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CHEMICAL CONSTITUENTS OF ALSTONIA VENENATA R.BR.

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A recent note (1) by A.B. Ray and Mrs. A. Chatterjee prompts us to publish our work on the chemical examination of Alstonia venenata R.Br. From its bark we have isolated stigmasterol (yield, 0.0006%), reserpine (0.02%) and two new indole alkaloids which we have named venenatine (0.09%) and isovenenatine (0.001%).

Venenatine, m.p. 123-126° (decomp.), $[\alpha]_D^{24}$ - 76.07°, as well as isovenenatine, m.p. 169-171°, $[\alpha]_D^{24}$ + 9.42°, possessed the molecular formula $C_{22}H_{28}N_2O_4$* (Molecular weight by mass spectrum, 384). Their homogeneity was established by thin layer as well as paper chromatography.

Venenatine, pKa 7.2, was a tertiary base and yielded a picrate, m.p. 243° (decomp.), a hydriodide, m.p. 255-257° (decomp.) and a methiodide, m.p. 285-290° (decomp.). The

* Satisfactory analyses were obtained for all compounds reported in this communication

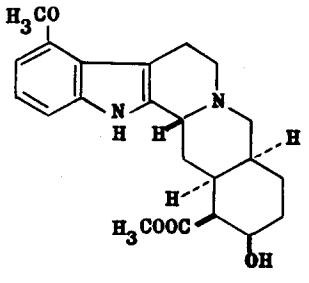
base had two methoxyl groups and two active hydrogens but no C-CH_3 or N-CH_3 groups. Its U.V. spectrum, λ max 226, 271 293 mμ (log ϵ 4.57, 3.92, 3.81), λsh 281 mμ (log ϵ 3.84), indicated it to possess a 2,3-disubstituted 4-methoxyindole chromophore (2). Its infra-red spectrum (methylene chloride) showed bands at 3600 (OH), 3460 (NH), 1725 (ester), 1620, 1595 and 1570 cm^{-1} (methoxylated aromatic nucleus). The base yielded an O-acetyl derivative, m.p. 98-101° (decomp.). The presence of a methoxycarbonyl group was shown by alkaline hydrolysis to venenatic acid which could be re-esterified with methanol and hydrogen chloride to give venenatine. Reduction of venenatine with lithium aluminium hydride gave venenatyl alcohol, $C_{21}H_{28}N_2O_3$, methiodide, m.p. 291-295° (decomp.). Venenatine, when refluxed with 3N-HCl, gave the phenolic nor-venenatic acid hydrochloride, $C_{20}H_{25}N_2O_4Cl$, m.p. 304-306° (decomp.), by demethylation of the aromatic methoxyl group. This gave a positive Gibb's test indicating the presence of an unsubstituted position <u>para</u> to the phenolic hydroxyl. Oxidation of venenatine with lead tetraacetate in acetic acid led to a tetradehydro derivative, λ max 260, 315, 360 mμ (log 4.79, 4.51, 4.20). Modified Oppenauer oxidation of venenatine with potassium tertiary butoxide and fluorenone gave in poor yield a ketone, $C_{20}H_{24}N_2O_2$, m.p. 140-142°, ν max 1705 cm^{-1}. Attempts to degrade venenatine by classical dehydrogenations failed to give any identifiable product.

The N.M.R. spectrum (at 60 mc, in $CDCl_3$) of venenatine possessed three-proton singlets at 223 ($COOCH_3$) and 233 c.p.s. (aromatic methoxyl). A multiplet at 252 c.p.s. is due to a

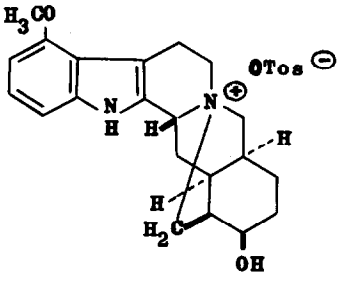
proton attached to the carbon bearing the hydroxyl group since it is shifted downfield to 322 c.p.s. in O-acetylvenenatine. A singlet at 496 c.p.s. is due to the indole N-H. The aromatic region of the spectrum showed the presence of three aromatic protons and was very similar to that of mitragynine (3), supporting the presence of a 5-methoxytetrahydro-β-carboline system.

The mass spectrum of venenatine was strikingly similar to that of 3-epi-α-yohimbine, the mass peaks between 156 and 184 in the latter being displaced in the spectrum of venenatine to 186, 199, 200 and 214 due to the increase in 30 mass units associated with the aromatic methoxyl group.

The above results lead to the gross structure (I) for venenatine.



I



II

Treatment of venenatine with t-butyl hypochlorite according to the procedure of Godtfredson and Vangedal (4) gave the C_7-chloroindolenine converted by methanolic hydrogen chloride to the Δ^3-compound. Reduction of the latter with sodium borohydride gave 3-epi-venenatine, m.p.

169-170°, identical in all respects with isovenenatine obtained from the plant. Isovenenatine, unlike venenatine, is readily oxidised by mercuric acetate to the Δ^3-derivative, isolated as the perchlorate, $C_{22}H_{27}N_2O_8Cl.1.5\ H_2O$, λ max 254, 344 mμ (logϵ 423, 4.31). Venenatine and isovenenatine must hence be C_3-epimers, the C_3-H being β (equatorial to ring C) in the former and α (axial to ring C) in the latter (5). As expected (6), isovenenatine, unlike venenatine, shows two peaks at 2800 and 2760 cm^{-1} in the infra-red spectrum.

Treatment of venenatyl alcohol with one mole of p-toluenesulphonyl chloride in pyridine gave the quaternary tosylate (II), m.p. 265-267° (decomp.), converted with aqueous potassium iodide to the corresponding quaternary iodide, m.p. 265° (decomp.). This was analogous to the case of reserpinol (7) and showed that the hydrogens at C_{15}, C_{16} and C_{20} were all cis-oriented.

Venenatine with p-toluenesulphonyl chloride in pyridine gave the O-tosyl derivative and not a quaternary salt as does 3-epi-α-yohimbine (8). This, as well as the infra-red and N.M.R. evidence, supports an axial C_{17}-β-OH group in venenatine. Venenatine hence possesses the structure and stereochemistry shown in (I), isovenenatine being its C_3-epimer.

From its melting point and published U.V. spectrum, alstovenine (1) appears to be identical with isovenenatine. The U.V., contrary to the authors' statement, supports a 5-methoxy- and not a 7-methoxytetrahydro-β-carboline moiety (2).

Venenatine and isovenatine represent growing additions to the class of monomethoxyyohimbines (9.10).

Fuller details of this work will be published elsewhere.

Acknowledgement: We thank Professor C. Djerassi for determining the mass spectra and drawing our attention to the similarity between venenatine and 3-epi-α-yohimbine. Thanks are also due to Dr. S. Selvavinayakam for microanalyses, Dr. B.S. Joshi for the N.M.R. spectrum of mitragynine and Dr. K. Nagarajan for the other N.M.R. spectra and some helpful discussions.

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