50-ml. fractions were collected. The material contained in fractions 5 and 6 was combined and crystallized from 3 ml. of ether to give 80 mg. (8% yield) of what is presumed to be **2α,21,21-tribromoprogesterone** (V) as white crystals, m.p. 147–149° dec. This material was recrystallized from acetone–petroleum ether to give 62 mg. of crystals, m.p. 145–146° dec., $[\alpha]^{24}D$ +162° (*c* 0.78, methanol); λ^{MeOH}_{max} 242 mμ (ε 14,700); λ_{max} 5.79, 5.92, 6.15 μ.

Anal. Calcd. for $C_{21}H_{27}Br_3O_2$: C, 45.76; H, 4.94; Br, 43.50. Found: C, 45.51; H, 5.20; Br, 43.09.

The material contained in fractions 8–14 was combined and crystallized from acetone–petroleum ether to give 0.200 g. (26% yield) of **2α,21-dibromoprogesterone** (VI) as white crystals, m.p. 160–161° dec. This material was recrystallized from acetone–petroleum ether to give 172 mg. of white crystals, m.p. 163–165° dec., $[\alpha]^{24}D$ +201° (*c* 0.71, chloroform); λ^{MeOH}_{max} 242 mμ (ε 18,100); λ_{max} 5.81, 5.92, 6.16 μ.

Anal. Calcd. for $C_{21}H_{28}Br_2O_2$: C, 53.41; H, 5.98; Br, 33.84. Found: C, 53.26; H, 6.15; Br, 33.81.

2α-Bromodeoxycorticosterone Acetate (X).—A mixture of 2.1 g. of potassium bicarbonate and 1.2 ml. of glacial acetic acid was thoroughly ground with a mortar and pestle. The resulting powder was added to a solution of 0.343 g. (0.73 mmole) of 2α,21-dibromoprogesterone (VI) in 25 ml. of acetone, and this mixture was magnetically stirred at room temperature for three days. The mixture was slowly diluted with water until the total volume was about 125 ml.; during the dilution all solid dissolved, and more solid then separated. This mixture was filtered, and the filtrate was extracted with 100 ml. of methylene chloride. The organic solution was washed with water (2 × 100 ml.), dried over magnesium sulfate and taken to dryness. The residue was combined with solid from above and recrystallized from acetone–petroleum ether to give 0.251 g. (79% yield) of white crystals, m.p. 176–178° dec. An additional recrystallization from acetone–petroleum ether gave white crystals, m.p. 173–175° dec., $[\alpha]^{25}D$ +174° (*c* 1.07, chloroform); λ^{MeOH}_{max} 243 mμ (ε 13,600); λ_{max} 5.71, 5.79, 5.92, 6.15, 8.11, 9.40 μ.

Anal. Calcd. for $C_{23}H_{31}BrO_4$: C, 61.20; H, 6.92; Br, 17.74. Found: C, 61.08; H, 7.14; Br, 17.71.

21-Acetoxy-1,4-pregnadiene-3,20-dione (**1-Dehydrodeoxycorticosterone Acetate**) (**XI**).—A solution of 0.190 g. (0.42 mmole) of 2α-bromodeoxycorticosterone acetate (X) and 3 ml. of 2,4,6-collidine was allowed to reflux for 45 minutes. Solid began separating from the solution when reflux temperature was reached, and the cooled mixture was distributed between 50 ml. of methylene chloride and 50 ml. of 10% sulfuric acid solution. The organic phase was washed further with 50 ml. of 10% sulfuric acid solution and then 50 ml. of water. After drying the solution over a mixture of magnesium sulfate and Norite, the solvent was removed to give a crystalline residue. This material was recrystallized from acetone–petroleum ether to give 0.065 g. (40% yield) of needles and rods, m.p. 200–201°, $[\alpha]^{25}D$ +131° (*c* 1.7, chloroform); λ^{MeOH}_{max} 243 mμ (ε 14,800); λ_{max} 5.72, 5.80, 6.00, 6.14, 6.23, 8.03, 9.38 μ. Reported[14] values are m.p. 202.6–204.0°, $[\alpha]D$ + 125.6° (ethanol), +134 ± 3° (chloroform)[14]; λ^{EtOH}_{max} 243 mμ (ε 15,400); $\lambda^{CS_2}_{max}$ 5.71, 5.79 μ; and $\lambda^{CHCl_3}_{max}$ 6.00, 6.17, 6.24 μ.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.48; H, 8.26.

Reaction of 2α,21,21-Tribromoprogesterone (V) with Sodium Methoxide.—A slurry of 0.285 g. (0.52 mmole) of V in 5 ml. of methanol was treated with 3.1 ml. of 1 *N* methanolic sodium methoxide; all of the solid dissolved and the yellow solution was allowed to stand at room temperature for four hours. The solution was diluted to a volume of 25 ml. with water and extracted with methylene chloride (2 × 25 ml.). The combined extracts were dried over magnesium sulfate and taken to dryness to give 0.147 g. of a glass. This material had λ^{MeOH}_{max} 231 mμ ($E^{1\%}_{1 cm.}$ 525); λ_{max} 5.83, 5.95, 6.18, 8.60 μ.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BOSTON UNIVERSITY]

Compounds Related to Podophyllotoxin. X. Synthesis of Picropodophyllin[1]

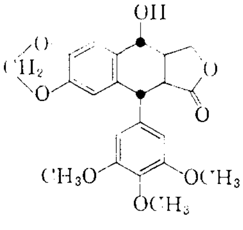
BY WALTER J. GENSLER, CARLOS M. SAMOUR, SHIH YI WANG AND FRANCIS JOHNSON

RECEIVED AUGUST 11, 1959

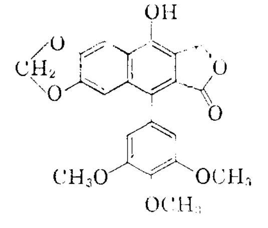
A total synthesis of picropodopyllin is described. 3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzophenone, from the Friedel–Crafts reaction of methylenedioxybenzene and trimethoxybenzoyl chloride, was condensed with ethyl succinate in the presence of potassium *t*-butoxide. Hydrolysis of the product gave two geometrically isomeric itaconic acids, one of which was carried through the subsequent steps. This acid was hydrogenated, and the resulting benzhydrylsuccinic acid cyclized to 1-trimethoxyphenyl-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoic acid. The corresponding ester was formylated, reduced with sodium borohydride, and hydrolyzed to DL-epiisopodophyllic acid. Dehydration furnished DL-β-apopicropodophyllin, which was hydrolyzed to DL-α-apopodophyllic acid. Resolution at this stage with quinine gave α-apopodophyllic acid. Lactonization to α-apopicropodophyllin followed by acid-catalyzed hydration furnished picropodophyllin. Reactions of the isomeric itaconic acid are recorded. Arguments concerning the mode of cyclization of the pertinent benzhydrylsuccinic acids are presented.

Introduction

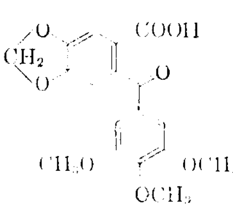
The lignan lactone picropodophyllin (I) has been obtained from several species of *Podophyllum*.[2]



picropodophyllin I



dehydropodophyllotoxin II



III

The more practical and convenient source, however, is through mild, base-catalyzed epimerization[3-6] of

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[1] This work was supported by Grants from American Cancer Society (CBC-6), and from National Cancer Institute, U. S. Public Health Service (CY2891).

[2] V. Podwyssotzki, *Ber.*, **15**, 377 (1882); M. V. Nadkarni, J. L. Hartwell, P. B. Maury and J. Leiter, THIS JOURNAL, **75**, 1308 (1953); S. C. Chakravarti and D. P. Chakraborty, *J. Am. Pharm. Assoc.*, **43**, 614 (1954) [*C. A.*, **49**, 569 (1955)]; A. Stoll, J. Renz and A. von Wartburg, *Helv. Chim. Acta*, **37**, 1747 (1954); A. von Wartburg, E. Angliker and J. Renz, *ibid.*, **40**, 1331 (1957); J. Bartek, H. Potěšilová, V. Mašínová and F. Šantavý, *Coll. Czechoslov. Chem. Comm.*, **21**, 392 (1956).

podophyllotoxin, a stereoisomer[7] found in relatively large amounts in the same plants. Whether picropodophyllin is a natural product, or whether it originates from podophyllotoxin as an artifact of isolation remains a moot point. Formulation I, proposed in 1932 by Borsche and Späth,[8] has found ample support in the known chemistry of picropodophyllin[9]; the stereochemistry as indicated in I was worked out later by Schrecker and Hartwell.[10]

Several syntheses directed to, or related to, picropodophyllin have been reported. DL-γ-Apopicropodophyllin[11,12] and dehydroanhydropicropodophyllin[11,13] have been prepared. An isomer of dehydroanhydropicropodophyllin[14] as well as other miscellaneous derivatives and analogs have also been described.[15–18] In syntheses somewhat more closely related to the present work, 2-(3′,4′,5′-trimethoxybenzoyl)-piperonylic acid (III), on the one hand, and benzhydrylsuccinic acids analogous to VIIIa on the other, occupy key positions. Starting with keto acid III, reactions suggest themselves that offer seemingly attractive and unambiguous routes for elaborating picropodophyllin compounds. Actually our first efforts were directed along these lines, which, however, we did not pursue. Independent attempts in other laboratories[19–21] to exploit keto acid III furnished useful and significant products, for example, cycloketo acid Xa, and dehydropodophyllotoxin (II).

Synthesis of picropodophyllin compounds by way of a step calling for cyclization of suitably substituted benzhydrylsuccinic acids (*e.g.*, VIIIa) was adumbrated by Borsche[15]; and closely related syntheses, making use of other benzhydrylsuccinic acids, have been realized.[22–24] However, in the syntheses actually carried through, *both* of the aryl groups of the intermediate benzhydrylsuccinic acids were the same. The problems entailed in working with a benzhydrylsuccinic acid such as VIIIa, in which the two rings are not the same, were recognized and clearly stated by Haworth.[11] One complication, for example, is that cyclization of an unsymmetrical benzhydrylsuccinic acid, *a priori*, could give rise to a mixture of four, or even more, isomeric cyclic keto acids. Nevertheless, these problems for the reasons presented below did not appear insurmountable, and we addressed ourselves to the synthesis of picropodophyllin with this general plan in mind. The present paper gives an account of this work which, as summarized in Chart 1, constitutes a total synthesis of picropodophyllin.[25]

Reactions Leading to Picropodophyllin.—Substituted benzophenone VI had been prepared before, either by decarboxylation of 2-(trimethoxybenzoyl)-piperonylic acid (III) which was available both as a degradation product[26] and as a synthetic material,[11,17,19,27] or by Friedel–Crafts acylation of methylenedioxybenzene (IV) with trimethoxybenzoyl chloride (V). The Friedel–Crafts process appeared much the more direct and, despite reports of very poor yields in this[26] as well as in closely related reactions,[15,28] we turned to this method. It was found that with stannic chloride in methylene dichloride solvent the desired product VI was formed in 80% yield.[29] The necessary trimethoxybenzoyl chloride (V) offered no problem.[28] However, our routine preparations of methylenedioxybenzene (IV) from catechol and methylene chlorobromide, although performed more conveniently than before,[32] furnished product in only 30–35% yield. The redeeming feature was that despite the modest yield, respectable quantities of methylenedioxybenzene could be obtained per run without resort to pressure equipment.[33,34]

Stobbe condensation of ketone VI followed by saponification furnished itaconic acids VII (a and b) as a mixture, which could be separated cleanly by fractional crystallization. The isomeric acids were obtained each in 39% yield. As discussed below, considerable attention was devoted to itaco-

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(3) R. Kürsten, *Arch. Pharm.*, **229**, 220 (1891); A. Viehoever and H. Mack, *J. Am. Pharm. Assoc.*, **27**, 632 (1938) [*C. A.*, **32**, 8075 (1938)]; N. L. Drake and E. H. Price, This Journal, **73**, 201 (1951).

(4) A. Robertson and R. B. Waters, *J. Chem. Soc.*, 83 (1933).

(5) W. Borsche and J. Niemann, *Ann.*, **494**, 126 (1932).

(6) E. Späth, F. Wessely and L. Kornfeld, *Ber.*, **65**, 1536 (1932).

(7) *Cf.* J. L. Hartwell and A. W. Schrecker, This Journal, **73**, 2909 (1951).

(8) W. Borsche and J. Niemann, *Ann.*, **499**, 59 (1932); E. Späth, F. Wessely and E. Nadler, *Ber.*, **65**, 1773 (1932).

(9) W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 957 (1955); M. G. Kelly and J. L. Hartwell, *J. Natl. Canc. Inst.*, **14**, 967 (1954); J. L. Hartwell and A. W. Schrecker, *Prog. in Chem. of Org. Nat. Prod.*, **15**, 83 (1958).

(10) A. W. Schrecker and J. L. Hartwell, This Journal, **75**, 5916 (1953); *J. Org. Chem.*, **21**, 381 (1956).

(11) R. D. Haworth and T. Richardson, *J. Chem. Soc.*, 348 (1936).

(12) A. W. Schrecker and J. L. Hartwell, This Journal, **74**, 5676 (1952).

(13) J. L. Hartwell and A. W. Schrecker, *ibid.*, **74**, 5672 (1952).

(14) R. D. Haworth, T. Richardson and G. Sheldrick, *J. Chem. Soc.*, 1576 (1935).

(15) W. Borsche, with S. Kettner, M. Gillies, H. Kühn and R. Manteuffel, *Ann.*, **526**, 1 (1936).

