DITERPENOIDS

X.* *cis-* AND *trans-*BIFORMENE

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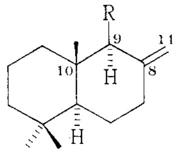
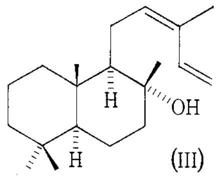
Summary

cis- and *trans-*Biformene have been synthesized by the dehydration of abienol, manool, and sclareol. Both *cis-* and *trans-*biformene are naturally occurring hydrocarbons.

INTRODUCTION

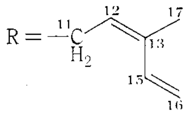
Biformene (I) has been isolated[1] from the wood of *Dacrydium biforme* and has been synthesized[1] by the dehydration of manool (II). Manool (II) is also present in *D. biforme* and, from biogenetic considerations, the naturally occurring biformene is expected to be a mixture of *cis* and *trans* isomers (Ia and Ib) and the synthetic product should also contain both isomers. This paper describes syntheses of both *cis-* and *trans-*biformene.



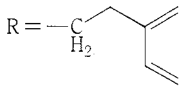


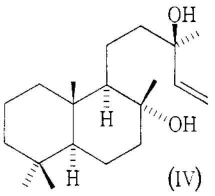
(III)

(Ia)



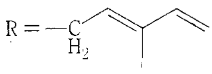
(Ic)



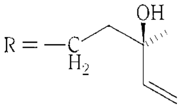


(IV)

(Ib)



(II)



DISCUSSION

Abienol (III) which is known[2] to have a *cis*-olefinic side-chain provides a good starting point for the synthesis of *cis*-labda-8(14),12,15-triene (Ia; *cis*-biformene). Dehydration of abienol with phosphorus oxychloride in pyridine[3] at 0° gave the

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* Part IX, *Aust. J. Chem.*, 1966, **19**, 2403.

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expected mixture of double-bond isomers.[4,5] Gas chromatography showed that the mixture contained about 90% of the exocyclic isomer (Ia) and about 10% of the 7(8)-trisubstituted and 8(9)-tetrasubstituted isomers. Chromatography of the mixture on silica gel impregnated with silver nitrate[6] gave the pure exocyclic isomer (Ia) as a low-melting crystalline solid whose physical constants (i.r., u.v., p.m.r. spectra) agree well with those recorded in the literature for similar *cis*-compounds[2,7,8] (see Table 1).

In an attempt to obtain the pure *trans*-isomer, manool (II) was dehydrated with phosphorus oxychloride in pyridine to give a mixture of double-bond isomers. Gas chromatography showed the mixture to consist of three major isomers. The first had a retention time identical with that of authentic *cis*-biformene and chromatography of the mixture over alumina impregnated with silver nitrate gave crystalline *cis*-biformene. Further chromatography of the mixture gave the second double-bond isomer, *trans*-labda-8(14),12,15-triene (Ib; *trans*-biformene). The third isomer was expected, by analogy with the mild dehydration of linalool and nerolidol,[9] to have the 8(14),13(17),15-triene structure (Ic) (sclarene[1]). A compound of this structure has been recently isolated[10] from the leaf oil of *Agathis australis* and a direct comparison of the compound from the two sources showed identical retention times on two gas chromatographic columns and an identical R_F on thin-layer chromatography. These three labdatriene isomers are also produced, together with other hydrocarbons, by the dehydration of the glycol sclareol (IV), using phosphorus oxychloride in pyridine.

