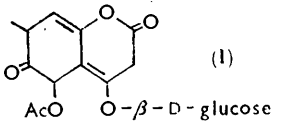
469. *Chemistry of the* Coprosma *Genus. Part XIII.*[1,2] *The Structure of Asperuloside*

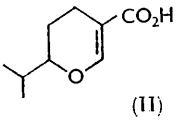
By Lindsay H. Briggs, B. F. Cain, P. W. Le Quesne, and James N. Shoolery

Re-interpretation of earlier evidence together with new chemical and spectral data have shown that asperuloside has the structure and absolute configuration depicted in (III).

In an earlier Paper [3] structure (I) was suggested for asperuloside, $C_{18}H_{22}O_{11}$. This was based on the assumption that the single ultraviolet peak, at 234·5 mμ (ε 6,800), was due to a transoid diene system with substituents linked through oxygen. Later it was concluded



(I)



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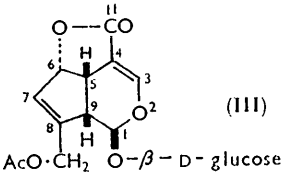


(III)

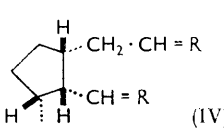
that this absorption arises from the grouping, RO·COC=C·OR', present in 3-carboxy-5,6-dihydro-6-isopropyl-4*H*-pyran (II),[4] and plumieride.[5] Re-interpretation of the existing evidence, coupled with further data, has shown that asperuloside is an iridoid [2] glucoside having the structure and absolute configuration depicted in (III). Grimshaw [6] and other workers [7] have also deduced the same general structure.

In agreement with Grimshaw,[6] a further Kuhn–Roth determination disclosed only one *C*-Me group, which the n.m.r. spectrum not only confirmed but also showed to be present in an acetoxyl function. The infrared spectrum in potassium bromide exhibited peaks at 1757 (γ-lactone), 1745 (acetate), 1704, and 1664 cm.$^{-1}$ (enol ether). The peak at 1704 cm.$^{-1}$ was absent from spectra measured in solution (pyridine or 1,2-dimethoxyethane) but in the spectra of the solid it appeared constant in position and intensity in all the samples examined. However, it was absent from the spectra of acylated derivatives of asperuloside measured on the solid state and in solution. Its presence is ascribed to intermolecular hydrogen bonding (cf. ref. 8). In the n.m.r. spectrum of asperuloside, the signal furthest downfield, at δ 7·20, is consonant with a single proton of the grouping RO·OC·C=CH·O·C (cf. genipin,[9] verbenalin, and loganin [10]). A one-proton signal at δ 5·67, slightly broadened by long-range couplings, implies a further trisubstituted double bond, while a two-proton singlet at δ 4·65 is assigned to an oxygen-substituted allylic methylene group (cf. genipin,[9] δ 4·29). The presence of an enol ether double bond was confirmed by preparation of the known [3] monobromomethoxide and a methoxymercuriacetate of tetra-acetylasperuloside. All eleven oxygen atoms of asperuloside are thus accounted for by the glucosyl residue, the grouping RO·CO·C=C·OR, which includes the lactone,[3] and the acetoxyl group.

