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REVISED STRUCTURE OF A STEROID OXIDE FROM *RHODODENDRON MACROPHYLLUM**

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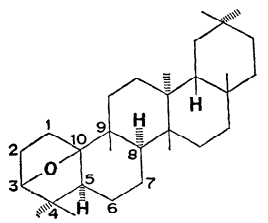
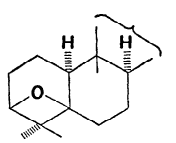
Key Word Index—*Rhododendron macrophyllum*; D:B-Friedoolean 3,5-oxide; D:B-Friedoolean-3,10-oxide; NMR oxide protons; steroid oxides.

Abstract—Updated NMR evidence is given that a previously reported triterpenoid oxide is not D:B Friedoolean-3,5-oxide, but is, instead, D:B-Friedoolean-3,10-oxide. A mechanistic explanation is given as to why the chemical evidence does not seem to support the NMR data.

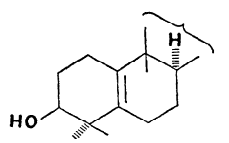
PREVIOUSLY we reported the isolation of a triterpenoid oxide from *Rhododendron macrophyllum.*[1] The MS spectrum indicated a MW of 426 and empirical formula of $C_{30}H_{50}O$. A search of the literature indicated that it was likely D:B-Friedoolean-3,10-oxide (I) or D:B-Friedoolean-3,5-oxide (II).



(I)



(II)



(III)

Rangaswami first reported campanulin as having a 3,10-oxide (I) based on IR evidence which no other workers, including ourselves, were able to obtain.[2] Arthur and Hui, whose reported IR spectrum was the same as ours, were undecided between the 3,10-oxide (I) and 3,5-oxide (II) for their epoxyglutinane. They leaned, however, towards the 3,5-oxide due to the reported conversion of their oxide to a mixture of the 5(10)-en-3α-ol, 5(10)-en-3β-ol (III), and 5-en-3α-ol following reduction of the ketone precursors.[3] Kimura *et al.* also reported the possibility of their oxide, dendropanpoxide, having structures I or II and chose the 3,5-oxide (II) because of conversion of their oxide into known derivatives having a 5(10)-en double bond.[4]

* Presented before the Pharmacognosy and Natural Products Section of the Academy of Pharmaceutical Sciences at the Annual Meeting of the American Pharmaceutical Association, April 1972, Abstracts, p. 98.

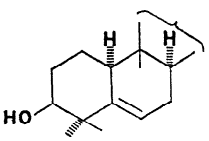
[1] G. H. CONSTANTINE, JR. and J. H. BLOCK, *Phytochem.* **9**, 1659 (1970).

[2] S. RANGASWAMI and K. SAMBAMURTHY, *Proc. Indian Acad. Sci.* **54A**, 132 (1961).

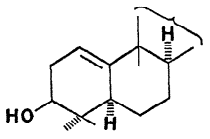
[3] H. R. ARTHUR and W. H. HUI, *J. Chem. Soc.* 551 (1961).

[4] K. KIMURA, Y. HASHIMOTO and I. AGATA, *Chem. Pharm. Bull. Japan* **8**, 1145 (1960).

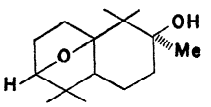
The chemical basis for differentiating between the two oxide linkages is to open the oxide ring using acidic conditions and examine the point of unsaturation in the resulting D:B-Friedooleanenol. Both I and II would be expected to yield D:B-Friedoolean-5(10)-en-3β-ol (III) using HCl in EtOH.[5] Treatment of epoxyglutinane with BF_3 etherate yielded D:B-Friedoolean-5-en-3β-ol (IV).[3] The same product is reported when dendropanoxide is treated with NaOAc and Zn–HoAc.[4] Compound IV is converted to III in acid due to migration of the double bond to the more stable 5(10) position.[4] It was assumed that a 3,10-oxide would form a 1(10)-en-3β-ol V with BF_3 etherate or NaOAc and Zn–HoAc treatment. Acid treatment of V could also be expected to give the 5(10)-en-3β-ol III. For these reasons, we concluded that our oxide must also be a 3,5-oxide.



