, 285 and 420.

Fraction (a) solidified and after crystallization from isopropyl ether melted at 71.7–72.5°.

*Anal.*⁹ Calcd. for C₉H₁₃NO: C, 71.49; H, 8.66. Found: C, 71.19, 71.15; H, 8.63, 8.49.

During attempts to crystallize the amine from a mixture of isopropyl alcohol and carbon tetrachloride, the hydrochloride was obtained, which softened at about 153° and melted at 173–174°.

Anal. Calcd. for C₉H₁₄ClNO: C, 57.60; H, 7.52. Found: C, 57.59, 57.64; H, 7.58, 7.55.

(7) Barrow and Ferguson, *J. Chem. Soc.*, 410 (1935).

(8) Fourneau and Tiffeneau, *Compt. rend.*, **140**, 1596 (1905).

(9) All carbon and hydrogen analyses are microanalyses by Dr. E. W. D. Huffman, Denver, Colo. All other analyses are by A. J. Castro.

(1) Abbott Laboratories Fellow, 1942–1944.

(1a) Noller and Kneeland, *THIS JOURNAL*, **68**, 201 (1946).

(2) Krasuskii, *Compt. rend.*, **146**, 236 (1908); Fourneau, *J. pharm. chim.*, [7] **2**, 109 (1910); *C. A.*, **5**, 3798 (1911).

(3) Levy and Sfras, *Compt. rend.*, **191**, 261 (1930).

(4) Mosettig, *Ber.*, **62**, 1271 (1929).

(5) Karrer, Thomann, Horlacher and Maeder, *Helv. Chim. Acta*, **4**, 97 (1921).

(6) Oeda, *Bull. Chem. Soc. Japan*, **13**, 465 (1938).

A mixture of isopropyl alcohol (99%) and carbon tetrachloride when shaken with water gave no test for halogen in the aqueous layer but if an identical mixture was heated on the water-bath for fifteen minutes and then shaken with water, the aqueous layer gave a positive test for halogen. Evidently the hydrochloride was formed because of the interaction of these solvents during the crystallization.

The hydrochloride was prepared directly from the crude amino alcohol by passing dry hydrogen chloride into an absolute ether solution or by treating the amino alcohol with aqueous hydrochloric acid and evaporating to dryness. After crystallization from absolute ethyl alcohol-ether mixture the product softened at about 153° and melted at 174–176°.

Anal. Calcd. for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; Cl, 18.89. Found: C, 57.64, 57.58; H, 7.57, 7.70; Cl, 18.75.

The monobenzoate was prepared by shaking an ether solution of the amino alcohol with aqueous sodium hydroxide solution and benzoyl chloride, and crystallized from ligroin (b. p. 100–140°) and from aqueous ethyl alcohol; m. p. 141.7–142.4°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.17, 75.04; H, 6.80, 6.84.

The dibenzoate and tribenzoate were obtained by the reaction of the amino alcohol with benzoyl chloride (mole ratio 1:3) in pyridine at room temperature. After filtering off the pyridine hydrochloride, the product was precipitated with water and washed with dilute sodium carbonate solution. Manipulation of the oil with a variety of solvents gave a solid fraction which on recrystallization from aqueous ethyl alcohol gave the tribenzoate, m. p. 89.5–90°.

Anal. Calcd. for $C_{30}H_{25}NO_4$: C, 77.73; H, 5.43. Found: C, 77.69, 77.64; H, 5.59, 5.49.

Evaporation of the mother liquors and recrystallization from isopropyl alcohol gave the dibenzoate, m. p. 103.2–103.7°.

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.85; H, 5.89. Found: C, 76.88, 76.80; H, 5.88, 5.79.

Neither of the above compounds gave a positive test for an alcoholic hydroxyl group¹⁰ indicating that they are the O,N, and the O,N,N derivatives.

