

desired compound. This modified procedure required a relatively short reaction time for the formation of the epoxide, and the alkali concentration was less than that used for the preparation of compound II. 17 β -Hydroxy-1 α ,2 α -epoxyandrostan-3-one was obtained by this modified procedure or by the alkaline hydrolysis of the corresponding acetoxy derivative (IV).

The infrared absorption for the epoxide group was at 11.44 and 12.48 for the epoxide II, 11.42 and 12.52 for the epoxide IV, and 11.38 and 12.52 for the 17 β -hydroxy-1 α ,2 α -epoxyandrostan-3-one (VI). The ultraviolet spectra of the epoxides exhibited end absorption and at high concentrations the C₃-ketone group could be demonstrated.

EXPERIMENTAL⁶

1 α ,2 α -Epoxyandrostan-3,17-dione (II). To a stirred solution of 1-androstene-3,17-dione (3 g.) in methanol (200 ml.) were added simultaneously and dropwise 4*N* sodium hydroxide (16.2 ml.) and 30% hydrogen peroxide (16.2 ml.). The mixture was maintained at 20° during the addition and stored overnight at 5°. The reaction mixture was diluted with water and extracted with benzene. The benzene solution was washed with 1% sodium hydroxide solution and then with water until the washings were neutral. The benzene solution was dried over anhydrous sodium sulfate, filtered, and the solvent removed under reduced pressure. The crystalline residue, still containing a small amount of benzene was dissolved in methylene chloride. On slow evaporation of the solvent, a crystalline solid was obtained. The solid was separated by filtration and washed with a small amount of methylene chloride. The yield was 2 g.; m.p. 246–247°; $[\alpha]_D^{20} +189^\circ$ (1% in chloroform).

Anal. Calcd. for C₁₉H₂₆O₃: C, 75.46; H, 8.67. Found: C, 75.61; H, 8.30; $\lambda_{\text{max}}^{\text{KBr}}$ 5.76, 5.90, 11.42 and 12.48 μ .

17 β -Acetoxy-1 α ,2 α -epoxyandrostan-3-one (IV). To a stirred solution of III⁷ (1.05 g.; m.p. 128–129°) in methyl alcohol (15 ml.) cooled to 10° was added 30% hydrogen peroxide (1 ml.). Then a 10% solution of sodium hydroxide (0.2 ml.) in methyl alcohol (5 ml.) was added. The temperature was kept between 15–20°. A crystalline precipitate was observed within 3 min. and after the reaction had proceeded for 10 min. the solid was separated by filtration and washed with methanol; yield was 300 mg.; m.p. 160–161°.

Anal. Calcd. for C₂₁H₃₀O₄: C, 72.80; H, 8.73. Found: C, 72.61; H, 9.04; $\lambda_{\text{max}}^{\text{KBr}}$ 5.74; 5.78 (sh), 7.26, 9.56, 9.72, 11.42 and 12.52 μ .

The mother liquor was allowed to stand at 15–20° for 45 min. and diluted with water. The solid which deposited, was filtered, dried to constant weight (400 mg.) in a vacuum oven, and recrystallized from methanol. The yield from the latter material was 250 mg.; m.p. 157–158°.

Hydrolysis of 17 β -acetoxy 1 α ,2 α -epoxyandrostan-3-one (IV). To a solution of IV (250 mg.) in ethyl alcohol (10 ml.; 2B) was added 5*N* sodium hydroxide (0.5 ml.) and the solution heated to gentle reflux for 10 min. The reaction mixture became slightly turbid during the treatment. The mixture was cooled, diluted with water (50 ml.) and the aqueous layer decanted from the gummy residue which deposited

on the sides of the flask. The gum was dissolved in methyl alcohol (5 ml.) and diluted with water (15 ml.). The filtered solid was dried to constant weight (220 mg.; m.p. 120–123°). The product was chromatographed over silica (45 g.). Elution was begun with benzene and followed by an ethyl acetate-benzene mixture (5.0-ml. fractions were collected). The first material eluted with 20% ethyl acetate was IV (70 mg.; m.p. 158–159.5°) followed by VI (90 mg.; m.p. 140–165°). Recrystallized from aqueous methyl alcohol gave pure IV (m.p. 160–161°); VI (m.p. 156–158°).

