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ANTIRHINE AND ANTIRHINE METHO-SALT FROM THE LEAVES OF *STRYCHNOS CAMPTONEURA*

N. G. BISSET and J. D. PHILLIPSON*

Pharmacognosy Research Laboratories, Department of Pharmacy, Chelsea College, University of London, Manresa Road, London SW3 6LX

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Key Word Index—*Strychnos camptoneura*; Loganiaceae; indole alkaloids; antirhine; antirhine metho-salt.

Abstract—The isolation of antirhine and antirhine metho-salt from the leaves of *Strychnos camptoneura* is described. The conformation of antirhine is discussed.

Strychnos camptoneura Gilg et Busse is a large liane occurring in West and northern Central Africa.[1] The stem-bark and root-bark alkaloids exhibit strong muscle-relaxant properties[2] and the isomeric heteroyohimbine anhydronium bases alstonine and serpentine have been isolated.[3] The stem-bark alkaloids have also yielded retuline *N*-oxide (a base of the akuammicine type) and camptoneurine (a base derived from tryptamine- and gentianine-like moieties).[4]

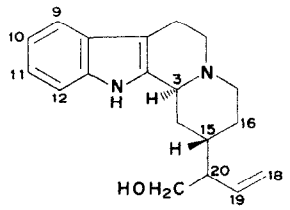
West African samples of *S. camptoneura* leaves contain up to 0·37% tertiary alkaloid[5] and from one sample we have obtained two bases. The MS of the major one points to an antirhine-type structure:[6] peaks at *m/e* 156, 169, 184 and 197 indicating an *ar*-unsubstituted tetrahydro-β-carboline moiety; the base peak at *m/e* 223 suggesting the presence of a fourth ring; and a peak at *m/e* 225 corresponding to loss of 71 m.u. from the mol.-ion peak at *m/e* 296. This conclusion is supported by examination of the other spectral data (see Experimental). The formula $C_{19}H_{24}N_2O$ (accurate mass measurement of the *m/e* 296 peak in the methiodide MS) and the α-configuration of H-3 (positive Cotton effects at 232 and 272 nm in the CD spectrum) suggest identity with antirhine itself (**1**); and this is confirmed by TLC and GLC comparison with the authentic base.

The two most likely conformations of antirhine have *trans* (**2**) and *cis* (**3**) quinolizidine ring junctions, respectively. The NMR signal for H-3 is broad and shows a large paramagnetic shift (δ 4·10, width at half height 10 Hz), which is indicative of a *cis* junction as in **3**;[7] this will be the most stable conformation since the bulky C-15 substituent will then be equatorial. However, weak Bohlmann bands in the IR spectrum at 2765, 2815 and

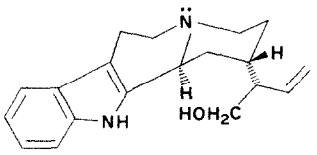
* Present address: Department of Pharmacognosy, School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX.

[1] LEEUWENBERG, A. J. M. (1969) *Meded. Landbouwhogesch. Wageningen* **69** (1), 75.
[2] SANDBERG, F., LUNELL, E. and RYRBERG, K. J. (1969) *Acta Pharm. Suec.* **6**, 79; SANDBERG, F., VERPOORTE, R. and CRONLUND, A. (1971) *Acta Pharm. Suec.* **8**, 341.
[3] VERPOORTE, R. and SANDBERG, F. (1971) *Acta Pharm. Suec.* **8**, 119.
[4] KOCH, M., GARNIER, J. and PLAT, M. (1972) *Ann. Pharm. Franc.* **30**, 299.
[5] BISSET, N. G. and PHILLIPSON, J. D. (1971) *Lloydia* **34**, 1.
[6] JOHNS, S. R., LAMBERTON, J. A. and OCCOLOWITZ, J. L. (1967) *Austral. J. Chem.* **20**, 1463.
[7] TRAGER, W. F., LEE, C. M. and BECKETT, A. H. (1967) *Tetrahedron* **23**, 365.

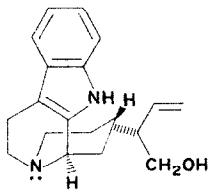
2853 cm^{-1} indicate that some of the conformer with the *trans* junction as in **2** is also present.



