[CONTRIBUTION NO. 1106 FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Racemizing Effect of the Phenyl Substituent of Optically Active Hydrogen 2-Phenyl-2-butyl Phthalate in Methanolytic Reaction[1]

BY HAROLD H. ZEISS

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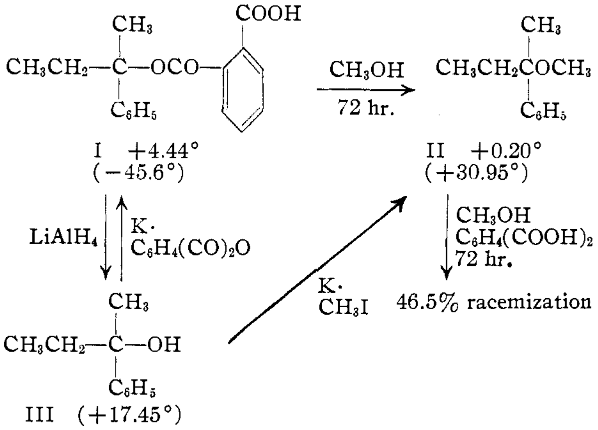
Replacement of the isobutyl group of hydrogen 2,4-dimethyl-4-hexyl phthalate, previously shown to undergo methanolysis with 54% inversion of configuration and 46% racemization, by the phenyl radical has led to a sharp increase in the extent of racemization in the methanolytic reaction. Resonance interaction of the phenyl group is considered to lower the activation energy required for frontside displacement of the phthalate fragment by solvent methanol.

Solvolysis of optically active hydrogen 2,4-dimethyl-4-hexyl phthalate in methanol gives rise to 4-methoxy-2,4-dimethylhexane with 54% inversion of configuration and 46% racemization.[2a] This result is interpreted in terms of a mechanistic hypothesis for the solvolysis reaction involving major participation of an asymmetric ntermediate in the formation of the methyl ether. This present paper is concerned with the methanolysis of optically active hydrogen 2-phenyl-2-butyl phthalate, in which a phenyl group replaces the isobutyl group attached to the tertiary carbon atom.

Hydrogen 2-phenyl-2-butyl phthalate (I) is almost quantitatively solvolyzed in anhydrous refluxing methanol within 72 hours. Comprehension of the stereochemical course of this reaction depends upon the establishment of the configurational relations of I and the methanolytic product, 2-methoxy-2-phenylbutane (II). The interconversion of (+)-I and (−)-2-phenylbutan-2-ol (III) without racemization or configurational change has been described earlier.[3] Similarly, (+)-II is prepared from (+)-III by the action of the potassium salt of the carbinol on methyl iodide. Neither reductive cleavage of the hydrogen phthalate with lithium aluminum hydride to carbinol nor the Williamson synthesis of the methyl ether from the carbinol are conversions conceivably involving alkyl–oxygen fission. Consequently, I and II of the same configuration have opposite signs of rotation. That alkyl–oxygen fission has occurred in the methanolysis of I is inherent in the formation of II. The possibility that acyl–oxygen cleavage has taken place with intermediate formation of III in the methanolysis is contraindicated by the absence of the characteristic O–H band in the infrared spectrum of the product, II.[4]



Optically active ester I, $[\alpha]^{24}\mathrm{D}$ +4.44°, in boiling methanol for 72 hours is converted to methyl ether II, $[\alpha]^{23}\mathrm{D}$ +0.20°. It is apparent that inversion of configuration has taken place in the formation of II with extensive loss (93.5%) of optical activity. That this loss of activity is not due exclusively to the mode of formation of II is found in the susceptibility of II to racemization under the conditions of the methanolysis. Optically active II, $[\alpha]^{22}\mathrm{D}$ −6.21°, after 72 hours of refluxing in methanol with phthalic acid, is recovered with 46.5% loss in optical rotation, $[\alpha]^{22}\mathrm{D}$ −3.32°. Correcting for this subsequent loss of activity in the methyl ether, the maximum amount of inversion occurring in the formation of II from I is 56%, accompanied by 44% retention of configuration, or 12% inversion and 88% racemization.[5]

