675. *The Isolation and Structure of Flavesone*

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Flavesone, a new β-triketone which is shown to have structure (II), has been found accompanying its higher homologue leptospermone (III) in the essential oils of *Leptospermum flavescens* Sm. and *Eucalyptus decorticans* Maiden.

The essential oils of certain *Leptospermum* species from Australia and New Zealand contain the carbonate-soluble β-triketone leptospermone, to which structure (I) was ascribed from degradative and synthetic evidence.[1,2] We have further examined the carbonate-soluble fraction of a sample of oil from *L. flavescens*, from which the original isolation of leptospermone was reported by Penfold.[1] The presence of two closely similar compounds was indicated by gas chromatography and supported by the mass spectrum, which showed ions of mass numbers 266 and 252. The loss of a methylene group from leptospermone would be most unexpected, so that the spectrum suggests the presence of a lower homologue of leptospermone along with leptospermone itself.

Attempts to separate the mixture by fractional distillation, by crystallisation of various derivatives, or by counter-current distribution of the copper salts were only partly successful. An almost complete separation was eventually achieved by preparative g.l.c., and the major component, present in almost double the amount of the minor, proved to be identical with an authentic specimen of leptospermone.

The minor component of the carbonate-soluble fraction, for which the name flavesone is proposed, gave analyses indicative of a lower homologue of leptospermone. From its u.v. spectrum flavesone has a conjugated structure and thus appears to exist largely as an enolic tautomer, (IIa) or (IIb). This conclusion is supported by its i.r. spectrum, which shows peaks at 1726 and 1672 cm.$^{-1}$, and a broad band at 1564 cm.$^{-1}$, corresponding to carbonyls which are unconjugated, conjugated, and conjugate-chelated, respectively. In its n.m.r. spectrum flavesone shows an absorption corresponding to one proton at δ 18·3—18·5 which is characteristic of enolic protons in a very strong chelated bond.[3,4] A symmetrical heptet centred at δ 3·82 (J = 7 c./sec.) is assigned to the methine proton of the

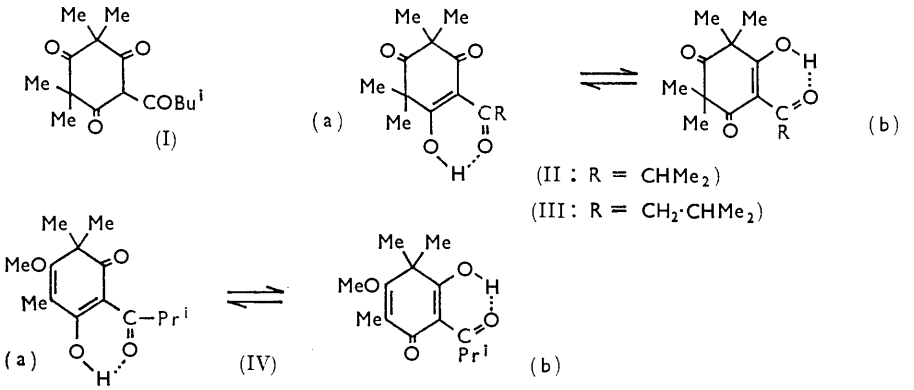
[1] A. R. Penfold, *J. Proc. Roy. Soc. New South Wales*, 1921, **45**, 51; W. F. Short, *J. Soc. Chem. Ind.*, 1926, **45**, 961; L. H. Briggs, A. R. Penfold, and W. F. Short, *J.*, 1938, 1193; L. H. Briggs, C. H. Hassall, and W. J. Taylor, *J.*, 1948, 383.

[2] L. H. Briggs, C. H. Hassall, and W. F. Short, *J.*, 1945, 706.

[3] R. O. Hellyer, I. R. C. Bick, R. G. Nicholls, and H. Rottendorf, *Austral. J. Chem.*, 1963, **16**, 703—708.

[4] S. Forsén and M. Nilsson, *Acta Chem. Scand.*, 1959, **13**, 1383; R. W. Hay and P. P. Williams, *J.*, 1964, 2270.

isobutyryl side-chain, while a doublet around δ 1·17 (J = 7 c./sec.) corresponds to the six adjacent *gem*-dimethyl protons. Two signals of almost equal intensity at δ 1·43 and 1·37, corresponding to twelve protons, are assigned to the ring methyls, and of these signals



it seems reasonable to assign the latter one to the pair of methyls between the carbonyl groups. Since a rapid interchange between the extreme ring conformations can be expected, each pair of methyls gives rise to a single time-averaged signal, as if the ring were, in fact, planar. On the other hand it is expected that the tautomeric enols (IIa) and (IIb) would interchange at a negligible rate in neutral solution; in the analogous case of tasmanone, it has been shown[3] that the chelated enols (IVa) and (IVb) are very stable and that tautomerism between them is very slow. In consequence, the ring methyls of flavesone appear as two separate signals.

