TABLE I

REDUCTION OF CHOLESTANONE BY LITHIUM ALUMINUM HYDRIDE AND ALUMINUM ALKOXIDES

Reducing agent	Temp., °C.	Time, hours	Yield, of α-cholestanol,[f] %	Total yield, %[g]
$LiAlH_4$	36[c]	8	12	80
$LiAlH_4$	36[c]	2	12	82
Aluminum-isopropoxide[a]	84[c]	7	28	93
	100[d]	7	27	92
	25[e]	7	22	56
Aluminum salt of diethylcarbinol[b]	115[c]	7	35	86
Aluminum salt of diisopropylcarbinol[b]	140[c]	7	22	93
	100[e]	7	45	95
	40[e]	7	23	68
Aluminum salt of di-*t*-butylcarbinol[b,h]	120[e]	7	55	90

[a] Distilled aluminum isopropoxide used. [b] Alkoxide solution prepared by dissolving aluminum with mercuric chloride and oxide in the carbinol. [c] Reflux temperature of solvent. [d] Carried out in a sealed tube. [e] Distillation carried out under reduced pressure in oil-bath at given temperature. [f] Yield based on amount of stanols isolated. [g] Based on cholestanone. [h] Di-*t*-butylcarbinol prepared in low yield using method in A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., 1943, p. 179, for preparation of di-*n*-butylcarbinol.

hydride) or for the other alkoxides by dissolving 400 mg. (14.8 millimoles) of aluminum, 50 mg. of mercuric chloride and 10 mg. of mercuric oxide in 50 ml. of the proper alcohol (dried over calcium hydride) and refluxing the mixture four hours after the reaction began, as evidenced by darkening of the solution. These alkoxide solutions were used directly without further purification. To the alkoxide solution was added 250 mg. (0.65 millimole) of cholestanone and the mixture was heated in an oil-bath three hours at the desired temperature. Then the reaction mixture was slowly distilled at the same temperature over a period of four hours, under reduced pressure where necessary. A negative ketone test on the distillate with 2,4-dinitrophenylhydrazine reagent[16] was obtained after about two hours in most cases. At the end of the distillation period any remaining alcohol was removed by rapid distillation, the residue taken up in 50 ml. of benzene and decomposed with 50 ml. of 6 *N* sulfuric acid. The organic layer was washed with three 50-ml. portions of water, dried over anhydrous sodium sulfate, and chromatographed on 10 g. of aluminum oxide as above. The results are reported in Table I.

Epimerization of β-Cholestanol.—Aluminum alkoxide solutions of isopropyl alcohol and diisopropylcarbinol were prepared as above and 500 mg. of β-cholestanol added with 0.1 ml. of cyclohexanone. The mixture was heated on the steam-bath for one hundred hours and worked up as above. The mixture yielded 16% α- and 84% β-cholestanol in both cases.

(16) R. Adams, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 200. For alcohols which are not completely soluble in water the modification applied to reactions run in toluene was used. See note p. 204.

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Glyoxylate Cyclizations. Methoxyindenes[1]

BY E. C. HORNING,[2] JOHN KOO[3] AND G. N. WALKER[4]

Applications of the Bougault cyclization in the preparation of methoxyindenes have been investigated. A new method of cyclization is described; the use of polyphosphoric acid as a cyclization agent leads to high yields of the indene ester, and the side reactions of sulfonation and ester-exchange are avoided. The indene esters are characterized by easy decarboxylation of the 3-carboxylic acid group during alkaline hydrolysis.

A method for preparing indenes involving the cyclization of a glyoxylate ester (derived from ethyl hydrocinnamate and ethyl oxalate) with sulfuric acid was first described by Bougault, and this general method was later extended by others to the synthesis of dihydronaphthalenes. In connection with studies on the structure of colchicine and its degradation products, particularly Windaus' anhydride,[5] we have used this approach for the synthesis of indenes, dihydronaphthalenes, and, in a new application, benzsuberenes. This paper describes the preparation of certain indenes.

The required ketoesters, IIA and IIB, were prepared by the condensation of ethyl oxalate with the corresponding hydrocinnamic esters IA and IB, using potassium or sodium ethoxides. The keto-ester IIA was cyclized with sulfuric–phosphoric acids to yield the indene IIIA; this compound was a colorless diester which was converted on alkaline hydrolysis to the indene monocarboxylic acid VA. The acid IVA, corresponding to IIIA, would not be expected to undergo easy decarboxylation, but this result may be expected if the unsaturation in the five-membered ring of IIIA or IVA shifts, under the influence of alkali, to that indicated for V. A similar result was described by Bougault[6] for diethyl indene-2,3-dicarboxylate. The fact that the 3-carboxylic acid group was lost rather than the 2-group was demonstrated here by the independent synthesis of VA from the formyl derivative VIA by sulfuric–phosphoric acid cyclization, followed by hydrolysis. This result does not establish the validity of the bond shift, since VA is symmetrical; it does confirm the identity of VA.