(16) R. G. Nelb and D. S. Tarbell, This Journal, **71**, 2936 (1949); K. N. Campbell and R. J. Boyle, Abstracts Am. Chem. Soc. Meeting, September, 1953, p. 14N; N. L. Drake and W. B. Tuemmler, This Journal, **77**, 1204 (1955); W. Reeve and P. J. Paré, *ibid.*, **79**, 675 (1957); E. A. Fehnel, *J. Org. Chem.*, **23**, 432 (1958).

(17) W. Reeve and W. M. Eareckson, III, This Journal, **72**, 5195 (1950).

(18) K. N. Campbell, J. A. Cella and B. K. Campbell, *ibid.*, **75**, 4681 (1953).

(19) W. Reeve and H. Myers, *ibid.*, **75**, 4957 (1953).

(20) G. N. Walker, *ibid.*, **75**, 3390 (1953).

(21) G. N. Walker, *ibid.*, **78**, 2316 (1956).

(22) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935).

(23) G. N. Walker, This Journal, **75**, 3387 (1953).

(24) N. L. Drake and W. B. Tuemmler, *ibid.*, **77**, 1209 (1955).

(25) W. J. Gensler, C. M. Samour and Shih Yi Wang, *ibid.*, **76**, 315 (1954); W. J. Gensler and Shih Yi Wang, *ibid.*, **76**, 5890 (1954).

(26) E. Späth, F. Wessely and E. Nadler, *Ber.*, **66**, 125 (1933).

(27) W. J. Gensler and C. M. Samour, This Journal, **73**, 5555 (1951).

(28) W. Reeve and J. D. Sterling, *ibid.*, **71**, 3657 (1949).

(29) The uniformly discouraging results in our first Friedel–Crafts experiments led us to explore an alternate preparation of ketone VI, *viz.*, addition of 3,4-methylenedioxyphenyllithium to 3,4,5-trimethoxybenzonitrile.[30] A practical preparation of the organolithium derivative was developed.[31] However, when the Friedel–Crafts reaction showed signs of becoming a practical process, work on this alternate preparation was discontinued. Note Added in Proof: Professor G. R. Pettit has informed us that the organolithium derivative with N-(trimethoxybenzoyl)-morpholine gives ketone VI in acceptable yields.

(30) *Cf.* V. J. Harding, *J. Chem. Soc.*, **105**, 2790 (1914); H. Stephen, *ibid.*, **127**, 1874 (1925); H. Richtzenhain and P. Nippus, *Chem. Ber.*, **82**, 408 1949; also *cf.* ref. 15.

(31) W. J. Gensler and J. E. Stouffer, *J. Org. Chem.*, **23**, 908 (1958).

(32) W. J. Gensler and C. M. Samour, *ibid.*, **18**, 9 (1953).

(33) *Cf.* K. N. Campbell, P. F. Hopper and B. K. Campbell, *ibid.*, **16**, 1736 (1951).

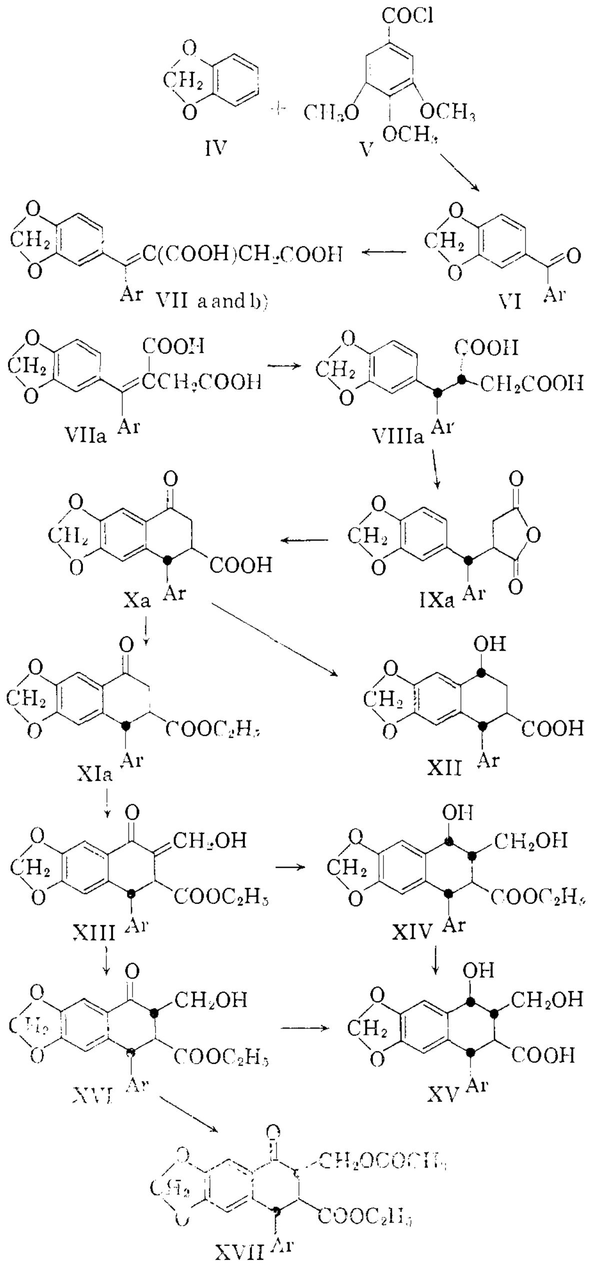
(34) Conversion of piperonal to methylenedioxybenzene (see Experimental section) offered little advantage in over-all yield and considerable disadvantage in the number of steps.

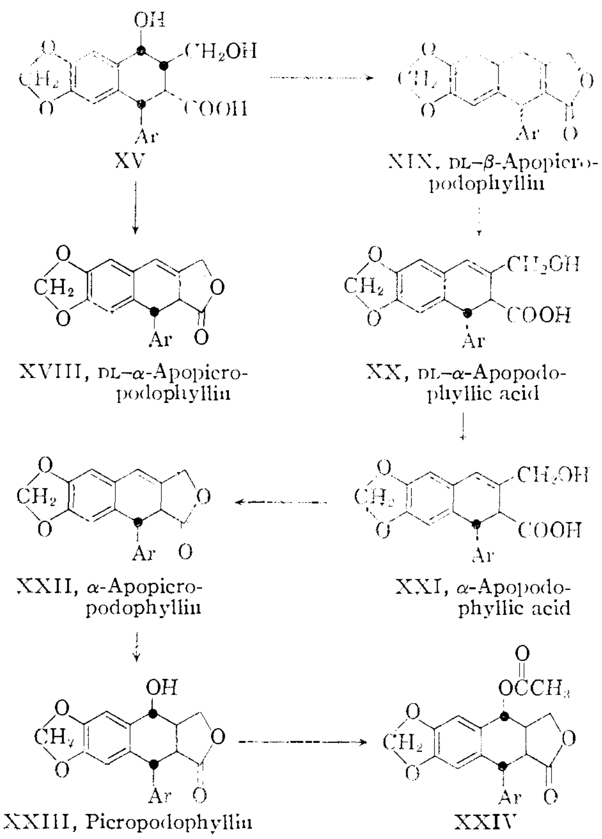
nic acid VIIb; however, the more useful compound proved to be the second isomer, to which provisional structure VIIa was assigned.

Itaconic acid VIIa could be converted to the corresponding anhydride, to the monomethyl ester, and to the dimethyl ester. Cyclization of acid VIIa with polyphosphoric acid led to a product, for which structure XXXIII is suggested (see Experimental section). Hydrogenation converted itaconic acid VIIa smoothly to 3,4-methylenedioxy-3′,4′,5′-trimethylbenzhydrylsuccinic acid (VIIIa). No sign of isomeric acid VIIIb was observed. Dehydration with acetyl chloride gave anhydride IXa, and treatment of the anhydride with stannic chloride in nitrobenzene gave tetralone acid Xa (67% yield) as the only isolated pure product. Other cyclization methods were less satisfactory. Cyclic keto acid Xa could be esterified readily to the ethyl (XIa) or to the methyl ester, and could be reduced with sodium borohydride to the corresponding hydroxy acid XII.

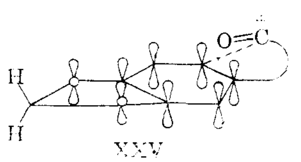
CHART I

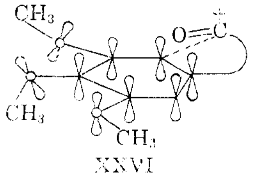
SYNTHESIS OF PICROPODOPHYLLIN
(Ar = trimethoxyphenyl)





Structure Xa is only one of several *a priori* possibilities for a cyclic keto acid derived from VIIIa. The arguments that led us to favor structure Xa as the one expected to form most readily rested foremost on the grounds that cyclization on the methylenedioxybenzene ring *para* to one of the methylenedioxybenzene oxygens[35] should be easier than cyclization on the trimethoxybenzene ring. We examined the transition states for ring closure making the simplifying assumptions that the acylium ion is the attacking species, and that the disposition of atoms in the transition states is close to that in the final products. Molecular models showed that while there is no steric interaction hindering cyclization on the methylenedioxybenzene ring, there is hindrance to cyclization on the trimethoxybenzene ring (*cf.* XXV and XXVI).


XXV


XXVI

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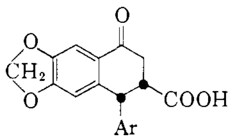
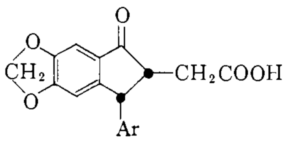
[35] Cyclization *ortho* to the methylenedioxy ring was largely discounted. Electrophilic substitution in catechol derivatives, *e.g.*, methylenedioxybenzene, tends to occur *para* rather than *ortho* to oxygen.

The oxygen atom of the carbonyl group is almost within contact distance of the oxygen atom of the adjacent methoxy group, and completely blocks the methyl of the methoxy group from coplanarity with the ring by rotation toward the carbonyl group. Electronic factors also operate to favor cyclization as in XXV over cyclization as in XXVI. The strain-free methylenedioxy ring is coplanar with the benzene ring. Accordingly, the oxygen p-orbitals are directed at right angles to the plane, and are always disposed for optimal overlap with the π-system of the ring (*cf.* XXV). In other words, the methylenedioxy grouping can be expected to effectively delocalize a plus charge originating in attack of a cationoid species across the ring. In the trimethoxybenzene system XXVI, each of the three oxygen atoms is within virtual contact distance to the neighboring oxygen. The only way all three of the methoxy groups can be coplanar with the benzene ring is to twist each group so that it points away from the carbonyl. Models show that this arrangement is possible, but only when the carbon atom of the methoxy group next to the carbonyl is in contact with, and two of the hydrogen atoms of this methoxy group overhang and straddle, the oxygen of the adjacent methoxy group. The same is true for the central methoxy group relative to the methoxy *para* to the carbonyl. It is questionable whether such an arrangement is energetically favorable, and reasonable to assume that the transition state will have the methoxyl groups *ortho* and *meta* to the developing carbonyl—possibly *para* as well–out of the plane of the ring to various degrees. The oxygen p-orbitals of these twisted methoxyls will be less effective in overlapping the ring π-system, and therefore will be less effective in stabilizing the transition state. Furthermore, since operation of the *electron-withdrawing inductive effect* of oxygen is independent of orbital overlap, the net effect of a methoxyl group with its methyl group out of the plane of the ring could be to *hinder* rather than to help electrophilic substitution.[36]

Accordingly, on the basis of both steric and stereoelectronic factors, we concluded that cyclization on the methylenedioxybenzene ring would occur in preference to the trimethoxybenzene ring. Formulations Xa, Xb, XXVII and XXVIII show the four possible cyclization products. Again considering the stability of the product to parallel the stability of the transition state, tetralone structure Xa, with adjacent substituents *trans* on a six-membered ring, was the most favored. Since the two *cis*, opposed, groups in indanone XXVIII are close to one another and are both rigidly axial, this form was ranked as least likely. The *cis*-disubstituted tetralone XXVII and the *trans*-disubstituted indanone Xb were clearly forms of intermediate stability. The experimental results were in accord with this analysis. One of the diastereoisomeric benzhydrylsuccinic acids (VIIIb) cyclized to give an indanone Xb in low yield (see below). The other stereoisomer, designated as VIIIa, gave tetralone Xa in good yield.[37]



XXVII



XXVIII

The structure of tetralone Xa is well established. The ketonic infrared absorptions of Xa and of its esters appear at 5.90–5.95 μ. This absorption is expected for a tetralone carbonyl, but not for an indanone carbonyl, which should absorb below 5.87 μ.[39] Independent evidence for the tetralone ring was obtained by aromatizing Xa to a naphthol.[40] All question about the correctness of structure Xa was removed when DL-α-apopicropodophyllin (XVIII) emerged in a later stage of the synthesis. With α-apopicropodophyllin related both to keto acid Xa and to picropodophyllin (I), the previously reported[26] oxidation of picropodophyllin to 2-(3',4',5'-trimethoxybenzoyl)-piperonylic acid (III) eliminated all possibility of cyclization of IXa on the trimethoxybenzene ring.[41] *trans*-Assignment to the groups in the tetralone intermediate Xa was supported by the fact that no sign of isomerization was noted when the keto acid Xa or its ester XIa was exposed to hot alkali. For example, no epimerization occurred after three hours in boiling 20% aqueous methanolic sodium hydroxide.[20] On the basis of the *trans* configuration in tetralone Xa, provisional stereochemical assignments for the precursor compounds were made. With Xa in the *trans* configuration, benzhydrylsuccinic acid VIIIa can be formulated as shown. Further, by the generalization that catalytic hydrogenation inserts

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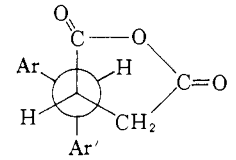
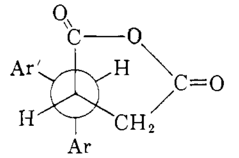
[36] Similar reasoning was followed by G. Baddeley, N. H. P. Smith and M. A. Vickars [*J. Chem. Soc.*, 2455 (1956)] in interpreting the 980:1 ratio of solvolysis rates for 5-chloromethylcoumaran and 3,5-dimethyl-4-methoxybenzyl chloride, and the 200:1 ratio of bromination rates for coumaran and 2,6-dimethylanisole. The same authors also present a detailed analysis of stereoelectronic interactions in both ground and activated states. Also *cf.* H. Hart and C. R. Wagner, *Proc. Chem. Soc.*, 284 (1958), and E. M. Arnett and C. Y. Wu, *Chemistry & Industry*, 1488 (1959). The fact that electrophilic substitution in methylenedioxybenzene is *slower* than in veratrole [G. Baddeley, G. Holt, N. H. P. Smith and F. A. Whittaker, *Nature*, **168**, 386 (1951)] is not directly pertinent to our situation; the more appropriate comparison would be between methylenedioxybenzene and trimethoxybenzene.

