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SESQUITERPENOIDS—III

THE CONSTITUTION AND STEREOCHEMISTRY OF VALDIVIOLIDE, FUEGIN, WINTERIN AND FUTRONOLIDE

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Abstract—The constitution and stereochemistry of three new bicyclofarnesol derivatives, valdiviolide, fuegin and winterin, isolated from *Drimys* species have been determined by interrelation with confertifolin.[3] A tentative structure is assigned to a fourth minor constituent, futronolide.

Comment is made on the U.V. spectra of $\Delta^{\alpha\beta}$-γ-hydroxybutenolides.

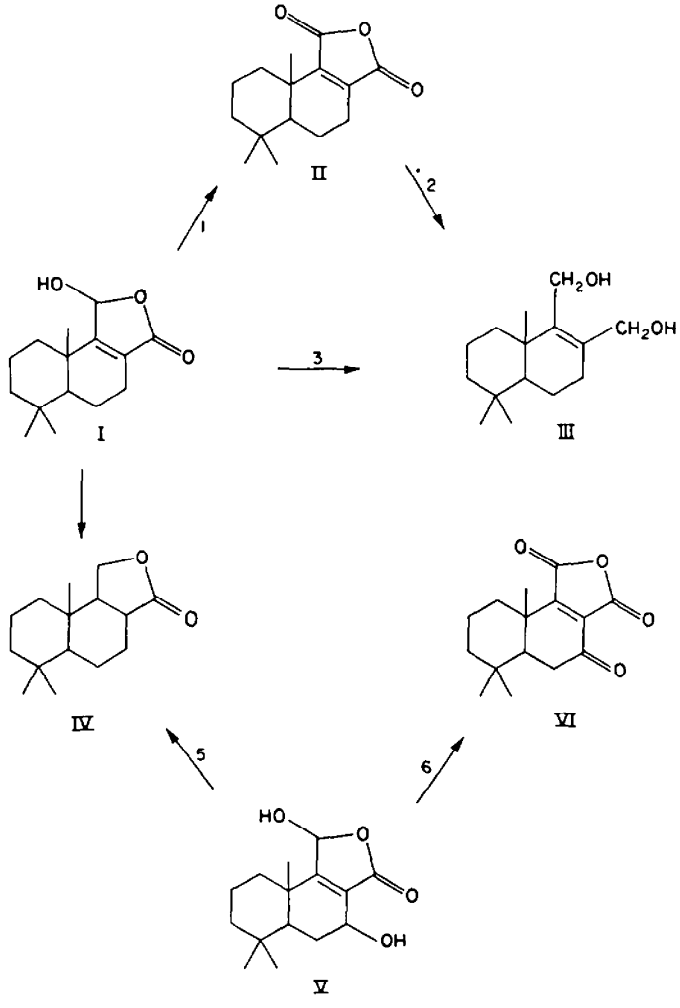
IT HAS been shown that the stem barks of South American *Drimys* species contain a number of biogenetically interesting bicyclofarnesol derivatives.[1,2] In our search for further structural variants, a large number of bark extracts, mainly of *D. winteri*, but also of *D. confertifolia*, collected in different regions of Chile were examined. As a result, four new bicyclofarnesol derivatives, all occurring in minor amounts were isolated and the distribution of the previously described major components is now better understood. Drimenol and confertifolin are encountered widely and in major amounts and frequently occur together. Isodrimenin appears more rarely, while drimenin, despite careful search, has to date been encountered in only one extract.[2] (It has been shown that the isolation procedure does not isomerize drimenin to isodrimenin). It is also interesting to note that while drimenol, confertifolin and isodrimenin coexisted in all the extracts that were examined in detail, one of the three was present only in trace amounts. We have not encountered isoconfertifolin (drim-7-ene-12,11-olide), the system corresponding to iresin, which was recently obtained[3] as a transformation product of the naturally occurring polygodial. Three of the new compounds, valdiviolide, fuegin and winterin, were obtained from a single *D. winteri* tree in the Valdivia region Fuegin had been previously isolated from a tree grown in Tierra del Fuego.[4] The fourth, futronolide occurred in bark collected in the Lago Ranco-Futrono region.