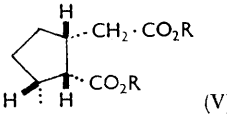
[1] Part XII, L. H. Briggs and P. W. Le Quesue, *J.*, 1963, 3471.
[2] Preliminary Communication: L. H. Briggs, B. F. Cain, P. W. Le Quesne, and J. N. Shoolery, *Tetrahedron Letters*, 1963, 69.
[3] L. H. Briggs and B. F. Cain, *J.*, 1954, 4182.
[4] F. Korte, K.-H. Büchel, and L. Schiffer, *Chem. Ber.*, 1958, **91**, 759.
[5] O. Halpern and H. Schmid, *Helv. Chim. Acta*, 1958, **41**, 1109.
[6] J. Grimshaw, *Chem. and Ind.*, 1961, 403.
[7] H. Inouye, T. Arai, Y. Miyoshi, and Y. Yaoi, *Tetrahedron Letters*, 1963, 1031. Professors A. J. Birch and H. Schmid have also kindly informed us of the same independent conclusion.
[8] J. A. Zderic, L. Cervantes, and M. T. Galvan, *J. Amer. Chem. Soc.*, 1962, **84**, 102.
[9] C. Djerassi, T. Nakano, A. N. James, L. H. Zalkow, E. J. Eisenbraun, and J. N. Shoolery, *J. Org. Chem.*, 1961, **26**, 1192.
[10] K. Sheth, E. Ramstad, and J. Wolinsky, *Tetrahedron Letters*, 1961, 394.

Treatment of asperuloside with lithium in liquid ammonia, either alone or in the presence of propan-1-ol,[11] gave intractable products which readily polymerised (cf. aucubin [12] and catalposide [13]), but tetra-acetylasperuloside readily underwent hydrogenolysis and hydrogenation with Adams catalyst to give acetic acid and the known [3] monobasic carboxylic acid, $C_{24}H_{32}O_{13}$. The u.v., i.r., and n.m.r. spectra of this compound showed that the $HO_2C{\cdot}\dot{C}{=}\dot{C}{\cdot}OR$ group has been retained, while the γ-lactone and acetoxyl groups and the second trisubstituted double bond had disappeared. A new secondary methyl group gave rise to a split n.m.r. signal at δ 0·97. Clearly, the carboxyl group arises by hydrogenolysis of the γ-lactone function of tetra-acetylasperuloside, while the acetic acid and the new methyl group result from hydrogenolysis of an allylic primary acetoxyl group. These reactions precede the saturation of the second trisubstituted (7,8) double bond.

The acidic hydrogenation product did not polymerise on treatment with acids, but was hydrolysed to the previously described [3] steam-volatile dicarbonyl compound, $C_9H_{14}O_2$, isolated as the bis-2,4-dinitrophenylhydrazone, $C_{21}H_{22}N_8O_8$. This derivative was identical in composition, melting point, u.v. spectrum, and optical rotation [3,7] with that derived by Djerassi and his co-workers [9] from genipin, and assigned the structure and absolute configuration [IV; R = 2,4-$(NO_2)_2C_6H_3{\cdot}NH{\cdot}N{=}$].* The infrared spectrum of the freshly



(IV)



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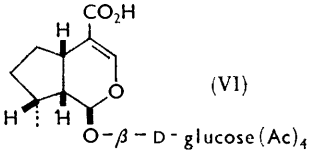


(VI)

prepared dicarbonyl compound indicated the presence of aliphatic aldehyde functions and a *C*-Me group, but the material gradually resinified and a new peak, at 1764 cm.,$^{-1}$ appeared in the infrared spectrum. Such changes are characteristic of 1,5-dialdehydes.[14] No products were isolated after attempted oxidation of this compound with silver oxide or Jones reagent,[15] but with alkaline potassium permanganate a dicarboxylic acid, $C_9H_{14}O_4$, was obtained. The composition, melting point, and optical rotation of this compound were identical with those reported by Djerassi and his co-workers for the acid (V; R = H) derived from genipin. Although direct comparison between the derivatives of asperuloside and genipin could not be made, methylation of the dicarboxylic acid from asperuloside gave a liquid ester with an infrared spectrum virtually identical with that of the ester (V; R = Me) from genipin. Hence the iridoid nature of the aglycone of asperuloside is established and the absolute configuration at C-5 and C-9 defined.