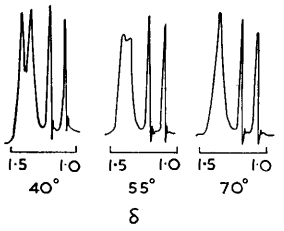
On the addition of a trace of base such as ammonia gas, the two ring-methyl peaks are replaced by a sharp singlet with a chemical shift (δ 1·40) which is the average of the two previous signals. This behaviour can be expected, if as a result of base catalysis, the rate of interconversion of the two tautomers (IIa) and (IIb) is sufficiently increased for a single time-averaged signal to be observed.[5] When a small amount of deuterodimethyl sulphoxide is added to the solution of flavesone, the two ring-methyl peaks (δ 1·42 and 1·38) and the enolic-proton peak (δ 18·3) are broadened and flattened. This probably results from a change in the hydrogen bonding of the enolic proton and an increase in the rate of interconversion of the two tautomers. As the temperature of the solution is increased to 70°, the two ring-methyl signals gradually coalesce into a single peak, indicating that the positions of the signals are dependent upon the rate of tautomerism (Figure). In the absence of deuterodimethyl sulphoxide two separate sharp signals are still observed even at 120° in 1,1,2,2-tetrachloroethane solution.

From its u.v. spectrum, leptospermone also exists largely as an enolic tautomer, (IIIa) or (IIIb).[2] This conclusion is supported by its i.r. spectrum, which shows peaks at 1718 and 1669 cm.$^{-1}$, and a broad band at 1535 cm.$^{-1}$ corresponding to the same types of carbonyls present in flavesone. An absorption corresponding to one proton at δ 18·3—18·5 (somewhat concentration dependent) in the n.m.r. spectrum of leptospermone indicates that it exists entirely in the chelated enolic form like flavesone. A doublet (δ 2·87; J = 7 c./sec.), equivalent to two protons, is assigned to the side-chain methylene group, flanked by a carbonyl and coupled to a methine proton, while another doublet (δ 0·98; J = 7 c./sec.), equivalent to six protons, is assigned to the side-chain *gem*-dimethyl coupled to the same methine proton. Two signals of almost equal intensity (δ 1·38 and 1·42), corresponding to twelve protons, are assigned to the ring methyls, as for flavesone.

[5] I. R. C. Bick and D. H. S. Horn, to be published.

Alkaline hydrolysis of flavesone gave isobutyric acid, identified by analytical g.l.c. and by preparation of the amide, and 1,1,3,3-tetramethylphloroglucinol, identified by comparison with an authentic sample. Synthetic flavesone, prepared by a method analogous to that of Jain and Seshadri [6] for leptospermone, was identical with the natural material in its g.l.c. retention time and its i.r. and n.m.r. spectra; the copper derivatives were identical (mixed melting point).

We have examined several other leptospermone-containing oils for flavesone. An alkali-soluble fraction of the oil from a New Zealand *Leptospermum* species, kindly provided



Effect of temperature on a portion of the n.m.r. spectrum of flavesone in $CDCl_3$ containing a trace of $(CD_3)_2SO$

by Professor L. H. Briggs, and the corresponding fraction from *Xanthostemon chrysanthus* F. Muell were each found by analytical g.l.c. to contain leptospermone only, but the corresponding fraction of the oil of *Eucalyptus decorticans* contained flavesone in 40 : 60 ratio with leptospermone.

Experimental

Microanalyses were carried out by Dr. K. W. Zimmermann, C.S.I.R.O. Microanalytical Laboratory, Melbourne. A Bodenseewerk Perkin-Elmer Fractometer model 116 was used for g.l.c. separations. N.m.r. spectra were run on a Varian Associates A60 spectrometer with tetramethylsilane as internal reference standard at δ 0·00; unless otherwise stated, measurements were made in deuterochloroform solution.

Isolation of Leptospermone and Flavesone.—(*a*) *From* Leptospermum flavescens. Leaves and terminal branchlets of *L. flavescens*, collected at Pymble, New South Wales, when steam-distilled in a tin-lined still yielded an oil (1·8%) which had the following constants: d_{15}^{15} 0·9235, n_D^{20} 1·4916, α_D^{20} +13·9°. The oil was dissolved in ether and washed first with saturated aqueous sodium hydrogen carbonate to remove acids, then with aqueous sodium carbonate (3 times, 5%). The oil recovered by acidifying the carbonate extracts amounted to 6% of the original oil; analytical g.l.c. indicated two compounds in the ratio 65 : 35. These were separated on a 6 ft. × ¼ in. aluminium column at 190° with Apiezon L as stationary phase and helium as carrier gas. The major fraction, collected at the outlet in a cooled trap, was identical with an authentic specimen of leptospermone in retention time and i.r. and n.m.r. spectra. The minor fraction consisted of flavesone.

