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Derivatives of Podocarpic Acid. IV. Reduction of the Aromatic Ring[1]

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Hydrogenation of the aromatic ring of podocarpic acid (Ia) gave the *trans-anti-cis*-perhydro derivative (IIa). This reduction product was converted by a series of reactions, in which the rearrangement of a bromo ketone (VII) during dehydrobromination was observed, to a compound having the *trans-anti-trans* skeleton (IVb). This same compound was prepared from the Birch reduction product of *O*-methylpodocarpinol (XI). The complete stereochemistry of the products has been elucidated by interconversions and by a study of the spectra and optical rotations.

In a search for compounds having biological activities, the availability and interesting structure of podocarpic acid[2] (Ia) led us to prepare a number of its derivatives. One area of our investigation was the reduction of the aromatic ring.

Sherwood and Short[2c] found in their early structural work that podocarpic acid in acetic acid did not absorb hydrogen over a platinum catalyst which was capable of promoting a rapid reduction of benzaldehyde. These workers considered this resistance to hydrogenation as evidence that podocarpic acid contained an aromatic ring but reported no further attempts to reduce the aromatic ring under more drastic conditions.

We have found that hydrogenation of podocarpic acid (Ia) proceeds over platinum in acetic acid at 60–70°, to give an easily-isolated perhydro derivative melting at 234–236°.[3] The formation of this perhydro podocarpic acid was accompanied by the formation of a mixture of isomeric C_{12} desoxy acids (m.p. 136–171°). Oxidation of the resulting hydroxy acid IIa gave the corresponding keto acid IIIa which in turn was easily converted to the keto ester IIIb. It was felt that much could be learned about the sterochemistry of the keto ester IIIb by the preparation of a compound having this same structure by an alternate method of reduction of the aromatic ring.

O-methylpodocarpinol[2a,4] (XI) was reduced with lithium and *t*-butyl alcohol in a mixture of tetrahydrofuran and ammonia.[5] Hydrolysis of the crude enol ether X followed by the separation of the ketonic and nonketonic fractions gave the conjugated ketone IXa along with the ring-C desoxy dodecahydropodocarpinol. It was reasonable to assume that the conjugated ketone obtained was the thermodynamically more stable (C-8β) form.

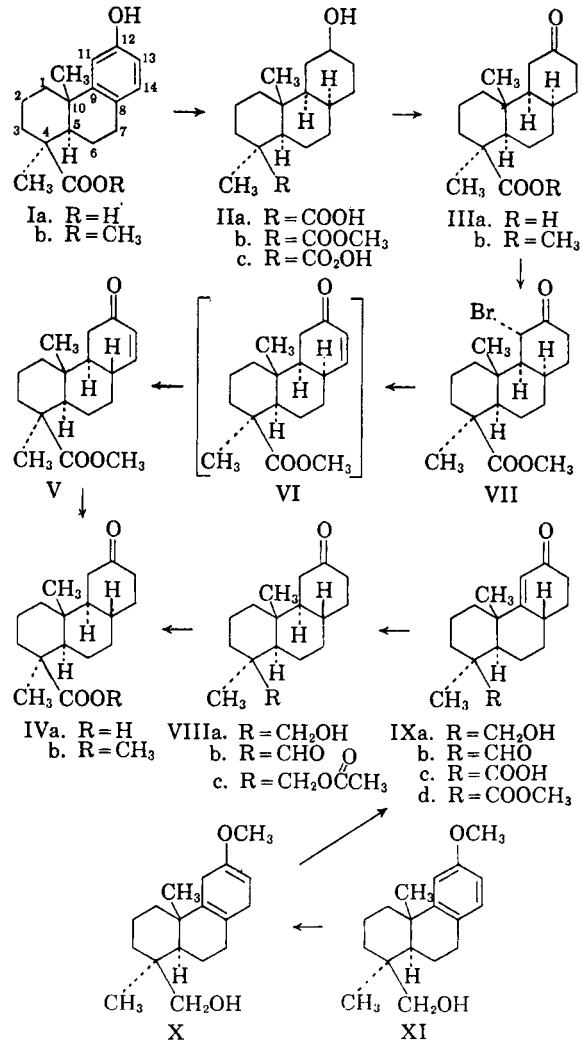

Figure 1

The position of the carbon-carbon double bond in the conjugated ketone IXa was clearly established by the position of the ultraviolet absorption maximum[6] (λ_{max} 240 mμ). Reduction of

(1) This work was presented in part at the 138th Meeting of the American Chemical Society, September 11–16, 1960, New York, N. Y. For previous papers in this series see (a) III, R. H. Bible, Jr., *Tetrahedron*, **11**, 22 (1960); (b) II, R. H. Bible, Jr., *Tetrahedron Letters*, No. 9, 20 (1960); (c) I, R. H. Bible, Jr., *J. Am. Chem. Soc.*, **79**, 3924 (1957).

(2)(a) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **64**, 928 (1942); (b) L. F. Fieser and W. P. Campbell, *J. Am. Chem. Soc.*, **61**, 2528 (1939); (c) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938).

(3) Hydrogenation over ruthenium oxide in ethanol at 100° follows a different steric course; this will be dealt with in a future communication.

(4) See H. H. Zeiss, C. E. Slimowicz, and V. Z. Pasternak, *J. Am. Chem. Soc.*, **70**, 1981 (1948).

(5) This technique was described by H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Cella, before the 126th meeting of the AAAS, Chicago, Ill. (1959).