[37] The above conclusions could also be reached on the assumption that the product is determined by the most likely conformation of the precursor compound.[38] Rotamer XXIX, the most stable conformation



XXIX



XXX

Ar = trimethoxyphenyl Ar = trimethoxyphenyl
Ar' = methylenedioxyphenyl Ar' = methylenedioxyphenyl

for anhydride IXa, has the appropriate groups oriented for cyclization to tetralone Xa. Rotamer XXX, the most stable conformation for anhydride IXb, has tbe approrpiate groups oriented for cyclization to indanone Xb.

[38] *Cf.* D. Lednicer and C. R. Hauser, THIS JOURNAL, **80**, 3409, 6364 (1958).

[39] Examples and generalizations are given, *inter alia*, by J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951); W. M. Schubert and W. A. Sweeney, THIS JOURNAL, **77**, 4172 (1955); J. Lecompte, *J. phys. radium*, **6**, 257 (1945); also *cf.* ref. 18, 23 and 38.

[40] To be published.

[41] Later, Dr. G. N. Walker very kindly supplied us with samples of cyclic keto acid Xa prepared from keto acid III by an unequivocal route.[20] Direct comparisons provided additional confirmation.

both hydrogen atoms on the same side of the ethylenic linkage, the geometry of itaconic acid VIIa is fixed.

Tetralone ester XIa was formylated with ethyl formate, using sodium hydride as catalyst. Bicarbonate-insoluble hydroxymethylene derivative XIII was obtained in 68% yield; small amounts of three bicarbonate-soluble materials, one of which is the acid XXXVIII corresponding to XIII,[42] also were formed. Hydroxymethylene compound XIII could be converted to dihydroxy ester XIV,[43] either in one step by sodium borohydride reduction,[44] or in two steps by catalytic hydrogenation to hydroxymethyl derivative XVI[46] followed by borohydride reduction. The absorption spectra of these compound were consistent with the assigned structures. The presence of hydroxyl in hydrogenation product XVI was substantiated by formation of an acetoxy derivative XVII.

Dehydration of dihydroxy acid XV gave rise either to DL-α-apopicropodophyllin (XVIII) or to DL-β-apopicropodophyllin (XIX). The former compound was obtained when the dihydroxy acid was warmed in 10% sulfuric acid, and the crude product crystallized in ethyl acetate containing traces of acid. DL-β-Apopicropodophyllin (XIX) was obtained when no precaution was taken to ensure an acid environment. The recognized rapid conversion of α- to β-apopicropodophyllin[4,12] under very mild base catalysis accounts for these results. The identity of the racemic materials was established by ultraviolet and infrared comparisons with optically active materials derived from the natural products.[4,12]

Resolution was effected at the DL-α-apopodophyllic acid (XX) stage, which was reached by saponification of DL-β-apopicropodophyllin (XIX). Both α-apopicropodophyllin *and* β-apopicropodophyllin are known to give the same α-apopodophyllic acid on saponification,[4,12] so that the location of the double bond in unsaturated lactones XVIII and XIX turned out to be not of great importance. Synthetic DL-α-apopodophyllic acid (XX) showed the same ultraviolet absorption as the optically active material; the significant differences in the infrared absorptions—determined with the two materials as mineral oil mulls—were attributed to intermolecular factors. The quinine salt of α-apopodophyllic acid separated smoothly from the racemic acid XX. Infrared absorption, mixed melting point and optical rotation comparisons between the quinine salt obtained from synthetic material and the quinine salt obtained from degradation of α-apopodophyllic acid showed that the two salts were the same. Synthetic, optically active, α-apopodophyllic acid (XXI), regenerated from its quinine salt, was likewise identical with authentic α-apopodophyllic acid; comparisons by melting points, mixed melting point, ultraviolet and infrared absorptions, and optical rotations all served to confirm the identity. After the identity was established, the remaining steps of the synthesis were conveniently carried out with readily accessible degradation material.

First α-apopodophyllic acid (XXI) was cyclized, either by heating at 180° [4] or by exposure to boiling 10% sulfuric acid, to α-apopicropodophyllin (XXII). Then hydration was effected by a process essentially the reverse of the acid-catalyzed dehydration of picropodophyllin.[48] Prolonged exposure of α-apopicropodophyllin (XXII) to glacial acetic acid containing hydrogen chloride, followed by treatment of the crude product with aqueous acetone and calcium carbonate afforded the desired picropodophyllin (XXIII). Its identity was established by melting point, mixed melting point and infrared absorption comparisons, as well as by similar comparisons of the derived acetate XXIV.[6] In the hydration process, combination of α-apopicropodophyllin with proton to give a *cis* fused lactone ring (as in picropodophyllin) rather than a *trans* fused ring reasonably could be expected. In the next stage a chloro group, or more likely an acetoxy group, would be attached to the carbonium carbon[10,48] next to the aromatic ring. The stereochemical problem at this point is simplified by the greater stability of the "normal" configuration of hydroxyl (as in picropodophyllin) over the epi configuration.[7] The low yield in the addition process was not unexpected considering the ease of dehydration of α-tetralols to dihydronaphthalenes. More specifically, in the equilibria between the unsaturated α-apopicropodophyllin and the saturated forms, the unsaturated molecule is distinctly favored.[48]

Reactions of Itaconic Acid VIIb (Chart 2).—Itaconic acid VIIb showed the same melting point as the first isomer, VIIa. The mixed melting point, however, was depressed by more than 20°. Dimethyl and monomethyl ester derivatives of itaconic acid VIIb were readily accessible. No isomerization of itaconic acid VIIb to VIIa occurred on exposure to hot acetic–hydrochloric acid. Instead a decarboxylation product, 4-(methylenedioxyphenyl)-4-(trimethoxyphenyl)-3-butenoic acid (XXXI), was obtained.[49] Itaconic acid VIIa under the same conditions gave the same product.

Hydrogenation of itaconic acid VIIb furnished a single material, 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic acid (VIIIb), in high yield. The dimethyl ester XXXII was formed with diazomethane, and the anhydride IXb with acetyl chloride. No epimerization occurred in either case, since saponification of either ester or anhydride regenerated unchanged acid VIIIb. In

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(42) In a similar process with a related keto ester, Drake and Tuemmler[24] reported appreciable quantities of bicarbonate-soluble product when the reaction period was extended.

(43) Evidence that this is ethyl DL-epiisopodophyllate, that is, that the sterochemistry is as indicated in XIV, will be published.

(44) Formation of 1,3-diols by reduction of enolic 1,3-dicarbonyls with lithium aluminum hydride gives poor results [*Cf.* A. S. Dreiding and J. A. Hartman, This Journal, **75**, 939, 3723 (1953); R. Vonderwahl and H. Schinz, *Helv. Chim. Acta*, **35**, 2368 (1952); F. Petuely and H. F. Bauer, *Monatsh.*, **83**, 758 (1952)]. Sodium borohydride is preferred.[24,45]

(45) G. N. Walker, This Journal, **75**, 3393 (1953).

(46) This conversion is similar to the platinum (alcohol) hydrogenation of 1-methyl-4-formyl-5-keto-2,3,4,5-tetrahydro-1-benzazepine[47] but not to the palladium-on-carbon (acetic acid) hydrogenation of a molecule very closely related to XIII.[45]

(47) B. D. Astill and V. Boekelheide, This Journal, **77**, 4079 (1955).

(48) A. W. Schrecker and J. L. Hartwell, *ibid.*, **76**, 752 (1954).

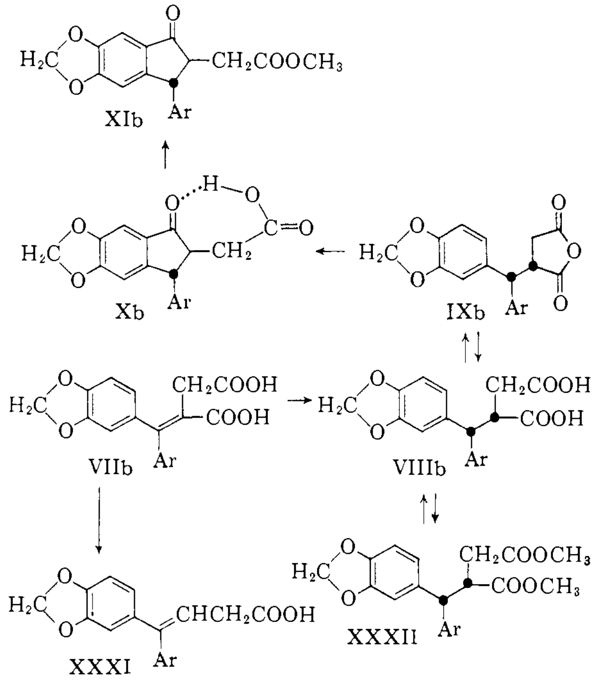
(49) *Cf.* W. S. Johnson and G. H. Daub, in R. Adams', "Organic Reactions," Vol. 6, John Wiley and Sons, Inc., New York, N. Y. 1951, p. 1.

an isolated experiment, in which anhydride IXb was exposed to temperatures of 240°, some epimerization was noted. Saponification led to a mixture from which succinic acid VIIIa could be separated. The salt of saturated acid VIIIb was stable to potassium *t*-butoxide in hot *t*-butyl alcohol.

Cyclization of succinic acid VIIIb was conspicuously unsatisfactory. The best results, obtained when anhydride IXb was treated with aluminum chloride in nitrobenzene, gave indanone acid Xb in less than 10% yield. The structure of Xb follows from the arguments presented above, and from infrared and ultraviolet absorption data. The acid Xb in chloroform solution showed only one carbonyl absorption peak at 5.86 μ, to which both the indanone carbonyl and the carboxylic acid carbonyl contributed.[39] The corresponding methyl ester XIb displayed the expected absorption peaks at 5.78 μ (ester carbonyl) and at 5.87 μ (indanone carbonyl). The ultraviolet absorption curve of Xb is similar to that of tetralone acid Xa and of its esters. This suggests that all these compounds have the same ultraviolet chromophore, and accordingly indicates the presence of an acylated methylenedioxybenzene system in Xb as in Xa. The *trans* arrangement in indanone Xb is in accord with the fact that no isomerization occurs when the ester XIb is exposed to alkali. In this connection, attempts to prepare stereoisomeric forms of other 2,3-disubstituted indanones by cyclization, for example, 2-ethyl-3-methylindanone,[50] 2-phenyl-3-benzylindanone,[38] or 2-phenyl-3-methylindanone,[51] have failed; in each case, the single form obtained is considered to be *trans*. The infrared absorption of Xb warrants comment. Although the keto acid Xb in solution absorbs as expected at 5.86 μ, the same compound *in a mull* shows two peaks, one at 5.71 and the other at 6.00 μ. If the molecule in the crystal is constrained to the configuration indicated in Xb (easily attained, and strain-free according to scale models), intramolecular hydrogen bonding will be strong. If so, the 6.00 μ peak can be ascribed to an abnormally high indanone carbonyl absorption, while the 5.71 μ peak can be ascribed to an abnormally low acid carbonyl absorption, one in fact resembling that of a six-membered lactone.[52]

CHART 2

REACTIONS OF ITACONIC ACID VIIb AND DERIVATIVES (Ar = trimethoxyphenyl)



Experimental[53]

Methylenedioxybenzene (IV).—Catechol (110 g., 1.0 mole), methylene chlorobromide (260 g., 2.00 moles), and ethylene glycol (300 ml.) were heated together in an oil-bath at 40°. Anhydrous potassium carbonate (150 g., 1.07 moles) was added, and the mixture was boiled for 8 hours. After the first 35 minutes a fresh portion of potassium carbonate (30 g.) was added, and after 65 minutes another 20 g. was added. The inside temperature of the boiling reaction mixture rose from 70° at the start to 130° at the end of the 8-hour period. More methylene chlorobromide (65 g.) and more potassium carbonate (30 g.) were added cautiously, and the mixture was held in the oil-bath at 125° (inside temperature 100°) for 12 hours.

The mixture was steam distilled, one liter of distillate being collected. After separation of the lower organic layer, the aqueous layer was extracted with two 100-ml. portions of chloroform. The extract was dried with magnesium sulfate, combined with the organic layer, the solvent was removed, and the oily residue was distilled. The fraction (42 g., 34%) boiling at 71–72° (10 mm.), $n^{25}\mathrm{D}$ 1.5360, was taken as methylenedioxybenzene.

