[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Glyoxylate Cyclizations. Methoxybenzsuberenes[1]

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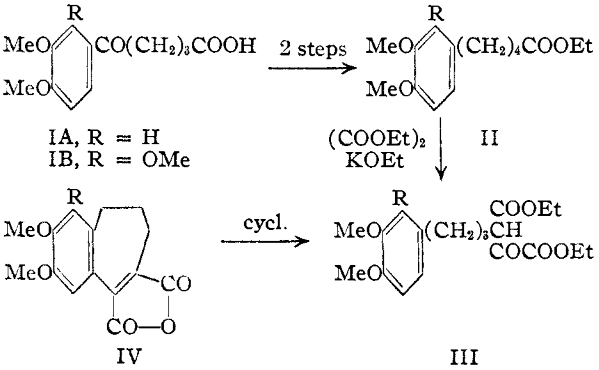
An investigation of the glyoxylate cyclization has shown that this method may be used for the preparation of benzsuberene dicarboxylic acid anhydrides; this route to ring systems is suitable for seven- as well as five- and six-membered rings.

The cyclization of an aryl-aliphatic glyoxylate ester to form a substituted indene, according to the general method of Bougault,[4] may be used for the preparation of dihydronaphthalenes as well as indenes. The extension of a cyclization method, suitable for rings of five or six members, to ring systems of more than six members often requires special conditions or modifications to discourage intermolecular reaction, but we have found that the glyoxylate cyclization may be utilized without major change for the preparation of a seven-membered ring system, leading to a benzsuberene dicarboxylic acid anhydride. This reaction provides a useful and direct route for the preparation of benzsuberenes, and has permitted identification of the ring system of Windaus' anhydride, a degradation product of colchicine.[5]

The esters required in this instance were obtained by using glutaric anhydride in a Friedel–Crafts reaction, followed by reduction of the carbonyl group (of the keto-acid or keto-ester) with a palladium–carbon catalyst at 60–70°, and subsequent condensation of the δ-arylvalerate with ethyl oxalate. The cyclization conditions require examination and trial for each specific compound, and in all cases in our experience a methoxyl group or groups provided activation at the site of ring closure. Too strong conditions generally resulted in sulfonation or loss of the keto-ester, but under the correct conditions the cyclization occurred in 50–70% yields, with subsequent ester-exchange or hydrolysis and dehydration to yield a cyclic anhydride as the product. The anhydrides, in the cases studied, are neutral, yellow, crystalline materials which are soluble in warm alkali. The alkaline solutions are colorless, and on acidification the solutions become turbid and deposit crystals of the original anhydride. The corresponding acids, in the indene series, do not form anhydrides. The corresponding dihydronaphthalenes yield anhydrides as a result of the cyclization reaction; the acids may be isolated by hydrolysis of the anhydrides, but on heating at moderate temperatures they are converted into the anhydrides, usually with a marked change in color.

The properties of the benzsuberenes reported here correspond with those of Windaus' anhydride,[5] which is now known to contain a seven-membered B-ring.

Acknowledgment.—We are indebted to Mrs. Sarah M. Woods for the analyses.



Experimental

All melting points are corrected.

Series A: R = H. **γ-(3,4-Dimethoxybenzoyl)-butyric Acid (IA).**—A modification of the succinic anhydride procedure was employed. To a chilled (0–5°), stirred mixture of 23.5 g. (0.17 mole) of veratrole, 20.0 g. (0.18 mole) of glutaric anhydride, 200 ml. of purified tetrachloroethane and 50 ml. of purified nitrobenzene, there was added slowly 48.0 g. (0.36 mole) of aluminum chloride. After standing three days at room temperature the usual isolation procedure was followed. The crude keto-acid was recrystallized from hot water to yield 13.5 g. (31%) of colorless needles, m.p. 138–140° (reported[6] m.p. 140–142°).

γ-(3,4-Dimethoxyphenyl)-valeric Acid.—A solution of 8.0 g. of IA in 150 ml. of acetic acid was hydrogenated at 60–70° with 3.0 g. of 5% palladium–carbon catalyst at 30–40 lb. pressure. The product was recrystallized from benzene to yield 6.0 g. (80%) of colorless acid, m.p. 75–77° (reported m.p.[6,7] 72°, 78°).

Ethyl δ-(3,4-Dimethoxybenzoyl)-butyrate.—A mixture of 13.5 g. of the keto-acid, 45 ml. of dry ethanol and 4.5 ml. of concd. sulfuric acid was refluxed for three hours. Most of the alcohol was distilled, and the residue was treated with water and ether. The ether solution was washed with 5% sodium bicarbonate solution and with water, and dried. The product was distilled under reduced pressure to provide a colorless oil, b.p. 179–180° (0.5 mm.), in 10.7 g. (71%) yield. The product solidified and was recrystallized from ether–ethyl acetate; m.p. 63°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.26; H, 7.19. Found: C, 64.17; H, 7.33.

