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Thalidoxine, a New Aporphine-Benzylisoquinoline Alkaloid[1]

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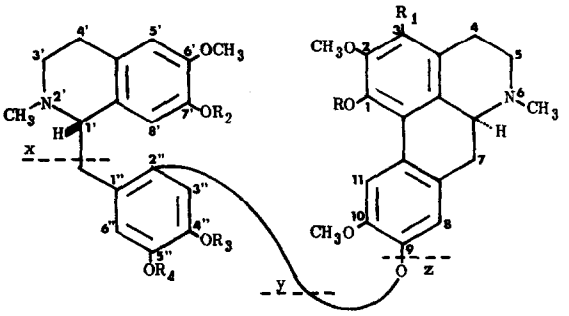
The dimeric alkaloid thalidoxine (1), $C_{40}H_{46}N_2O_3$, $[\alpha]_D^{25}$ +113° (c 0.2 MeOH) has been obtained from Thalictrum dioicum L. (Ranunculaceae) as an amorphous base. The ir spectrum ($CHCl_3$) contained phenolic hydroxyl absorbance at 3540 cm^{-1}. The uv spectrum λ_{max}^{MeOH} 275, 296sh and 310sh (log ε 4.23, 4.08 and 4.02) was reminiscent of that for the well-known thalicarpine (3),[2] and gave no bathochromic shift in base. The mass spectrum m/e 682 (M^+), 476 (M - x), 340 (M - y), 324 (M - z) and 206 (x, base), pointed to the fact that thalidoxine was an aporphine-benzylisoquinoline dimer with a phenolic function located on the benzylisoquinoline ring C. The nmr spectrum (Table), with signals for six methoxyl groups indicated that 1 was an O-demethyl analog of thalicarpine (3), and indeed diazomethane O-methylation afforded a crystalline product, identical in terms of tlc R_f values, uv, ir, nmr and mass spectra, mp and ord curves, with authentic thalicarpine (3). The two possible expressions for thalidoxine at this stage were 1 and 2. The choice between these two isomeric structures was forthcoming from the study of the nmr spectrum of thalidoxine acetate (4), mp 128-129° ($CHCl_3$), prepared by pyridine-acetic anhydride treatment of 1.

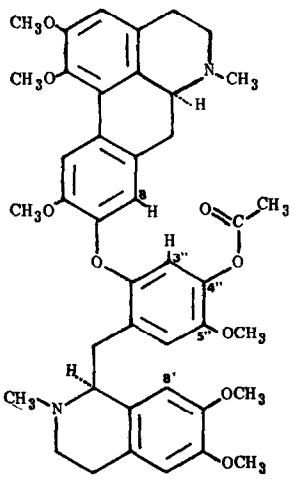
The nmr spectrum ($CDCl_3$) of thalidoxine acetate (4) contained singlets for one acetate methyl group at δ2.25, two N-methyl groups at δ2.57 and 2.61, six aromatic methoxyls at δ3.54, 3.67, 3.70, 3.84, 3.85 and 3.90, one shielded C-8' proton at δ6.13, five aromatic protons at δ6.40, 6.54 (2), 6.60 and 6.87, and a deshielded C-11 proton at δ8.14. It is well established that a proton ortho to a phenolic function is shifted downfield by 0.3 ppm upon O-acetylation;[3] however, the δ6.77 signal in the spectrum of the phenol 1 (Table) was shifted only to δ6.87 in the acetate 4.

The most striking feature in the nmr spectrum of thalidoxine acetate (4)[4] was that although the chemical shift of the C-8' proton indicated little conformational change from 1 or 3 within the isoquinoline moiety, there was present at δ6.40 an aromatic proton signal which corresponded

to one of the signals originally at δ6.50 or 6.57 in the spectrum of 1. This upfield shift must be attributed to a through-space shielding effect of the acetate carbonyl. Inspection of molecular models showed that an acetate carbonyl at C-4" can be located in close proximity to both the C-8 proton of the aporphine system and the C-3" proton as shown in expression 9, and can thus exert a shielding effect of 0.1-0.2 ppm on these aromatic protons, as observed experimentally.[5] Conversely, if the acetate function had been located at C-5", the carbonyl could not have approached,



1, R = R_2 = R_4 = CH_3; R_1 = R_3 = H
2, R = R_2 = R_3 = CH_3; R_1 = R_4 = H
3, R = R_2 = R_3 = R_4 = CH_3; R_1 = H
4, R = R_2 = R_4 = CH_3; R_1 = H; R_3 = $COCH_3$
5, R = R_3 = R_4 = CH_3; R_1 = R_2 = H
6, R = R_1 = H; R_2 = R_3 = R_4 = CH_3
7, R = R_1 = R_2 = H; R_3 = R_4 = CH_3
8, R = R_2 = R_3 = R_4 = CH_3; R_1 = OCH_3



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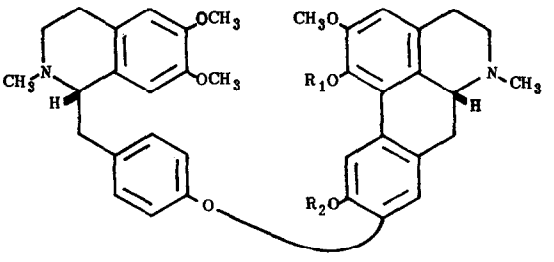
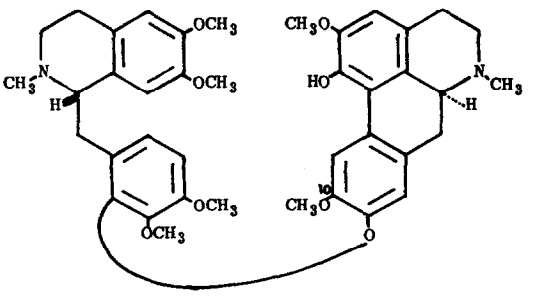