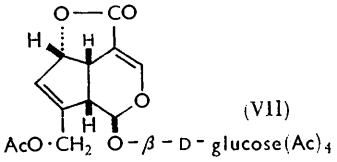
The very ready loss of the sugar residue in the hydrolysis both of asperuloside and of the acidic hydrogenation product suggests that the 1,5-dialdehyde structure of the C_9-dicarbonyl compound arises from the grouping $HO_2C{\cdot}\dot{C}{=}\dot{C}{\cdot}O{\cdot}\dot{C}H{\cdot}O{\cdot}$ glucose (Ac_4) by hydrolysis and decarboxylation. Hence the acidic hydrogenation product is assigned the structure (VI). The n.m.r. spectrum of this acid possessed complex signals at *ca.* δ 1·55 and 2·30 assigned to the methine and methylene protons of the cyclopentane ring.

In tetra-acetylasperuloside, the trisubstituted double bond to which both hydrogenolysable groups are allylic can lie only between C-7 and C-8, and the primary allylic acetoxyl

* *Note Added in Proof.*—It would appear from the work of H. Inouye and his collaborators (*Tetrahedron Letters*, 1963, 1031; *Chem. Pharm. Bull.*, 1964, **12**, 888, 901, 968) that our suggested configurations of the reduction products of asperuloside and its derivatives at C-8 should be reversed. Specifically, the C-8 epimers of (V) have almost identical melting points and other physical properties and our assignment was made without direct comparison.

[11] K. Heusler, H. Heusser, and R. Anliker, *Helv. Chim. Acta*, 1953, **36**, 652.
[12] A. J. Birch, J. Grimshaw, and H. R. Juneja, *J.*, 1961, 5194.
[13] W. H. Lunn, D. W. Edward, and J. T. Edward, *Canad. J. Chem.*, 1962, **40**, 104.
[14] G. W. K. Cavill, D. L. Ford, and H. D. Locksley, *Austral. J. Chem.*, 1956, **9**, 288; G. W. K. Cavill, D. L. Ford, H. Hinterberger, and D. H. Solomon, *ibid.*, 1961, **14**, 276.
[15] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J.*, 1946, 39.

group only at C-10. Hence the alkyl oxygen atom of the γ-lactone group could be attached either at C-6 or C-9. Stereochemical considerations show that attachment at C-9 would be improbable, so that tetra-acetylasperuloside may be represented by structure (VII).



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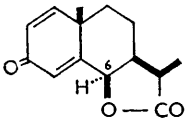


(VIII)

This structure is fully supported by the n.m.r. spectrum, which has earlier been discussed in detail.[2] The n.m.r. spectrum of asperuloside, measured in deuterium oxide, was analogous to that of the acetate. The only significant difference appeared in the signal of the C-1 proton at δ 6·03 (cf. δ 5·68 for the acetate, in deuterochloroform).

The total stereochemistry of asperuloside follows from the established absolute configuration at C-5 and C-9. Dreiding models indicate that the glucosyl residue suffers less steric hindrance from the aglycone in the quasi-equatorial β- than in the quasi-axial α-orientation. From the known co-planarity of the atoms –C·CO·O·C– in γ-lactones,[16] the alkyl oxygen bond from C-6 must have the quasi-axial α-configuration, which is in accord with the spin-coupling of 6 c./sec. between the resonances of the C-5 and C-6 protons in the n.m.r. spectrum. A neutral product of hydrogenation of tetra-acetylasperuloside over platinum has been obtained in 2—4% yield which is isomeric with the acid (VI), and contains a saturated γ-lactone function. The preponderance of initial hydrogenolysis over hydrogenation in this reaction is further evidence of the quasi-axial character of the C-6 alkyl oxygen bond [cf. 6-epi-α-santonin (VIII)[17]].

The above evidence establishes the structure and absolute configuration (III) for asperuloside. Some further reactions of asperuloside and its derivatives are now considered in the light of this formulation.

