Tetrahedron Letters No. 26, pp 2427 - 2430.
©Pergamon Press Ltd. 1979. Printed in Great Britain.
0040-4039/79/0622-2427$02.00/0

REVISED STRUCTURES OF PIPOXIDE AND PIPOXIDE CHLOROHYDRIN*

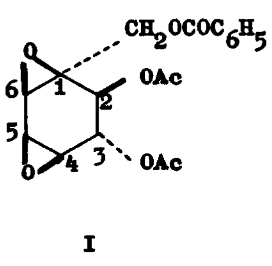
B.S. Joshi,[+] D.H. Gawad
CIBA-GEIGY Research Centre, Goregaon, Bombay 400 063, India
and
H. Fuhrer
CIBA-GEIGY Limited, Basle, Switzerland

Summary - The structures assigned earlier to pipoxide and pipoxide chlorohydrin have been revised on the basis of 360 MHz PMR spectral evidence and decoupling experiments.

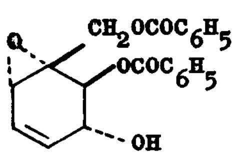
In the course of chemical investigation of Piper species,[1-5] we have examined four plants viz., P. attenuatum, P. galeatum, P. hookeri and P. nigrum.

Hexane extraction of the whole plant of P. attenuatum, P. galeatum and P. hookeri afforded a crystalline compound m.p. 150°, $[\alpha]_D$ + 74° which was shown to be identical with crotepoxide (I), known to possess significant antitumour activity in Lewis lung carcinoma[6].

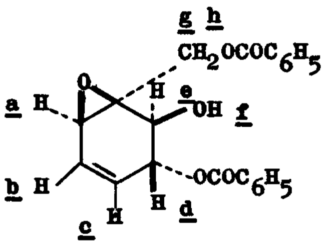
Chromatographic separation of the hexane extracts of P. hookeri and P. nigrum afforded colourless plates, m.p. 154°, $[\alpha]_D$ - 49° (C 2; $CHCl_3$), $C_{21}H_{18}O_6$, M^+ at $^m/e$ 366; λ_{max} (EtOH) 228, 274, 280 nm (log ϵ, 4.46, 3.29, 3.19), ν_{max} (nujol) 3440, 1722, 1680, 1600 cm^{-1}, tlc (sigel) R_f 0.24 ($CHCl_3$:2% MeOH). This was found to be identical with pipoxide[7]. As pipoxide was reported to have a rotation $[\alpha]_D^{20°}$ + 24.5°, the ORD curves of both compounds were determined which showed them to be superimposable. ORD (C 0.05, $CHCl_3$) $[\phi]_{600}$ - 100; $[\phi]_{292}$ - 1219; $[\phi]_{283}$ - 1096; $[\phi]_{255}$ - 4550; $[\phi]_{242}$ - 6501; $[\phi]_{230}$ + 18030; $[\phi]_{226}$ + 12720.



I



II



III

---

* Contribution No.549 from CIBA-GEIGY Research Centre

Table 1 : NMR Spectrum of Pipoxide (III)

H	δ	Multiplicity	Coupling J Hz		Decoupling
a	3.60	d,d	H_a, H_b H_a, H_c	3.75 1.75	↓ Irr.
b	6.10	d,d,d	H_b, H_c H_a, H_b H_b, H_d	10.0 3.75 2.5	↑ Change
c	5.9	d,t	H_b, H_c H_c, H_d H_a, H_c	10.0 2.0 1.75	↑ Change
d	5.68	d,t	H_d, H_e H_c, H_d H_b, H_d	8.0 2.0 2.5	⇑ Change
e	4.32	d,d	H_d, H_e H_e, H_f	8.0 6.0	⇓ Irr.
f	3.24	d	H_e, H_f	6.0	
g, h	5.1, 4.48	AB	H_g, H_h	12.00	
10 Aromatic protons	7.3-8.1	m	-		

δ in ppm vs. TMS

d = doublet; t = triplet; m = multiplet; AB = AB spectrum; Irr. = Irradiation

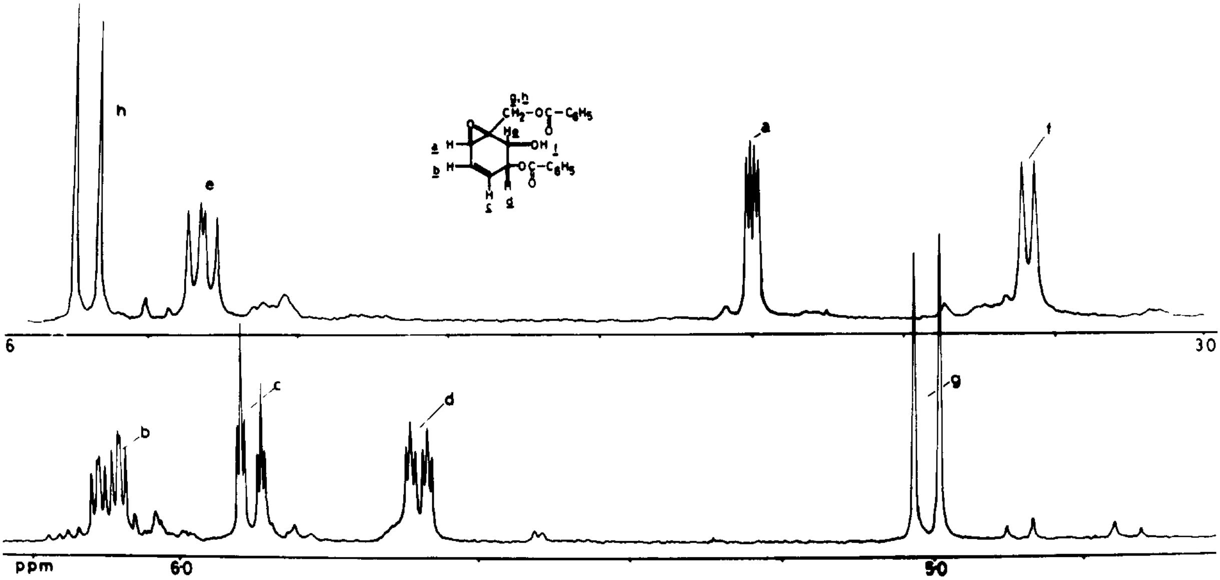
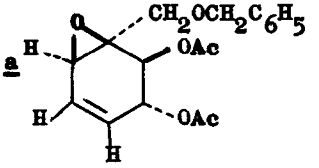
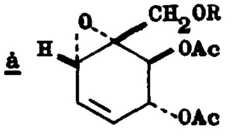


