195. *Diterpenes. Part III. The Diterpenes from* Podocarpus ferrugineus.

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The diterpene fraction of the essential oil of *Podocarpus ferrugineus* has been found to contain (+)-phyllocladene, (+)-kaurene, and a new dextrorotatory isomer, m. p. 59—60°. A re-examination of crude " mirene " and " mirene hydrochloride " (Hosking and Short, *Rec. Trav. chim.*, 1928, **47**, 834) showed them to contain phyllocladene and kaurene hydrochloride, respectively. It is evident that " mirene " was not homogeneous, and was probably impure *iso*phyllocladene. The name mirene has been transferred to the new isomer.

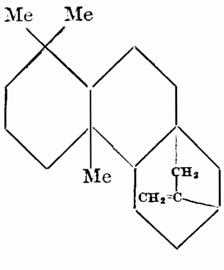
From the essential oil of *Podocarpus ferrugineus* (" miro ") Hosking and Short (*Rec. Trav. chim.*, 1928, **47**, 834) isolated an apparently new diterpene, mirene, m. p. 102—104°, $[\alpha]_{5461}^{15}$

+27·15°,[*] forming a monohydrochloride, m. p. 97—98°, from which the hydrocarbon was regenerated on treatment with alcoholic potassium hyroxide, and a dihydro-derivative, m. p. 73—74° (Hosking, *Rec. Trav. chim.*, 1930, **49**, 1036). Following an observation by one of us (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) that the m. p. of dihydromirene was the same as that of α-dihydrophyllocladene, suggesting a relationship between mirene and phyllocladene, samples of mirene hydrochloride and dihydromirene were submitted by Dr. J. R. Hosking to Mr. C. W. Brandt with the suggestion that they would prove identical with phyllocladene hydrochloride and α-dihydrophyllocladene, respectively. No depressions in m. p. were observed (Brandt, *New Zealand J. Sci. Tech.*, 1938, **20**, 8B) thus confirming the suggestion. Brandt also obtained a hydrocarbon, m. p. 103°, by treating the hydrochloride with alcoholic potassium hydroxide, which did not depress the m. p. of *iso*phyllocladene. His regenerated hydrocarbon was reported as lævorotatory, however, whereas *iso*phyllocladene is dextrorotatory, and from our experience in the kaurene series a strong depression should have been observed with the enantiomorphs. Brandt, however, in a private communication, has informed us that the rotation of his regenerated hydrocarbon was done on a micro-scale, and he would not insist that the rotation was negative under the experimental conditions.

It would appear therefore that mirene is an impure form of *iso*phyllocladene, the purest specimen of which has m. p. 112° (Briggs and Sutherland, *J. Org. Chem.*, 1942, **7**, 397).

With the kind permission of the late Dr. J. R. Hosking we have continued the investigation of the diterpene fraction of the essential oil of this species. In contrast with the results of Hosking and Short we have isolated, by fractional crystallisation, three diterpenes, (+)-phyllocladene, identified by mixed m. p. and Debye–Scherer patterns, (+)-kaurene, identified by Debye–Scherer patterns and conversion into (+)-*iso*kaurene, and a new diterpene, m. p. 59—60°, $[\alpha]_D^{20}$ +43·8° (monohydrochloride, m. p. 82°, and dihydro-derivative, m. p. 63—64°). Since the original mirene from this oil has been shown to be *iso*phyllocladene, we have transferred the name mirene to the new isomer. Like rimuene (McDowall and Finlay, *J. Soc. Chem. Ind.*, 1925, **44**, 42T), phyllocladene (Aitken, *J. Soc. Chem. Ind.*, 1928, **47**, 223T), and cupressene (Briggs and Sutherland, *loc. cit.*), mirene is isomerised by glacial acetic acid into *iso*phyllocladene. Mirene gives a strong m. p. depression when mixed with rimuene and its Debye–Scherer pattern shows that it is neither identical with nor an enantiomorph of α-cryptomerene from *Cryptomeria japonica* (Uchida, *Bull. Forest Expt. Stat. Meguro, Tokyo*, 1915, Reprint) for a sample of which we are greatly indebted to Professor Uchida.

Through the courtesy of Professor L. Ruzicka, to whom we are greatly indebted, we have been able to re-examine some of the original material of Hosking and Short. A sample of " crude mirene," m. p. 60—70°, on crystallisation afforded (+)-phyllocladene, identified through mixed m. p., rotation, and conversion into *iso*phyllocladene and α-dihydrophillocladene. On the other hand, a sample of " mirene hydrochloride," m. p. 94°, yielded (+)-kaurene hydrochloride, m. p. 116°, on crystallisation, identified through its m. p., rotation, and conversion into (+)-*iso*kaurene, undepressed in m. p. by an authentic specimen. With the small amount of material at our disposal it was not possible to examine the mother liquors for mirene.



Brandt [already reported by one of us (Briggs, *Proc. Roy. Soc. New South Wales*, 1947, **80**, 154)] has adduced evidence for the inset structure for phyllocladene. Four stable geometrical isomerides of this structure may occur, each in (+)- and (—)-forms, and it would appear that a number of naturally occurring diterpenes are stereoisomers of the same general pattern.