(6) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941).

this conjugated ketone (IXa) with lithium and *t*-butyl alcohol in a mixture of tetrahydrofuran and ammonia[5] gave the saturated ketone VIIIa. Here again, the method of formation strongly indicated that the isomer obtained was the more stable form.[7] It is of interest that the keto group in VIIIa was not reduced even though alcohol was present.[8] Oxidation of the primary alcohol group in VIIIa with chromic acid–sulfuric acid in acetone[9] gave the aldehyde VIIIb. Oxidation of either VIIIa or crude VIIIb with chromic acid and acetic acid gave the keto acid IVa. This keto acid (IVa) was easily converted to a keto ester (IVb) which was shown to be different from IIIb by direct comparison of the two substances. That IVb had the *trans-anti-trans* arrangement expected by its method of formation was clearly demonstrated by its strongly positive Cotton effect (amplitude +70).[10] Of the four possible isomers of different configurations at C_8 and C_9 (Fig. 2), IVb alone would be expected by the octant rule[11] to give a positive Cotton effect.

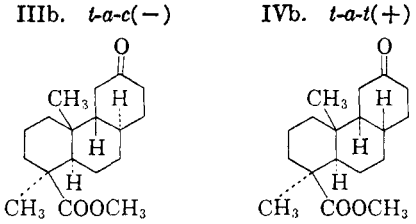

Fig. 2. Predicted Cotton Effects

It seemed reasonable that the hydrogenation of podocarpic acid had proceeded to give the $C_{8\alpha}$, $C_{9\alpha}$ ring junction, an assumption consistent with the observed[10] negative Cotton effect of the keto ester IIIb. If this were indeed the case, then the keto ester IIIb should be convertible to the keto ester IVb by epimerization at C_8. Introduction of a double bond either at $C_{9(11)}$ or at $C_{13(14)}$ in the keto ester IIIb should permit a test of this hypothesis. Bromination of the keto ester IIIb with *N*-bromosuccinimide in carbon tetrachloride at room temperature gave an axial bromo ketone VII (λ_{max} 310 mμ).[12] This bromo ketone, which will be discussed in the sequel, on dehydrobromination either with lithium chloride–lithium carbonate[13] or with collidine followed by equilibration over basic alumina gave the unsaturated keto ester V. The position of the ultraviolet absorption maximum[6] (230 mμ) was conclusive evidence that the double bond was in the indicated position. Hydrogenation of V gave a saturated keto ester (IVb) which was identical with the saturated keto ester prepared by way of the Birch reduction.

The conversion of IIIb to IVb clearly demonstrated that the difference in these two compounds resided in a difference in sterochemistry at C_8. This interconversion together with the observed Cotton effects proved that the skeletal sterochemistry of the keto ester IIIb and IVb were those predicted on chemical grounds.

The establishment of the skeletal stereochemistry of the reduction products of podocarpic acid permitted a further examination of the orientation of the substituents on ring C. The introduction of the axial bromine atom in IIIb to give VII was accompanied by a large *dextro* contribution to the molecular rotation[14] and a positive Cotton effect (amplitude +210).[10,11] As the nature of the B/C ring junction had been established and thus the complete absolute configurations were known,[15] the newly introduced bromine atom had to be assigned the C-11α position. The rearrangement observed in the dehydrobromination of VII to V is consistent with similar observations in other series.[16]

Equilibration of the bromo ketone VII gave (Fig. 3) an equatorial bromo ketone (λ_{max} 280

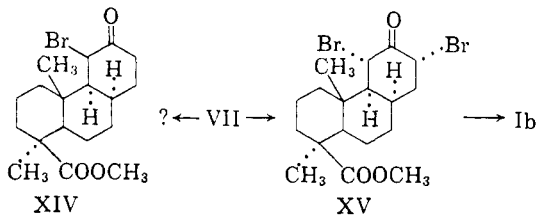

Fig. 3. Equilibration of the bromo ketone VII

(7) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(8) A number of examples of the reduction of a conjugated ketone to the saturated ketone by lithium in ammonia *in the absence of alcohol* have been reported [see F. Sondheimer, R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 2696 (1952); and A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, **79**, 4556 (1957)].

(9) This reagent was prepared by dissolving chromic acid (136.2 g.) and concd. sulfuric acid (110 ml.) in water (total volume = 500 ml.) see K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(10) We are indebted to Dr. William Klyne of the Postgraduate Medical School, University of London, London, England, for the determination and interpretations of the rotary dispersion curves.

(11) W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne, and C. Djerassi, unpublished observation; see C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw Hill Book Co., New York, 1960, Chapter 13, and W. Klyne, *Advances in Organic Chemistry* (1960), **1**, 333.

(12) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(13)(a) R. Joly and J. Warnant, *Bull. Soc. Chim. France*, 367 (1958); (b) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(14) See E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc.*, **77**, 3667 (1955).

(15) See W. Klyne in *Determination of Organic Structures by Physical Methods*, E. A. Braude and F. C. Nachod, ed., Academic Press, New York, 1955, p. 122.

(16) See, for example, B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959); M. Gates and G. M. K. Hughes, *Chem. & Ind.*, 1506 (1956); and J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

