379. *The Constitutions of Dammarenolic and Nyctanthic Acid.*[*]

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and (*c*) Carl Djerassi, J. S. Mills, and R. E. Wolff.

Dammarenolic and nyctanthic acid have been shown to be formed by an additional step of triterpenoid biogenesis in which the oxygenated position 3 in ring A is attacked to afford a carboxyl group with fission of the ring. This conclusion has been confirmed by photochemical cleavage of the tris-norlactone of hydroxydammarenone-II to give the dihydro-derivative of dammarenolic acid trisnorlactone and by the same cleavage of β-amyrone to furnish dihydronyctanthic acid. Conclusive evidence for the presence of an isopropenyl group in dammarenolic acid has also been adduced.

A preliminary communication describing this work has already appeared.[1]

The dammar triterpenoid dammarenolic acid, $C_{30}H_{50}O_3$, has been characterised as a tricyclic compound containing a carboxyl group, two ethylenic linkages, and a non-acetylatable hydroxyl group.[2] One of the ethylenic linkages was regarded from its infra-red bands as $>C=CH_2$; the other was formulated as $-CH=CMe_2$ because on oxidation by chromic acid methyl dammarenolate gave acetone and a methyl ester trisnor-γ-lactone, $C_{28}H_{44}O_4$. This ready oxidation is characteristic of a side chain, as in (I),[2,3] which is present in many of the neutral dammar triterpenoids.[3] The nature of the carboxyl group was not investigated further.

In the present paper we first report some additional experiments on the chemistry of dammarenolic acid. In agreement with the presence of two ethylenic linkages methyl dammarenolate was readily hydrogenated to a tetrahydro-derivative. Ozonolysis of the methyl ester trisnor-γ-lactone, $C_{28}H_{44}O_4$, mentioned above, gave formaldehyde, confirming chemically the presence of the grouping $>C=CH_2$. Hydrogenation of the methyl ester lactone gave an oily dihydro-derivative which, on reduction with lithium aluminium hydride, furnished a nicely crystalline triol, $C_{27}H_{50}O_3$, m. p. 150—152°, to which further reference is made below.

The oxidation of methyl dammarenolate by chromic acid (see above) has been investigated by us in more detail than before. Besides the methyl ester γ-lactone referred to above, there was isolated a saturated ketone, $C_{27}H_{42}O_5$, characterised as its 2,4-dinitrophenylhydrazone, and an acid, $C_{26}H_{40}O_6$, which contained, from its infrared bands, a γ-lactone and a methoxycarbonyl group. The formation of this acid suggested the presence of an isopropenyl grouping, $-CMe=CH_2$, in dammarenolic acid. In confirmation, the ketone $C_{27}H_{42}O_5$ was shown to be a methyl ketone from its nuclear magnetic resonance spectrum. A 10% solution in [^{2}H]chloroform (with tetramethylsilane as an internal standard) showed peaks at 6·45 (OMe), 7·89 (COMe), 8·69 (Me·C·O·), and 8·99, 9·07, and 9·14 (three saturated C-Me)τ.[*] Except for an irregularity in the 327—300 mμ region, this ketone gave a nearly plain rotatory dispersion curve. This is inconsistent with any ring ketone structure[5] but compatible with the presence of a methyl ketone grouping.[6] The

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[*] This paper represents Part XLI in a series of papers on Terpenoids by one author (C. D.) and his collaborators (for Part XL, see *J. Amer. Chem. Soc.*, 1959, **81**, 2914). It is also to be regarded as Part VIII in a series of papers by D. H. R. B. and his colleagues on Photochemical Transformations (for Part VII, see *J.*, 1960, 511).

[†] We thank Dr. L. M. Jackman of Imperial College for the determination and interpretation of this spectrum. The measurements were made with a Varian Associates Instrument and a 40 Mc./sec. oscillator. For the definition of τ see Tiers.[4]

[1] Arigoni, Barton, Bernasconi, Djerassi, Mills, and Wolff, *Proc. Chem. Soc.*, 1959, 306.

[2] Mills and Werner, *J.*, 1955, 3132.

[3] Mills, *J.*, 1956, 2196.

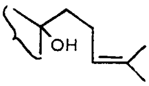
[4] Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.