(1)



(2)



(3)

The spectral properties of the minor alkaloid (see Experimental) are similar to those of antirhine. However, in the MS there is an extra peak at *m/e* 310 indicating the presence of an additional CH_2 group; this peak is attributed to the ion formed by loss of HX from an antirhine-type metho-salt. The MS also establishes that the only halogen present is bromine. Positive Cotton effects at 227 and 267 nm in the CD spectrum of the base again indicate that H-3 has the α-configuration. The alkaloid is therefore identified as antirhine methobromide.

This identification is supported by the similarity of the MS and TLC properties with those of prepared antirhine methiodide. The compound isolated was the bromide salt, but it is not certain that this is the naturally-occurring form of the base, as halogenated solvents were used in the work-up.[8]

Since only one spot was noted on TLC of the natural and prepared antirhine metho-salts, it appears that only one metho-compound is formed. In view of the NMR evidence for the *cis* quinolizidine junction in antirhine, it may be suggested that in the metho-salts the quaternary methyl group has the α-configuration.[9]

Among indole alkaloids antirhine-type bases are unusual in that H-15 has the less common β-configuration. Antirhine itself has previously been found in the Rubiaceae (*Antirhea*)[6] and the Apocynaceae (*Rhazya*),[10] and it is now reported present in the Loganiaceae (*Strychnos*). Bases of the same skeletal type occur in four other genera of the Apocynaceae.[11] With this type of alkaloid the simultaneous presence of the tertiary and corresponding N_b-methyl quaternary bases has not been observed before.*

EXPERIMENTAL

The TLC was carried out using neutral silica-gel G (Merck) plates run in one of the following systems: (a) $CHCl_3$–MeOH (9:1); (b) MeOH; (c) EtOAc-*iso*PrOH-conc. NH_4OH (60:35:5); and (d) EtOAc-*iso*PrOH-5·5% NH_4OH (45:35:20). The GLC was performed as previously described.[5] The 100 MHz NMR spectrum was recorded in $CDCl_3$ at 50° with TMS ($\delta = 0$) as internal standard. The MS were determined with an A.E.I. MS902 high-resolution mass spectrometer operating at 70 eV.

Authentication of the plant material. Dr. A. J. M. Leeuwenberg, Laboratory for Plant Systematics and Plant Geography, Agricultural University, Wageningen, The Netherlands, collected the *Strychnos camptoneura* leaves *ca* 15 km east of Dimako, Cameroun, and also identified them. Material under no. *Leeuwenberg* 5826 is deposited in the herbarium at Wageningen.

* *Added in proof.* In a paper (SAKAI, S., OHTANI, H., IDO, H. and HAGINIWA, J. (1973) *Yakugaku Zasshi* **93**, 483) which appeared after the present note had been submitted for publication, antirhine and antirhine methochloride are listed among the alkaloids isolated from the roots of *Amsonia elliptica* (Thunb.) Roem. et Sch. (Apocynaceae).

[8] PHILLIPSON, J. D. and BISSET, N. G. (1972) *Phytochemistry* **11**, 2547.

[9] SAWA, Y. K. and MATSUMARA, H. (1969) *Tetrahedron* **25**, 5319, 5329.

[10] BANERJI, A., MAJUMDER, P. L. and CHATTERJEE, A. (1970) *Phytochemistry* **9**, 1491; SILVA, K. T. D. DE, SMITH, G. N. and WARREN, K. E. H. (1971) *Chem. Commun.* 905.

[11] HESSE, M. (1964) *Indolalkaloide in Tabellen*, pp. 101–102, Springer, Berlin; (1968) *Ergänzungswerk*, pp. 173–175, Springer, Berlin.