When the ester IIB was subjected to Bougault conditions, the diester IIIB could not be obtained. Ester exchange or hydrolysis paralleled or followed cyclization, and the best conditions found gave an acid-ester. In searching for alternate methods of cyclization, polyphosphoric acid[7] was employed. With this reagent, the ester IIIB was obtained in 90% yield from IIB, indicating that polyphosphoric

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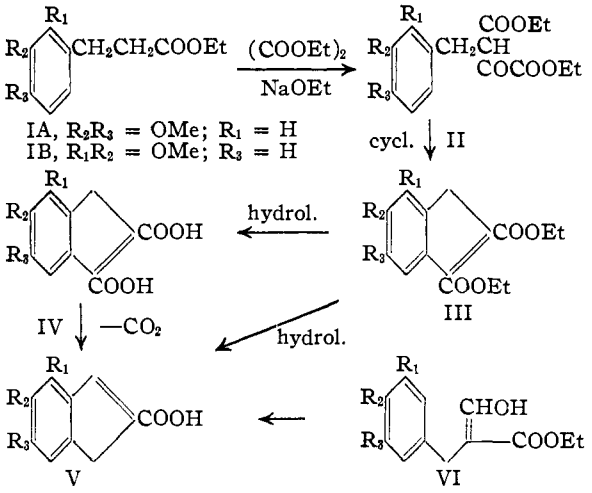
(5) A. Windaus, *Ann.*, **439**, 59 (1924).

(6) J. Bougault, *Compt. rend.*, **159**, 745 (1914).

(7) H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2962, 2965 (1950).



acid was functioning exclusively as a cyclizing agent, and not as a hydrolytic or ester-exchange agent as well. This reagent may be the agent of choice for Bougault cyclizations in general, particularly where sulfuric acid leads to ester-exchange or extensive sulfonation.

The acid VB, obtained by alkaline hydrolysis, is believed to have the structure indicated; the position of the carboxylic acid group is chosen by analogy with VA and assumes a bond shift.

The properties of these indene derivatives do not resemble the properties of Windaus' anhydride. The easy decarboxylation of the carboxylic acid group adjacent to the A-ring in indenes has no counterpart in similar compounds with six or seven-membered B-rings.

An attempt was made to prepare diethyl 1-methyl-4,5,6-trimethoxyindene-2,3-dicarboxylate according to the method described in the experimental section. The glyoxylate condensation resulted in this case in a bicarbonate-soluble material which corresponded on analysis to a ketoacid-ester rather than a ketodiester, and which was destroyed under cyclization conditions.

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

Experimental

All melting points are corrected.

Series A: R_2, R_3 = OMe; R_1 = H. **3,4-Dimethoxycinnamic acid** was prepared through the condensation of veratraldehyde with malonic acid (2 equiv.) in pyridine with catalytic amounts of piperidine. The colorless product (m.p. 180°, 86% yield) was satisfactory for esterification or hydrogenation without recrystallization.

β-(3,4-Dimethoxyphenyl)-propionic acid was prepared by hydrogenation of the cinnamic acid in acetic acid at 60–70° with a 5% palladium–carbon catalyst at 20–40 lb. pressure. Quantitative yields were obtained through removal of the solvent by distillation, and the residual crystalline hydrocinnamic acid was esterified without further purification.

Ethyl β-(3,4-Dimethoxyphenyl)-propionate (IA).—A mixture of 32.0 g. of the acid, 100 ml. of dry ethanol and 10 ml. of concd. sulfuric acid was boiled for three hours. Most of the alcohol was removed by distillation; the residue was treated with water and ether. The ether solution was washed with sodium bicarbonate solution and with water, and dried; the product was isolated by distillation as a colorless oil, b.p. 124° (0.4 mm.) in 27.5 g. (73%) yield.

Ethyl α-Keto-β-carbethoxy-γ-(3,4-dimethoxyphenyl)-butyrate (IIA).—The method of Hershberg and Fieser[8] was employed. A mixture of alcohol-free potassium ethoxide from 1.6 g. (0.04 mole) of potassium, 9.0 g. (0.06 mole) of ethyl oxalate and 10.0 g. (0.04 mole) of ethyl β-(3,4-dimethoxyphenyl)-propionate in dry ether (50 ml.) was stirred under reflux for one hour. Iced water was added and the aqueous layer was separated, acidified, and extracted with ether. After drying and evaporation of the ether there remained 8.5 g. (60%) of the keto-ester as a viscous yellow oil, which was used immediately for cyclization.

