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D:B-FRIEDOOLEAN-3,5-OXIDE IN *RHODODENDRON MACROPHYLLUM**

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Abstract—The triterpenoid epoxide present in the title plant has been isolated previously from species of *Dendropanax* and other Rhododendrons and given different names, i.e. epoxyglutinane, dendropanoxide, and possibly campanulin. Previously conflicting evidence regarding the position of the epoxide group and the nomenclature of the compound have now been clarified.

INTRODUCTION

Rhododendron macrophyllum (western Rhododendron) which is native to California, Oregon and Washington was previously examined for the presence of the grayanotoxins, toxic diterpenoids. These were isolated from methanolic extracts.[1] Since the publication of these results, further studies have been conducted on the petroleum ether soluble materials.

RESULTS AND DISCUSSION

Isolated from the petroleum ether fraction was a compound with m.p. 203–5° and $[\alpha]_D^{25°}$ +67°. The mass spectrum indicated a mol. wt. of 426 and empirical formula of $C_{30}H_{50}O$. This empirical formula would indicate either extensive unsaturation or presence of a polycyclic compound. The presence in the mass spectrum of two hydrocarbon fragment ions of 231 ($C_{17}H_{27}$) and 217 ($C_{16}H_{25}$) are indicative of those derived from a saturated diterpenoid structure.[2] Further there was no evidence of unsaturation in the i.r. or NMR. The Liebermann–Burchard and $SbCl_3$ tests were also positive.

The i.r. spectrum (KBr and $CHCl_3$) had a pair of bands at 1380 and 1360 cm^{-1} indicative of *gem*-dimethyl or isopropyl and strong absorption in the 980–1000 cm^{-1} region suggestive of an ether bond since there were no hydroxyl or carbonyl bands. The NMR spectrum showed a doublet at 3·7 δ (1H). The integration for one proton, the doublet nature of the signal, the lack of any hydroxyl in the i.r. and the absence of any other downfield signal strongly pointed

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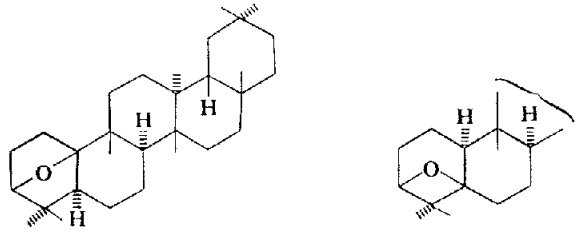
[1] G. H. CONSTANTINE, JR., K. SHETH and P. CATALFOMO, *J. Pharm. Sci.* **56**, 1518 (1967).

[2] F. W. MCLAFFERTY, *Mass Spectral Correlations*, pp. 76, 80, Advances in Chemistry Series, No. 40, American Chemical Society, Washington, D.C. (1963).

to the following type of structures: CH_2–CH–O–C–. Since protons attached to epoxides normally resonate in the 3·1 δ region, the cyclic ether appeared to be a four membered ring or larger.[3] Further, the compound was unreactive to $LiAlH_4$ under forcing conditions.

A search of the literature for compounds with the same empirical formula, m.p. range and optical rotation produced two D:B-friedooleanoxides (I and II) containing cyclic ethers



(I) (II)

which were also unreactive to $LiAlH_4$. As noted in Table 1, m.p. and rotation will not distinguish between the two isomers.

Rangaswami based his assignment of a 3,10-oxide on the i.r. spectrum of campanulin which had a band at 1098 cm^{-1} analogous to a tetrahydrofuran structure.[4] A trimethylene oxide (3,5-oxide) would be expected to show a band at 970–980 cm^{-1}.[5] While Rangaswami did not mention what solvent his oxide was in when the spectrum was taken, the band for our oxide remained in the 980 cm^{-1} region in KBr, $CHCl_3$ and mineral oil. This corresponds with the i.r. spectrum reported by Arthur and Hui for their oxide.[6]*