The crystalline mixture of compounds obtained from the Valdivia extract by fractional distillation under reduced pressure and solvent treatment (see Experimental), was separated by chromatography over activated alumina into mainly (85%) confertifolin (light petroleum → chloroform) and minor quantities of valdiviolide (chloroform–ethyl acetate → ethyl acetate), fuegin (acetic acid) and winterin (aqueous acetic acid).

The most polar compound, winterin, $C_{15}H_{20}O_3$ (from combustion analysis and mass spectroscopic molecular weight), was identified as a maleic anhydride by its

[1] H. H. Appel, C. J. W. Brooks and K. H. Overton, *J. Chem. Soc.* 3322 (1959).
[2] H. H. Appel, J. D. Connolly, K. H. Overton and (in part) R. P. M. Bond, *J. Chem. Soc.* 4658 (1960).
[3] C. S. Barnes and J. W. Loder, *Austral. J. Chem.* **15**, 322 (1962).
[4] M. de la Horra (Thesis, Universidad Tecnica, Valparaiso, 1962).

I.R. spectrum [$\nu_{max}^{CCl_4}$, 1847, 1776 (anhydride COs) and 1668 (conjugated olefinic linkage) cm^{-1}], while the substitution of this function was indicated by the resemblance of the U.V. spectrum (λ_{max} 257 mμ; ε, 3820) to that of the simple methyl ethyl maleic anhydride[5] and also of the mould products byssochlamic and glauconic acids[6] which contain di-substituted maleic anhydride systems. If one assumes a structural relationship with confertifolin, then winterin is drim-8-enc-11,12-dioic acid anhydride (II). In support of this, the lowest signal in the N.M.R. spectrum of winterin is at τ 7·54 (C_7 allylic methylene), and the constitution is further confirmed by reduction of winterin with lithium aluminium hydride to drim-8-ene-11,12-diol (III),



Reagents. 1, CrO_3. 2, $LiAlH_4$. 3, $LiAlH_4$. 4, H_2/Pt
5, H_2/Pt. 6, CrO_3

[5] H. M. Muir and A. Neuberger, *Biochem. J.* **45**, 165 (1949).
[6] J. E. Baldwin, D. H. R. Barton, J. L. Bloomer, L. M. Jackman, L. Rodriguez-Hahn and J. K. Sutherland, *Experientia* **8**, 345 (1962).

previously obtained[2] from both isodrimenin and confertifolin, and the oxidation of valdiviolide (I) to winterin (see below).

The two less polar compounds, valdiviolide and fuegin, are related to each other and to confertifolin (IX) as shown by their U.V. and I.R. spectra.

Valdiviolide: λ_{max} 221 mμ (ε, 10,300) ν_{max}^{KCl} 3360, $\nu_{max}^{CHCl_3}$ 1769 and 1680 cm^{-1}.

Fuegin. λ_{max} 217 mμ (ε, 6,500), $\nu_{max}^{CHCl_3}$ 3605, 3476; $\nu_{max}^{CCl_4}$ 1767 and 1687 cm^{-1}.

Confertifolin. λ_{max} 217 mμ (ε, 11,750) $\nu_{max}^{CCl_4}$ 1769 and 1677 cm^{-1}.

