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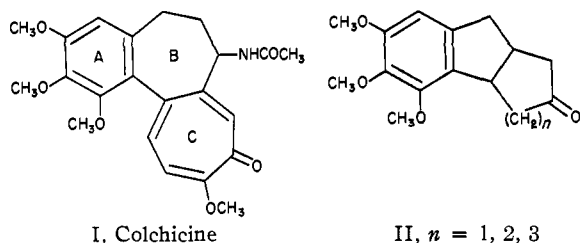
## The Synthesis of 4,5,6-Trimethoxyindene- and 4,5,6-Trimethoxyindanecarboxylic Acids and Esters<sup>1</sup>

BY JOHN KOO<sup>2</sup>

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A series of 4,5,6-trimethoxyindene- and -indanecarboxylic acid and esters has been synthesized. The structure of 4,5,6-trimethoxyindene-2-carboxylic acid has been proved by independent synthesis.

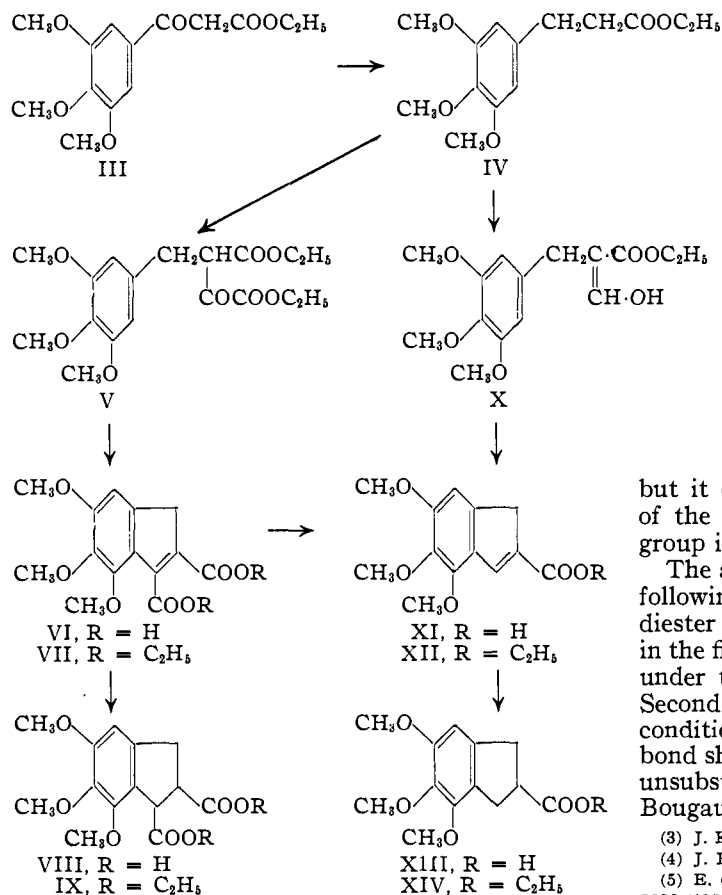
In connection with the study of analogs of colchicine (I) and related compounds, the synthesis of compounds with the general structure of II appeared desirable. In these compounds the benzo-



I, Colchicine

II,  $n = 1, 2, 3$ 

suberan A/B ring system of colchicine would be replaced by the indane structure, which, in turn, would be attached to a five-, six- or seven-membered ring.



VI, R = H  
VII, R = C<sub>2</sub>H<sub>5</sub>

(1) Some early experiments in this paper were carried out at the John Harrison Laboratory of the University of Pennsylvania.

(2) Special Research Fellow of the National Cancer Institute, National Institutes of Health.

The first objective of this project was to prepare intermediates containing the trimethoxyindane ring system with one or two reactive groups on which C-rings of various sizes could be constructed. The development of a general synthetic route for appropriate indenenes or indanes might be applicable for the synthesis of benzosuberones or benzosuberans, possibly leading to the ring structure of colchicine itself. The present report covers the synthesis of some 4,5,6-trimethoxyindene- and -indanecarboxylic acids and esters.