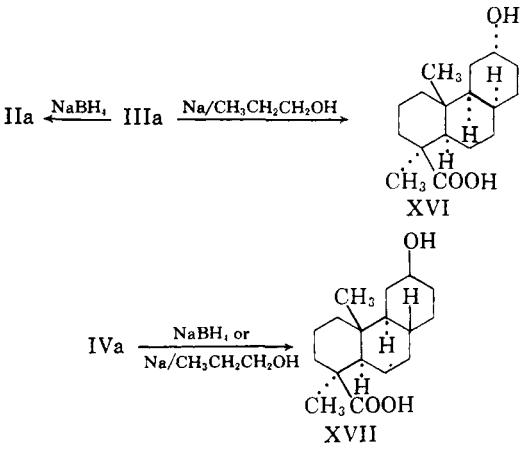

Fig. 4. Reduction of the keto acid IIIa

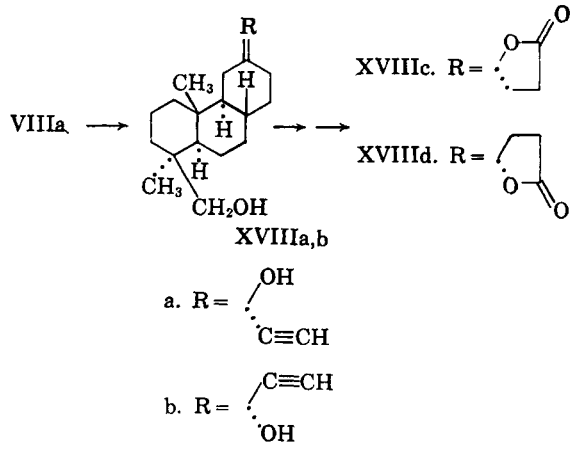

Fig. 5. Addition of acetylene to the keto alcohol VIIIa

mμ)[12] which must be either XIV or the isomeric $C_{13\beta}$ bromo compound. Unfortunately, the molecular rotatory dispersion cannot be employed in this case to establish the location of the bromine atom. Further bromination of VII yielded an α,α'-diaxial bromo derivative (XV; λ_{max} 342 mμ)[12] for which only one formulation is possible. Dehydrobromination of XV gave the known methyl podocarpate (Ib)[2c] in high yield.

Reduction of the keto acid IIIa (Fig. 4) with sodium in *n*-propyl alcohol gave a new hydroxy acid XVI in 65% yield while reduction with sodium borohydride gave a mixture of the hydroxy acid IIa and XVI in a ratio of 70:30. Since reduction with sodium in *n*-propyl alcohol is known to give a mixture of alcohols corresponding to the ratio of their thermodynamic stabilities,[17a] the new hydroxy acid XVI must have the hydroxy group in the equatorial ($C_{12\alpha}$) position. The hydroxy group in IIa must then be assigned the axial ($C_{12\beta}$) position which is consistent with its formation from the ketone IIIa by the approach of the reducing agent from the less hindered side. In contrast, the isomeric keto acid IVa yielded the same hydroxy acid by either reduction with sodium in *n*-propyl alcohol or by sodium borohydride. Accordingly, the hydroxyl in XVII was assigned the equatorial (β) position.

The addition of acetylene to the keto alcohol VIIIa congruously with the *trans-anti-trans* skeleton of VIIIa and the relatively low steric requirements of the reagent, (Fig. 5) gave a mixture of isomeric acetylenic hydroxy compounds (XVIIIa and XVIIIb). These substances were converted by a series of reactions to the saturated spirolactones[18] (XVIIIc and XVIIId).

The hydroxy acid IIa and its acetate displayed interesting anti-inflammatory properties in animals.[19] The details of the investigation of these properties will be reported elsewhere.

EXPERIMENTAL[20]

Except where noted, rotations were determined using 1% ethanol solutions and ultraviolet absorption spectra were run on methanol solutions. All melting points were taken on a Fisher-Johns block and were corrected using standard compounds.

trans-anti-cis-Perhydropodocarpic acid (IIa). A solution of podocarpic acid[2c] (50.0 g.) in acetic acid (250 ml.) was agitated under an atmosphere of hydrogen (965–875 lb./sq. in.) with platinum oxide (1.5 g.) at 60–76°. The uptake of hydrogen ceased after 2 hr. After 4.75 hr., the reaction mixture was filtered. Fresh catalyst (1.0 g.) was added. The mixture was stirred in an atmosphere of hydrogen (875–820 lb./sq. in.; 55–78°) for 5.5 hr. Removal of the catalyst and solvent gave a residual tan glass. This residue was refluxed for 2 hr. with a solution of potassium hydroxide (50 g.) in water (50 ml.) and methanol (200 ml.). Dilution of the reaction mixture with water followed by acidification with 5% hydrochloric acid gave a tan solid. Two recrystallizations from aqueous isopropyl alcohol (charcoal) gave *trans-anti-cis*-perhydropodocarpic acid (IIa); m.p. 230–233°; 14.2 g. A sample for analysis was obtained by two further recrystallizations; m.p. 234.5–236°; $[\alpha]_D$ +23°; λ_{max} 2.98 and 5.94 μ (KBr); no detectable band in the region 220–300 mμ at a concentration of 10 mg./100 ml.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.80; H, 9.98.

The material remaining in the mother liquor (23 g.) after removal of a second crop (7.0 g.; m.p. beginning at 155°) was chromatographed over silica (350 g.). Elution with 2% ethyl acetate in benzene gave desoxyperhydropodocarpic acid; 3.3 g.; m.p. 136–171°. The melting point of this material was not changed rapidly by recrystallization from aqueous methanol. A sample for analysis was obtained by one recrystallization from aqueous methanol; $[\alpha]_D$ +52°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.44; H, 10.56.

The *acetate* of *trans-anti-cis-perhydropodocarpic acid* was prepared by heating the hydroxy acid (25.0 g.; IIa) in acetic

(17)(a) For references see D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (b) E. P. Oliveto, H. L. Herzog, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 1505 (1953).

(18) See J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(19) The determinations of the biological properties of these substances have been made by the staff of the Division of Biological Research of G. D. Searle and Company.

(20) All ultraviolet and infrared spectra and rotations were performed by the Analytical Department of G. D. Searle and Company under the direction of Dr. R. T. Dillon. Elementary analyses were determined by the Analytical Department and by Micro-Tech, Skokie, Ill.

anhydride (50 ml.) containing hydrochloric acid (0.1 ml.) at 80° for 30 min. The solid which formed on standing after dilution of the reaction mixture with water was collected and washed with water. Recrystallization from aqueous methanol gave the acetate of *trans-anti-cis*-perhydropodocarpic acid; m.p. 134.5–136°; $[\alpha]_D$ −11°; λ_{max} 5.78 and 5.91 μ (KBr); no detectable band in the region 220-370 mμ at 40 mg./100 ml.; ϵ 198 at 220 mμ.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.97; H, 9.60.

