[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Isolation of an Epoxyether from the Reaction of an α-Haloketone with Base[1]

BY CALVIN L. STEVENS, WALI MALIK AND RICHARD PRATT

Recently Temnikova and Kropacheva[2] have reported the preparation of 1-phenyl-1-methoxy-1,2-epoxypropane (II) from the reaction of α-bromopropiophenone and sodium methoxide. The epoxyether (II) was characterized by reaction with phenylhydrazine in glacial acetic acid to give III and by hydrolysis with 5% sulfuric acid to give phenylacetylcarbinol and methylbenzoylcarbinol. II polymerized at room temperature and gave a crystalline dimer, 2,5-dimethoxy - 2,5 - dimethyl - 3,6 - diphenyl - *p*-dioxane, when treated with methyl alcohol containing 3% hydrogen chloride.

$$\underset{\text{I}}{C_6H_5COCHBrCH_3} + NaOCH_3 \longrightarrow C_6H_5C(O)CHCH_3 + NaBr$$

(II: $C_6H_5C(OCH_3)(O)CHCH_3$)

$$\text{III: } C_6H_5C(=N-NHC_6H_5)-CH(NH-C_6H_5)CH_3$$

The publication of the Russian workers has prompted us to report here the results of an investigation initiated in November, 1948, of 1,2-epoxy-1-ethers. This investigation resulted in the independent isolation of the epoxyether (II) by the same type of reaction employed by the Russian workers. The epoxide ring of II was cleaved rapidly with alcohol and benzoic acid with the formation of an α-hydroxyketal and an α-ketobenzoate, respectively, and the structures of these two products were proven. Although II polymerized readily at room temperature, it was stable for many weeks as a solid at −15°.

The epoxyether (II) was prepared in 66% yield from α-chloropropiophenone and had essentially the same physical properties reported by the Russian workers. However, our preparation was further characterized as one of the two possible racemic mixtures by a sharp melting point at −7 to −5°.

Warm methyl alcohol containing a catalytic amount of sodium methoxide cleaved the epoxide ring of II with the formation of α-hydroxypropiophenone dimethyl acetal[3] (IV).

The epoxyether (II) reacted exothermically with benzoic acid with the formation of α-hydroxypropiophenone benzoate (V) in 31% yield. This reaction undoubtedly proceeded by cleavage of the epoxide ring with loss of methyl alcohol to give the ketobenzoate (V).

$$\text{II} + HOCH_3 \xrightarrow{\ominus OCH_3} C_6H_5C(OCH_3)_2CHOHCH_3 \quad \text{IV}$$

$$\text{II} + HOCC_6H_5 \longrightarrow C_6H_5C(OCC_6H_5)(O)CHCH_3 \quad \text{V}$$

The hydroxyketal (IV) could be converted to the ketobenzoate (V) by benzoylation of the hydroxyl group with benzoyl chloride in pyridine followed by preferential acid hydrolysis of the ketal groups with dilute hydrochloric acid.

The ketobenzoate (V) obtained from both cleavage reactions was identical with the compound prepared from α-chloropropiophenone and sodium benzoate in aqueous alcohol.[4] Evidence for the structure of the α-hydroxypropiophenone benzoate was obtained by a comparison of its ultraviolet absorption spectrum with the ultraviolet absorption spectrum of the isomeric α-hydroxy-α-phenylacetone benzoate (VIII) prepared by reactions VI to VIII. The ultraviolet absorption spectrum of V (Fig. 1, Curve 2)

$$\underset{\text{VI}}{C_6H_5CH_2COCH_3} + Br_2 \longrightarrow$$

$$\underset{\text{VII}}{C_6H_5CHBrCOCH_3} \xrightarrow{\ominus OCC_6H_5}$$

$$\text{VIII: } C_6H_5CH(OCC_6H_5)(O)COCH_3$$

showed a maximum at 2400 Å. (ε 23,000) indicating conjugation of a carbonyl group with a benzene ring. VIII showed an ultraviolet absorption maximum (Fig. 1, Curve 1) similar to an ester of benzoic acid, maximum 2300 Å. (ε 16,200). Additional evidence was obtained by treating V with excess phenylmagnesium bromide. Triphenylcarbinol and 1,1-diphenylpropanediol-1,2 were produced in about equal amounts. The glycol was identical with an authentic sample prepared from ethyl lactate and phenylmagnesium bromide.[5]

(1) Presented before the Organic Division at the 117th meeting of the American Chemical Society in Philadelphia, Pa., April 12, 1950. Sponsored in part by the Research Corporation.

