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SHORT NOTES

Further Studies on the Major Alkaloids of the Stem-bark of *Alstonia Venenata* R.Br. Structure and Stereochemistry of Alstovenine and its Congeners

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The attention of the authors has been drawn to a recent publication by Govindachari *et al*[1]. on the chemical constituents of *Alstonia venenata* R.Br. (Fam. Apocynaceae). As the work on the same plant has been in progress in our laboratory for some time past and some preliminary results[2] have already been published on alstovenine and its congeners isolated therefrom, further physical and chemical evidences collected in elucidating their structures are reported in this communication.

A rigorous *p*H-gradient separation technique was adopted for the isolation of the bases present in *A. venenata*, resulting in the isolation of nine alkaloids in the pure and crystalline state. Structure elucidation of some of these bases are complete and will be the subject matter of a forthcoming publication.

The C-3 epimer of alstovenine[2] has been named venenatine* by Govindachari *et al*[1]. The interrelationship of these two alkaloids has been independently demonstrated by the conversion of alstovenine into venenatine, as will be discussed later.

Venenatine, $C_{22}H_{28}O_4N_2$, m.p. 130° (decomp.), $[\alpha]_D^{30°}$, −82.4° − λ_{max} 226, 272, 294 mμ (log ε, 4.53, 3.87, 3.80), is a monoacidic tertiary base containing two methoxyl groups and two active hydrogen atoms. The I R spectrum shows presence of a saturated ester group (5.78μ), an -NH (3.00μ), and a hydroxyl function (2.78μ) in this compound. It readily forms a methiodide, $C_{23}H_{31}O_4N_2I$, MeI, m.p. 288° (decomp.), confirming the tertiary nature of the basic nitrogen atom.

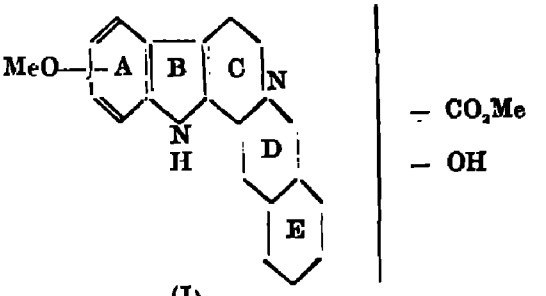
Venenatine forms an amorphous perchlorate, m.p. 235° (decomp.), and a crystalline picrate, m.p. 242° (decomp.). With acetic anhydride and pyridine in the cold, the base forms an *O*-acetyl derivative, which crystallises from aqueous methanol in plates, m.p. 112° (decomp.). The base, heated under reflux with 2*N*-KOH-MeOH, yields venenatic acid, $C_{21}H_{26}O_4N_2$, crystallising from ethanol in shining needles, m.p. 245° (decomp.), reconvertible to the parent alkaloid by the action of diazomethane.

1. *Tetrahedron Letters*, 1964, No. 16, 901.
2. Ray & Chatterjee, this *Journal*, 1963 **40**, 1043.

* *Govindachari and his co-workers have assigned a 9-methoxy-yohimbine structure to this alkaloid mainly on the basis of its mass and N M R spectral analyses. Although a direct comparison of their alkaloid with ours has not been made as yet, the reported constants for this base suggest the identity of venenatine with our alkaloid, 3-epi-alstovenine. Our results furnish an independent chemical proof for an aromatic methoxyl-substituted yohimbine structure for this compound.*

Selenium dehydrogenation of venenatine did not furnish any identifiable product, but similar dehydrogenation of venenatic acid at 300°, followed by the methylation of the degraded base and subsequent chromatgraphy over Brockmann alumina, yielded yobyrine[3], $C_{19}H_{16}N_2$ (Mass No. 272), m.p. 210°, and a methoxy-yobyrine, $C_{20}H_{18}ON_2$ (Mass No. 302), m.p. 229°. As expected, the latter base was found to contain one methoxyl and a *C*-methyl function. Methoxy-yobyrine showed λ_{max}^{EtOH} 219, 247, 289, 334, 348 mμ (log ε, 4.45, 4.62, 4.09, 3.74, 3.76 respectively). comparable with that of 5-methoxy-1-methyl-β-carboline[4].

The isolation of yobyrine thus provides a direct chemical evidence of the pentacyclic ring system of yohimbine type, on the basis of which the partial structure of venenatine may be expressed as (I).