Methylenedioxybenzene also was prepared according to the sequence: piperonal oxime (84%) from piperonal, dehydration with acetic anhydride to piperonylonitrile (93%), Radziszewski (peroxide) hydration to piperonylamide (95%), sodium hypochlorite degradation to 3,4-methylenedioxyaniline (73%), and deamination by hypophosphorous acid reduction of the diazotized material to methylenedioxybenzene (72%). The one-step preparation from catechol was preferred over the five-step preparation from piperonal since, despite satisfactory yields at each stage, the over-all yield (39%) from piperonal was about the same as from catechol.

3,4,5-Trimethoxybenzoyl Chloride (V).—Dimethyl sulfate (402 ml., 4.3 moles) was added dropwise over a period of 2–3 hours to a cold stirred solution of 150 g. (0.798 mole) of gallic acid and 240 g. (6.0 moles) of sodium hydroxide in 1.5 l. of water. Oxygen-free nitrogen blanketed the reaction mixture throughout the preparation. The mixture was stirred further for 20 minutes at room temperature, for 2 hours at the boiling point, and, after addition of 60 g. of sodium hydroxide dissolved in 90 ml. of water, for another 2 hours at the boiling point. Acidification of the cooled mixture precipitated the product, which was collected, washed with water, and pressed to a cake. A solution of the damp solid in methanol, after treatment with decolorizing carbon (Darco), was cooled. Colorless crystalline 3,4,5-trimethoxybenzoic acid, m.p. 167–168°, was obtained in 81% yield (152 g.).

A mixture of 144 g. of 3,4,5-trimethoxybenzoic acid (0.678 mole), 360 ml. of dry benzene and 177 ml. of thionyl chloride (2.46 moles) was boiled for 18 hours. All material volatile at steam-bath temperatures and water-pump pressures was removed. The residue was dissolved in 200 ml. of boiling benzene and treated with decolorizing carbon. The decolorized solution, concentrated to a volume of approximately 150 ml. and diluted with 150 ml. of ligroin (dens. 0.72–0.74), was cooled. The precipitated 3,4,5-tri-

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(50) R. Granger, M. Corbier, J. Vinas and P. Nau, *Bull. soc. chim. France*, 810, 815 (1957).

(51) A. A. Plentl and M. T. Bogert, THIS JOURNAL, **63**, 989 (1941).

(52) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1958, p. 186.

(53) Elementary analyses were performed by Carol K. Fitz, 115 Lexington Ave., Needham Heights, Mass., and by S. M. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass.

methoxybenzoyl chloride (V), after drying, weighed 139 g. (89%) and showed m.p. 79–80°. Distillation of the product although possible (b.p. 79–80° at 23 mm.) was unnecessary.

3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzophenone (VI).—To methylenedioxybenzene (89.5 g., 0.735 mole) in 600 ml. of methylene chloride that had been distilled from phosphorus pentoxide was added 239 g. (107 ml., 0.92 mole) of stannic chloride. The apparatus was protected from atmospheric moisture, and the reaction mixture was agitated continuously with a stirrer carrying a Teflon blade. A solution of 182 g. (0.79 mole) of 3,4,5-trimethoxybenzoyl chloride (V) in 600 ml. of methylene chloride was added dropwise over a 1-hour period to the mixture cooled in an ice-bath. After 24 hours, during which time the temperature had been allowed to come to 25°, 540 ml. of concentrated hydrochloric acid was added over a 30-minute period. The reaction mixture was stirred further for 24 hours. During addition of the hydrochloric acid and for some time thereafter large amounts of hydrogen chloride were evolved.

Aqueous sodium chloride solution (10%, 2 to 4 l.) was added to help break the emulsion, and the lower organic layer was separated and washed with three 1200-ml. portions of 10% potassium hydroxide solution. The acid and the alkaline washings were extracted separately with methylene chloride, and all the organic solutions were combined. This solution was shaken with 120 ml. of 2% aqueous sodium chloride solution and then was filtered through a layer of diatomaceous earth (Celite) and dried with calcium chloride. Solvent was removed from the dry dark brown solution by distillation on the steam-bath, and the residue, dissolved in 1.5 l. of benzene, was allowed to flow through a column (2″ diameter) containing 425 g. of Merck acid-washed alumina. The column was rinsed by passage of 2 l. of fresh benzene. The combined benzene solutions were distilled under reduced pressure to remove all volatile material. A solution of the tan residual solid in 200 ml. of chloroform and 1200 ml. of methanol was distilled until the volume was 800 ml. Allowing this solution to stand first at room temperature and then at 5° afforded two crops of crystals, which were collected and washed on the funnel with ice-cold methanol. The white 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzophenone (VI) so obtained, m.p. 124–126°, weighed 185 g. (80%), and showed an absorption maximum at 315 mμ (log ε 4.45) in 2×10^{-5} *M* absolute alcohol solution. The carbonyl absorption peak appeared at 6.05 μ. The same compound was reported before with m.p. 125–127°.[26,27]

When tetrachloroethane was used as solvent instead of methylene chloride, the same product was obtained in 65% yield. Other combinations of catalysts (aluminum chloride and stannic chloride) and solvents (carbon disulfide and benzene) at various temperatures gave much poorer results.

3,4-Methylenedioxy-3′,4′,5′-trimethoxydiphenylitaconic Acids A and B (VIIa and b).—To a scrupulously dried 5 l. three-necked flask provided with a stirrer and reflux condenser was added 1500 ml. of *t*-butyl alcohol that had been distilled first from calcium hydride and then from lithium aluminum hydride. Dry nitrogen was passed through the apparatus before adding the *t*-butyl alcohol, and thereafter throughout the course of the experiment. A moisture trap was fitted to the top of the condenser. Pieces of clean potassium (30.2 g., 0.77 g. atom) were weighed in xylene, quickly blotted with filter paper, and dropped into the flask against a stream of nitrogen. The potassium dissolved after heating and stirring the mixture for 0.5 hour. 3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzophenone (195 g., 0.62 mole) was added as quickly as possible, and was dissolved by boiling the mixture for 0.5 hour. Freshly distilled ethyl succinate (204 g., 1.18 moles) was added rapidly, and the reaction was allowed to proceed at reflux temperatures for 15 hours.

The cooled mixture was treated with 190 ml. of 5 *N* hydrochloric acid, was concentrated by distillation under reduced pressures to a volume of 600 ml., and was diluted with 1 l. of water. The product was extracted first with three 400-ml. portions of ether, and then from the ether into three 500-ml. portions of saturated aqueous sodium bicarbonate solution. The bicarbonate solution was added to 350 ml. of concentrated hydrochloric acid containing 800 g. of ice, and the resulting oil extracted with three 400-ml. portions of ether. The combined ethereal solutions, after drying with calcium chloride, were warmed to remove solvent.

Saponification of the Stobbe half-ester product was effected by boiling a mixture of the residual brown gum (272 g.) with 375 ml. of methanol, 600 ml. of water and 120 g. of sodium hydroxide for 18 hours. A portion of the solvent (400 ml.) was removed by distillation, and the concentrate was added dropwise to a stirred mixture of 360 ml. of 10 *N* hydrochloric acid and 1200 g. of ice. The precipitated itaconic acids were collected on the funnel and washed free of chloride ion with ice-water. Trituration of the wet, somewhat sticky solid with ether furnished powdery, pale yellow material, which was collected by filtration. More product could be obtained from the various washings by ether extraction. The crude itaconic acids, after air-drying, weighed 240 g.

Isomers VIIa and VIIb were separated by boiling a mixture of the crude product with 1450 ml. of methanol and 635 ml. of acetone until almost all of the solid had dissolved. After filtration to remove some insoluble extraneous material, the solution was distilled until the vapor temperature reached 62.5°. Methanol (250 ml.) was added and distillation was continued until the vapor temperature was 64°. The solution was seeded with a crystal of itaconic acid VIIa, and was allowed to stand at room temperature for 20 hours. The crystalline precipitate was removed by filtration, washed with 50 ml. of ice-cold methanol, and was dried *in vacuo* at 80°. This fraction of itaconic acid VIIa weighed 89 g. and showed m.p. 196–198°.

The filtrate and washings were taken to dryness by distillation under reduced pressures. The residue was crystallized by solution in excess acetone, concentration of the solution to approximately 250 ml., and cooling. Crystals of itaconic acid VIIb were collected, washed on the funnel with 50 ml. of ice-cold acetone, and air-dried. This crop, m.p. 195–198°, weighed 89.7 g. Reworking the various mother liquors furnished an additional 12 g. of itaconic acid VIIa, m.p. 196–198°, and 10 g. of itaconic acid VIIb, m.p. 196–198°. The two isomers were accordingly obtained in equal amounts, each in 39% yield.

Recrystallization of VIIa from methanol furnished material, m.p. 200–201° dec. The analytical sample was dried at 140° *in vacuo*.

Anal. Calcd. for $C_{21}H_{20}O_9$: C, 60.57; H, 4.84; neut. equiv., 208.2. Found: C, 60.5; H, 4.8; neut. equiv., 207.5.

When the sample was dried *in vacuo* over phosphorus pentoxide at 56°, material with the same melting point but containing methanol of crystallization was obtained. In absolute alcohol (3.8×10^{-5} *M*), absorption maxima appeared at 217 mμ (log ε 4.43), 292 mμ (log ε 4.07), and an inflection at 250 mμ. A mull with mineral oil showed absorption at 5.87, 5.95 and 3.00 μ.

Anal. Calcd. for $C_{21}H_{20}O_9 \cdot CH_3OH$: C, 58.92; H, 5.40; methanol, 7.14; neut. equiv., 224.2. Found: C, 59.0; H, 5.3; loss in weight on drying at 140°, 7.2%; neut. equiv., 223.

Recrystallization of itaconic acid VIIb from acetone brought the melting point to 200° dec.

Anal. Calcd. for $C_{21}H_{20}O_9$: C, 60.57; H, 4.84; neut., equiv., 208.2. Found: C, 60.8; H, 4.8; neut. equiv. 208.8.

In alcohol solution (3.9×10^{-5} *M*), itaconic acid VIIb showed absorption maxima at 210 mμ (log ε 4.66), 291 mμ (log ε 4.14) and an inflection point at 250 mμ; mulled with mineral oil the compound showed absorption peaks at 5.79 and 5.92 μ.

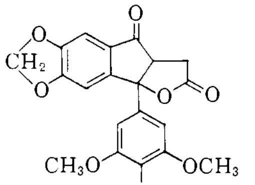
The mixture melting point of the two itaconic acids was 172–178°.

Action of Polyphosphoric Acid on 3,4-Methylenedioxy-3′,4′,5′-trimethoxydiphenylitaconic Acid (VIIa).—An intimate mixture of 1.0 g. of itaconic acid VIIa and 12 g. of polyphosphoric acid was allowed to stand at 25° for 2 days. Water (40 ml.) was added to the black mass, the mixture was filtered, and the solids were washed on the funnel with water, saturated sodium bicarbonate solution, and water. The black solid, after drying *in vacuo* over phosphorus pentoxide, was dissolved in 50 ml. of benzene and the solution allowed to flow through a 12 × 1 cm. column of Merck acid-washed alumina (15 g.). The column was eluted with fresh benzene. Removal of all solvent from the eluate by distillation at reduced pressure on the steam-bath furnished a dark gummy residue. This was crystallized twice (decolorizing carbon was employed once) by solution in a small volume of chloroform, dilution with hot methanol, concentration, and cooling. The small pearly plates (47 mg., m.p. 221–222°) were crystallized again to give the analytical sample, m.p. 222°.

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.0; H, 4.5.

Infrared absorption bands appeared at 5.62 and 5.82 μ. The compound in absolute alcohol (2.5 × 10^{-5} *M*) showed ultraviolet absorption maxima at 208 mμ (log ε 4.55), 235 (4.35), 271 (3.72) and 316 (3.79).

A structure consistent with the available information on the 221–222° melting product is keto lactone XXXIII,[54] in which the lactonic and ketonic carbonyl groups might be expected to absorb, respectively, at 5.62 and 5.82 μ. The ultraviolet absorption curve of XXXIII is very similar to that of indanone Xb, and both resemble that of tetralone acid Xa as well as its ethyl (XIa) and methyl ester.[55]



XXXIII

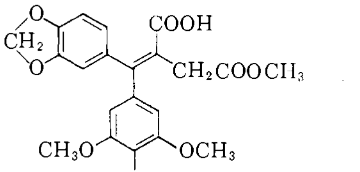
3,4-Methylenedioxyphenyl-3′,4′,5′-trimethoxyphenylitaconic (VIIa) Anhydride.—Acetyl chloride (10 ml.) containing 1.0 g. of itaconic acid VIIa was boiled for 20 minutes. Excess reagent was removed by distillation, and the yellow residue was dissolved in 30 ml. of benzene and washed with aqueous sodium bicarbonate solution, and with water. The solution was dried with magnesium sulfate. Removal of benzene under reduced pressure at 95° left a yellow oil, which crystallized on cooling to a solid (0.95 g.), m.p. 164°. Two crystallizations from benzene–petroleum ether (b.p. 30–60°) furnished lumpy yellow crystals, m.p. 163–164°. The infrared absorption curve of this itaconic anhydride from VIIa showed peaks characteristic for a five-membered cyclic anhydride at 5.44 and 5.65 μ.

Anal. Calcd. for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.6, 63.3; H, 4.77, 4.3.