The chemical basis for differentiating between the oxide linkages is to open the oxide ring and examine the point of unsaturation in the resulting D:B-friedooleanenol. Treatment of compounds I or II in essentially anhydrous acid media yields D:B-friedoolean-5(10)-en-3β-ol IIIa.[6,7,11,13] It is also possible to treat compound II with BF_3 etherate or NaOAc, Zn dust in HOAc and obtain a mixture of the 5(10)-en-3β-ol IIIa and 5-en-3β-ol IVa.[6,13] Treatment with acid will convert (IVb) to (IIIb).[14]

Using the Rangaswami method,[7] the unknown oxide yielded the 5(10)-en-3β-ol (IIIa) whose physical properties (m.p. 227–230°, $[\alpha]_D^{25°}$ −37°) corresponded well with the reported

* We take exception to the epilogue of Ref. 4 in which the authors state that campanulin is the same compound as the oxide reported by Arthur and Hui.[6] As Table 1 shows, m.p. and $[\alpha]_D$ are not differentiating. More importantly the reported i.r. spectra are different in the two papers. Finally, Arthur and Hui presumably obtained the mixture of 5-en-3β-ol (IVa) and 5(10)-en-3β-ol (IIIa) which would not have resulted had their oxide possessed a 5,10-oxide linkage (see below). A disturbing piece of information is the report by the authors of Ref. 12 who stated that there was no m.p. depression in a mixed m.p. of their campanulin and another sample of campanulin (from Rangaswami) and epoxy-glutinane (source not given).

[3] J. R. DYER, *Applications of Absorption Spectroscopy of Organic Compounds*, p. 86. Prentice-Hall, Englewood Cliffs, N.J. (1965).
[4] S. RANGASWAMI and K. SAMBAMURTHY, *Proc. Indian Acad. Sci.* **54A**, 132 (1961).
[5] G. M. BARROW and S. SEARLES, *J. Am. Chem. Soc.* **75**, 1175 (1953).
[6] H. R. ARTHUR and W. H. HUI, *J. Chem. Soc.* 551 (1961).
[7] S. RANGASWAMI and K. SAMBAMURTHY, *Proc. Indian Acad. Sci.* **46A**, 245 (1957).
[8] S. RANGASWAMI and K. SAMBAMURTHY, *Proc. Indian Acad. Sci.* **53A**, 98 (1961).
[9] S. RANGASWAMI and K. SAMBAMURTHY, *J. Sci. Ind. Res. India* **20B**, 544 (1961).
[10] S. RANGASWAMI and K. SAMBAMURTHY, *J. Sci. Ind. Res. India* **20B**, 610 (1961).
[11] S. RANGASWAMI and P. VENKATESWARLU, *Proc. Indian Acad. Sci.* **62A**, 224 (1965).
[12] P. C. MAITI, S. K. KANJI and R. CHATTERJEE, *J. Inst. Chem. India* **39**, 165 (1967).
[13] K. KIMURA, Y. HASHIMOTO and I. AGATA, *Chem. Pharm. Bull. Tokyo* **8**, 1145 (1960).
[14] P. SENGUPTA, S. GHOSH and L. J. DURHAM, *Tetrahedron* **22**, 3469 (1966).

TABLE 1.

Compound	Trivial name	Source	m.p.	$[\alpha]_D$	Temp.*	References
I	Campanulin	*Rhododendron falconeri* Hook.	198°	+71·9° ± 3°	29°	7
		R. campanulatum D. Don.	204°	+75·2° ± 2°	29°	8
			201–3°			
			200–2°			
		R. barbatum Wall	202–4°	+69·1° ± 2°	30°	9
		R. decipiens Lacaita	202–4°	+65·7° ± 3°	30°	10
		R. grande Wight	202–3°	+82·1°	35°	11
		R. campanulatum, falconeri, barbatum and *arboreum* var. *nilagiricum*,	206–8°	+75·2°	29°	12†
II	Dendropanoxide (3β,5β-epoxyalnusane)	*Dendropanax trifidus* Makino	206–7°	+68·4°	28°	13
	Epoxyglutinane	*R. westlandii*	201–2°	+74·8°		6‡

* All rotations were in $CHCl_3$.

