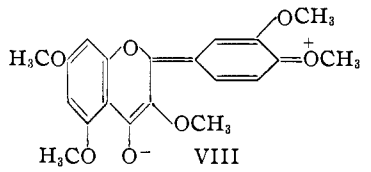
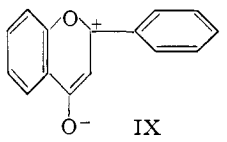
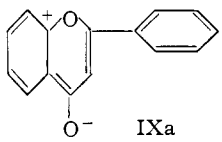
than that of the corresponding flavanone derivative. The lowering is due, at least partially, to increased conjugation, as in VIII, which is not possible in the flavanones. The chemical behavior of flavones (the formation of salts, difficulty of carbonyl derivative formation, etc.) and the infrared spectra indicate that flavones are not closely analogous to flavanones, chalcones or acetophenones. This may be due to the importance of resonance structures, such as IX and IXa, in which conjugation between the carbonyl group and the 5- and 7-position is not favored.



VIII



IX



IXa

Comparison of our results with studies of the polarographic reduction of the carbonyl group in flavones, flavanones and chalcones by Geissman and his co-workers[18] indicates that the same factors that are operative in altering the infrared frequency of the carbonyl group are responsible for the ease of reduction of this group.

(18) Engelkemeir, Geissman, Crowell and Friess, THIS JOURNAL, **69**, 155 (1947); Geissman and Friess, *ibid.*, **71**, 3893 (1949).

CORVALLIS, OREGON

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

The Synthesis of 2,3,4-Trimethoxybenzosuberene- and 2,3,4-Trimethoxybenzosuberancarboxylic Acids and Esters

BY JOHN KOO[1] AND JONATHAN L. HARTWELL

RECEIVED OCTOBER 9, 1952

The synthesis of several different types of 2,3,4-trimethoxybenzosuberene and -benzosuberancarboxylic acids and esters, which are of possible importance for the construction of the C-ring of colchicine and its related compounds, is described. The cyclization of these seven-membered ring compounds was accomplished with ease and in high yield by the use of polyphosphoric acid. The conversion of ethyl α-ethoxalyl-δ-(3,4,5-trimethoxyphenyl)-valerate to 2,3,4-trimethoxybenzosuber-5-ene-5-carboxylic acid in one operation, in good yield, is reported.

The successful synthesis of *dl*-colchinol methyl ether[2] and of deaminocolchinic acid anhydride[3] by two independent groups has eliminated any reasonable doubt as to the nature of ring B of colchicine. Our synthetic work on colchicine and its related compounds since then has been directed toward building ring C. One plan for this purpose consists in first preparing a compound containing the fused A/B ring system with ring A appropriately substituted, and with ring B bearing one or two reactive groups through which ring C may then be constructed. In this communication we wish to report the synthesis of a series of 2,3,4-trimethoxybenzosuber-5-ene and -suberancarboxylic esters and acids. Since these compounds contain the required fused A/B ring system and reactive groups, they are possible starting materials for the preparation of colchicine as well as of related compounds.

A search of the literature reveals that naphthalene or tetralin carboxylic acids and esters are relatively common, but little is known about the synthesis of their seven-membered analogs. Apparently, all types of bicyclic compounds described in this paper, containing three methoxyl groups on the benzene ring and with a mono- or dicarboxylic acid on one or both of the α- and β-positions of the seven-membered ring, are unreported. In the benzosuberene series, either mono- or diacids or their esters should prove applicable for subsequent work, and the position of the double bond may add to their suitability.

Condensation of ethyl δ-(3,4,5-trimethoxyphenyl)-valerate[3b] (I) with ethyl formate in the presence of dry potassium ethoxide yielded the formyl derivative (II) in 50% yield. Previously,[3,4] in connection with another study of the colchicine problem, many dimethoxy or trimethoxy five-membered, six-membered and seven-membered compounds were cyclized by a mixture of sulfuric acid and 85% phosphoric acid with difficulty and in varying yields. Our general experience with this reagent[4] is (1) that dimethoxy compounds are usually cyclized more easily than their trimethoxy analogs, and (2) that seven-membered compounds containing the same groups are more difficult to cyclize than their five- or six-membered analogs.[5] The difficulty in achieving cyclization of seven-membered compounds lies in the fact that it can be carried out only under certain rigid conditions (concentration of sulfuric acid, temperature and time), and the conditions used for one compound may not be applicable to another. Moreover, in many cases, sulfuric acid causes destruction or