This suggests in both compounds the presence of a butenolide system as in confertifolin, and additional hydroxyl groups. Valdiviolide, $C_{15}H_{22}O_3$, has one and fuegin, $C_{15}H_{22}O_4$, two oxygens in addition to the lactone. That both compounds contain a lactonol as in (I), is evident from their U.V. spectra in basic solution, which differ from that of confertifolin (discussed below), and from the presence in their N.M.R. spectra of a signal (1 proton) at τ 3·85, attributable to an allylic proton attached to carbon (C_{11}), bearing two singly bonded oxygens. Valdiviolide must be one of two possible lactonols derived from winterin (II) since reduction of valdiviolide (I) with lithium aluminium hydride yields drim-8-ene-11,12-diol (III), and oxidation with chromic anhydride in acetic acid yields winterin (II). The correct structure (I) not (X) is confirmed by hydrogenolysis of (I) with platinum oxide in acetic acid to dihydroconfertifolin (IV).

The fourth oxygen atom of fuegin, $C_{15}H_{22}O_4$, is probably present as an additional hydroxyl group or as an ether function and not as a ketone, since the carbonyl region of the I.R. spectrum resembles that of valdiviolide. The position of a multiplet (1 proton) in the N.M.R. spectrum centred at τ 5·33, suggests that the additional secondary hydroxyl or ether function is attached allylically to the butenolide double bond, that is at C_7. The constitution (V) for fuegin is confirmed by conversion to dihydroconfertifolin (IV) (hydrogenolysis of both allylic hydroxyl groups and reduction of the ethylenic linkage) when the compound in acetic acid is hydrogenated in presence of Adams' catalyst.

Oxidation of fuegin with 2·15 oxygen equivalents of chromium trioxide in acetic acid did not proceed smoothly, but the crystalline oxidation product isolated in small yield has spectral properties [ν_{max}^{KCl} 1787, 1778 (anhydride), 1689 (enone) and 1641 (ethylenic linkage) cm^{-1} and λ_{max}^{EtOH} 230 mμ (ε, 7,750), $\lambda_{max}^{1NKOH/EtOH}$ 238, 278 mμ (ε, 2,780, 3,710)] which suggests the anticipated structure of drim-8-ene-7-one-11,12-dioic acid anhydride (VI).

The stereochemistry of the C_7 hydroxyl group is not readily deduced from the available data and lack of material precluded further investigation. The C_{11} hydroxyl group in fuegin and valdiviolide may be assumed to be in the thermodynamically more stable configuration (probably α) since equilibration through the aldehydo-acid should take place without difficulty.

One additional new Drimys constituent, futronolide, was isolated from a tree in the Lago Ranco-Futrono region and separated chromatographically from the confertifolin, which constitutes more than 99% of the crystalline material and altogether 5 mg of futronolide were available for investigation.

The molecular weight of 250 determined by mass spectrometry, shows futronolide to be isomeric with valdiviolide (I). The close similarity of the U.V. spectrum both in neutral (λ_{max} 218 mμ; ε, 10,700) and basic (λ_{max} 231 mμ; ε, 5,100) solutions to that of confertifolin establishes the presence of a butenolide as in confertifolin, and also

clearly shows that the third oxygen, whilst hydroxylic (I.R.), is not, as in valdiviolide, part of a lactonol (See Table 1). This conclusion is supported by the absence in the N.M.R. spectrum* of a signal at τ 3·35, attributed to the C_{11} proton in valdiviolide and fuegin. Futhermore, the absence of a vinylic proton signal necessitates a $\Delta^{8,9}$ butenolide. The rest of the spectrum (Fig. 1), particularly when compared with that of confertifolin, may be interpreted as follows:

TABLE 1

	Neutral solution		Basic solution	
	$\lambda_{max.}$ (mμ)	ε	$\lambda_{max.}$ (mμ)	ε
$\Delta^{\alpha\beta}$-Butenolides				
Confertifolin (IX)	217	11,750	232	4,350
Isodrimenin (XI)	218	10,000	230	11,000
Futronolide (VII)	218	10,700	231	5,100
$\Delta^{\alpha\beta}$-γ-Hydroxy Butenolides				
Valdiviolide (I)	221	10,300	228	5,000
			257	10,300
Fuegin (V)	217	6,500	233	5,050
			258	6,150
$\Delta^{\alpha\beta}$-α-Hydroxy Butenolides				
α-Keto Butyrolactone[7]	226	4,000	261	2,600
β-Ionone Oxidation Product (XV)[8]	238	11,400	274	10,000
Iresin Ozonolysis Product (XVI)[9]	240	8,000	274	1,100