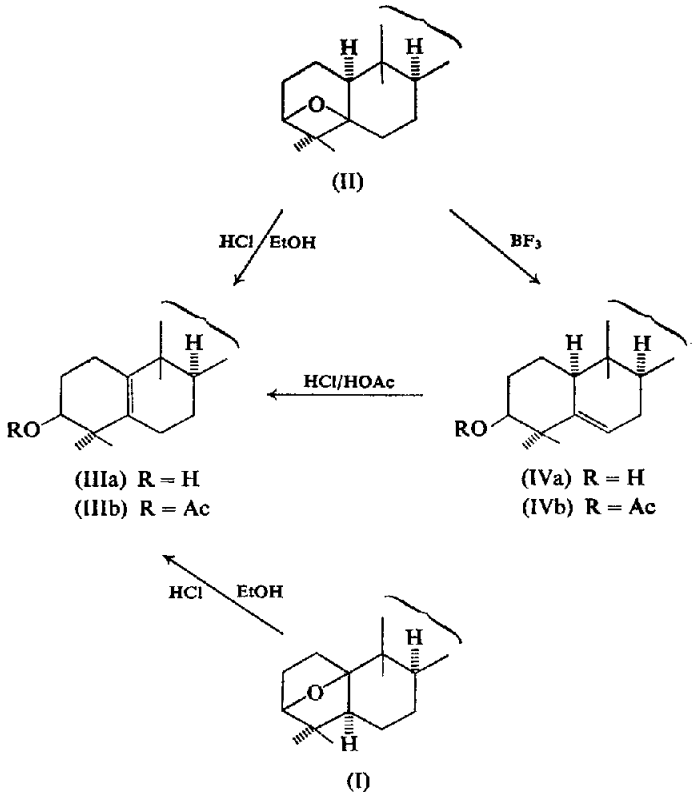
† The constants refer to the sample isolated from *R. campanulatum*.

‡ Arthur and Hui did not decide between structures I and II, but their results strongly suggest II (see below).

Table 2.

Chemical abstracts name[15]	Trivial name	m.p.	$[\alpha]_D$	Temp.*	References
D:B-Friedoolean-5(10)-en-3α-ol	Glut-5(10)-en-3α-ol	256–259°	−38°		14
	Glutin-5(10)-en-3α-ol	258–259°	−42°		16
D:B-Friedoolean-5(10)-en-3β-ol (IIIa)	—	248–250°	−30·5° ± 2°	30°	7
	Campanulol	241–243°	−38·8°	35°	11
	Alnus-5(10)-en-3ξ-ol	240–242°	−39·4°	28°	13
	Glutin-5(10)-en-3β-ol	243–244·5°	−35·7°		6
	Glut-5(10)-en-3β-ol	242–244°	−40°		14
	Glutin-5(10)-en-3β-ol	244–245°	−42·5°		16
	Alnus-5(10)-en-3ξ-ol	241–242°	−42°		17
D:B-Friedoolean-5(10)-en-3α-acetate	Glutin-5(10)-en-3α-yl Acetate	209–210°	−49°		16
D:B-Friedoolean-5(10)-en-3β-acetate (IIIb)	Alnus-5(10)-en-3ξ-yl Acetate	284–287°	−26·5°	28°	13
	—	300–302°	−18°		6
	Glutin-5(10)-en-3β-yl Acetate	299–301°	−20·7°		6
	—	286–288°	−17·6° ± 2°	29°	4
	—	285–287°	−14·8° ± 3°	28°	4
	Glut-5(10)-en-3β-yl Acetate	291–295°	−18°		14
	Glutin-5(10)-en-3β-yl Acetate	297–299°	−23°		16
	Alnus-5(10)-en-3ξ-yl Acetate	290–293°	−27°		17
D:B-Friedoolean-5-en-3α-ol	Glut-5-en-3α-ol	200–203°	+63°		14
	Glutin-5(6)-en-3α-ol	201–203°	+62°		16
D:B-Friedoolean-5-en-3β-ol (IVa)	Glut-5-en-3β-ol	206–208°	+62°		14
	Glutin-5(6)-en-3β-ol	210·5–211·5°	+64°		16
D:B-Friedoolean-5-en-3α-acetate	Glutin-5-en-3α-yl Acetate	226–229°	+42·9°		6
D:B-Friedoolean-5-en-3β-acetate (IVb)	Glutin-5-en-3β-yl Acetate	191–193°	+70·7°		6
	Glutin-5-en-3β-yl Acetate	192–194°	+79°		16