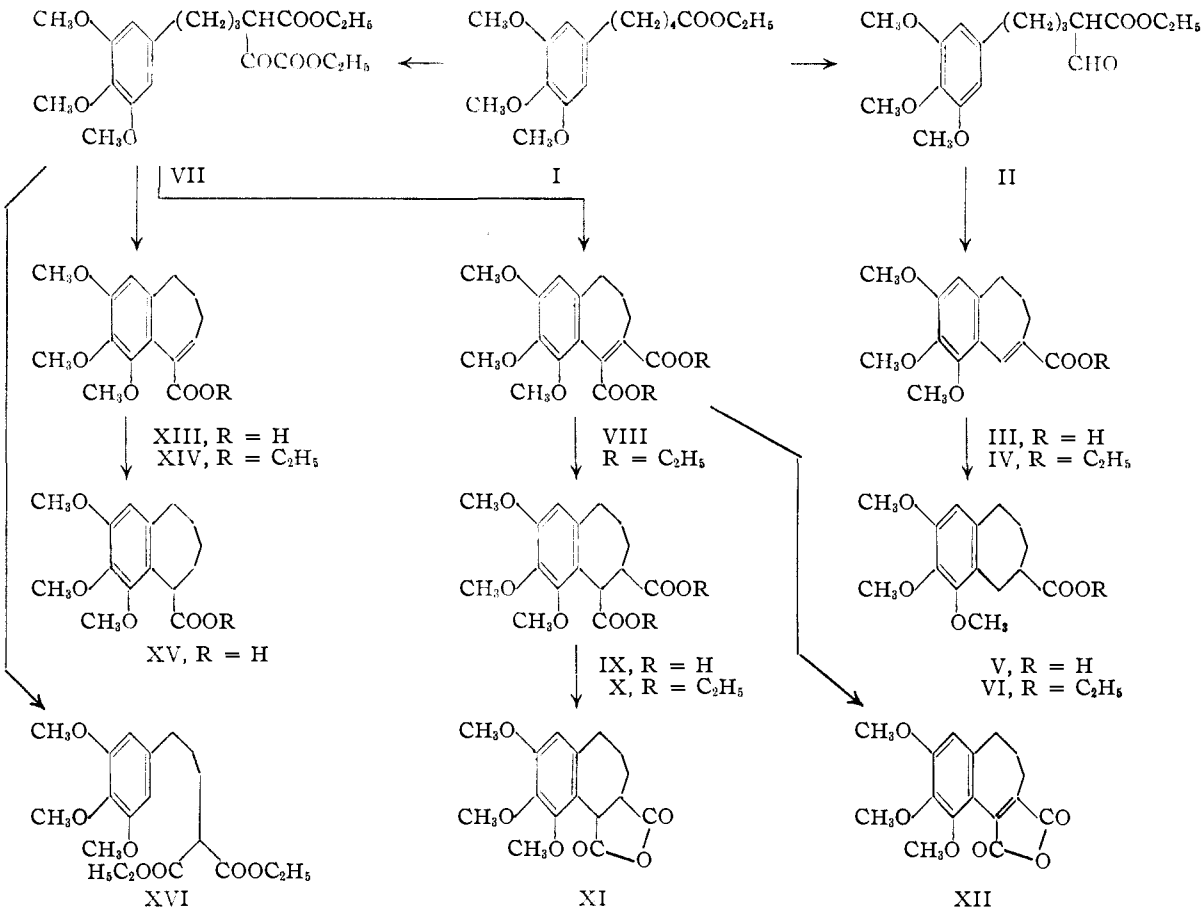
(1) Special Research Fellow of the National Cancer Institute, National Institutes of Health.

(2) H. Rapoport, A. R. Williams and M. E. Cisney, THIS JOURNAL, **73**, 1414 (1951).

(3) (a) E. C. Horning, M. G. Horning, J. Koo, M. S. Fish, J. A. Parker, G. N. Walker, R. M. Horowitz and G. E. Ullyot, *ibid.*, **72**, 4840 (1950); (b) J. Koo, *ibid.*, **75**, 720 (1953).

(4) E. C. Horning, J. Koo and G. N. Walker, *ibid.*, **73**, 5826 (1951); E. C. Horning and J. Koo, *ibid.*, **73**, 5828, 5830 (1951); J. Koo, *ibid.*, **75**, 723 (1953); J. Koo, *ibid.*, **75**, in press (1953).