The multiplet (1H) centred at τ 5·55, absent in confertifolin, must arise from an allylic proton situated on carbon bearing oxygen. Assuming a butenolide as in confertifolin, the hydroxyl group must be attached at C_7 suggesting the constitution (VII) for futronolide; the observed fine structure of the C_7H signal is in keeping with this. Moreover, the triplet centred in confertifolin at τ 5·36 (J = 3 c.p.s.), arising from the C_{11} methylene group, interacting through the double bond with two nonequivalent protons at C_7, is in futronolide replaced by a doublet centred at τ 5·26 (J = 5 c.p.s.), as would be expected on the basis of structure (VII).

The U.V. spectra of the two lactonols (I and V), deserve futher comment. In neutral ethanolic solution they resemble the conjugated butenolides isodrimenin (XI), confertifolin (IX), and futronolide (VII) but in basic ethanolic solution, their behaviour differs from these simple lactones. Whereas the latter exhibit (see Table 1) a single maximum, shifted ca. 13 mμ to the red (arising presumably from the $\alpha\beta$-unsaturated carboxylate ion), the lactonols have two absorption bands in basic solution: one corresponds to the band at ca. 230 mμ present in the lactones, but in

* We are particularly indebted to Dr. A. Melera, Varian AG, Zurich, for this N.M.R. spectrum, obtained on ca. 3 mg of futronolide.

[7] H. Hift and H. R. Mahler, *J. Biol. Chem.* **198**, 907 (1957).

[8] C. J. W. Brooks, G. Eglinton and D. Magrill, *J. Chem. Soc.* 308 (1961).

[9] C. Djerassi and W. Rittel, *J. Amer. Chem. Soc.* **79**, 3528 (1957).

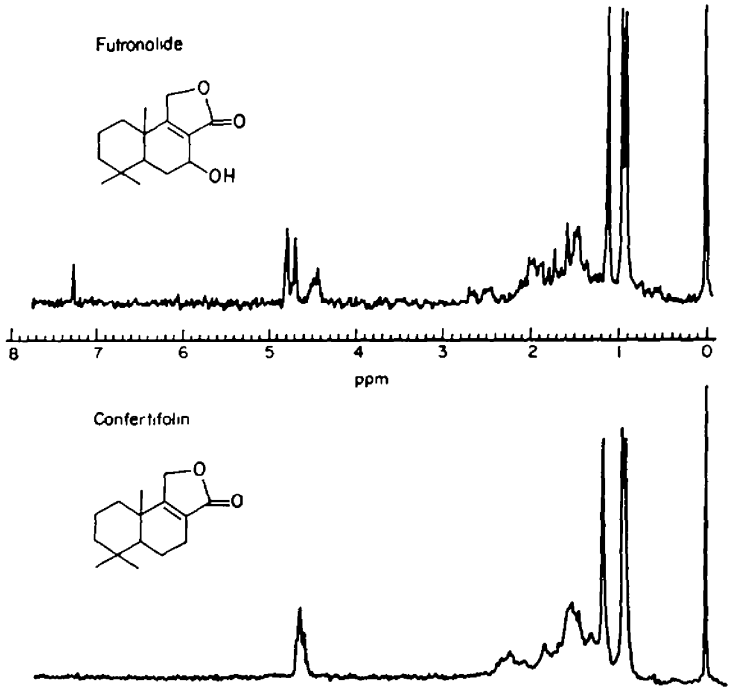
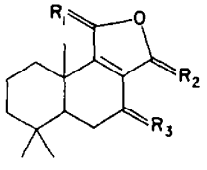


FIG. 1. N.M.R. Spectra of Futronolide and Confertifolin in $CDCl_3$ (60 Mc).