TABLE 1

COMPARISON OF *cis* AND *trans* ISOMERS

Compound	Chemical Shift (τ)				J_{AB} (c/s)	U.V.	
	C16	C16′	C15	C12		λ_{max}	ε
cis-Biformene (Ia)	4·90	4·97	3·17	4·75	≃2	236·5	20500
trans-Biformene (Ib)	5·07	5·16	3·74	4·63	≃1	231	26000
cis-Methyl communate[2]	4·93	5·00	3·18	4·80	—	235	—
trans-Methyl communate[7]	4·98	5·15	3·72	4·60	1	232	27600
cis-Abienol[2,8] (III)	4·93	5·00	3·15	4·55	≃2	235	19800

The dehydration of manool (II) with acid has been previously used[1] to synthesize biformene. Repetition of this experiment using manool or sclareol gave a hydrocarbon fraction which, by gas chromatography, was a mixture of at least seven compounds

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[7] Norin, T., *Acta chem. scand.*, 1965, **19**, 1020.

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[9] Connell, D. J., personal communication.

[10] Thomas, B. R., personal communication.

(cf.[11]). Chromatography of the mixture on silica gel/silver nitrate gave a partial separation. The first fraction eluted was a 1 : 1 mixture of hydrocarbons. From the work of Bory and Asselineau[12] and by analogy with the acid-catalysed dehydration of linalool[13] in which monocyclic hydrocarbons are produced, this first fraction is probably a mixture of tricyclic diterpene hydrocarbons. Further elution gave both pure *cis*- and *trans*-biformene. The presence of sclarene (Ic) in the mixture was indicated by gas chromatography.

Sclarene and the biformene isomers are very unstable, particularly toward oxygen. A sample of pure crystalline *cis*-biformene after 10 weeks at −5° in a sealed (but not evacuated) glass vessel gave polymeric material together with a volatile extract which contained only 90% *cis*-biformene (gas chromatography). The isomers rapidly decompose at room temperature with the initial formation of a skin over the surface followed by polymerization to give brittle solids insoluble in hexane.

Hydrogenation of either *cis*- or *trans*-biformene over palladium on charcoal produces hexahydrobiformene. Gas chromatographic analysis of this product showed it to be a mixture of two compounds. Assuming addition of hydrogen to the olefinic centre at C 8 from the less hindered β-face of the molecule, the product should be a mixture of the C 13 isomers, 8*S*,13*R*-labdane and 8*S*,13*S*-labdane.

A survey[11,14] of the diterpene hydrocarbon content of the genus *Dacrydium* has shown the presence of considerable amounts of phyllocladene and lesser amounts of isophyllocladene. *Dacrydium biforme* has been previously reported[15] to contain phyllocladene. Gas chromatographic analysis and thin-layer chromatography of the neutral components of *D. biforme* now indicates that both *cis*- and *trans*-biformene are present in the heartwood and that sclarene (Ic) is also present in detectable amounts.

Since the *cis*-alcohol abienol (III) can be isolated from Canada balsam,[8] it was of interest to examine the same balsam for biformene isomers. The oleoresin contains *cis*-biformene but no *trans*-biformene in detectable amounts. Since the balsam contains no detectable amount of *trans*-abienol, it seems likely that the *cis*-biformene is formed in this species by the dehydration of the corresponding *cis*-alcohol.

The molecular rotations of both *cis*- and *trans*-biformene ($[M]_D$ +127 and $[M]_D$ +129 respectively) are of the magnitude predicted for this type of compound.[16] This result suggests that the *cis*-Δ^{12} double bond in these hydrocarbons has little effect upon the optical rotation. Therefore the anomalous rotation[2] of abienol can best be explained through an interaction between the C 8 hydroxyl and the Δ^{12} double bond. The infrared spectrum of abienol in dilute solution provides some evidence for this view as it shows concentration-independent hydroxyl vibrations at 3610 and 3560 cm^{-1}.

[11] Aplin, R. T., Cambie, R. C., and Rutledge, P. S., *Phytochemistry*, 1963, **2**, 205.

[12] Bory, S., and Asselineau, C., *Bull. Soc. chim. Fr.*, 1961, 1355.

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[15] Briggs, L. H., *J. chem. Soc.*, 1937, 79.