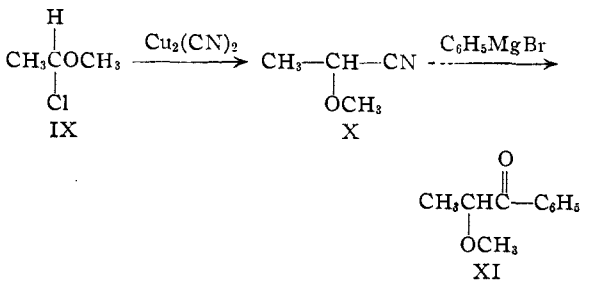
(2) Temnikova and Kropacheva, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **19**, 1917 (1949); *C. A.*, **44**, 1929 (1950).

(3) This ketal, m. p. 35–37°, is isomeric with the hydroxyketal, $C_6H_5CHOHC(OCH_3)_2CH_3$, m. p. 62–63°, prepared by McPhee and Klingsberg (ref. 7) by the action of alcoholic sodium methoxide with α-chloro-α-phenylacetone. Both ketals gave the 2,4-dinitrophenylosazone of methylphenylglyoxal.

(4) Temnikova, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1022 (1938).

(5) Roger, *Biochem. Z.*, **230**, 320 (1931).

The structure of the ketobenzoate (V) furnishes evidence for the structure of the α-hydroxyketal (IV) and for the structure assigned to the epoxyether (II). Further, α-methoxypropiophenone (XI), the compound predicted from a metathetical reaction of the haloketone (I) and sodium methoxide, was synthesized by reactions IX to XI and shown to be different in chemical and physical properties from the epoxyether (II).



The isolation of the epoxyether and the rapid reaction of this compound with alcohol to give an α-hydroxyketal confirms the mechanism postulated by Ward and by Kohler[6] for the formation of α-hydroxyketals from certain α-haloketones with alcoholic sodium alkoxides, *via* epoxyether intermediates.

Epoxyethers have been postulated as intermediates in the rearrangement of certain α-haloketones to acids or esters in the presence of base[7] under essentially the same conditions as described above for the formation of the epoxyether. However, no evidence for rearrangement of this epoxyether to an ester could be obtained during its formation or isolation. Work is under way to determine the mechanism of this rearrangement.

Acknowledgment.—We are indebted to Mr. J. French and Mr. E. Farkas of Wayne for the analysis and to Miss Denise Lundquest of Parke, Davis Company for the ultraviolet spectra.

Experimental

α-Chloropropiophenone.—This chloroketone was prepared in 50% yield from α-chloropropionyl chloride, benzene and aluminum chloride,[8] b. p. 123–125° (17 mm.); $n^{25}D$ 1.5402; d^{25}_4 1.156.

1-Phenyl-1-methoxy-1,2-epoxypropane (II).—Dry sodium methoxide prepared from 3.6 g. of sodium and methyl alcohol was stirred as an ether suspension and 15 g. of α-chloropropiophenone added slowly at room temperature. After heating for two hours at reflux, the salts were separated by centrifugation and the ether evaporated under reduced pressure. Distillation of the residue gave 10.0 g. (66%) of the epoxyether (II), b. p. 75–76° (1 mm.); m. p. −7 to −5°; $n^{25}D$ 1.5002; d^{25}_4 1.052.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37; CH_3O, 18.9; mol. wt., 164.2. Found: C, 73.00; H, 7.43. CH_3O, 18.5; mol. wt. (camphor) 157, (cryoscopic in benzene) 160.

(6) Ward, *J. Chem. Soc.*, 1544 (1929); Kohler and Addinall, THIS JOURNAL, **52**, 3728 (1930).

(7) Favorski, *J. Russ. Phys.-Chem. Soc.*, **26**, 559 (1894); Aston, *et al.*, THIS JOURNAL, **62**, 2590 (1940); **64**, 300 (1942); McPhee and Klingsberg, *ibid.*, **66**, 1132 (1944).

(8) Baker and Barkenbus, THIS JOURNAL, **58**, 263 (1936).

