THE CHEMISTRY OF THE DITERPENOIDS

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ALTHOUGH impure specimens of abietic acid and the primary resin acids were the subject of investigations more than a century ago, a full understanding of the chemistry of the diterpenoids has been developed only in the last twenty years. This period has seen remarkably rapid progress and, apart from certain minor points of stereochemistry, the structures of all the major diterpenoids have now been elucidated with certainty.

The importance of the method of dehydrogenation in establishing the nature of the carbon skeleton in sesquiterpenoid compounds is well known. This method is of even greater importance in the study of diterpenoids, and the whole chemistry of the group depends upon basic experiments involving dehydrogenation to aromatic compounds. Indeed, the first application of the dehydrogenation method was made in the diterpenoid field by A. Vesterberg [1] who obtained retene (I) from abietic acid by heating it with sulphur. Retene was later isolated in a similar manner by the dehydrogenation of levopimaric acid.[2] A different derivative of phenanthrene called pimanthrene, 1 : 7-dimethylphenanthrene (II), was first obtained by L. Ruzicka and Balas [3] by the dehydrogenation of dextropimaric acid, and this hydrocarbon results also, usually together with other hydrocarbons, from the dehydrogenation of a number of other diterpenoids. The most numerous group of diterpenoids gives, either on direct dehydrogenation or dehydrogenation of suitable derivatives, 1 : 7 : 8-trimethylphenanthrene, which was first obtained in this way by L. Ruzicka and J. R. Hosking [4] from a derivative of agathenedicarboxylic acid.

It is possible to make a classification of diterpenoids (omitting phytol and a few miscellaneous diterpenoids) into bicyclic and tricyclic groups, but since the members of the bicyclic group, after suitable cyclisation, give the same dehydrogenation products as do those of the tricyclic group, it would seem preferable to adopt a system based purely on dehydrogenation experiments as has been done in the case of sesquiterpene compounds.[5] One must distinguish therefore three main classes of diterpenoid, those giving retene, those giving pimanthrene, and those giving 1 : 7 : 8-trimethylphenanthrene, recognising also that a number of diterpenoids give both pimanthrene and 1 : 7 : 8-trimethylphenanthrene.

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[1] *Ber.*, 1903, **36**, 4200.

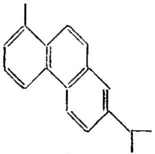
[2] L. Ruzicka, Balas, and Vilim, *Helv. Chim. Acta*, 1924, **7**, 458.

[3] *Ibid.*, 1923, **6**, 677.

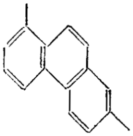
[4] *Ibid.*, 1931, **14**, 203.

[5] J. L. Simonsen and D. H. R. Barton, "The Terpenes", Vol. III, Cambridge Univ. Press.

The structures of retene, pimanthrene, and 1 : 7 : 8-trimethylphenanthrene have been rigidly proved by synthesis.[6]



(I.)



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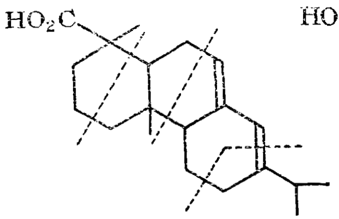

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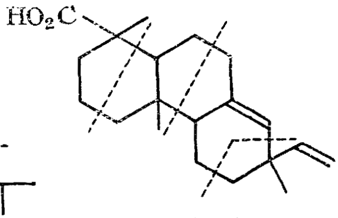

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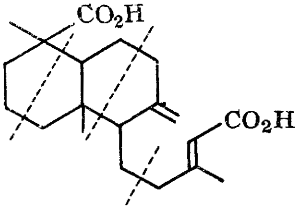

(V.)

All the diterpenoids whose constitutions have so far been elucidated obey the " isoprene rule ", as illustrated by the formulæ for abietic acid (III), dextropimaric acid (IV), and agathenedicarboxylic acid (V).

Diterpenoid Resin Acids.[6a]—These acids constitute the major non-volatile portion of many oleoresins, especially those obtained from conifers. Abietic acid, the best known of the resin acids, is prepared from colophony (rosin) by treatment with acidic reagents.[7] It is a so-called " secondary " resin acid, being formed from a precursor, levopimaric acid, by isomerisation. Dextropimaric acid is also present in colophony, but is most easily isolated from French " galipot " * obtained from the cluster pine (*Pinus pinaster ; P. maritima*). Fossil rosins are formed when resin-exuding trees decay under anaerobic conditions. The copal and kauri copal of various tropical trees are obtained largely as fossilised material and yield the diterpenoid

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[6] R. D. Haworth, B. M. Letsky, and C. R. Mavin, *J.*, 1932, 1784 ; J. C. Bardhan and S. C. Sengupta, *ibid.*, p. 2520 ; R. D. Haworth and C. R. Mavin, *ibid.*, p. 2720.

[6a] Cf. G. C. Harris, *J. Amer. Chem. Soc.*, 1948, **70**, 3671.

[7] G. Dupont, *Bull. Soc. chim.*, 1921, **29**, 727 : 1924, **35**, 879 ; G. Dupont and R. Uzac, *ibid.*, 1924, **35**, 394 ; L. L. Steele, *J. Amer. Chem. Soc.*, 1922, **44**, 1333 ; S. Palkin and T. H. Harris, *ibid.*, 1934, **56**, 1935 ; G. C. Harris and T. F. Sanderson, *ibid.*, 1948, **70**, 334.

* Galipot is that portion of the untreated oleoresin which crystallises spontaneously on standing at room temperature.

resin acid, agathenedicarboxylic acid. Many fossil rosins from decayed pine trees have been examined, and in the majority of cases the presence of retene and fichtelite (p. 60) has been established.

Abietic acid. Abietic acid, which may be obtained in a state of purity by crystallisation of the quarter sodium salt [8] or, with greater efficiency, of the salts it gives with various amines [8a] especially diamylamine,[9] is a doubly unsaturated, tricyclic acid, $C_{20}H_{30}O_2$. The two ethylenic linkages are in conjugation [10] and, although abietic acid gives the same philodiene adducts as levopimaric acid,[10, 11] they must be distributed in two different rings as shown by the ultraviolet absorption spectrum.[12]

As mentioned above, abietic acid (VI; R = H) gives retene in high yield on dehydrogenation. The carboxyl group, which is eliminated in this reaction, has been shown to be tertiary in character [13] and to be attached at the 1-position in the retenoid skeleton. The evidence for this is briefly summarised as follows. Bouveault–Blanc reduction of methyl abietate (VI; R = Me) afforded abietinol (VII), dehydrated by phosphorus pentachloride to methylabietin, $C_{20}H_{30}$. The latter gave homoretene on dehydrogenation with sulphur or selenium.[14] Although homoretene was at first considered to be a dimethyl*iso*propylphenanthrene, it was subsequently realised [15] that the formation of methylabietin (VIII) from abietinol involved a molecular rearrangement and that homoretene was 1-ethyl-7-*iso*propylphenanthrene (IX). This was confirmed by R. D. Haworth's synthesis of homoretene.[16]

An important clue to the position of the double bonds in abietic acid was furnished at an early date by the observation that trimellitic acid (X) was produced by oxidation with a variety of reagents.[17] Having regard to

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[8] G. Dupont, L. Desalbres, and A. Bernette, *Bull. Soc. chim.*, 1926, **39**, 488; C. C. Kesler, A. Lowy, and W. F. Faragher, *J. Amer. Chem. Soc.*, 1927, **49**, 2898; S. Palkin and T. H. Harris, *loc. cit.*, ref. (7).

[8a] F. Balas, *Časopis Česk. Lékarnictva*, 1927, **7**, 320; S. Palkin and T. H. Harris, *loc. cit.*; compare V. N. Krestinskii and I. I. Bardyshev, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 1894; I. I. Bardyshev, *ibid.*, 1941, **11**, 996; R. Lombard and J.-M. Frey, *Bull. Soc. chim.*, 1948, **15**, 1194.

[9] G. C. Harris and T. F. Sanderson, *loc. cit.*, ref. (7).

[10] L. F. Fieser and W. P. Campbell, *J. Amer. Chem. Soc.*, 1938, **60**, 159.

[11] L. Ruzicka, P. J. Ankersmit and B. Frank, *Helv. Chim. Acta*, 1932, **15**, 1289; B. A. Arbusow, *J. Gen. Chem. U.S.S.R.*, 1932, **2**, 806; compare H. Wienhaus and W. Sandermann, *Ber.*, 1936, **69**, 2202; L. Ruzicka, R. G. R. Bacon, R. Lukes, and J. D. Rose, *Helv. Chim. Acta*, 1938, **21**, 583.

[12] K. Kraft, *Annalen*, 1935, **520**, 133; H. Wienhaus, H. Ritter, and W. Sandermann, *Ber.*, 1936, **69**, 2198; L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, 1938, **21**, 565; W. Sandermann, *Ber.*, 1941, **74**, 154.

[13] W. Fahrion, *Z. angew. Chem.*, 1901, **14**, 1197; P. Levy, *Z. anorg. Chem.*, 1913, **81**, 147.

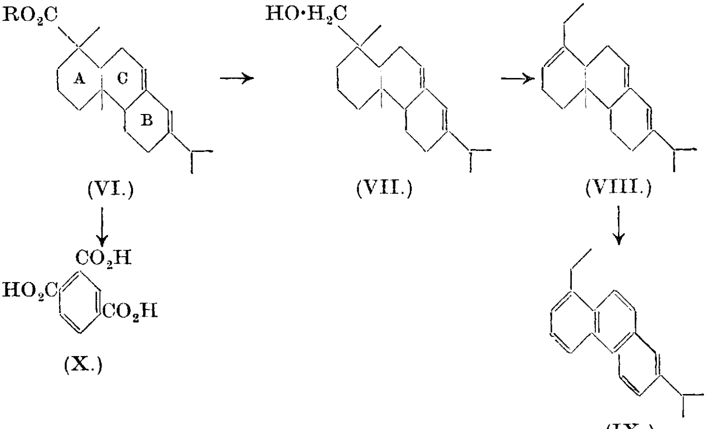
[14] L. Ruzicka and J. Meyer, *Helv. Chim. Acta*, 1922, **5**, 581; L. Ruzicka and H. Jacobs, *Rec. Trav. chim.*, 1938, **57**, 509.

[15] F. Vocke, *Annalen*, 1932, **497**, 247; L. Ruzicka, G. B. R. de Graaff, and H. J. Müller, *Helv. Chim. Acta*, 1932, **15**, 1300.

[16] *J.*, 1932, 2717.

[17] J. Schreder, *Annalen*, 1874, **172**, 93; O. Emmerling, *Ber.*, 1879, **12**, 1441; L. Ruzicka, H. Schinz, and J. Meyer, *Helv. Chim. Acta*, 1923, **6**, 1077; L. Ruzicka and M. Pfeiffer, *ibid.*, 1925, **8**, 632.

the formula of retene, this was taken to imply that at least one of the ethylenic linkages must be in ring B. Support for this view was the fact that *iso*butyric acid could be obtained on energetic oxidation with potassium permanganate.[18] Rigid proof of the position of the conjugated ethylenic linkages as shown in (VI) has been provided only comparatively recently by the elegant experiments of L. Ruzicka and L. Sternbach.[19] When abietic acid is oxidised under mild conditions the first product of the reaction is dihydroxyabietic acid (XI),[20] which then appears to be further attacked with formation of oxidodihydroxyabietic acid (XII). This oxide is unstable in aqueous media and is rapidly hydrated to γ-tetrahydroxyabietic acid.* By treatment with dilute hydrochloric acid the latter was converted almost quantitatively into the stable chlorotrihydroxyabietic acid (XIII), whilst with dilute sulphuric acid it afforded the α-tetrahydroxyabietic acid (XIV), which had been obtained previously by P. Levy.[21] γ-Tetrahydroxyabietic acid underwent a slow mutarotation in neutral aqueous solution to afford β-tetrahydroxyabietic acid, converted, like the γ-isomer, into the α-acid with dilute sulphuric acid. It appears, therefore, that the usual product isolated from the potassium permanganate oxidation of abietic acid under mild conditions is a mixture of dihydroxyabietic acid and γ-tetrahydroxyabietic acid, and that Levy's α-tetrahydroxyabietic acid is an artefact formed



(VI.) (VII.) (VIII.) (X.) (IX.)