Esterification of IIa with dimethylsulfate and sodium hydroxide in aqueous methanol[20] gave *methyl trans-anti-cis-perhydropodocarpate* (IIb). The product, which did not crystallize, was distilled at about 154° (0.15 mm.) to give the methyl ester as a colorless glass; $[\alpha]_D$ +31°; λ_{max} 2.77 and 5.83 μ ($CHCl_3$).

Anal. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.28; H, 10.07.

Methylation of the acetate of perhydropodocarpic acid with dimethyl sulfate and sodium hydroxide in aqueous methanol[20] followed by recrystallization of the product from aqueous methanol gave the acetate of *methyl trans-anti-cis-perhydropodocarpate;* m.p. 82–84°; $[\alpha]_D$ −1°; λ_{max} 5.78; ϵ 198 at 220 mμ.

Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59; OCH_3, 9.22. Found: C, 71.35; H, 9.33; OCH_3, 8.95.

4β-Carboxy-4α,10β-dimethyl-trans-anti-cis-perhydro-12-phenanthrone (IIIa). The hydroxy acid IIa (100 g.) in acetone (40 ml.) was oxidized by the slow addition of an 8N chromic acid solution[9] (150 ml.). The solid which separated on dilution of the reaction mixture with water was collected, washed with water, and then recrystallized three times from aqueous methanol; m.p. 167.5–174°; 93.5 g.; $[\alpha]_D$ +35°; λ_{max} 3.18, 5.82, and 5.95 μ (broad) (KBr) and 281 mμ (ϵ 21.2).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.03; H, 9.27.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-cis-perhydro-12-phenanthrone (IIIb). Methylation of the keto acid IIIa with dimethyl sulfate and sodium hydroxide in aqueous methanol[20] gave the corresponding keto ester IIIb. Recrystallization from aqueous methanol gave either a lower melting point (110–113°) crystalline modification or a higher (120–121.5°) form. The lower melting form could be obtained by sublimation at reduced pressure; $[\alpha]_D$ +41°; λ_{max} 5.83 μ ($CHCl_3$) and 281 mμ (ϵ 24).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.07; H, 9.51.

4β-Methoxycarbonyl-4α,10β-dimethyl-11α-bromo-trans-anti-cis-perhydro-12-phenanthrone (VII). *N*-Bromosuccinimide (8.81 g.) was added to a solution of IIIb (14.5 g.) in carbon tetrachloride (70 ml.). Exposure of the reaction mixture to diffused sunlight initiated a reaction which was moderated by occasional cooling in an ice bath. The reaction was complete in about 30 min. After removal of the solid by filtration, the solvent was distilled using a rotating flask evaporator under reduced pressure over a warm (35°) water bath. Addition of hexane to the residual glass gave a crystalline solid which on three recrystallizations from hexane gave the pure bromo ketone; m.p. 152–153°; 6.7 g.; $[\alpha]_D$ +167°; λ_{max} 5.82 μ (KBr) and 310 mμ (ϵ 130).

Anal. Calcd. for $C_{18}H_{27}BrO_3$: C, 58.22; H, 7.33; Br, 21.52. Found: C, 58.63; H, 7.37; Br, 20.94.

Hydrogenation of the material in the mother liquor over 5% palladium on calcium carbonate (10 g.) in ethanol (200 ml.) at 25° gave the starting keto ester IIIb which, after two recrystallizations from aqueous methanol amounted to 4.9 g.; m.p. 116.5–121.5°.

Isomerization of the axial bromo ketone VII. A solution of the bromo ketone VII (1.79 g.) and 48% hydrobromic acid (6 ml.) in acetic acid (60 ml.) was allowed to stand at room temperature for 48 hr. The reaction mixture, after dilution with water, was extracted with ether. The ether solution was washed with water. Distillation of the ether followed by azeotropic drying of the residue with benzene gave a residual glass. Recrystallization of this residue from hexane (charcoal) gave the equatorial bromo ketone XIV; 0.210 g.; m.p. 143.5–147°; $[\alpha]_D$ +59 ± 4°; λ_{max} 5.83 μ ($CHCl_3$) and 280 mμ (ϵ 45).

Anal. Calcd. for $C_{18}H_{27}BrO_3$: C, 58.22; H, 7.33; Br, 21.52. Found: C, 58.08; H, 7.23; Br, 21.89.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-trans-1,2,-3,4,5α,6,7,8β,9α,10,11,12-dodecahydro-12-phenanthrone (V). (A) The bromo ketone VII (4.31 g.) was added under nitrogen with stirring to redistilled collidine (50 ml.) which had been preheated to reflux temperature. The reaction mixture was stirred and heated at reflux temperature for an additional 30 min. The product was extracted into ether after dilution of the reaction mixture with 2% hydrochloric acid. The ether solution was washed with water and then dried over anhydrous sodium sulfate. Removal of the drying agent and solvent gave the crude material as a light yellow glass.

The residue was stirred in benzene (200 ml.) with basic aluminum oxide (Woelm; activity grade I; 20 g.) at reflux temperature for 35 min. The aluminum oxide was filtered off and washed with benzene. Removal of the solvent from the combined filtrates gave a light yellow crystalline solid which was recrystallized from aqueous methanol (charcoal); 0.52 g.; m.p. 117–123°. Two further recrystallizations from aqueous methanol gave the pure conjugated ketone V as flat blades; m.p. 126.5–129°; $[\alpha]_D$ +72°; λ_{max} 5.79, 5.95 (broad), 6.24, and 11.36 (broad) μ and 230 mμ (ϵ 8,710).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.29; H, 9.03.