[5] Cf. Djerassi, " Optical Rotatory Dispersion: Applications to Organic Chemistry," New York, 1960, McGraw-Hill Book Co., Chap. 4—6.

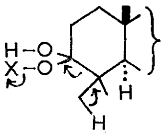
[6] See, for example, Fig. 4 in Djerassi, Mitscher, and Mitscher, *J. Amer. Chem. Soc.*, 1959, **81**, 947.

formation of a methyl ketone on chromic acid oxidation of an isopropenyl group has analogy in lupeol chemistry.[7]

Further evidence for the presence of an isopropenyl group was obtained by oxidation of the trisnor-γ-lactone ester with selenium dioxide. This gave an $\alpha\beta$-unsaturated aldehyde [$\cdot C(:CH_2)\cdot CHO$] comparable with analogous compounds obtained in the same way by similar oxidation of lupeol acetate.[8,9]

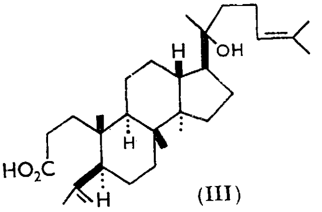


(I)



(II)

Now one of the most interesting features of dammarenolic acid is that it contains no hydroxyl or ketone group at a 3-position in a triterpenoid nucleus such as is found almost without exception in plant triterpenoids. It occurred to us that perhaps the carboxyl group of dammarenolic acid might result from the cleavage of a normal triterpenoid 3-ketone according to a new biogenetic process illustrated in (II) (X = a suitable electronegative departing group) or equivalent process. Dammarenolic acid would then be



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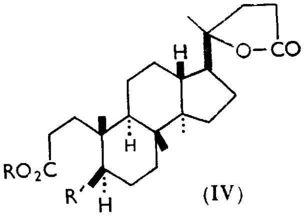
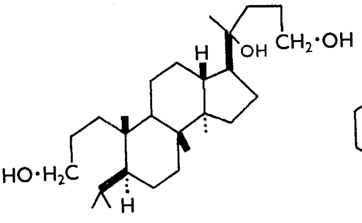
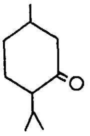


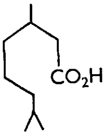
(IV)



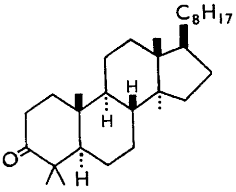
(V)



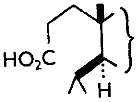
(VI)



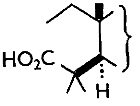
(VII)



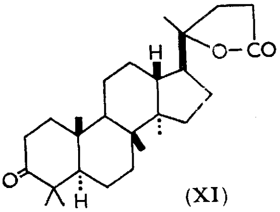
(VIII)



(IX)



(X)



(XI)

(III), the derived methyl ester trisnor-γ-lactone would be (IV; R = Me, R′ = $-CMe{:}CH_2$), the methyl ketone $C_{27}H_{42}O_5$ would be (IV; R = Me, R′ = Ac), and the corresponding acid would be (IV; R = Me, R′ = CO_2H). The dihydro-derivative of the methyl ester trisnor-γ-lactone would be represented as (IV; R = Me, R′ = Pr^i), and the triol of m. p. 150—152° resulting therefrom by reduction would be (V). In the event, it was a simple matter to show that these formulæ were indeed correct.

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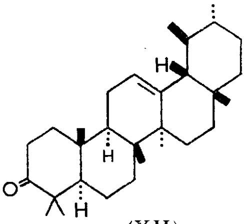
[7] Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1939, **22**, 778.

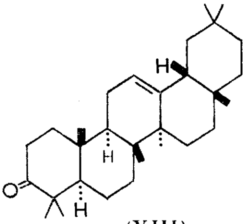
[8] Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311.

[9] Jones and Meakins, *J.*, 1940, 1335.

