Methoxyindan and Methoxytetralin Esters[1]

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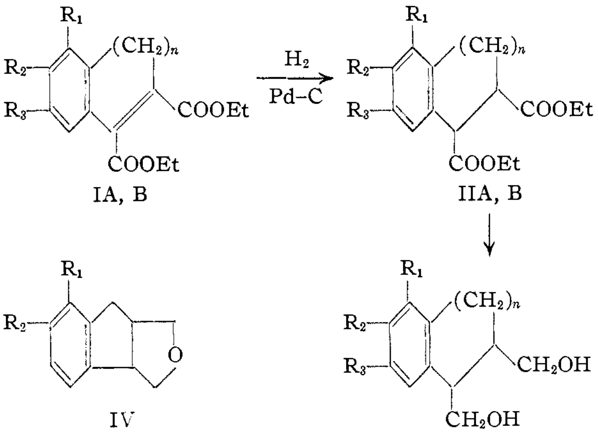
In the course of studying colchicine and its degradation products, several methoxyindene, methoxydihydronaphthalene and methoxybenzsuberene derivatives were prepared through the glyoxylate cyclization method. These compounds were bicyclic systems in which the B-ring was five, six or seven-membered, and the two acid groups were in the same relative position in each case. A route was sought for the introduction of a C-ring, using as a starting point 1,4-diols derived from these materials.

Compound IA and an acid–ester corresponding to IA were prepared as described earlier.[3] Compound IB was prepared by the polyphosphoric acid cyclization of the glyoxylate derived from ethyl γ-(3,4-dimethoxyphenyl)-butyrate. The sole product of the cyclization (in 92% yield) was the diester IB. This may be compared with the effect produced by the use of concentrated sulfuric acid in the cyclization; under such circumstances the product is the corresponding anhydride. This again demonstrates that polyphosphoric acid is capable of inducing glyoxylate cyclizations without transesterification or hydrolysis of the ester group.

The unsaturated esters IA and IB, as well as the acid–ester related to IA, were hydrogenated with ease (5% palladium–carbon catalyst). A related benzsuberan, 2,3,4-trimethoxybenzsuberan-5,6-dicarboxylic acid, was obtained by the catalytic reduction of a synthetic sample of 2,3,4-trimethoxybenzsuber-5-ene-5,6-dicarboxylic anhydride, followed by hydrolysis of the anhydride group. This seven-membered dicarboxylic acid may be converted to its anhydride by heating with acetic anhydride, but the acid is quite stable. This behavior may be contrasted with that of the corresponding seven-membered dicarboxylic acid containing a 5,6-double bond; this acid is unknown owing to its ready dehydration to form the corresponding anhydride.

With these materials as possible starting points, model experiments were carried out with IIA and IIB for the next step. Lithium aluminum hydride reduction in both cases gave the expected 1,4-diol, IIIA and IIIB. Compound IIIA was chosen for further model experiments directed to the lengthening of the carbon chains for C-ring formation. With phosphorus tribromide, a halogen-containing intermediate was formed, but attempts to use this product in alkylation reactions or in reaction with sodium cyanide gave in each case a neutral crystalline solid corresponding in properties and analysis to the tricyclic ether IV. While this was an interesting result, it was not in the desired direction, and this phase of the work was discontinued.

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



A: R_1, R_2 = OCH_3; R_3 = H; n = 1

B: R_2, R_3 = OCH_3; R_1 = H; n = 2

Experimental[4]

Diethyl 6,7-Dimethoxy-3,4-dihydronaphthalene-1,2-dicarboxylate.—A mixture of 2.0 g. of glyoxylate (prepared from the condensation of ethyl oxalate with ethyl γ-(3,4-dimethoxyphenyl)-butyrate in ether with sodium ethoxide, 81% yield) and 8 g. of polyphosphoric acid was stirred vigorously. When the warm solution cooled to room temperature (10 minutes), the mixture was treated with ice and water and the product was extracted with ethyl acetate. The chilled extract was washed in turn with 5% sodium hydroxide solution, water, 5% acetic acid solution and 5% sodium bicarbonate solution. Evaporation of the solvent, after drying, gave 1.7 g. (92%) of crude crystalline ester. Recrystallization from methanol gave pale yellow crystals, m.p. 103–105°.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.61; H, 6.61.

Hydrolysis of the diester with 15% sodium hydroxide solution (two hours at 95–100°), followed by dilution and acidification gave a yellow solution which on heating deposited red crystals of the anhydride, m.p. 192–193°, in agreement with the literature.