The starting material, ethyl  $\beta$ -(3,4,5-trimethoxyphenyl)-propionate (IV), was obtained in 90% yield by hydrogenation of ethyl 3,4,5-trimethoxybenzoylacetate<sup>3</sup> (III). Condensation of IV by a modification of the Bougault reaction<sup>4</sup> using ethyl oxalate in the presence of potassium ethoxide, yielded the keto diester (V) as a viscous oil in 73% yield. This was then cyclized to the indene diester (VII) by two different agents, a sulfuric acid and 85% phosphoric acid mixture giving a 77% yield of product, and polyphosphoric acid giving 92% yield in a much smoother and more convenient manner. Hydrogenation of VII with 5% palladium-on-carbon catalyst readily produced the indane diester (IX) in 94% yield, from which the corresponding indane diacid (VIII) was obtained by alkaline hydrolysis.

Direct alkaline hydrolysis of VII yielded the indene monoacid (XI) instead of the desired indene diacid (VI), a result not surprising in view of previous work.<sup>4,5</sup> This result was not encountered in the six-membered<sup>6</sup> and seven-membered<sup>7</sup> analogs, but it could be explained on the basis of a shift of the double bond<sup>8</sup> leaving the 3-carboxylic acid group in an unstable allylic position, as shown.

The above explanation receives support from the following facts. First, as already noted, the indane diester (IX), which does not possess a double bond in the five-membered ring, yielded the diacid (VIII) under the same conditions of alkaline hydrolysis. Second, by acid hydrolysis, which, unlike alkaline conditions, is known not to be favorable to double bond shifts in three-carbon tautomeric systems, the unsubstituted indene diacid was obtained by Bougault<sup>4</sup> from the corresponding diester.

(3) J. Koo, *THIS JOURNAL*, **75**, 720 (1953).

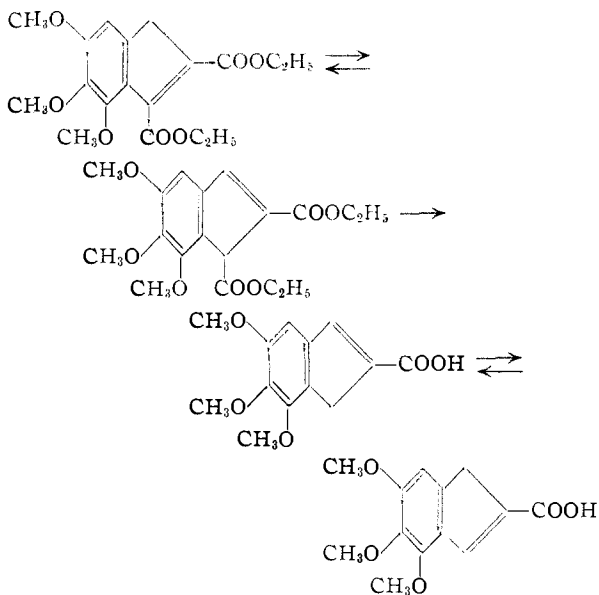
(4) J. Bougault, *Compt. rend.*, **159**, 745 (1914).

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

(6) E. C. Horning and J. Koo, *ibid.*, **73**, 5828 (1951).

(7) J. Koo and J. L. Hartwell, *ibid.*, **75**, 1625 (1953).

(8) Cf. J. W. Baker, "Tautomerism," George Routledge and Sons, Ltd., London, 1934, pp. 95-97.



The acid (XI) was then hydrogenated smoothly to the corresponding indane acid (XIII). Attempts to obtain the indene diacid (VI) directly from VII by hydrolysis with a mixture of acetic acid and hydrochloric acid resulted in decomposition; only a trace of material could be isolated. This was apparently caused by the interference of methoxyl groups, a condition not present in Bougault's work.<sup>4</sup>

In an alternative path, the ester (IV) was condensed with ethyl formate and potassium ethoxide to yield the formyl derivative (X). This derivative was cyclized by means of sulfuric acid and polyphosphoric acid to give the indene ester (XII) in 68 and 91% yields, respectively. Saponification of this ester with potassium hydroxide yielded the corresponding acid, with properties identical with the monoacid (XI) obtained by alkaline hydrolysis of the indene diester (VII). Moreover, hydrogenation of XII to XIV followed by hydrolysis also gave an acid identical with XIII. These two independent synthetic routes firmly established the structure of the indene monocarboxylic acid (XI).