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[18] P. Levy, *Ber.*, 1909, **42**, 4305 ; L. Ruzicka, J. Meyer, and M. Pfeiffer, *Helv. Chim. Acta*, 1925, **8**, 637 ; L. F. Fieser and W. P. Campbell, *loc. cit.*, ref. (10).

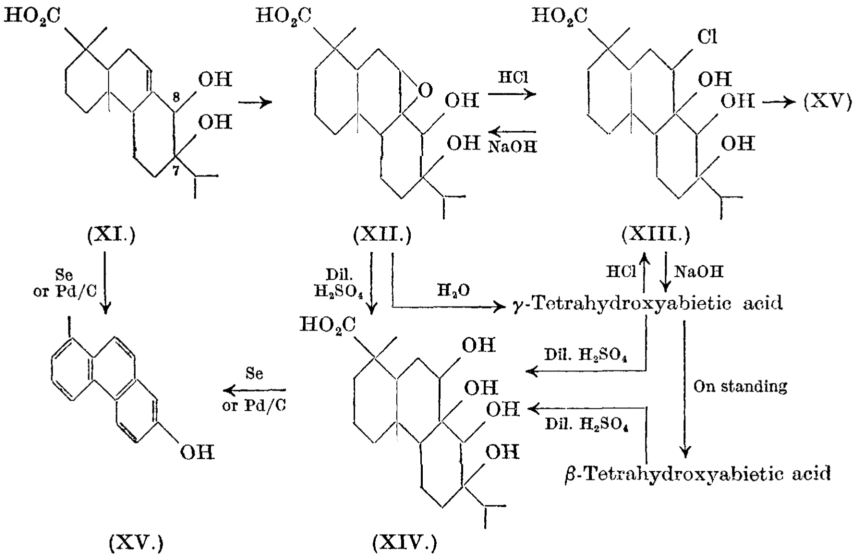
[19] *Helv. Chim. Acta*, 1938, **21**, 565 ; 1940, **23**, 333, 341, 355 ; 1941, **24**, 492 ; 1942, **25**, 1036 ; L. Ruzicka, L. Sternbach, and O. Jeger, *ibid.*, 1941, **24**, 504.

[20] L. Ruzicka and J. Meyer, *ibid.*, 1923, **6**, 1097 ; compare O. Aschan, *Ber.*, 1921, **54**, 867 ; L. Ruzicka, J. Meyer, and M. Pfeiffer, *loc. cit.*, ref. (18).

[21] *Ber.*, 1909, **42**, 4305 ; 1926, **59**, 1302 ; 1928, **61**, 616 ; 1929, **62**, 2497 ; compare O. Aschan and P. Levy, *ibid.*, 1927, **60**, 1923.

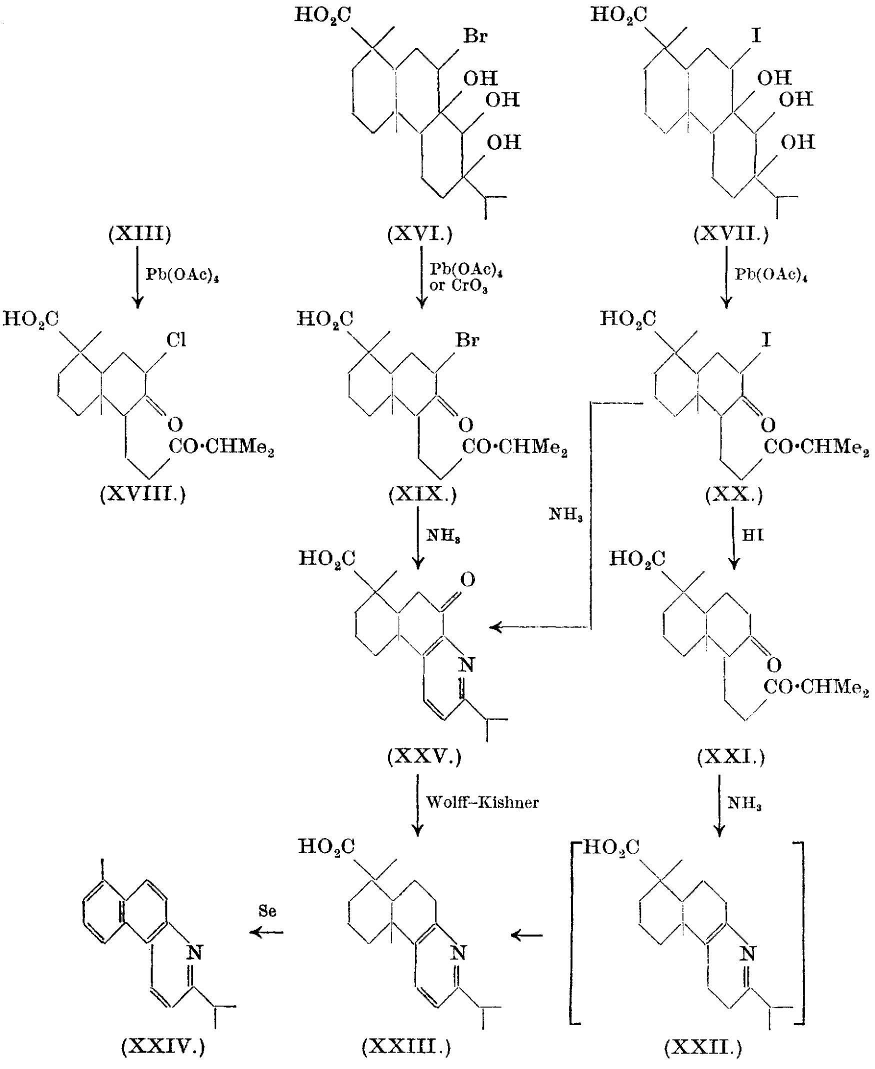
* Strictly, this name is incorrect and should be replaced by γ-tetrahydroxytetrahydroabietic acid. Similarly, many of the other names used in this article are logically incorrect, but are retained because of the familiar usage in the literature.

during working up. Both the β- and the γ-tetrahydroxyabietic acid must be regarded merely as stereoisomers of the α-acid. By dehydrogenation, (XI), (XII), (XIII), and (XIV) all gave 7-hydroxy-1-methylphenanthrene (XV). These experiments place with certainty one of the hydroxyl groups in all these compounds at C_7 and thus prove the relative position of the *iso*propyl group and one of the ethylenic linkages in abietic acid.



When γ-tetrahydroxyabietic acid was treated with hydrobromic or hydriodic acid it gave bromo- (XVI) or iodo-trihydroxyabietic acid (XVII) respectively. All three halogenotrihydroxyabietic acids afforded the corresponding halogenodiketo-acids, (XVIII), (XIX), and (XX), on oxidation with two molecular proportions of lead tetra-acetate. With hydriodic acid (XX) was reduced to the diketo-acid (XXI), which by treatment with ammonia gave, presumably *via* the dihydropyridine (XXII), followed by disproportionation, 8-azadehydroabietic acid (XXIII). Selenium dehydrogenation of the latter furnished 8-azaretene (XXIV), the identity of which was confirmed by its synthesis. Both (XIX) and (XX) underwent an unusual reaction when treated with ammonia, giving 9-keto-8-azadehydroabietic acid (XXV), from which (XXIII) was obtained on reduction by the Wolff–Kishner method. This last series of reactions proves in a particularly elegant manner the correctness of the double bond positions in the abietic acid formula (VI; R = H).

The experiments described above constitute an unambiguous proof of the main structural features of the abietic acid molecule and leave undecided only the position of the quaternary methyl group. The following is the more important evidence with regard to this feature. By energetic oxidation abietic acid affords two homologous tricarboxylic acids, (XXVI)



and (XXVII).[22] Dehydrogenation of these with selenium gave, respectively, *m*-xylene (XXVIII) and hemimellitene (XXIX). This proves the 1 : 3-relationship of the two methyl groups in (XXVI) and (XXVII) and hence the position of the quaternary methyl group in (VI) as shown.[23]

A further proof of this relationship was provided by L. Ruzicka and

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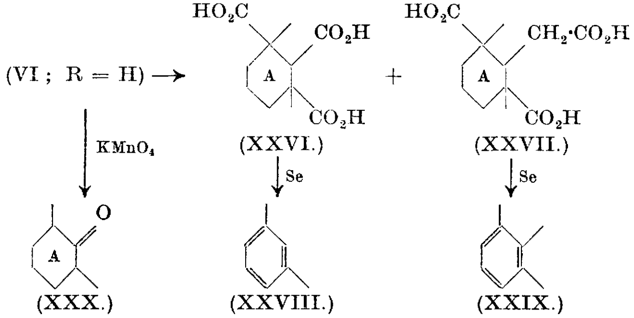
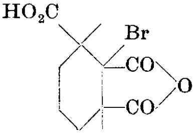
[22] L. Ruzicka, J. Meyer, and M. Pfeiffer, *loc. cit.*, ref. (18); P. Levy, *Ber.*, 1929, **62**, 2497; L. Ruzicka, M. W. Goldberg, H. W. Huyser, and C. F. Seidel, *Helv. Chim. Acta*, 1931, **14**, 545; compare J. Schreder, *loc. cit.*; O. Emmerling, *loc. cit.*; P. Levy, *loc. cit.*; O. Aschan and P. Levy, *loc. cit.*

[23] L. Ruzicka, M. W. Goldberg, H. W. Huyser, and C. F. Seidel, *loc. cit.*

H. Waldmann,[24] who showed that vigorous oxidation of abietic acid also afforded 1 : 3-dimethyl*cyclo*hexan-2-one (XXX).



Additional evidence on this point was given by F. Vocke [25] who treated (XXVI) with red phosphorus and bromine and isolated, amongst other products, two bromo-anhydrides, (XXXI) and (XXXII), both of which furnished an unsaturated acid (XXXIII) with sodium hydroxide. Although at the time these experiments were carried out they were open to a different interpretation,[26] H. N. Rydon's synthesis [27] of (XXXIII) has confirmed Vocke's formulation.



(XXXI.)

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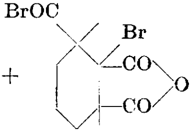

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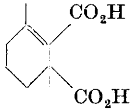
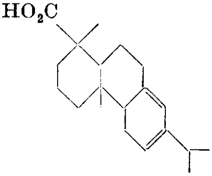


(XXXIII.)



(XXXIV.)

*Levopimaric acid.** This resin acid was first isolated in a state of purity by A. Vesterberg,[28] but little progress was made with its chemistry until G. Dupont [29] had described a reliable method for its preparation from French galipot. The most convenient method of isolation is by crystallisation of the butanolamine salt.[9] S. Palkin and T. H. Harris [30] isolated pure levopimaric acid from the primary resin acids of *Pinus palustris* and of *P. caribbea*, and it is now certain that the acid is a primary constituent of all resins from pine and fir trees. It has also been shown that the so-called

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[24] *Helv. Chim. Acta*, 1933, **16**, 842. [25] *Loc. cit.*

[26] L. Ruzicka, H. Waldmann, P. J. Meier, and H. Hösli, *Helv. Chim. Acta*, 1933, **16**, 169.

[27] *J.*, 1937, 257. [28] *Ber.*, 1887, **20**, 3248

[29] *Compt. rend.*, 1921, **172**, 923, 1184 ; *Bull. Soc. chim.*, 1921, **29**, 718 ; compare L. Ruzicka and Balas, *loc. cit.* ; L. Ruzicka, Balas, and Vilim, *loc. cit.*

[30] *J. Amer. Chem. Soc.*, 1935, **55**, 3677.

