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THE STRUCTURE AND STEREOCHEMISTRY

OF THE DITERPENES

AND

THE GLYCOALKALOID FROM SOLANUM NIGRUM.

A Thesis

presented to the University of New Zealand
for the Degree of Doctor of Philosophy

by

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August, 1957.

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I N T R O D U C T I O N .

The diterpenoids are fairly widely distributed in nature. The best known members are the resin acids obtained from the non-volatile portion of many oleoresins, especially those obtained from conifers. Diterpenoid acids, alcohols, lactones, phenols, and alkaloids have been obtained from a variety of sources. The hydrocarbons are more restricted in occurrence; all are found in New Zealand and all but two (camphorene and cupressene) in endemic species. Their reported occurrences are almost solely limited to countries bordering on the Pacific.

The literature on the subject up till 1949, and, in part, until mid-1953, has been well reviewed by Barton ("Chemistry of Carbon Compounds," Elsevier Publishing Co., Amsterdam, 1953, Vol. IIB, p.696). The oxygenated and basic diterpenoids will be discussed in the relevant sections where they concern the present work. The hydrocarbons, the subject of this thesis, are considered in this introduction.

PHYLLOCLADENE.

The tetracyclic diterpene, phyllocladene, was first isolated, from *Phyllocladus rhomboidalis*, by Baker and Smith ("Pines of Australia," Technological Museum, Sydney, 1910, p.419). It has since been isolated from *P. alpinus* (Briggs, *J. Soc. Chem. Ind.*, 1937, 56, 137T), *Dacrydium cupressinum* (Hosking, private

communication), D. Kirkii (Briggs and Taylor, J. Org. Chem., 1947, 12, 551), Podocarpus hallii (Briggs, Trans. Roy. Soc. N.Z. 1940, 70, 173), P. ferrugineus (Briggs, Cawley, Loe and Taylor, J., 1950, 955), P. spicatus (Briggs and Loe, J., 1950, 958). Briggs (J., 1937, 79, 830) has shown that it is identical with 'dacrene' from Dacrydium biforme (Goudie, J. Soc. Chem. Ind., 1923, 42, 357T; Aitken, *ibid.*, 1928, 47, 223T) and D. colensoi (Blackie, *ibid.*, 1929, 48, 357T) and with 'sciadopitene' from Sciadopitys verticillata (Nishida and Uota, J. Agric. Chem. Soc. Japan, 1935, 11, 489; 1936, 12, 308). Phyllocladene also occurs with the related isophyllocladene (see below) in Araucaria excelsa (Briggs, J. Soc. Chem. Ind., 1941, 60, 222; Briggs and Taylor, *ibid.*, 1947, 66, 168) and Phyllocladus trichomanoides (Briggs and Sutherland, J. Org. Chem., 1948, 13, 1). Isophyllocladene occurs in Cupressus macrocarpa (*idem*, *ibid.*, 1942, 7, 397). The physical constants of a diterpene hydrocarbon isolated from Sciadopitys verticillata by Kawamura (Bull. Imp. Forestry Exp. Sta. Tokyo, 1931, No. 31, 93) suggest that it is the optical antipode of isophyllocladene.

Phyllocladene, m.p. 98° , $[\alpha]_{\text{D}}^{25^{\circ}} + 15.8^{\circ}$ (CHCl_3), $\text{C}_{20}\text{H}_{32}$, has one double bond and is therefore tetracyclic. It forms a hydrochloride, m.p. 106° , $[\alpha]_{\text{D}}^{20^{\circ}} + 7.8^{\circ}$, a hydrobromide, m.p. $141 - 142^{\circ}$ (decomp.), $[\alpha]_{\text{D}}^{17^{\circ}} + 9.3^{\circ}$, a nitrosochloride, m.p. 128° , a nitrosate, m.p. 129.5° , a nitrosite, m.p. $132 - 133^{\circ}$, a dibromide, m.p. 122° , and two epimeric dihydro derivatives, ' α ' and ' β ' having m.p. $74 - 74.5^{\circ}$, $[\alpha]_{\text{D}}^{16^{\circ}} + 23.9^{\circ}$ (CHCl_3) and m.p. $55 - 56^{\circ}$, $[\alpha]_{\text{D}}^{16^{\circ}} + 12.5^{\circ}$ (CHCl_3) respectively (Briggs, J., 1937, 79). α - Dihydrophyllocladene has been shown to be

identical with iosene obtained from lignites (Briggs, J., 1937, 1035).

