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## ALKALOIDS OF *SIDA CORDIFOLIA*\*<sup>†</sup>

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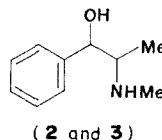
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**Key Word Index**—*Sida cordifolia*; Malvaceae;  $\beta$ -phenethylamines; carboxylated tryptamines; quinazoline alkaloids;  $\beta$ -phenethylamine; ephedrine;  $\psi$ -ephedrine; *S*-(+)-*N*<sub>b</sub>-methyltryptophan methyl ester; hypaphorine; vasicinone; vasicine; vasicinol; sympathomimetic amines; bronchodilator principle.

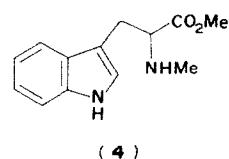
*Sida cordifolia* L. (Malvaceae) is distributed along with other species of this genus throughout the tropical and sub-tropical plains of India. Extracts of different parts of the plant are reported to be used in the Ayurvedic system of medicine for a variety of purposes [1]. Ghosh and Dutta previously isolated [2] ephedrine and  $\psi$ -ephedrine from the aerial parts of this plant, while Dutta reported [3] the presence of appreciable quantities of  $H_2O$ -soluble alkaloids but could not isolate them. Reports on nitrogenous constituents of this family of over 700 species are very few. *Gossypium* is the only other genus where the presence of two biogenic amines, viz. 5-hydroxytryptamine [4], and histamine [5] has been reported. No true alkaloids have been previously described in the malvaceae.

From the roots of this plant, we have now isolated three  $\beta$ -phenethylamines, viz.  $\beta$ -phenethylamine (1), ephedrine (2), and  $\psi$ -ephedrine (3), 2 carboxylated tryptamines, *S*-(+)-*N*<sub>b</sub>-methyltrypto-

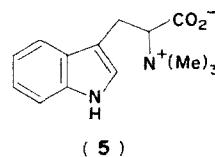
phan methyl ester (4) and hypaphorine (5), and three quinazoline alkaloids, vasicinone (6), vasicine (7) and vasicinol (8). In addition, liberal amounts of choline and betaine have been obtained from the  $H_2O$ -soluble alkaloid fraction.



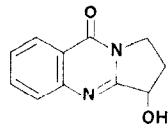
epimeric at the  $\beta$ -position



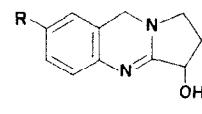
(4)



(5)



(6)



(7) R = H

(8) R = OH

\* Part I in the projected series "Chemical Constituents of Malvaceae".

The stems and leaves contain essentially the same alkaloids as are present in the roots, but in different amounts. Ephedrine and  $\psi$ -ephedrine constitute the major bases in the aerial parts, but occur as minor components in the roots. Another interesting quantitative variation has been observed with ageing. The roots of 6-month-old plants afford quinazoline alkaloids as the major alkaloids and only traces of the carboxylated tryptamines. The situation is reversed in roots of 2-yr-old plants, which contain carboxylated tryptamines in place of the quinazoline alkaloids. Also, the amount of alkaloids considerably declines in older plants. The occurrence of true alkaloids in a member of the Malvaceae has thus been demonstrated for the first time.

The favourable combination of 3 sympathomimetic amines ( $\beta$ -phenethylamine, ephedrine, and  $\psi$ -ephedrine) and a potent bronchodilator principle (vasicinone) [6] in this species would account for the major therapeutic uses of the plant extract in the Ayurvedic system of medicine.

## EXPERIMENTAL

*Extraction of alkaloids.* The bases in the  $C_6H_6$  extract was separated into 4 fractions by column chromatography over neutral alumina (Brockmann, activity grade *ca* III) followed by PLC (Si gel G, E. Merck, 2 mm thickness). The alkaloid mixtures from the EtOH extract were broadly divided into 4 groups [7]:  $CHCl_3$ -soluble acetates,  $CHCl_3$ -soluble moderately strong bases,  $EtOAc$ -soluble polar bases, and  $H_2O$ -soluble bases. The mixture of  $EtOAc$ -soluble bases was separated into phenolic and non-phenolic entities by passing its MeOH soln over a column (1  $\times$  20 cm) of Amberlite IRA-400 ( $\ominus OH$ ) resin [8]. For TLC and PLC, 2 solvents were used: 1 (*n*-BuOH- $HOAc$ - $H_2O$ , 4:1:2) and 2 ( $CHCl_3$ -MeOH, 9:1). Dragendorff, Ehrlich- and ninhydrin reagents were used for staining purposes. The identity of the pure compounds was established by their mp, mmp, co-TLC with reference samples; by chemical transformation into suitable derivatives and from correspondence of optical rotation, UV, IR, PMR, and MS spectra of the alkaloids with those reported in literature.

Air-dried and milled roots of *S. cordifolia*\* (3.5 kg) were processed and the descriptions of the alkaloids are given here in order of their isolation. The brown basic gum (458 mg), obtained from the  $C_6H_6$  extract, was chromatographed over alumina (2  $\times$  30 cm) using  $C_6H_6$  and mixtures of  $C_6H_6$  and  $CHCl_3$  as eluents.