* The names levo- and dextro-pimaric acid do not, of course, denote optical antipodes. They were originally introduced by A. Vesterberg [28] and have not been altered here because to do so at this stage might prove confusing.

sapinic acids, formerly thought to be primary constituents of the oleoresin, all contain levopimaric acid.[31] *

Levopimaric acid, $C_{20}H_{30}O_2$ (XXXIV), is readily isomerised by heat or by acids to abietic acid [32] and, like abietic acid, it gives retene on dehydrogenation.[33] The presence of two double bonds and therefore of three rings, as implied by the above observations, has been proved by hydrogenation [34] and by per-acid titration.[35] In addition, the two double bonds must be in conjugation, for levopimaric acid reacts quantitatively with maleic anhydride at room temperature to afford the same adduct as is obtained from abietic acid under more vigorous conditions.[36] Since levopimaric acid shows an absorption maximum in the ultraviolet at 272·5 mμ,[37] it follows that these two conjugated ethylenic linkages must be contained in one ring, as indeed would be expected from the ease of addition of maleic anhydride. Levopimaric acid gives *iso*butyric acid on ozonolysis.[38] Therefore it is probable that the *iso*propyl grouping is attached directly to one of the ethylenic linkages. This has been rigidly proved by the elegant experiments of L. Ruzicka and S. Kaufmann,[39] the most important of which may be briefly summarised as follows. Ozonolysis of the trimethyl ester (XXXV) derived from the maleic anhydride adduct of levopimaric acid gave, amongst other products, a mono-unsaturated keto-tricarboxylic acid trimethyl ester (XXXVI) in which the double bond was in the $\alpha\beta$-position to the keto-group as shown by the ultraviolet absorption spectrum. On oxidation with hypobromite (XXXVI) was smoothly degraded (and hydrolysed) to an $\alpha\beta$-unsaturated acid (XXXVII), the absorption spectrum of the tetramethyl ester of which confirmed the double bond position in (XXXV). Rigid chemical proof that the acetyl grouping of (XXXVI) was formed from the *iso*propyl group was obtained (*a*) by Clemmensen reduction to (XXXVIII) followed by dehydrogenation to 1-methyl-7-ethylphenanthrene (XXXIX) and (*b*) by reaction with ethylmagnesium iodide to give (XL),† dehydrogenation of which afforded 1-methyl-7-*sec*.-butyl-

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[31] T. Hasselstrom and M. T. Bogert, *ibid.*, 1935, **57,** 2118 ; K. Kraft, *Annalen*, 1935, **520,** 133 ; 1936, **524,** 1 ; G. C. Harris and J. Sparks, *J. Amer. Chem. Soc.*, 1948, **70,** 3674 ; compare F. Vocke, *Annalen*, 1933, **508,** 11 ; W. Sandermann, *Ber.*, 1938, **71,** 2005.

[32] *Inter al.*, G. Dupont, *Compt. rend.*, 1921, **172,** 923, 1373 ; *Bull. Soc. chim.*, 1921, **29,** 718, 727 ; L. Ruzicka, Balas, and Vilim, *loc cit.* ; R. Lombard, *Bull. Soc. chim.*, 1948, **15,** 1186.

[33] *Idem.*, *ibid.* ; W. Sandermann, *Ber.*, 1941, **74,** 154.

[34] L. Ruzicka and R. G. R. Bacon, *Helv. Chim. Acta*, 1937, **20,** 1542 ; compare L. Ruzicka, Balas, and Vilim, *loc. cit.*

[35] K. Kraft, *Annalen*, 1936, **524,** 1.

[36] B. A. Arbusow, *loc. cit.* ; L. Ruzicka, P. J. Ankersmit, and B. Frank, *loc. cit.* ; L. Ruzicka and R. G. R. Bacon, *loc. cit.* ; H. Wienhaus and W. Sandermann, *Ber*, 1936, **69,** 2202.

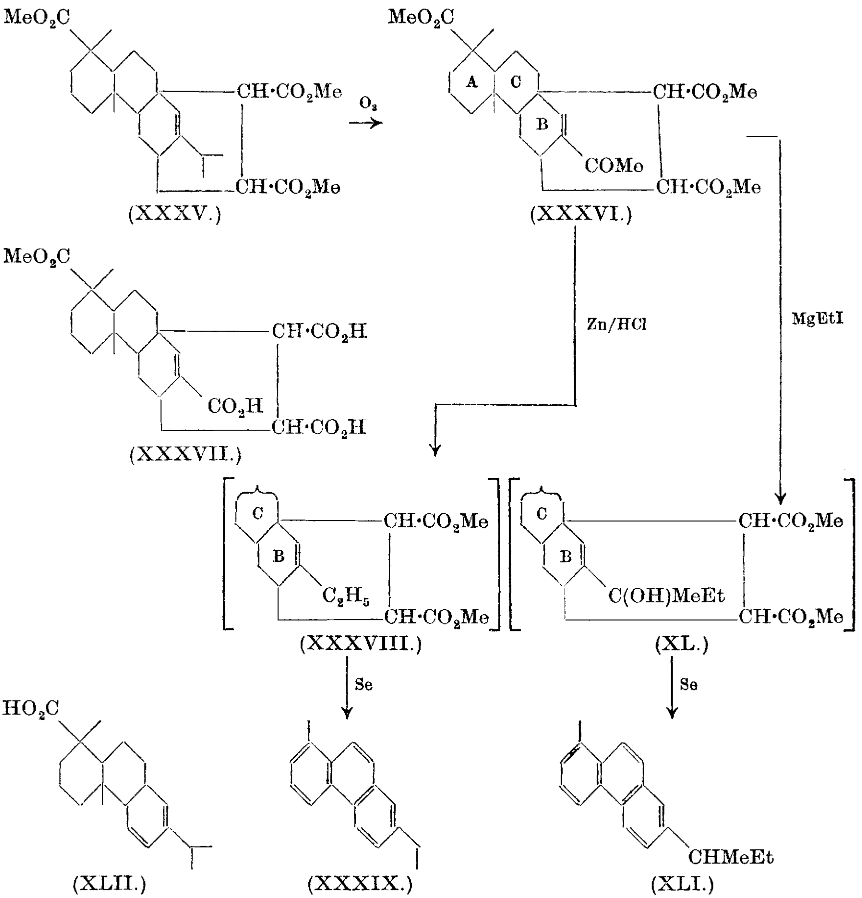
[37] K. Kraft, *Annalen*, 1935, **520,** 138 ; G. C. Harris and T. F. Sanderson, *loc. cit.*.

[38] L. Ruzicka, R. G. R. Bacon, R. Lukes, and J. D. Rose, *loc. cit.*

[39] *Helv. Chim. Acta*, 1940, **23,** 1346 ; 1941, **24,** 939.

* R. Lombard's recently isolated dextrosapinic acid may be an exception to this generalisation (p. 45).

† The carbomethoxyl groupings in (XXXVI) may also have reacted with the Grignard reagent but this does not affect the argument.


(XXXV.) (XXXVI.) (XXXVII.) (XXXVIII.) (XL.) (XLII.) (XXXIX.) (XLI.)

phenanthrene (XLI). The formation of (XXXIX) and (XLI) shows beyond doubt that the double bond of the adduct (XXXV) must be adjacent to the *iso*propyl grouping. Only the formulæ (XXXIV) and (XLII), therefore, are possible representations of levopimaric acid, and of these the former is much to be preferred as it explains more readily the ease of rearrangement to abietic acid. The formula (XXXIV) is also supported by various theoretical arguments which have been advanced by W. Sandermann.[40] *

neo*Abietic acid.* This interesting resin acid is a primary constituent of the oleoresin of *Pinus palustris* and has been isolated therefrom as the

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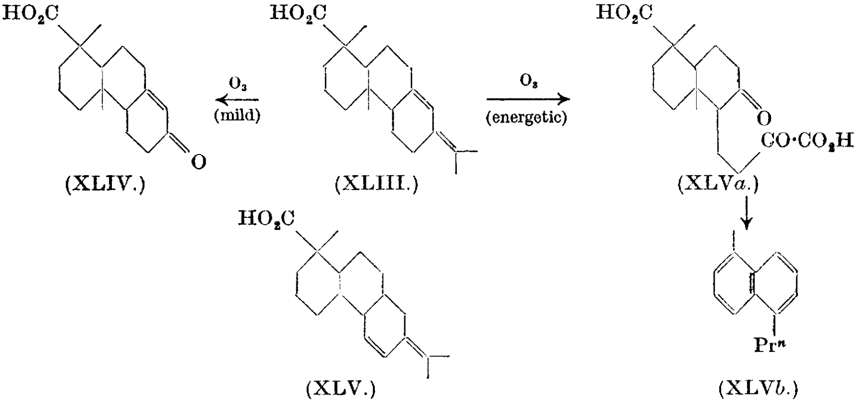
[40] *Ber.*, 1941, **74**, 154 ; W. Sandermann and R. Hohn, *ibid.*, 1943, **76**, 1257 ; compare L. Ruzicka and S. Kaufmann, *Helv. Chim. Acta*, 1941, **24**, 1425.

[41] *Chem. Zentr.*, 1942, ii, 892, 893.

* Formula (XXXIV) for levopimaric acid is said to be proved by certain experiments of B. A. Arbusow,[41] who has shown that the α-naphthaquinone adduct, on dehydrogenation with air in alcoholic potash solution followed by pyrolysis and then oxidation with nitric acid, affords anthraquinone-1 : 3-dicarboxylic acid. The Reviewer has not had access to Arbusow's original memoirs.

butanolamine salt by G. C. Harris and T. F. Sanderson,[42] as well as from the resin of this tree. It is also conveniently prepared by heating abietic acid at 300° in an inert atmosphere for short periods. The structure of *neo*abietic acid as (XLIII) has been established by G. C. Harris and T. F. Sanderson [43] in the following way. *neo*Abietic acid gave retene on dehydrogenation, absorbed two molecular proportions of hydrogen on catalytic hydrogenation, showed an intense band in the ultraviolet at 250mμ and, like levopimaric acid, was almost quantitatively isomerised to abietic acid by the action of mineral acid. It must, therefore, be a simple double-bond isomer of abietic acid in which the double bonds are in conjugation with each other, but not in the same ring of the carbon skeleton. On ozonolysis *neo*abietic acid afforded acetone and an $\alpha\beta$-unsaturated ketone, $C_{17}H_{24}O_3$ (XLIV), thus showing the presence of an *iso*propylidene group. It was possible to distinguish between the alternative formulæ (XLIII) and (XLV), both of which explain this observation, since drastic ozonolysis of *neo*abietic acid and dehydrogenation of the reaction product, presumably (XLV*a*), gave 1-methyl-5-*n*-propylnaphthalene (XLV*b*).



(XLIV.) (XLIII.) (XLV*a*.)

(XLV.) (XLV*b*.)

The relationship of *neo*abietic acid to the dextrosapinic acid recently isolated by R. Lombard [44] as a primary constituent of the galipot of *Pinus halepensis* is uncertain, but, like *neo*abietic acid, dextrosapinic acid is said to be isomerised by acids to abietic acid.

Dextropimaric acid. This acid was first obtained in a state of purity by A. Vesterberg [45] by crystallisation of the sparingly soluble sodium salt, but it is best isolated, after removal of levopimaric acid as the maleic anhydride adduct, by crystallisation of the butanolamine salt.[46] Dextropimaric acid is probably present to a greater or less extent in all resins

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[42] *Loc. cit.*

[43] *J. Amer. Chem. Soc.*, 1948, **70**, 339.

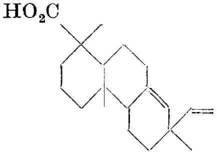
[44] *Compt. rend.*, 1944, **219**, 587 ; 1944, **219**, 253 ; 1946, **222**, 237 ; *Bull. Soc. chim.*, 1945, **12**, 395.

[45] *Ber.*, 1885, **18**, 3331 ; 1886, **19**, 2167 ; compare *idem, ibid.*, 1887, **20**, 3248 ; 1905, **38**, 4125 ; G. Dupont, *Bull. Soc. chim.*, 1921, **29**, 718 ; L. Ruzicka and Balas, *loc. cit.* ; L. Ruzicka, Balas, and Vilim, *loc. cit.*

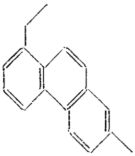
[46] G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 2079.

obtained from conifers, but it is not always possible to separate it from the accompanying isomeric resin acids. Thus it has been detected in the resins from *Pinus caribbea*, *P. tæda*, *P. serotina* and *Picea excelsa*,[47] as well as in the oleoresins of *P. palustris* [48] and *P. sylvestris*.[49] Unlike most of the other primary resin acids, dextropimaric acid is comparatively stable to heat and is not isomerised by treatment with mineral acids.