On treatment with 10% alcoholic sulphuric acid or on regeneration from its hydrochloride, phyllocladene is converted into isophyllocladene, m.p. 111 - 112°, $[\alpha]_D^{17} + 23.4^\circ$ (CHCl₃). The isomerisation involves only the shift of the double bond as both isomers give the same two dihydro derivatives and the same hydrochloride and hydrobromide. Isophyllocladene forms a discrete dibromide, m.p. 133 - 134°.

Dehydrogenation of phyllocladene with selenium gives a mixture of retene and pimanthrene (Brandt, N.Z.J.Sci.Tech., 1938, 20, 8).

Uota (J.Dept.Agric.,Kyushu Imp.Univ.Japan, 1937, 5, 117) carried out degradative experiments on phyllocladene and isophyllocladene obtaining, and partially characterising, a number of oxidation and dehydrogenation products. Much of this work was repeated by Brandt (N.Z.J.Sci.Tech., 1952, 34, 46) who, as a result of his investigations postulated structures for the two hydrocarbons. Cain (Research Report, 1954, unpublished work), in a continuation of this work, obtained several new degradation products and characterised others more fully. Their results are summarised in Fig.1.

Bottomley, Cole and White (J., 1955, 2624) examined the infrared spectra of phyllocladene and some of its derivatives. Their observations tended to confirm the structures postulated by Brandt (loc.cit.). In particular, the exocyclic double bond in phyllocladene was shown to be attached to a slightly strained