(B) A mixture of the bromo ketone VII (6.7 g.), lithium chloride (1.34 g.), and lithium carbonate (1.0 g.) was heated at reflux temperature in dimethylformamide (142 ml.) for 6 hr.[13] The reaction mixture was diluted with water (total volume 1.5 l.). Three recrystallizations of the resulting solid from aqueous methanol (charcoal) gave the conjugated ketone V (1.13 g. m.p. 122.5–126.5°) which was identical with the material obtained by Method A. Further work-up of the mother liquors gave an additional amount of V; 0.32 g.; m.p. 121–126.5°.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-trans-perhydro-12-phenanthrone (IVa). The conjugated ketone V (0.30 g.) was hydrogenated in ethanol (30 ml.) in the presence of 5% palladium-charcoal (0.030 g.) at room temperature. The absorption of hydrogen amounted to 92% of the required theoretical amount. The crystalline residue, which was obtained after removal of the catalyst and solvent, was recrystallized twice from aqueous methanol followed by one recrystallization from aqueous acetone (charcoal) to give the saturated ketone IVa; m.p. 116.5–121.5°; 0.16 g.; $[\alpha]_D$ +48° (0.5% ethanol). This compound was identical (no depression of melting point on admixture; identical infrared absorption spectra) with the saturated ketone prepared below by means of the Birch reduction.

4β-Hydroxymethylene-4α,10β-dimethyl-trans-anti-cis-perhydro-12-phenanthrol (IIc). Reduction of the hydroxy acid IIa (5.0 g.) in ether (200 ml.) with lithium aluminum hydride (3.0 g.) at room temperature for 4 days[4] gave both starting material (1.8 g.) and *trans-anti-cis*-perhydropodocarpinol (1.2 g.). Recrystallization of the perhydropodocarpinol from aqueous methanol followed by drying of the product at 100° (0.1 mm.) gave the pure material; m.p. 120–123°; $[\alpha]_D$ −52°; λ_{max} 3.96 μ (KBr).

Anal. Calcd. for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.79; H, 11.36.

4β-Methoxycarbonyl-4α,10β-dimethyl-11α,13α-dibromo-trans-anti-cis-perhydro-12-phenanthrone (XV). The keto ester VII (10.0 g.) in carbon tetrachloride (100 ml.) was brominated with *N*-bromosuccinimide (12.2 g.) at room temperature in diffused sunlight. The product, worked up by the procedure given above for the monobromo ketone, and recrystallized three times from aqueous methanol, melted at 162–164.5°; 1.44 g.; $[\alpha]_D$ +5°; λ_{max} 5.82 μ and 342 mμ (ϵ 180).

Anal. Calcd. for $C_{18}H_{26}Br_2O_3$: C, 48.02; H, 5.82; Br, 35.50. Found: C, 47.97; H, 6.20; Br, 34.82.

Dehydrobromination of the dibromoketone XV. A solution of XV (0.50 g.) in dimethyl formamide (6 ml.) was refluxed with lithium chloride (0.282 g.) for 1.5 hr.[13b] Recrystallization of the product from aqueous methanol gave methyl podocarpate; 0.27 g.; m.p. 204.5–208°. This compound was identical with an authentic sample of methyl podocarpate[2c] (no depression of the melting point on admixture; identical infrared spectra; identical ultraviolet spectra).

4β-Carboxy-4α,10β-dimethyl-trans-anti-cis-perhydro-12α-phenanthrol (XVI). A solution of the keto acid IIIa (0.50 g.) in *n*-propyl alcohol (25 ml.) was maintained at the reflux temperature during the addition of 2.5 g. of sodium.[17b] The reaction mixture was maintained at the reflux temperature for 1 hr. after the addition of the sodium was completed and was then treated successively with methanol, water, and 5% hydrochloric acid. The residue remaining after removal of the solvents was stirred with water and then collected. Two recrystallizations from aqueous methanol gave the hydroxy acid XVI; 0.33 g.; m.p. 253–256°. A sample for analysis was obtained by sublimation under reduced pressure; $[\alpha]_D$ +52°; λ_{max} 2.97 and 5.93 μ (KBr); no detectable band in the region 220–370 mμ at 11 mg./100 ml.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.64; H, 10.21.

An admixture of the two isomeric hydroxy acids IIa and XVI melted in between the melting points of the two pure substances.

Reduction of the keto acid IIIa *with sodium borohydride.* A solution of sodium borohydride (2.80 g.) in water (10 ml.) was added slowly to a warm solution of the ketone IIIa (5.10 g.) and sodium hydroxide (0.74 g.) in ethanol (53 ml.). The reaction mixture was allowed to stand at room temperature for 40 hr. The mixture was diluted with water (total volume = 2 l.). Acetic acid and then 10% hydrochloric acid were added. The resulting solid was collected, washed with water, and then dried overnight in the steam-oven; 4.98 g.; m.p. 235–240°; $[\alpha]_D$ +23°. The infrared absorption spectrum of this material resembled very closely the spectrum of a mechanical mixture of IIa (70%) and XVI (30%) which exhibited a melting point of 234–244° and $[\alpha]_D$ +30°.

4β-Hydroxymethylene-4α,10β-dimethyl-12-methoxy-1,2,3,4,-5α,6,7,10,11,14-decahydrophenanthrene (X). Ten grams of lithium wire was added during a 12 min. period to stirred solution of 20 g. of *O*-methylpodocarpinol (XI)[2a,4] in 250 ml. of *t*-butyl alcohol, 250 ml. of tetrahydrofuran and 600 ml. of ammonia[5] contained in a 3-l. three-necked flask fitted with a sealed stirrer and a Dry Ice cooled condenser. The deep blue solution topped by a bronze liquid amalgam phase decolorized spontaneously after about 1 hr. After the addition of 50 ml. of methanol, the ammonia was evaporated and 500 ml. of water was added. Vacuum distillation of about 500 ml. of the mixed solvent caused the separation of a waxy solid which was then collected on a filter, rinsed free of alkali and dried at room temperature. The crude mixture weighed 19.3 g. The ultraviolet spectrum at 100 mg./100 ml. showed the absence of aromatic compounds. Crystallization of a sample from hexane gave small needles, m.p. 100–103°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.80; H, 10.49.