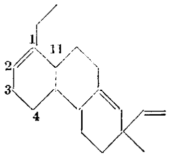
As mentioned above (p. 36), dextropimaric acid (XLVI) gives pimanthrene (II) on dehydrogenation. The position of the carboxyl group has been proved by a similar series of experiments to those recorded (p. 38) for abietic acid.[50] Thus, Bouveault–Blanc reduction of ethyl pimarate afforded dextropimarinol, dehydrated by phosphorus pentachloride to methyl dextropimarin which on dehydrogenation gave an aromatic hydrocarbon, $C_{17}H_{16}$. Although the latter was at first considered to be a trimethylphenanthrene, it was subsequently shown by L. Ruzicka, G. B. R. de Graaff, and H. J. Müller,[51] to be 7-methyl-1-ethylphenanthrene (XLVII) and this identity has been confirmed by synthesis.[52] From this, it follows that methyldextropimarin must be represented by (XLVIII), its formation involving a rearrangement similar to that observed in the dehydration of abietinol.* A further indication of the position of the carboxyl group and a proof of the points of attachment of the two quaternary methyl groups in ring A are that vigorous oxidation of dextropimaric acid gives the same two tricarboxylic acids, (XXVI) and (XXVII), as are obtained in the same way from abietic acid (p. 40).[53]



(XLVI.)



(XLVII.)



(XLVIII.)

Dextropimaric acid is doubly unsaturated, as shown by catalytic hydrogenation [54] and by per-acid experiments.[54, 55] Since it has the formula $C_{20}H_{30}O_2$ it must be tricyclic, in agreement with the dehydrogenation evidence. The two double bonds are not in conjugation and differ greatly

[47] *Inter al.*, T. Hasselstrom and M. T. Bogert, *loc. cit.*; K. Kraft, *Annalen*, 1935, **520**, 133; 1936, **524**, 1; W. Sandermann, *Ber.*, 1938, **71**, 2005; 1942, **75**, 174.

[48] S. Palkin and T. H. Harris, *loc. cit.*; K. Kraft, *loc. cit.*

[49] A. Vesterberg, *Ber.*, 1905, **38**, 4125.

[50] L. Ruzicka and Balas, *Helv. Chim. Acta*, 1924, **7**, 875.

[51] *Loc. cit.*

[52] R. D. Haworth, *J.*, 1932, 2717.

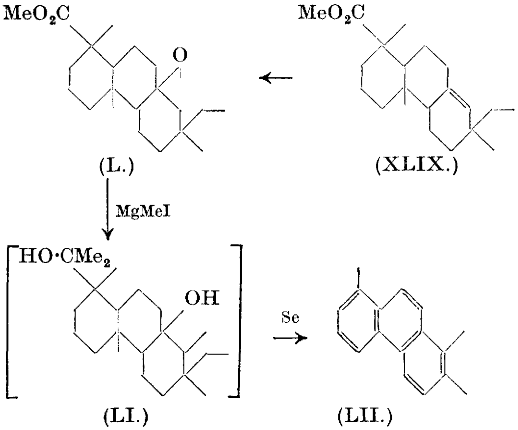
[53] L. Ruzicka, G. B. R. de Graaff, M. W. Goldberg, and B. Frank, *Helv. Chim. Acta*, 1932, **15**, 915.

[54] L. Ruzicka, H. W. Huyser, and C. F. Seidel, *Rec. Trav. chim.*, 1928, **47**, 363.

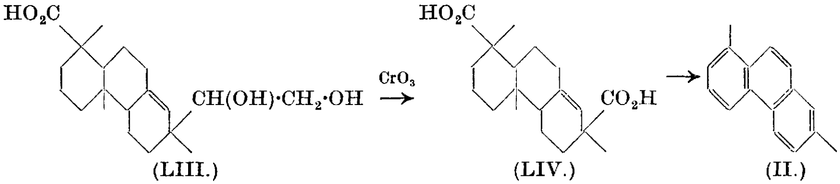
[55] L. Ruzicka and B. Frank, *Helv. Chim. Acta*, 1932, **15**, 1294; K. Kraft, *Annalen*, 1936, **524**, 1; L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, 1940, **23**, 124.

* It should be pointed out that the 1(2)-position of the ethylenic linkage in methyldextropimarin and in methylabietin has not been proved and it may well be at 1(11) instead.

in reactivity. Partial hydrogenation gives a very insoluble and characteristic dihydrodextropimaric acid (XLIX),[54, 56] which has been used by L. Ruzicka and L. Sternbach [57] in an elegant demonstration that the less reactive double bond is in the 7(8) or 8(14)-position. Their evidence is briefly as follows. By treatment of the oxide of methyl dihydrodextropimarate (L) with methylmagnesium iodide an alcohol (LI) was prepared, which on dehydrogenation gave 1 : 7 : 8-trimethylphenanthrene (LII).



The more reactive of the two ethylenic linkages is present as a tertiary vinyl grouping. This is proved by the facts that dextropimaric acid may be oxidised by potassium permanganate to a glycol (LIII) which on further oxidation by chromic acid gives a dicarboxylic acid, $C_{19}H_{28}O_4$ (LIV), containing one carbon atom less,[58] which is dehydrogenated by selenium to pimanthrene (II).[53] As would be expected, ozonolysis of dextropimaric acid gives a high yield of formaldehyde.[59]



The experiments described above, taken in conjunction with the "isoprene rule", indicate that dextropimaric acid must be represented by either (XLVI) or (LV). Conclusive evidence in favour of the former

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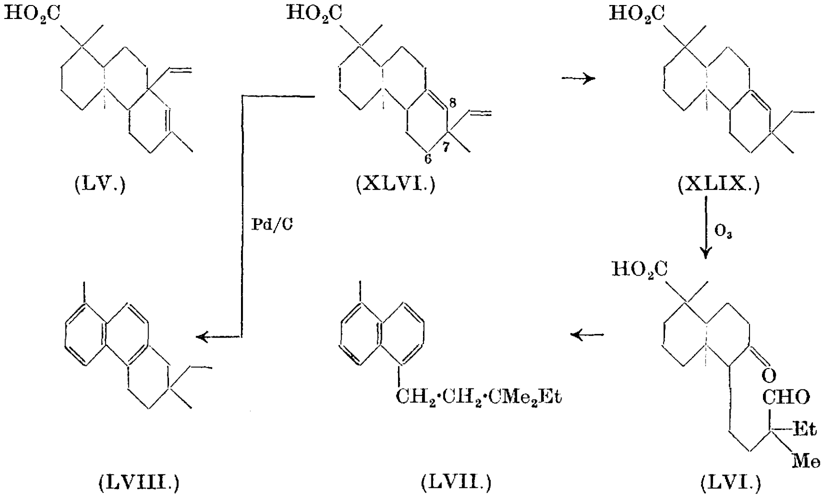
[56] L. Ruzicka and Balas, *ibid.*, 1923, **6**, 681 ; L. Ruzicka and B. Frank, *loc. cit.* ; S. Palkin and T. H. Harris, *loc. cit.* ; T. Hasselstrom and M. T. Bogert, *loc. cit.* ; compare L. Tschugaeff and P. Teearu, *Ber.*, 1913, **46**, 1773.

[57] *Loc. cit.*

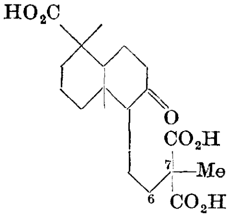
[58] L. Ruzicka and Balas, *Annalen*, 1928, **460**, 202 ; compare P. Levy, *Ber.*, 1928, **61**, 616.

[59] L. Ruzicka and Balas, *loc. cit.* ; compare L. Ruzicka, C. F. Seidel, H. Schinz, and M. Pfeiffer, *Helv. Chim. Acta*, 1947, **30**, 1807.

of these has been reported recently by G. C. Harris and T. F. Sanderson.[60] Dihydrodextropimaric acid (XLIX) was ozonised to give the keto-aldehyde (LVI) (negative iodoform test), which was reduced by the Wolff–Kishner method and then dehydrogenated to give a C_{18} disubstituted naphthalene (LVII). The keto-aldehyde from (LV) would have given a positive iodoform test and would have been converted into a C_{16} trisubstituted naphthalene. Further proof for the correctness of (XLVI) was provided by partial dehydrogenation of dextropimaric acid, which gave a C_{18} trisubstituted naphthalene (LVIII).



*iso**Dextropimaric acid.* This interesting resin acid has been isolated recently [46] as the butanolamine salt during the preparation of dextropimaric acid. G. C. Harris and T. F. Sanderson [60] regard it as the C_7 epimeride of dextropimaric acid on the basis of the following evidence. When *iso*dextropimaric acid was subjected to the same series of degradations as was applied to dextropimaric acid, the same hydrocarbons (LVII) and (LVIII) were obtained, racemisation at C_7 being presumed to occur during the formation of (LVIII). Also, when dextropimaric acid and *iso*dextropimaric acid were ozonised and the products oxidised with hydrogen peroxide, the same tricarboxylic acid (LIX), in which the asymmetry at C_7 had been destroyed, was isolated in both cases. Although Harris and Sanderson's interpretation of the experimental evidence is logical, it should be pointed out that *iso*dextropimaric acid and its butanolamine salt were found to be optically inactive in all solvents and to give an optically inactive dihydro-acid. This would be unexpected unless it were the racemate corresponding to dextropimaric acid.



(LIX.)

G. C. Harris and T. F. Sanderson [60a] have also

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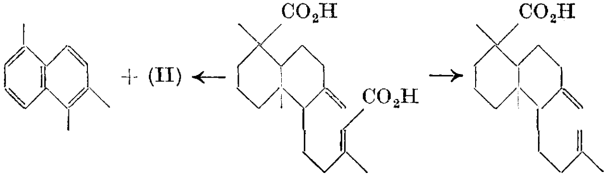
[60] *J. Amer. Chem. Soc.*, 1948, **70**, 2081.

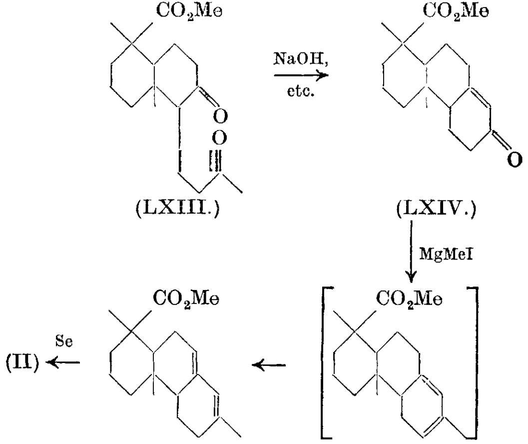
[60a] *Ibid.*, p. 3870.

isolated the aldehyde corresponding to *iso*dextropimaric acid from the neutral fractions of commercial gum and wood rosins. It is probably identical with cryptopinone obtained by N. A. Sörensen and T. Bruun [60b] from the twig roots and resinified trunks of pine trees.

Agathenedicarboxylic acid. This bicyclic resin acid was first isolated in a state of purity by L. Ruzicka and J. R. Hosking [61] from Kauri copal and from the soft and hard grades of Manila copal. The structure (LX) which has been assigned to this acid is due entirely to the experiments of L. Ruzicka and his collaborators,[62] and is based on the following evidence. The carbon skeleton present in the acid is indicated by its dehydrogenation with sulphur or selenium to give 1 : 5 : 6-trimethylnaphthalene (LXI) and pimanthrene (II). The formation of the latter results presumably from the presence of an unsaturated side chain which appears partially in the naphthalene hydrocarbon as a methyl group. The acid contains two ethylenic linkages, one of which must be in the αβ-position with respect to one of the carboxyls. This is shown by the absorption spectrum and by the ease with which carbon dioxide is split out on pyrolysis to give noragathenemonocarboxylic acid (LXII).



(LXI.) (LX.) (LXII.)



(LXIII.) (LXIV.)