Monomethyl Ester of 3,4-Methylenedioxyphenyl-3′,4′,5′-trimethoxyphenylitaconic (VIIa) Acid.—The anhydride of itaconic acid VIIa (0.2 g.) was allowed to react in 5 ml. of dry boiling methanol for 24 hr. Complete solution was evident after 2 hours, and the initial yellow color of the mixture gradually faded and disappeared altogether after 8 hours. When the colorless glassy material remaining after removing all solvent was crystallized from aqueous methanol, colorless rods (0.19 g.), m.p. 126–127° with preliminary sintering, were obtained. Recrystallization from benzene–petroleum ether (b.p. 30–60°) gave analytically pure half methyl ester, m.p. 127–128°.

Anal. Calcd. for $C_{22}H_{22}O_9$: C, 61.39; H, 5.15. Found: C, 61.17; H, 5.39.

Infrared absorption bonds at 5.73 and 5.83 μ corresponded to saturated ester and α,β-unsaturated acid groupings, respectively. The half-ester was soluble in saturated aqueous sodium bicarbonate solution. Structure XXXVII is consistent with the available experimental facts.



XXXVII

Dimethyl Ester of 3,4-Methylenedioxyphenyl-3′,4′,5′-trimethoxyphenylitaconic (VIIa) Acid.—A distilled ethereal solution (55 ml.) of diazomethane (excess) was poured onto 0.5 g. of itaconic acid VIIa. After the acid had dissolved, the solution in a loosely stopped flask was allowed to stand at 5° for 16 hours. Glacial acetic acid was added dropwise to discharge the yellow color, and the solvent was removed *in vacuo* at temperatures up to 100°. Crystallization of the residue from methanol gave 0.46 g. of the dimethyl ester of VIIa, m.p. 116–117°. Further crystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{23}H_{24}O_9$: C, 62.15; H, 5.44. Found: C, 62.4; H, 5.4.

This dimethyl ester, which was insoluble in aqueous bicarbonate, showed absorption maxima (3.68 × 10^{-5} *M* alcohol solution) at 211 mμ (log ε 4.61), 297 (4.11), and an inflection point at 246 (4.17). Infrared absorption peaks at 5.75 and at 5.88 μ corresponded to saturated and α,β-unsaturated ester groupings, respectively.

3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic Acid (VIIIa).—A warm mixture of 500 ml. of absolute alcohol and 12.0 g. (0.0289 mole) of itaconic acid VIIa, most of which was in solution, was placed in an atmosphere of hydrogen. The mixture was stirred at 70° until all the solid had dissolved. A slurry of 3 g. of 5% palladium-on-charcoal catalyst with 20 ml. of absolute alcohol was introduced through a side-arm. Reducing the hydrogen pressure inside the apparatus to just below atmospheric facilitated the addition. Hydrogenation of the stirred reaction mixture at a temperature of 60° was allowed to proceed for 1.5 hours, at which time absorption of hydrogen ceased. The amount of hydrogen taken up corresponded to 117% of the theoretical.

The cooled hydrogenation mixture was filtered, and solvent was removed from the filtrate by distillation on the steam-bath under reduced pressure. The residue was dissolved in 40 ml. of hot chloroform, 400 ml. of ether was added, and the solution was filtered without delay through diatomaceous earth to remove a small amount of flocculent solid. Removal of all solvent afforded 3,4-methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic acid (VIIIa), which precipitated during the evaporation in the form of a white powder (11.5 g. or 96%), m.p. 200°. Crystallization from concentrated ether solution did not change the melting point.

Anal. Calcd. for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 60.2; H, 5.3.

The compound in alcohol solvent showed an ultraviolet absorption maximum at 283 mμ (log ε 3.62) with a shoulder at 242 mμ.

Hydrogenation over a palladium catalyst in acetic acid solvent was possible, but offered little advantage. No hydrogen was absorbed over Adams catalyst in ethanol, in ethyl acetate, in ethyl acetate containing a few drops of 70% perchloric acid, or in glacial acetic acid. Hydrogenation of the disodium salt of itaconic acid VIIa in an aqueous system over Raney nickel was likewise ineffective.

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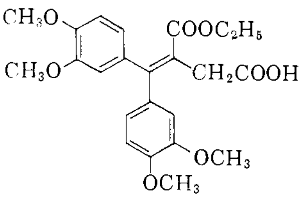
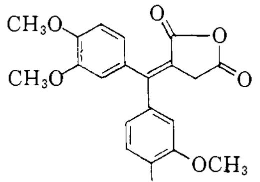
(54) *Cf.* H. Stobbe and W. Vieweg, *Ber.*, **35**, 1727 (1902); also see ref. 15.

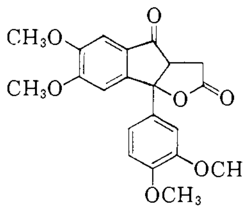
(55) In this connection, half-ester XXXIV on treatment with polyphosphoric acid has been reported[23] to give anhydride XXXV. The



XXXIV



XXXV



XXXVI

observed infrared absorption peaks for the product at 5.60 and 5.83 μ were regarded as the pair of absorption peaks expected of anhydrides. However, the peaks for anhydrides of type XXXV might be expected to appear at significantly lower wave lengths. For example, the two peaks for the structurally similar anhydride of itaconic acid VIIa are displayed at 5.44 and 5.65 μ. It is possible that the compound reported as anhydride XXXV is in fact keto lactone XXXVI.

3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic Anhydride (IXa).—A solution of 0.5 g. of succinic acid VIIIa in 10 ml. of acetyl chloride was boiled for 25 minutes. Excess reagent was removed by distillation, and the residue was held at 100° under reduced pressure for 2 hours. The orange-red glassy residue, which could not be induced to crystallize, was distilled at 0.01 mm. in a creased test-tube still. The succinic anhydride IXa was collected at 200–230° (external temperature) as a practically colorless, viscous, almost glassy oil (0.4 g.).

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 63.0; H, 5.2.

Anhydride IXa could be hydrolyzed to unchanged succinic acid VIIIa. The anhydride from 0.2 g. of succinic acid VIIIa was allowed to stand for 6 days in a mixture of 12 ml. of dioxane and 7 ml. of 0.25 *N* sodium hydroxide solution. The solution was acidified with dilute hydrochloric acid, was diluted with water, and cooled for several days. The precipitated crystals of succinic acid VIIIa, after washing and drying *in vacuo*, weighed 0.17 g. and showed the correct melting point.

1-(3′,4′,5′-Trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoic Acid (Xa).—A mixture of redistilled acetyl chloride (80 ml.) and 18.0 g. (0.043 mole) of succinic acid VIIIa was boiled for 3 hours, after which period the bulk of the acetyl chloride was removed by distillation. A solution of the residual anhydride in 100 ml. of benzene was shaken with two 100-ml. portions of saturated bicarbonate solution and then with 50 ml. of water. The dried (magnesium sulfate) solution was distilled at reduced pressures on the steam-bath, and all solvent was removed from the remaining anhydride IXa by pumping at 2 mm.

This anhydride, dissolved in 100 ml. of dry, distilled nitrobenzene, was added over a period of 20 minutes to a magnetically stirred solution of stannic chloride (28.8 g., 0.118 mole) in 100 ml. of nitrobenzene. During the addition as well as during the subsequent 5-hour period of stirring, the temperature was held at 0°. The mixture gradually acquired a deep-red color.

Cold 5 *N* hydrochloric acid (100 ml.) was added gradually with stirring to the cold reaction mixture. The upper organic layer was separated, and was washed with 100 ml. of 5 *N* hydrochloric acid followed by three 50-ml. portions of water. Methylene chloride (150 ml.) was added, and the acidic material was extracted into three 100-ml. portions of saturated aqueous sodium bicarbonate. The combined bicarbonate extracts were washed once with ether, and then added dropwise to a stirred mixture of concentrated hydrochloric acid (100 ml.) and crushed ice (400 g.). The solid was collected, washed on the funnel with ice-water until free of chloride ion, and then pressed and sucked until most of the water was removed.

A solution of the damp cake in 300 ml. of methanol, after concentration to a volume of 150 ml., was allowed to stand at room temperature. The precipitated feathery needles were collected, washed first with ice-cold methanol and then with ether (25 ml.), and finally were dried *in vacuo* at 50°. Almost white 1-(3′,4′,5′-trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoic acid (11.6 g. or 67%) was obtained, with m.p. 219–220° dec. Recrystallization from ether containing a small amount of methanol, or from ether–petroleum ether (b.p. 30–60°), did not change the melting point significantly.

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 63.0; H, 5.2.

The same product Xa was prepared from anhydride IXa by cyclization with aluminum chloride in nitrobenzene (59% yield), as well as from the diacid VIIIa by cyclization with polyphosphoric acid[56] either at 23° (7% yield) or at 80° (6% yield). The ultraviolet absorption curve (2×10^{-5} *M* in alcohol) showed maxima at 234 mμ (log ε 4.11), 275 (3.60) and a plateau at 314–330 (3.51).

When mixed with keto acid Xa prepared in a different way,[20,41] the material showed m.p. 218–219° dec.

Ethyl 1-(3′,4′,5′-Trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate (XIa).—A solution of 11.2 g. (0.028 mole) of keto acid Xa in 150 ml. of absolute alcohol containing 1 ml. of concentrated sulfuric acid was boiled under a moisture-protected reflux condenser for 4 hours. Decolorizing carbon (0.5 g.) was added, and after another half-hour of boiling the mixture was filtered through a filter acid (Celite), and the filtrate concentrated by distillation to a volume of 120 ml. The cooled solution was diluted with 500 ml. of ice-water, and the white precipitate was removed by filtration, and washed on the funnel first with water and then with saturated sodium bicarbonate solution. The solid product, after drying *in vacuo* at 90° for 4 hours, was crystallized from methylene chloride to furnish 9.9 g. (83%) of keto ester XIa, m.p. 152–153°. Repeated crystallization from ethanol raised the melting point to 162–163°.

Anal. Calcd. for $C_{23}H_{24}O_8$: C, 64.48; H, 5.65. Found: C, 64.2; H, 5.4.

The 152–153° melting product gave a satisfactory analysis (C, 64.3; H, 5.7), and an infrared absorption curve identical with that from the 162–163° material. Both curves showed peaks for ester carbonyl (5.78 μ) and tetralone carbonyl (5.90 μ). Ultraviolet absorption maxima were observed in a 1.85×10^{-5} *M* alcohol solution at 207 mμ (log ε 4.78), 236 (4.51), 275 (3.99) and 318 (3.93).

Saponification of the ethyl ester XIa in boiling aqueous methanolic sodium hydroxide solution led to keto acid Xa (80% yield after crystallization) that did not depress the melting point of an authentic sample.

Methyl 1-(3′,4′,5′-Trimethoxyphenyl)-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate.—Absolute methanol (20 ml.) containing 0.21 g. of keto acid Xa and 2 ml. of concentrated sulfuric acid was boiled under a condenser for 12 hours. The hot solution was filtered, 60 ml. of water was added to the filtrate, and the mixture, after cooling in the ice-bath for 2 hours, was filtered. The solids were washed successively with water, saturated sodium bicarbonate solution, and water. The air-dried product (0.21 g., 98%), m.p. 174–175°, after two recrystallizations from methanol, weighed 0.17 g. and melted at 178–178.5°.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.5; H, 5.3.

The methyl ester of Xa admixed with the same material synthesized in a different way[20,41] (m.p. 173–175°) showed m.p. 177.5–178.5°.

The infrared absorption peaks at 5.95 and 5.77 μ corresponded to the ketonic and ester carbonyls, respectively. Ultraviolet absorption maxima at 236 mμ (log ε 4.45), 275 (3.94) and 320 (3.87) were evident in 3.54×10^{-5} *M* alcohol solution. The methyl ester of Xa also could be prepared by treating cyclic keto acid Xa with ethereal diazomethane.

1-(3′,4′,5′-Trimethoxyphenyl)-4-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoic Acid (XII) from Keto Acid Xa.—A solution of 0.7 g. (0.019 mole) of sodium borohydride in 12 ml. of water was added dropwise to a cold aqueous solution of 0.50 g. of cyclic keto acid Xa in 11.9 ml. of 0.105 *N* sodium hydroxide solution. The mixture, after standing at room temperature for one hour, was treated with 6 *N* hydrochloric acid, which decomposed excess reagent and precipitated a gelatinous solid. The mixture was cooled and filtered, and the solids were washed with cold water and dried *in vacuo*. Crystallization from methanol afforded 0.33 g. of hydroxy acid XII in two crops with m.p. 178–182°. One recrystallization brought the melting point to 181.4–182°.

Anal. Calcd. for $C_{21}H_{22}O_8$: C, 62.70; H, 5.5. Found: C, 62.7; H, 5.7.

Hydroxy acid XII in 2×10^{-5} *M* absolute alcohol solution had λ_{max} 291 mμ (log ε 3.73).

Lactonization did not occur[45] and the hydroxy acid XII was recovered unchanged after exposure to boiling 10% sulfuric acid for 2 hours.

Ethyl 1-(3′,4′,5′-Trimethoxyphenyl)-3-hydroxymethylene-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate (XIII).—Sodium hydride (4.4 g., 0.183 mole) was added to a solution of dry ethanol (5.2 ml., 0.113 mole) and benzene (375 ml.) that had been distilled from lithium aluminum hydride, and the mixture was stirred magnetically for 3 hours at room temperature. An atmosphere of oxygen-free dry nitrogen was maintained in the reaction flask during the entire preparation. Ethyl formate (19 ml., 0.237 mole) that had been dried over potassium carbonate and freshly distilled was added in a thin stream. Stirring was continued for another half-hour. A solution of 16.5 g. (0.0386 mole) of cyclic keto ester XIa in 250 ml. of absolute benzene was added dropwise to the stirred reaction mixture over a

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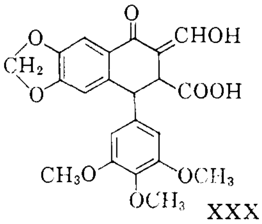
(56) *Cf.* J. Koo, This Journal, **75**, 1891 (1953).

period of 1 hour. The rusty-red mixture was stirred further for 12 hours.