(5) This phenomenon has also been found for the Friedel–Crafts cyclization. *Cf.* W. S. Johnson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 117–118.



sulfonation of compounds and results in a poor yield or even no product at all. It is therefore interesting that in our work two carboxyl derivatives were first cyclized to benzosuberenes by the employment of polyphosphoric acid with excellent results not only in high yield but also in ease of operation. The cyclization of the formyl derivative was carried out by two methods. With polyphosphoric acid, a 90% yield of ethyl 2,3,4-trimethoxybenzosuber-5-ene-6-carboxylate (IV) was obtained at room temperature in 30 minutes. With a mixture of sulfuric acid and 85% phosphoric acid, the corresponding acid (III) was produced in 71% yield. The ester was hydrogenated over palladium–charcoal catalyst to give a 90% yield of the corresponding benzosuberan derivative (VI). Hydrogenation of the benzosuberene acid (III) in a similar manner, or hydrolysis of the benzosuberan ester (VI), afforded the same product, 2,3,4-trimethoxybenzosuberan-6-carboxylic acid (V).

In another series, ethyl δ-(3,4,5-trimethoxyphenyl)-valerate (I) was condensed with ethyl oxalate to yield the ethoxalyl derivative (VII), which upon treatment with polyphosphoric acid, readily cyclized to produce in 95% yield diethyl 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylate (VIII). The corresponding benzosuberan diester (X) was obtained by hydrogenation of the benzosuberene diester with palladium–charcoal catalyst (88% yield). Subsequent hydrolysis of X gave 2,3,4-trimethoxybenzosuberan-5,6-dicarboxylic acid (IX) in 80% yield. Windaus[6] obtained the benzoylamino derivative of this acid (IX) by reduction with zinc dust and acetic acid of N-benzoylcolchinic anhydride. The diacid was converted to the anhydride (XI) by heating with acetic anhydride.

In another series of reactions involving treatment of the above ethoxalyl derivative (VII) with dilute sulfuric acid, an 86–91% yield of 2,3,4-trimethoxybenzosuber-5-ene-5-carboxylic acid (XIII) was conveniently afforded in one step. This acid was esterified to give a low-melting ethyl ester (XIV), and was hydrogenated to yield the benzosuberan acid (XV). On heating, VII yielded ethyl γ-(3,4,5-trimethoxyphenyl)-propylmalonate (XVI).

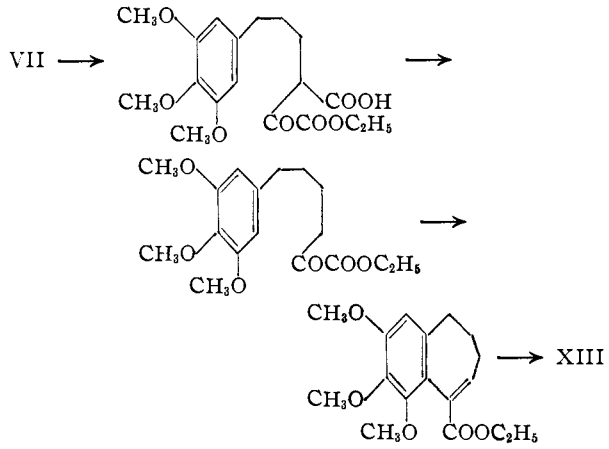
The formation of the seven-membered 2,3,-4-trimethoxybenzosuber-5-ene-5-carboxylic acid (XIII) in a single step by simultaneous hydrolysis, decarboxylation and cyclization in high yield seemed interesting in comparison with some previous parallel syntheses for six-membered compounds.[7]

In order to gain information on the mechanism of the reaction whereby XIII is formed from VII, VIII was treated under reaction conditions similar to VII. However, starting material was recovered unchanged. Apparently cyclization is

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

(7) L. F. Fieser and H. L. Holmes (THIS JOURNAL, **58**, 2319 (1936)) prepared a dihydronaphthalene acid from the corresponding ethoxalyl derivative in three steps, while R. D. Haworth, B. P. Moore and P. L. Pauson (*J. Chem. Soc.*, 327 (1949)) obtained a diester instead of the proposed dihydronaphthalene acid.

preceded by hydrolysis and by decarboxylation of the carboxyl group attached to the CH group, as



Alkaline hydrolysis of VIII, followed by acidification, yielded 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylic anhydride (XII). This gave conclusive proof of the structure of VIII.

Attempts were made to reduce the above anhydride to the corresponding benzosuberandicarboxylic anhydride (XI) by palladium–charcoal in acetic acid and by Raney nickel in dilute sodium hydroxide solution. In these cases no hydrogen was absorbed and all of the starting material was recovered.