4β-Hydroxymethylene-4α,10β-dimethyl-1,2,3,4,5α,6,7,8β,-10,12,13,14-dodecahydro-12-phenanthrone (IXa). The crude enol ether X was dissolved in 153 ml. of methanol containing 10.2 ml. of 12*M* hydrochloric acid and 6.8 ml. of water and stored at room temperature for 2 hr. Dilution with 600 ml. of water precipitated a viscous oil which failed to crystallize and was therefore recovered by chloroform extraction to yield 18 g. of a clear yellow glass. A solution of the latter in 180 ml. of anhydrous alcohol containing 18 g. of Girard's T reagent and 18 ml. of acetic acid was refluxed for 0.5 hr. The cooled mixture was then poured into a solution of 25.2 g. of sodium bicarbonate in 720 ml. of water. The curdy precipitate was recovered by extraction with three 200-ml. portions of ether and removal of the solvent to give 6.0 g. of a non-ketonic fraction as a colorless glass. The aqueous alkaline solution from the above extraction was acidified to a *p*H of about 2.0 with 6*M* hydrochloric acid. After 2.0 hr. the mixture was extracted with three 200-ml. portions of ether and the extract was washed with water, dried and evaporated to yield 10.6 g. of a viscous yellow oil which crystallized on standing. Recrystallization from 30 ml. of ethyl acetate and 30 ml. of isopropyl ether gave 7.4 g. of IXa melting at 105–107°. An analytical sample, crystallized from ethyl acetate, melted at 111–112°; λ_{max} 240 mμ (ϵ 16,250).

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.53; H, 9.78.

The *semicarbazone* melted at 255° with decomposition after crystallization from alcohol.

Anal. Calcd. for $C_{18}H_{29}N_3O_2$: N, 13.15. Found: N, 13.26.

The crude non-ketonic fraction was dissolved in benzene and chromatographed over 420 g. of silica gel. Elution with benzene afforded 4.5 g. of *4β-hydroxymethylene-4α,10β-dimethyldodecahydrophenanthrene,* which upon crystallization from 80% methanol (charcoal), melted at 108–109° and weighed 3.2 g.

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 81.98; H, 11.50.

4β-Methoxycarbonyl-4α,10β-dimethyl-1,2,3,4,5α,6,7,8β,-10,12,13,14-dodecahydro-12-phenanthrone (IXd). The alcohol IXa (10.6 g.) was oxidized in acetone (500 ml.) with a standard solution of chromic acid-sulfuric acid (23 ml.).[9] After the excess oxidant was decomposed by the addition of isopropyl alcohol, about two-thirds of the solvent was distilled under reduced pressure. The residue was diluted with water and the product was then extracted into chloroform. Removal of the solvent gave the crude aldehyde IXb; 10 g.; λ_{max} 3.61, 5.79, 5.97, and 6.22 μ ($CHCl_3$).

A solution of the crude aldehyde IXb (10 g.) in acetic acid (100 ml.) was treated at 15–20° with a solution of chromic acid (3.2 g.) in 66% acetic acid (12 ml.). The reaction mixture, after standing overnight, was diluted with water (2 l.). The resulting mixture was heated to 80° and then cooled. The solid was collected, washed with water, and then dried to give the crude acid IXc; 7.5 g.; λ_{max} 2.81, 5.86, 5.97, and 6.22 μ ($CHCl_3$).

The crude acid IXc (7.0 g.) was methylated with dimethyl sulfate and sodium hydroxide in 50% methanol.[2c] The ester was extracted into ether from an alkaline aqueous mixture. The ether extract was washed with water and then evaporated to give the crystalline ester IXd (5.5 g.) which, after two recrystallizations from methanol amounted to 1.42 g.; m.p. 116–118°; $[\alpha]_D$ −8°; λ_{max} 5.78, 5.98, 6.25, and 11.36 μ ($CHCl_3$) and 238.5 mμ (ϵ 15,800).

Anal. Calcd. for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.64; H, 9.13.

4β-Hydroxymethylene-4α,10β-dimethyl-trans-anti-trans-perhydro-12-phenanthrone (VIIIa). A solution of 2 g. of the unsaturated ketone IXa in 25 ml. of *t*-butyl alcohol, 25 ml. of tetrahydrofuran and 60 ml. of ammonia was reduced with 1.0 g. of lithium as described above. Spontaneous decoloration occurred after 3.0 hr., whereupon 20 ml. of methanol was added and the ammonia was permitted to evaporate. Addition of 50 ml. of water, followed by vacuum distillation of solvent and extraction with ether gave 2.0 g. of crude VIIIa as a pale yellow glass. The infrared spectrum showed a strong band at 5.83 μ indicating that the carbonyl group had not been reduced.

Acetylation with acetic anhydride and pyridine at room temperature provided the acetate VIIIc which melted at 114.5–116° after crystallization from hexane; $[\alpha]_D$ +13.5°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.61; H, 10.02.

Saponification of this acetate gave the carbinol VIIIa which, after crystallization from ethyl acetate, melted at 105°; $[\alpha]_D$ +18.8°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.37; H, 10.64.

4β-Carboxyl-4α,10β-dimethyl-trans-anti-trans-perhydro-12-phenanthrone (IVa). A solution of 3.0 g. of chromic anhydride in 2.0 ml. of water and 8.0 ml. of acetic acid was added during a 20-min. period at 15–20° to a stirred solution of 5.3 g. of the crude keto alcohol (VIIIa) in 50 ml. of acetic acid. The dark mixture was stirred for 20 min. longer, stored overnight, and then diluted with 1 l. of hot water. After several hours the finely divided precipitate was collected on a filter, rinsed well with water, and dried to yield 3.0 g. of crude acid (IVa). This crude acid was used without further purification.