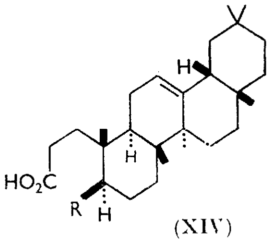
Many years ago Ciamician and Silber[10] discovered the photochemical cleavage of menthone (VI) to the acid (VII). We found that lanostanone (VIII) was smoothly cleaved on irradiation with ultraviolet light in aqueous acetic acid into a carboxylic acid. From analogy, and because the desired methyl ester was readily hydrolysed, this acid is formulated as in (IX) and not as in (X) where the carboxyl group would be much more hindered. This cleavage reaction was then applied to the γ-lactone (XI) from hydroxydammarenone-II.[2,3,11] The resultant acid (IV; R = H, R′ = Pr^i) was obtained crystalline but its methyl ester remained oily (cf. above). This ester was, however, readily hydrolysed back to the parent acid in agreement with the presence of a primary methoxycarbonyl group. Reduction of this ester γ-lactone with lithium aluminium hydride then afforded the same nicely crystalline triol (V) as had been obtained earlier from dammarenolic acid (see above). The proof of structure (III) for the latter was thus complete.



(XII)



(XIII)



(XIV)

Another triterpenoid acid which presents the same problem of biogenesis as dammarenolic acid is the tetracyclic nyctanthic acid.[12] It occurred to us that this substance might be derived from either α- (XII) or β-amyrone (XIII) by the same sort of ring fission (II). It was then a simple matter to subject these two ketones to photochemical cleavage to give acids [as (IX)]. The acid (XIV; R = Pr^i) from β-amyrone was identical with dihydronyctanthic acid. Since nyctanthic acid itself contains the grouping ($\rangle$C=CH$_2$) it must be formulated as in (XIV; R = –CMe:CH$_2$). The same conclusion as to the constitution of nyctanthic acid has been reached independently by a non-photochemical method.[13]

EXPERIMENTAL

M. p.s were taken on a Fisher–Johns or a Kofler block. Infrared spectra were measured with a Perkin–Elmer model 21 double-beam instrument, and rotatory dispersion curves with a Rudolph spectropolarimeter with mechanically oscillating polariser. $[\alpha]_D$ refer to CHCl$_3$ solutions, and ultraviolet absorption spectra to EtOH solutions unless specified to the contrary. Light petroleum refers to the fraction of b. p. 40—60°.

Methyl Dammarenolate.—The material, isolated as described by Mills and Werner[2] and recrystallised from aqueous methanol, had m. p. 87·5—89·5°, $[\alpha]_D$ +44° (*c* 1·31), R.D. in methanol (*c* 0·106), plain positive dispersion curve: $[\alpha]_{589}$ +45°, $[\alpha]_{500}$ +79°, $[\alpha]_{400}$ +115°, $[\alpha]_{300}$ +265°, $[\alpha]_{260}$ +370°. Infrared bands (KBr) were at 3470, 1730, 1640, and 894 cm.$^{-1}$.

Methyl Tetrahydrodammarenolate.—Quantitative microhydrogenation of methyl dammarenolate with platinum oxide and acetic acid resulted in the uptake of 2·1 mol. of hydrogen. In a preparative experiment, the ester (2·01 g.) was hydrogenated at room temperature and atmospheric pressure (570 mm.) in glacial acetic acid (150 ml.) in the presence of platinum oxide (532 mg.). The catalyst was filtered off, the filtrate poured into water (450 ml.), and the product extracted with ether, washed with water, sodium hydrogen carbonate solution, and water, dried and recovered quantitatively as a colourless solid. Two recrystallisations from aqueous methanol led to *methyl tetrahydrodammarenolate*, m. p. 103—105°, $[\alpha]_D$ +31° (*c* 1·05), $\nu_{max.}$ (in

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[10] Ciamician and Silber, *Ber.*, 1907, **40**, 2419; 1909, **42**, 1510.

[11] See also Mills, *Chem. and Ind.*, 1956, 189; Cosserat, Ourisson, and Takahashi, *ibid.*, p. 190; Godson, King, and King, *ibid.*, p. 190; Crabbé, Ourisson, and Takahashi, *Tetrahedron*, 1958, **3**, 279; Biellmann, Crabbé, and Ourisson, *ibid.*, p. 303.

[12] Turnbull, Vasistha, Wilson, and Woodger, *J.*, 1957, 569.

[13] Whitham, *Proc. Chem. Soc.*, 1959, 271.

$CHCl_3$) 3534 and 1727 cm.$^{-1}$ (Found: C, 78·0; H, 11·55. $C_{31}H_{56}O_3$ requires C, 78·1; H, 11·8%).