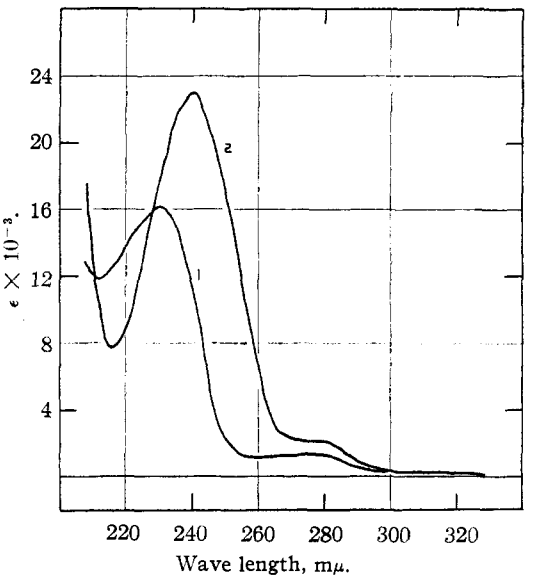


Fig. 1.—Ultraviolet absorption spectrum of α-hydroxy-α-phenylacetone benzoate (VIII, Curve 1) and α-hydroxypropiophenone benzoate (V, Curve 2) in 95% alcohol.

α-Hydroxypropiophenone Dimethyl Ketal (IV).—To a solution of 0.1 g. of sodium in 50 ml. of methyl alcohol was added 8.5 g. of the epoxyether (II). The alcohol was heated gently and then allowed to stand for 24 hours. The excess alcohol was distilled at reduced pressure and the residual liquid distilled at 0.5 mm. The yield of hydroxyketal was 8.0 g. (79%); b. p. 94–95° (0.5 mm.); m. p. 36–37°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; CH_3O, 31.1. Found: C, 67.11; H, 8.45; CH_3O, 31.0.

The hydroxyketal gave a 70% yield of the 2,4-dinitrophenylosazone of methylphenylglyoxal, m. p. 254–256° (*cf.* ref. 3), on treatment with acidic 2,4-dinitrophenylhydrazine reagent.

α-Hydroxypropiophenone Benzoate (V).—To 1.2 g. (0.01 mole) of benzoic acid was added 1.6 g. (0.01 mole) of the epoxyether (II). Heat was evolved and the reaction became homogeneous. On cooling a solid crystallized, after which the reaction mixture was taken up in ether, washed with sodium carbonate and then the ether evaporated. The resulting solid was recrystallized from heptane, m. p. 108–109°. A mixed melting point with the ketobenzoate made from the α-chloropropiophenone and sodium benzoate[4] was not depressed, m. p. 108–109°. The yield of pure ketobenzoate was 0.8 g. (31%).

Conversion of the Hydroxyketal (IV) **to the Ketobenzoate** (V).—The ketal (0.5 g.) was treated with 0.4 g. of benzoyl chloride in 10 ml. of pyridine. After heating for three hours on a steam-bath the reaction was poured into water and the organic layer washed with water and hydrolyzed by heating one-half hour with 5 ml. of concentrated hydrochloric acid dissolved in 20 ml. of methyl alcohol. After the reaction was poured onto ice and the solid filtered and recrystallized, 0.4 g. of ketobenzoate was obtained, m. p. 107–109°, mixed m. p. with V, 107–109°.

1,1-Diphenylpropanediol-1,2.—The Grignard reagent was prepared from 4.0 g. (0.025 mole) of bromobenzene and 0.5 g. of magnesium. An ether solution of 1.7 g. (0.0066 mole) of the ketobenzoate (V) was added rapidly. The mixture was refluxed for four hours and then decomposed with ammonium chloride solution. The ether layer was dried and concentrated to give 1.0 g. of solid material. The solid was separated by fractional recrystallization from heptane into about equal portions of triphenylmethyl carbinol, m. p. 158–160°; mixed m. p. with an authentic sample, 158–160°, and 1,1-diphenylpropanediol-1,2,

m. p. 94–96°. A mixed m. p. with the authentic glycol made from ethyl lactate and phenylmagnesium bromide[9] was not depressed; m. p. 94–96°.

α-Hydroxy-α-phenylacetone Benzoate (VIII).—Phenylacetone (10 g., 0.075 mole) was brominated in 50 ml. of carbon tetrachloride with 12 g. (0.075 mole) of bromine. After the carbon tetrachloride had been evaporated under reduced pressure, a solution of 11.4 g. (0.08 mole) of sodium benzoate in 100 ml. of water and 100 ml. of alcohol was added. The reaction was refluxed for ten hours, after which time the volume of the solvent was reduced to 100 ml. After cooling the reaction mixture, the solid was filtered, washed with dilute hydrochloric acid and dilute sodium hydroxide, and finally recrystallized from 50% alcohol to give 11 g. (58%) of α-hydroxy-α-phenylacetone benzoate, m. p. 57–58°.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.31; H, 5.32.