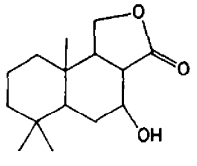
VII $R_1 = H_2$; $R_2 = O$; $R_3 = H,OH$.

IX $R_1 = R_3 = H_2$; $R_2 = O$.

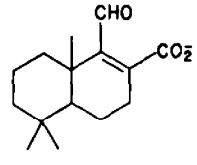
X $R_1 = O$; $R_2 = H,OH$; $R_3 = H_2$.

XI $R_1 = O$; $R_2 = R_3 = H_2$.

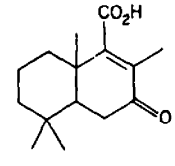
XIV $R_1 = R_3 = O$; $R_2 = H_2$.



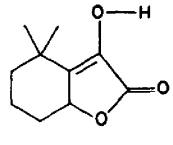
VIII



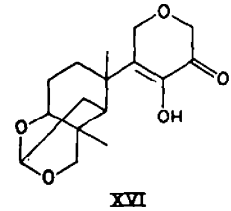
XII



XIII



XV



XVI

addition there is a more intense band at ca. 260 mμ. It is tempting to ascribe this new band to the anion of the ring-opened αβ-unsaturated γ-aldehydo acid (XII); in this connection it is worth recalling that the acid (XIII)[1] and the lactone (XIV)[2] have in basic solution $\lambda\lambda_{max}$ 260 (ε, 11,600) and 259 (ε, 5,600) mμ respectively. It must however, be understood that in these cases the ene-1,4-dione chromophore is *transoid*, whereas it is *cisoid* in (XII). These spectral characteristics clearly distinguish $\Delta^{\alpha\beta}$-butenolides from their γ-hydroxy derivatives, a point which provides a very welcome criterion for the scarcely available futronolide (see above). Also the spectra clearly differentiate between γ-hydroxy and α-hydroxy-$\Delta^{\alpha\beta}$-butenolides, these compounds (see Table 1) in basic solution showing a single absorption band shifted about 35 mμ to the red.

The newly described Drimys constituents considered together with those previously isolated by us and the recently published polygodial (tadeonal?[12])(originally[3] from the botanically unrelated *Polygonum hydropiper* but more recently[10] also from *Drymis lanceolata*) form an impressive array of oxygenation patterns on carbon atoms 11 and 12 of the drimane skeleton.

EXPERIMENTAL

M.ps were determined on the Kofler block. I.R. solution and KCl disc spectra were kindly recorded by Mrs. F. Lawrie with a Unicam S.P. 100 double-beam spectrometer and are accurate to ±1 cm^{-1}. U.V. spectra were recorded in ethanol solution on a Perkin–Elmer 137 spectrometer, except where specified to the contrary. N.M.R. spectra were taken either on a Varian A60 spectrometer through the courtesy of Dr. A. Melera, Zürich, or on an A.E.I.2 spectrometer by Miss M. Mackay, Glasgow. Mass spectra were taken by Dr. R. I. Reed and his colleagues, Glasgow, on a Metropolitan-Vickers Ltd. MS2 Mass-spectrometer. For column chromatography, Woelm alumina deactivated to the appropriate Brockmann grade was used. Chromatoplates for thin-layer chromatography were prepared according to Stahl,[11] using Kieselgel G (Merck, Darmstadt) as adsorbent. Extractions were kindly carried out by Sr. J. Olivares (Universidad Tecnica Federico Santa Maria, Valparaiso, Chile). Microanalyses are by Mr. J. M. L. Cameron, B.Sc., and his staff, Glasgow.