Oxidation of Methyl Dammarenolate by Chromium Trioxide.—The conditions employed by Mills and Werner for the oxidation of methyl dammarenolate to the trisnorlactone (IV; R = Me, R′ = $\cdot$CMe:CH$_2$) were modified by the omission of benzene. At least three products were isolated.

Methyl dammarenolate (13 g.) in glacial acetic acid (200 ml.) was treated dropwise at room temperature with chromium trioxide (10·4 g.) in glacial acetic acid (120 ml.). After being kept overnight, the mixture was poured into ice-water (2 l.), and the amorphous precipitate was collected and dissolved in ether. The ether solution was washed successively with ice-water, a small amount of sodium hydrogen carbonate solution, and water, dried, and evaporated. The residue (9·65 g.) was chromatographed on silica gel (300 g.; Davidson Chemical Co., Baltimore, grade 922).

(*a*) Elution with benzene–ether (95 : 5) provided methyl dammarenolate trisnorlactone (2·85 g.) which on recrystallisation from aqueous methanol had m. p. 125—126°, $[\alpha]_D$ +51° (*c* 2·73); R.D. in methanol (*c* 0·103), plain positive dispersion curve: $[\alpha]_{589}$ +45°, $[\alpha]_{500}$ +76°, $[\alpha]_{400}$ +118°, $[\alpha]_{300}$ +260°, $[\alpha]_{262\cdot5}$ +349°, very similar to that of methyl dammarenolate. Identity with the lactone of Mills and Werner[2] was established by mixed m. p. determination and infrared comparison: $\nu_{max.}$ (in KBr) 1767, 1739, 1645, and 881 cm.$^{-1}$ [the last two bands are due to $>$C:CH$_2$].

(*b*) Elution with benzene–ether (90 : 10) gave the *nor-ketone* (IV; R = Me, R′ = Ac) (1·0 g.); recrystallised twice from acetone–hexane this had m. p. 154—156°, $[\alpha]_D$ +29° (*c* 1·01), $\lambda_{max.}$ (in EtOH) 286 mμ (ε 28), $\nu_{max.}$ (in KBr) 1770, 1741, and 1690 cm.$^{-1}$; R.D. curve in methanol (*c* 0·29): $[\alpha]_{700}$ +12°, $[\alpha]_{589}$ +14°, $[\alpha]_{327-300}$ +110° (shoulder), $[\alpha]_{255}$ +256° [Found: C, 72·45; H, 9·3; O, 18·45; OMe, 6·85%; *M* (Rast), 454. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5; O, 17·9; OMe, 6·95%; *M*, 447]. The derived 2,4-*dinitrophenylhydrazone* (methanol–sulphuric acid), recrystallised from ethanol–chloroform, had m. p. 267—269°, $\lambda_{max.}$ in $CHCl_3$ 364 mμ (ε 22,730) (Found: C, 63·4; H, 7·65. $C_{33}H_{46}O_8N_4$ requires C, 63·25; H, 7·4%).

(*c*) Elution with benzene–ether (1 : 1) afforded an oil (3·13 g.) which led to crystals (350 mg.; m. p. 230—233°) on crystallisation from acetone–hexane. Four additional recrystallisations gave the colourless *acid* (IV; R = Me, R′ = CO_2H), m. p. 257—259°, $[\alpha]_D$ +17° (*c* 1·01), $\nu_{max.}$ (in $CHCl_3$) 3350, 1757, 1730, and 1709 cm.$^{-1}$ (general appearance of an acid) (Found: C, 69·7; H, 9·2. $C_{26}H_{40}O_6$ requires C, 69·6; H, 9·0%).

Ozonolysis of Trisnorlactone Methyl Ester (IV; R = Me, R′ = $\cdot$CMe:CH$_2$).—Ozone was passed at room temperature for 10 min. through a solution of 1·0 g. of the lactone in acetic acid (50 ml.); then ferrous sulphate (3 g.) and water (140 ml.) were added. The mixture was distilled until about one-third of its volume had been collected in a solution of 2,4-dinitrophenylhydrazine (0·59 g.) in concentrated sulphuric acid (10 ml.) and water (40 ml.). The yellow precipitate was chromatographed in chloroform over alumina (100 g.). Elution with the same solvent and recrystallisation provided formaldehyde 2,4-dinitrophenylhydrazone (110 mg.), m. p. 166—167° (mixed m. p.; correct infrared spectrum).

