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ALKALOIDS OF THE LEAVES OF *VOACANGA GRANDIFOLIA**

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Key Word Index—*Voacanga grandifolia*; Apocynaceae; alkaloids; vobtusine; vobtusine–lactone; deoxyvobtusine.

Abstract—Besides vobtusine and vobtusine–lactone, deoxyvobtusine was isolated from the leaves of *Voacanga grandifolia* (Miq.) Rolfe. Spectral and chemical evidence, not reported earlier, but pertaining to the structure and stereochemistry of the alkaloid are presented.

INTRODUCTION

IT IS clear from previous investigations of some nine species that the genus *Voacanga* elaborates indole alkaloids of diverse skeletal patterns.[1] This has interested us to chemically investigate a new species, *V. grandifolia* (Miq.) Rolfe,[2] a native of Java and cultivated in the Indian Gardens, which has not been previously examined. The present communication discusses the isolation and characterization of the leaf alkaloids of this plant.

RESULTS AND DISCUSSION

From the leaves of *V. grandifolia* was isolated, besides vobtusine (**1**)[3,4] and vobtusine–lactone (**2**),[5]* another dimeric base, $C_{43}H_{50}N_4O_5$ (M^+ 702), in poor yield, which was identified as deoxyvobtusine, an alkaloid reported[6] by Poisson *et al.* from *V. africana*. The same alkaloid, designated as goziline was simultaneously reported[7,8] by Schmid *et al.* from *Hedranthera barteri*.

Mainly from spectral data, these authors proposed the structure (**3**) for the alkaloid. In the present communication, we place on record our independent chemical and spectral observations bearing on the structure and stereochemistry of the alkaloid. The structural similarity of deoxyvobtusine with vobtusine prompted us to establish chemical correlation between these two bases. Accordingly, deoxyvobtusine was subjected to sealed-tube acid-catalyzed decarboxylation[9] to afford decarbomethoxydeoxyvobtusine (**4**), $C_{41}H_{48}N_4O_3$

* Preliminary report of this work was presented in the "Convention of Chemists", CSIR, India, (1972), Abstract p. 81.

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[3] POISSON, J., PLAT, M., BUDZIKIEWICZ, H., DURHAM, L. J. and DJERASSI, C. (1966) *Tetrahedron* **22**, 1075.

[4] GORMAN, A. A., AGWADA, V., HESSE, M., RENNER, U. and SCHMID, H. (1966) *Helv. Chim. Acta.* **49**, 2072.

[5] KUNESCH, N., POISSON, J. and DAS, B. C. (1968) *Tetrahedron Letters* 1745; *The position of the OH group in vobtusine–lactone has since been revised as being similar to that in vobtusine (**1**) [Personal communication with Dr. B. C. Das].

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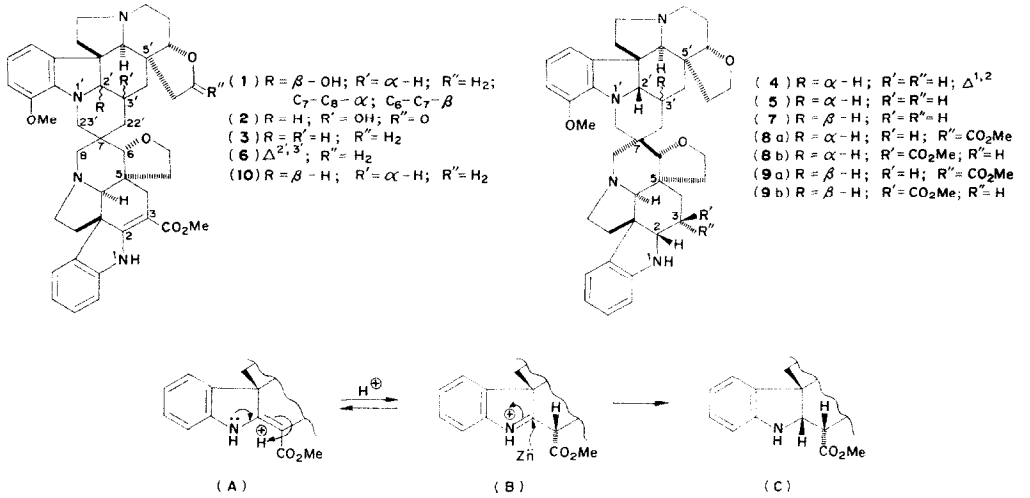
(M^+ 644) λ_{max}^{EtOH} 223, 264 and 298–303 (sh) (log ϵ, 4·90, 4·12 and 3·42) nm. Reduction of (**4**) with zinc and 10% methanolic H_2SO_4 gave dihydrodecarbomethoxydeoxyvobtusine (**5**), $C_{41}H_{50}N_4O_3$ (M^+ 646), as indicated from its UV, λ_{max}^{EtOH} 219, 262 and 307 (log ϵ, 4·41, 4·08 and 3·60) nm and MS data. In a parallel experiment, vobtusine was converted[4] to anhydrovobtusine (**6**). Sealed-tube acid-catalyzed decarboxylation of the latter followed by reduction of the decarboxylated product with zinc and 10% methanolic H_2SO_4 afforded tetrahydrodecarbomethoxyanhydrovobtusine (**7**), $C_{41}H_{50}N_4O_3$ (M^+ 646) which is isomeric with (**5**) and exhibits similar UV. λ_{max}^{EtOH} 220, 258 and 298–300 (log ϵ, 4·38, 4·07 and 3·66) nm and MS behaviour. TLC of (**5**) and (7) showed them to be different.