(*b*) *From* Eucalyptus decorticans. From leaves and terminal branchlets of *E. decorticans*, collected at Yarraman, Queensland, an oil (0·25%) with the following constants was obtained by steam-distillation: d_{15}^{15} 0·9105, n_D^{20} 1·4855, α_D^{20} +8·0°. It contained 14% of a mixture of leptospermone and flavesone in the ratio 60 : 40, which was separated as before. The *copper salt* of leptospermone, prepared by the method of Birch and Elliott [7] and recrystallised from methanol, gave royal blue crystals, m. p. 163·5—164° (Found: C, 60·8; H, 6·8. $C_{30}H_{42}CuO_8$ requires C, 60·6; H, 7·1%).

Isolation of Leptospermone from Xanthostemon chrysanthus.—Leaves and terminal branchlets of *X. chrysanthus* collected at Babinda, Queensland, yielded, on a steam-distillation, an oil (0·4%) with the following constants: d_{15}^{15} 1·046, n_D^{20} 1·4987. The crude oil was found by the above extraction methods to contain 90% of leptospermone. No flavesone was detected in the carbonate-soluble portion.

[6] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1955, **42***A*, 279.
[7] A. J. Birch and P. Elliott, *Austral. J. Chem.*, 1956, **9**, 95.

Characterisation of Flavesone.—*Flavesone* is a very pale yellow, rather viscous liquid, almost odourless, b. p. 134°/10 mm., d_4^{20} 1·098, n_D^{20} 1·5010, $\lambda_{max.}$ 234, 280 mμ (log $\varepsilon_{max.}$ 4·6, 4·5, in cyclohexane), $\nu_{max.}$ 2989, 2942, 2885, 1726, 1672, 1564b, 1470, 1457, 1385, 1378, 1326, 1242, 1186, 1095, 1060, 1010, 967, 943, 895, 862, 841, 805, 781 cm.$^{-1}$ (liquid) (Found: C, 66·5; H, 7·8. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%). The *copper salt*, prepared by the method of Birch and Elliott,[7] afforded dark blue prisms, m. p. 203—204°, and pale blue needles, m. p. 182—184°, when recrystallised from methanol (Found, for prisms: C, 59·7; H, 6·8. $C_{28}H_{38}CuO_8$ requires C, 59·4; H, 6·8%). The *needle form*, when dried at 50° *in vacuo*, gave the prism form (Found, for needles: loss on drying, 2·8. $C_{28}H_{38}CuO_8,H_2O$ requires H_2O, 3·1%). p-*Toluidinoflavesone*, prepared by a method similar to that of Briggs, Hassall, and Short,[2] crystallised from light petroleum as prisms, m. p. 121—123° (Found: C, 74·0; H, 7·7; N, 4·1. $C_{21}H_{27}NO_3$ requires C, 73·8; H, 8·0; N, 4·1%).

Degradation of Flavesone.—A solution of flavesone (110 mg.) in hydrochloric acid (30 c.c.; 10N) was refluxed for an hour, diluted with water, and partly distilled. The distillate (25 c.c.) was extracted with ether, the ether solution re-extracted with aqueous sodium hydrogen carbonate (5%), and the sodium hydrogen carbonate solution acidified and again extracted with ether. Removal of the ether left an acidic oil (20 mg.) which was in part converted into its methyl ester by heating in a sealed tube with methanol and boron trifluoride. The ester on gas chromatography, gave a single peak the retention time of which was identical with that of methyl isobutyrate. The remainder of the oil was converted into the amide, m. p. 127—128°. The residual solution from the above distillation was filtered and extracted with chloroform (4 × 10 c.c.). The solid residue left after removal of the chloroform was recrystallised from aqueous methanol (1 : 1) and sublimed (at 170° at atmospheric pressure). The product (10 mg.) had m. p. 180—182°, alone and in admixture with an authentic sample of 1,1,3,3-tetramethylphloroglucinol.

Synthesis of Flavesone.—A solution of phloroisobutyrophenone (3·7 g., prepared by a Hoesch synthesis [8]) in methanolic sodium methoxide (3·0 g. Na; 40 c.c.) was refluxed with methyl iodide (20 c.c.) for 3 hr. After removal of the solvents *in vacuo*, the residue was treated with dilute hydrochloric acid and extracted with ether. The ether solution was washed with dilute aqueous sodium sulphite, dried (Na_2SO_4), and evaporated. Distillation of the residue afforded a main fraction (2·2 g.), b. p. 134°/10 mm., identical with flavesone in g.l.c. retention time and i.r. and n.m.r. spectra. The m. p. of the copper derivative was not depressed on admixture with that from natural flavesone.

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[8] K. C. Gulati, S. R. Seth, and K. Venkataraman, *Org. Synth.*, 1935, **15**, 70; P. E. Spoerri and A. S. DuBois, *Org. Reactions*, 1949, **5**, 387.