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EXPERIMENTAL

Melting points are uncorrected. n-Hexane had b.p. 68°. Ultraviolet spectra were recorded with a Cary 14 spectrophotometer. Infrared spectra were measured on a Perkin–Elmer 237 spectrophotometer. Optical rotations were recorded on a Perkin–Elmer 141 polarimeter. Measurements were made on solutions in absolute ethanol and isooctane. The p.m.r. spectra were recorded at 60 Mc/s on a Varian A60 spectrometer with tetramethylsilane as internal reference. Measurements were made in carbon tetrachloride solution. Thin-layer chromatograms were run on silica gel (Shandon)/silver nitrate (4 : 1) in n-hexane/acetone (10 : 3), and sulphuric acid (98%) used to detect the spots. All gas chromatograms were obtained on an Aerograph Hi-Fi 600-B with flame-ionization detector using stainless steel coiled columns, 5 ft long and 1/8 in. o.d. The solid support was acid-washed Chrom W 60/80 (SF 96) and 80/100 (EGS and Versamid) mesh. Gas-inlet pressure (nitrogen) was 15 lb/in^2. Other details are set out in Table 2. Retention volumes for the diterpenoids are listed in Table 3.

TABLE 2

DATA FOR GAS CHROMATOGRAPHY

Column Data	Silicone Oil SF 96	Ethylene Glycol Succinate	Versamid
Ratio liquid : support (w/w)	5 : 100	5 : 100	10 : 100
Column temperature	155°	140°	170°
Injection temperature	170°	170°	180°

TABLE 3

RETENTION TIMES OF DITERPENE HYDROCARBONS RELATIVE TO MANOOL (= 1)

Hydrocarbons	5% E.G.S.	5% SF 96	10% Versamid
cis-Biformene (Ia)	0·24	0·75	0·385
trans-Biformene (Ib)	0·29	0·835	0·44
Sclarene (Ic)	0·18	0·61	0·305

Dehydration of Abienol with Phosphorus Oxychloride/Pyridine

Abienol (III) [m.p. 40–41°, $[\alpha]_D$ +23·5° (*c*, 1·5 in $CHCl_3$), ν_{max} (CCl_4, 0·005M) 3610, 3560 cm^{-1}] (13·5 g) in pyridine (200 ml) at 0° was treated with a mixture of $POCl_3$ (70 ml) in pyridine (100 ml). After 18 hr at 0° the mixture was poured slowly into an ice-cold aqueous solution of $NaHCO_3$. The neutral product (13·2 g) was isolated with ether, chromatographed on neutral alumina (200 g), and eluted with n-hexane to give a colourless oil (12·9 g, n_D^{20} 1·5275) (gas chromatography showed two components in the ratio 1 : 9). The oil (5 g) was further chromatographed on silver nitrate/silica gel (200 g). Elution with ether/hexane (1 : 5) gave cis-*labda-8(14),12,15-triene* (1·1 g) as a viscous oil which crystallized on standing, m.p. 18°, $[\alpha]_D$ +46·5° (*c*, 0·972 in $CHCl_3$), +49° (*c*, 1·48 in isooctane) (Found: C, 88·1; H, 11·9. $C_{20}H_{32}$ requires C, 88·2; H, 11·8%). λ_{max} 236·5 mμ (ϵ 20500 in absolute ethanol). ν_{max} (film) 3085s, 1800m, 1649s, 1602m, 1345w, 1280m, 1225m, 1201s, 1190m, 1110s, 1095s, 1055w, 1039m, 990s, 970m, 940w, 902s, 890s, 850s, 820s, 752w, 690m, 670s cm^{-1}. P.m.r. spectrum: 3·17 (C 15; quartet), 4·75 (C 12; broadened triplet), 4·90, 4·97 (C 16, C 16′; three broadened lines; $J_{15,16}$ 18 c/s, $J_{15,16'}$ 10·5 c/s, $J_{16,16'}$ 2 c/s), 5·23, 5·56 (C 14, C 14′), 7·83 (C 11; complex), 8·32 (C 17 methyl; fine doublet; $J \simeq 1$ c/s), 9·15, 9·20, 9·29 (C 18, C 19, C 20 methyls) τ.