### Experimental<sup>9</sup>

**Ethyl  $\beta$ -(3,4,5-Trimethoxyphenyl)-propionate (IV).**—A mixture of 10 g. of ethyl 3,4,5-trimethoxybenzoylacetate,<sup>3</sup> 60 ml. of acetic acid and 3 g. of 5% palladium-carbon catalyst was shaken under hydrogen at 40 lb. pressure. The hydrogenation proceeded readily at room temperature, and 1.2 moles of hydrogen was absorbed in the first hour before the reaction slowed down. The temperature was then raised to 60°, and another 0.83 mole of hydrogen was taken up in 3 hours. Removal of catalyst and solvent by filtration and distillation yielded a colorless oil weighing 8.6 g. (90%), b.p. 142–145° (0.3 mm.).

*Anal.* Calcd. for  $C_{14}H_{20}O_5$ : C, 62.66; H, 7.42. Found: C, 62.87; H, 7.80.

Alkaline hydrolysis of the ester and recrystallization of the residue from 50% ethanol yielded  $\beta$ -(3,4,5-trimethoxyphenyl)-propionic acid as fine colorless crystals, m.p. 102–103° (reported, 98°<sup>10</sup> and 100–102°<sup>11</sup>).

(9) All melting points are corrected. Infrared measurements were made with a Perkin-Elmer model 21 spectrometer in chloroform solution, unless otherwise stated.

(10) K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

(11) J. W. Cook, W. Graham, A. Cohen, R. W. Lapsley and C. A. Lawrence, *J. Chem. Soc.*, 322 (1944).

**Ethyl  $\alpha$ -(Ethoxalyl)- $\beta$ -(3,4,5-trimethoxyphenyl)-propionate (V).**—Potassium (1.2 g.) was dissolved portionwise in 15 ml. of absolute ethanol and the excess ethanol was removed by heating *in vacuo*. After cooling, 6.6 g. of ethyl oxalate in 30 ml. of dry ether was added with shaking, causing the mixture to turn yellow with evolution of gas. Immediately, a solution of 8.5 g. of ethyl  $\beta$ -(3,4,5-trimethoxyphenyl)-propionate in 30 ml. of dry ether was added. The flask was shaken 1 to 2 minutes, gently refluxed 3 hours and allowed to stand at room temperature for 10 hours. Cold water was added to the flask to dissolve the resulting reddish-brown semi-solid. The water layer was separated from the ether and acidified, and the resulting oil extracted with ether. The combined ether extracts were washed with water, then dilute sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation of the ether left the product as a light yellowish oil weighing 8 g. (73%). It was not further purified because of its instability.

**Diethyl 4,5,6-Trimethoxyindene-2,3-dicarboxylate (VII).**—This compound was obtained by cyclization of the above ethoxalyl derivative with two different agents. (a) **Cyclization with Sulfuric Acid.**—A 3-g. sample of the oil was dissolved in 5 ml. of 85% phosphoric acid, and 15 ml. of concd. sulfuric acid was added with stirring at 0°. The mixture was allowed to stand at 10–15° for an hour and then poured into ice-water. The product separated immediately as a colorless solid, weighing 2.2 g. (77%).

(b) **Cyclization with Polyphosphoric Acid.**—An 8-g. sample of the oil was mixed with 30 g. of polyphosphoric acid at 0–5°. The viscous mixture turned reddish-brown in 3 minutes and after 10 minutes it was poured into ice-water to give a colorless precipitate weighing 7 g. (92%). The products obtained from both cyclizations could be recrystallized from benzene-petroleum ether or dilute ethanol to yield fine colorless crystals, m.p. 120–121°.

*Anal.* Calcd. for  $C_{18}H_{22}O_7$ : C, 61.70; H, 6.33. Found: C, 61.76; H, 6.17.

**Infrared Spectrum.**—Conjugated ester band was shown at 5.87  $\mu$ .

**Diethyl 4,5,6-Trimethoxyindane-2,3-dicarboxylate (IX).**—Diethyl 4,5,6-trimethoxyindene-2,3-dicarboxylate (1 g.) in 15 ml. of acetic acid with 0.5 g. of 5% palladium-carbon catalyst was hydrogenated at 60° under slightly above atmospheric pressure. The absorption of hydrogen ceased in 6 hours and 1.01 mole of hydrogen was taken up. Filtration of the catalyst and evaporation of the solvent left a viscous oil weighing 0.94 g. (94%). It was crystallized from ether-pentane as colorless fine crystals, m.p. 39–40°.

*Anal.* Calcd. for  $C_{18}H_{24}O_7$ : C, 61.35; H, 6.87. Found: C, 61.15; H, 6.56.