The previously reported[3] bisbromomethoxide of asperuloside was not obtained on treatment of asperuloside with methanolic bromine. The reaction products readily polymerised even under weakly basic conditions and the authentic sample[3] could not be investigated owing to decomposition. This material may have been a mixture of several initially-formed bromination products, and the reported presence of an infrared peak at 810 cm.$^{-1}$, due to a trisubstituted double bond, in the authentic sample is in accord with this supposition. The monobromomethoxide, $C_{27}H_{33}BrO_{16}$, of tetra-acetylasperuloside, mentioned above, showed only terminal ultraviolet absorption, and lacked the enol-ether peak in the infrared spectrum. The γ-lactone carbonyl frequency was increased to 1805 cm.$^{-1}$, indicating[18] an α-electronegative substituent, and the band at 808 cm.$^{-1}$, due to a trisubstituted double bond, was retained. The structure (IX; R = Me) is therefore assigned to this compound. The stereochemistry shown is imposed by the lactone group and by the *trans*-addition process.

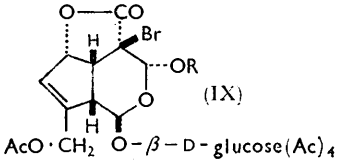
Tetra-acetylasperuloside was also reported[3] to react with bromine in acetic acid to form a monobromoacetoxylate, m. p. 183·5—184°. This product was not obtained in the present work; several experiments yielding high-melting needles for which, despite consistent melting points and analyses, no reasonable formula could be derived. Bromination

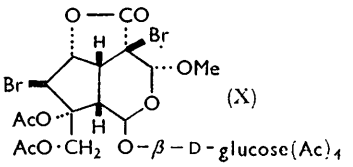
[16] J. F. McConnell, A. McL. Mathieson, and B. P. Schoenborn, *Tetrahedron Letters*, 1962, 445; A. McL. Mathieson and J. C. Taylor, *ibid.*, 1961, 590; *Acta Cryst.*, 1963, **16**, 524; J. Fridrichsons and A. McL. Mathieson, *ibid.*, 1962, **15**, 119; E. J. Gabe, *ibid.*, 1962, **15**, 759; G. A. Barclay, R. A. Eade, H. V. Simes, J. J. H. Simes, and J. C. Taylor, *Chem. and Ind.*, 1963, 1206.

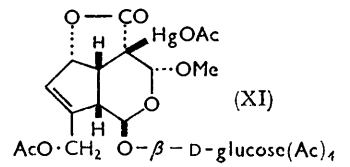
[17] D. H. R. Barton, J. E. D. Levisalles, and J. T. Pinhey, *J.*, 1962, 3472; W. G. Dauben, W. K. Hayes, J. S. P. Schwarz, and J. W. McFarland, *J. Amer. Chem. Soc.*, 1960, **82**, 2232; cf. also W. Cocker, B. Donnelly, H. Gobinsingh, T. B. H. McMurry, and M. A. Nisbet, *J.*, 1963, 1262.

[18] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, p. 187; F. Korte, H. J. Niessen, and K. Trautner, *Annalen*, 1961, **648**, 140.

under these conditions may lead to several products (cf. dihydropyran [19]), and some bromination of the trisubstituted double bond may also occur. However, by treatment of tetra-acetylasperuloside with bromine in acetic acid containing excess sodium acetate,[20] a monobromoacetoxylate, m. p. 178·5—179·5°, was obtained. Similar considerations to those above allow the assignment of the structure (IX; R = Ac).



