with ice and water, and the product was extracted with ether–ethyl acetate (1:4). The organic layer was washed with water, with 5% sodium hydroxide solution and with 3% aqueous acetic acid, with 5% sodium bicarbonate solution and with water. A crude yield of 43.8 g. (90%) of colorless IIIB resulted after drying and removal of the solvents. Recrystallization from methanol gave colorless needles, m.p. 77–79°.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.83; H, 6.20.

Monoethyl Ester of 6,7-Dimethoxyindene-2,3-dicarboxylic Acid.—A solution of 34.7 g. of the keto ester IIB in 40 ml. of 85% phosphoric acid was chilled in Dry Ice, and treated with a chilled mixture of 45 ml. of sulfuric acid and 30 ml. of 85% phosphoric acid. After standing six days at room temperature the mixture was treated with ice and water, and an acidic product (17.2 g.) was isolated. Repeated recrystallizations yielded a yellow bicarbonate-soluble indenecarboxylic acid, m.p. 140–142° (dec.), which corresponded on analysis to an acid ester.

Anal. Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.80; H, 5.69.

Variations in conditions did not lead to IIIB, but more vigorous conditions gave increasing quantities of IVB.

6,7-Dimethoxyindene-2,3-dicarboxylic Acid (IVB). Hydrolysis Method.—To a warm (50°) solution of 3.0 g. of sodium hydroxide in 80 ml. of water there was added 3.0 g. of the acid ester. After standing at 50–60° for 4 minutes, the product was isolated by acidification and recrystallization from methanol. The yield was 1.9 g. (71%) of bright yellow acid IVB, m.p. 221–223° (dec.).

Anal. Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.36; H, 4.74.

Cyclization Method.—A mixture of 1.6 g. of the keto ester IIB in 4 ml. of concd. sulfuric acid and 6 ml. of 85% phosphoric acid was heated at 90–100° for 30 minutes, and then allowed to stand for three days at room temperature. A bright yellow ether-insoluble acid, m.p. 217–220° (dec.), was isolated; it was identical with the acid obtained by hydrolysis of the monoester.

4,5-Dimethoxyindene-2-carboxylic Acid (VB).—Hydrolysis of the acid ester in aqueous alcoholic sodium hydroxide solution, under reflux, gave the colorless acid VB, m.p. 230–231° after recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.50. Found: C, 65.61; H, 5.70.

Series C: 3,4,5-Trimethoxybenzoyl Chloride.—3,4,5-Trimethoxybenzoic acid was converted into the acid chloride with thionyl chloride in the usual way; the product was distilled *in vacuo* as a colorless oil, b.p. 193–197° (22–24 mm.), which solidified immediately; m.p. 79–82° (reported[9] b.p. 185° (18 mm.)).

3,4,5-Trimethoxyacetophenone.—A Grignard reagent was prepared from 80 g. of methyl iodide and 9.3 g. of magnesium in dry ether. A total of 60.0 g. of powdered anhydrous cadmium chloride was added slowly with good stirring. After one hour of refluxing, most of the ether was replaced by benzene, and a benzene solution containing 50.0 g. of 3,4,5-trimethoxybenzoyl chloride was added dropwise. The stirred mixture was refluxed for 1.5 hours and allowed to stand overnight. The crude product was distilled *in vacuo* to yield (a) 1.4 g., b.p. to 144° (1.4 mm.), and (b) 19.2 g., b.p. 145–151° (1.4 mm.). By trituration of (a) with pentane, an additional 0.8 g. of crystalline ketone was obtained. The total yield, 20.0 g. (44%), was a colorless crystalline material (m.p. 66–75°) which was not purified further, and which has been described previously (reported[10] m.p. 77–79°). The red **2,4-dinitrophenylhydrazone** was recrystallized from benzene, m.p. 245–245.5°.

Anal. Calcd. for $C_{17}H_{18}O_7N_4$: C, 52.30; H, 4.65. Found: C, 52.50; H, 4.86.

Ethyl β-(3,4,5-Trimethoxyphenyl)-butyrate.—A Reformatsky reaction was carried out in the usual way with 15.3 g. of 3,4,5-trimethoxyacetophenone, 21 g. of ethyl bromoacetate and 24 g. of 30-mesh zinc. The product was a viscous oil, b.p. 159–170° (1–1.2 mm.), which was hydrogenated in ethyl acetate solution with a 5% palladium–carbon catalyst. A yield of 10.7 g. (56%) of product was obtained at this point; it was a colorless oil which was not characterized, but was converted directly into the ethyl oxalate condensation product.