α-Methoxypropiophenone (XI).—The method used recently by Henze, Benz and Sutherland[9] for the preparation of fifteen different α-methoxyketones was used in this synthesis with slight modification. α-Chloroethylmethylether, b. p. 66–68°, prepared in 48% yield from paraldehyde, methyl alcohol, and dry hydrogen chloride, reacted with cuprous cyanide without solvent to give 27% of α-methoxypropionitrile, b. p. 110–113°; $n^{20}D$ 1.3822. Phenylmagnesium bromide converted the nitrile in 50% yield to α-methoxypropiophenone, b. p. 76–77° (0.8 mm.); $n^{25}D$ 1.5220; d^{25}_4 1.095.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.13; H, 7.38. Found: C, 72.79; H, 7.22.

The semicarbazone of α-methoxypropiophenone melted sharply at 161–162°.

Anal. Calcd. for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.83; CH_3O, 14.0. Found: C, 59.82; H, 6.89; CH_3O, 14.1.

The methoxyketone was stable to warm methyl alcohol and did not react with benzoic acid at room temperature.

(9) Henze, Benz and Sutherland, THIS JOURNAL, **71**, 2122 (1949).

Summary

A reactive epoxyether (II), isolated from the reaction of α-chloropropiophenone and sodium methoxide, was cleaved rapidly with methyl alcohol and benzoic acid to give an α-hydroxyketal (IV) and an α-ketobenzoate (V), respectively. The structures of these derivatives were proven. The epoxyether gave no evidence of rearrangement to an ester during the formation or isolation.

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[CONTRIBUTION FROM THE PHARMACEUTICAL RESEARCH DIVISION, COMMERCIAL SOLVENTS CORPORATION]

Carboxy Derivatives of Benzylpenicillin[1]

BY R. P. HOLYSZ AND HOMER E. STAVELY

Until recently no chemical derivatives of benzylpenicillin had been reported except esters prepared with diazoalkanes. These esters were active parenterally only in species which were able to hydrolyze them to benzylpenicillin.[2] No data have been presented concerning their activity following oral administration.

The relationship of structure to antibiotic activity in derivatives of the free carboxyl group of penicillin has been of interest to a number of investigators. Prompted by the observation that certain penicilloic acid derivatives reacted with isobutyryl chloride in the presence of pyridine to form N-isobutyrylpenicilloic isobutyric anhydride (unpublished experiments) it was decided to investigate the formation of benzylpenicillinic alkanecarboxylic anhydrides and their utilization in the formation of benzylpenicillinic esters and amides. The publication on benzylpenicillinic anhydride[3] afforded an alternative method of approach to these derivatives. Subsequently, the preparation of benzylpenicillinic alkanecarboxylic anhydrides and the preparation of benzylpenicillinamide were reported.[4]

In the present work both procedures for the preparation of some carboxy derivatives of benzylpenicillin were investigated. Under the conditions employed benzylpenicillinic anhydride has proved to be superior to benzylpenicillinic acetic anhydride as an intermediate. The best yields (60–90%) of benzylpenicillinic anhydride, with minimum discoloration of the reaction mixture, were obtained by a modification of the method of Carpenter.[3] The anhydride was prepared by allowing thionyl chloride to react with triethylammonium benzylpenicillinate at −10 to 10° in chloroform solution. For every mole of penicillin salt approximately three-fourths of a mole of thionyl chloride was used. The anhydride was not isolated from such a solution, but the appropriate amine or alcohol was added, either as a solution or suspension in chloroform, and the reaction was allowed to proceed for a few hours at room temperature. The properties of the compounds prepared in this manner are listed in Table I.

$$2RCO_2^-HN^+Et_3 + SOCl_2 \longrightarrow (RCO)_2O + 2Et_3N^+HCl^- + SO_2$$

The product obtained by the addition of anhydrous hydrazine to the benzylpenicillinic anhydride solution was insoluble in most common organic solvents. Nitrogen analysis and its insolubility in acids supported the symmetrical structure, RCONHNHCOR. An attempt was made to prepare the monosubstituted hydrazine by reverse addition. Two products were isolated, one insoluble in ethyl acetate and identical with the disubstituted hydrazine, and the other soluble

(1) Presented in part before the Medicinal Chemistry Division, A. C. S., Atlantic City, New Jersey, September, 1949.

(2) Richardson, *et al.*, *Proc. Soc. Exptl. Biol. Med.*, **60**, 272 (1945); Kirchner, *et al.*, *J. Org. Chem.*, **14**, 388 (1949).

(3) Carpenter, THIS JOURNAL, **70**, 2964 (1948).

(4) Cooper and Binkley, *ibid.*, **70**, 3966 (1948).