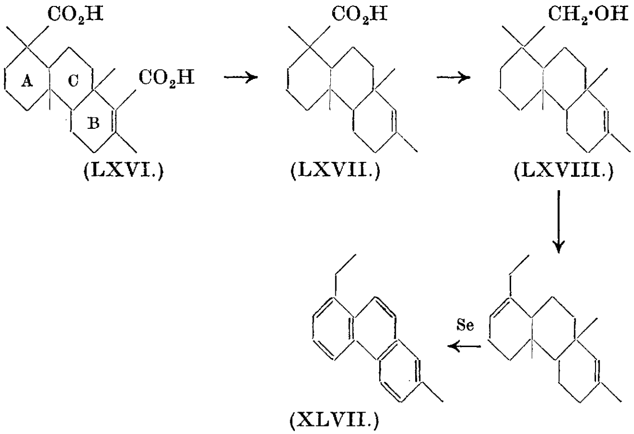
(LXV.)

[60b] *Acta chem. scand.*, 1947, **1**, 112.

[61] *Annalen*, 1929, **469**, 147.

[62] L. Ruzicka, R. Steiger, and H. Schinz, *Helv. Chim. Acta*, 1926, **9**, 962 ; L. Ruzicka and J. R. Hosking, *ibid.*, 1930, **13**, 1402 ; 1931, **14**, 203 ; L. Ruzicka and H. Jacobs, *loc. cit.* ; L. Ruzicka, E. Bernold, and A. Tallichet, *Helv. Chim. Acta*, 1941, **24**, 223 ; L. Ruzicka and E. Bernold, *ibid.*, p. 931, 1167 ; compare L. Ruzicka and E. Rey, *ibid.*, 1943 **26**, 2136.

The position of the two olefinic linkages in agathenedicarboxylic acid was proved by a study of the ozonolysis products of the dimethyl ester. The most important of these was a 1 : 5-diketone (LXIII) which readily underwent intramolecular dehydration on treatment with alkali to give a tricyclic $\alpha\beta$-unsaturated ketone (LXIV). By reaction with methylmagnesium iodide,* the latter afforded a conjugated diene (LXV), dehydrogenated by selenium to give pimanthrene. These experiments also indicate the position of the carboxyl group which is easily eliminated on pyrolysis. The position of the other carboxyl group was proved in the following manner. When agathenedicarboxylic acid was digested with formic acid it was isomerised to a tricyclic acid, *iso*agathenedicarboxylic acid (LXVI). This, like its progenitor, possessed an $\alpha\beta$-unsaturated carboxyl group readily eliminated by heat to give *iso*noragathenemonocarboxylic acid (LXVII). Reduction of the methyl ester of the latter † by a modified Bouveault–Blanc method furnished *iso*noragathenol (LXVIII), which was dehydrated and then dehydrogenated to give 7-methyl-1-ethylphenanthrene (XLVII) identical with the hydrocarbon prepared similarly from dextropimaric acid (p. 46).



Podocarpic acid. Although podocarpic acid is not strictly a member of the diterpenoid resin acids, its chemistry is closely related to that of the diterpenoids. It is convenient, therefore, to give a short account of it here. Podocarpic acid, $C_{17}H_{22}O_3$ (LXIX ; R = H), was first isolated by A. C. Oudemans [63] from the resin of *Podocarpus cupressinum* and was obtained later [64] from *P. dacrydioides* and from *Dacrydium cupressinum.* It is a phenolic carboxylic acid which gives 1-methylphenanthrene and 6-hydroxy-

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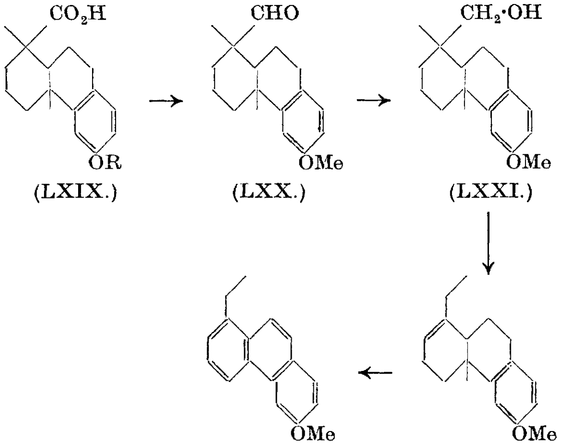
[63] *Ber.*, 1873, **6**, 1122, 1125 ; *Annalen*, 1873, **170**, 214 ; *J. pr. Chem.*, 1874, **9**, 385.

[64] Compare I. R. Sherwood and W. F. Short, *J.*, 1938, 1006.

* The tertiary carbomethoxyl group in (LXIV) is strongly hindered sterically and does not react.

† More recent experiments have shown that (LXVII) was not homogeneous ; this does not affect the validity of the conclusions reached here because the inhomogeneity depended only on isomerism in ring B.

1-methylphenanthrene on dehydrogenation.[65] Although these facts are explicable by other formulæ besides (LXIX ; R = H), the correctness of the latter was proved by W. P. Campbell and D. Todd [66] in the following way. Podocarpic acid methyl ether (LXIX ; R = Me) was reduced by the Rosenmund method to podocarpinal methyl ether (LXX), which was further hydrogenated to podocarpinol methyl ether (LXXI). This was dehydrated and then dehydrogenated to give 6-methoxy-1-ethylphenanthrene (LXXII).



(LXIX.) (LXX.) (LXXI.)

(LXXII.)

Miropinic acid and iso*miropinic acid*.* These acids were isolated by C. W. Brandt and L. G. Neubauer [69] from the resin exuded by the Miro tree (*Podocarpus ferrugineus*). Miropinic acid, $C_{20}H_{30}O_3$, is tricyclic, has two ethylenic linkages, and gives pimanthrene on dehydrogenation. It is partly isomerised to *iso*miropinic acid by treatment with methanolic hydrogen chloride.

Vouacapenic acid. The heartwood of *Vouacapoua americana* Aubl. contains the methyl ester of vouacapenic acid, $C_{20}H_{28}O_2$. This acid has two ethylenic linkages ; the third oxygen atom is probably ethereal.[70]

Cativic acid. The oleoresin from *Prioria copaifera*, Griseb. (the cativa tree) contains the interesting resin acid cativic acid, $C_{20}H_{34}O_2$, which occurs in the resin both in the free state and esterified with the corresponding primary alcohol, cativyl alcohol. Although cativic acid is probably

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[65] H. Plimmer, W. F. Short, and P. Hill, *ibid.*, p. 694 ; I. R. Sherwood and W. F. Short, *loc. cit.*

[66] *J. Amer. Chem. Soc.*, 1942, **64**, 928.

[67] *J. Pharm. Soc. Japan*, 1937, **57**, 69.

[68] J. R. Hosking and C. W. Brandt, *Ber.*, 1935, **68**, 1313 ; J. R. Hosking, *New Zealand J. Sci. Tech.*, 1937, **19**, 208.

[69] *J.*, 1940, 683.

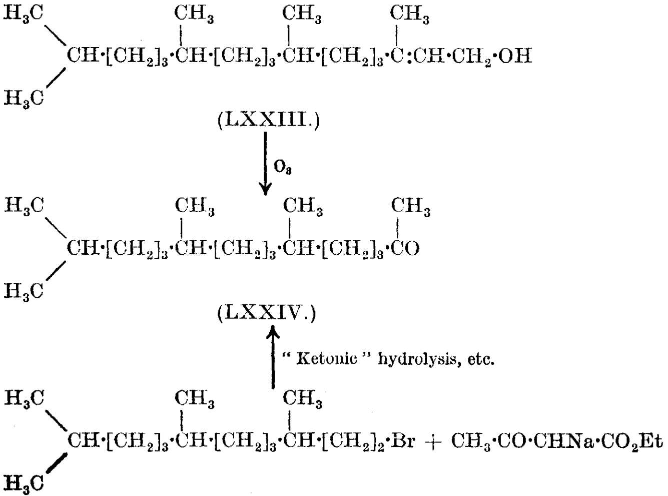
[70] D. B. Spoelstra, *Rec. Trav. chim.*, 1930, **49**, 226.

* Miropinic acid is possibly identical with cryptopimaric acid isolated by S. Keimatsu, T. Ishiguro, and G. Fukui [67] from *Cryptomeria japonica*, and with an acid obtained from *Dacrydium biforme* and *D. kirkii*.[68]

diterpenoid it differs from abietic acid and related acids in that its carboxyl group is readily esterfied.[71]

Diterpenoid Alcohols and Phenols.—These compounds have received comparatively little attention.

Phytol. The mono-unsaturated aliphatic diterpenoid alcohol phytol, $C_{20}H_{40}O$, was discovered by R. Willstätter [72] to be the alcoholic moiety of the chlorophyll molecule. The initial degradational experiments [73] did not lead to a successful elucidation of the structure of phytol, and this was only effected later by the synthetic experiments of F. G. Fischer,[74] who found that phytol (LXXIII), which had been already recognised as a primary alcohol, gave a saturated ketone (LXXIV) and glycollic aldehyde on ozonolysis, thus showing the double bond to be in the $\alpha\beta$-position to the alcoholic grouping. The structure of (LXXIV) as 2 : 6 : 10-trimethylpentadecan-14-one was proved by its synthesis as indicated * from hexahydrofarnesyl bromide (LXXV).



(LXXV.)

Natural phytol usually has a negligibly small optical rotation and this has been taken to imply that it is a racemate.[75] However, Karrer *et al.*[76]

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[71] N. L. Kalman, *J. Amer. Chem. Soc.*, 1938, **60**, 1423.

[72] R. Willstätter and F. Hocheder, *Annalen*, 1907, **354**, 205; R. Willstätter, F. Hocheder, and E. Hug, *ibid.*, 1909, **371**, 1; R. Willstätter and A. Oppé, *ibid.*, 1911, **378**, 1.

[73] R. Willstätter, E. W. Mayer and E. Hüni, *ibid.*, p. 73; R. Willstätter, O. Schuppli, and E. W. Mayer, *ibid.*, 1918, **418**, 121.

[74] *Ibid.*, 1928, **464**, 69; F. G. Fischer and K. Löwenberg, *ibid.*, 1929, **475**, 183.

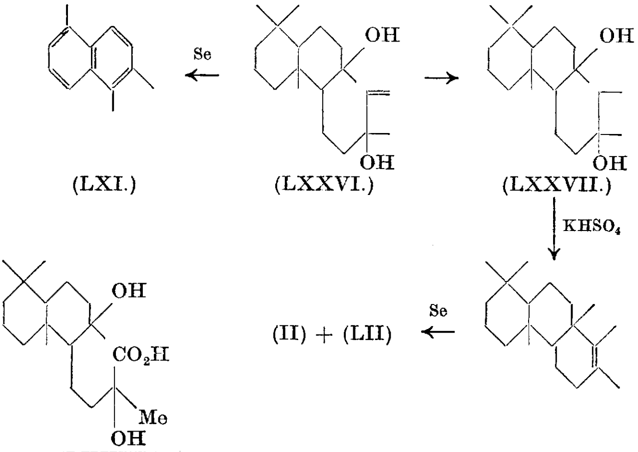
[75] F. G. Fischer and K. Löwenberg, *loc. cit.*; T. Wagner-Jauregg, *Z. physiol. Chem.*, 1933, **222**, 21.

[76] P. Karrer, A. Geiger, H. Rentschler, E. Zbinden, and A. Kugler, *Helv. Chim. Acta*, 1943, **26**, 1741.

* For later syntheses, see L. I. Smith and J. A. Sprung, *J. Amer. Chem. Soc.*, 1943, **65**, 1276; P. Karrer, *et al.*, *Helv. Chim. Acta*, 1943, **26**, 1741.

have recently described the isolation of an optically active phytol, $[\alpha]_D^{18^\circ} + 0{\cdot}20$—$0{\cdot}21^\circ$, from nettles and have synthesised a lævorotatory phytol, $\alpha_D - 0{\cdot}18^\circ$. This synthetic phytol and the dextrorotatory phytol are not, as might have been thought, optical antipodes ;[77] it is concluded that phytol is not a racemate but a latently optically active compound.