Diethyl 5,6-Dimethoxyindene-2,3-dicarboxylate (IIIa).—The keto-ester IIA (3.4 g., 0.01 mole) was added slowly to a mixture of 15 ml. of concd. sulfuric acid and 15 ml. of 85% phosphoric acid at 0–5°. After standing at room temperature for three hours the mixture was poured on chopped ice. The product separated slowly in crystalline form; it was removed, dried and recrystallized from benzene–hexane. The yield of colorless diester, m.p. 159–160°, was 1.8 g. (55%). This was the only product obtained under varying cyclization conditions with sulfuric–phosphoric acids.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.44; H, 6.28.

5,6-Dimethoxyindene-2-carboxylic Acid (VA).—The diester IIIA was saponified in aqueous alcoholic potassium hydroxide solution (25%; three hour reflux period). The crude acidic product was recrystallized from aqueous methanol to yield the pale yellow monocarboxylic acid VA, m.p. 242–244°.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.50. Found: C, 65.37; H, 5.40.

Ethyl α-Formyl-β-(3,4-dimethoxyphenyl)-propionate (VIA).—A mixture of alcohol-free potassium ethoxide from 1.0 g. (0.025 mole) of potassium, 2.75 g. (0.037 mole) of ethyl formate, and 6.0 g. (0.025 mole) of ethyl β-(3,4-dimethoxyphenyl)-propionate in 40 ml. of dry ether was stirred at −15° for four hours, and then allowed to stand for two days at room temperature. The mixture was treated with ice water, and the product isolated as usual. A yield of 3.1 g. (45%) of viscous oil was obtained; this formyl compound was used immediately for cyclization.

Ethyl 5,6-Dimethoxyindene-2-carboxylate.—A solution of 2.7 g. of the formyl ester VIA in 10 ml. of concd. sulfuric acid and 30 ml. of 85% phosphoric acid was maintained at 0–10° for 1.5 hours. The mixture was treated with ice and water, and the product was separated, washed, and dried. The yield of colorless ester was 1.9 g. (77%), m.p. 103.5–104.5 after recrystallization from ether–pentane.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.54; H, 6.43.

This ester was hydrolyzed in aqueous alcoholic potassium hydroxide solution to yield an acid, m.p. 242–243° after recrystallization from aqueous methanol. A mixed m.p. with VA obtained from IIIA showed no depression.

Series B: R_1, R_2 = OMe; R_3 = H. **2,3-Dimethoxycinnamic acid** was prepared from 2,3-dimethoxybenzaldehyde and malonic acid in the usual way in 85–95% yield. The crude product, m.p. 174–178°, was used without further purification.

Ethyl 2,3-Dimethoxycinnamate.—A mixture of 50.0 g. of the acid and 180 ml. of dry methanol was saturated with hydrogen chloride, and the solution was refluxed for two hours. Isolation of the product gave 36.9 g. (65%) of the ester as a colorless oil, b.p. 146–147° (0.8 mm.).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.94; H, 6.91.

Ethyl β-(2,3-Dimethoxyphenyl)-propionate (IB).—Hydrogenation of the cinnamic ester was effected in ethyl acetate solution with a 5% palladium–carbon catalyst in 97% yield; the product was a colorless oil and was used without purification.

Ethyl α-Keto-β-carbethoxy-γ-(2,3-dimethoxyphenyl)-butyrate (IIB).—A mixture of 102 g. of the ester IB, 82 g. of ethyl oxalate and alcohol-free sodium ethoxide from 21.0 g. of sodium, in 400 ml. of dry ether, was allowed to stand at room temperature for 22 hours. The keto-ester was isolated as usual; there was obtained 131 g. (91%) of viscous orange oil which was used immediately for cyclization.

Diethyl 6,7-Dimethoxyindene-2,3-dicarboxylate (IIIB).—A mixture of 51.3 g. of IIB and 145 g. of polyphosphoric acid was stirred vigorously; an exothermic reaction occurred (the temperature rose to 87°), and a deep red color developed. After 25 minutes, the mixture was treated

(8) E. B. Hershberg and L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 194.

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.

(9) W. H. Perkin and C. Weizmann, *J. Chem. Soc.*, **89**, 1655 (1906).
(10) V. J. Harding, *ibid.*, **105**, 2796 (1914).

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Glyoxylate Cyclizations. Methoxydihydronaphthalenes[1]

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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-

(1) Supported in part by a grant-in-aid from the American Cancer Society recommended by the Committee on Growth of the National Research Council.
(2) National Heart Institute, Bethesda, Md.
(3) American Cancer Society Postdoctoral Fellow, 1948–1950.
(4) Bougault, *Compt. rend.*, **159**, 745 (1914).
(5) A. Windaus, *Ann.*, **439**, 59 (1924).
(6) L. F. Fieser and E. B. Hershberg, THIS JOURNAL, **58**, 2314 (1936).