SCHEME-1: MECHANISM OF REDUCTION OF CARBOMETHOXY-α-METHYLENEINDOLINE ALKALOIDS WITH $Zn/MeOH-H_2SO_4$.

In another set of experiments, deoxyvobtusine itself was reduced with zinc and 10% methanolic H_2SO_4 to give two isomers, $C_{43}H_{52}N_4O_5$ (M^+ 704), the UV [(**8**a, major): λ_{max}^{EtOH} 220, 262 and 303 (log ϵ, 4·56, 3·90 and 3·36) nm and (**8**b, minor): λ_{max}^{EtOH} 220, 262 and 302 (log ϵ, 4·72, 3·95 and 3·66) nm], IR and MS data of which correspond to 2,3-dihydrodeoxyvobtusines, (**8**a) and (**8**b). The formation of two such epimers from compounds containing β-anilinomethacrylate chromophore under the above reaction conditions has recently been reported by Kutney *et al.*[10] Similar reduction of anhydrovobtusine (**6**) also afforded two isomeric tetrahydroanhydrovobtusines (**9**a) and (**9**b) $C_{43}H_{52}N_4O_5$ (M^+ 704) [(**9**a, major): λ_{max}^{EtOH} 220, 258 and 302 (log ϵ, 4·30, 4·11 and 3·94) nm and (**9**b, minor): λ_{max}^{EtOH} 220, 257 and 300 (log ϵ, 4·26, 4·14 and 3·80) nm]. Only one isomer was previously reported[4] in this reduction. But here again, in spite of their isomeric nature and close similarity in UV, IR and MS data, the four compounds (**8**a), (**8**b), (**9**a) and (**9**b),are chromatographically different. This is also in conformity with the observation that deoxyvobtusine is not identical with 2',3'-dihydroanhydrovobtusine obtained[8] by catalytic hydrogenation of anhydrovobtusine (**6**).

From their specific rotation values, similar ORD curves and from biogenetic consideration, it appears that vobtusine and deoxyvobtusine belong to the same stereochemical

[10] KUTNEY, J. P., BROWN, R. T., PIERS, E. and HADFIELD, J. R. (1970) *J. Am. Chem. Soc.* **92**, 1708.

series. The above observations can then be rationalized in the following manner. From the mechanism (see Scheme 1) recently postulated[11,12] by Le Men *et al.* for similar reductions of the carbomethoxy-α-methyleneindoline alkaloids, stereospecific reduction of the 2′,3′double bond in decarbomethoxyanhydrovobtusine is ensured by an initial thermodynamically controlled process (cf. A → B) involving the uptake of a proton at C-3′ from the axial β-side. This is then followed by the reduction of the resulting immonium ion (cf. B → C). Simultaneous reduction of the other indolenine system gives (**7**). The nonidentity of (**7**) with (**5**) implies that the latter must have an opposite configuration at C-3′. The same mechanistic argument also applies in the reduction of anhydrovobtusine (**6**) to (**9a**) and (**9b**). It seems, therefore, that both (**9a**) and (**9b**) have the same configuration at C-3′ [C-3′ H, β and axial] and that they differ only in the stereochemistry at C-3. Likewise, (**8a**) and (**8b**) are also epimeric at C-3.