Sclareol. The ditertiary glycol sclareol, $C_{20}H_{36}O_2$ (LXXVI), was first isolated by Y. Volmar and A. Jermstad[78] from the leaves of *Salvia sclarea* L. It was recognised as a diterpenoid by M. M. Janot,[79] who showed, by catalytic hydrogenation to the saturated dihydrosclareol (LXXVII), that it must be bicyclic and contain only one ethylenic linkage. The carbon skeleton of sclareol was partly characterised by L. Ruzicka and M. M. Janot's observation[80] that sclareol gave 1 : 5 : 6-trimethylnaphthalene (LXI) on dehydrogenation with selenium. When dihydrosclareol was treated with potassium hydrogen sulphate it furnished, amongst other products, dihydro*cyclo*sclarene (LXXVIII), which was dehydrogenated to a mixture of 1 : 7 : 8-trimethylphenanthrene (LII) and pimanthrene.[80] The presence of a methylene grouping in sclareol was shown by the high yield of formaldehyde on ozonolysis and by the formation of a C_{19} dihydroxy-acid (LXXIX), amongst other products, on oxidation with potassium permanganate.[80, 81] In view of these experimental facts, particularly the isolation of (LII) on dehydrogenation of (LXXVIII), a carbon skeleton similar to that in agathenedicarboxylic acid (p. 49) was suggested. The two uncharacterised oxygen atoms must be present as tertiary alcoholic groups and are placed as indicated in order best to account for the formation of (LXXVIII) on dehydration. Some recent work on manoöl (p. 55) discussed later constitutes an indirect proof of the correctness of the sclareol formula.



(LXI.) (LXXVI.) (LXXVII.)

(LXXIX.) (LXXVIII.)

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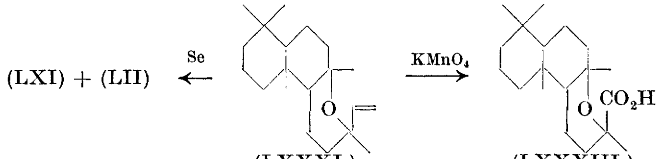
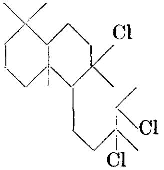
[77] P. Karrer, H. Simon, and E. Zbinden, *ibid.*, 1944, **27**, 313.
[78] *Compt. rend.*, 1928, **186**, 517, 783. [79] *Ibid.*, 1930, **191**, 847 ; 1931, **192**, 845.
[80] *Helv. Chim. Acta*, 1931, **14**, 645 ; M. M. Janot, *Ann. Chim.*, 1932, **17**, 5.
[81] L. Ruzicka, C. F. Seidel, and L. L. Engel, *Helv. Chim. Acta*, 1942, **25**, 621.

Manoöl, manoyl oxide, and ketomanoyl oxide. Because of a very close relationship in structure it is convenient to treat these three substances together. The diterpenoid alcohol manoöl, $C_{20}H_{34}O$ (LXXX), was isolated by J. R. Hosking and C. W. Brandt [82] from the wood oil of the yellow pine (*Dacrydium biforme*). The same authors also reported the isolation of manoyl oxide, $C_{20}H_{34}O$ (LXXXI),[83] and of ketomanoyl oxide (LXXXII)[84] from the wood oil of the silver pine (*Dacrydium colensoi*; otherwise *D. westlandicum*).

The accepted structure for manoyl oxide was established by Hosking and Brandt [85, 86] in the following manner. Manoyl oxide contained only one ethylenic linkage, and the oxygen atom, which could not be characterised, was assumed correctly to be part of an oxide ring. On dehydrogenation with selenium, manoyl oxide afforded 1 : 5 : 6-trimethylnaphthalene (LXI) and 1 : 7 : 8-trimethylphenanthrene (LII). The presence of an exocyclic methylene group was proved by the formation of formaldehyde in high yield on ozonolysis, and by oxidation with potassium permanganate, which gave a C_{19} acid (LXXXIII). This acid is important because it shows that the oxide ring in (LXXXI) is correctly formulated. On treatment with hydrogen chloride both manoyl oxide and sclareol gave the same trichloro-compound (LXXXIV), thus confirming the structure assigned to the former.



(LXXXI.) (LXXXIII.)



(LXXXIV.)

The formula (LXXX) for manoöl was deduced by Hosking and Brandt [82, 86] from the following evidence. Since manoöl gave the same product (LXXXIV) by treatment with hydrogen chloride as was obtained from manoyl oxide, they must possess the same carbon skeleton. Catalytic hydrogenation of manoöl furnished the saturated tetrahydromanoöl (LXXXV) and thus showed the presence of two ethylenic linkages. The action of hydrogen chloride on (LXXXV) afforded a chloride yielding, on digestion with aniline, a mixture of two hydrocarbons, (LXXXVI) and (LXXXVII). On ozonolysis this mixture gave a C_{18} ketone (LXXXVIII)

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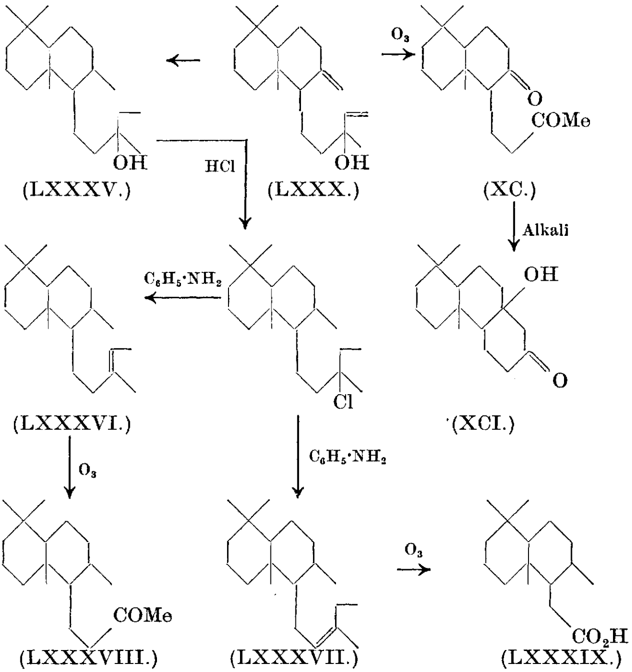
[82] *Ber.*, 1935, **68**, 1311; *New Zealand J. Sci. Tech.*, 1936, **17**, 755.
[83] *Ber.*, 1934, **67**, 1173; *New Zealand J. Sci. Tech.*, 1936, **17**, 750.
[84] *Ber.*, 1934, **67**, 1173; 1935, **68**, 286; *New Zealand J. Sci. Tech.*, 1936, **17**, 750.
[85] *Ber.*, 1935, **68**, 37.
[86] *Ibid.*, 1936, **69**, 780.

and a C_{16} acid (LXXXIX). The formation of these two degradation products provides conclusive proof that the hydroxyl group in manoöl must be as in (LXXX), and also indicates indirectly the position of one of the ethylenic linkages as shown. The position of the other ethylenic linkage



was proved by ozonolysis of manoöl itself, which gave a C_{17} diketone (XC). The keto-groups must have been in the 1 : 5-relationship in the latter because of the ease with which it was cyclised by alkali to the hydroxy-ketone (XCI).

The formula (LXXX) for manoöl has recently received confirmation by the establishment of a direct relationship with abietic acid.[87] The hydroxy-ketone (XCI) was reacted with *iso*propylmagnesium bromide to give the dihydric alcohol (XCII), which was dehydrated to the corresponding diene, possibly (XCIII), and then dehydrogenated by bromosuccinimide to the hydrocarbon (XCIV). This hydrocarbon was identical with dehydroabietane obtained from abietic acid, since both gave the same 6 : 8-dinitrodehydroabietane on nitration. The synthesis of dehydroabietane had been carried out earlier by W. P. Campbell and D. Todd,[66] starting with dehydroabietic acid (XCVI).* This was reduced by the Rosenmund method to

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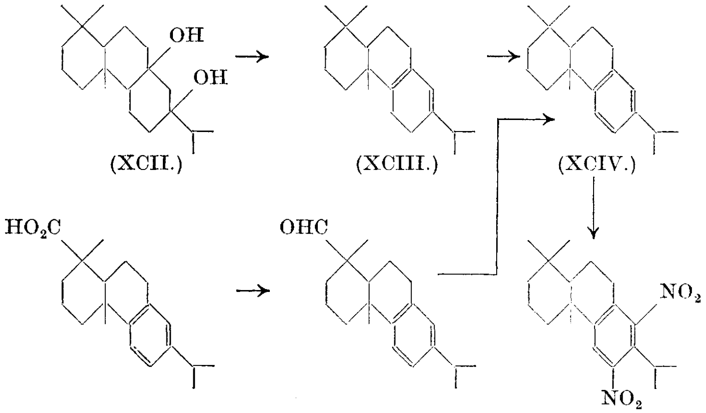
[87] O. Jeger, O. Dürst, and G. Büchi, *Helv. Chim. Acta*, 1947, **30**, 1853.

* Dehydroabietic acid was first obtained in a state of purity by L. F. Fieser and W. P. Campbell.[10] It is a major constituent of the so-called pyroabietic acid formed by the action of heat on abietic acid.[10, 88] Although much interesting work of a preparative nature has been done in recent years on dehydroabietic acid,[89] space restrictions do not justify a detailed account here.

dehydroabietinal (XCVII), which on further reduction by the Wolff–Kishner method gave dehydroabietane.



(XCII.) (XCIII.) (XCIV.)

(XCVI.) (XCVII.) (XCV.)

The formula (LXXXII) for ketomanoyl oxide has been elegantly demonstrated by the experiments of Hosking and Brandt.[84, 86] Reduction of this oxide by the Wolff–Kishner method afforded manoyl oxide (LXXXI), thus leaving only the position of the keto-group to be established. With methylmagnesium iodide, (LXXXII) furnished, *via* the carbinol (XCVIII) and catalytic hydrogenation, (XCIX), the oxide ring of which was split by hydrogen chloride to give (C). Removal of hydrogen chloride from the latter by heating with aniline, followed by dehydrogenation, gave a mixture of 1 : 3 : 5 : 6-tetramethylnaphthalene (CI) and, probably, 1 : 3 : 7 : 8-tetramethylphenanthrene (CII), thus proving the original keto-group to have occupied the 3-position.

Ferruginol. This phenolic diterpenoid comprises the major part of the resin of the Miro tree and was isolated therefrom by C. W. Brandt and L. G. Neubauer.[90] Ferruginol, $C_{20}H_{30}O$, gave 6-hydroxyretene (CIII; $R = H$) on dehydrogenation with selenium,[90, 91] from which result the formula (CIV) was deduced. The correctness of this formula was shown by W. P. Campbell and D. Todd [66] by partial synthesis of ferruginol (*a*) from dehydroabietic acid and (*b*) from podocarpic acid (p. 50). (*a*) 6-Methoxydehydroabietic acid (CV) was reduced by the Rosenmund method to

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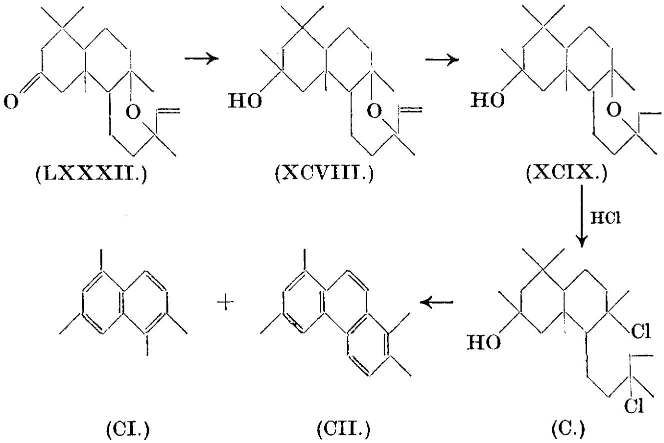
[88] *Inter al.*, E. E. Fleck and S. Palkin, *J. Amer. Chem. Soc.*, 1937, **59**, 1593; 1938, **60**, 921; 1939, **61**, 247; L. Ruzicka, R. G. R. Bacon, L. Sternbach, and H. Waldmann, *Helv. Chim. Acta*, 1938, **21**, 591; R. Lombard, *Compt. rend.*, 1939, **208**, 1321; 1941, **213**, 793; *Bull. Soc chim.*, 1942, **9**, 833; T. Hasselstrom, E. A. Brennan, and S. Hopkins, *J. Amer. Chem. Soc.*, 1941, **63**, 1759.