Isolation of valdiviolide, fuegin and winterin. Air-dried powdered bark of *D. Winteri*, collected in the Valdivia region of Chile, was exhaustively extracted with light petroleum (b.p. 70–80°) in a Soxhlet apparatus. The oil, after solvent removal in *vacuo* (400 g), was distilled at 10^{-4} mm and 4 fractions were collected: (1) 130–180°; (2) 180–210°; (3) 210–240° and (4) 240–260°. Fractions 2 and 3, diluted with light petroleum, deposited crystalline material (10·4 g), m.p. 155–170°. Adsorption of this on activated alumina (III, 210 g) and elution with light petroleum–chloroform mixtures of increasing polarity afforded confertifolin (8·6 g), m.p. 153°. $[\alpha]_D$ +70° (*c*, 1·13 in $CHCl_3$) identical in m.p., mixed m.p. and I.R. spectrum with an authentic specimen.[2] Elution with ethyl acetate–chloroform (1:4) → ethyl acetate gave material (439 mg) which after several crystallizations from benzene afforded valdiviolide (11-hydroxyconfertifolin) (218 mg; prisms from benzene) m.p. 177–178°, $[\alpha]_D$ +111° (*c*, 1·18 in $CHCl_3$) (Found: C, 71·9; H, 8·7; m.wt. 250 (mass spectrometric). $C_{15}H_{22}O_3$ requires: C, 71·95; H, 8·85%; m.wt. 250).

Elution with AnalaR acetic acid gave a semi-crystalline oil (807 mg), which on repeated crystallization, first from benzene and subsequently from methylene chloride-light petroleum, gave prisms of *fuegin* (*7,11-dihydroxyconfertifolin*) (155 mg), m.p. 170–172°, $[\alpha]_D$ +76° (*c*, 1·12 in $CHCl_3$). (Found: C, 67·85; H, 8·0; m.wt 266 (mass spectrometric). $C_{15}H_{22}O_4$ requires: C, 67·65; H, 8·35%; m.wt. 266).

Elution with water-acetic acid (1:9) gave *winterin* (*11-oxoconfertifolin, drim-8-ene-11,12-dioic acid anhydride*) (156 mg; plates from ether) m.p. 158°, $[\alpha]_D$ +109° (*c*, 2·52 in $CHCl_3$). (Found: C, 72·45; H, 8·05; m.wt. 248 (mass spectrometric). $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·1; m.wt. 248).

[10] J. W. Loder, *Austral. J. Chem.* **15**, 389 (1962).

[11] E. Stahl, *Chem. Zt.* **82**, 323 (1958).

[12] A. Ohsuka, *J. Chem. Soc., Japan* **83**, 757 (1962).

Isolation of futronolide. The residue from an extract of *D.winteri* bark, collected in the region of Lago Ranco–Futrono and obtained as above, was fractionally distilled at 10^{-3} mm, and the fraction collected at 200–240° diluted with an equal volume of n-hexane. The crystalline material which separated (3·1 g) was chromatographed over alumina (III; 90 g). Elution with *n*-hexane–benzene (4:1) gave confertifolin (2·97 g) (identified by m.p., mixed m.p. and I.R. spectrum). Continued elution with the same solvent then gave a further small crystalline fraction, which on repeated crystallization from methylene chloride–benzene afforded prisms of futronolide (7-hydroxyconfertifolin?) (5 mg) m.p. 215–217°. [$\nu_{max}^{CHCl_3}$ 3604, 3476, 1758, 1749 and 1699 cm^{-1} λ_{max} (EtOH) 218 mμ (ε, 10,000); λ_{max} (0·1N KOH–EtOH) 231 mμ (ε, 5,100). M.wt. 250 (mass spectrometric). $C_{15}H_{22}O_3$ requires 250].

Reactions of valdiviolide (11-(*Hydroxyconfertifolin*)

Oxidation with chromium trioxide. Valdiviolide (13 mg) and chromium trioxide (5 mg; 1·5 O) in AnalaR acetic acid (4 ml) were kept at 18° for 16 hr. Working up in the usual way gave from ether 11 mg of neutral product, m.p. 156–157°, undepressed on admixture with winterin (see below) and showing identical mobility on a chromatoplate.