The formation of (**9a**) and (**8a**) in excess over (**9b**) and (**8b**) does not violate the above mechanism but only indicates that the reduction of the β-anilinomethacrylate chromophore leading to their formation is not completely stereospecific as in the case of the other anilinoenamine system. Now, the fact that (**9a**) and (**9b**) are not identical with (**8a**) and (**8b**) demands that the two pairs have opposite configuration at C-3′. Consequently, the configuration of the C-3′ hydrogen of deoxyvobtusine should in all probability be expressed as (**10**).

There is a further point of interest in the UV spectra of (**5**), (**7**), (**8a**), (**8b**), (**9a**) and (**9b**). Although the overall feature of these spectra are very similar, the spectra of (**5**), (**8a**) and (**8b**) compare excellently with those reported for N_a-alkyldeacetylaspidospermines[13] while those of the vobtusine-derived compounds, (**7**), (**9a**) and (**9b**) exhibit hypsochromic shifts of 3–6 nm in the longer wave band. This small but finite difference in UV spectra of the two series of compounds is evidently due to their different stereochemistry, although the nature of the actual contributing factors is not clear.

EXPERIMENTAL

M.ps were determined on a Köfler block and are uncorrected. Brockmann alumina was used for column chromatography and silica gel G for TLC. UV spectra were measured using 95% aldehyde-free EtOH and IR spectra were run in Nujol mulls unless otherwise stated. Anhyd. Na_2SO_4 was used for drying and petrol used had the b.p. 60–80°. The reagent, CAS is a 0·1% solution of ceric ammonium sulphate in (1:1) aq. H_3PO_4. The homogeneity of the compounds was checked by TLC and MS.

Isolation of deoxyvobtusine (**10**), *vobtusine* (**1**) *and vobtusine–lactone* (**2**). Air-dried powdered leaves (1 kg) of *Voacanga grandifolia* were successively extracted with petrol. and $CHCl_3$. Both the extracts were concentrated, churned separately with 5% aq. citric acid, filtered and the filtrates fractionated into C_6H_6-soluble citrate (BSC) and $CHCl_3$-soluble citrate (CSC) fractions by successive extraction with C_6H_6 and $CHCl_3$. The BSC and CSC fractions were washed with NH_4OH, dried and concentrated. The remaining aq. citrate fractions (SB) were basified with NH_4OH, extracted with $CHCl_3$, dried and concentrated. The CSC fraction of the petrol extract was chromatographed. C_6H_6–$CHCl_3$ (6:1) eluate gave a solid which on repeated chromatography afforded deoxyvobtusine (**10**). A further quantity of (**10**) was also isolated from the CSC fraction of $CHCl_3$ extract (total yield, 0·003%). C_6H_6–$CHCl_3$ (4:1) eluate yielded a solid which on chromatography furnished vobtusine (**1**), m.p. 303° (dec.) $[\alpha]_D$ −311° (*c* 0·29; $CHCl_3$) (identified from UV, IR, PMR, MS and comparison with authentic sample). (**1**) was also obtained from the BSC and SB fractions of both petrol and $CHCl_3$ extracts (total yield, 0·03%). C_6H_6–$CHCl_3$ (3:1) eluate afforded a solid which on preparative TLC on silica gel plates gave vobtusine–lactone (**2**) (yield, 0·0002%) (identified by m.p., $[\alpha]_D$, UV, IR and MS).

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[13] WITKOP, B. and PATRICK, J. B. (1954) *J. Am. Chem. Soc.* **76**, 5603.

