Synthetic Studies on Oxirane Compounds. I. Ammonolysis of 2,3-Epoxyl-3-pheny-1-propanol

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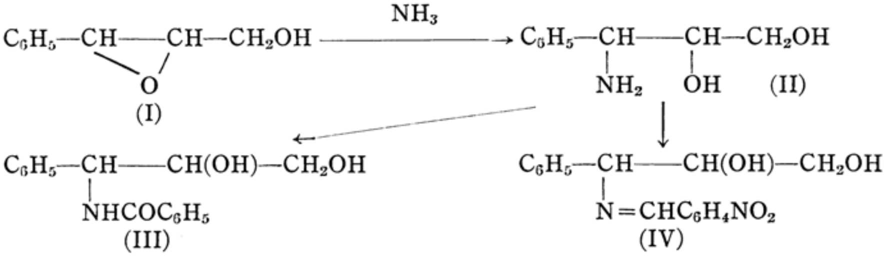
(Received December 20, 1955)

The study described in the present communication was a part of a program involving synthetic studies on chloramphenicol which is an important antibiotic found by the scientists of Parke, Davis and Co.. An attractive synthetic path to chloramphenicol involves the opening of the oxide ring of 1-phenylglycidol with ammonia. Although it has been shown recently by Fusco and Trave[1] that 1-*p*-nitrophenyl-1-amino-2,3-propanediol is obtained by the action of ammonia on 1-*p*-nitrophenylglycidol, the substituent exerts often a profound effect on the direction of opening of the oxide ring, an example apparently being found in the reaction of nitrostyrene oxide[2] with hydrogen chloride. The direction of opening is opposite to that observed with styrene oxide[3]. This possibility made it desirable to attempt the ammonolysis of 1-phenylglycidol. The experiments described here established, however, the fact that 1-phenyl-1-amino-2,3-propanediol (II) is obtained by the action of methanolic ammonia on 1-phenylglycidol, the direction of opening being much the same as that observed with 1-*p*-nitrophenylglycidol.



1-Phenylglycidol was prepared from cinnamyl alcohol and perbenzoic acid and had essentially the same boiling point with that reported by Platt and Hibbert[4]. By treatment with an excess of ammonia in absolute methanol in an autoclave, the epoxide ring of 1-phenylglycidol was split with the formation of 1-phenyl-1-amino-2,3-propanediol (II), m. p. 90–91°, which depressed the melting point of the authentic sample of DL-threo-1-phenyl-2-amino-1,3-propanediol, m. p. 87–88°. Treatment of II with *p*-nitrobenzaldehyde gave a Schiff base (IV), m. p. 149–150°, which also depressed the melting point of the corresponding Schiff base (V), m. p. 143–145°, prepared similarly from DL-threo-1-phenyl-2-amino-1,3-propanediol.

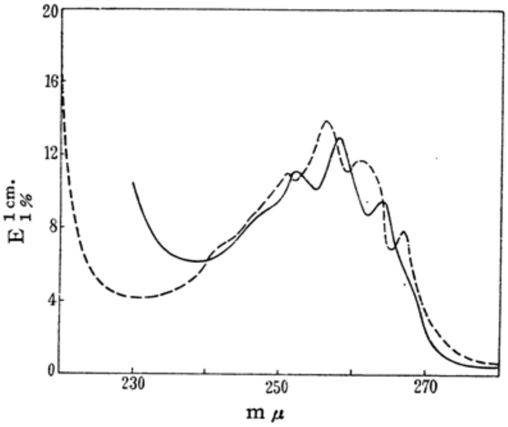


Fig. 1. Ultraviolet spectra of 1-phenyl-1-amino-2,3-propanediol.
(----- : in 1 N hydrochloric acid;
——— : in ethanol)

To establish the identity of 1-phenyl-1-amino-2,3-propanediol (II) the known 1-phenyl-1-benzamido-2,3-propanediol was synthesized by the method of Lott[5] from cinnamyl benzoate bromohydrin and ammonia and did not depress the melting point of the benzoyl

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[1] R. Fusco and R. Trave, *Gazz. chim. ital.*, 80, 366 (1950).

[2] F. Arndt, B. Eistert and W. Partale, *Ber.*, 61 B, 1107 (1928).

[3] C. Golumbic and D. L. Cottle, *J. Am. Chem. Soc.*, 61, 996 (1939).

[4] M. E. Platt and H. Hibbert, *Can. J. Research*, 7, 629 (1932); *C. A.*, 27, 1334.

[5] Lott, U.S. patent 2,103,266. The structure was elucidated by Controulis et al., who found that the migration of benzoyl group from O to N takes place during ammonolysis. *J. Am. Chem. Soc.*, 71, 2463 (1949).

derivative (III) of the product (II) from the cleavage of 1-phenyl-glycidol (I). Ultraviolet absorption (Fig. 1) agreed in every respect with that obtained by Controulis et al..

On treatment of II with hot acetone an *iso*-propylidene derivative was produced which regenerated II readily by hydrolysis with hydrochloric acid at room temperature.