Catalytic Reductions.—Hydrogenation of IA[3] in ethyl acetate with a 5% palladium–carbon catalyst proceeded smoothly at room temperature under low pressure (30–40 lb.) to yield (quantitative) **1,2-dicarbethoxy-4,5-dimethoxyindan** as an oil. This ester was not characterized but was used immediately for further reaction. The reduction of an acid-ester corresponding to IA, prepared as described previously,[3] was carried out in the same way in acetic acid solution. The product in this case was 1-carboxy-2-carbethoxy-4,5-dimethoxyindan (based on the most probable structure for the acid-ester precursor) as a colorless solid, m.p. 149–151° (from methanol) (*Anal.* Calcd. for $C_{15}H_{18}O_6$: C, 61.21; H, 6.16. Found: C, 61.29; H, 6.09). The diester IB was hydrogenated in ethyl acetate solution in the same way as IA; the product was 1,2-dicarbethoxy-6,7-dimethoxytetralin, as a colorless solid, m.p. 73–74.5° (from ether) (*Anal.* Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.48; H, 6.87). A sample of synthetic 2,3,4-trimethoxybenzsuber-5-ene-5,6-dicarboxylic anhydride[5] was hydrogenated in ethyl acetate solution at 60°; the crude product was hydrolyzed with hot sodium hydroxide solution, and after acidification there was isolated **2,3,4-trimethoxy-5,6-dicarboxybenzsuberan** as a colorless solid, m.p. 188–189.5° (from aqueous methanol). (*Anal.* Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.10; H, 6.33.) From this acid by heating with acetic anhydride there was obtained the corresponding anhydride, **2,3,4-trimethoxybenzsuberan-5,6-dicarboxylic anhydride**, as a colorless solid, m.p. 176–178.5° (from ethyl acetate). (*Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.73; H, 5.92. Found: C, 63.00; H, 5.88.)

1,2-Di-(hydroxymethyl)-4,5-dimethoxyindan.—A solution of 47.2 g. of 1,2-dicarbethoxy-4,5-dimethoxyindan in

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[2] From the doctoral thesis of G. N. Walker submitted to the Graduate School of the University of Pennsylvania.

[3] E. C. Horning, J. Koo and G. N. Walker, THIS JOURNAL, **73**, 5826 (1951).

[4] All melting points are corrected.

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

400 ml. of dry ether was added dropwise to a stirred mixture of 15.0 g. of lithium aluminum hydride in 400 ml. of ether over one hour. After stirring for an additional half-hour, the mixture was chilled and treated with water and dilute sulfuric acid. The product was isolated in the usual way as a crude red oil. Trituration with ether with chilling gave 29.1 g. (84%) of nearly colorless crystalline product. Recrystallization from water provided a colorless analytical sample, m.p. 100–102°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.64; H, 7.56.

The same diol was obtained in 38% yield by the lithium aluminum hydride reduction of the monoethyl ester of 1,2-dicarboxy-4,5-dimethoxyindan. To determine whether a different stereochemical configuration would result when a chemical reduction was carried out with 1,2-dicarbethoxy-4,5-dimethoxyindan, the following experiment was performed. A 5.0-g. quantity of IA was reduced with zinc dust in 20 ml. of aqueous acetic acid (2:1 aq.) at 95–100°. The neutral product, 4.4 g. of oil, was reduced with lithium aluminum hydride (2.0 g.) in 250 ml. of ether. The product was identical with that obtained from IIA; a mixed melting point was not depressed.

1,2-Di-(hydroxymethyl)-6,7-dimethoxytetralin.—The reduction of 4.0 g. of 1,2-dicarbethoxy-6,7-dimethoxytetralin with 2.1 g. of lithium aluminum hydride in dry ether yielded 2.3 g. (77%) of colorless crystalline product (by trituration with ether). An analytical sample was secured by recrystallization from water; m.p. 127–128.5°.

Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.34; H, 7.82.

6,7-Dimethoxy-3,3a,8,8a-tetrahydroindeno(1,2-c)furan (*R.I. 1437*).—Treatment of 5.0 g. of 1,2-di-(hydroxymethyl)-4,5-dimethoxyindan with 20.5 g. of phosphorus tribromide in 75 ml. of dry benzene under reflux for 45 minutes gave a neutral oil (2.5 g.) as a product. This material gave an immediate precipitate with alcoholic silver nitrate solution. Numerous efforts were made to replace the halogen by reaction under standard conditions with sodium cyanide and with ethyl malonate. In each case the product was a colorless crystalline solid, m.p. 82–83.5° (from ether). This material was halogen-free; it did not react with bromine or potassium permanganate solutions, and was recovered unchanged after refluxing with 25% potassium hydroxide solution. From these properties and the analytical data, structure IV was assigned to this material.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.51; H, 7.28.