Anal. (VI) Calcd. for C₁₉H₂₆O₃: C, 74.96; H, 9.27. Found: C, 75.09; H, 9.46; $\lambda_{\text{max}}^{\text{KBr}}$ 2.87, 5.82, 9.43, 9.6, 10.78, 11.38, 12.51 μ .

17 β -Hydroxy-1 α ,2 α -epoxyandrostan-3-one (VI). To a stirred solution of V^{7b} (0.9 g.; m.p. 152–153°) in methyl alcohol cooled to 10° was added 30% hydrogen peroxide (1 ml.). Then a 10% solution of sodium hydroxide in methyl alcohol (0.2 ml.) was added. The temperature was kept between 14–18°. After 10 min., the reaction mixture was diluted with water (45 ml.) and the solid that crystallized from the solution was separated by filtration and dried. The product (m.p. 157–158°) weighed about 700 mg. and was crystallized to constant m.p. from 90% methyl alcohol (m.p. 161–162°). This product showed no absorption in the 220–300 μ region.

Anal. Calcd. for C₁₉H₂₆O₃: C, 74.96; H, 9.27. Found: C, 74.95; H, 9.17; $\lambda_{\text{max}}^{\text{KBr}}$ 2.86, 5.83, 9.44, 9.51, 10.78, 11.38 and 12.52 μ .

DIVISION OF CHEMICAL RESEARCH
G. D. SEARLE AND Co.
Box 5110
CHICAGO 80, ILL.

Isomeric 2-Phenoxypropylcarboxylic Acids¹

J. H. LOOKER AND LOREN L. BRAUN

Received January 6, 1958

Recently, a series of 2-aryloxypropylcarboxylic acids was prepared by hydrolysis of the ethyl esters, initially formed through reaction of ethyl diazoacetate with a suitable arylvinyl ether.² In all cases only one acid was reported. The present communication describes the two theoretically possible diastereomeric 2-phenoxypropylcarboxylic acids, as well as infrared spectra of the isomeric acids.

Although we employed the same reactants as Julia and Tchernoff,² our experimental procedure (similar to that of Burger and Yost³) differed from that of the French workers in several respects: reaction period, absence of copper catalyst, method for isolation of the ester, hydrolysis medium, and purification procedure. No attempt was made to obtain the pure diastereomeric ethyl esters, which were hydrolyzed in ethanolic sodium hydroxide.

(1) Abstracted from a portion of a thesis submitted by Loren L. Braun in partial fulfillment of the requirements for the Ph.D. degree, University of Nebraska, 1956.

(2) M. Julia and C. Tchernoff, *Bull. soc. chim. France*, 181 (1956).

(3) A. Burger and W. L. Yost, *J. Am. Chem. Soc.*, 70, 2198 (1948).

(6) The author expresses his appreciation to Dr. R. T. Dillon and his staff on the analytical department of the G. D. Searle and Co. for the analytical data presented in this paper. The melting point determinations were observed on a Fischer-Johns block.

(7) (a) A. Butenandt and H. Dannenberg [*Ber.*, 71, 1681 (1938)] describe this compound with a melting point 117–118°. (b) *Ber.*, 73, 206 (1940).