Dehydration of Manool using Phosphorus Oxychloride/Pyridine

Manool (II) (6 g) in pyridine (100 ml) at −5° was treated with a mixture of $POCl_3$ (35 ml) in pyridine (50 ml). After 24 hr at −5°, the mixture was poured into ice-cold bicarbonate solution. The oil (5·95 g), isolated with n-hexane, was chromatographed over alumina (100 g). Elution with n-hexane gave a colourless oil (5·7 g) (n_D^{20} 1·5108) (gas chromatography showed three components in the ratio 7 : 2 : 9). This olefinic mixture (3 g) was chromatographed over silver nitrate/alumina (15%; 200 g). Elution with ether/n-hexane (9 : 1) gave *cis*-labda-8(14),12,15-triene (0·35 g) as a colourless oil which crystallized on standing, m.p. 18°, $[\alpha]_D$ +46·7° (*c*, 1·92 in $CHCl_3$), +49·2° (*c*, 1·525 in isooctane) (Found: C, 88·1; H, 11·9%). The u.v., i.r., and p.m.r. spectra were identical with those described above. Further elution with ether/methanol (4 : 1) gave, as a colourless oil, trans-*labda-8(14),12,15-triene* (0·45 g), n_D^{20} 1·5293, $[\alpha]_D$ +47·3 (*c*, 1·54 in $CHCl_3$), +50·2 (*c*, 1·65 in isooctane) (Found: C, 88·1; H, 11·9. $C_{20}H_{32}$ requires C, 88·2; H, 11·85%). λ_{max} 231 mμ (ε 26000 in absolute ethanol). ν_{max} (film) 3085s, 1785m, 1640s, 1605s, 1455s, 1435s, 1410m, 1382s, 1360s, 1340m, 1290w, 1270w, 1220w, 1195m, 1125m, 1105w, 1082m, 1030w, 980s, 965m, 940w, 880s, 850w, 820w, 800w, 665w cm^{-1}. P.m.r. spectrum: 3·74 (C 15; quartet), 4·63 (C 12; broadened triplet), 5·07, 5·16 (C 16, C 16′; three broadened lines; $J_{15,16}$ 19 c/s, $J_{15,16'}$ 8 c/s, $J_{16,16'}$ 1 c/s), 5·27, 5·57 (C 14, C 14′), 7·73 (C 11; complex), 8·30 (C 17 methyl; fine doublet; $J \simeq 1$ c/s), 9·13, 9·18, 9·29 (C 18, C 19, C 20 methyls) τ.

Dehydration of Sclareol with Phosphorus Oxychloride/Pyridine

Sclareol (IV) was treated with phosphorus oxychloride/pyridine as for manool above, to give an oil from which after chromatography over alumina and silver nitrate/alumina *cis*-biformene and *trans*-biformene were isolated as described. The u.v., i.r., and p.m.r. spectra for both compounds were identical with those described above.

Dehydration of Manool with Glacial Acetic Acid

Manool (II) (12 g) in glacial acetic acid (120 ml) was refluxed for 1 hr. Isolation of the product with ether gave a straw-coloured oil (11·8 g) which was chromatographed on neutral alumina (300 g). Elution with n-hexane gave a colourless oil (4·5 g). Further elution with n-hexane/ether (10 : 1) gave the allylic acetate (2·5 g) previously described.[1] Elution with n-hexane/ether (1 : 2) gave unchanged manool (3·7 g).