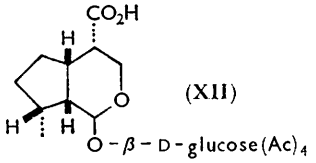


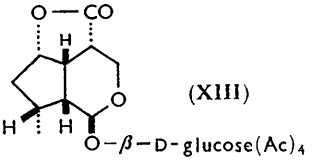


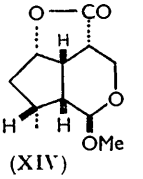
Tetra-acetylasperuloside monobromomethoxide (IX; R = Me) also reacted slowly with bromine in acetic acid to give the known [3] tetra-acetylbromomethoxydihydroasperuloside bromoacetoxylate, $C_{29}H_{36}Br_2O_{18}$, the infrared spectrum of which showed carbonyl peaks at 1789 (α-bromo-γ-lactone), 1748, and 1736 cm.$^{-1}$ (acetate), but no peak near 810 cm.$^{-1}$ due to a trisubstituted double bond. The structure (X) is suggested for this compound on the basis of sterically favoured bromination from above at C-7, followed by *trans*-addition of the acetoxyl group at C-8. Analogy exists [21] for this reaction but after treatment of tetra-acetylasperuloside monobromomethoxide (IX; R = Me) with bromine in methanol-pyridine the starting material was recovered.

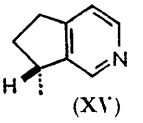
The methoxymercuriacetate of tetra-acetylasperuloside mentioned above showed infrared carbonyl peaks at 1754 (γ-lactone), 1739 (acetate), and 1577 cm.$^{-1}$. This compound is assigned the structure (XI) since methoxymercuration of enol ether double bonds has been shown to give *trans*-products.[22] The relatively low γ-lactone carbonyl frequency is due to the electron contributing α-mercuriacetoxyl substituent.

The acid (VI) did not form a bromomethoxide with methanolic bromine but was slowly hydrogenated over Adams catalyst to give a dihydro-derivative, $C_{24}H_{34}O_{13}$, having no selective ultraviolet absorption. This compound is assigned the structure and stereochemistry (XII) on the basis of hydrogenation from the β-face of the molecule (cf. hexahydrodesoxyplumieride).[5]









The neutral product of hydrogenation of tetra-acetylasperuloside, mentioned above, had the molecular formula $C_{24}H_{32}O_{13}$. Although sparingly soluble in cold alkali, it dissolved in warm 2N-sodium hydroxide. It had no selective ultraviolet absorption and lacked an infrared peak near 1650 cm.$^{-1}$, indicating saturation of the enol ether function, which was confirmed by an increase in γ-lactone carbonyl frequency [23] from 1764 to 1773 cm.$^{-1}$. The n.m.r. spectrum showed no signals due to olefinic protons. A secondary *C*-Me gave rise to a doublet resonance (centre δ 0·97), and four acetyl groups gave signals at δ 1·97—2·05. The structure (XIII) is therefore assigned.

Treatment of this lactone with methanolic hydrogen chloride gave a lactonic acetal, $C_{11}H_{16}O_4$, the infrared spectrum of which showed a single carbonyl peak at 1773 cm.$^{-1}$,

[19] W. A. Bonner, P. J. Werth, and M. Roth, *J. Org. Chem.*, 1962, **27**, 1575.
[20] D. H. R. Barton, H. T. Cheung, A. D. Cross, L. M. Jackman, and M. Martin-Smith, *J.*, 1961, 5061.
[21] W. Bockemüller and F. W. Hoffmann, *Annalen*, 1935, **519**, 165.
[22] H. W. W. Ehrlich, *J.*, 1962, 509.
[23] M. Horák and J. Plíva, *Chem. and Ind.*, 1960, 102.

and a sharp peak at 1370 cm.$^{-1}$ (C–Me). The structure (XIV), fully consistent with the n.m.r. spectrum, is proposed for this compound. A complex signal appears at *ca.* δ 5·0, due to the proton on C-6 coupled to those on C-7, C-5, and possibly C-4. A one-proton signal at δ 4·73 is assigned to the quasi-axial C-1 proton having the α-configuration. A two-proton signal at δ 4·0 is assigned to the C-3 methylene protons, while the resonance of the methoxyl group falls at δ 3·40. The secondary methyl group at C-8 gives rise to a doublet centred at δ 1·03. The formation of this compound by acid-catalysed methanolysis of the lactone (XIII) is characteristic of the saturated 2-alkoxytetrahydropyran system.[5]

The 1,5-dialdehyde structure of the C-9 dicarbonyl compound (IV; R = O) was confirmed by conversion of its bis-2,4-dinitrophenylhydrazone with hydrochloric acid–acetic acid into the pyridine (XV), epi-4-noractinidine. This reaction, which is reminiscent of the conversion of 1,5-glutardialdoxime into pyridine with hydrochloric acid,[24] has been employed by Cavill and his co-workers [25] for the synthesis of actinidine.