(IV)



(V)



(VI)

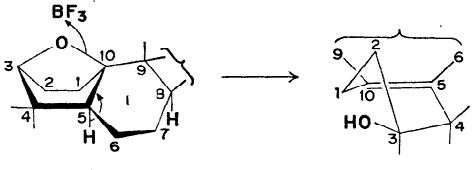
After publishing our results we received a personal communication informing us that our NMR datum for the proton at position 3(3·7 δ) was consistent for a 3,10-oxide (5-membered ring) rather than a 3,5-oxide (4-membered ring). The oxide proton of the four membered oxide ring of the diterpenoid baccatin-V resonates at 4·9 δ and the C-3β proton in 3α,5α-epoxycholestane is found at 4·53 δ. The oxide proton of the 1,4-oxide (VI) has a signal at 3·83 δ.[6] Finally, the oxide protons of trimethylene oxide have a signal at 4·73 δ as compared to 3·75 δ for the oxide protons of tetrahydrofuran.[7]

This new, and previously unpublished information prompted us to carry out a complete reevaluation of our work and that of others reporting the oxide. The methyl signals for our oxide were at 0·91, 0·96, 0·98, 0·99, 1·01 δ (15 H) and 1·14, 1·17, and 1·19 δ (9 H). These are consistent for a 3,10-oxide (I) since the three methyl groups downfield from the remaining five can be assigned to the two methyls at position four and the methyl at position nine. Both carbons 4 and 9 are each one carbon away from the carbons bonded to the oxide oxygen (carbon 4 is attached to carbon 3, and carbon 9 is attached to carbon 10). The three downfield methyls shifted upfield to the expected methyl region in all the derivatives obtained by opening the oxide ring. Our oxide and those previously reported are unreactive to $LiAlH_4$ under forcing conditions.[1,3,4] This would eliminate from consideration a 1,2-oxide, strongly suggest a 3,10-oxide (I) and possibly question the 3,5-oxide (II) assignment. Our oxide gave an identical spectrum when compared with a sample of epoxyglutinane.[8] As we reported in our previous publication, the acetate of 5(10)-en-3β-ol (III) gave an NMR spectrum identical to that already published.[9] The NMR and IR spectra of our 5-en-3β-ol (IV) obtained by BF_3 etherate oxide opening were identical to those spectra obtained from an authentic sample.[10] The NMR spectrum of the acetate of IV was identical to the spectrum obtained from a sample obtained from a laboratory different from the one that provided the

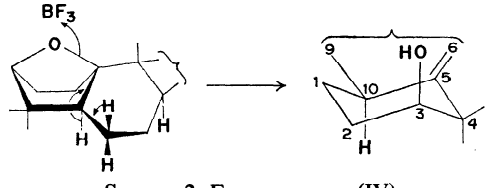
[5] See Ref. 1 for a complete literature review and tables of physical constants.
[6] T. G. HALSALL, personal communication. We are very grateful to Dr. Halsall for sending us his NMR data prior to publication. See T. G. HALSALL, *et al.*, *Chem. Commun.* 1382 (1970).
[7] Spectra No. 33 and 77, Varian Spectra Catalog, Varian Associates, Palo Alto (1962).
[8] Graciously supplied by Miss W. H. HUI.
[9] P. SENGUPTA, S. GHOSH and L. J. DRUHAM, *Tetrahedron* **22**, 3469 (1966).
[10] Graciously supplied by Professor P. SENGUPTA.

free alcohol.[11] The carbinol proton signal for the alcohol and acetate have a half-width of 8–9 Hz (equatorial proton) indicating an axial hydroxyl or acetate.[12,13]

The problem is how to rationalize the NMR evidence which points strongly to a 3,10-oxide (I) with the chemical evidence from opening the oxide ring which indicates a 3,5-oxide (II). This can be done by assuming that two mechanisms are operating simultaneously during the opening of the oxide ring. One involves the expected generation of a tertiary carbonium ion at position 10 followed by elimination of the proton at position 5 (Scheme I). The second mechanism involves the concerted migration of the C-5 proton which is *trans* to the C-10 oxide linkage, to position 10 as the oxygen carbon at position 10 bond is breaking. This is followed by *trans* elimination of the axial proton at position 6 (Scheme 2).