* All rotations were in $CHCl_3$.



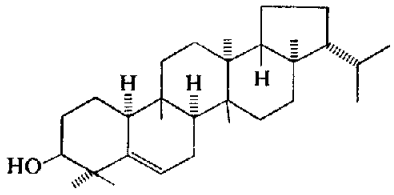
values (Table 2). The NMR spectrum of IIIa showed the disappearance of the oxide proton at 3·7 δ and the appearance of a carbinol proton at 3·33 δ (1H). There were no vinyl signals, but there was the appearance of allylic protons at 2·0 δ (3–4H). Acetylation of IIIa yielded the 5(10)-en-3β-acetate (IIIb) whose physical properties (m.p. 294–6°, $[\alpha]_D^{25°}$ −20·7°) corresponded well with the reported values (Table 2). The NMR spectrum of IIIb corresponded with that reported by Sengupta *et al.*[14] including the expected downfield shift to 4·7 δ (1H) of an acetylated carbinol proton.[18] The band width at 1/2 the peak height (W_H) was 33–38 cps indicating an equatorial hydroxyl (as the acetate ester),[19,20] which agrees with the stereochemistry reported by chemical means.[14,16]

Treatment of the unknown oxide with BF_3 etherate yielded a mixture of alcohols which were acetylated; fractional crystallization yielded a proportionally large amount of the 5(10)-en-3β-acetate (IIIb) and a lesser amount of a mixture of (IIIb) and the 5-en-3β-acetate (IVb). The NMR of this mixture showed a vinyl signal at 5·4 δ. Refluxing this mixture in HOAc-conc. HCl converted IVb to IIIb. Thus our oxide most probably possesses the 3,5-oxide linkage as represented by II.

[15] For an explanation of this system of nomenclature, see: S. ALLARD and G. OURISSON, *Tetrahedron* **1**, 277 (1957).
[16] A. C. PATON, F. S. SPRING and R. STEVENSON, *J. Chem. Soc.* 2640 (1958).
[17] J. M. BEATON, F. S. SPRING, R. STEVENSON and J. L. STEWART, *Tetrahedron*, **2**, 246 (1958).
[18] J. N. SHOOLERY and M. T. ROGERS, *J. Am. Chem. Soc.* **80**, 5121 (1958).
[19] R. U. LEMIEUX, R. K. KULLNIG, W. J. BERNSTEIN and W. G. SCHNEIDER, *J. Am. Chem. Soc.* **80**, 6098 (1958).
[20] E. W. GARBISCH, JR., *J. Org. Chem.* **27**, 4249 (1962).

We strongly advise other workers investigating this genus who isolate a triterpenoid oxide to obtain an i.r. spectrum and look for bands in the region of 1090–1100 cm^{-1} (3,10-oxide) or 970–980 cm^{-1} (3,5-oxide).* A further confirmation would be ring opening using conditions that might yield a 5-en-3β-ol IVa depending on the location of the oxide ring.†

Recently, there has also been isolated from another rhododendron, *R. simiarium* (Ericaceae) simiarenol (V), a member of the neogammacerane series. Of potential chemo-



(V)

taxonomic interest would be a survey of these two types in *Rhododendron*. Arthur had already done this for the *Rhododendron* indigenous to Hong Kong;[21] only one species has a neogammacerane (*R. simiarium*) and one other a triterpenoid oxide (*R. westlandii*).