Ethyl δ-(3,4-Dimethoxyphenyl)-valerate (A).—A solution of 10.0 g. of the keto-ester in 80 ml. of acetic acid was hydrogenated at 60–70° under 30 lb. pressure with 4.0 g. of 5% palladium-carbon catalyst. Removal of the catalyst and distillation of the solution under reduced pressure provided 8.8 g. (95%) of the colorless ester, b.p. 148–151° (0.5 mm.).

(B).—A mixture of 6.0 g. of the acid, 25 ml. of dry ethanol and 2.5 ml. of concd. sulfuric acid was refluxed for three hours. The ester was isolated as usual as a colorless oil, b.p. 143–144° (0.4 mm.), in 4.3 g. (66%) yield.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.34; H, 8.77.

Ethyl α-Keto-β-carbethoxy-ε-(3,4-dimethoxyphenyl)-caproate (IIIA).—Following the usual method, 3.8 g. (0.025 mole) of ethyl oxalate was condensed with 4.0 g. (0.017 mole) of IIA, using potassium ethoxide from 0.60 g. (0.17 mole) of potassium, in ether. The yield of viscous keto-diester was 2.3 g. (37%).

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[2] National Heart Institute, Bethesda, Md.

[3] American Cancer Society Postdoctoral Fellow 1948–1950.

[4] J. Bougault, *Compt. rend.*, **159**, 745 (1915).

[5] E. C. Horning, M. G. Horning, J. Koo, M. S. Fish, J. A. Parker, G. N. Walker, R. Horowitz and G. E. Ullyot, THIS JOURNAL, **72**, 4840 (1950).

[6] R. D. Haworth and J. R. Atkinson, *J. Chem. Soc.*, 797 (1938).

[7] D. Caunt, W. D. Crow, R. D. Haworth and C. A. Vodoz, *ibid.*, 1631 (1950).

2,3-Dimethoxybenzsuber-5-ene-5,6-dicarboxylic Anhydride (IVA).—A chilled solution of 2.3 g. of IIIA in 30 ml. of 85% phosphoric acid and 10 ml. of concd. sulfuric acid was kept at 0–5° for 24 hours, and then allowed to warm to room temperature over 2 hours. Isolation of the neutral product provided a crude yellow crystalline material which was recrystallized from ethyl acetate–pentane to give 1.1 g. (50%) of IVA; bright yellow, m.p. 164–165°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.14. Found: C, 65.34; H, 5.24.

This anhydride dissolved in warm sodium hydroxide solution to yield a colorless solution; acidification returned the yellow anhydride.

Series B: R = OMe. **1,2,3-Trimethoxybenzene.**—Pyrogallol trimethyl ether (m.p. 43–46°) was obtained in 97% yield by methylation of pyrogallol with dimethyl sulfate and potassium hydroxide solution, using simultaneous addition of both reagents.

γ-(2,3,4-Trimethoxybenzoyl)-butyric Acid (IB).—The general method was employed, using 34.0 g. (0.20 mole) of 1,2,3-trimethoxybenzene, 23.0 g. (0.20 mole) of glutaric anhydride and 60 g. of aluminum chloride in 200 ml. of tetrachloroethane and 60 ml. of nitrobenzene. The crude product was separated by ether treatment into two fractions (a) an ether-soluble fraction of 32 g. (57%) of IB, purified by precipitation from sodium bicarbonate solution, as a nearly colorless crystalline acid, m.p. 70–75° (reported[8] m.p. 73–75°), and (b) a crystalline ether-insoluble acid, m.p. 168–181°, 13 g. (24%) yield, which was probably identical with the hydroxydimethoxyvaleric acid fraction described by Haworth.[8] Methylation of fraction (b) with dimethyl sulfate and sodium hydroxide solution yielded an additional 10 g. of IB, m.p. 76–77°, after recrystallization from cyclohexane.

Ethyl γ-(2,3,4-Trimethoxybenzoyl)-butyrate.—A mixture of 18.0 g. (0.64 mole) of IB, 50 ml. of dry ethanol and 5 ml. of concd. sulfuric acid was refluxed for three hours. Isolation of the neutral product in the usual way yielded 12.0 g. (60%) of colorless ester, b.p. 166–167° (0.3 mm.).

Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.90; H, 7.15.