The dialdehyde (IV; R = O) was originally considered to be a methyl ketone, partly on the basis of a positive iodoform test. This result has been confirmed, but Seelye and Turney [26] have drawn attention to the unspecific nature of the iodoform reaction.

Finally, a comparative survey of iridoid compounds indicates that potential or actual double bonds in both rings as well as an oxygenated substituent in the cyclopentane ring are necessary for polymerisation.

Experimental

Analyses were by Dr. A. D. Campbell and his associates, University of Otago, New Zealand. Melting points were determined in an electrically heated copper block. Light petroleum refers to the fraction of b. p. 40—60°. Infrared spectra were determined on Beckman IR2 or Perkin-Elmer Infracord instruments, and ultraviolet spectra on a Perkin-Elmer 137 u.v. instrument. N.m.r. spectra were measured in dilute solution in deuterochloroform unless otherwise specified. Peak positions were measured in c./sec. relative to tetramethylsilane as internal reference by the audio side band method. Varian HR 60 and 100 spectrometers were used.

Bromination of Tetra-acetylasperuloside.—(*a*) *With bromine in acetic acid.* Bromine (3·75 g.) in acetic acid (12·5 ml.) was added dropwise with stirring to a solution of tetra-acetylasperuloside (500 mg.) in acetic acid (5 ml.). After 1 hr. at 20° the solution was heated for 15 min. at 100° and poured into ice–water (250 ml.). The product (237 mg.) was repeatedly crystallised from methanol to give needles, m. p. 220—222° after softening above 215° (Found: C, 41·4; 40·8; H, 4·2, 4·0; Br, 22·2, 22·2; Ac, 36·0%).

(*b*) *With bromine in acetic acid and sodium acetate.* Bromine (150 mg.) in acetic acid (0·5 ml.) was added to a solution of tetra-acetylasperuloside (500 mg.) and sodium acetate (2·5 g.) in acetic acid (10 ml.). After 1 hr. at 20° the solution was poured on cracked ice, and the product (551 mg., 81%) repeatedly crystallised from ethanol to give fine needles of *tetra-acetylasperuloside monobromoacetoxylate* (IX; R = Ac), m. p. 178·5—179·5° (Found: C, 46·4; H, 4·6; Br, 11·1. $C_{28}H_{33}BrO_{17}$ requires C, 46·6; H, 4·6; Br, 11·1%); ν (KBr) 1792 (α-bromo-γ-lactone), 1761 (acetate), and 807 cm.$^{-1}$ (C:CH).

Tetra-acetylasperuloside Methoxymercuriacetate (XI).—Solutions of mercuric acetate (160 mg.) in methanol (8 ml.) and tetra-acetylasperuloside (291 mg.) in methanol (8 ml.) were mixed and kept at 20° for 22 hr. After a little mercuric oxide had been filtered off, the filtrate was concentrated to 5 ml., and during 40 hr. at 3° deposited a crystalline product (165 mg., 38%). A further slow crystallisation from methanol gave *tetra-acetylasperuloside monomethoxymercuriacetate* (XI) as small plates, m. p. 173—175° (decomp.) (Found: C, 39·0; H, 4·45. $C_{29}H_{36}HgO_{18},H_2O$ requires: C, 39·1; H, 4·3%); ν ($CHCl_3$) 3448 (O–H of water), 1754 (γ-lactone), 1739 (acetate), and 1577 cm.$^{-1}$ (mercuriacetoxyl CO; cf. mercuric acetate, ν ($CHCl_3$) 1577 cm.$^{-1}$).