Experimental

1-Phenylglycidol (I) (2, 3-Epoxy-3-phenyl-1-propanol).—To a solution of 8.8 g. of perbenzoic acid in 100 cc. of chloroform was added 8.0 g. of cinnamyl alcohol. The solution was kept at 0° for about twenty-four hours and was shaken frequently during the first hour. The benzoic acid was removed from the chloroform solution by shaking with an excess of 10% sodium hydroxide solution, the alkali was removed by washing with water, and the chloroform solution was dried with sodium sulfate. It was then fractionated. Removal of the chloroform left a practically colorless liquid which distilled at 117–118°/1.5 mm. The yield was 4.5 g. (45% of the theoretical amount). Platt and Hibbert[4] described already the b. p. 136–137°/5 mm.

1-Phenyl-1-amino-2, 3-propanediol (II) (Cleavage of I with Ammonia).—The phenylglycidol (I) (13.6 g.) was heated with 350 cc. of a saturated solution (at 0°) of ammonia in absolute methanol at 80–90° for five hours in a stainless-steel autoclave. The solution was concentrated to a dark brown gum under reduced pressure which crystallized on trituration with ether. The ether-mixture was kept in a stoppered flask for about twenty hours. The crystals formed 9 g. and were collected on a filter. Three times of recrystallization from chloroform-ethylacetate (1: 1) gave colorless needless melting at 90–91°. (Found: N, 8.22. Calcd. for $C_9H_{13}O_2N$: N, 8.38%.)

This depressed the melting point of an authentic sample of DL-threo-1-phenyl-2-amino-1, 3-propanediol, m. p. 87–88°.

1-Phenyl-1-benzamido-2, 3-propanediol (III).—0.5 g. Sample of the above described product (II) was treated with a small excess of benzoyl chloride in 1 N sodium hydroxide. The precipitate was recrystallized from water, colorless needles, m. p. 163–164°. This did not depress the melting point of 1-phenyl-1-benzamido-2, 3-propanediol, m. p. 163–164°, prepared by the method of Lott[5] from cinnamyl benzoate bromohydrin and ammonia.

1-Phenyl-1-(*p*-nitrobenzylidene)-amino-2, 3-propanediol (IV).—1.0 g. Sample of (II), m. p. 89–90° was mixed with 0.9 g. of *p*-nitrobenzaldehyde in 5.0 cc. of ethylacetate and warmed. Soon the resulting clear solution began to precipitate pale-yellow crystals. After standing overnight at room temperature the crystals were collected on a filter, washed with ethylacetate and ether, m. p. 140–143°. The yield was 1.0 g. Further recrystallization from methanol gave pale-yellow needles, m. p. 149–150°. (Found: N, 9.23. Calcd. for $C_{13}H_{16}O_4N_2$: N, 9.33%.)

1-Phenyl-2-(*p*-nitrobenzylidene)-amino-1, 3-propanediol.—The condensation of *p*-nitrobenzaldehyde with DL-threo-1-phenyl-2-amino-1, 3-propanediol was carried out exactly as described above and led to 1-phenyl-2-(*p*-nitrobenzylidene)-amino-1, 3-propanediol, pale-yellow needles, m. p. 137–140°, 1.0 g. Recrystallization from acetone gave pale-yellow needles, m. p. 143–145°. (Found: N, 9.44. Calcd. for $C_{16}H_{16}O_4N_2$: N, 9.33%.)

This depressed the melting point of a sample of IV.

***iso*-Propylidene Derivative of II.**—A portion of 0.5 g. of the dark brown gum from which 1-phenyl-1-amino-2, 3-propanediol (II) described above was isolated, was dissolved in acetone by warming on a steam-bath. After standing at room temperature a colorless crystalline precipitate 0.3 g. was obtained, m. p. 93–96°. After recrystallization from acetone, the *iso*-propylidene derivative melted at 102.5–103°. (Found: N, 6.47. Calcd. for $C_{12}H_{17}O_2N$: N, 6.76%).

A sample of 0.2 g. of the *iso*-propylidene derivative was hydrolyzed with 1 cc. of 2 N hydrochloric acid at room temperature in a few minutes. The hydrolysate was neutralized with potassium carbonate and evaporated to dryness under reduced pressure. The colorless residue was dissolved in 1 cc. of water, made alkaline to pH 10 and extracted with ethylacetate. The ethylacetate solution was dried over sodium sulfate and evaporated to a syrupy residue, 0.1 g., which crystallized from ether. Recrystallization from ethylacetate-chloroform (1: 1) gave colorless needles, 0.05 g., m. p. 89.5–90°. The mixed melting point with an authentic sample of II showed no depression.

An attempt was made to prepare *iso*-propylidene derivative from DL-threo-1-phenyl-2-amino-1, 3-propanediol by the same procedure described above. However, only a syrup was obtained.

Summary

1-Phenyl-1-amino-2, 3-propanediol, m. p. 90–91°, was obtained by ammonolysis of 2, 3-epoxy-3-phenyl-1-propanol. Several derivatives of this compound were described.

A part of the cost of the present research has been defrayed from the Scientific Research Encouragement Grant from the Ministry of Education, to which the authors' thanks are due.

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