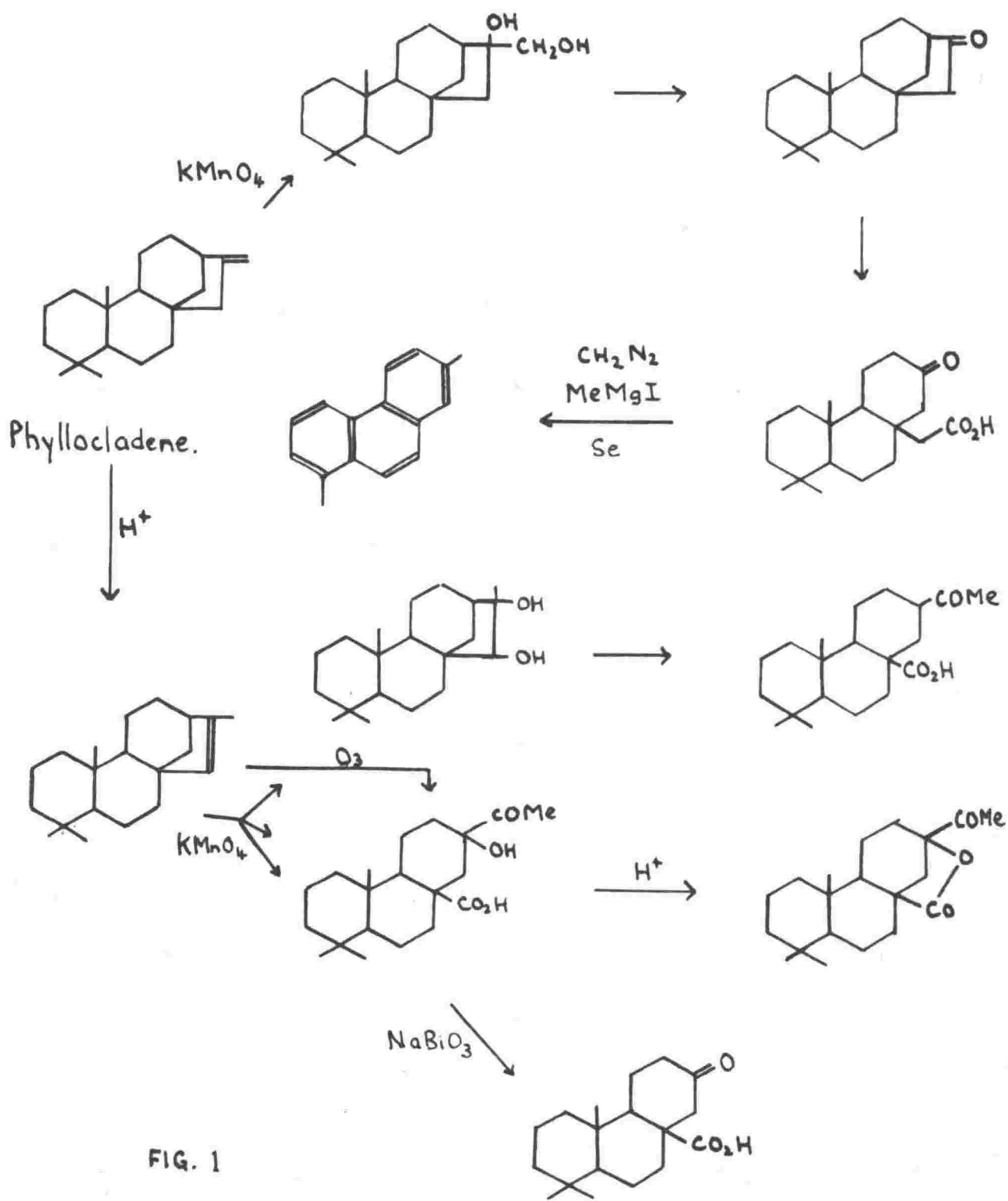


FIG. 1

ring which, by examination of the derived nor-ketone, was shown to be five-membered. Quantitative studies on this ketone showed that there was one methylene group adjacent to the carbonyl group.

The presence of a trisubstituted double bond in a strained ring was indicated in isophyllocladene and from intensity measurements on the spectrum of this compound, they concluded that the molecule contained a gem dimethyl group and an angular methyl group between two six membered rings. In isophyllocladene an extra methyl group, produced on isomerisation, is present; a small band in the phyllocladene spectrum due to a methylene group adjacent to the vinylidene double bond disappears on isomerisation.

KAURENE.

This hydrocarbon has been isolated, in laevorotatory form, from *Agathis australis*, 'Kauri' (Hosking, *Rec. Trav. Chim.*, 1928, 47, 578; 1930, 49, 1036; Briggs and Cawley, *J.*, 1948, 1888) and as podocarpene, from *Podocarpus macrophylla*, Don. (Nishida and Uota, *J. Agric. Chem. Soc. Japan*, 1931, 7, 157), *P. spicatus* (Butler and Holloway, *J. Soc. Chem. Ind.*, 1939, 58, 223), and *Sciadopitys verticillata* (Kawamura, *Bull. Imp. Forestry Exp. Sta. Tokyo*, 1931, No. 31, 93). *Podocarpus ferrugineus* yields d-kaurene (Briggs, Cawley, Loe and Taylor, *J.*, 1950, 955).

Kaurene, $C_{20}H_{32}$, is tetracyclic and contains one double bond and it is obviously very similar to phyllocladene. Thus Cain (Thesis, University of New Zealand, 1954) has shown that it forms two saturated dihydro derivatives, gives a high yield of formaldehyde on ozonolysis, and gives a mixture of pimanthrene

and retene on dehydrogenation.

Again, it forms a hydrochloride which on treatment with basic reagents yields the isomeric isokaurene. The infrared spectra show that the double bonds in the two isomers are unsymmetrically disubstituted and trisubstituted, respectively.

Wilmshurst (Thesis, University of New Zealand 1953) has shown that isokaurene is identical with α -cryptomerene obtained by Uchida from *Cryptomeria japonica* Don. (J. Amer. Chem. Soc., 1916, 38, 687). Briggs, Cawley, Loe and Taylor (loc. cit.) have shown that isokaurene is the product of mild acid isomerisation of Kaurene.