Kaurene is isomerised by boiling glacial acetic acid into *iso*kaurene but with boiling alcoholic sulphuric acid it is converted into the γ-isomer, m. p. 196—198°, reported by Nishida and Uoda (*Bull. Agric. Soc. Japan*, 1930, **1**, Nos. 1—3), under conditions which left *iso*phyllocladene unchanged. *iso*Kaurene does not depress the m. p. of kaurene and forms a eutectic containing 60% kaurene and 40% *iso*kaurene.

EXPERIMENTAL.

The leaves and terminal branchlets of *Podocarpus ferrugineus* (140 lb.), collected at Mangapehi in June through the courtesy of Mr. G. R. Hammond, State Forest Service, to whom we are greatly indebted, produced 95 g. (0·15% yield) of a pale yellow oil on steam distillation. The oil was distilled

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[*] The lævorotation of mirene reported by one of us (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) and Brandt (*New Zealand J. Sci. Tech.*, 1938, **20**, 8B) is an error.

in a Bower and Cooke type of column (*Ind. Eng. Chem. Anal.*, 1943, **15**, 290), the lower terpene fractions at 20 mm. and the higher fractions at 3·5 mm., the bath temperature not rising above 215° at any stage. No attempt was made to separate the constituents below the diterpene fraction. The following major fractions were obtained :

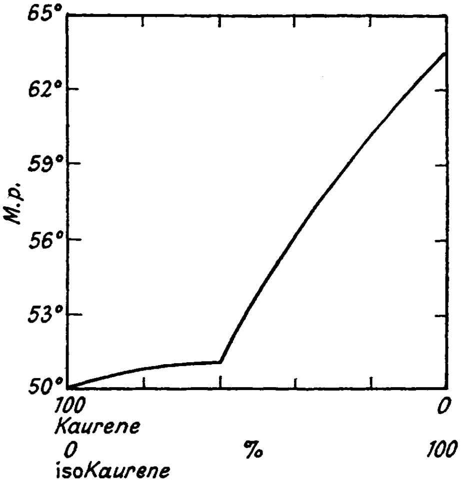
Fraction.	B. p.	n_D^{25}.	Wt., g.
I	<47°/20 mm.	1·464	37·8
II	45—125/3·5 mm.	1·464 ~ 1·492	11·3
III	130—160/3·5 mm.	1·514	13·0

The residual brown oil (45 g.) solidified (m. p. *ca.* 40—45°) and was investigated for diterpenes. Separation of this material into three constituents was only achieved by a long series of systematic fractional crystallisations from ethyl acetate and both alcohol and absolute alcohol. Coloured material which hindered crystallisation was removed at certain stages by chromatographing solutions in light petroleum through a 20 × 1 cm. column of alumina. By this means the following constituents were obtained.

(+)-*Phyllocladene.*—The small amount of pure material (<400 mg.) had m. p. and mixed m. p. with authentic (+)-phyllocladene (from *Araucaria excelsa*) 96°, whilst the Debye–Scherer diagrams were identical.

(+)-*Kaurene.*—Only 1·1 g. were obtained in a pure state ; it had m. p. 49° and $[\alpha]_D^{20}$ +101° ($l = 1$; c, 1·5 in chloroform). It gave a m. p. depression when mixed with (−)-kaurene (from *Agathis australis*) but the Debye–Scherer diagrams were identical.

A sample of the diterpene isolated from the essential oil of *Podocarpus spicatus* by Butler and Holloway (*J. Soc. Chem. Ind.*, 1939, **58**, 223) was kindly sent to us for comparison. It proved to be lævorotatory whilst the Debye–Scherer diagram indicated that it was mixture of kaurene and *iso*kaurene.



The melting-point diagram for mixtures of kaurene and *iso*kaurene, showing a eutectic at 40% kaurene + 60% *iso*kaurene, is given in the figure.

Isomerisation of Kaurene.—(a) *With glacial acetic acid.* (−)-Kaurene (100 mg., from *Agathis australis*), dissolved in glacial acetic acid (6 c.c.), was gently heated under reflux for 1¼ hours. The product separating on cooling, after repeated crystallisation from alcohol, formed plates, m. p. and mixed m. p. with (−)-*iso*kaurene 64°. The enantiomorph, of the same m. p., was similarly obtained from (+)-kaurene.

(b) *With alcoholic sulphuric acid.* (−)-Kaurene (100 mg.), dissolved in alcohol (9 c.c.) and concentrated sulphuric acid (3 drops), was heated under reflux for 6½ hours. The material separating on cooling was crystallised repeatedly from alcohol and then formed prismatic needles, m. p. 196—198° [Found : *M* (micro-Rast), 266, 268. Calc. for $C_{20}H_{32}$: *M*, 272].