TABLE I
 INFRARED ABSORPTION MAXIMA^{a,b} OF CYCLOPROPANECARBOXYLIC ACIDS

	Cyclopropanecarboxylic Acid ^c	2-Phenoxy-cyclopropanecarboxylic Acid A ^d	Acid B ^d
Carboxyl C=O ^e	1690 (1694 in CCl ₄)	1683 (1692 in CCl ₄)	1697 (1708 in CCl ₄)
Carboxyl OH ^e	2560, 2670, 931	2630 (wk), 920	2550, 2685 (wk), 957
Oxide ^e	—	1257 (1224 ?)	1253 (1225 ?)
Aromatic:			
Phenyl C=C ^e	—	1602, 1589, 1496	1603, 1592, 1491
C—H out of plane deformation ^e	—	750, 687	756, 682
Methylene ^e	1460	1452	1450
Cyclopropyl ^f	1032	1051 or 1020	1032 or 1018

^a Spectra were determined with a Perkin-Elmer Model 21 recording spectrophotometer. ^b Band locations are given in cm.⁻¹ Bands are of medium or strong intensity, except where otherwise indicated. Weak bands are denoted by (wk). ^c As pure liquid. ^d In KBr disks. ^e Band-structure correlations are in accordance with L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, N. Y., 1954, pp. 5-9. ^f Several workers have suggested that the cyclopropyl group displays a band in the region 1000-1020 cm.⁻¹ (Ref. e, pp. 27-28). The region 1000-1050 cm.⁻¹ has been suggested by V. A. Slabey [*J. Am. Chem. Soc.*, **76**, 3604 (1954)], and the region 1000-1040 cm.⁻¹ by E. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderly [*J. Am. Chem. Soc.*, **79**, 3467 (1957)]. See, however, A. R. H. Cole [*J. Chem. Soc.*, 3807 (1954)], who states that a band at 1010 cm.⁻¹ is unreliable when oxygen functions are present. C. F. H. Allen, T. J. Davis, W. J. Humphlett, and D. W. Stewart [*J. Org. Chem.*, **22**, 1291 (1957)] have questioned the fact that the 2.3 μ or 9.8 μ (ca. 1020 cm.⁻¹) affords a clear indication of the presence or absence of the cyclopropyl group.

The diastereomeric acids obtained were then separated by fractional crystallization from water. The less soluble Acid A possessed a melting point of 113-113.7°, which is in reasonable agreement with the previously reported value of 112°. ² The more soluble Acid B was obtained by benzene extraction of the aqueous mother liquors, and had a melting point of 135-137°. The latter acid apparently was not obtained by Julia and Tchernoff. ² The yield of Acid A was roughly twice that of Acid B.

The method of synthesis, combustion analyses and negative results from two standard chemical tests for the ethylenic linkage indicate with reasonable certainty the structural nature and identity of Acids A and B. The infrared absorption spectra of the two acids, some of the more important bands of which are reported in Table 1, confirm the structural nature of the two acids. In addition, the acid carbonyl bands for the acids in carbon tetrachloride solution can be used to assign configuration by taking advantage of the generalization of Mohrbacher and Cromwell. ⁴ In accordance with the latter, Acid A has the lower carbonyl band frequency and is the *trans* isomer. Acid B, then, is assigned the *cis*-configuration. Acid A and cyclopropanecarboxylic acid in carbon tetrachloride solution have virtually identical carbonyl band frequencies, a fact which is interpreted as indicating less steric interaction between phenoxy and carboxyl groups in Acid A, the *trans* isomer, than in Acid B. This configurational assignment finds confirmation in our isolation of the more stable Acid A in considerably greater yield than Acid B, and in the isolation of Acid A as the sole reaction product by Julia and Tchernoff. ²

(4) R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 406 (1957).

Possible ring-closure of Acids A and B in polyphosphoric acid, under conditions which gave 8-bromo-1-benzo[*f*]chromanone from β -(6-bromo-2-naphthoxy)propionic acid, ⁵ was investigated. However, all ring-closure attempts were unsuccessful.