Deoxyvobtusine (**10**). M.p. 290° (dec.) [MeOH–$CHCl_3$]; $[\alpha]_D$ −303° (*c* 0·3; $CHCl_3$); CAS: blue colouration; λ_{max} 225, 268, 302 and 327 (log ε, 4·56, 4·09, 4·13 and 4·20) nm; differential UV of (**10**) with echitovenine,[14] λ_{max} 266 and 303 (log ε, 3·96 and 3·39) nm [cf. N_a-ethyl–deacetyl aspidospermine:[13] λ_{max} 268 and 312 (log ε, 3·98 and 3·43) nm]; ν_{max} 3400 (–NH), 1680 and 1610 (–N–C=C–C(=O)–OMe) cm^{-1}; δ (60 MHz, $CDCl_3$, TMS as internal standard): 8·90 (1 H, *s*, NH, disappeared on deuteriation), 7·30–6·61 (7 H, *m*, Ar–H), 5·38 (1 H, *d*, *J* 14 Hz: one of the C-8H), 3·83 (3 H, *s*, Ar–OCH_3), 3·76 (3 H, *s*, $-CO_2CH_3$) and 4·10–0·60 (41 H); *m/e* (abundance %): 702 (M^+, 100) 674 (8), 644 (10), 488 (71), 377 (65), 363 (10), 351 (M^{2+}, 11), 331 (6·5), 252 (18), 188 (19), 176 (11), 174 (24·5), 168 (12), 162 (18), 150 (11), 138 (85) and 110 (12·5); ORD: [(*c* 0·013; dioxan): 270–400 nm; *P*—peak; *T*—trough; *a*—amplitude] $[\Phi]^P_{305}$ +73570, $[\Phi]^T_{346}$ − 51632, *a* − 125202; [cf. vobtusine (*c* 0·013; dioxan): $[\Phi]^P_{304}$ + 84365, $[\Phi]^T_{346}$ − 57562, *a* − 141927] (Found: C, 73·27; H, 7·05; N, 7·88. calc. for $C_{43}H_{50}N_4O_5$: C, 73·50; H, 7·12; N, 7·98%).

Decarbomethoxydeoxyvobtusine (**4**). A soln of (**10**) (0·15 g) in 3 N HCl (12 ml) was heated in an evacuated sealed tube at 105–110° for 11 hr. Work up gave decarbomethoxydeoxyvobtusine (**4**) (0·085 g) eluted by C_6H_6–$CHCl_3$ (1:2). R_f 0·4 in EtOAc–EtOH (4:1); CAS: bluish violet colouration; λ_{max} 223, 264 and 298–303 (*sh*) (log ε, 4·90, 4·12 and 3·42) nm; ν^{KBr}_{max} 2810 (CH) and 1584 (>C=N–) cm^{-1}; *m/e* (abundance %): 644 (M^+, 100), 506 (1), 488 (3), 377 (16), 331 (6), 322 (M^{2+}, 14), 305 (22), 208 (11), 188 (11), 156 (6), 174 (31), 144 (5), 138 (100) and 110 (11) (Found: C, 76·62; H, 7·39; N, 8·59. $C_{41}H_{48}N_4O_3$ requires: C, 76·40; H, 7·45; N, 8·70%).

Dihydrodecarbomethoxydeoxyvobtusine (**5**). A soln of (**4**) (0·06 g) in 10% MeOH–H_2SO_4 (20 ml) was reduced with Zn dust (0·8 g) under reflux for 10 hr. Unreacted Zn was filtered off, MeOH was removed under reduced pressure, the soln diluted with H_2O, basified with NH_4OH, extracted with $CHCl_3$, dried, concentrated and chromatographed. The C_6H_6-eluate gave dihydrodecarbomethoxydeoxyvobtusine (**5**) (0·03 g). R_f 0·5 in EtOAc–EtOH (4:1); CAS: pink colouration; λ_{max} 219, 262 and 307 (log ε, 4·41, 4·08 and 3·60) nm; $\lambda^{1N\ HClO_4\ EtOH}_{max}$ 218, 257 and 305 (log ε, 4·20, 3·78 and 3·35) nm; *m/e* (abundance %): 646 (M^+, 100), 488 (10), 377 (20), 333 (24), 323 (M^{2+}, 30), 307 (8), 210 (11), 188 (17), 174 (59), 158 (39), 144 (27), 138 (100) and 110 (21) (Found: C, 76·36; H, 7·68; N, 8·58. $C_{41}H_{50}N_4O_3$ requires: C, 76·17; H, 7·74; N, 8·67%).