TABLE I

INFRARED CARBONYL BANDS IN CHLOROFORM

The shift of the absorption band due to conjugation is apparent in comparing III with V, IV with VI, VIII with X, XII with XI, and XIII with XV. The regular anhydride double band is shown by XI and XII, while the dicarboxylic acids and esters—VIII, IX and X—show only one sharp band each.

Compound	Wave length, μ	Compound	Wave length, μ
III	5.97	X	5.78
IV	5.92	XI	5.38; 5.62
V	5.87	XII	5.43; 5.66
VI	5.79	XIII	5.92[a]
VIII	5.83	XIV	5.86
IX	5.90[a]	XV	5.87

[a] Nujol mull.

Experimental[8]

Ethyl α-Formyl-δ-(3,4,5-trimethoxyphenyl)-valerate (II).—Potassium (2.6 g.) was dissolved in 30 ml. of absolute ethanol; the excess ethanol was removed by suction and 30 ml. of dry ether was added. While this ether solution was cooling to −20°, a mixture of 10 g. of ethyl δ-(3,4,5-trimethoxyphenyl)-valerate (I) and 6 g. of ethyl formate in 60 ml. of ether was added dropwise with stirring. Half an hour later, the temperature was raised to about −15° and the stirring was continued for four hours. A pale yellow paste formed which was permitted to stand at room temperature for 3 days. Cold water was added to dissolve the salt; the water solution was acidified and extracted with ether, and the ether solution was washed with water, dilute sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the ether left a bright yellowish oil weighing 5.4 g. (50%). It could not be distilled without decomposition.

Ethyl 2,3,4-Trimethoxybenzosuber-5-ene-6-carboxylate (IV).—The formyl ester (II) (3.4 g.) was mixed with 30 g. of polyphosphoric acid at 5°. The mixture was maintained at room temperature for 30 minutes and then was poured into ice-water. The precipitate, after filtration, washing and drying, weighed 2.9 g. (90%). The product was recrystallized from dilute ethanol to yield a felt of colorless needles, m.p. 67–68°.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.66; H, 7.19. Found: C, 66.76; H, 7.19.

2,3,4-Trimethoxybenzosuber-5-ene-6-carboxylic Acid (III).—The formyl ester (II) (3 g.) was dropped into a mixture of 10 ml. of 85% phosphoric acid and 20 ml. of concd. sulfuric acid at 0–5°. After standing at room temperature for 2.5 hours, the mixture was poured into ice-water. The resulting crystalline precipitate was filtered, washed and dried; yield 1.9 g. (73%), m.p. 175–178°. It was purified by recrystallization from dilute ethanol to give colorless small scales, m.p. 179–180°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.75; H, 6.47. Found: C, 64.86; H, 6.51.

This acid was also obtained by saponification of ethyl 2,3,4-trimethoxybenzosuber-5-ene-6-carboxylate (IV) with 15% alcoholic potassium hydroxide. The yield was 85%, m.p. 179–180°. The mixed melting point of this compound with the acid obtained from cyclization showed no depression.

Ethyl 2,3,4-Trimethoxybenzosuberan-6-carboxylate (VI). To a solution of 1 g. of the ester (IV) in 20 ml. of acetic acid was added 2 g. of palladium–carbon catalyst, and the mixture was hydrogenated at 60° for 90 minutes. Filtration and removal of the solvent by suction on a steam-bath left an oil weighing 0.9 g. (90%). An analytical sample was obtained by crystallization of the oil in ethyl acetate–pentane, cooling in Dry Ice for a week; colorless, fine crystals resulted, m.p. 31–32.5°.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.96; H, 7.85.

2,3,4-Trimethoxybenzosuberan-6-carboxylic Acid (V).—The ester (VI) (0.9 g.) was boiled with 10 ml. of 15% alcoholic potassium hydroxide for two hours. Insoluble impurities were removed by filtration, and the alkaline solution was diluted with a little cold water and acidified. A small amount of reddish crystals mixed with a dark gum separated. This material was collected and dissolved in dilute sodium hydroxide solution. Some charcoal was added and the mixture warmed on a steam-bath for 10 minutes; filtration and acidification followed. The product (0.6 g., 71%) was filtered off and recrystallized from 60% ethanol to give colorless bright scales, m.p. 165–167°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.28; H, 7.14. Found: C, 64.29; H, 7.31.