Mirene.—This is apparently the diterpene occurring in the greatest amount, and 3·2 g. of pure material were obtained. No alteration in m. p. could be achieved by repeated crystallisation from ethyl acetate or alcohol from which *mirene* separated in rectangular plates, or in any fraction after chromatographing the solution through a 20-cm. column of alumina (Brockmann, grade I). The Debye–Scherer diagram also indicated homogeneity and proved that it was not identical with cryptomerene of similar m. p. (Found : C, 88·5; H, 12·3. $C_{20}H_{32}$ requires C, 88·2 ; H, 11·8%), $[\alpha]_D^{20}$ +43·8° ($l = 1$, c, 4·1 in chloroform).

Isomerisation of mirene to iso*phyllocladene.* Mirene (100 mg.) was heated in glacial acetic acid solution (10 c.c.) for 6 hours. The solid separating on cooling, after recrystallisation from alcohol (charcoal), formed needles, m. p. 110°, undepressed by *iso*phyllocladene, $[\alpha]_D^{20}$ +23·08° ($l = 0·25$, $c = 0·2$ in chloroform). Briggs (*J.*, 1937, 79) records $[\alpha]_D^{17}$ +23·4° for *iso*phyllocladene.

Dihydromirene. A solution of mirene (100 mg.) in glacial acetic acid (15 c.c.) was hydrogenated at 34 lb. per sq. in. pressure for 16 hours in the presence of palladised charcoal (100 mg.). After concentration of the filtered solution, *dihydromirene* separated in plates which, after repeated crystallisation from glacial acetic acid, had m. p. 63—64° (Found : C, 87·4; H, 12·7. $C_{20}H_{34}$ requires C, 87·6; H, 12·4%).

Mirene hydrochloride. Dry hydrogen chloride was passed through a solution of mirene (100 mg.) in glacial acetic acid (2 c.c.) and dry ether (0·5 c.c.) cooled in ice. The colourless solid which formed was washed with glacial acetic acid and ethyl acetate and recrystallised from ethyl acetate to a constant m. p. The *hydrochloride* had m. p. 82°, $[\alpha]_D^{15}$ +59·9° ($l = 1$; c, 0·4 in chloroform) (Found : Cl, 12·0. $C_{20}H_{32}$,HCl requires Cl, 11·5%).

Re-examination of Hosking and Short's Material.—Isolation of phyllocladene. A sample (450 mg.) of Hosking and Short's material, labelled " crude mirene," had m. p. 60—70°. On crystallisation from absolute alcohol this formed plates, m. p. 91—93° (yield, 400 mg.), raised by further crystallisation to m. p. 95—96° (yield, 300 mg.) and two further crystallisations to a constant m. p. 96—97°, undepressed by authentic (+)-phyllocladene, $[\alpha]_D^{16}$ +15·5° ± 2° ($l = 1$; c, 2·27 in chloroform).

The purified material (40 mg.) was heated under reflux with alcoholic sulphuric acid (2 c.c. ; 10% solution) for ½ hour. The plates separating on cooling, after recrystallisation from absolute alcohol, formed needles, m. p. 111—112°, undepressed by authentic (+)-*iso*phyllocladene, $[\alpha]_D^{16}$ +23·5° ± 2° ($l = 1$; c, 1·92 in chloroform).

The purified material (60 mg.) was hydrogenated in glacial acetic acid solution in the presence of platinum oxide. Concentration of the filtered solution afforded needles, which, after recrystallisation from the same solvent, had m. p. 70—71°, undepressed by an authentic sample of (+)-α-dihydrophyllocladene (Found: C, 87·1; H, 12·4. Calc. for $C_{20}H_{34}$: C, 87·5; H, 12·5%), $[\alpha]_D^{13}$ +21° ± 2° ($l = 1$; c, 1·12 in chloroform).

Isolation of kaurene derivatives. A sample of Hosking and Short's "mirene hydrochloride" had m. p. 94°, raised to 115—116° by a single crystallisation from ethyl acetate and to 116° by a further crystallisation (Found: C, 77·7; H, 10·9. Calc. for $C_{20}H_{32}$,HCl: C, 77·8; H, 10·8%), $[\alpha]_D^{21}$ +38·5° ± 1° ($l = 1$; c, 2·0 in chloroform). In Part I (*J.*, 1948, 1888) values of m. p. 114—115° and $[\alpha]_D^{20}$ −40·0° are recorded for (−)-kaurene hydrochloride.

The hydrochloride (100 mg.) was heated under reflux with alcoholic sodium hydroxide (5 c.c.; 3% solution) for 3 hours. After addition of water, the diterpene was extracted with chloroform and repeatedly crystallised from absolute alcohol, from which it separated in plates or needles, m. p. 64—65°, undepressed by authentic (+)-*iso*kaurene (Found: C, 88·0; H, 11·7. Calc. for $C_{20}H_{32}$: C, 88·2; H, 11·8%), $[\alpha]_D^{21}$ +31° ± 2° ($l = 1$; c, 1·79 in chloroform). In Part I (*loc. cit.*) a value of $[\alpha]_D^{20}$ −25·9° is recorded for (−)-*iso*kaurene.

The analyses are by Drs. Weiler and Strauss, Oxford, Mr. Manser, Zürich, and Mr. Seelye of this department.

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