The racemizing effect of aryl and alkenyl groups in hydrolysis and alcoholysis reactions of optically active secondary esters has been recognized by Kenyon, Balfe and co-workers,[6] the extent of which is dependent upon the substituents and the basicity of the reaction medium. For example, the hydrogen phthalate ester of phenylmethylcarbinol is hydrolyzed with retention of configuration in concentrated alkali and with slight racemization in dilute alkali; but it does not react with ethanol. However, the same ester of phenyl-*p*-anisylcarbinol is racemized in either concentrated or dilute alkaline solution and undergoes ethanolysis also with racemization. It is apparent that increased electron accession to the reacting center causes not only increased reactivity but also increased racemization. It is to be expected, then, that a tertiary ester should be even more sensitive to substituent effect, and that

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(1) Presented at the Chicago Meeting of the American Chemical Society, September, 1950; Abstracts of Papers, p. 50N.

(2) (a) W. von E. Doering and H. H. Zeiss (submitted for publication); (b) W. von E. Doering and A. Streitwieser, Jr., Abstracts of 119th Meeting, American Chemical Society, 1951, p. 45 M; *Ann. Reports*, **48**, 122 (1951).

(3) H. H. Zeiss, THIS JOURNAL, **73**, 2391 (1951).

(4) In reference (2) it is shown that reaction between 2,4-dimethylhexan-4-ol and methanol in the presence of phthalic acid to form 4-methoxy-2,4-dimethylhexane is very slow in comparison to the rate of formation of ether from the methanolysis of the hydrogen phthalate. Consequently, the presence of carbinol would be expected in the methyl ether had it been an intermediate.

(5) This correction is made using the inaccurate assumption that the maximum concentration of phthalic acid is obtained in zero time. The corrected value is necessarily an upper limit of extent of inversion.

(6) M. P. Balfe, H. W. J. Hills, J. Kenyon, H. Phillips and B. C. Platt, *J. Chem. Soc.*, 556 (1942); M. P. Balfe, M. A. Doughty, J. Kenyon and R. Poplett, *ibid.*, 605 (1942); M. P. Balfe, E. A. W. Downer, A. A. Evans, J. Kenyon, R. Poplett, C. E. Searle and A. L. Târnoky, *ibid.*, 797 (1946); M. P. Balfe, A. Evans, J. Kenyon and K. N. Nandi, *ibid.*, 803 (1946); M. P. Balfe, J. Kenyon and R. Wicks, *ibid.*, 807 (1946).

this is the case as shown by the sharp increase in racemization to 88% in the methanolysis of I as compared with the 46% observed with hydrogen 2,4-dimethyl-4-hexyl phthalate.

The racemizing effect of a phenyl group *vis-á-vis* an isobutyl group is considered to be in agreement with the mechanistic concept newly developed for solvolyses.[2] Increased internal stabilization of the forming reaction intermediate by phenyl group interaction would result in a decrease in the activation energy associated with frontside solvation, in an increase in the rearward solvating energy and in decreased asymmetry in the intermediate. While the stereochemical result obtained here does not distinguish uniquely between an interpretation of the solvolytic reaction in terms of activation energies and other concepts involving lifetimes of intermediate carbonium ions, the former hypothesis is preferred on the grounds of greater specificity.

Experimental[7]

Methanolysis of (+)-Hydrogen 2-Phenyl-2-butyl Phthalate (I).—A solution of 11 g. of hydrogen 2-phenyl-2-butyl phthalate, $[\alpha]^{24}\text{D}$ +4.44°, in 150 ml. of absolute methanol was refluxed for 72 hours. The methanolic solution was poured into 1.5 l. of water, followed by extraction with ether. After washing the ether solution thoroughly with dilute sodium carbonate solution and acidification of the combined alkaline washes, no unreacted acid ester was separated, indicating that reaction had reached completion. The ether solution of 2-methoxy-2-phenylbutane (II) was washed with water and dried over potassium carbonate. After removal of the solvent there remained 5.5 g. (92%) of II which was evaporatively distilled at room temperature and 1 mm.: $[\alpha]^{23}\text{D}$ +0.20° (α +0.19°), $n^{25}\text{D}$ 1.4981, d^{25}_4 0.940.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.61; H, 9.85.

Racemization of (−)-2-Methoxy-2-phenylbutane (III).—Methyl ether (2.8 g.), $\alpha^{22}\text{D}$ −5.84° (l = 1), in 60 ml. of absolute methanol containing 2.4 g. of phthalic acid, was refluxed for 72 hours, after which the methyl ether was recovered by the isolation procedure described above including final purification by evaporative distillation. A 46.5% loss in optical activity had occurred during the 72-hour period: $\alpha^{22}\text{D}$ −3.12° (l = 1).