O,N-Dibenzoate of 3-Phenyl-2-aminopropanol-1.—The crude amino alcohol obtained by the reduction with sodium and butyl alcohol of ethyl 2-acetylamino-3-phenylpropionate⁷ was reacted with benzoyl chloride and sodium hydroxide according to the same procedure which gave the monobenzoate described above. The product was a dibenzoate which melted at 150.8–151.4° after crystallization from ligroin (b. p. 100–140°) and from aqueous ethyl alcohol.

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.85; H, 5.89. Found: C, 76.72, 76.60; H, 6.08, 6.14.

3-Phenyl-1-aminopropanol-2 and Derivatives.—In a 500-cc., three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer, and surrounded by an ice-salt cooling mixture was placed 56.9 g. (0.47 mole) of phenylacetaldehyde, b. p. 70–83° (3 mm.), prepared from ethyl orthoformate and phenylmagnesium bromide,¹¹ 28.7 g. (0.47 mole) of nitromethane and 82 cc. of 95% ethyl alcohol. When the temperature of the solu-

tion reached 8°, 47.5 cc. of a 10 N solution of sodium hydroxide was added dropwise with stirring at such a rate that the temperature did not rise above 11°. An additional 50 cc. of alcohol was added to permit adequate mixing, and stirring was continued for thirty minutes. The mixture was diluted with ice-water and made neutral to litmus with acetic acid. After standing overnight in the refrigerator, the yellow oil was separated and the aqueous layer extracted three times with ether. The oil and ether extracts were washed three times with water, the ether removed, and the residue distilled. The fraction boiling at 161–169° (7 mm.) was a red oil and proved to be the nitro alcohol. The yield was 19.9 g. or 23% of the calculated amount.

A solution of 10 g. of the red oil in 30 cc. of alcohol was shaken with a palladium-charcoal catalyst containing 0.4 g. of palladium¹² in the presence of hydrogen at an initial gage pressure of 40 lb. At the end of an hour hydrogen was no longer absorbed so an additional like amount of catalyst was added and shaking continued. At the end of fifteen hours the calculated amount of hydrogen had been absorbed.

After removal of the catalyst the clear filtrate was acidified with 5% aqueous hydrochloric acid, the alcohol removed and the aqueous solution extracted with ether. Evaporation of the aqueous layer to dryness under reduced pressure gave the hydrochloride as a pale wine-red liquid, weighing 8 g. Addition of absolute alcohol and ether, and standing overnight in the refrigerator, gave 4.4 g. of white crystals, and an additional 0.3 g. was obtained from the mother liquor. The total yield was 56.4% of crude product. After four crystallizations from absolute alcohol-ether the product softened at about 154° and melted at 175–177°.

Anal. Calcd. for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; Cl, 18.89. Found: C, 57.67, 57.73; H, 7.63, 7.71; Cl, 18.62.

When 0.5 g. of the crude hydrochloride was benzoylated with benzoyl chloride and sodium hydroxide, the monobenzoate was obtained; m. p. 142.1–142.6° after five crystallizations from aqueous alcohol.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.26, 75.22; H, 6.76, 6.78.

When the benzoate was tested in dioxane with ammonium hexanitratocerate, a red color was produced indicating the presence of a free alcoholic hydroxyl group.¹⁰ N-Benzoyl-(2-phenylethyl)-amine did not respond to the test. The above hydrochloride and monobenzoate did not depress the melting point of the corresponding derivatives of the amino alcohol derived from benzylethylene oxide and ammonia.

Summary

The amino alcohol formed by the reaction of one mole of benzylethylene oxide with one mole of ammonia is identical with that obtained by the reduction of the nitro alcohol formed by the condensation of phenylacetaldehyde with nitromethane, and hence is 1-amino-2-hydroxy-3-phenylpropane.

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(11) Bodroux, *Bull. soc. chim.*, [3] **31**, 585 (1904).

(12) Ott and Eichler, *Ber.*, **55**, 2661 (1922).