**Infrared Spectrum.**—Ester band was shown at 5.78  $\mu$ .

**4,5,6-Trimethoxyindane-2,3-dicarboxylic Acid (VIII).**—The diester (IX) (0.5 g.) was refluxed with 10 ml. of 15% alcoholic potassium hydroxide for 5 hours. The alkaline solution was diluted and acidified. After a few minutes the solution became turbid and then gradually a colorless crystalline precipitate separated weighing 0.32 g. (78%). Recrystallization from 70% ethanol gave fine crystals, m.p. 225–226°.

*Anal.* Calcd. for  $C_{14}H_{16}O_7$ : C, 56.75; H, 5.40. Found: C, 56.77; H, 5.40.

**Infrared Spectrum.**—Acid band was shown at 5.87  $\mu$  (nujol mull).

**4,5,6-Trimethoxyindene-2-carboxylic Acid (XI).**—A mixture of 1.5 g. of indene diester (VII) in 5 ml. of ethanol and 15 ml. of 20% potassium hydroxide was refluxed for three hours. The resulting dark solution was shaken with ether and acidified. The dark semi-solid which separated was dissolved in sodium carbonate solution, warmed a while with Norit, filtered and again acidified. The precipitate obtained was recrystallized from 50% ethanol to give colorless fine needles weighing 0.7 g. (66%), m.p. 169–170°. The analysis indicated that the product was an indene monoacid. The position of the carboxylic acid group, presumed to be at carbon atom 2, was confirmed later by direct synthesis of this compound.

*Anal.* Calcd. for  $C_{13}H_{14}O_5$ : C, 62.40; H, 5.60. Found: C, 62.48; H, 5.77.

**Infrared Spectrum.**—Conjugated acid band was shown at 5.94  $\mu$ .

**4,5,6-Trimethoxyindane-2-carboxylic Acid (XIII).**—Hydrogenation of the indene monoacid (XI) in acetic acid using a 5% palladium-on-charcoal catalyst proceeded readily at 50° and 40 lb. pressure and ceased after two hours with the absorption of 1.01 moles of hydrogen. After filtering, the solvent was distilled, and the residue, melting at 100–105°, was recrystallized from 50% ethanol to give a 92% yield of the indane acid as colorless fine crystals, m.p. 110–111°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>16</sub>O<sub>5</sub>: C, 61.89; H, 6.35. Found: C, 61.89; H, 6.38.

**Infrared Spectrum.**—Acid band was shown at 5.84  $\mu$ .

**Attempted Preparation of 4,5,6-Trimethoxyindene-2,3-dicarboxylic Acid (VI).**—A solution of the indene diester (VII) in acetic acid with a slight amount of hydrochloric acid<sup>4</sup> was warmed on the steam-bath for 30 minutes. A very small amount of crystalline precipitate, which separated from the dark red-brown reaction mixture, was collected. It melted at 132–135° with gas evolution, which apparently was caused by decarboxylation of the dicarboxylic to the mono-carboxylic acid on heating.<sup>4</sup> No product could be isolated from the filtrate.

**Ethyl  $\alpha$ -Formyl- $\beta$ -(3,4,5-trimethoxyphenyl)-propionate (X).**—A suspension of potassium ethoxide was prepared by dissolving 2.4 g. of potassium in 20 ml. of absolute ethanol, removing excess solvent by heating under reduced pressure for 45 minutes and adding 30 ml. of dry ether. The mixture was cooled to –20° and a solution of 8 g. of ethyl  $\beta$ -(3,4,5-trimethoxyphenyl)-propionate and 4.6 g. of ethyl formate in 30 ml. of ether was added dropwise with stirring during a 30-minute interval. Stirring was continued for another 4 hours at –20°, then the reaction mixture allowed to stand at room temperature for 3 days. Cold water was added to dissolve the dark-reddish gum; the alkaline solution was acidified and the oil which separated extracted with ether, washed with water and dilute sodium bicarbonate solution, then dried over magnesium sulfate. Evaporation of the ether gave 5.1 g. (57%) of a clear reddish oil. This was used for the next preparation without further purification.