Direct hydrogenation of 2,3,4-trimethoxybenzosuberene-6-carboxylic acid (III) in a manner similar to that for the ester (IV) gave a 95% yield of benzosuberan acid (V), which was identical with that obtained by saponification of the hydrogenated ester.

Ethyl 2,3,4-Trimethoxybenzosuber-5-ene-5,6-dicarboxylate (VIII).—The ethoxalyl derivative (VII)[3b] (3.6 g.) was mixed with 40 g. of polyphosphoric acid at 5° and the mixture was stirred for a few minutes. After the mixture turned a dark red, it was poured into ice-water. The colorless product, after filtration and drying, weighed 3.3 g. (97%), m.p. 70–74°. An analytical sample was purified by recrystallization from 70% ethanol to give colorless, small needles, m.p. 76–77.5°.

Anal. Calcd. for $C_{20}H_{26}O_7$: C, 63.47; H, 6.92. Found: C, 63.60; H. 6.95.

Ethyl 2,3,4-Trimethoxybenzosuberan-5,6-dicarboxylate (X).—To a solution of 1 g. of the benzosuberene diester (VIII) in 15 ml. of acetic acid, 1 g. of palladium–carbon catalyst was added, and the mixture was hydrogenated at *ca.* 50° and under 40 lb. pressure for 6 hours. The heating and stirring, which were stopped overnight, were applied the next day for another 6 hours. The catalyst was filtered off and the solvent was removed under reduced pressure. A colorless thick oil (0.88 g., 88%) was obtained, which was crystallized from ether–pentane to give colorless, fine crystals, m.p. 65–66°.

Anal. Calcd. for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.00; H, 7.41.

2,3,4-Trimethoxybenzosuberan-5,6-dicarboxylic Acid (IX).—The diester (X) (0.5 g.) was refluxed with 10 ml. of 15% alcoholic potassium hydroxide for 5 hours. The small

(8) Melting points were taken on the Hershberg apparatus and are corrected values. Analyses were carried out by the Microanalytical Laboratory, under the direction of Dr. W. C. Alford.

amount of dark residue was removed by filtration. The solution was diluted and acidified to turbidity, which, after standing in the ice-box all day, changed to a colorless crystalline precipitate, weighing 0.35 g. (80%). The analytical sample was obtained by recrystallization from 40% ethanol to give colorless fine crystals, m.p. 190–192° (shrinking at 185°).

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.10. Found: C, 59.36; H, 6.26.

2,3,4-Trimethoxybenzosuberan-5,6-dicarboxylic Anhydride (XI).—The benzosuberan diacid (IX) (2 g.) was refluxed with 10 ml. of acetic anhydride for two hours. The excess solvent was evaporated under vacuum, leaving a thick oil weighing 1.52 g. (82%), which was recrystallized from acetic acid to give colorless needles, m.p. 176.5–177.5°.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.79; H, 5.93. Found: C, 63.00; H, 6.13.

2,3,4-Trimethoxybenzosuber-5-ene-5-carboxylic Acid (XIII).—A mixture of 3 g. of VII and 40 ml. of 16% sulfuric acid was refluxed with stirring for 5 hours, causing some yellowish solid to separate gradually. After cooling in the ice-box for a few hours, the residue was filtered off and dissolved in dilute sodium hydroxide solution. Since very little insoluble material separated, the solution was acidified. The colorless crystalline precipitate was filtered off and dried; yield 2 g. (91%), m.p. 195–198°. Recrystallization of the crude product from dilute ethanol gave colorless small scales, m.p. 198–200°. In another run, the starting material weighed 5.5 g. and the yield of acid was 3.4 g. (86%).

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 64.75; H, 6.47. Found: C, 64.82; H, 6.50.

Ethyl 2,3,4-Trimethoxybenzosuber-5-ene-5-carboxylate (XIV).—The acid (XIII) (1 g.) was refluxed with 10 ml. of absolute ethanol and 1 ml. of concd. sulfuric acid for 5 hours. The resulting mixture was diluted with cold water and extracted with ether. The ether solution, after being washed with 5% sodium bicarbonate solution and then water, was evaporated to yield an oil weighing 1.27 g. (77%), which was crystallized from dilute ethanol. After standing in the ice-box for 2 weeks, the oil which first separated on cooling, solidified partially to crystals. Recrystallization in the same manner was repeated twice to give colorless fine crystals, m.p. 44–45°.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.66; H, 7.19. Found: C, 66.64; H, 7.36.