α-Keto-β-carbethoxy-γ-(3,4,5-trimethoxyphenyl)-valeric Acid.—A condensation was effected in the usual way between 2.0 g. of ethyl oxalate and 2.2 g. of ethyl β-(3,4,5-trimethoxyphenyl)-butyrate with sodium ethoxide from 0.30 g. of sodium. The reaction was rapid; after 20 minutes the product was isolated as a crystalline yellow bicarbonate-soluble material (1.0 g., 34%) which was recrystallized from methanol; m.p. 96.5–98°.

Analysis indicated that the product was an ester-acid rather than a diester. It gave a dark red enol test with ferric chloride solution. Variations in the conditions affected the yield, but did not give a diester. The product was assumed to be the corresponding substituted valeric acid. It was destroyed under cyclization conditions.

Anal. Calcd. for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.66; H, 6.05.

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

Glyoxylate Cyclizations. Methoxydihydronaphthalenes[1]

BY E. C. HORNING[2] AND JOHN KOO[3]

The 3,4-dihydronaphthalene-1,2-dicarboxylic anhydrides IVA and IVB have been prepared using the Bougault cyclization procedure. The anhydride IVB is a six-membered analog of the system present in Windaus' anhydride, a degradation product of colchicine.

The glyoxylate cyclization procedure of Bougault[4] may be applied to the synthesis of 3,4-dihydronaphthalene-1,2-dicarboxylic anhydrides. In order to obtain six-membered analogs of the anhydride system of Windaus' anhydride,[5] a degradation product of colchicine, the anhydrides IVA and IVB were prepared, using this general method. Compound IVA was described by Fieser and Hershberg[6]; this anhydride was obtained by cyclization of the glyoxylate ester IIIA with concentrated sulfuric acid. The deep-red anhydride yielded a yellow acid after hydrolysis; this acid was stable at room temperature but on heating to 80–90° or on attempted recrystallization it was converted to IVA.

For the preparation of IVB, it was necessary to secure β-(3,4,5-trimethoxybenzoyl)-propionic acid. This was obtained by alkylation of ethyl 3,4,5-

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(3) American Cancer Society Postdoctoral Fellow, 1948–1950.

(4) Bougault, *Compt. rend.*, **159**, 745 (1914).

(5) A. Windaus, *Ann.*, **439**, 59 (1924).

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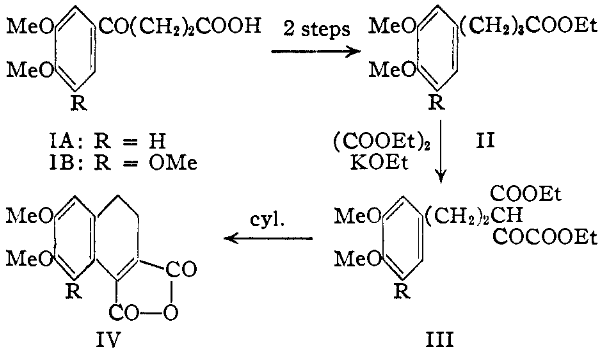

trimethoxybenzoylacetate with ethyl bromoacetate, followed by hydrolysis with diluted sulfuric acid. After esterification, the carbonyl group was reduced by hydrogenation with 5% palladium–carbon catalyst at 60–70° in acetic acid. This general reduction procedure[7] is particularly well suited for the reduction of polymethoxy acids or esters of this general nature, where the strongly acid or alkaline conditions of the Clemmensen or Wolff–Kishner reduction lead to demethylation or destruction of the compound. The keto-diester IIIB was obtained as usual by condensation of ethyl oxalate with the ester IIB. The cyclization to IVB was effected with concentrated sulfuric acid. A somewhat similar cyclization, employing 18% sulfuric acid, has been described,[8] but the product in this case was the corresponding diethyl ester, from which a half-ester but not the anhydride IVB could be obtained. From other experiments we have found that a methoxyl group in the 8-position is responsible for this effect; the group which resists hydrolysis is very likely the 1-carboxylic ester. In the present experiments, the concentrated sulfuric acid employed for cyclization also leads to hydrolysis or ester-exchange to yield IVB as the final product. The latter compound is a six-membered analog of Windaus' anhydride; when the B-ring is seven-membered, the corresponding acids or acid esters have not been isolated.

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Experimental

All melting points are corrected.

Series A: R = H. **β-(3,4-Dimethoxybenzoyl)-propionic acid** (IA) was prepared in the usual way, using 28.0 g. (0.20 mole) of veratrole, 25.0 g. (0.25 mole) of succinic anhydride, 200 ml. of tetrachloroethane, 75 ml. of nitrobenzene and 60 g. (0.45 mole) of aluminum chloride. The yield of recrystallized colorless product, m.p. 157–158° was 27.0 g. (62%).

γ-(3,4-Dimethoxyphenyl)-butyric Acid.—A solution of 10.0 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 catalyst was removed, and the solution was concentrated under reduced pressure to about 20 ml. volume, and cold water was added. The crystalline product, 9.0 g. (97%), m.p. 56–58° (reported[9] m.p. 57–59°), was used without further purification.