[89] *Inter al.*, T. Hasselstrom, E. A. Brennan, and J. D. McPherson, *ibid.*, 1938, **60**, 1267; T. Hasselstrom and J. D. McPherson, *ibid.*, p. 2340; L. F. Fieser and W. P. Campbell, *ibid.*, p. 2631; 1939, **61**, 2528; W. P. Campbell and M. Morgana, *ibid.*, 1941, **63**, 1838; T. Hasselstrom and S. Hopkins, *ibid.*, p. 421; L. Ruzicka and S. Kaufmann, *Helv. Chim. Acta*, 1940, **23**, 288.

[90] *J.*, 1939, 1031.

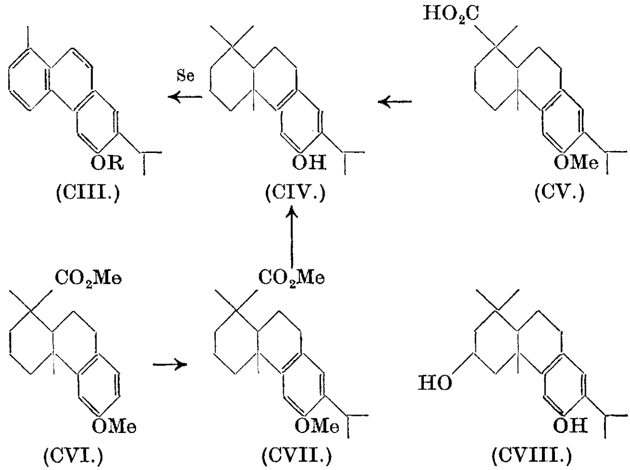
[91] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, 1940, **62**, 1287.



(LXXXII.) (XCVIII.) (XCIX.)

(CI.) (CII.) (C.)

the corresponding aldehyde, which on further reduction by the Wolff–Kishner procedure gave ferruginol. (*b*) Podocarpic acid methyl ester methyl ether (CVI) underwent the Friedel–Crafts reaction with acetyl chloride to give the 7-acetyl derivative, converted by reaction with methylmagnesium chloride followed by dehydration of the resulting tertiary



(CIII.) (CIV.) (CV.)

(CVI.) (CVII.) (CVIII.)

carbinol* into the 7-*iso*propenyl derivative, which on hydrogenation furnished 7-*iso*propylpodocarpic acid methyl ester methyl ether (CVII). The corresponding acid was then reduced as described above for 6-methoxydehydroabietic acid and gave ferruginol. These partial syntheses are not only a proof of the structure of ferrigunol but also show that the carboxyl group in abietic acid is epimeric to that in podocarpic acid.

Hinokiol. The diterpenoid phenolic alcohol hinokiol, $C_{20}H_{30}O_2$, was

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* The carbomethoxyl group of methyl podocarpate is very hindered sterically and did not react with the Grignard reagent.

first isolated by Y. Yoshiki and T. Ishiguro[92] as one of the crystalline constituents of the resin extracted from the heartwood of *Chamæcyparis obtusa*, Sieb. et Zucc. The chemistry of hinokiol has been extensively studied.[92, 93] On dehydrogenation with selenium, hinokiol furnished, amongst other products, a substance which is undoubtedly 6-hydroxyretene (CIII; R = H),[90, 91] and which accounts for the phenolic hydroxyl in hinokiol. The second hydroxyl is secondary, as shown by oxidation of hinokiol to the corresponding ketone, hinokione, which is also a constituent of *Chamæcyparis obtusa* resin. It is probably attached at the 3-position,[94] as shown in the formula (CVIII).

Sugiol. The only known phenolic ketone, sugiol, $C_{20}H_{28}O_2$, was isolated by S. Keimatsu, T. Ishiguro, and G. Fukui[95] from *Cryptomeria japonica* D. Don. Some progress has been made towards the elucidation of its structure.[96] On reduction by the Clemmensen method and dehydrogenation of the product, sugiol methyl ether afforded a substance which is undoubtedly 6-methoxyretene (CIII; R = CH_3). Sugiol probably differs therefore from hinokione only in the position of the ketonic oxygen function.

Totarol. The diterpenoid alcohol totarol, $C_{20}H_{30}O$, isolated from the wood of the totara tree (*Podocarpus totara*), has been investigated by W. F. Short and H. Stromberg.[97] Totarol is probably a secondary alcohol and it contains three ethylenic linkages. On dehydrogenation it gives 7-hydroxy-1-methylphenanthrene, which has been synthesised.[98]

Diterpenoid Hydrocarbons.—These constitute a numerous group of diterpenoids which, apart from camphorene, are of unknown structure. They are not, at present, of any economic importance.

Camphorene. Camphorene was found by F. W. Semmler and I. Rosenberg[99] to occur in the higher-boiling hydrocarbon fraction of camphor oil. Later,[100] it was recognised as identical with the dimyrcene prepared by C. Harries[101] by the action of heat on myrcene. It can also be prepared by similar pyrolytic methods from other substances.[102] Camphorene is monocyclic and has four ethylenic linkages, as shown by its catalytic hydrogenation to octahydrocamphorene (CIX). The latter, on oxidation with manganese dioxide and sulphuric acid, furnished terephthalic acid.

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[92] *J. Pharm. Soc. Japan*, 1933, **53**, 11; *Chem. Zentr.*, 1933, i, 3203.

[93] S. Keimatsu and T. Ishiguro, *J. Pharm. Soc. Japan*, 1935, **55**, 45; *Chem. Zentr.*, 1935, ii, 3664; G. Huzii and T. Tikamori, *J. Pharm. Soc. Japan*, 1939, **59**, 116.

[94] L. F. Fieser and M. Fieser, "The Chemistry of Natural Products related to Phenanthrene", New Edition, 1949. The Reviewer is much indebted to Professor L. F. Fieser for an opportunity to read the text of the new edition before publication.

[95] *J. Pharm. Soc. Japan*, 1937, **57**, 92; *Chem. Zentr.*, 1937, ii, 596.

[96] G. Huzii and T. Tikamori, *J. Pharm. Soc. Japan*, 1939, **59**, 124; *Chem. Abs.*, 1939, **33**, 4592.

[97] *J.*, 1937, 516.

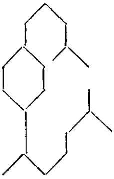
[98] W. F. Short, H. Stromberg and A. E. Wiles, *J.*, 1936, 319.

[99] *Ber.*, 1913, **46**, 768.

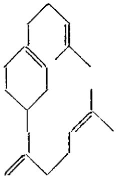
[100] F. W. Semmler and K. G. Jonas, *ibid.*, p. 1566; 1914, **47**, 2068.

[101] *Ibid.*, 1902, **35**, 3264.

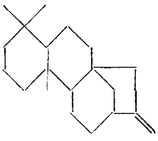
[102] F. W. Semmler and K. G. Jonas, *ibid.*, 1914, **47**, 2068; K. Kafuku, T. Oyamada, and M. Nishi, *J. Chem. Soc. Japan*, 1933, **54**, 364; L. A. Goldblatt and S. Palkin, *J. Amer. Chem. Soc.*, 1941, **63**, 3517.



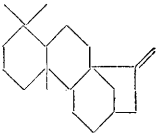
(CIX.)



(CX.)



(CXI.)



(CXII.)

This is in agreement with formula (CX) for camphorene [103] derived from consideration of its method of formation by the polymerisation of myrcene.

Phyllocladene and iso*phyllocladene.* The diterpene phyllocladene, $C_{20}H_{32}$, has been isolated from numerous essential oils,[104, 105, 106] and may occur together with *iso*phyllocladene.[106] Both phyllocladene and *iso*phyllocladene are tetracyclic and contain one ethylenic linkage. They give the same hydrochloride and are related to each other respectively as are β- and α-pinene.[105] Phyllocladene gives, amongst other products, pimanthrene and retene on dehydrogenation, and it has been suggested [107] that phyllocladene may be represented by (CXI) or (CXII), of which the former explains better the degradation to retene. α-Dihydrophyllocladene, produced along with the β-isomer by the catalytic hydrogenation of phyllocladene, is identical with iosene obtained from lignites.[108]

*iso*Phyllocladene is probably the optical antipode of the diterpene mirene isolated by J. R. Hosking and W. F. Short [109] from the leaf oil of *Podocarpus ferrugineus* (the Miro tree).

α-Podocarprene. This tetracyclic mono-unsaturated diterpene, $C_{20}H_{32}$, has been isolated from various essential oils.[110] It gives a monohydrochloride which with potassium acetate affords δ-podocarprene. α- and δ-Podocarprenes are probably related in the same way as phyllocladene and *iso*phyllocladene.

The diterpene kaurene, isolated by J. R. Hosking [111] from the leaf oil of the Kauri pine (*Agathis australis*), is probably an artefact formed by the action of heat or metallic sodium on α-podocarprene, which is the substance isolated from the oil under mild conditions.[112]

Rimuene. This tricyclic diterpene, $C_{20}H_{32}$, isolated from the essential

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[103] L. Ruzicka and M. Stoll, *Helv. Chim. Acta*, 1924, **7**, 271.

[104] B. H. Goudie, *J. Soc. Chem. Ind.*, 1923, **42**, 357T ; H. A. A. Aitken, *ibid.*, 1928, **47**, 223T ; W. J. Blackie, *ibid.*, 1929, **48**, 357T ; 1930, **49**, 26T ; L. H. Briggs, *J.*, 1937, 79 ; compare C. W. Brandt, *New Zealand J. Sci. Tech.*, 1938, **20**, 8.

[105] K. Nishida and H. Uoda, *J. Agric. Chem. Soc. Japan*, 1935, **11**, 489 ; 1936, **12**, 308 ; H. Uoda, *J. Dept. Agric. Kyushu Imp. Univ. Japan*, 1937, **5**, 117.

[106] L. H. Briggs and M. D. Sutherland, *J. Org. Chem.*, 1948, **13**, 4.

[107] C. W. Brandt, *loc. cit.*, ref. (104).

[108] L. H. Briggs, *J.*, 1937, 1035.

[109] *Rec. Trav. chim.*, 1928, **47**, 834 ; J. R. Hosking, *ibid.*, 1930, **49**, 1036 ; compare J. Kawamura, *Bull. Imp. Forestry Exp. Sta. Tokyo*, 1931, No. 31, 93.

[110] K. Nishida and H. Uoda, *J. Agric. Chem. Soc. Japan*, 1931, **7**, 157 ; J. Kawamura, *loc cit.* ; L. H. Briggs and R. W. Cawley, *J.*, 1948, 1888.

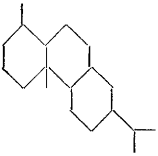
[111] *Rec. Trav. chim.*, 1928, **47**, 578 ; 1930, **49**, 1036.

[112] L. H. Briggs and R. W. Cawley, *loc. cit.*, ref. (110).

oil of the Rimu tree (*Dacrydium cupressinum*)[113] and, as totarene, from that of the Totara tree (*Podocarpus totara*),[114] gives pimanthrene on dehydrogenation and is isomerised to *iso*phyllocladene on digestion with formic acid.[107] It contains a methylene group and a further, unidentified, olefinic linkage.

Miscellaneous Diterpenoids.—*Fichtelite.* Although fichtelite is not strictly a diterpenoid, it is very closely related to abietic acid and so may be considered here. It was first isolated by C. Bromeis[115] from the decayed wood of conifers, in which it owes its presence to the decomposition of resin acids under anaerobic conditions. Although this saturated hydrocarbon was the subject of numerous investigations,[116] it was not until L. Ruzicka, F. Balas, and H. Schinz[117] had shown that it afforded retene on dehydrogenation with sulphur that real progress could be made with its formulation. Subsequently, L. Ruzicka and H. Waldmann[118] found by quantitative dehydrogenation with palladised charcoal that its (previously disputed) formula must be $C_{19}H_{34}$, and this was confirmed by *X*-ray analysis.[119]

In view of the relationship of fichtelite to abietic acid and to retene, Ruzicka and Waldmann suggested that it is most probably represented by (CXIII).


(CXIII.)