The reaction mixture was poured onto a vigorously stirred mixture of 200 ml. of 2 N sulfuric acid and 100 g. of ice. After 5 minutes of stirring, the benzene layer was separated and was washed with two 100-ml. portions of water. The aqueous layer and washings were extracted with 50 ml. of benzene, which was combined with the original benzene layer. The benzene solution was extracted with saturated aqueous sodium bicarbonate solution (2 × 100 ml.), and the aqueous extract reserved for further treatment, as described below. The weakly acidic hydroxymethylene product XIII then was removed from the benzene solution by two extractions, each time with 100 ml. of 1% aqueous sodium hydroxide solution and 100 g. of ice. Without delay, the alkaline extracts were poured into 400 ml. of water containing 5 ml. of concentrated sulfuric acid and 500 g. of ice. The yellow precipitate was extracted with 600 ml. of ether–methylene chloride (5:1) and then with 150 ml. of ether–methylene chloride (2:1). The extracts were washed with water and dried with sodium sulfate. Removal of all solvent by distillation under reduced pressures at temperatures no higher than 100° left a viscous glassy red residue. Crystallization of this crude product from 30 ml. of methanol gave three crops of yellow hydroxymethylene derivative XIII (total yield 12.9 g. or 68%), m.p. 134–137°. The product as a mull showed infrared absorption peaks at 5.77, 6.13, 6.19 and 6.28 μ. Further crystallization of hydroxymethylene derivate XIII from methanol gave an analytical sample, m.p. 137–138°, which was dried overnight *in vacuo* at 80°. Analysis showed the presence of a mole of methanol.

Anal. Calcd. for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30. Calcd. for $C_{24}H_{24}O_9 \cdot CH_3OH$: C, 61.47; H, 5.78. Found: C, 61.4; H, 5.8.

Three bicarbonate-soluble products were obtained in the formylation experiments as follows. The above-mentioned bicarbonate wash was added without delay to 300 ml. of water containing 10 ml. of concentrated sulfuric acid. The precipitate was extracted with methylene chloride, the extract was washed with water, dried over magnesium sulfate, and evaporated to dryness. The residue (2.35 g.) on crystallization from ether and then from acetone–ether furnished red-brown rosettes (0.13 g.) that softened at 245°, showed shrinking and charring above 250°, but did not melt up to 360°. These melting point characteristics remained the same after two additional crystallizations from acetone–ether, or when the melting point was determined with the material in an evacuated sealed capillary. Infrared absorptions were evident at 3.10 (very weak), 3.84 (very weak), 5.81, 5.86 and 6.04 μ (weak). Structure XXXVIII is suggested for this material.



XXXVIII

Anal. Calcd. for $C_{22}H_{20}O_9$: C, 61.68; H, 4.71. Found: C, 61.9; H, 4.4.

When the mother liquors from these crystallizations were processed, and the gummy red residue crystallized from methanol, slow-crystallizing, white, thick squares (0.22 g.), m.p. 204–207° (softens 198°), were obtained. Another crystallization brought the melting point to 210–215° (dec., softening at 200°), which did not change on further crystallization. Infrared peaks appeared at 5.85 and 5.98 μ, but none in the hydroxyl region.

Anal. Found: C, 62.0; H, 5.7.

In another formylation experiment, the sodium hydride condensation mixture was quenched in water containing no acid, and the resulting aqueous alkaline solution was allowed to stand at room temperature for 1 hour. Subsequent treatment in the usual way led to a bicarbonate-soluble material, which after several crystallizations from ether–petroleum ether and from methanol melted at 164–165°.

Anal. Found: C, 61.4; H, 5.0.

Ethyl 1-(3′,4′,5′-Trimethoxyphenyl)-3-hydroxymethyl-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate (XVI).—Ethanol (20 ml.) containing 0.8 g. of hydroxymethylene derivative XIII and 0.1 g. of platinum oxide catalyst was stirred under an atmosphere of hydrogen for 3 hours. More catalyst (0.1 g.) was added, and the mixture was stirred for another 12 hours at which point only two-thirds of the calculated amount of hydrogen had been absorbed. Catalyst plus considerable precipitated product (which coated the catalyst and interfered with the hydrogenation) was removed by filtration, fresh catalyst was added, and hydrogenation was continued for an additional 4 hours. The total amount of hydrogen absorbed corresponded to 1.12 molar proportions. The hydrogenation mixture was filtered, and the filtrate which contained only a trace of non-volatile material discarded. The combined solids were treated with chloroform and filtered to remove catalyst. Hot ethanol was added to the concentrated chloroform filtrate, the mixture was concentrated further to a volume of 15 ml., and crystallization effected. Tetralone compound XVI (0.5 g.) separated as colorless blades, m.p. 225–227° (dec., softening at 217°). The ultraviolet absorption spectrum of the product in alcohol (4.15 × 10^{-5} M) showed λ_{max} 237 mμ (log ϵ 4.42), 277.5 (3.89), and 322 (3.89). Peaks were evident in the infrared at 2.90 (hydroxyl), 5.78 (ester carbonyl) and 6.03 μ (tetralone carbonyl, possibly hydrogen bonded).

Anal. Calcd. for $C_{24}H_{26}O_9$: C, 63.87; H, 5.72. Found: C, 63.6; H, 5.90.

Attempts to improve the melting point by two recrystallizations of the product from methylene chloride–methanol solvent gave material with m.p. 226.5–228°.

Ethyl 1-(3′,4′,5′-Trimethoxyphenyl)-3-acetoxymethyl-4-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydro-2-naphthoate (XVII).—Hydroxymethyl compound XVI (56 mg.) was dissolved in 1 ml. of pure anhydrous warm pyridine. Acetic anhydride (0.5 ml.) was added, the mixture was warmed on the steam-bath for 3 minutes, and then allowed to stand at room temperature for 3 hours. The reaction mixture was added dropwise to 15 ml. of ice-water, and the white precipitate collected, washed with water, and partially dried on the funnel. Crystallization from methanol afforded 48 mg. of acetylated product XVII in the form of glistening plates, m.p. 164.5–165.5° (softening at 161°). The melting point was unchanged after two additional crystallizations from the same solvent. The infrared absorption spectrum of XVII showed no peaks ascribable to hydroxyl, but did show carbonyl peaks at 5.76 (ester) and 6.03 μ (tetralone).

Anal. Calcd. for $C_{26}H_{28}O_{10}$: C, 62.39; H, 5.64. Found: C, 62.4; H, 5.5.

Ethyl DL-Epiisopodophyllate (XIV) from Sodium Borohydride Reduction of Hydroxymethylene Derivative XIII.—Hydroxymethylene derivative XIII (1.0 g., 0.00205 mole) in 20 ml. of absolute methanol was treated at room temperature with a solution of 1.5 g. (0.04 mole) of sodium borohydride in 20 ml. of absolute methanol. The initial vigorous effervescence soon ceased. At hourly intervals a solution of 0.3 g. of sodium borohydride in 5 ml. of methanol was added. After the fifth such addition the mixture was allowed to stand for 1 hour.

The reaction mixture was acidified with 0.5 N hydrochloric acid. The solution then was adjusted to pH 8 and extracted three times with ether. The ether extracts were dried with sodium sulfate, and freed of all volatile material. The crystalline residue, crystallized from methanol, weighed 0.50 g. (53%) and showed m.p. 183–184°. Further crystallization of this ethyl DL-epiisopodophyllate (XIV) did not change the melting point.

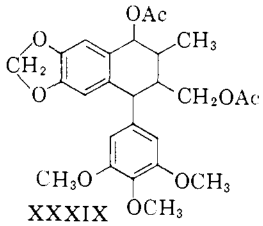
Anal. Calcd. for $C_{24}H_{28}O_9$: C, 62.60; H, 6.13. Found: C, 62.5; H, 6.2.

DL-Epiisopodophyllic Acid (XV) by Saponification of Its Ethyl Ester XIV.—A solution of 0.30 g. of ethyl DL-epiisopodophyllate (XIV) in 5 ml. of methanol containing 5 ml. of 4% aqueous sodium hydroxide was boiled for 1.5 hours. Acidification by addition of the saponification mixture to cold 0.5 N hydrochloric acid deposited a voluminous precipitate, which on standing became more compact and crystalline. The solids were collected, air-dried, and recrystallized from methanol to give 0.24 g. (85%) of DL-epiisopodophyllic acid (XV), m.p. 232–234°. Infrared absorption peaks at 2.96, 3.07 and 5.89 μ were evident. In 2×10^{-5} *M* absolute alcohol solution, the compound showed λ_{max} 292 mμ (log ϵ 3.57), and an ultraviolet absorption curve practically the same as that obtained with podophyllic acid.

Anal. Calcd. for $C_{22}H_{24}O_9$: C, 61.10; H, 5.59. Found: C, 61.1; H, 5.7.

DL-Epiisopodophyllic Acid (XV) from Hydroxymethylene Derivative XIII.—A cold suspension of hydroxymethylene derivative XIII (5.0 g., 0.0102 mole) in 50 ml. of methanol and 100 ml. of water was treated portionwise with 10 g. (0.26 mole) of sodium borohydride. The mixture was stored for 7 days in the cold. Aqueous acetic acid (1:1) was added dropwise until no effervescence was noted. Potassium hydroxide (3 g. in 10 ml. of water) was added, the alkaline solution was boiled for 2 hours, and then slowly distilled on the steam-bath (2 hours) until 30 ml. of distillate was collected. The cooled solution was extracted with ether to remove some solid, and then added dropwise to hydrochloric acid (20 ml.) plus ice (100 g.). The isolated solids were crystallized from dioxane–propanol to give 2.5 g. (57%) of DL-epiisopodophyllic acid (XV), m.p. 233–236°.

The ether extract containing alkali-insoluble material was dried with magnesium sulfate and was evaporated to dryness. The residue, a white amorphous solid (0.2 g.), m.p. 140–180°, could not be crystallized. A portion (50 mg.) was mixed with 1 ml. of acetic anhydride and 2 ml. of pyridine and was allowed to stand at room temperature for 6 hours. The mixture was poured into 20 ml. of water, and the precipitated solids were crystallized from methanol to give 27 mg. of acetylated product, m.p. 160–162° (soften at 158°). The analytical sample, obtained after further recrystallizations, was in the form of thick needles, m.p. 162–163.5°. Infrared absorption peaks were observed at 5.76 and 5.80 μ. A provisional structure for this material is XXXIX or an isomeric form.[57]



XXXIX

Anal. Calcd. for $C_{26}H_{30}O_9$: C, 64.18; H, 6.22. Found: C, 63.8; H, 5.9.

DL-Epiisopodophyllic Acid (XV) from Sodium Borohydride Reduction of Hydroxymethyl Derivative XVI.—Sodium borohydride (0.25 g.) was added to a solution of 0.13 g. of hydroxymethyl ester derivative XVI in ethanol (40 ml.). After a reaction period of 20 hours at room temperature, excess reagent was decomposed with acetic acid and the mixture processed thereafter essentially according to the preceding experiment. Crystallization of the crude product (105 mg., m.p. 220–222°) from chloroform–methanol afforded 75 mg. of pure DL-epiisopodophyllic acid (XV), melting alone or admixed with the material obtained in the preceding experiment at 231–233°. The infrared absorption curves confirmed the identity of the two samples.

DL-α-Apopicropodophyllin (XVIII) from DL-Epiisopodophyllic Acid (XV).—A mixture of 100 mg. of DL-epiisopodophyllic acid (XV), 10 ml. of water, 1 ml. of alcohol and 0.6 ml. of concentrated sulfuric acid was heated on the steam-bath for 18 hours. The cooled mixture was filtered, and the solids were washed thoroughly on the funnel first with water and then with ether. Crystallization of the resulting white powder from ethyl acetate containing a trace of hydrochloric acid gave needle-like crystals of DL-α-apopicropodophyllin (32 mg.), m.p. 232–234° (softening at 226°). Two recrystallizations from acidified ethyl acetate brought the melting point to 232–234° (softening at 230°).

Anal. Calcd. for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found: C, 66.4; H, 5.00.

This DL-α-apopicropodophyllin (XVIII) as a 7.8×10^{-5} *M* solution in slightly acidified 95% alcohol showed λ_{max} 300 mμ (log ϵ 3.86) and 312.5 mμ (log ϵ 3.88); the absorption curve was the same as that of degradation α-apopicropodophyllin. The infrared absorption spectra of racemic and optically active α-apopicropodophyllin, when both compounds were in methylene chloride solutions, were identical. However, when the spectra were taken with the materials as mulls with mineral oil, the 5.62 μ lactone absorption observed for the solutions shifted to 5.68 μ in the case of the racemic material and to 5.63 μ in the case of the optically active material.

DL-β-Apopicropodophyllin (XIX) from DL-Epiisopodophyllic Acid (XV).—A mixture of DL-epiisopodophyllic acid (30 mg.) with *either* 200 ml. of distilled water *or* 200 ml. of 10% sulfuric acid was boiled for 20 hours. The crystalline solid formed on cooling the mixture was collected, washed first with bicarbonate solution, and then with water, and finally air-dried. The dry material was dissolved in 1:1 absolute alcohol–benzene and passed through a column of alumina (Merck, "For chromatography"). Evaporation of solvent on the steam-bath left 14.5 mg. (53%) of product (XIX), which after three crystallizations from ethyl acetate showed m.p. 214–215°. A transition of the crystals of DL-β-apopicropodophyllin from clear and shiny to frost-like and translucent was noted at approximately 130°. The ultraviolet absorption spectra [λ_{max} 290 mμ (log ϵ 3.73)] of racemic and optically active β-apopicropodophyllin were practically the same. The infrared absorption curves were the same.