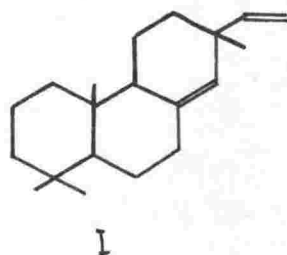
γ -Kaurene, obtained by the action of alcoholic sulphuric acid on kaurene or of alcoholic potash on Kaurene hydrochloride, is an alcohol, $C_{20}H_{34}O$. Treatment with dry hydrogen chloride gives Kaurene hydrochloride (Cain, loc. cit.). Physical constants. Kaurene, m.p. $50^{\circ} [\alpha]_D^{11} - 72^{\circ}$, isokaurene, m.p. $65^{\circ} [\alpha]_D^{11} - 27.1^{\circ}$; α -dihydrokaurene, m.p. $86 - 87^{\circ}$, $[\alpha]_D^9 - 29.3^{\circ}$; β -dihydrokaurene, m.p. 52° , $[\alpha]_D^{19} - 49^{\circ}$.

Isokaurene forms the same hydrochloride and gives α -dihydrokaurene, but the nitrosate m.p. 126° (decomp.) (Kawamura, loc. cit.) is apparently distinct from that of Kaurene, m.p. 140° (decomp.).

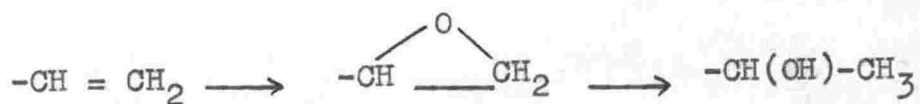
RIMUENE.

The tricyclic diterpene rimuene, $C_{20}H_{32}$, has been isolated from the leaf oils of *Dacrydium cupressinum*, 'rimu' (McDowall and Finlay, J. Soc. Chem. Ind., 1925, 44, 42T) and *Podocarpus totara* (Beath, J. Soc. Chem. Ind., 1933, 52, 338T).

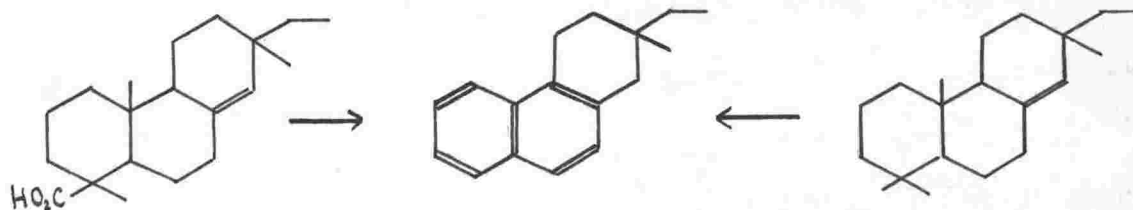
The structure (I) has been proposed by Wilmshurst (loc.cit.) and Cain (loc.cit.).



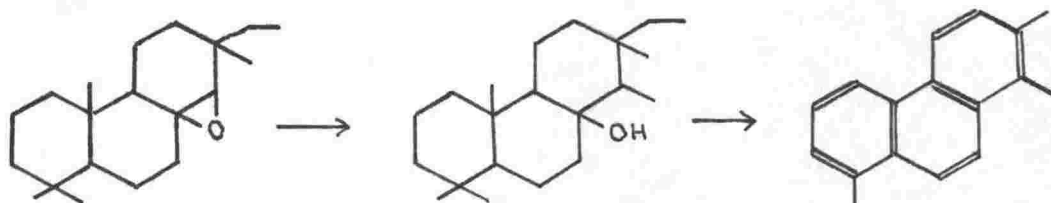
The nature of the double bonds is indicated by the infrared spectra. A dihydro and a saturated tetrahydro derivative have been prepared. The vinyl double bond gave formaldehyde on ozonolysis, while treatment of rimuene with perbenzoic acid, followed by lithium aluminium hydride reduction, yielded material giving a positive iodoform reaction.



Selenium dehydrogenation gave pimanthrene (Brandt, N.Z.J. Sci.Tech., 1938, 20, 8), while partial catalytic dehydrogenation of dihydrorimuene gave a naphthalene hydrocarbon apparently identical with that obtained by Harris and Sanderson (J. Amer. Chem. Soc., 1948, 70, 208) by similar treatment of the two dihydro-dextropimaric acids.



Treatment of the epoxide or dibromide of dihydrorimuene with methyl magnesium iodide and subsequent selenium dehydrogenation gave 1:2:8-trimethylphenanthrene.



