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PARVINE, A NEW ANGUSTINE-TYPE ALKALOID FROM *NAUCLEA PARVA**

MALCOLM SAINSBURY and BRIAN WEBB

School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, England

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Abstract—The bark of *Nauclea parva* contains several alkaloids, the most abundant of which, parvine, is of the corynanthé-type. The proof of structure of this alkaloid is given and its synthesis from harmalan and nicotinoyl chloride is described.

INTRODUCTION

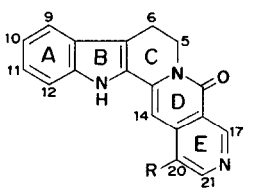
The genus *Nauclea* L. (*Sarcocephalus* Afzel ex R.Br.) of the family Rubiaceae is widely distributed in tropical regions yet, prior to the studies of McLean and his co-workers [1a–e] on *N. diderrichii*, little phytochemical work had been conducted upon members of this group. From this plant McLean has isolated a wide variety of alkaloids including simple β-carbolines, pyridines, indole pyridines and glycosidic alkaloids and recently a British group [2] have shown that pyridino-indolo-quinolizidone structures occur in the leaves of *N. coadunata*.

We now report upon the structure and synthesis of parvine the major alkaloid of *N. parva* Merrill (syn. *Sarcocephalus parvus*), a small tree indigenous to Sarawak

RESULTS

The bark of *N. parva* contains a number of alkaloids, but individual compounds are present in very low concentrations; thus the most abundant alkaloid, parvine, represents only 0·001% of an air dried sample.

Parvine ($C_{18}H_{13}N_3O$) is an orange coloured cystalline solid which has an UV spectrum, λ_{max} (ε) nm 222 (32,356), 252 (25,740), 374 (36,480) and 392 (37,500), very similar to that of angustoline (1), λ_{max} (ε) nm 221 (30,900), 251 (23,440), 289 (13,490), 308 (8,710), 375 (38,900) and 395 (39,810), an alkaloid first isolated from an Apocynaceous plant *Strychnos angustiflora* Benth [3]. Both parvine and angustoline show bands at 1650 cm^{-1} in the IR spectra and on this basis we allocated, provisionally, structure (**2**) to parvine

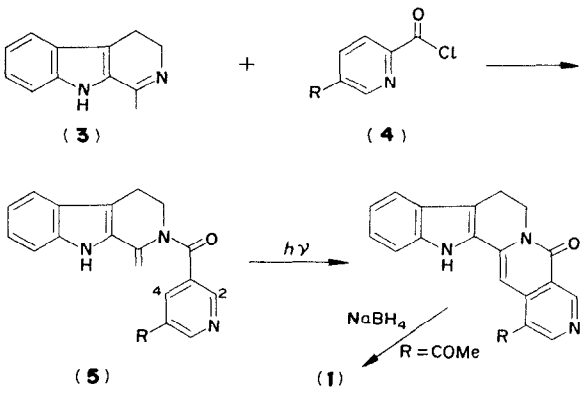


(**1**) R = MeCH(OH)–
(**2**) R = H

Parvine is very insoluble in most solvents, so that it was necessary to determine its PMR spectrum in trifluoroacetic acid most of the features of this spectrum (see experimental) are in accord with structure (**2**), but because of N-protonation in this solvent and consequential coupling with the adjacent H atoms, the position of the N atom in ring E was not established with certainty. Furthermore, because of the very small amount of material available the preparation of suitable derivatives to overcome this problem was not possible.