Anal. Calcd. for $C_{22}H_{20}O_7$: C, 66.66; H, 5.09. Found for the product from the water experiment: C, 66.48; H, 5.37. Found for the product from the 10% sulfuric acid experiment: C, 66.68; H, 5.25.

Both DL-α and DL-β-apopicropodophyllin hold solvent tenaciously, and considerable difficulty was encountered with analyses.

DL-α-Apopodophyllic Acid (XX) from DL-β-Apopicropodophyllin (XIX).—DL-β-Apopicropodophyllin (0.16 g.) was exposed for 1 hour to a boiling solution of 0.16 g. of sodium hydroxide in 2 ml. of water and 2 ml. of alcohol. The solution was filtered, and the filtrate to which 5 g. of ice had been added was acidified with an ice-cold solution of glacial acetic acid (0.5 ml.) in water (5 ml.). The acid mixture containing solid was extracted with four 10-ml. portions of chloroform. The extracts were passed through a bed of magnesium sulfate, and the bed was rinsed carefully with more solvent, which was combined with the first filtrate. The chloroform solution was concentrated to approximately 10 ml. and, after dilution with 10 ml. of dry benzene, was allowed to stand at room temperature. Crystals of DL-α-apopodophyllic acid (XX) were collected, washed with a small amount of benzene, and dried. The melting point, 170–171°, of this material (0.13 g. or 78%) did not change on recrystallization.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.5; H, 5.2.

A mixture of this racemic acid and optically active α-apopodophyllic acid (m.p. 168–169°) derived from natural materials melted at 168–169°. The racemic material XX in 3.87×10^{-5} *M* alcohol (95%) solution showed λ_{max} 310.5 mμ (log ϵ 3.86) and a flat λ_{max} at 296.5 mμ (log ϵ 3.86). Although the ultraviolet absorption curves of racemic and optically active acids were the same, the infrared absorption curves taken with mulls of the crystalline materials showed appreciable differences.[60]

DL-α-Apopodophyllic acid (XX) could be prepared most conveniently by boiling 100 ml. of 5% sulfuric acid solution containing 150 mg. of DL-epiisopodophyllic acid (XV) for 20 hours. The cooled mixture deposited crystalline solid, which was collected, treated directly with sodium hydroxide, and processed essentially as described above to give 95 mg. (66%) of DL-α-apopodophyllic acid, m.p. 170–171°.

Anal. Found: C, 63.5; H, 5.2.

Quinine Salt of α-Apopodophyllic Acid. (a) From Synthetic DL-α-Apopodophyllic Acid (XX).—The clear solution

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(57) An analogous product was observed when a structurally related hydroxymethylene derivative was treated with lithium aluminum hydride.[45,58] While sodium borohydride generally does not reduce esters, exceptions are known.[59]

(58) *Cf.* C. S. Rondestvedt, This Journal, **73**, 4509 (1951).

(59) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 503 and 531.

(60) We are indebted to Subodh C. Chakravarti for his assistance in preparing samples of racemic and resolved α-apopodophyllic acid, and for taking their infrared absorption curves.

obtained by combining 4.80 mg. of quinine (0.0148 mmole) in 1 ml. of acetone with 12.4 mg. of DL-α-apopodophyllic acid (0.03 mmole) in 1.5 ml. of acetone was allowed to stand in the cold overnight. The crystals were collected, washed with a small amount of acetone, and dried. This quinine salt (7.6 mg., 70%) of synthetic α-apopodophyllic acid showed m.p. 213–214° and $[\alpha]^{27}\mathrm{D}$ −232° (*c* 0.42 in pyridine).

Anal. Calcd. for $C_{42}H_{46}N_2O_{10}$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.1; H, 6.2; N, 3.9.

The mixture melting point with the quinine salt (m.p. 214–215°) of α-apopodophyllic acid from natural products (see below) was 213–214°. The infrared absorption curves of the two salts, as mulls with mineral oil, were identical.

(b) **From α-Apopodophyllic Acid Derived from Natural Products.**—A hot solution of 0.20 g. of α-apopodophyllic acid (0.48 mmole) and 0.18 g. of quinine (0.58 mmole) in 20 ml. of acetone was cooled and allowed to stand at room temperature. The precipitated quinine salt (high yield) melted at 214–215° and showed $[\alpha]^{27}\mathrm{D}$ −235° (*c* 0.51 in pyridine).

Anal. Calcd. for $C_{42}H_{46}N_2O_{10}$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.0; H, 6.3; N, 3.8.

Optically Active Synthetic α-Apopodophyllic Acid XXI from Its Quinine Salt.—The quinine salt (80 mg.) was shaken with 10 ml. of 2% sodium hydroxide solution and 5 ml. of ether. The alkaline aqueous layer, after further extraction with two portions of ether, was kept cold and acidified with a cold solution of 0.5 ml. of glacial acetic acid in 5 ml. of water. The mixture was stored in the cold for two days. The precipitate was collected, washed on the funnel with water, and air-dried. This crude synthetic α-apopodophyllic acid (38 mg., m.p. 161–165°) was dissolved in 5 ml. of boiling 95% alcohol, the solution was diluted slowly with 15 ml. of water, and was allowed to stand in the cold overnight. The precipitated crystals after collection and drying (29 mg., 65%) melted at 168–169° both before and after admixture with authentic α-apopodophyllic acid (m.p. 168–169°), and showed $[\alpha]^{26}\mathrm{D}$ −158° (*c* 0.59 in chloroform). A specific rotation of $[\alpha]^{27}\mathrm{D}$ −159.5° was observed for the authentic acid. The ultraviolet absorption curve of the synthetic α-apopodophyllic acid (XXI), which curve was the same as that of authentic α-apopodophyllic acid, had $\lambda_{\max}$ 295 mμ (log ϵ 3.89; flat) and 310 mμ (log ϵ 3.90) (3.78×10^{-5} *M* in 95% alcohol).

For infrared work a sample of synthetic acid XXI was recrystallized from benzene–chloroform. The melting point was unchanged. Degradation α-apopodophyllic acid (m.p. 169–170°) was likewise brought out of benzene–chloroform, and the infrared absorption curves of the two samples as mineral oil mulls were taken and compared.[60] All of the 20 or more features of the two curves were substantially the same, with the exception of two. The degradation material showed minor absorption maxima at 7.72 μ (T = 45%, with base line 51%) and at 13.2 μ (T = 60%, with base line 75%) that were not evident in the synthetic material. These two maxima were ascribed to trace impurities in the degradation acid.

α-Apopicropodophyllin (XXII) by Cyclization of α-Apopodophyllic Acid (XXI). (a) **Cyclization with Acid.**—Sulfuric acid (10%, 50 ml.) containing 120 mg. of α-apopodophyllic acid (XXI) was boiled for 18 hours. The mixture after a 4-hour period in the cold was filtered, the solids were washed with water and dried. Two crystallizations of the crude α-apopicropodophyllin (100 mg., m.p. 220–222°) from ethyl acetate containing a trace of concentrated hydrochloric acid furnished 80 mg. of product, melting alone or mixed with authentic α-apopicropodophyllin (m.p. 235–237°) at 233–235°.

(b) **Cyclization with Heat.**—A small flask containing 160 mg. of α-apopodophyllic acid (XXI) was held in a bath at 180° for 15 minutes. Resolidification of the initial melt was observed after 10 minutes of heating. Two crystallizations of the glassy product from ethyl acetate containing some hydrochloric acid gave 70 mg. of crystalline α-apopicropodophyllin (XXII), m.p. 232–234°. The mixture melting point with authentic α-apopicropodophyllin was 232–234°.

Picropodophyllin (XXIII) from α-Apopicropodophyllin (XXII).—Hydrogen chloride gas that had been passed over dry calcium chloride was bubbled into a mixture of α-apopicropodophyllin (0.5 g.) and glacial acetic acid (10 ml., 99.8%) for 35 minutes. The suspension was then boiled gently until all solids had dissolved (*ca.* 5 minutes). Hydrogen chloride was introduced at room temperature for 1 hour, and the mixture allowed to stand thereafter at room temperature for 12 hours. Hydrogen chloride was bubbled in for 1 hour, and after 24 hours bubbled in again for 3 hours. After an additional day at room temperature, the clear solution was added dropwise to 50 ml. of ice-water. The precipitate was collected, washed on the funnel with water, and dried.

The dry solid (0.37 g.) was boiled for 1.5 hours with a mixture of 6 ml. of acetone, 6 ml. of water and 0.16 g. of calcium carbonate. The hot mixture was filtered, and most of the acetone removed in a stream of air. Addition of 18 ml. of ice-water gave a precipitate, which was collected, dried *in vacuo*, and recrystallized twice from methanol.

This product (190 mg.) in 10 ml. of benzene–petroleum ether (9:1) was passed through an alumina column (7.2 × 0.9 cm.) made up of 5 g. of Merck acid-washed alumina. Elution with benzene or with benzene–ether mixtures gave no picropodophyllin. However, elution with 150 ml. of ether containing 2% of methanol removed 28 mg. of crystalline solid from the column. One crystallization from methanol furnished 10 mg. of the desired product (XXIII), m.p. 216–221°. Another crystallization gave picropodophyllin melting either alone or with authentic material at 223–224°. The infrared absorption spectrum was the same as that of authentic picropodophyllin.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.5; H, 5.4.

Acetylpicropodophyllin (XXIV).[6]—A mixture of 4.9 mg. of picropodophyllin (XXIII) derived from α-apopicropodophyllin, 3 drops of dry pyridine and 4 drops of acetic anhydride was allowed to stand for 18 hours. About 3 g. of ice was added, the mixture was stirred for a short time, and then filtered. The solid was washed with water and dried over phosphorus pentoxide. Crystallization from ethyl acetate afforded 3.9 mg. of acetylpicropodophyllin (XXIV), m.p. 209–210°, $[\alpha]^{26}\mathrm{D}$ +26.5° (*c* 1.26 in chloroform).

Acetylpicropodophyllin, prepared in the same way from authentic picropodophyllin, showed m.p. 210–211° and $[\alpha]^{28}\mathrm{D}$ +28.8° (*c* 0.59 in chloroform). A mixture of the two acetyl derivatives melted at 209–210°. The infrared absorption curves were identical.

Action of Hydrogen Chloride on Itaconic Acids VIIa and b.—Dry hydrogen chloride was bubbled for 2 hours into a boiling acetic acid solution (25 ml.) of itaconic acid VIIb (0.4 g.). The deep-orange solution was distilled to dryness *in vacuo* on the steam-bath, and the dark residual gum was crystallized from 2.5 ml. of acetone. The product (69 mg., m.p. 195–205° with decomposition) after two further crystallizations from acetone appeared as colorless plates (36 mg.), m.p. 206–207°.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.2; H, 5.4.

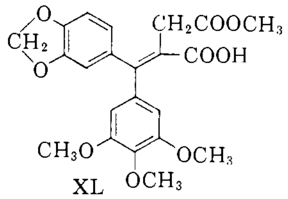
An alcohol solution of the product (2.2×10^{-5} *M*) showed $\lambda_{\max}$ 210 mμ (log ϵ 4.66), 260 (4.13) and 298 (3.83). The product as a mineral oil mull had infrared absorption peaks at 5.82, 5.875 (main) and 5.92 μ. The material was soluble in saturated sodium bicarbonate solution.

The same procedure starting with 0.4 g. of itaconic acid VIIa afforded 48 mg. of crystalline product, melting before or after addition of the material from isomer b at 206–207°. The infrared absorption spectra of the products from itaconic acid isomers a and b were identical. Structure XXXI is suggested for this material.

Monomethyl Ester of 3,4-Methylenedioxyphenyl-3′,4′,5′-trimethoxyphenylitaconic Acid (VIIb).—Itaconic acid VIIb (1.0 g.) was converted to its anhydride in essentially the manner described for the corresponding conversion of itaconic acid VIIa. The glassy, orange anhydride, as obtained by removal of solvent from a benzene solution, was dissolved in 20 ml. of dry methanol, and the solution was boiled for 18 hours. Removal of solvent by distillation on the steam-bath left an orange oil that crystallized with scratching. A solution of the product in methanol was treated with decolorizing carbon, the filtrate was concentrated to 7 ml., and cooled. The long needle-like crystals were collected and recrystallized twice from methanol to give 0.75 g. of monomethyl ester of itaconic acid VIIb, m.p. 186–187°.

Anal. Calcd. for $C_{22}H_{22}O_9$: C, 61.39; H, 5.15; neut. equiv., 430.4. Found: C, 61.32, 61.7; H, 5.36, 5.2; neut. equiv., 431.7.

Ultraviolet absorption maxima were noted at 209 mμ (log ε 4.61) and 292 mμ (log ε 4.08); an inflection appeared at 250 mμ. The compound showed infrared absorption peaks at 5.96 (α,β-unsaturated acid) and at 5.77 μ (saturated ester). The half-ester, for which structure XL is suggested, was soluble in saturated bicarbonate solution.



XL

The half-ester could be saponified by holding a mixture of 0.3 g. of the half-ester, 25 ml. of dioxane, 25 ml. of water and 5 g. of sodium hydroxide at 80° for 10 hours. The reaction mixture was diluted with 150 ml. of water, treated with 20 ml. of concentrated hydrochloric acid, and extracted with ether. The ether solution was washed with water and dried with magnesium sulfate. Removal of the ether solvent left a gum, which on crystallization from acetone afforded 0.14 g. of itaconic acid VIIb as thick plates. The melting point and mixture melting point were 199–200°.