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Substitution in Polymethylbenzenes. III. A New Route to Isodurene Derivatives[1]

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In connection with kinetic studies now in progress on hindered nitrohydrocarbons, we have found that 4-nitroisodurene[2] can be obtained by reduction of 4,6-dinitroisodurene and subsequent deamination of the resulting 4-nitro-6-aminoisodurene by the method previously described[3] for the preparation of 3-nitrodurene.

4,6-Dinitroisodurene has been reported by a number of early workers,[4] but the melting point given by Jannasch and Weiler, 180–181°, is different from the values ranging from 156 to 165°, given by the other authors, and appears never to have been duplicated. We have nitrated isodurene in chloroform solution with nitric acid in sulfuric acid under essentially the same conditions as for the nuclear nitration of durene.[1] Our results are in good agreement with those of Jannasch and Weiler.

Since pure isodurene is not a readily available compound,[5] we have also tried to prepare 4,6-dinitroisodurene from other sources. Smith and Cass[6] have shown that the tetramethylbenzene fraction obtained from the distillation of the product of methylation of xylene is a mixture of durene and isodurene, from which most of the durene can be frozen out. Thermal analysis of the system durene–isodurene[5a] shows that at the eutectic point, −28.1°, the system contains only 8% of durene. Smith and Taylor[7] have already used isodurene-rich mixtures for the preparation of isodurene compounds, by mercuration of the mixture and purification of the acetoxymercuriisodurene thus obtained by differential crystallization. We have found that on nitration of a durene–isodurene mixture with a composition close to the one corresponding to the eutectic point, a crude 4,6-dinitroisodurene is obtained which can be purified by only three crystallizations from ethanol. The yield of the dinitro compound, m.p. 181.5–183.5°, was 43% based on the isomeric starting material. Since preliminary experiments with identical samples of isodurene-rich isomeric mixtures indicated that nitration was a more reliable route than mercuration for the preparation of certain isodurene derivatives, 4,6-dinitroisodurene, rather than 4-acetoxymercuriisodurene, was chosen as the starting material for the preparation of 4-nitroisodurene.

On reduction of 4,6-dinitroisodurene by sodium disulfide we have obtained pure 4-nitro-6-aminoisodurene in quantitative yields. The latter compound, m.p. 139.5–140.5°, proved to be different from the product obtained by Noelting and Stoecklin,[8] m.p. 87–88°, on nitration of isoduridine and described as nitroaminoisodurene. Noelting and Stoecklin reported results of analyses but gave no proof of structure for their product. Since nitration of polymethylbenzenes often led to side-chain substitution depending on experimental conditions[9] and nitration of arylamines may give arylnitramines,[10] the compound of Noelting and Stoecklin could be either a ω-nitroisoduridine or isodurylnitramine. On the other hand, the structure of the compound described in this paper as 4-nitro-6-aminoisodurene appears to be conclusively established both by the specific method of preparation used here and by its deamination to 4-nitroisodurene.

Crude, low-melting 4-nitroisodurene was effectively decolorized and purified with the least loss

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[1] Part II of this series: G. Illuminati and M. Palmucci Illuminati, THIS JOURNAL, **75**, 2159 (1953).

[2] L. I. Smith and F. L. Taylor, *ibid.*, **57**, 2460 (1935).

[3] G. Illuminati, *ibid.*, **74**, 4951 (1952).

[4] E. Ador and A. Rilliet, *Ber.*, **12**, 329 (1879); O. Jacobsen, *ibid.*, **15**, 1853 (1882); W. R. Orndorff and Young, *Am. Chem. J.*, **15**, 267 (1890); P. Jannasch and M. Weiler, *Ber.*, **27**, 3441 (1894).

[5] (a) L. I. Smith and F. H. MacDougall, THIS JOURNAL, **51**, 3001 (1929); (b) S. F. Birch, R. A. Dean, F. A. Fidler and R. A. Lowry, *ibid.*, **71**, 1362 (1949); (c) C. D. Shacklett and H. A. Smith, *ibid.*, **73**, 766 (1951); (d) D. A. McCaulay and A. P. Lien, *ibid.*, **74**, 6246 (1952).

[6] L. I. Smith and O. W. Cass, *ibid.*, **54**, 1609 (1932).

[7] L. I. Smith and F. L. Taylor, *ibid.*, **57**, 2370 (1935).

[8] E. Noelting and L. Stoecklin, *Ber.*, **24**, 564 (1891).

[9] R. Willstätter and H. Kubli, *ibid.*, **42**, 4151 (1909).

[10] See, for example, W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., London, 1948, p. 320.