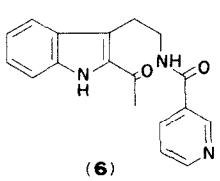
* Since going to press Prof J L Pousset has isolated from *Nauclea latifolia* an alkaloid nauclefine which is identical with parvine (1975) *Phytochemistry* **14**, 1407

(±)-Angustoline has recently been synthesised [4] by the following route:



In the penultimate step two products might arise through cyclisation of the exocyclic $-CH_2-$ group of (**5**, R=COMe) with either C_2 or C_4 of the pyridine ring. In practice, however, only one product (**1**) was isolated

Clearly parvine may be synthesised by a similar sequence using nicotinoyl chloride (**4**, R=H), rather than (**4**, R=COMe) and omitting the last step When harmalan (**3**) and nicotinoyl chloride were combined in dimethylformamide solution and the product worked up by extraction with aqueous acid the 2-acetylindole (**6**) was obtained rather than the required intermediate (**5**, R=H) Presumably this product arises from (**5**, R=H) by hydrolysis, for when aqueous conditions of isolation are avoided the amide (**5**, R=H) is obtained in fair yield Oxidative cyclisation of (**5**, R=H) by irradiation with "soft" UV light then afforded a single compound identical in mp, mmp, IR spectroscopy with parvine



To check that cyclisation of (**5**, R=H) had occurred via C_4 to give (**2**) the methiodide of the latter was prepared and its PMR spectrum in trifluoroacetic acid determined. The result demonstrates most clearly that the structure (**2**) for parvine is correct, for now the H atom attached to C_{17} resonates as a singlet at δ 9·5, and C_{20}-H and C_{21}-H form an AB system with doublets (J 6Hz) at δ 7·9 and 8·4 respectively

The bark of *N. parva* also contains β-sitosterol, campesterol and stigmasterol as well as traces of a terpenoid acid, mp 293·5° (MeOH) (measured mass 588·400, calc for $C_{35}H_{56}O_3$, 588·403 and for $C_{42}H_{52}O_2$, 588·397). Two other alkaloids $C_{20}H_{20}N_2O_3$ (measured mass 336·148, calc mass 336·147) and $C_{20}H_{14}N_2O_2$ (measured mass 314·104, calc 314·106) occur in very small amounts in the bark and the structures of these will be examined further when more plant material becomes available

DISCUSSION

The occurrence of pyridino-indolo-quinolizidones in Rubiaceous plants and also in species from the Loganaciae is taxonomically interesting, although their ubiquity in the latter [2] has caused their authenticity as alkaloids to be questioned and there has been some discussion as to their origins either as natural products or as artefacts [1d,2,3]

In our work the use of nitrogenous reagents or basic conditions during the isolation procedure were avoided and chromatographic analysis indicated the presence of parvine at the very earliest stages of the work up, thus although this is not conclusive evidence, we tend to the view that parvine is a true alkaloid of *N. parva*.

EXPERIMENTAL

Isolation of parvine Air dried bark (400 g) was pulverized and extracted (Soxhlet) with MeOH (10 l.) Removal of solvent afforded a brown gum (10 g) which was applied to a column of Si gel and eluted first with $CHCl_3$ petrol mixtures and then with $CHCl_3$–MeOH 60:80 in 175 10-ml fractions. Early fractions, on work up yielded a mixture of campesterol β-sitosterol and stigmasterol as well as traces of a terpenoid acid (see above) Fractions 62–71 (1·5% MeOH in $CHCl_3$) were combined and after removal of the solvent the residue was further purified by chromatography on 1 m plates coated with 2 mm thick layers of Si gel eluting with Et_2O The major band, R_f 0·5–0·6 was removed and extracted with MeOH to yield 0·3 mg of a highly fluorescent solid mp 230–40° dec, molecular formula $C_{20}H_{14}N_2O_2$ λ_{max} 265, 295, 350, 372, 415 nm ν_{max} 3360, 1690, 1630, 1600 cm^{-1} (nujol mull) Similarly fractions 72–89 (5–10% MeOH in $CHCl_3$) when combined and rechromatographed on plates, yielded, as the major component, a yellow gum (0·1 mg) $C_{20}H_{20}N_2O_3$, λ_{max} 316, 405 nm, ν_{max} 3240, 1740, 1650, 1600 cm^{-1} Fractions 89–123 (10–15% MeOH in $CHCl_3$), on combination and removal of solvent, gave a brown gum (10 mg) this was separate by TLC on Si gel eluting with 5% MeOH in $CHCl_3$ The major band