2,3,4-Trimethoxybenzosuberan-5-carboxylic Acid (XV).—A mixture of 0.5 g. of 2,3,4-trimethoxybenzosuber-5-ene-5-carboxylic acid (XIII) in 10 ml. of acetic acid was hydrogenated over 1 g. of palladium–carbon catalyst at 60° and 40 lb. pressure for 5 hours; stirring without heating was continued for another 4 hours. Filtration of catalyst followed by evaporation of the solvent left a gum weighing 0.45 g. (90%), which was recrystallized from dilute ethanol once to yield colorless fine crystals, m.p. 138–140°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.28; H, 7.14. Found: C, 64.38; H, 6.98.

Ethyl γ-(3,4,5-Trimethoxyphenyl)-propylmalonate (XVI).—The keto diester (VII) (4.0 g.) was heated in a distilling flask under vacuum. When the metal-bath temperature reached 130°, the substance simultaneously started to bubble and evolve a gas. The reaction was finished at the end of the 1.5 hr. taken to raise the bath temperature to 150°. The product was then distilled at 187–188° (0.7 mm.) to give 2.3 g. (62%) of a colorless viscous oil.

Anal. Calcd. for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.96; H, 7.86.

Alkaline and Acid Hydrolysis of Ethyl 2,3,4-Trimethoxybenzosuber-5-ene-5,6-dicarboxylate (VIII) (a).—The diester (0.5 g.) was refluxed with 10 ml. of 15% sodium hydroxide for 5 hours. Very little neutral material was removed with ether, and the solution was acidified with dilute hydrochloric acid to yield at first a yellowish turbidity which gradually changed to a light yellow precipitate. This was recrystallized once from ether–pentane to give yellow needles of XII, weighing 0.32 g. (80%), m.p. 119–120°, no depression on admixture with an authentic sample[3] of 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylic anhydride.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.89; H, 5.32.

(b).—The diester (1 g.) was refluxed with 15 ml. of 16% sulfuric acid for 15 hours. After cooling, an oil separated; this was taken up with ether and the resulting ether solution was washed with dilute $NaHCO_3$ solution and then with water. Acidification of the $NaHCO_3$ solution yielded nothing. The ether solution was worked up, and almost all of the starting material was recovered unchanged.

Attempted Hydrogenation of the Anhydride (XII).—Hydrogenation of 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylic anhydride (XII) in acetic acid with palladium–carbon catalyst at 60° and 40 lb. pressure for 10 hours was unsuccessful. No hydrogen was absorbed and all of the starting material was recovered.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

Hormonal Antimetabolites. I. Derivatives of *meso*-2,2′-Dithienylhexane

BY JEAN SICÉ AND MORTON MEDNICK

RECEIVED AUGUST 18, 1952

As a first step toward the eventual procurement of sex hormone antagonists, the thiophene isolog of hexestrol and related analogs of progesterone and desoxycorticosterone have been prepared from dithienylhexane (III), obtained by coupling of thienylhalopropanes. None of these substances showed any estrogenic activity in mice.

To date a few unsuccessful attempts to find direct antagonists to sexual and cortical hormones have been reported. Because of the interest of this Laboratory in hormone-dependent tumors, a different approach to this problem has been undertaken. Estrogens inhibit normal growth but produce cancer in many organs; androgens partially inhibit the effect of estrogens. Estrogens cause regression of certain human cancers of the prostate and breast. Androgens may accelerate the growth of prostatic cancer and depress the activity of some mammary carcinoma.[1] The sex hormones used clinically overstimulate the secondary sex characteristics, thereby producing some objectionable side effects (feminization or masculinization); direct antagonists should provide a therapeutic action free from secondary effects.

The correlation of the chemical structure with the physiological activity of the stilbenic estrogens brings out the essential role of both the hydrocarbon skeleton and the phenolic groups; the purpose of this study is to determine whether an alteration in the electronic distribution of the aromatic nuclei, in this series, can produce an antagonistic analog (antiestrogen or antiandrogen) of these substances.[2] Lacassagne and Buu-Hoï[3] have shown that the

(1) *Cf.* C. Huggins, *Yale J. Biol. Med.*, **19**, 319 (1947); *J. Urology*, **68**, 875 (1952).

(2) *Cf.* D. W. Woolley, "A Study of Antimetabolites," John Wiley and Sons, Inc., New York, N. Y., 1952.

(3) L. Corre, M. de Clercq, Ng. Ph. Buu-Hoï, Ng. Hoán and A. Lacassagne, *Bull. soc. chim. biol.*, **30**, 674 (1948).