Hydrogenation of Methyl Dammarenolate Trisnorlactone (IV; R = Me, R′ = $\cdot$CMe:CH$_2$).—Hydrogen consumption (1 mol.) stopped after 15 min. when the lactone (300 mg.) in acetic acid (40 ml.) was hydrogenated over platinum oxide (100 mg.). The product (IV; R = Me, R′ = Pr^i) was isolated as described above for methyl tetrahydrodammarenolate, but was not crystalline even after chromatography on silica gel.

For adequate characterisation the above methyl dihydrodammarenolate trisnorlactone (240 mg.) was left overnight at room temperature with lithium aluminium hydride (300 mg.) in anhydrous tetrahydrofuran (15 ml.). The mixture was poured on ice, and N-hydrochloric acid was added until a slightly acid reaction was obtained. Extraction with ether, washing until neutral, drying (Na_2SO_4), and evaporation gave an oil which crystallised from acetone–hexane (200 mg.; m. p. 150—152°). Two recrystallisations from the same solvents provided the *triol* (V), m. p. 150—152°, $[\alpha]_D$ 45° (*c* 1·30), which exhibited no infrared carbonyl absorption. The substance appears to be hygroscopic and it was dried at 50°/0·01 mm. for two days before analysis (Found: C, 76·75; H, 12·1. $C_{27}H_{50}O_3$ requires C, 76·7; H, 11·9%).

Oxidation of Methyl Dammarenolate Trisnorlactone (IV; R = Me, R′ = –CMe:CH$_2$) *by Selenium Dioxide.*—A solution of the lactone (500 mg.) and freshly sublimed selenium dioxide (500 mg.) in acetic acid (25 ml.) was heated under reflux for 2 hr., filtered through Celite, diluted with water, and extracted with ether. The ethereal solution was washed with water, ice-cold 2% aqueous sodium hydroxide, and water, dried, and evaporated. The yellow crystalline residue (400 mg.; $\lambda_{\max.}$ 220 mμ) was passed in acetone through a small column of alumina and then stirred with mercury in order to remove colloidal selenium. The material was then chromatographed on 15 g. of silica gel and eluted with benzene–ether (4 : 1), yielding crystals (360 mg.), m. p. 185—187°. Two recrystallisations from acetone–hexane gave the αβ-unsaturated *aldehyde* [IV; R = Me, R′ = $\cdot C(:CH_2)\cdot CHO$], m. p. 186—188°, $\lambda_{\max.}$ 222 mμ (log ε 3·81), $\nu_{\max.}$ 1760 (γ-lactone), 1736 (CO_2Me), and 1693 (αβ-unsaturated aldehyde) cm.$^{-1}$; R.D. (*c* 0·070) in dioxan: $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +25°, $[\alpha]_{357\cdot5}$ −311°, $[\alpha]_{300}$ +806° (Found: C, 73·1; H, 9·2; O, 17·25. $C_{28}H_{42}O_5$ requires C, 73·3; H, 9·25; O, 17·45%).

Photochemical Cleavage of Lanostanone.—The ketone (1·0 g.) in acetic acid–water (9 : 1) (250 ml.) was irradiated in a Pyrex flask at reflux temperature under nitrogen with a bare mercury-arc lamp (125 w) for 12 hr. The course of the reaction was followed by the decrease in intensity of the Zimmermann test characteristic [14] of triterpenoid 3-ketones. The solvent was removed *in vacuo* and the residue chromatographed over acid-washed alumina (30 g.; Grade III). Elution with chloroform–methanol afforded the *seco-acid* (as IX) (350 mg.), m. p. (from light petroleum) 186—188°, $[\alpha]_D$ +14° (*c* 1·00), no ultraviolet absorption, $\nu_{\max.}$ 1710 (broad) cm.$^{-1}$ (CO_2H) (Found: C, 80·75; H, 12·15. $C_{30}H_{54}O_2$ requires C, 80·65; H, 12·2%). With diazomethane this gave the methyl ester which, crystallised with difficulty from methanol, had m. p. (solvated) 79—83°, $[\alpha]_D$ +16° (*c* 1·00), no ultraviolet absorption, $\nu_{\max.}$ 1739 (CO_2Me) cm.$^{-1}$. The methyl ester (130 mg.) in dioxan–ethanol (1 : 1) (50 ml.) was refluxed with 2% potassium hydroxide (5 ml.) for 30 min. Separation into acidic and neutral (negligible) fractions, and crystallisation from light petroleum, gave back the seco-acid (100 mg.).