R_f 0·55–0·61 was removed and extracted with MeOH to yield parvine as an orange coloured solid (4 mg) mp 292–4 (aq MeOH) *m/e* 287 (100%), 286 (80%), 272 (15%) δ (TFA) 9·65 broad doublet [1H] (H-17), 8·45 *m*, [1H] (H-21), 8·05–7·20 *m* [6H] (aromatics) 4·78 *t*, *J* 7Hz, [2H] (H_2-5), 3·22·6 *J* 7Hz, [2H] (H_2-6), ν_{max} 3250, 1650, 1610 1600 cm^{-1} [Found C, 75·0, H, 4·4, $C_{18}H_{13}N_3O$ requires C, 75·2, H, 4·6%]

Synthesis of parvine Reaction of harmalan with nicotinoyl chloride Nicotinoyl chloride, generated *in situ* from its hydrochloride (0·8 g) salt by treatment with a 4-fold excess of triethylamine, was reacted with harmalan (1 g) in DMF soln Solvent was removed under red pres and residue extracted with 2M HCl, basification of the extracts afforded the indole (6) mp 160–5° (EtOH), 0·6 g *m/e* 307 (10%) 264 (5%), 185 (100%) δ (D_6-DMSO) 9·0 *bs* [2H], 8·8 *bs* [1H], 8·7 *bd* [1H], 8·2 *bd* [1H], 7·85–7·0 *m* [5H], 3·5 *m* [4H], 2·62 *s* [3H] ν_{max} 3340, 1665, 1640 cm^{-1} [Found C, 70·5, H, 5·5, N, 13·5 $C_{18}H_{17}N_3O_2$ requires C, 70·3, H, 5·6, N, 13·7%]. When this reaction was repeated, this time using CH_2Cl_2 as solvent instead of DMF and the residue, after evaporation of the solvent, applied to a column packed with Si gel and eluted with 2% MeOH in dry Et_2O the required product (**5**) was obtained Yield 0·65 g, almost colourless plates, mp 101–5° (dec) (softens at ~80°) *m/e* 289 (50%), 288 (25%), 261 (65%), 260 (100%), 106 (45%) ν_{max} 3300, 1645, 1610, 1590 cm^{-1} δ ($CDCl_3$) 9·3 [1H] *s* (NH), 8·74 [2H] *bs*, 7·95–7·10 [6H], 5·15 [1H] *m*, 4·3 [1H] *m*, 4·25 [2H] *t*, *J* 7Hz, 3·08 [2H] *t*, *J* 7Hz. [Found C, 74·6, H, 5·0, N, 14·3 $C_{18}H_{15}N_3O$ requires C, 74·7, H, 5·2, N, 14·5%] This product (0·4 g) in MeOH (500 ml) was irradiated with "soft" UV light during 24 hr Solvent was reduced in vol to *ca* 50 ml and cooled, crystals of parvine formed around the edges of the flask, these were collected and recrystallized from MeOH Yield 48% mp 292–4°, mmp with natural parvine 293–4° [Found C, 75·2, H, 4·5, N, 14·3 Calc for $C_{18}H_{13}N_3O$ C, 75·2, H, 4·6, N 14·6% Methiodide yellow crystalline solid mp 330° δ (TFA) 9·5 [1H] *s* (17-H), 8·3 [1H] *d*, *J* 6Hz (21-H), 7·9 [1H] *d*, *J* 6Hz (20-H); 7·68–7·2 [4H] *m* (9-H, 10-H, 11-H, 12-H), 7·20 [1H] *s* (14-H), 4·75 [2H] *t*, *J* 7Hz (5-H_2), 3·4 [2H] *t*, *J* 7Hz (6-H_2), 4·4 [3H] *s* (N-Me) [Found C, 53·1, H, 3·8, N, 10·0 $C_{19}H_{16}N_3OI$ requires C, 53·2, H, 3·75, N, 9·8%] Parvine, at 50 mg/kg, showed no effect *in vivo* (mice), *in vitro* it produced non-specific contractions of the guinea pig ileum, and reduced the tone and activity of the rabbit duodenum preparation

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