**Ethyl 4,5,6-Trimethoxyindene-2-carboxylate (XII).**—This indene monoester was obtained in the same manner as the analogous diester (VII) by cyclization of the formyl derivative (X) with two different agents. (a) A 3-g. sample of the above oil was added dropwise to a mixture of 10 ml. of concentrated sulfuric and 20 ml. of 85% phosphoric acid at 0° and, after stirring 5 minutes, the mixture was allowed to stand at room temperature for 1.5 hours. It was then

poured into ice-water and the oily gum which separated was washed with water and dried; wt. 1.9 g. (68%). (b) Four grams of the oil was added to 40 g. of polyphosphoric acid at 10° with stirring. The mixture turned dark brown in a few minutes and was poured into ice-water after standing at room temperature for ten minutes. The oil which separated from the resulting emulsion solidified upon stirring. This solid was filtered; yield 3.4 g. (91%). The products from the two cyclization procedures were recrystallized separately from dilute ethanol to give similar colorless fine needles, m.p. 56–58°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>18</sub>O<sub>5</sub>: C, 64.73; H, 6.47. Found: C, 64.74; H, 6.18.

**Infrared Spectrum.**—Conjugated ester band was shown at 5.90  $\mu$ .

Hydrolysis of this ester with 15% alcoholic potassium hydroxide gave a 73% yield of the corresponding acid, which separated from dilute ethanol as colorless fine crystals, m.p. 169–170°. It was identical in melting point with the acid (XI) previously obtained from hydrolysis of diethyl 4,5,6-trimethoxyindene-2,3-dicarboxylate, and a mixed melting point with this acid showed no depression.

**Ethyl 4,5,6-Trimethoxyindane-2-carboxylate (XIV).**—A mixture of 1 g. of the indene ester (XII), 15 ml. of acetic acid and 1 g. of 5% palladium-carbon catalyst was hydrogenated at 60° and 5 lb. pressure. After 2.5 hours, 0.99 mole of hydrogen was absorbed. The catalyst was removed and the acetic acid evaporated under reduced pressure giving 0.93 g. (93%) of an oily product (XIV). All attempts to crystallize the oil were unsuccessful.

Saponification of the oil with 20% aqueous sodium hydroxide yielded the corresponding acid which separated from dilute ethanol in colorless fine crystals, m.p. 110–111°. It was proved to be identical with the sample (XIII) obtained by hydrogenation of 4,5,6-trimethoxyindene-2-carboxylic acid, by comparison of melting points and mixed melting point.

**Acknowledgments.**—The author wishes to express his thanks to Dr. J. L. Hartwell for his encouragement and to Dr. A. W. Schrecker for assistance in revising the manuscript. Analyses were carried out by the Microanalytical Laboratory under the direction of Dr. W. C. Alford.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMICAL PHARMACOLOGY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

## Studies in Polyphosphoric Acid Cyclizations

By JOHN KOO<sup>1</sup>

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An extensive study of cyclizations with polyphosphoric acid (PPA) has been made and this acid has been found to be the reagent of choice in the synthesis of various 1-indanones, 1-tetralones, benzosuber-5-ones and anthraquinones from aryl-aliphatic and aroyl-aromatic acids. It has been further applied advantageously to the preparation of various substituted indenones from aryl-substituted aliphatic ketones. Improved and detailed experimental conditions and techniques required for PPA cyclizations have been described.

During the course of an investigation dealing with the synthesis of degradation products of colchicine and of some analogous compounds, it became necessary to develop procedures for the preparation of di- and trimethoxybenzosuberene derivatives by the cyclization of aryl-aliphatic carbonyl compounds.<sup>2</sup> In the original experiments, the appropriate  $\alpha$ -ethoxalyl esters were treated with a

mixture of concentrated sulfuric and 85% phosphoric acids to yield substituted benzosuberencarboxylic anhydrides.<sup>2a,b,c</sup> This procedure was well suited for the preparation of indenones<sup>3,4</sup> and dihydronaphthalene,<sup>5</sup> but proved to be somewhat less satisfactory in the preparation of seven-membered ring compounds because of the sensitivity of the reaction product to the cyclizing agent or because of the occurrence of side-reactions,<sup>2c</sup> such as sulfonation or ester cleavage.

(1) Special Research Fellow of the National Cancer Institute, National Institutes of Health.

(2) (a) E. C. Horning and J. Koo, *THIS JOURNAL*, **73**, 5830 (1951); (b) J. Koo, *ibid.*, **75**, 720 (1953); (c) **75**, 723 (1953); (d) J. Koo and J. L. Hartwell, *ibid.*, **75**, 1625 (1953).

(3) E. C. Horning, J. Koo and G. N. Walker, *ibid.*, **73**, 5826 (1951).

(4) J. Koo, *ibid.*, **75**, 1889 (1953).

(5) E. C. Horning and J. Koo, *ibid.*, **73**, 5828 (1951).