EXPERIMENTAL⁶

Phenylvinyl ether. This compound was prepared by the method of Lauer and Spielman. ⁷

Ethyl diazoacetate. Ethyl diazoacetate was prepared by the general procedure of Womack and Nelson. ⁸

2-Phenoxy-cyclopropanecarboxylic acids A and B. The procedure used to prepare these acids was similar to that of Burger and Yost⁹ for synthesis of phenylcyclopropanecarboxylic acids A and B.

In a three necked flask, equipped with mechanical stirrer, reflux condenser, and dropping funnel, was placed a 30 g. (0.25 mole) quantity of phenylvinyl ether. To the stirred reaction mixture there was added, over a 15 hr. period, a solution of 57 g. (0.5 mole) of ethyl diazoacetate in 60 g. (0.50 mole) of phenylvinyl ether. The temperature was maintained at 146-154°. Gas evolution began with the addition of ethyl diazoacetate. The reaction mixture soon began to darken, and after 2 hr. was black. When addition of the diazoacetate solution was complete, the reaction mixture was distilled through a 24-inch Podbielniak column. Four fractions were collected at 6-10 mm.: (1) 51.8 g., b.p. 52-56°; (2) 2.5 g., b.p. 57-120°; (3) 1 g., b.p. 120-129°, and (4) 30 g., b.p. 129-140°.

Fractions 3 and 4 were combined and placed in a solution prepared by dissolving 8.8 g. of sodium hydroxide in a mixture of 11 ml. of water in 82 ml. of 95% ethanol. The alkaline mixture was heated under reflux for 9 hr., and then most of the alcohol was removed by distillation. The residue was

(5) L. L. Braun and J. H. Looker, *J. Am. Chem. Soc.*, **80**, 359 (1958).

(6) Melting points, observed in capillary tubes, are uncorrected.

(7) W. M. Lauer and M. A. Spielman, *J. Am. Chem. Soc.*, **55**, 1573 (1933).

(8) E. B. Womack and A. B. Nelson, *Org. Syntheses, Coll. Vol. 3*, 392 (1955).

diluted with a small volume of water and the resulting mixture acidified with concentrated hydrochloric acid. An oil separated, which solidified upon strong cooling of the mixture. The solid was collected by filtration and recrystallized from boiling water, of which about 2 l. were required. Several more recrystallizations from water yielded 6.5 g. (7.3%) of white, flaky crystals of Acid A, m.p. 110–113°. The combined mother liquors were extracted with benzene. The benzene extract was concentrated under reduced pressure, petroleum ether (b.p. 30–60°) added, and the resulting mixture permitted to stand in the refrigerator. The crystals which formed were recrystallized several times from water to give 3.0 g. (3.4%) of white crystals of Acid B, m.p. 134–137°. Repeated crystallization from water gave the analytically pure acids: Acid A, m.p. 113–113.7°; Acid B, m.p. 135–137°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.42; H, 5.65. Found: (for Acid A): C, 67.35; H, 5.67. (For Acid B): C, 67.58; H, 5.69.

Acid A in carbon tetrachloride did not decolorize 5% bromine in carbon tetrachloride. In acetone solution, Acid A gave no decoloration with a 2% solution of potassium permanganate. Acid B gave similar results with the preceding reagents. Phenylvinyl ether gave instantaneous decolorization with both reagents.

A 1-g. quantity of Acid A, m.p. 110–114°, was heated in 11.35 g. of polyphosphoric acid at 70–80° for 2 hr. with mechanical stirring and exclusion of moisture. The reaction mixture was poured into cold water and the resulting mixture extracted with benzene. The benzene solution was washed with 5% sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the benzene revealed neither solid nor liquid residue. Acid B gave similar results with polyphosphoric acid.

Acknowledgment. The financial support of this investigation by the Research Corporation of New York is gratefully acknowledged.

AVERY LABORATORY
THE UNIVERSITY OF NEBRASKA
LINCOLN, NEB.