(I)

Potash fusion of venenatic acid furnished isophthalic acid besides several unidentified indolaceous compounds along with a very small amount of a basic substance. Isolation of isophthalic acid indicates the *cis*-fusion[5] of rings D and E in venenatine.

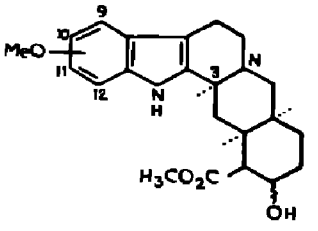
The reduction of the methoxycarbonyl function by $LiAlH_4$ and subsequent tosylation of the reduction product in pyridine at the room temperature furnished a quaternary tosylate, m.p. 260° (decomp.). The latter on treatment with sodium iodide in aqueous solution readily formed an iodide, m.p. 265° (decomp.). The formation of this inner quaternary salt[6] indicates that the hydrogens at C_{15} and C_{16} in venenatine are *cis*.

The NMR spectrum of venenatine exhibits two one-proton signals downfield from the two methoxyl peaks. Of these, the one appearing at 5.74*T* is attributed to the C*H*-OH and the other at 5.55*T* to the C-3 equatorial proton (C-3 equational proton of pseudoyohimbine[7] appears at 5.67*T*). The reluctance of venenatine to undergo dehydrogenation on controlled oxidation with mercuric acetate supports the equatorial nature of the C-3 hydrogen.

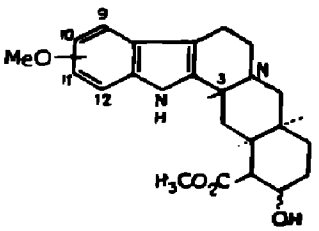
Alstovenine[2], $C_{22}H_{28}O_4N_2$, m.p. 172°, $[\alpha]_D^{30}$ +10.2°, shows striking similarity with venenatine in all its spectral as also in chemical properties. It furnishes a crystalline hydrochloride, m.p. 287-88° (decomp.). With acetic anhydride and pyridine at the room temperature, alstovenine forms an *O*-acetyl derivative, $C_{24}H_{30}O_5N_2$ (m.p. 180°) and on

3. Chatterjee and Pakrashi, this *Journal*, 1954, **31**, 25.
4. Doig *et al.*, *J. Chem. Soc.*, 1952, 3912.
5. Chatterjee (Nee Mookerjee), this *Journal*, 1943, **20**, 11; Schlittler, "Rauwolfia: Botany, Pharmacognosy, Chemistry & Pharmacology", Little, Brown & Co., Boston, Toronto, 1957, p. 78.
6. Huebner *et al.*, *J. Amer. Chem. Soc.*, 1955, **77**, 4180.
7. Albright *et al.*, *J. Org. Chem.*, 1963, **28**, 38.

alkali hydrolysis, to alstovenic acid, m.p. 252° (decomp.). On treatment with CH_2N_2, this acid regenerates the parent alkaloid in quantitative yield. Unlike venenatine, alstovenine suffers facile dehydrogenation with mercuric acetate with the formation of a Δ^3-base. The latter has been isolated as its perchlorate, crystallising from methanol in plates, m.p. 230° (decomp); λ_{max}^{EtOH} 256, 348mμ (log ε, 4.12, 4.21); λ_{max}^{Nujol} 6.12μ, 6.35μ, and 6.48μ) Reduction of Δ^3-alstovenine with zinc dust in acetic acid according to the method of Weisenborn and Diassi[6] furnished a mixture of alstovenine (60%) and venenatine (40%). Venenatine is thus a C-3 epimer of alstovenine, the C-3 hydrogen being axial in the latter. The axial nature of the C-3 hydrogen in alstovenine is also apparent from its NMR spectrum as it lacks any alicyclic proton signal other than that present for C*H*-OH (5.80τ) downfield from the methoxyl peaks. Thus alstovenine (II) belongs to an aromatic methoxyl-substituted allo-yohimbine and venenatine (III) to the corresponding *epi-allo* series. The carbomethoxyls in these compounds are equatorial, as indicated from (*a*) saponification and (*b*) tosylation experiments.



(II)



(III)

The aromatic methoxyl function is tentatively assigned to the 9-position in ring A on the basis of the UV spectral data[4] of methoxy-yobyrine. But confirmation to such an assignment awaits further chemical evidences for which synthesis of 5-methoxy-yobyrine has been undertaken for its direct comparison with the methoxy-yobyrine, isolated from the selenium-dehydrogenation product of venenatic acid.

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