Fig.1: 360 MHz proton spectrum of pipoxide

Pipoxide has been assigned the structure (II) on the basis of spectroscopic evidence and some chemical reactions[7]. Alternative structures were not considered and we have found that the 60 MHz NMR spectrum does not give clear separation of all the protons. We have determined the 100 MHz spectrum and also carried out decoupling experiments (Table 1). This data together with the 360 MHz spectrum (Fig.1) clearly is in agreement with the structure (III) for pipoxide. The correct structure is a positional as well as a configurational isomer of the earlier structure (II) as H_e shows no coupling with H_c or H_b. On deuteration H_e appears as a doublet with the disappearance of the signals at δ 3.24. After the addition of trichloroacetylisocyanate to the solution, the PMR shows a dramatic change of the AB spectrum due to the methylene protons H_g, H_h, and H_e appears downfield at around δ 5.8. The OH group must therefore be in the neighbourhood of the side chain attached to C-1.

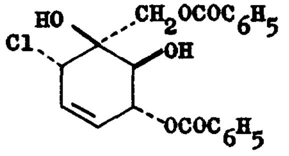


IV



V : R = $CH_2C_6H_5$

VI : R = COC_6H_5



VII

Configuration for the epoxide was assigned on the basis of a comparison of the chemical shift of H_a which appears at δ 3.6 when compared to the corresponding proton at δ 3.6 in (IV), 3.68 in crotepoxide (I) and at δ 3.47 and δ 3.44 respectively in the synthetic compound (V) and senepoxide (VI)[8,9].

From the methanol extract of P. hookeri and P. nigrum we isolated a compound $C_{21}H_{19}ClO_6$, m.p. 203-4°[7,10], λ_{max} (EtOH) 230, 274 and 281 nm (log ϵ, 4.44, 3.28 and 3.19); ν_{max} (KBr), 3540, 1688, 1600, 1580 cm^{-1}. $[\alpha]_D$ + 93° (C 0.5; MeOH) (Lit.[10] $[\alpha]_D$ + 14°), identical with pipoxide chlorohydrin which should now be constituted as (VII). Pipoxide chlorohydrin (VII) on treatment with dilute methanolic potassium bicarbonate[9] afforded pipoxide (III) indicating the stereochemistry of the chlorine atom with respect to the tertiary hydroxyl group.

Acknowledgements : We are grateful to Professor Kupchan and Dr. Atal for authentic samples, Dr. P.C. Parthasarathy for helpful discussions, Dr. S. Selvavinayakam and coworkers for the analytical and spectral data and Dr. P. Moser for the ORD curves.

References

1. B.S. Joshi, V.N. Kamat and A.K. Saksena, Tetrahedron Letters, 2395 (1968).
2. B.S. Joshi, N. Viswanathan, D.H. Gawad and W. von Philipsborn, Helv. Chim. Acta, 58, 1551 (1975).
3. B.S. Joshi, N. Viswanathan, D.H. Gawad, V. Balakrishnan, W. won Philipsborn and A. Quick, Experientia, 31, 880 (1975).
4. N. Viswanathan, V. Balakrishnan, B.S. Joshi and W. von Philipsborn, Helv. Chim. Acta, 58, 2026 (1975).
5. B.S. Joshi, N. Viswanathan, D.H. Gawad, V. Balakrishnan and W. von Philipsborn, Helv. Chim. Acta, 58, 2295 (1975).
6. S.M. Kupchan, R.J. Hemingway, P. Coggon, A.T. McPhail and G.A. Sim, J. Am. Chem. Soc., 90, 2982 (1968).
7. J. Singh, K.L. Dhar and C.K. Atal, Tetrahedron, 26, 4403 (1970).
8. M.R. Demuth, P.E. Garrett and J.D. White, J. Am. Chem. Soc., 98, 634 (1976).
9. R. Hollands, D. Becher, A. Gaudemer and J. Polonsky, Tetrahedron, 24, 1633, (1968).
10. J. Singh, K.L. Dhar and C.K. Atal, Indian J. Pharm., 33, 50 (1971).

(Received in UK 1 March 1979)