*$\beta$ -Phenethylamine (1).* PLC (Solvent 2) of the early  $C_6H_6$  eluates afforded, from the upper preparative zone ( $R_f \sim 0.8$ ),  $\beta$ -phenethylamine as a brown liquid (42 mg), co-TLC, IR, and PMR spectra established its identity.

The middle preparative zone ( $R_f \sim 0.65$ ) from the later  $C_6H_6$  and  $C_6H_6$ - $CHCl_3$  eluates gave a mixture of ephedrine and  $\psi$ -ephedrine. These were separated by fractional crystallization of their hydrochlorides from EtOH.

*Ephedrine (2).* The alkaloid hydrochloride crystallized from a small volume of EtOH as colourless needles (22 mg), mp and mmp 220° (co-TLC of the base, IR).

*$\psi$ -Ephedrine (3).* The EtOH mother liquor, after separation of ephedrine hydrochloride, was evaporated. The residue was washed with  $CHCl_3$ , the base was liberated and crystallized from aq. EtOH as colourless crystals (13 mg), mp and mmp 117-118° (co-TLC, IR).

*S-(+)- $N_b$ -Methyltryptophan methyl ester (4).* The lower PLC zone ( $R_f \sim 0.3$ ) from the  $CHCl_3$  eluates gave a pale yellow gum (57 mg); the spectral data ( $M^+$ , *m/e* and PMR) are consistent with those reported in the literature [9], the base hydrochloride crystallized from EtOH as needles, mp 168-170°;  $[\alpha]_D^{25} + 47.8^\circ$  (*c* 0.48, MeOH). The IR spectrum was superimposable with an authentic sample of *S*-(+)- $N_b$ -methyltryptophan methyl ester hydrochloride, prepared from abrine [10].

A further crop (22 mg) of a mixture of ephedrine and  $\psi$ -ephedrine was obtained from the  $CHCl_3$ -soluble acetates. The  $CHCl_3$ -soluble moderately strong base fraction on crystallization from AcMe afforded a mixture of 2 alkaloids,  $R_f$  0.48 and 0.64 (Solvent 1). It was dissolved in EtOH, to which ethereal HCl was added.

*Vasicinone (6).* Vasicinone, HCl first crystallized out as colourless needles (126 mg), mp 228-230°. The mp and mmp of the base-hydrochloride were identical with those of an authentic sample of vasicinone, HCl. The free base crystallized from EtOH as colourless needles, mp and mmp 198-200°; co-TLC ( $R_f$  0.64);  $[\alpha]_D^{25} - 78^\circ$  (*c* 0.52,  $CHCl_3$ ); UV; IR; MS (*m/e*) [11]; PMR [12] spectra of the base corresponded well with those of literature values. It appears that vasicinone obtained from this species is a mixture of l- and dl-forms [6].

The EtOH mother liquor, after separation of vasicinone, HCl, was evaporated. The free base, obtained from the hydrochloride, was dissolved in  $CHCl_3$  (10 ml) and chromatographed over a column of alumina (1.8  $\times$  24 cm). The early  $C_6H_6$  eluates afforded a further crop (11 mg) of vasicinone.

*Vasicine (7).* The  $Et_2O$  eluates from the column afforded vasicine (37 mg), mp 192-194°; co-TLC ( $R_f$  0.48);  $[\alpha]_D^{25} 0^\circ$ ; UV; IR; MS (*m/e*); PMR spectra of the compound corresponded well with the values reported in the literature [11-14].

*Vasicinol (8).* The  $EtOAc$ -soluble bases were separated into phenolic and non-phenolic bases [8] when vasicinol [13] was obtained from the phenolic alkaloid fraction as cream coloured crystals (31 mg); mp 270-273° (dec.);  $[\alpha]_D^{25} + 2.5^\circ$  (*c* 0.32,  $AcOH$ ); 6-O-methyl ether with ethereal  $CH_2N_2$  (monitored with TLC), mp 208-210° (lit. [14] mp 216-218°); UV; IR; MS data of this compound corresponded well with those reported in the literature [11, 14].

The mixture of water-soluble bases, after separation of choline (76 mg) in the usual way [7], was converted to the corresponding hydrochlorides by stirring an EtOH soln of their reineckates with Amberlite IRA-400 ( $Cl^-$ ).

*Hypaphorine (5).* The EtOH soln of the regenerated hydrochlorides/chlorides on concn afforded hypaphorine, HCl (14 mg), mp and mmp 230-232°; co-TLC; UV and IR spectra of the compound were consistent with those of an authentic sample [7].

*Betaine* The EtOH mother liquor, after separation of hypaphorine, HCl, was evaporated. The residue crystallized from a small vol. of MeOH-AcMe as colourless needles (84 mg) mp and mmp with betaine, HCl, 285-288°; co-TLC carried out in 3 solvents systems also indicated its identity.

\* The identity of the plants was confirmed by Dr. C. S. P. Rao, Department of Botany, Banaras Hindu University.

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