

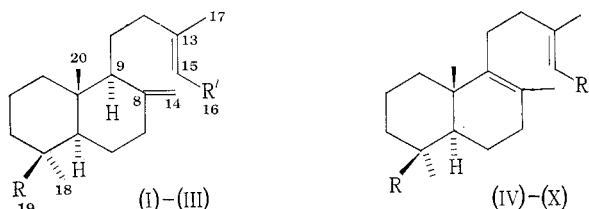
## DITERPENOIDS

### XX.\* 16,19-DIOXYGENATED LABDA-8,13(15)-DIENES

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During attempts<sup>1</sup> to synthesize C16-monomethyl agathate (I) (16-methoxycarbonyl-*trans*-labda-8(14),13(15)-dien-19-oic acid)‡ we followed the published<sup>3</sup> method of treating agathic acid (II) with sulphuric acid in methanol. This method failed to give the required monoester (I), but gave rather the  $\Delta^{8(9)}$  isomer (IV) which, from p.m.r. studies, comprised more than 80% of the equilibrium mixture. Attempted separation of the equilibrium mixture by silica gel chromatography was unsuccessful. However, hydrolysis gave the disodium salt (V) which could be recrystallized, and the free acid (VI) was regenerated by ion-exchange chromatography.



	R	R'		R	R'
(I)	COOH	COOMe	(IV)	COOH	COOMe
(II)	COOH	COOH	(V)	COONa	COONa
(III)	CH <sub>2</sub> OH	COOH	(VI)	COOH	COOH
			(VII)	COOMe	COOH
			(VIII)	COOMe	COOMe
			(IX)	CH <sub>2</sub> OH	CH <sub>2</sub> OH
			(X)	CH <sub>2</sub> OH	COOH

Since the migration of the 8(14) double bond of agathic acid into the endocyclic position is an acid-catalysed reaction in a series where such reactions are biogenetically important, we felt it desirable to synthesize a series of  $\Delta^{8(9)}$  compounds and to look for these derivatives in nature. The monoesters (IV) and (VII), the diester

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‡ The nomenclature of the diterpenoids is under review (Rowe, J. W., personal communication). Systematic names in this paper follow those laid down<sup>2</sup> for earlier papers in this series.

<sup>1</sup> Carman, R. M., and Marty, R. A., *Aust. J. Chem.*, 1966, **19**, 2403.

<sup>2</sup> Carman, R. M., *Aust. J. Chem.*, 1966, **19**, 629.

<sup>3</sup> Arya, V. P., Erdtman, H., and Kubota, T., *Tetrahedron*, 1961, **16**, 255.

(VIII), and the diol (IX) were prepared by procedures similar to those used for agathic acid derivatives. Isomerization of agathic acid (III) with sulphuric acid in methanol yields the corresponding isomer (X).

Compounds in the  $\Delta^{8(9)}$  series gave infrared spectra practically superimposable upon the spectra of their 8(14) analogues, with the exception that the endocyclic compounds showed no 890 or 3080  $\text{cm}^{-1}$  bands. The p.m.r. spectra of endocyclic isomers are listed in Table 1. As expected,<sup>2</sup> the compounds of the  $\Delta^{8(9)}$  series all had large positive rotations with  $[M]_D$  around  $+380^\circ$  for derivatives with a C19 ester or acid function, and with  $[M]_D$  about  $+200^\circ$  for the C19 alcohols.