Photochemical Cleavage of the Lactone (XI) *from Hydroxydammarenone*-II.—The lactone [3] (500 mg.) in acetic acid–water (9 : 1) (150 ml.) was irradiated as above, and the resulting gum separated by cold aqueous sodium hydroxide into neutral and acidic fractions. The latter (460 mg.) was chromatographed over silica gel (46 g.). Elution with light petroleum–benzene (2 : 1) afforded the *seco-acid lactone* (IV; R = H, R′ = Pr^i) (50 mg.), m. p. (from ether–methanol) 99—104°, $[\alpha]_D$ +43° (*c* 1·25), no ultraviolet absorption, $\nu_{\max.}$ 1770 (γ-lactone) and 1710 (CO_2H) cm.$^{-1}$ (Found: C, 74·85; H, 10·55. $C_{27}H_{44}O_4$ requires C, 74·95; H, 10·25%).

With diazomethane the acid lactone gave the methyl ester which did not crystallise. Hydrolysis of the oily methyl ester (80 mg.) in dioxan–ethanol (1 : 1) with 2% potassium hydroxide in ethanol (5 ml.) under reflux for 30 min. gave back unchanged acid (50 mg.).

The oily ester-lactone (IV; R = Me, R′ = $\cdot CMe:CH_2$) (200 mg.) in tetrahydrofuran (20 ml.) was treated with lithium aluminium hydride (500 mg.) in the same solvent (10 ml.) for 78 hr. at room temperature. The product was chromatographed over Grade V alumina. Elution with ether–chloroform (4 : 7) afforded the triol (V), $[\alpha]_D$ +48° (*c* 0·80), m. p. (from acetone–light petroleum) 150—152° alone or mixed with the triol obtained (see above) from dammarenolic acid. The infrared spectra of the two specimens (in $CHCl_3$) were identical.

Photochemical Cleavage of α-Amyrone (XII).—The ketone (1·0 g.) in acetic acid water (9 : 1) (250 ml.) was irradiated as in the prior examples. Working up as before and chromatography of the acidic fraction (800 mg.) over silica gel (100 g.) gave, on elution with light petroleum–benzene (4 : 1), the desired *seco-acid* (as IX) (400 mg.), m. p. (from ethanol) 170—172°, $[\alpha]_D$ +73° (*c* 1·50), end absorption in the ultraviolet, $\nu_{\max.}$ 1710 (CO_2H) cm.$^{-1}$ (Found: C, 81·85; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

Photochemical Cleavage of β-*Amyrone* (XIII).—The ketone (1·0 g.) was irradiated and worked up as for α-amyrone (see above). The derived seco-acid (XIV), recrystallised from ethanol, had m. p. 194—196°, $[\alpha]_D$ +82° (*c* 1·40), end absorption in the ultraviolet, $\nu_{\max.}$ 1710 (CO_2H) cm.$^{-1}$ (Found: C, 81·4; H, 11·4. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%). The acid was undepressed in m. p. on admixture with dihydronyctanthic acid of the same m. p.; the two specimens showed the same infrared spectra in $CHCl_3$, different from that of the seco-acid from α-amyrone.

The acid was converted into its amorphous methyl ester with diazomethane, and this (250 mg.) in tetrahydrofuran (30 ml.) was treated with lithium aluminium hydride (600 mg.) in the same solvent (20 ml.) for 10 hr. at room temperature. The product was chromatographed over alumina Grade V. Elution with benzene–ether (9 : 1) gave the expected alcohol, m. p. 149—151°, $[\alpha]_D$ +85° (*c* 1·50) (lit.,[12] m. p. 153°, $[\alpha]_D$ +90°).

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[14] Barton and de Mayo, *J.*, 1954, 887.

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