Isolation of the alkaloids. The dry, ground leaves (2·2 kg) were moistened with 10% NH_4OH and macerated with two successive lots of EtOAc. The combined extracts were concentrated under reduced pressure and shaken with four successive quantities of 2% H_2SO_4. The combined acid extracts were washed with EtOAc, basified with NH_4OH, and shaken with three successive portions of CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with H_2O, dried over anhyd. Na_2SO_4, and taken to dryness to yield 6·2 g (0·28%) total crude alkaloid as a brown solid. This material gave off-white crystals (0·95 g) from CH_2Cl_2. Prep. TLC of a 0·2 g portion using silica-gel plates run in the system CH_2Cl_2–MeOH (95:5) afforded a main band, the residue (0·13 g) from which crystallized in Me_2CO and was shown by TLC to comprise 1 major and 1 minor component. Treatment with dry Et_2O of a 70-mg portion yielded a soluble part (41 mg) which crystallized in MeOH and was identified as antirhine; the Et_2O-insoluble part was identified as antirhine methobromide.

Antirhine. λ_{max}^{EtOH} 226, 275, 283, 290 nm, λ_{max}^{EtOH} 248 nm; ν_{max}^{Nujol} 3260 (OH), 3075 (NH), 920 (vinyl), 740 (*o*-disubstituted C_6H_6) cm^{-1}, ν_{max}^{KCl} 2765, 2815, 2853 cm^{-1} (weak Bohlmann bands); δ 7·76 (1H, br.m, disappearing on deuteration; NH), 7–7·50 (4H, *m*; H-9, H-10, H-11, H-12), *ca* 5·62 (1H, octet; H-19), 5·26 (1H, *dd*, *J* 3, *J'* 9 Hz; H-18), 5·11 (1H, *dd*, *J* 3, *J'* 19 Hz; H-18), 4·10 (1H, *m*, width at half height 10 Hz; H-3), 3·64 (2H, *m*; 2 × H-21); MS (205°) *m/e* 296 (M^+; 50%), 295 (58), 265 ($M^+ - 31$; 13), 225 ($M^+ - 71$; 84), 223 (100), 197 (17), 184 (17), 169 (27), 156 (22), 144 (13), 143 (14), 130 (9); CD (MeOH) $[\theta]_{272} + 5{,}500$, $[\theta]_{232} + 19{,}300$; TLC: R_f values system *a* 0·08, *b* 0·35, *c* 0·61, identical with those of authentic antirhine; on heating with $Ce(SO_4)_2$ spray reagent identical pale lilac colour; GLC: R_{Stry}^{270} 0·99, identical with that of authentic antirhine.

Methiodide. ν_{max}^{Nujol} 3360 (OH) and 3240 (NH) cm^{-1}; MS (260°) *m/e* 310 ($M^+ - HI$; 14%), 296 (52), 295 (65), 265 (17), 225 (92), 223 (85), 197 (20), 184 (24), 169 (78), 156 (24), 144 (24), 143 (20), 142 (MeI^+; 100), 130 (17), 127 (I^+; 31); accurate mass measurement: found 296·1886, calc. for $C_{19}H_{24}N_2O$ 296·1889.

Acetate. Prepared from antirhine by treatment with Ac_2O/pyr. at 100°; λ_{max}^{EtOH} unchanged; ν_{max}^{Nujol} 1720 cm^{-1}.

Antirhine methobromide. λ_{max}^{EtOH} 222, 272, 280, 289 nm, λ_{min}^{EtOH} 242 nm; ν_{max}^{Nujol} 3330 (OH), 3190 (NH); MS (225°) *m/e* 310 ($M^+ - HBr$; 18%), 296 (55), 295 (67), 265 (20), 225 (100), 223 (96), 197 (16), 184 (34), 169 (38), 156 (37), 144 (29), 143 (27), 130 (22), 96 ($MeBr^+$; 37), 94 (38), 82 (HBr^+; 15), 80 (15); accurate mass measurement: found 310·2053, calc. for $C_{20}H_{26}N_2O$ 310·2045; found 296·1887, calc. for $C_{19}H_{24}N_2O$ 296·1889; found 295·1805, calc. for $C_{19}H_{23}N_2O$ 295·1810; CD (70% MeOH) $[\theta]_{267} + 9{,}040$, $[\theta]_{227} + 9{,}040$; TLC: R_f value system *d* 0·30, identical with that of antirhine methiodide; on heating with $Ce(SO_4)_2$ spray reagent identical grey–green colour.

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