Tetrahydrodecarbomethoxyanhydrovobtusine (**7**). Tetrahydrodecarbomethoxyanhydrovobtusine (**7**) was prepared from (**6**) by the method of Schmid *et al.*[4] M.p. 208° (MeOH); (M^+ 646); λ_{max} 220, 258 and 298–300 (log ε, 4·38, 4·07 and 3·66) nm; $\lambda^{1N\ HClO_4\ EtOH}_{max}$ 220, 255 and 299 (log ε, 4·20, 4·02 and 3·61) nm.

Dihydrodeoxyvobtusines (**8***a*) *and* (**8***b*). (**10**) (0·15 g) in 10% MeOH–H_2SO_4 (40 ml) was treated with Zn dust (1·5 g) and the mixture was refluxed for 7·5 hr. The solution was filtered hot, MeOH removed under reduced pressure, diluted with H_2O, basified with NH_4OH, extracted with $CHCl_3$, dried, concentrated and chromatographed. C_6H_6–$CHCl_3$ (10:1) eluate gave the major dihydrodeoxyvobtusine (**8a**) (0·06 g) while C_6H_6–$CHCl_3$ (6:1) fractions yielded the minor dihydrodeoxyvobtusine (**8b**) (0·02 g). (**8a**). R_f 0·3 in EtOAc–EtOH (3:1); CAS: bluish-pink colouration; λ_{max} 220, 262 and 303 (log ε, 4·56, 3·90 and 3·36) nm; ν_{max} 3400 (–NH), 1700 (–CO_2Me), 1610 and 1587 (indoline bands) cm^{-1}; *m/e* (abundance %): 704 (M^+, 100), 646 (2), 488 (16), 391 (5), 377 (25), 365 (12), 352 (M^{2+}, 30), 188 (10), 174 (24), 144 (13), 138 (49) and 130 (10) (Found: C, 72·98; H, 7·30; N, 7·83. $C_{43}H_{52}N_4O_5$ requires: C, 73·28; H, 7·39; N, 7·95%). (**8b**). R_f 0·2 in EtOAc–EtOH (3:1); CAS: blue colouration; λ_{max} 220, 262 and 302 (log ε, 4·72, 3·95 and 3·66) nm; ν^{KBr}_{max} 3400 (–NH), 2875 (CH), 1700 (–CO_2Me), 1608 and 1583 (indoline bands) cm^{-1}, *m/e* (abundance %): 704 (M^+, 100), 646 (5), 488 (1), 391 (7), 377 (18), 365 (12), 352 (M^{2+}, 24), 188 (9), 174 (21), 144 (9), 138 (43) and 130 (5) (Found: C, 73·10; H, 7·28; N, 7·85. $C_{43}H_{52}N_4O_5$ requires: C, 73·28; H, 7·39; N, 7·95%).

Tetrahydroanhydrovobtusines (**9**a) *and* (**9**b). Anhydrovobtusine (**6**) was prepared from (**1**) according to the method[4] of Schmid *et al.* A soln of (**6**) (0·2 g) in 10% MeOH–H_2SO_4 (50 ml) was reduced with an excess of Zn dust (2·5 g) under reflux for 8 hr. Work up and chromatography gave the major isomer of tetrahydroanhydrovobtusine (**9**a) (0·07 g) in the first C_6H_6 fractions; later fractions furnished the minor isomer (**9**b) (0·025 g). (**9**a). (M^+ 704); R_f 0·45 in EtOAc–EtOH (3:1); λ_{max} 220, 258 and 302 (log ε, 4·30, 4·11 and 3·94) nm; ν_{max} 3300 (–NH), 1700 (–CO_2Me), 1610 and 1590 (indoline bands) cm^{-1} (Found: C, 72·95; H, 7·31; N, 7·87. $C_{43}H_{52}N_4O_5$ requires: C, 73·28; H, 7·39; N, 7·95%). (**9**b). (M^+ 704); R_f 0·38 in EtOAc–EtOH (3:1); λ_{max} 220, 257 and 300 (log ε, 4·26, 4·14 and 3·80) nm (Found: C, 72·87; H, 7·27; N, 7·82. $C_{43}H_{52}N_4O_5$ requires: C, 73·28; H, 7·39; N, 7·95%).

(6:1) fractions yielded the minor dihydrodeoxyvobtusine (**8b**) (0·02 g). (**8a**). R_f 0·3 in EtOAc–EtOH (3:1); CAS:

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