2-Methoxy-2-phenylbutane (II).—2-Phenylbutan-2-ol (1.8 g.), $[\alpha]^{26}\text{D}$ +16.68°, was stirred vigorously with 0.5 g. of potassium sand in 100 ml. of hot benzene for four hours. To this solution was next added 2 g. of methyl iodide in 20 ml. of benzene. The slow precipitation of potassium iodide was allowed to proceed overnight. A blanket of nitrogen was maintained over the reaction mixture while water was added to destroy any unreacted potassium metal and to dissolve the inorganic salt. After separation of the aqueous layer the benzene solution was washed, dried and the solvent benzene removed by atmospheric distillation. The residual liquid was evaporatively distilled to give 1.1 g. (56%) of 2-methoxy-2-phenylbutane: $[\alpha]^{27}\text{D}$ +29.58°; $n^{26}\text{D}$ 1.4991; d^{25}_4 0.940; b.p. 201–202° (760 mm.). This methyl ether contained a trace of unreacted carbinol as reflected in a slightly higher refractive index than that of II obtained from the methanolysis and in the appearance of a weak O–H band in its infrared spectrum. Removal of carbinol by boiling the methyl ether over molten potassium resulted in some decomposition. However, the infrared spectra of II contaminated with carbinol or after treatment with potassium and of II resulting from methanolysis compared so closely as to warrant the conclusion that the extent of contamination was not large enough to be of appreciable significance in the calculation of configurational changes.

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(7) Optical rotations of methylethylphenylcarbinol and of its methyl ether II were measured without solvent. The rotation of its hydrogen phthalate I was determined in absolute ethanol.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND COMPANY]

Base-catalyzed Condensation Reactions of *p*-Hydroxybenzaldehyde and Higher Keto Acids

BY GEORGE M. PICHA

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The condensation products resulting from the base-catalyzed reactions of *p*-hydroxybenzaldehyde with some higher aliphatic (ω-1)-keto acids have been shown to be the isomers which result from reaction of the terminal methyl group, in accordance with a generally applicable principle governing such condensations. These products have also served as intermediates in the preparation of a series of amino ester hydrochlorides differing both in the length of the aliphatic chain and the nature of the nitrogen-containing group.

The investigation of the condensation reactions of unsymmetrical ketones has been one of the classical problems of organic chemistry. The nature of the reaction products resulting from the condensation of aromatic aldehydes with aliphatic keto acids has constituted one of the major aspects of this investigation.

Variant formulations given in the early literature[1] for the condensation products of benzaldehyde and levulinic acid, one of the first such reaction pairs to be studied, gave rise to confusion, dispute and occasionally polemics.

Of the various individuals studying this and similar reaction systems shortly before the turn of the century, Erdmann was the most successful in establishing the correct structures of these compounds. He demonstrated that condensation reactions effected by acidic and basic catalysts gave rise to different benzallevulinic acids, only one of which could be cyclodehydrated to 3-acetyl-1-naphthol. Several lines of evidence were adduced to prove that these were not *cis–trans* isomers, of which the most convincing was that the saturated keto acids produced by hydrogenation of the double bond were not identical.

Largely on the evidence of dehydration to a naph-

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(1) (a) E. Erlenmeyer, Jr., *Ber.*, **23**, 74 (1890); (b) H. Erdmann, *ibid.*, **18**, 3441 (1885); (c) H. Erdmann, *ibid.*, **21**, 635 (1888); (d) H. Erdmann, *Ann.*, **254**, 182 (1889); (e) H. Erdmann, *ibid.*, **258**, 129 (1890); (f) H. Erdmann, *Ber.*, **24**, 3201 (1891); (g) A. Ludwig and E. A. Kehrer, *ibid.*, **24**, 2776 (1891); (h) E. A. Kehrer, *ibid.*, **24**, 4104 (1891); (i) E. A. Kehrer and W. Kleberg, *ibid.*, **26**, 345 (1893). The conclusions of Erdmann were apparently based in large part on the laboratory work contained in the Inaugural Dissertation (Halle, 1891) of F. Henke. This paper is not available to the author, and seems never to have been published elsewhere as an independent article.