Oxidation of the keto alcohol VIIIa in acetone with chromic acid–sulfuric acid gave the crude keto aldehyde VIIIb (λ_{max} 3.63 μ in $CHCl_3$).[21] Further oxidation of this aldehyde with chromic anhydride in acetic acid gave the keto acid IVa.

4β-Methoxycarbonyl-4α,10β-dimethyl-trans-anti-trans-12-phenanthrone (IVb). The crude acid IVa (2.22 g.) was methylated with dimethyl sulfate and sodium hydroxide in 50% methanol.[2c] After extraction with chloroform, the extract was washed well with water and the solvent was vacuum distilled to give 2.0 g. of a dark oil which crystallized on standing. Vacuum sublimation (120°/0.3 mm.) followed by two crystallizations from methanol produced 0.65 g. of the methyl ester IVb melting at 119–120°; $[\alpha]_D$ +51° (ethanol); λ_{max} 5.83 μ.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.99; H, 9.58. Found: C, 73.88; H, 9.68.

The melting point of this material was depressed on admixture with IIIb.

4β-Carboxy-4α,10β-dimethyl-trans-anti-trans-perhydro-12β-phenanthrol (XVII). Method A. A solution of 3 g. of the crude acid (IVa) in 100 ml. of ethanol containing 0.8 g. of sodium hydroxide was heated to reflux and treated with a solution of 1.8 g. of sodium borohydride in 25 ml. of 80% ethanol. The stirred mixture was refluxed for 2 hr., cooled and cautiously acidified with 20 ml. of 6*M* hydrochloric acid. Dilution with 500 ml. of water gave a granular white precipitate which was collected on a filter, rinsed and dried. The crude acid XVII was recrystallized twice from ethyl acetate, yielding 1.0 g. of colorless spikes; m.p. 248–250°; $[\alpha]_D$ +41.4° λ_{max} 2.97 and 5.89 μ (KBr).

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.75; H, 10.13. Found: C, 72.53; H, 9.88.

Method B. Reduction of the crude keto acid IVa with sodium in *n*-propyl alcohol gave XVII which was identical (no depression of the melting point on admixture identical infrared absorption spectra) with the material prepared by Method A.

Acetylation of 530 mg. of the carbinol XVII with acetic anhydride in pyridine at room temperature gave 436 mg. of the acetate of *4β-carboxy-4α,10β-dimethyl-trans-anti-trans-perhydro-12β-phenanthrol* melting at 152–154° after crystallization from hexane; $[\alpha]_D$ +5.5°; λ_{max} 2.83 (weak), 5.78, 5.89, and 7.92 μ.

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 71.03; H, 9.40.

4β-Hydroxymethylene-4α,10β-dimethyl-12ξ-ethynyl-trans-anti-trans-perhydro-12ξ-phenanthrol (XVIIIa *and* XVIIIb).[22] A solution of 35 g. of potassium in 800 ml. of dry *t*-butyl alcohol (prepared under nitrogen atmosphere) was diluted with 200 ml. of dry toluene, chilled to 5°, and saturated with acetylene. A solution of 25 g. of the ketone VIIIa in 200 ml. of dry toluene was added all at once to the stirred mixture, after which the treatment with acetylene under a slight positive pressure was continued at 0–5° for 5 hr. After dilution with 2 l. of water, the toluene layer was separated and the aqueous layer was extracted with 2 × 600 ml. of ether. The combined extracts were washed with water, dried, and evaporated to yield 28.5 g. of a brittle yellow glass (no carbonyl band in infrared). Crystallization from 300 ml. of ethyl acetate (charcoal) and concentration of the mother liquor to a volume of 100 ml. gave two crops of crystals (total of 7.1 g.) each of which melted at 180–220°. These were combined and recrystallized twice from ethanol to give 3.03 g. of XVIIIa (or b); colorless needles; m.p. 217–219°; $[\alpha]_D$ +3.5°; λ_{max} 2.79, 2.90–2.95 (doublet), 3.1 and 4.76 μ ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.51; H, 10.46. Found: C, 77.99; H, 10.21.

All mother liquors were combined and evaporated, yielding 22 g. of viscous oil which was dissolved in benzene and chromatographed over 1.5 kg. of silica gel. The 85% benzene–15% ethyl acetate eluate produced 5.07 g. of crystalline XVIIIb (or a) which, after crystallization from 40 ml. of acetonitrile (charcoal), weighed 4.33 g., and melted at 165°; $[\alpha]_D$ +39.5°; λ_{max} 2.72 and 3.0 μ ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.51; H, 10.46. Found: C, 78.08; H, 10.40.

The 80% benzene–20% ethyl acetate yielded 3.64 g. of XVIIIa (or b) melting at 216–218°.

4β-Hydroxymethylene-4α,10β-dimethyl-12ξ-carboxyethyl-trans-anti-trans-perhydro-12ξ-phenanthrol α-lactone (XVIIIc *and XVIIId*).[22] A solution of 2.95 g. (0.01 mole) of the ethynyl derivative XVIIIa in 40 ml. of tetrahydrofuran was added during a 5-min. period to a stirred solution of 0.15 mole of methylmagnesium bromide in tetrahydrofuran. The mixture was refluxed and stirred for 24 hr. (positive color test for RMgX) and then treated with carbon dioxide just above the stirred liquid surface at room temperature for 24 hr. A trap with a 1-in. head of mercury was used to prevent undue loss of solvent during carbonation. The gray suspension was poured onto 500 ml. of 5% sulfuric acid and then about 200 ml. of solvent was removed by vacuum distillation. After decanting the supernatant liquor, the resinous crude acid was taken up in 140 ml. of water containing 3 ml. of diethanolamine at 65°. The nearly clear hot solution was filtered through Celite and the hot filtrate was acidified. The solid white acid was collected on a filter, rinsed with water, and dried to yield 1.52 g. of crude *4β-hydroxymethylene-4α,-10β-dimethyl-12ξ-carboxyethynyl-trans-anti-trans-perhydro-12ξ-phenanthrol* which was used without further treatment.