EXPERIMENTAL

M.ps are uncorrected. Rotations were obtained in $CHCl_3$, NMR spectra in deuterated chloroform. Petroleum ether refers to the mixture b.p. 30–60°. TLC was carried out with Silica Gel G and compounds were detected with 10% w/w $SbCl_3$ in $CHCl_3$ and the plates were heated to 110° for 10 min.

Isolation. A typical extraction was to take 1 kg of dried ground leaves and extract in a Soxhlet for 12 hr with petrol ether (PE). The extract (6·1 g) was chromatographed on alumina and 500 ml fractions collected as follows:

Fractions	Solvent	R_f in $CHCl_3$–Me_2CO (9:1)
1–4	PE	0·9
5–8	PE:$CHCl_3$ (9:1)	0·8, 0·9
9–12	PE:$CHCl_3$ (4:1)	—
13–16	PE:$CHCl_3$ (1:1)	0·18, 0·24, 0·50, 0·60
17–20	CH_3OH	—

Fractions 5–8 were combined and partitioned between EtOH–H_2O and Et_2O (1:1) in which the oxide was found in the ether phase. Recrystallization from acetone yielded 22 mg of pure material. More material was obtained by redissolving the waxy residue from evaporation of the acetone liquors in fresh acetone and allowing to stand. The pure material had m.p. 203–205°; $[\alpha]_D^{25°}$ + 67° ($c = 6$); i.r. (mineral oil) cm^{-1} 1020, 1004, 992, 974, ($CHCl_3$) 1460, 1386, 1364, 1000, (KBr) 1468, 1452, 1383, 1362, 1020, 1005, 994, 975; NMR δ 0·89, 0·99, 1·13, 1·16, 1·25, 1·39, 1·76, 1·87, 3·7 (d, 1H).

Opening of the oxide ring. HCl in ethanol. 100 mg of the oxide, 20 ml EtOH, and 0·8 ml conc HCl were refluxed for 30 min. The product was isolated in the usual way and recrystallized from EtOH, yielding 80 mg of the 5(10)-en-3β-ol (IIIa), m.p. 227–230°; $[\alpha]_D^{25°}$ −37° ($c = 1$); i.r. (mineral oil) cm^{-1} 3480 broad, 1030 broad and absence of the oxide bands at 1000; NMR δ 0·94, 1·01, 1·19, 1·27, 1·38, 1·97, 3·33 (m, 1H). Acetylation of IIIa with Ac_2O/pyridine gave a product, which crystallized from $CHCl_3$–MeOH, yielded the 5(10)-en-3β-acetate (IIIb), m.p. 294–296°; $[\alpha]_D^{25°}$ −20·7° ($c = 0·2$); NMR consistent with the published spectrum.[14]

Opening of the oxide ring. BF_3. A solution of the oxide (72 mg) in 12·6 ml anhydrous ether and 0·16 ml of 98% BF_3–ether complex was allowed to stand at room temp. for 14 hr. after which 13 ml of water was added. The product (75 mg) was acetylated yielding 108 mg of a chromatographically defined mixture,

* As far as we can determine, Rangaswami has reported only one i.r. spectrum.[4] All subsequent identifications have been restricted to m.ps and optical rotations.

† Treatment of a 3-10-oxide with BF_3 might be expected to yield a 1(10)-en-3β-ol. In our search of the literature, we have been unable to find such a compound in order to compare physical properties with the known 5(6)-en-3β-ol (IV).

[21] H. R. ARTHUR, S. W. TAM and (in part) V. ANGSUSINGH, *Australian J. Chem.* **13**, 506 (1960).

R_f 0·35 and 0·38 (hexane–acetone, 120:1). The upper spot was chromatographically identical to IIIb. Repeated recrystallizations from $CHCl_3$–MeOH yielded pure 5(10)-en-3β-acetate (IIIb). The NMR of the residue (38 mg) strongly indicated a mixture of IIIb and IVb. The mixture was heated for 2 hr at 100° in 7·2 ml HOAc and 1·2 ml of conc HCl, yielding eventually a chromatographically identical product to IIIb with m.p. 280–5°.

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