Ethyl δ-(2,3,4-Trimethoxyphenyl)-valerate (IIB).—A solution of 11.0 g. of the keto-ester in 60 ml. of acetic acid was hydrogenated at 60–70° with 4 g. of palladium–carbon catalyst at 35–40 lb. pressure. The product was isolated as a colorless oil in 5.5 g. (53%) yield by fractionation *in vacuo;* b.p. 148–152° (0.4 mm.).

Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.69; H, 8.10.

Ethyl α-Keto-β-carbethoxy-ε-(2,3,4-trimethoxyphenyl)-caproate (IIIB).—The condensation of 2.9 g. (0.02 mole) of ethyl oxalate and 5.3 g. (0.018 mole) of IIB was carried out with potassium ethoxide obtained from 0.70 g. (0.018 mole) of potassium, to yield 3.4 g. (48%) of IIIB.

1,2,3-Trimethoxybenzsuber-5-ene-5,6-dicarboxylic Anhydride (IVB).—A solution of 1.0 g. of IIIB in 9 ml. of 85% phosphoric acid and 3 ml. of concd. sulfuric acid was kept at 0–5° for 24 hours. An additional 12 ml. of concd. sulfuric acid was added, and the mixture was heated to 50°. The neutral product was then isolated; there resulted a crude yellow crystalline material which was recrystallized from ether–pentane to give 0.71 g. (70%) of IVB, m.p. 111–113°. An alkaline solution of the anhydride was colorless; acidification returned the yellow anhydride.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.34; H, 5.47.

PHILADELPHIA, PENNA.

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[8] R. D. Haworth, B. P. Moore and P. L. Pauson, *J. Chem. Soc.*, 1045 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

The Addition of Some Phenols to 1,1-Difluoroethylenes[1,2]

BY PAUL TARRANT AND HENRY C. BROWN

Phenol has been found to add across the double bond of $CF_2{=}CClF$, $CF_2{=}CCl_2$, $CF_2{=}CHCl$ and the cresols to $CF_2{=}CClF$. The resulting aryl chlorofluoroethyl ethers vary considerably in stability. The ether obtained from phenol and chlorotrifluoroethylene was hydrolyzed to chlorofluoroacetic acid, indicating that phenols add across the double bond of 1,1-difluoroölefins to give α,α-difluoroethers.

As part of a research program in this Laboratory dealing with the addition of organic molecules to fluoroölefins, a study has been made of the reaction of cresols and phenols to certain 1,1-difluoroethylenes.

Although there are several reports on the addition of alcohols to such olefins,[3,4] apparently the only reference to the addition of phenol[3] mentions its addition to tetrafluoroethylene under anhydrous conditions in an autoclave to give 1,1,2,2-tetrafluoro-1-phenoxyethane.

Aryl fluoroethers have been prepared in some number by the action of sodium phenolate on the saturated chlorofluoroethanes in what seems to be a Williamson type of reaction. For example, McBee and Bolt[5] prepared $C_6H_5OCF_2CHCl_2$ by the reaction of sodium phenolate with $CF_2ClCHCl_2$ and $C_6H_5OCF_2CH_2Cl$ by the reaction of sodium phenolate on CF_2ClCH_2Cl. In these reactions involving the saturated compound, it appears that the chlorine of the $-CF_2Cl$ had been displaced by the phenoxy group. This would be somewhat unusual, and McBee and Bolt make this statement concerning it: "General concepts of the chemistry of the organic chlorofluorides indicate that the chlorine atom on the carbon holding no fluorine atoms should be replaceable. However, this group apparently resists attack, and, in fact, seems to have an activating effect on the adjacent fluorinated grouping." Since the results of the present investigation indicates the reactivity of fluoroolefins toward phenol, it seems reasonable to assume that the replacement of the firmly held chlorine atom of the $-CF_2Cl$ group did not occur as a simple displacement reaction. In a basic solution a proton may be removed from the carbon atom adjacent to the $-CF_2Cl$ group, causing the elimination of chlorine to give hydrogen chloride and an olefin. McBee and Bolt found such un-

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[2] The material in this paper is abstracted in part from a dissertation submitted by Henry C. Brown to the Graduate Council of the University of Florida, August, 1950, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy.

[3] Hanford and Rigby, U. S. Patent 2,409,274 (1946).

[4] (a) Miller, Fager and Griswold, THIS JOURNAL, **70**, 431 (1948). (b) Park, Vail, Lea and Lacher, *ibid.*, **70**, 1550 (1948). (c) Barr, Rapp, Pruett, Bahner, Gibson and Lafferty, *ibid.*, **72**, 4480 (1950). (d) Park, Snow and Lacher, *ibid.*, **73** 861 (1951). (e) Tarrant and Brown, *ibid.*, **73**, 1781 (1951).

[5] McBee and Bolt, *Ind. Eng. Chem.*, **39**, 412 (1947).