Dimethyl Ester of 3,4-Methylenedioxyphenyl-3′,4′,5′-trimethoxyphenylitaconic Acid (VIIb).—An ethereal solution (60 ml.) containing diazomethane in excess was poured into a cold suspension of itaconic acid VIIb (1.0 g.) in 50 ml. of ether. Vigorous evolution of gas accompanied dissolution of the solid, which required 7 minutes. The mixture, in a loosely stoppered flask, was held at 5° for 10 hours. After decomposition of excess reagent with glacial acetic acid all volatile material was removed. Crystallization of the oily residue from methanol gave thick needles (0.88 g.) with m.p. 114–115°. This product was insoluble in a saturated solution of sodium bicarbonate. The melting point of the dimethyl ester of VIIb was raised to 120–121° after two recrystallizations from benzene–petroleum ether (b.p. 30–75°).

Anal. Calcd. for $C_{23}H_{24}O_9$: C, 62.15; H, 5.44. Found: C, 61.9; H, 5.2.

The dimethyl ester in 1.6 × 10^{-5} *M* alcohol solution showed absorption maxima at 208 mμ (log ε 4.60) and 295 mμ (log ε 4.12). Carbonyl absorptions were noted at 5.77 and 5.86 μ. A mixture of dimethyl esters from itaconic acids VIIa and VIIb melted at 102–104°.

The monomethyl ester of itaconic acid VIIb could be converted to dimethyl ester by following essentially the directions as given above. The melting point of the resulting diester as well as the mixture melting point was 118–119°. The infrared absorption curves of the dimethyl ester derived from the acid VIIb or from its monomethyl ester were identical.

The dimethyl ester of VIIb (153 mg.) could be saponified by treatment with a boiling solution of methanol (25 ml.), water (20 ml.) and potassium hydroxide (5 g.) for 3 hours. The acid VIIb was isolated in the usual way, and was crystallized from acetone to give 53 mg. of product, m.p. 200–200.5°. The mixture melting point with itaconic acid VIIb was 200–201°.

3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic Acid (VIIIb).—Hydrogenation of itaconic acid VIIb (0.010 mole or 4.15 g.) was conducted in a manner similar to the hydrogenation of itaconic acid VIIa. After 20 minutes of hydrogenation at 23°, absorption of hydrogen ceased. The amount of hydrogen taken up corresponded to 115% of the theoretical. Crystallization of the product from ether afforded bulky cubic crystals, which were air-dried. This material (4.2 g.), containing ether of crystallization,[61] melted to a glass at 78–90° with evolution of gas and with preliminary sintering; the melt became more mobile at approximately 130°. The melting point behavior was not changed after three recrystallizations from ether.

Anal. Calcd. for $C_{21}H_{22}O_9 \cdot (C_2H_5)_2O$: C, 60.96; H, 6.55; ether, 15.0%; neut. equiv., 246.3. Found: C, 61.1; H, 6.6; neut. equiv., 247.5.

When the etherate of succinic acid (VIIIb) was held at 60° until the weight became constant, the loss in weight was 13.7%. The ether-free material melted to a glass at 79–100° dec.

Anal. Calcd. for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 59.8; H, 5.3.

In another experiment the etherate was heated at 100° (0.02 mm.) for 3 hours, and the resulting glass analyzed. Found: C, 60.2; H, 5.4. When the etherate was crystallized from chloroform solvent, the crystals, although solvent-free, still melted over a range, 115–127° dec. Found: C, 60.4; H, 5.4.

The etherate of acid VIIIb showed absorption maxima in 2.3 × 10^{-5} *M* alcohol solution at 207 mμ (log ε 4.59), 285 (3.60) and an inflection at 242 (3.88). Infrared absorption peaks were evident at 5.82 and 5.87 μ.

3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic Anhydride (IXb).—A solution of freshly distilled acetyl chloride (6 ml.) and 1.0 g. of succinic acid VIIIb was boiled for 1 hour. Removal of volatile material by distillation on the steam-bath left a yellow residue, which was dissolved in 20 ml. of benzene. The benzene solution was washed with 20 ml. of sodium bicarbonate solution, then with 20 ml. of water, and was dried with magnesium sulfate. Solvent was removed, and the glassy, almost colorless anhydride IXb held at 100° (0.1 mm.) for 5 hours.

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 63.03; H, 4.99.

Distillation was possible in a creased test-tube still at an external temperature of 190–230° (0.01 mm.). The somewhat amber, glassy distillate gave proper analytical figures (Found: C, 62.9; H, 5.1), and an infrared absorption curve practically identical with that of succinic anhydride IXa. Absorption peaks were evident in a mineral oil mull at 5.37 and 5.62 μ.

No change in configuration occurred since anhydride IXb could be hydrolyzed to succinic acid VIIIb as follows. Anhydride IXb from 1 g. of VIIIb was allowed to stand at room temperature with 50 ml. of acetone and 10 ml. of 1 *N* sodium hydroxide solution for 4 days. The reaction mixture was processed in the usual way, and succinic acid VIIIb (0.9 g., m.p. 82–90°, was obtained by crystallization from ether–petroleum ether (b.p. 30–60°) solvent in the form of large colorless crystals. In a second hydrolysis experiment recovered acid VIIIb was obtained with melting point and mixture melting point 70–90° (effervescence).

In another experiment some indication of partial conversion of anhydride IXb to anhydride IXa was obtained. Anhydride IXb from 1.0 g. of succinic acid VIIIb was distilled twice at air-bath temperatures of 235–240° (0.01 mm.). The yellow glassy distillate (0.9 g.) on saponification as described above gave acidic material, from which approximately 36 mg. of ether-crystallized product, m.p. 188–193° (soften at 185°), could be obtained. Admixture with succinic acid VIIIa gave material with m.p. 191–196° (soften 185°). The infrared absorption curve of the crystalline saponification product was similar to that of succinic acid VIIIa.

Dimethyl Ester (XXXII) of 3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic Acid (VIIIb).—A solution of 0.55 g. (0.0011 mole) of the etherate of acid VIIIb in 20 ml. of ether was treated with excess diazomethane in 40 ml. of ether, and the mixture was allowed to stand at 5° for 12 hours. After addition of 1.5 ml. of glacial acetic acid, all solvent was removed, and the residue was crystallized from methanol. The resulting dimethyl succinate XXXII (0.35 g., m.p. 60–65°) on two further crystallizations was obtained in the form of fine needles, m.p. 63–65°.

Anal. Calcd. for $C_{23}H_{26}O_9$: C, 61.87; H, 5.87. Found: C, 61.6; H, 5.8.

This dimethyl ester in 3.7 × 10^{-5} *M* alcohol solution showed λ_{max} 209 mμ (log ε 4.64) and 285 mμ (log ε 3.69) and a shoulder at 242 mμ (log ε 3.98). The material was insoluble in aqueous bicarbonate.

In one preparation, dimethyl ester XXXII was obtained in the form of clusters of thick rods, m.p. 81.5–83.5°. A supersaturated solution of this material, seeded with the lower melting form, deposited the more familiar needle-like crystals, m.p. 63–65°.

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(61) Interestingly, unsubstituted benzhydrylsuccinic acid has been reported[24] to crystallize with half a molecule of benzene.

Reconversion to the acid was carried out by boiling a solution of ester XXXII (70 mg.) in 10 ml. of methanol and 5 ml. of water containing 0.7 g. of potassium hydroxide for 3.5 hours. The saponification mixture was processed in the usual way to yield succinic acid VIIIb, which after crystallization from ether weighed 45 mg. and showed m.p. 78–91° (effervescence). The characteristic melting point behavior was noted for this product before or after admixture with the starting succinic acid VIIIb.

Attempted Isomerization of Succinic Acid VIIIb to Succinic Acid VIIIa.—Freshly cut potassium (2.0 g.) and 40 ml. of *t*-butyl alcohol that had been distilled from lithium aluminum hydride were stirred and heated under a reflux condenser for 1.5 hours to dissolve the metal. The apparatus was scrupulously dried; dry nitrogen blanketed the reaction mixture throughout the experiment. A solution of succinic acid VIIIb etherate (0.3 g.) in 10 ml. of anhydrous butanol was added, and the mixture was stirred and boiled for 18 hours. Concentrated hydrochloric acid (10 ml.) was added to the cold mixture, and solvent was removed by distillation under reduced pressure. Water (100 ml.) was added to the residue, and organic acids were isolated in the usual manner. After crystallization from ether, the recovered succinic acid (0.25 g. or 83%) showed m.p. 79–92° (effervescence); when mixed with starting material VIIIb, the product showed m.p. 79–82° (effervescence).

Friedel–Crafts Cyclization of 3,4-Methylenedioxy-3′,4′,5′-trimethoxybenzhydrylsuccinic Anhydride (IXb) to Indanone Xb.—A solution of 12.3 g. of succinic acid VIIIb etherate in 40 ml. of acetyl chloride was boiled for 3 hours. Most of the reagent was removed by distillation. The sirupy residue, dissolved in 50 ml. of benzene, was washed with two 30-ml. portions of saturated sodium bicarbonate solution, and was dried with magnesium sulfate. Benzene was removed by distillation under reduced pressures at 100°, and by pumping at 1 mm.

A cold solution of this anhydride IXb in redistilled nitrobenzene (40 ml.) was added dropwise during 10 minutes to a stirred solution of 9.0 g. of aluminum chloride in 100 ml. of nitrobenzene. The reaction flask was held in an ice-bath during the addition; thereafter the mixture was allowed to stand at room temperature for 20 hours.

The reaction mixture was stirred with 80 ml. of 5 *N* hydrochloric acid for 2 hours. The organic layer was separated and was shaken first with 40 ml. of 5 *N* hydrochloric acid and then with two 80-ml. portions of saturated sodium bicarbonate solution. The combined bicarbonate solutions, after one ether wash, were added dropwise to a mixture of 100 ml. of 10 *N* hydrochloric acid plus 150 g. of ice. The tan precipitate was collected, washed on the funnel with ice-water until free of acid, and then taken up in 100 ml. of ether. The dried (magnesium sulfate) solution was evaporated to dryness, and the gummy residue was triturated with 30 ml. of cold ether until a fine white powder formed. The mixture was filtered, and the powder (0.85 g.) was crystallized thrice from small volumes of methanol to give 0.2 g. of cyclized product Xb, m.p. 187–188°. Methanol–ether, acetone–ether and chloroform–ether also served as recrystallization solvents.

Anal. Calcd. for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 62.76; H, 5.26.

The compound Xb in alcohol solution showed λ_{max} 232 mμ (log ϵ 4.52), 267 (3.95) and 318 (3.98). The compound as a mull with mineral oil showed infrared absorption peaks at 5.71, 6.00, 6.21 and 6.28 μ; the chloroform solution showed absorption peaks at 5.86, 6.21 and 6.28 μ.

Other cyclization experiments gave either negative or even less satisfactory results than those described above. The reagents tried with the succinic anhydride include aluminum chloride in tetrachloroethane, stannic chloride in nitrobenzene, and aluminum chloride in methylene chloride. Cyclization reagents tried with the free succinic acid VIIIb include liquid hydrofluoric acid, concentrated sulfuric acid and polyphosphoric acid.

Methyl Ester XIb of Indanone Xb.—The cyclization product Xb (approximately 100 mg.) was treated with ethereal diazomethane in excess, and the yellow solution allowed to stand at 5° for 2.5 hours. Dropwise addition of glacial acetic acid destroyed the unused diazomethane, after which action volatile material was removed in a jet of dry air. The somewhat sticky residue was dissolved in a very small amount of acetone, ether was added, and the faint turbidity was removed by filtration through Celite filter aid. Concentration and cooling gave small, thick, faintly yellow plates, m.p. 153–154° with sintering at 144°. Since recrystallizations did not improve the melting point, the methylated product was chromatographed using a 0.5 × 2″ column of acid-washed alumina (4 g.). The material (41 mg.) was placed on the column as a solution with 25 ml. of carbon tetrachloride. Eluate was collected in 25-ml. portions and each portion processed separately. No solid appeared after passage of a total of 450 ml. of solvents made up of carbon tetrachloride, various mixtures of carbon tetrachloride and benzene, and of benzene. However 150 ml. of benzene–ether (4:1) served to remove 40 mg. of crystalline material, which on crystallization from ether containing a small amount of ethyl acetate gave 23 mg. of ester XIb, m.p. 159–161°. A further crystallization did not change the melting point.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.9; H, 5.3.

Ultraviolet absorption maxima appeared at 209 mμ (log ϵ 4.59), 233 (4.44), 268 (3.875) and 318 (3.99) when a 2×10^{-5} *M* solution in absolute alcohol was taken. Infrared absorption peaks at 5.78 and 5.87 μ were indicative of an ester carbonyl and an α,β-unsaturated cyclopentenone carbonyl, respectively.

Hydrolysis of ester XIb regenerated the original cyclized acid. A mixture of 27 mg. of XIb, 4 ml. of methanol, 2 ml. of water and 50 mg. of potassium hydroxide was boiled for 3 hours. The saponification mixture, after concentration, was diluted with water and acidified with dilute hydrochloric acid. The organic acid was taken up in ether, the ether solution was washed with water, dried with magnesium sulfate, and warmed to remove solvent. A methanol solution of the residue was filtered, solvent was removed from the filtrate, and the solid residue was crystallized first from ether and then from methanol–ethanol. The material Xb so obtained showed m.p. 187–188°; the mixture melting point with the original indanone acid Xb was 185–187°.

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