10, R_1 = R_2 = H
11, R_1 = CH_3; R_2 = H
12, R_1 = R_2 = CH_3



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intramolecularly, any aromatic proton to exert an overall shielding effect. It follows that thalidoxine acetate must be represented by expression 9, and that the low field aromatic proton signal at δ6.77 in the nmr spectrum of 1, which was shifted to δ6.87 in the spectrum of 4, must be assigned to the C-3" proton. By analogy, the singlet furthest downfield in the region δ6.60-6.78 in the nmr spectra of other thalicarpine-type dimeric alkaloids is also probably due to the C-3" aromatic proton.

Additionally, the large number of variously substituted aporphine-benzylisoquinoline dimers now known allows the clarification of the assignments of several methoxyl resonances. Inspection of the Table clearly shows that contrary to prior assignments[2] the highest field methoxyl resonance near δ3.58 is characteristic of a C-7' methoxyl group, while the peak at δ3.71 is due to the aporphine C-1 methoxyl.

Table

NMR Resonances of Thalicarpine Type Alkaloids in δ Values ($CDCl_3$)

	Thalicarpine[6] (3)	Thalmelatine[2] (5)	Thalictropine[7] (6)	Thalictrogamine[7] (7)	Adiantifoline[8] (8)	Thalidoxine (1)
N-CH_3	2.45, 2.48	2.42, 2.48	2.47, 2.50	2.49, 2.52	2.44, 2.47	2.47, 2.48
C-7' OCH_3	3.58	-	3.58	-	3.59	3.57
C-1 OCH_3	3.71	3.72	-	-	3.78	3.70
C-10 OCH_3	3.95	3.95	3.92	3.95	3.94 or 3.96	3.90
Other methoxyl groups: C-2, C-6', C-3" and C-4"	3.80	3.79	3.78	3.79	3.78	3.75
	3.80	3.79	3.78	3.83	3.78	-
	3.83	3.79	3.82	3.83	3.82	3.78
	3.91	3.88	3.88	3.92	3.89	3.88
C-8' H	6.21	6.43	6.20	6.40	6.24	6.23
C-3" H	6.67	6.68	6.67	6.78	6.60	6.77
C-11 H	8.19	8.18	8.18	8.18	8.08	8.15
Other aromatic protons: C-3, C-8, C-5' and C-6"	6.53	6.52	6.55	6.51	-	6.50
	6.56	6.55	6.55	6.57	6.55	6.50
	6.60	6.60	6.55	6.57	6.55	6.50
	6.62	6.60	6.59	6.57	6.60	6.57

Comparison of the data in the thalicarpine series (Table) with those of the pakistanine[9] and the fetidine[10] series further revealed that the aporphine C-10 methoxyl group in all of these aporphine-benzylisoquinoline dimers resonates downfield from δ3.90. The spectra of pakistanine (10) and 1-O-methylpakistanine (11) are devoid of a methoxyl peak in this region. But the spectrum of 1,10-di-O-methylpakistanine (12) shows a C-10 methoxyl singlet at δ3.91. In the spectrum of fetidine (13), the C-10 methoxyl peak is located at δ3.97.

References

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2. For a recent review as well as for lead references on the aporphine-benzylisoquinoline dimers see M. Shamma, "The Isoquinoline Alkaloids", Academic Press Inc., New York (1972), p. 232.
3. R.J. Highet and P.F. Highet, J. Org. Chem., 30, 902 (1965).
4. The chemical shifts for the spectra of 1 and 4 were concentration, temperature and time dependent, so that average values are reported here. This phenomenon has been observed with other dimeric isoquinoline bases: cf. M. Curcumelli-Rodostamo and M. Kulka in "The Alkaloids", ed. by R.H.F. Manske, Vol. 9, Academic Press, New York (1967), p. 133; and T. Kametani, H. Iida, K. Sakurai, S. Kano and M. Ihara, Chem. Pharm. Bull. Japan, 17, 2120 (1969).
5. L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford (1969), p. 88.
6. S.M. Kupchan and N. Yokoyama, J. Amer. Chem. Soc., 85, 1361 (1963); M. Tomita, S.-T. Lu and Y.Y. Chen, J. Pharm. Soc. Japan, 86, 763 (1966); and N.M. Mollov and H.B. Dutschewska, Tetrahedron Letters, 853 (1966).
7. M. Shamma and J.L. Moniot, Tetrahedron Letters, in press (1973).
8. R.W. Doskotch, P.L. Schiff, Jr., and J.L. Beal, Tetrahedron Letters, 4999 (1968).
9. M. Shamma, J.L. Moniot, S.Y. Yao, G.A. Miana and M. Ikram, J. Amer. Chem. Soc., 95, 1381 (1972).
10. M.P. Cava and K. Wakisaka, Tetrahedron Letters, 2309 (1972); and M.P. Cava, private communication.