SCHEME 1. FORMATION OF (III).



SCHEME 2. FORMATION OF (IV).

Treatment of the 5(10)-en-3β-ol (III) with BF_3 etherate yielded only starting material, indicating that BF_3 does not cause a migration of the double bond from the 5(10) position back to the 5(6) location, nor does BF_3 cause the formation of an equilibrium mixture of double bond isomers.

An alternative structure that might be proposed would be the 3,8-oxide. This can be eliminated since the NMR spectrum of our oxide integrates for only one proton attached to a carbon with an oxide bond. Any other linkage would involve changes in the size of rings A and B plus a rearrangement during oxide opening.

From the above, we conclude that current NMR evidence points to the 3,10-oxide (I), and ring opening with BF_3 etherate and NaOAc and Zn–HOAc is not necessarily conclusive of a 3,5-oxide. Future investigation might include an X-ray examination of the oxide and study of methods for controlling the route of ring opening.

EXPERIMENTAL

M.ps are uncorrected. NMR spectra in $CDCl_3$. TLC was carried out with Silica Gel G and compounds were detected with 10% w/w $SbCl_3$ and heating the plates to 110° for 10 min. Column chromatography was carried out with J. T. Baker silica gel.

D:B-Friedoolean-5-en-3β-ol. (IV). The oxide (754 mg) was dissolved in 135 ml Et_2O and 1·72 ml of 98% BF_3–etherate complex added. After standing overnight, 100 ml of H_2O was added and the Et_2O phase removed. The aqueous portion was extracted with additional Et_2O. The extracts were combined and dried over anhydrous sodium sulfate. Removal of the Et_2O yielded 716 mg, a mixture of two components (benzene–EtOAc, 2:1). The mixture was chromatographed on a 2 × 30 mm silica gel column using *n*-hexane–EtOAc (12:1) as the eluant and collected in 100 ml fractions. Fractions 5–7 yielded 25 mg pure D:B-Friedoolean-5-en-3β-ol (IV) (m.p. 212–215°). Fractions 8–9 contained two components, and fractions 10–12 contained 150 mg of D:B-Friedoolean-5(10)-en-3β-ol (III) (m.p. 227–228°). The NMR of IV showed signals at δ 0·85 (3H), 0·97 (3H), 1·00 (6H), 1·04 (3H), 1·10 (3H), 1·14 (3H), 1·16 (3H), 3·48 (1H, $w_{1/2}$ 8 Hz, eq C-3 carbinol proton), 5·64 (1H, C-6 vinyl proton). The acetate of IV showed signals at δ 0·84 (3H)), 0·94 (3H), 0·98 (3H)

[11] Graciously supplied by Professor J. MCLEAN.

[12] R. U. LEMIEUX, R. K. KULLNIG, W. J. BERNSTEIN and W. G. SCHNEIDER, *J. Am. Chem. Soc.* **80**, 6098 (1958).

[13] E. W. GARBISCH, JR., *J. Org. Chem.* **27**, 4249 (1962).

1·00 (3H), 1·04 (3H), 1·06 (3H), 1·10 (3H), 1·16 (3H), 2·00 (3H, acetate), 4·70 (1H, $w_{1/2}$ 7 Hz, eq C-3 carbinol, proton), 5·56 (1H, C-6 vinyl proton).

BF_3-*etherate treatment of D:B-Friedoolean-5*(10)-*en-3β-ol* (III). A solution containing 72 mg of the 5(10)-en-3β-ol (III) in 12·6 ml Et_2O and 0·16 ml of 98% BF_3–etherate complex was allowed to stand at room temp. overnight after which H_2O was added. The Et_2O phase was removed and the aqueous portion extracted with additional Et_2O. The Et_2O extracts were combined and dried over anhydrous $MgSO_4$. Removal of the ether yielded a single product which was chromatographically identical to the starting material.

Acknowledgement—We thank Dr. J. D. White, Dept. of Chemistry, Oregon State University for discussions on BF_3 rearrangements.