Beath, Lea (unpublished work, quoted by Beath), Wilmshurst and Cain (loc.cit.) have all shown that rimuene may be isomerised to isophyllocladene although the best yield recorded is only 8.5%, by the last worker.

Cain attempted a partial synthesis of rimuene from a sample of isodextropimaric acid, m.p. $162 - 164^{\circ}$, $[\alpha]_D^{17} - 1.5^{\circ}$ (C 8.21), $[\alpha]_D^{17} \pm 0^{\circ}$ (1% soln.) by conversion of the carboxyl group to a methyl group. The resulting hydrocarbon was obtained as an oil, b.p. $130^{\circ}/0.1$ m.m., $[\alpha]_D^{17} + 3.5^{\circ}$ (CHCl_3) whose infrared spectrum was very similar to, but in details distinct from, that of rimuene.

However, further work showed the starting acid to be non-homogeneous as optical resolution and recrystallisation gave two fractions. One had m.p. $163 - 165^{\circ}$, $[\alpha]_D^{17} - 84.8^{\circ}$; the other had m.p. $163-165^{\circ}$ $[\alpha]_D^{17} + 24.3^{\circ}$.

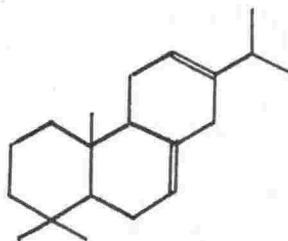
Robertson (Thesis, University of New Zealand.1956) converted a tetrahydroisodextropimaric acid to an oily hydrocarbon whose infrared spectrum differed fairly widely from that of tetrahydrorimuene, in particular, the bands due to the gem dimethyl group were absent.

Thus although degradative work has established the structure of rimuene with a reasonable degree of certainty, the partial synthesis awaits the preparation of pure resin acids. Physical constants. Rimuene, m.p. 55.5° , $[\alpha]_D$ 53.7° ; hydrochloride m.p. 63° ; nitrosochloride, m.p. $86 - 88^{\circ}$ (decomp.); tetrabromide, m.p. $55 - 60^{\circ}$; dihydrorimuene, m.p. 31° ; tetrahydrorimuene, m.p. 77° .

CUPRESSENE.

This minor diterpene was isolated by Briggs and Sutherland (J. Org. Chem., 1942, 7, 397) from the essential oil of *Cupressus macrocarpa*. The hydrocarbon, m.p. $74 - 75^{\circ}$, $[\alpha]_D$ $25^{\circ} + \text{lit.}$ $- 59.2^{\circ}$ (CHCl_3), gave a tetrahydro derivative, m.p. $56 - 57.5^{\circ}$, $[\alpha]_D$ $17^{\circ} + 62^{\circ}$ (CHCl_3) and a hydrochloride, m.p. $80 - 82^{\circ}$. Attempted dehydrogenation with a palladium catalyst at $270 - 280^{\circ}$ gave isophyllocladene as the sole product, isolated in 35% yield.

From examination of spectral data Cain showed that the diterpene is tricyclic and contains either two trisubstituted, or a tri- and a tetra-substituted double bond. From the ease of hydrogenation and isomerisation he deduced (2) as a possible structure.



(2)

MIRENE.

This tetracyclic hydrocarbon, $\text{C}_{20}\text{H}_{32}$, was obtained

from the essential oil of *Podocarpus ferrugineus*, 'miro,' (Briggs, Cawley, Loe and Taylor, J., 1950, 955, compare Hosking and Short, *Rec. Trav. Chim.*, 1928, 47, 834; Hosking, *ibid.*, 1930, 49, 1036 and Brandt, *N.Z.J. Sci. Tech.*, 1938, 20, 8).

The infrared spectrum of mirene is almost identical with that of phyllocladene (Wilmshurst, *loc.cit.*) and mirene is isomerised by acids to isophyllocladene. This worker has suggested that mirene has the same structure as phyllocladene, except that the hydrogen at C-13 occupies the equatorial configuration. Properties: Hydrocarbon, m.p. 59 - 60°, $[\alpha]_D^{20} + 43.8^\circ$ (CHCl_3); dihydro derivative, m.p. 65.6 - 66°; hydrochloride, m.p. 82° $[\alpha]_D^{15} + 59.9^\circ$ (CHCl_3).