2,2-Diaryl-*p*-dioxanes

R. K. SUMMERBELL, JAMES P. SETTLE, AND MATHILDE KLAND-ENGLISH

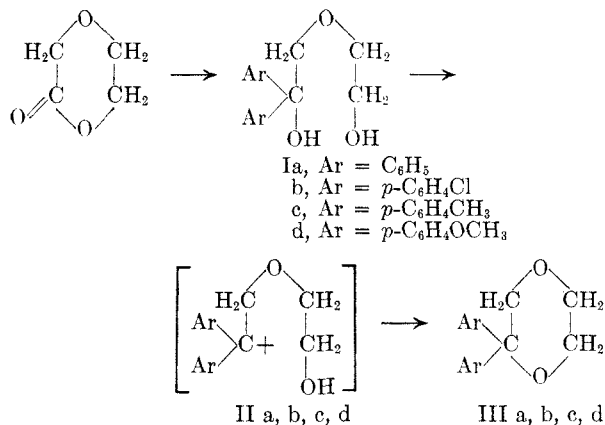
Received January 6, 1958

Two recent publications from our laboratory^{1,2} have made use of 2,2-diphenyl-*p*-dioxane as the reference compound in proving structures. This note details the original synthesis of this and other 2,2-diaryl-*p*-dioxanes.

Treatment of *p*-dioxanone with the appropriate Grignard reagent resulted in the formation of fair yields of α,α -diphenyldiethylene glycol, Ia, α,α -di-*p*-chlorophenyldiethylene glycol, Ib, and α,α -di-*p*-tolyl-diethylene glycol, Ic. These glycols were converted to dioxanes by treatment in benzene solution with anhydrous hydrogen chloride and calcium chloride at room temperature.

(1) R. K. Summerbell and Hans E. Lunk, *J. Am. Chem. Soc.*, **79**, 4802 (1957).

(2) R. K. Summerbell and Hans E. Lunk, *J. Am. Chem. Soc.*, **80**, 604 (1958).



The ease of formation of the dioxane rings contrasts with the difficulty of closing similar 4-methylmorpholine rings with acid,³ presumably because in the latter case the carbonium ion corresponding to II would have two positive charges. As would be expected from the proposed carbonium ion mechanism, Ib was not converted to the dioxane as easily as Ia or Ic. On the other hand, Id was not even isolated. Either the dioxane III d was formed in solvent evaporation or under the extremely mild acid conditions of the hydrolysis of the Grignard reaction product with aqueous ammonium chloride, or it was a direct product formed before hydrolysis. Such direct formation of ethers from aliphatic lactones by treatment with Grignard reagents seems to be rare.⁴

When a butyl Grignard reagent was treated with *p*-dioxanone, a compound of correct composition for the expected glycol resulted, but starting material was recovered when ring closure to the dioxane was attempted by the method successfully employed for aromatic derivatives.

EXPERIMENTAL

p-Dioxanone. Small yields of this compound were obtained by each of the methods attempted.⁵⁻⁷ None was satisfactory, and our modifications did not improve matters importantly. The compound was always distilled immediately before use in order to be certain that it was in the monomeric form. A convenient method for the laboratory preparation of this compound was found later in our laboratory, and has now been published.²

(3) I. A. Geissman, M. Bassin, and E. V. Zeilberger, *J. Am. Chem. Soc.*, **73**, 5874 (1951).

(4) M. S. Kharasch and Otto Reinmuth, *Grignard Reactions of Non-metallic Substances*, Prentice Hall, New York, 1954, pp. 574–578.

(5) C. A. Bischoff and P. Walden, *Ber.*, **26**, 263 (1893); *Ann.*, **279**, 47 (1894).

(6) W. H. Carothers, C. L. Dorough, and F. J. Van Natta, *J. Am. Chem. Soc.*, **54**, 771 (1932).

(7) R. W. McNamee and C. M. Blair, U. S. Patent 2,142,033, *Chem. Abstr.*, **33**, 2542 (1939).