Marrubiin. The diterpenoid lactone marrubiin, $C_{20}H_{28}O_4$, which constitutes the bitter principle of the horehound (*Marrubium vulgare* L.), although known for many years, was not isolated in a state of purity until 1932.[120] The chemistry of marrubiin has been investigated by various workers[121] and some progress has been made with the elucidation of its structure. It contains two ethylenic linkages and is bicyclic, giving 1 : 5 : 6-trimethylnaphthalene (LXI) on dehydrogenation. Two of the oxygen atoms are present as a lactone ring, one as a tertiary hydroxyl group, and the fourth, probably, as an oxide ring. It is possibly related, therefore, to the 1 : 7 : 8-trimethylphenanthrene group of diterpenoids.

Stereochemistry of the Diterpenoids.—Some progress has already been made in our knowledge of the stereochemistry of the diterpenoids, and it is possible to present a tentative scheme covering the more important centres in those compounds of established structure.

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[113] F. H. McDowall and H. J. Finlay, *J. Soc. Chem. Ind.*, 1925, **44**, 42T ; M. S. Carrie, *ibid.*, 1932, **51**, 367T.

[114] G. B. Beath, *ibid.*, 1933, **52**, 338T ; compare H. A. A. Aitken, *ibid.*, 1929, **48**, 344T.

[115] *Annalen*, 1841, **37**, 304 ; compare J. B. Trommsdorff, *ibid.*, 1837, **21**, 126.

[116] *Inter al.*, T. E. Clark, *ibid.*, 1857, **103**, 236 ; C. Hell, *Ber.*, 1889, **22**, 498 ; E. Bamberger, *ibid.*, p. 635 ; C. Liebermann and L. Spiegel, *ibid.*, p. 779 ; L. Spiegel, *ibid.*, p. 3369 ; E. Bamberger and L. Strasser, *ibid.*, p. 3361.

[117] *Helv. Chim. Acta*, 1923, **6**, 692.

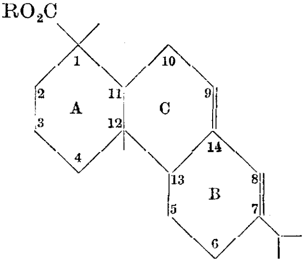
[118] *Ibid.*, 1935, **18**, 611.

[119] D. Crowfoot, *J.*, 1938, 1241.

[120] L. J. Mercier and F. Mercier, *Compt. rend.*, 1932, **195**, 1102.

[121] H. M. Gordin, *J. Amer. Chem. Soc.*, 1908, **30**, 265 ; A. Lawson and E. D. Eustice, *J.*, 1939, 587 ; F. Hollis, J. H. Richards, and A. Robertson, *Nature*, 1939, **143**, 604.

It was mentioned on pp. 40, 46, that vigorous oxidation of abietic (VI ; R = H) and dextropimaric acids gives a $C_{11}H_{16}O_6$ tricarboxylic acid derived from ring A. This acid is optically inactive and must, therefore, possess a plane of symmetry, *i.e.*, the 1- and the 3-carboxyl group must be in the *cis*-relationship to each other. The carboxyl attached at position 2 has recently been shown by D. H. R. Barton and G. A. Schmeidler,[122] from a study of dissociation-constant data, to be related in the *trans*-sense to the other two carboxyl groups, so that the A/C ring fusion in abietic acid and related acids must also be *trans*.* The remaining asymmetric centre in abietic acid at C_{13} (see VI) is probably in the *trans*-relationship to the C_{12} methyl group. This is so because it would be anticipated that treatment with acidic reagents (as in the preparation of abietic acid) would provide a mechanism for the assumption of the more stable configuration at this centre. There is support for this argument in the work of W. Sandermann,[124] who prepared an isomer of abietic acid by pyrolysis of the levopimaric acid maleic anhydride adduct and from abietic acid dihydrobromide. He called this isomer *iso*-abietic acid and showed that it was possibly epimeric with abietic acid at the C_{13} position. On treatment with hydrogen chloride it was rearranged to abietic acid. From the strong lævorotation of abietic and levopimaric acids it is probable that they have the same configuration at C_{13}. *neo*Abietic acid, which is strongly dextrorotatory (p. 44), must by this reasoning have the opposite configuration to abietic acid at C_{13}.[94]



(VI.)

Since manoöl has been related directly to dehydroabietic acid (p. 55) it must have the same configurations as abietic acid at C_{11} and C_{12}. This also establishes the configurations of manoyl oxide (p. 54), ketomanoyl oxide (p. 54), and sclareol (p. 53) at these centres.

Very recently,[125] L. Ruzicka, R. Zwicky, and O. Jeger have shown that agathenedicarboxylic acid has the same ring fusion as for rings A/C of abietic acid. When the agathenedicarboxylic acid derivative (LXV) (p. 49) was dehydrogenated by the bromosuccinimide method, it gave the corresponding dehydro-derivative (CXIV), converted by standard methods into the

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[122] *J.*, 1948, 1197. [123] D. H. R. Barton, *Chem. and Ind.*, 1948, 638.

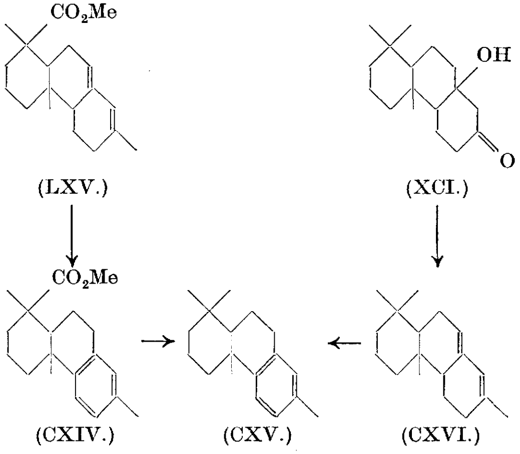
[124] *Ber.*, 1943, **76**, 1257, 1261.

[125] *Helv. Chim. Acta*, 1948, **31**, 2143 ; the author is indebted to Dr. O. Jeger for a copy of this paper before its publication.

* Treatment of the various dihydroabietic acids with strongly acid reagents gives an isomeric lactone, $C_{20}H_{32}O_2$, m.p. 130—131°, $[\alpha]_D$ *ca.* − 2° (in alcohol). This substance is usually considered to be lactonised at the C_{13} position. Its formation in this way has been taken to support a *cis* A/C ring fusion, since it cannot possibly be built up on models if the A/C fusion is *trans*. The accepted formula for this lactone must be in error, and it has been suggested elsewhere [123] that its formation involves a migration of the C_{12} methyl group comparable to that taking place in the genesis of Westphalen's diol.

partly aromatic hydrocarbon (CXV), which was obtained also from the manoöl derivative (XCI) (p. 55) by reaction with methylmagnesium iodide to give the diene (CXVI) and dehydrogenation of the latter with bromosuccinimide. These experiments also provide an unambiguous proof of the point of attachment of the C_{12}-methyl group in agathenedicarboxylic acid. Both the agathenedicarboxylic acid derivative (LXV) and the manoöl derivative (CXVI) have strong lævorotations similar to that shown by abietic acid. For this reason they probably have the same configuration at C_{13} as in abietic acid. *Assuming that inversion at this centre has not occurred during their preparation,* this may be taken as evidence for the same configuration at C_{13} in agathenedicarboxylic acid, manoöl, manoyl oxide, ketomanoyl oxide, and sclareol as in abietic acid.

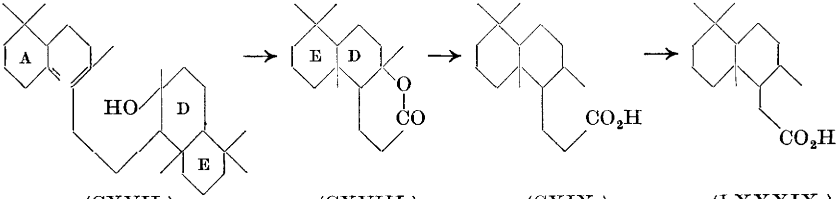
These conclusions on stereochemistry are summarised in the table.



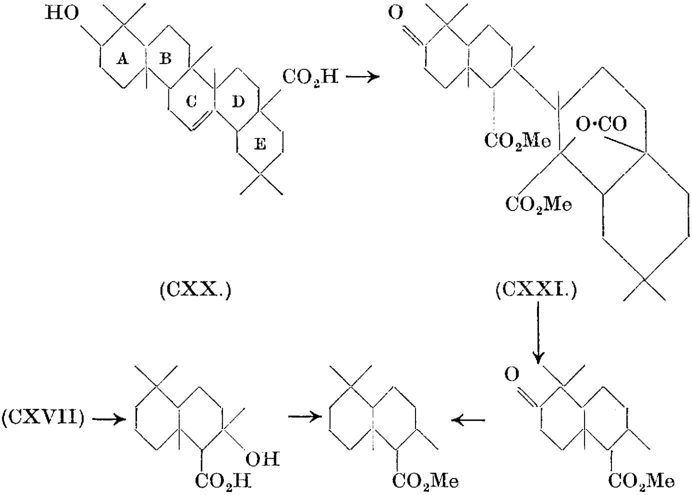
Diterpenoid.	Relationship between :		
	CO_2H at C_1 and H at C_{11}.	H at C_{11} and Me at C_{12}.	Me at C_{12} and H at C_{13}.
Abietic acid	*cis*	*trans*	*trans*
*iso*Abietic acid	*cis*	*trans*	*cis* ?
*neo*Abietic acid	*cis*	*trans*	*cis* ?
Dextropimaric acid . . .	*cis*	*trans*	?
Levopimaric acid . . .	*cis*	*trans*	*trans*
Podocarpic acid	*trans*	*trans*	—
Agathenedicarboxylic acid.	*trans*	*trans*	*trans* ?
Manoöl	—	*trans*	*trans* ?
Manoyl oxide	—	*trans*	*trans* ?
Ketomanoyl oxide . . .	—	*trans*	*trans* ?
Sclareol	—	*trans*	*trans* ?
Ferruginol	—	*trans*	—

Relationships between Di- and Tri-terpenoids.—This is a field of the greatest importance for the final clarification of the structures of the triterpenoids. Important advances can be expected therein in the near future.

The formulation of rings D and E of ambrein (CXVII)[126] has been elegantly confirmed by the experiments of L. Ruzicka, O. Dürst, and O. Jeger.[127] When ambrein is oxidised it affords,[128] amongst other products, a saturated lactone (CXVIII) which can be degraded through the corresponding saturated acid (CXIX) to an acid identical with that (LXXXIX), obtained previously from manoöl. These experiments also establish that the ring fusion between rings D and E in ambrein is *trans* (see above).



(CXVII.) (CXVIII.) (CXIX.) (LXXXIX.)



(CXX.) (CXXI.)

(CXXIV.) (CXXIII.) (CXXII.)

A similar important correlation has now been established between oleanolic acid, probably (CXX), and manoöl through a common degradation product of the former and of ambrein.[129] Pyrolysis of the keto-lactone (CXXI), obtained from oleanolic acid, afforded, amongst other products,

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[126] E. Lederer and D. Mercier, *Experientia*, 1947, **3**, 188 ; O. Jeger, O. Dürst, and L. Ruzicka, *Helv. Chim. Acta*, 1947, **30**, 1859.

[127] *Ibid.*, 353.

[128] L. Ruzicka and F. Lardon, *ibid.*, 1946, **29**, 912 ; E. Lederer, F. Marx, D. Mercier, and G. Perot, *ibid.*, 1354.

[129] L. Ruzicka, H. Gutmann, O. Jeger, and E. Lederer, *ibid.*, 1948, **31**, 1746 ; the author is indebted to Dr. O. Jeger for a copy of this paper before its publication.

a keto-ester (CXXII) reduced by the Wolff–Kishner method to the saturated acid (CXXIII). The latter was also prepared from ambrein in the following way. Oxidation of ambrein with potassium permanganate gave, amongst other products, the saturated hydroxy-acid (CXXIV) which, by dehydration and then hydrogenation, was converted into (CXXIII). These experiments show that the A/B ring fusion in oleanolic acid must be *trans*, in agreement with the *X*-ray data of G. Giacomello.[130] *

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[130] *Gazzetta*, 1938, **68**, 363 ; compare L. Ruzicka and H. Gubser, *Helv. Chim. Acta*, 1945, **28**, 1054.

* An account of the chemistry of the minor diterpenoids, cryptomerene and cupressene, will be found elsewhere.[5] Cafestol (cafesterol) and kahweol have not been considered in the present Review although they are possibly diterpenoid in character.[94]