TABLE 1  
P.M.R. VALUES ( $\tau$ )  
d, doublet; t, triplet

Com- pound	Sol- vent	C20- CH <sub>3</sub>	C18- CH <sub>3</sub>	C14- CH <sub>3</sub>	C17- CH <sub>3</sub>	C15- CH	Others
(IV)	CCl <sub>4</sub>	9.17	8.75	8.42	7.85	4.37	6.37 (OCH <sub>3</sub> )
(VI)	CDCl <sub>3</sub>	9.14	8.75	8.42	7.82	4.34	
(VII)	CCl <sub>4</sub>	9.25	8.84	8.40	7.82	4.34	6.40 (OCH <sub>3</sub> )
(VIII)	CCl <sub>4</sub>	9.22	8.79	8.35	7.79	4.25	6.40, 6.37 ( $2 \times \text{OCH}_3$ )
(IX)	CDCl <sub>3</sub>	9.07	9.02	8.45	8.30	4.59*	6.54, 6.26 (C19, $2 \times d$ , $J$ 11 Hz), 5.86 (C16, $d$ , $J$ 7 Hz)
(X)	CDCl <sub>3</sub>	9.04	8.99	8.40	7.79	4.27	6.49, 6.23 (C19, $2 \times d$ , $J$ 10 Hz)

\* t,  $J$  7 Hz.

Gas chromatographic studies of the resins of black kauri and of *Agathis robusta*<sup>4</sup> failed to show the presence of any members of the  $\Delta^{8(9)}$  series.

### Experimental

P.m.r. spectra were recorded at 60 MHz with tetramethylsilane as an internal standard. Infrared spectra were obtained in Nujol mulls except where indicated. Optical rotations and ultraviolet spectra were measured in ethanol solutions.

#### Isomerization of Agathic Acid

Agathic acid (II) (5 g), absolute methanol (125 ml), and conc. sulphuric acid (2.5 ml) were refluxed for 5 hr. The reaction mixture was poured into iced water (1 l.) and extracted with ether (6  $\times$  100 ml). The combined ether extracts were concentrated at reduced pressure to give a yellow viscous oil,  $[\alpha]_D +71^\circ$ . Filtration through a charcoal column gave a clear oil,  $[\alpha]_D +76^\circ$ , with p.m.r. spectrum superimposable on that of 16-methoxycarbonyl-*trans*-labda-8,13(15)-dien-19-oic acid (see below) but with additional signals (vinyl impurities) at 5.08 and 5.4  $\tau$ . Chromatography on silica gel gave the unseparated mixture from hexane-acetone (19:1).

#### *trans*-Labda-8,13(15)-diene-16,19-dioic Acid

The crude monomethyl esters (5 g), methanol (125 ml), and aqueous sodium hydroxide (25%, 20 ml) were refluxed for 15 min. The reaction mixture was concentrated to 20 ml at reduced pressure and the sodium salts allowed to crystallize. After two recrystallizations from aqueous *t*-butanol (water : *t*-butanol 1 : 4), the sodium salt was passed through a Zeocarb 225 ion-exchange column (in the acid form) in aqueous methanol (1 : 1). Slow removal of the methanol gave fine needles, which on recrystallization (aqueous acetone) gave *trans*-labda-8,13(15)-diene-16,19-dioic

<sup>4</sup> Cowley, D. E., Ph.D. Thesis, University of Queensland, 1967.

acid (VI), m.p. 178–180°,  $[\alpha]_D +112^\circ$  (Found: C, 71.7; H, 9.1.  $C_{20}H_{30}O_4$  requires C, 71.8; H, 9.0%).  $\lambda_{\max}$  215 m $\mu$  ( $\epsilon$  16000).  $\bar{\nu}$  1690, 1630, 1250, 1190, 1160, 910, 860, 790  $\text{cm}^{-1}$ .

*16-Methoxycarbonyl-trans-labda-8,13(15)-dien-19-oic Acid*

The acid (VI) (1 g, 0.003 mole) in ether was treated with ethereal diazomethane (0.003 mole). The ether was removed at reduced pressure and the residue extracted with hexane. The hexane-soluble fraction was distilled (150°/0.1 mm) to give *16-methoxycarbonyl-trans-labda-8,13(15)-dien-19-oic acid* (IV) as a viscous oil;  $[\alpha]_D +106^\circ$  (Found: C, 72.6; H, 9.5.  $C_{21}H_{32}O_4$  requires C, 72.4; H, 9.3%).  $\lambda_{\max}$  215 m $\mu$  ( $\epsilon$  14700).  $\bar{\nu}$  (film) 1725, 1690, 1645, 1260, 1230, 1150, 1040, 920, 860  $\text{cm}^{-1}$ .