Catalytic Hydrogenation of Tetra-acetylasperuloside.—A suspension of tetra-acetylasperuloside (3·50 g.) and Adams catalyst (350 mg.) in ethanol (150 ml.) was shaken under hydrogen at 20° and 47 lb./sq. in. for 22 hr., during which all the starting material dissolved. After removal of the frequently pyrophoric catalyst the filtrate was concentrated to a gum smelling strongly of

[24] B. D. Shaw, *J.*, 1937, 300.
[25] G. W. K. Cavill and D. L. Ford, *Austral. J. Chem.*, 1960, **13**, 296.
[26] R. N. Seelye and T. A. Turney, *J. Chem. Educ.*, 1959, **36**, 572.

acetic acid. Most of the gum dissolved in saturated sodium hydrogen carbonate solution during 12 hr., leaving a white suspension which was filtered off (127 mg., 4%) and repeatedly crystallised from ethanol to give the neutral *lactone* (XIII) as rods, m. p. 196·5—197° (Found: C, 54·8; H, 6·4; Ac, 30·6. $C_{24}H_{32}O_{13}$ requires C, 54·5; H, 6·1; 4Ac, 32·6%); ν (KBr) 1773 (saturated γ-lactone), 1742 (acetate); ν ($CHCl_3$) 1754, 1739 cm.$^{-1}$.

The sodium hydrogen carbonate solution was acidified and the gummy product either filtered off or obtained *via* ether, and crystallised from 50—60% aqueous methanol to give needles (740 mg., 21%) of the acid (VI), m. p. 184·5°; ν ($CHCl_3$) 3448, 2695 (acid O–H), 1757 (acetate), 1748 (acid CO), and 1695 cm.$^{-1}$ (C–O–C:C–); δ ($CDCl_3$) 7·45 (C-3 proton), 1·03 and 0·90 (doublet, secondary Me), no olefinic proton near 5·75 p.p.m.; $\lambda_{max.}$ (EtOH) 234 mμ (ε 5000). Considerable variation in the catalyst–substrate ratio did not alter the proportions of products obtained.

Hydrogenation of the Acid (VI).—The acid (VI) (100 mg.) and Adams catalyst (200 mg.) in methanol (60 ml.) were shaken under hydrogen at 20° and 49 lb./sq. in. for 120 hr. Removal of solvent gave a product the crystalline portion (39 mg.) of which was repeatedly crystallised from aqueous methanol to give the *dihydro-acid* (XIII) as hexagonal plates, m. p. 175—176° (Found: C, 54·3; H, 6·5; $C_{24}H_{34}O_{13}$ requires: C, 54·1; H, 6·6%); ν (KBr) 1764 (acetate), 1754 cm.$^{-1}$ (acid CO); no selective ultraviolet absorption.

Hydrolysis and Decarboxylation of the Acid (VI).—A suspension of the acid (6·15 g.) in 2N-hydrochloric acid (120 ml.) was steam-distilled for 6 hr. Extraction of the steam-distillate (1·51) with ether yielded *cis,cis*-3-methyl-2-formylcyclopentyl acetaldehyde (IV; R = O) (780 mg., 43%) as an oil which was immediately used in the subsequent oxidation. ν (CCl_4) 2695 (aldehyde), 1724 (aldehyde), 1375 cm.$^{-1}$ (Me); in stored samples, a further peak at 1764 cm.$^{-1}$ appeared. Addition of 0·25M-2,4-dinitrophenylhydrazine in ethanolic phosphoric acid [27] to the aqueous solution remaining after the extraction gave an orange precipitate of the previously obtained bis-2,4-dinitrophenylhydrazone [IV; R = 2,4-$(NO_2)_2C_6H_3$·NH·N=], obtained from ethyl acetate as clusters of orange needles, m. p. 218·5—219·5° [lit.,[3] 224·5—225°, lit.,[9] m. p. 219·5—220·5°, $[\alpha]_D$ −21·8° (*c* 0·22 in $CHCl_3$), lit.,[7] m. p. 216—218°, $[\alpha]_D^{17}$ −22·5° ($CHCl_3$)].