The initial fraction (4·5 g) was rechromatographed on silver nitrate/silica gel (200 g). Elution with n-hexane/ether (5 : 1) gave three major fractions. The first, a colourless mobile oil, had n_D^{20} 1·5285, b.p. 110°/0·15 mm, $[\alpha]_D$ +22·5° (*c*, 0·435 in isooctane). ν_{max} (film) 3085m, 2940s, 1640m, 1456s, 1396s, 1376s, 1206w, 1030m, 996m, 966m, 961w, 936w, 906s, 851w, 806m cm^{-1}. Gas chromatography showed the oil to be a mixture of two components in the ratio 1:1. The second fraction from the silver nitrate/silica gel column crystallized to give *cis*-labda-8(14)12,15,-triene (0·25 g), m.p. 18°, $[\alpha]_D$ +46·0° (*c*, 0·99 in $CHCl_3$) +48·5° (*c*, 1·05 in isooctane) (Found: C, 88·1; H, 11·9%). The u.v., i.r., and p.m.r. spectra were identical with those described above. The third fraction gave, as a colourless oil, *trans*-labda-8(14),12,15-triene, n_D^{20} 1·5295, $[\alpha]_D$ +47·1° (*c*, 1·15 in $CHCl_3$), +49·8° (*c*, 1·25 in isooctane) (Found: C, 88·05; H, 12·0%). The u.v., i.r., and p.m.r. spectra were identical to those described above.

The forerun of the third fraction contained a compound which was not further purified. Direct comparison of gas chromatography retention times and R_F values on thin-layer chromatography indicated that the compound was identical with authentic sclarene (Ic) from *Agathis australis* leaf oil.

Dehydration of Sclareol with Glacial Acetic Acid

Sclareol (IV) was dehydrated with glacial acetic acid as for manool above. *cis*- and *trans*-Biformene were isolated from the product by chromatography over alumina and silver nitrate/silica gel as described above. The u.v., i.r., and p.m.r. spectra for both compounds were identical with those described above.

Neutral Compounds from Canada Balsam

Canada balsam (F. W. Berk Ltd, London) (5 g) in ether (20 ml) was extracted with aqueous 2% sodium hydroxide. The straw-coloured neutral fraction (2·7 g) in n-hexane was chromatographed over neutral alumina (100 g). Elution with n-hexane/ether gave a colourless oil. This fraction showed peaks on gas chromatography, one of which corresponds to *cis*-biformene (0·3% of neutrals) on all the columns used. Thin-layer chromatography also indicated the presence of a spot with the same R_F as *cis*-biformene. No spots or peaks corresponding to *trans*-biformene were detected.

Neutral Compounds from Dacrydium biforme *Chips*

Dacrydium biforme chips (70 g) were treated with n-hexane at room temperature for 100 hr. The extract was filtered and evaporated to dryness at low temperature to give a straw-coloured oil (3·5 g) which was chromatographed over alumina (70 g). Elution with n-hexane/ether gave an oil which showed five major peaks on gas chromatography. One of these corresponded in retention time to *cis*-biformene (0·4% of neutrals), the second to *trans*-biformene (2·5% of neutrals), the third to sclarene (2% of neutrals), and the fourth to manool (90% of neutrals). Thin-layer chromatography on silver nitrate/silica gel showed again the correspondence of the three hydrocarbons.

Hydrogenation of cis-*Labda-8(14),12,15-triene*

The olefin (0·95 g) in absolute ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of palladium (20% on charcoal). The product was chromatographed over alumina to give a colourless mobile oil (0·93 g) from n-hexane. Distillation gave the saturated product, n_D^{20} 1·4900, $[\alpha]_D$ +25° (*c*, 0·96 in isooctane) +24° (*c*, 1·05 in $CHCl_3$). Infrared spectrum showed only C–C and C–H absorption. Gas chromatography indicated two components in the ratio 1 : 1 (Found: C, 86·25; H, 13·75. Calc. for $C_{20}H_{38}$: C, 86·3; H, 13·75%).

Hydrogenation of trans-*Labda-8(14),12,15-triene*

The olefin was hydrogenated and treated as above. The saturated mixture was identical on gas chromatography to that obtained from *cis*-isomer (Found: C, 86·3; H, 13·8%).

ACKNOWLEDGMENTS

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