A solution of 1.50 g. of the crude acetylenic acid in 100 ml. of alcohol was hydrogenated at atmospheric pressure. The filtered solution was treated with 4 ml. of 10% sodium hydroxide, boiled down to a volume of about 25 ml., and cooled to *ca.* 25°. Four milliliters of 6*N* hydrochloric acid was added and the solution was allowed to stand for 5 min. (to insure complete lactone formation). Dilution with 500 ml. of water gave a viscous product which soon granulated. The crude lactone (1.32 g.) was crystallized from 7 ml. of ethyl acetate (charcoal) to obtain 0.8 g. of pure XVIIIc (or d); m.p. 179–180°; $[\alpha]_D$ +17°; λ_{max} 2.72 and 5.64 μ ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.91; H, 10.07. Found: C, 74.54; H, 9.98.

Carboxylation of 4.3 g. of the acetylenic alcohol XVIIIb (or a) was conducted in the above manner to furnish 1.4 g. of crude acid which upon hydrogenation yielded 1.23 g. of crude lactone XVIIId (or c). Crystallization from 100 ml. of ethyl acetate (charcoal) gave 1.17 g. of lusterous white plates, m.p. 235–240°; $[\alpha]_D$ +23.6°; λ_{max} 2.72 and 5.65 μ ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{32}O_3$: C, 74.91; H, 10.07. Found: C, 74.94; H, 9.95.

(21) This observation led to the employment of this procedure in the preparation of *O*-methyl-7-methylpodocarpinal Ref. 1a and 1b.

(22) This sequence of reactions was patterned after that described in Ref. 18.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Naturally Occurring Oxygen Heterocyclics. X.[1] 4-Phenyl-5,7-dihydroxy-6-isovaleryl-8-isopentenylcoumarin[2,3]

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The yellow toxic principle isolated from the peelings of the fruits of *Mammea americana L.* is shown to be 4-phenyl-5,7-dihydroxy-6-isovaleryl-8-isopentenylcoumarin(III).

In a recent report[6] from this laboratory, mammein, the insecticidal constituent isolated[7] from the seeds of *Mammea americana L.* (family *Guttiferae*) was shown to possess structure I. Through the generous cooperation of Dr. Murrell P. Morris of the U. S. Department of Agriculture Experiment Station of Mayaguez, Puerto Rico, we have obtained a supply of a yellow toxic[8] principle isolated from the peelings of the fruits of the same plant, and the present article is concerned with its structure elucidation.

Repeated chromatography and recrystallization of the yellow substance led to homogeneous samples with wide melting point ranges, apparently due to solvation. The analytical specimen had m.p. 98–109°, was optically inactive, gave a dark brown color with ferric chloride and was soluble in aqueous sodium hydroxide but insoluble in dilute hydrochloric acid.

The analytical results were consistent with the empirical formula $C_{25}H_{26}O_5$ which was confirmed by the preparation of a beautifully crystalline diacetate, m.p. 122–124° ($C_{29}H_{30}O_7$) and dimethyl ether, m.p. 86–89° ($C_{27}H_{30}O_5$). The ultraviolet and infrared spectral data (see Experimental) were reminiscent of a coumarin structure similar to that of mammein,[6] while the analytical data suggested the replacement of the *n*-propyl substituent in the latter by a phenyl substituent. Indeed, the presence of a mono-substituted phenyl group was indicated by infrared absorbtion bands at 776 and 698 cm.$^{-1}$ (carbon disulfide). Along with the spectral and analytical data, the recovery of the unchanged yellow compound after treatment with alkali under conditions previously[9] used to effect isomerization[10] of mammein (I) to isomammein (II) led us to consider structure III for this substance. All details of this structure (III) were verified by the experiments discussed below.

The presence of a double bond in the side chain was indicated by the facile uptake of one mole of hydrogen to yield a yellow dihydride, m.p. 99–103°, which was characterized as its diacetate derivative, m.p. 98–102°. The ultraviolet and infrared spectra of the dihydride IV were very similar to those of III, thus showing that the reactive olefinic link is not conjugated with the main chromophoric system. Ozonization of III, followed by reductive work up of the ozonide, led to the isolation of acetone (69% yield as the 2,4-dinitrophenylhydrazone) unaccompanied by formaldehyde, as well as the aldehydic moiety V, whose empirical formula substantiated its formation by simple fission of the double bond.

A more drastic, as well as more infomative, breach of the molecule was accomplished by prolonged refluxing of III with aqueous potassium hydroxide. Under these conditions, III was degraded to a mixture from which acetophenone (79% yield), isovaleric acid (57% yield), and two

(1) Paper IX, C. Djerassi, J. D. Gray, and F. A. Kincl, *J. Org. Chem.*, **25**, 2174 (1960).

(2) For preliminary communication, see R. A. Finnegan and C. Djerassi, *Tetrahedron Letters*, No. 13, 11 (1959).

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(6) C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *J. Org. Chem.*, **25**, 2164 (1960).

(7) M. P. Morris and C. Pagan, *J. Am. Chem. Soc.*, **75**, 1489 (1953).

(8) For a discussion of the toxicity of this fruit see M. P. Morris, C. Pagan, and J. Garcia, *Revista de Agricultura de Puerto Rico, Suplemento-Seccion, Alimentos Nutricion*, Vol. XLIII, No. 1, 288a (1952).

(9) C. Djerassi, E. J. Eisenbraun, B. Gilbert, A. J. Lemin, S. P. Marfey, and M. P. Morris, *J. Am. Chem. Soc.*, **80**, 3686 (1958).

(10) For discussion of the nature of this isomerization, see Ref. 6.