Oxidation of cis,cis-3-*Methyl*-2-*formylcyclopentylacetaldehyde* (IV; R = O).—Potassium permanganate (1·3 g.) was added during 3 hr. in small portions with stirring to a suspension of the dialdehyde (780 mg.) in 5% potassium carbonate solution at 0°. After 1 hr. the temperature was gradually raised to 36°, stirring continued for a further 2 hr., and the reaction mixture kept overnight. After removal of manganese dioxide the filtrate was extracted with ether to remove a small quantity of a sweet-smelling oil [ν (CCl_4) 3580 (O–H), 1785, 1770 cm.$^{-1}$]. The solution was then acidified and extracted with ether to give a gum, which crystallised from ether–hexane as thick rods of *cis,cis*-3-methyl-2-carboxycyclopentylacetic acid (V; R = H) (89 mg., 10%), m. p. mainly at 107·5—108°, after beginning at 101·5°, $[\alpha]_D$ +18° (MeOH), plain positive R.D. curve (Found: C, 58·0; H, 7·3; O, 34·2. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6; O, 34·4%) [Djerassi and his co-workers [9] quote m. p. 99·5—105° (104·5—107·5° after drying for 3 days at 0·5 mm. over P_2O_5), $[\alpha]_D$ +20° (*c* 0·21 in MeOH)]. This acid (20 mg.) was methylated with diazomethane and the product distilled to give a colourless oil of virtually identical infrared spectrum with that obtained by Djerassi and his co-workers [9] [ν ($CHCl_3$) 1730 cm.$^{-1}$ (aliphatic ester); cf. lit.,[9] ν ($CHCl_3$) 1730 cm.$^{-1}$].

Action of Hydrochloric Acid–Acetic Acid on the Bis-2,4-*dinitrophenylhydrazone* [(IV); R = 2,4-$(NO_2)_2C_6H_3$·NH·N=].—Concentrated hydrochloric acid (1 ml.) was added to a suspension of the bis-2,4-dinitrophenylhydrazone (250 mg.) in acetic acid (5 ml.) and the mixture heated under reflux for 2 hr. The cooled yellowish-brown solution became blood-red after the addition of N-potassium hydroxide solution (100 ml.). Steam distillation gave a sweet-smelling distillate (500 ml.) from which a pale yellow oil containing 8-*epi*-4-*noractinidine* (XV) was extracted with chloroform. The *picrate*, prepared in concentrated ethanolic solution at 100°, crystallised from chloroform–carbon tetrachloride as nacreous golden plates, m. p. 115·5—116° (50 mg.; 28%) (Found: C, 49·4; H, 4·0; N, 15·5. $C_{15}H_{14}N_4O_7$ requires: C, 49·7; H, 3·9; N, 15·5%). A crystal modification, large plates of m. p. 129—130°, was obtained from dichloromethane–ethanol.

Methanolysis of the Lactone (XIII).—A solution of the lactone (XIII) (100 mg.) in 0·1N-absolute methanolic hydrogen chloride was heated under reflux in a dry atmosphere for 3 hr.,

[27] G. D. Johnson, *J. Amer. Chem. Soc.*, 1951, **73**, 5888.

cooled, and neutralised with silver carbonate. Concentration of the neutral filtrate and methanolic washings gave a colourless crystalline mass, which was partitioned between water and benzene. The benzene-soluble product was crystallised from hexane containing a little benzene to give the *acetal* (XIV) (16 mg., 43%) as rods, m. p. 151·5—152·5° (Found: C, 62·2; H, 7·6. $C_{11}H_{16}O_4$ requires: C, 62·25; H, 7·6%), ν ($CHCl_3$) 1773 (saturated γ-lactone) and 1370 cm.$^{-1}$ (CMe).

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