*Dimethyl trans-Labda-8,13(15)-diene-16,19-dioate*

The acid (VI) was methylated with excess diazomethane in the usual manner. Chromatography of the product over neutral alumina gave a clear oil (from hexane), which was rapidly distilled (0.1 mm) to give *dimethyl trans-labda-8,13(15)-diene-16,19-dioate* (VIII),  $[\alpha]_D +112^\circ$  (Found: C, 72.8; H, 9.5.  $C_{22}H_{34}O_4$  requires C, 72.9; H, 9.5%).  $\lambda_{\max}$  215 m $\mu$  ( $\epsilon$  16500).  $\bar{\nu}$  (film) 1725, 1645, 1355, 1330, 1225, 1145, 1035, 920, 860, 770  $\text{cm}^{-1}$ .

*19-Methoxycarbonyl-trans-labda-8,13(15)-dien-16-oic Acid*

The dimethyl ester (VIII) (0.6 g) in ether (20 ml) was stirred with aqueous sodium hydroxide (40%, 5 ml) in a stoppered flask for 3 days at 25°. The mixture was diluted with water, washed with ether, and the aqueous layer then treated with excess Zeocarb 225 ion-exchange resin (in the acid form). Extraction with ether gave the crude monomethyl ester. Slow distillation (0.1 mm) gave *19-methoxycarbonyl-trans-labda-8,13(15)-dien-16-oic acid* (VII) as an oil which crystallized, m.p. 116–119°,  $[\alpha]_D +110^\circ$  (Found: C, 72.1; H, 9.3.  $C_{21}H_{32}O_4$  requires C, 72.4; H, 9.3%).  $\lambda_{\max}$  215 m $\mu$  ( $\epsilon$  13700).  $\bar{\nu}$  1730, 1700, 1640, 1265, 1245, 1180, 1160, 1150, 1040, 910, 870, 770, 600  $\text{cm}^{-1}$ .

*trans-Labda-8,13(15)-diene-16,19-diol*

To the dimethyl ester (VIII) (1 g) in dry ether (60 ml) lithium aluminium hydride (1 g) was added with shaking. The reaction mixture was refluxed for 6 hr and stood for a further 24 hr. Normal work-up procedure gave *trans-labda-8,13(15)-diene-16,19-diol* (IX), m.p. 148.5–149.5° (from diisopropyl ether),  $[\alpha]_D +70^\circ$  (Found: C, 78.6; H, 11.3.  $C_{20}H_{34}O_2$  requires C, 78.4; H, 11.2%).  $\bar{\nu}$  3250, 1045, 1030, 1005  $\text{cm}^{-1}$ .

*19-Hydroxy-trans-labda-8,13(15)-dien-16-oic Acid*

Agatholic acid (III) (1 g), absolute methanol (25 ml), and sulphuric acid (0.5 ml) were refluxed for 5 hr. Aqueous sodium hydroxide (5% 15 ml) was added and reflux continued for 4 hr. The reaction mixture was poured into water, acidified (2N HCl), and extracted with ether. The ether extract gave a crystalline product, which on recrystallization (ethyl acetate) and sublimation (0.1 mm) gave *19-hydroxy-trans-labda-8,13(15)-dien-16-oic acid* (X), m.p. 130–132°,  $[\alpha]_D +62^\circ$ . (Found: C, 75.0; H, 10.0.  $C_{20}H_{32}O_3$  requires C, 75.0; H, 10.1%).  $\lambda_{\max}$  210 m $\mu$  ( $\epsilon$  12500).  $\bar{\nu}$  3325, 1700, 1645, 1250, 1030  $\text{cm}^{-1}$ .

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