Ethyl γ-(3,4-dimethoxyphenyl)-butyrate (IIA) was obtained from the acid by esterification with ethanol–sulfuric acid as a colorless oil, b.p. 138–143° (0.3 mm.) in 73% yield.

Ethyl α-keto-β-carbethoxy-δ-(3,4-dimethoxyphenyl)-valerate (IIIA) was prepared by the condensation of IIA with ethyl oxalate, using potassium ethoxide, in 60% yield.

6,7-Dimethoxy-1,2-dihydronaphthalene-3,4-dicarboxylic Anhydride (IVA).—A solution of 5.5 g. (0.16 mole) of IIIA in 50 ml. of concd. sulfuric acid was kept at 25–30° for two hours. Isolation of the neutral product yielded 3.1 g. (68%) of red anhydride, m.p. 190.5–191.5° (reported[6] m.p. 192.5–193°) after recrystallization from benzene–hexane.

Hydrolysis of the anhydride in alcoholic potassium hydroxide solution yielded the yellow acid corresponding to IVA; the acid was stable at room temperature but was converted on heating at about 80–90° to the red anhydride. Attempted purification of the acid from various solvents generally resulted in a product containing a few crystals of the red anhydride.

Series B: R = OCH_3. **β-(3,4,5-Trimethoxybenzoyl)-propionic Acid.**—To a solution of 3.0 g. (0.13 mole) of sodium in 225 ml. of dry ethanol there was added 24.9 g. (0.088 mole) of ethyl 3,4,5-trimethoxybenzoylacetate, followed by the dropwise addition of 15 g. (0.09 mole) of ethyl bromoacetate at 10–15°. After standing for two days at room temperature, the mixture was diluted with water, and the product was extracted with ether. There was obtained 22.9 g. (71%) of crude, colorless oil which was not purified further, but which was hydrolyzed immediately.

A mixture of 22.9 g. of the crude ester and 250 ml. of 20% sulfuric acid was heated under reflux for 48 hours. The mixture was chilled, and the crude product was separated. Preliminary purification was effected by solution in alkali, extraction with ether of neutral material, and reprecipitation of the crystalline acid. The product, 12.5 g. (75%, or 53% over-all) was recrystallized from benzene–pentane to give colorless small crystals, m.p. 130.5–131.5° (reported[8] m.p. 122°).

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.00. Found: C, 57.95; H, 6.17.

Ethyl β-3,4,5-Trimethoxybenzoylpropionate.—A mixture of 11.0 g. (0.041 mole) of IB, 70 ml. of dry ethanol and 7 ml. of concd. sulfuric acid was heated under reflux for three hours. The neutral product was separated to yield 10.5 g. (78%) of crystalline material, m.p. 54.5–55.5° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{15}H_{20}O_6$: C, 60.81; H, 6.75. Found: C, 60.68; H, 6.70.

Ethyl γ-(3,4,5-Trimethoxyphenyl)-butyrate (IIB).—A solution of 9.5 g. (0.032 mole) of the keto-ester in 60 ml. of acetic acid was hydrogenated at 60–70° and 35–40 lb. pressure with 4.0 g. of 5% palladium–carbon catalyst. The catalyst was removed, and the mixture distilled to yield 8.9 g. (99%) of colorless oil, b.p. 165–170° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{22}O_5$: C, 63.47; H, 7.80. Found: C, 63.31; H, 7.73.

Ethyl α-Keto-β-carbethoxy-δ-(3,4,5-trimethoxybenzoyl)-valerate (IIIB).—To an ether (20 ml.) suspension of potassium ethoxide from 0.83 g. (0.021 mole) of potassium there was added 5.0 g. (0.033 mole) of ethyl oxalate and 6.0 g. (0.021 mole) of IIB in 20 ml. of ether. The mixture was heated under reflux for three hours, and then allowed to stand for 12 hours. The enolic fraction was isolated as usual to yield 4.5 g. (56%) of bright yellow oil which was used immediately for cyclization.

3,4-Dihydro-6,7,8-trimethoxynaphthalene-1,2-dicarboxylic Anhydride.—A solution of 0.9 g. (0.0023 mole) of the ester IIIB in 8.0 ml. of concd. sulfuric acid was maintained at 30–35° for 30 minutes. The dark solution was diluted with ice-water, and the neutral product isolated by extraction with ether and the usual washes. The crude product was recrystallized from ether–pentane (Dry Ice) to yield 0.5 g. (75%) of small dark yellow crystals, m.p. 120–121°.

Anal. Calcd. for $C_{15}H_{14}O_6$: C, 62.07; H, 4.83. Found: C, 62.10; H, 4.80.

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