Catalytic hydrogenation. Valdiviolide (10 mg) in acetic acid (5 ml) was hydrogenated with Adams catalyst (14 mg) at 20°/1 atm.; 1·05 mole hydrogen were absorbed during 16 hr. Further catalyst (10 mg) was added and hydrogenation continued for 2 days. Chromatography of the product, obtained in the usual way, over alumina (III; 600 mg) gave on elution with light petroleum–benzene (1:1) dihydroconfertifolin (9·5 mg) m.p. (alone and mixed) 133–135°, having an I.R. spectrum superimposable on that of authentic material.

Reduction with lithium aluminium hydride. Valdiviolide (33 mg) in dry ether (10 ml) was added slowly to a slurry of lithium aluminium hydride (118 mg) in ether (15 ml) and the reaction completed by refluxing during 0·5 hr. Working up in the usual way gave drim-8-ene-11,12-diol (24 mg; plates from benzene); m.p. 121–123° (alone and mixed); I.R. spectrum superimposable on that of authentic material.

Reactions of fuegin (7,11-*Dihydroxyconfertifolin*)

Oxidation with chromium trioxide. Fuegin (37 mg) in AnalaR acetic acid (2 ml; distilled from CrO_3) was treated dropwise and with stirring with chromium trioxide (19·5 mg; 2·15 O) in acetic acid (10 ml). The solution was kept at 20° during 16 hr and excess oxidant destroyed by addition of methanol. Repeated crystallization of the residue from chloroform gave drim-8-ene-7-one-11,12-dioic acid anhydride (?) (4 mg), m.p. 147–150°; λ_{max} (EtOH) 230 mμ (ε, 7,750); (0·1N KOH–EtOH) 238, 278 mμ (ε, 2,780, 3,710). ν_{max} (KCl disc) 1780, 1689 and 1641 $cm.^{-1}$

Catalytic hydrogenation. Fuegin (9 mg) in acetic acid (5 ml) was hydrogenated with Adams catalyst (53 mg) at 20° and 1 atm; 2·4 mole of hydrogen were absorbed during 2 days. A second quantity of catalyst (12 mg) was added and hydrogenation continued for 12 hr more. Working up in the usual way afforded a neutral oil (8 mg), which on chromatography over alumina (III; 600 mg) and elution with light petroleum–benzene (1:1) gave dihydroconfertifolin, (needles from light petroleum; 4 mg) m.p. 132–134° (alone and mixed), I.R. spectrum identical with that of authentic material.

Reduction of winterin (*drim-8-ene-11,12-dioic acid anhydride*) *with lithium aluminium hydride.* Winterin (14 mg) in ether (2 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (150 mg) in ether (10 ml), and the suspension subsequently refluxed for 0·5 hr. Working up in the usual way afforded, on crystallization from benzene, drim-8-ene-11,12-diol (3 mg) m.p. 120–121°, undepressed on admixture with authentic material and indistinguishable from it by thin layer chromatography.

Hydrogenation of futronolide (*7-hydroxyconfertifolin*?). Futronolide (3·5 mg) in acetic acid (5 ml) was hydrogenated with two successive lots of Adams catalyst (17 mg and 22 mg, each for 7 hr). Working up as usual gave a gum (3 mg) which on chromatography over alumina (III, 100 mg) and elution with benzene–chloroform (4:1) afforded 7-hydroxy-dihydroconfertifolin? (needles from benzene) m.p. 164–165° (ca. 1 mg) $\nu_{max}^{CHCl_3}$ 3609, 3509, 1768 $cm.^{-1}$

Acknowledgements—We are indebted to Professor G. Kenner, Liverpool, for the N.M.R. spectrum of confertifolin, and to Dr. A. L. Porte, Glasgow, for discussion of N.M.R. spectra. One of us (R. P. M. B.) thanks the Carnegie Trust for financial assistance.