Tetrahedron Letters No. 16, pp 1357 - 1358, 1975. Pergamon Press. Printed in Great Britain.

ISOLATION AND STRUCTURE OF AKAGERINE; A NEW TYPE OF INDOLE ALKALOID

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(Received in UK 3 March 1975; accepted for publication 13 March 1975)

The roots of Strychnos usambarensis are used as arrow poison in Central Africa. Early investigations have shown that the active principles were divided into tertiary and quaternary alkaloids[1]. We now record the isolation of an additionnal tertiary alkaloid: akagerine[2].

The tertiary crude bases were purified by a column chromatography over Al_2O_3 (activity II-III) and eluted with ether. 20- ml fractions were collected. After check TLC, the fractions 72-98 were combined and gave amount of the pure akagerine which crystallized in hexane, as plaquettes; m.p. 188°C (dec.); ORD (c:0,004-MeOH) $[\phi]$ +8100° at 280-284 nm; CD (MeOH) $[\theta]_{265}$ = +13200.

The molecular formula has been established by mass spectrometry (high resolution) = m/e (relative abundance) 324 $M^+[C_{20}H_{24}N_2O_2]$ (51), 309(9), 306 $[C_{20}H_{22}N_2O]$ (44), 277 $[C_{19}H_{21}N_2]$ (21), 263 (13), 241 (14), 223 (13), 214 (30), 213 $[C_{13}H_{13}N_2O]$ (36), 198 $[C_{13}H_{12}NO]$ (27), 186 (11), 185 $[C_{12}H_{13}N_2]$ (100 = base peak), 184 (56), 183 (28), 180 (18), 172 (13), 171 $[C_{11}H_9NO]$ (80), 156 (11), 144 (8), 143 (10), 130 (6).

The U.V. spectrum $[\lambda_{nm}^{MeOH}$ (log ε) 227 (4.51), 276 (3.82), 283 (3.82), 293 (3.73)] indicates the presence of an indole (tetrahydro-β-carboline) system.

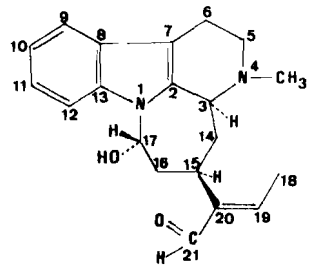
The I.R. spectrum $[\nu_{max}^{KBr}$ 3450, 3050, 2930, 2850, 2700, 1680, 1628, 1445, 1370, 1350, 1305, 1295, 1280, 1200, 1110, 890 and 742 cm^{-1}], shows bands which can be assigned to unsaturated carbonyl (1680) and indole (742).

The N.M.R. spectrum (in $CDCl_3$) shows characteristic signals at δ 9.19 (aldehydic proton), δ 6.45 and δ 2 (ethylidene side chain), δ 2.33 (N-CH_3), δ 7.4-7 (four aromatic protons), δ 4.45 (proton exchangeable with D_2O).

Mild acetylation (Ac_2O-C_5H_5N-RT) afforded the acetylated akagerine which showed characteristic absorption of OAc bands in the I.R. and N.M.R. spectra. The lack of proton exchangeable with D_2O is also obvious.

X-Ray cristallography of the base has confirmed the previous results but has mainly established the relative configuration of akagerine. Crystals of akagerine recrystallized from hexane are tetragonal, space group $P\,4_12_12$ or $P\,4_32_12$ with 8 molecules in an unit cell of dimensions a = b = 9.255 Å, c = 42.165 Å.

Akagerine is a tetracyclic indole alkaloid possessing a perhydroazepine ring coupled to tetrahydro-β-carboline, by an original N_1-C_{17} bond [3]. Indeed, it is the first time that such an alkaloid has been found. Moreover, a cis-relationship between H_3, H_{15}, OH_{17} and the electrons lone pair of N_4 is detected by this X-Ray analysis [4].



AKAGERINE $C_{20}H_{24}O_2N_2$

Examination of molecular stereomodels formed by condensation of N_b-methyl-tryptamine and a monoterpene unit derived from loganic acid, has shown that the 15α-configuration for $C_{15}H$ agrees with the biosynthetic hypothesis [5 to 8]. From these data, the complete absolute stereochemistry of akagerine could be depicted as that shown above.

Akagerine should be the precursor of more sophisticated alkaloids (bisindole and heptacyclic compounds) that would be obtained by reaction with tryptamine. These new produots would be different from usambarensine [1,9].

The results of this research are presented to Prof. A. Denoël for his 60th birthday.

Acknowledgements: We thank sincerely Drs N.G. Bisset, P.J. Hylands, as well MM. D. Carter and G. MacDonough (University of London) for their collaboration in this work.

References and complementary notes

1. L. Angenot : Diss. Abstr. Intern., 34, 11, 338 (1974).
2. The name akagerine was chosen because Strychnos usambarensis was collected in the National Park of Akagera (Rwanda), where the plant is abundant.
3. In this letter, the numbering system is that of J. Le Men and W.I. Taylor : Experientia, 21, 508-510 (1965).
4. For full details about cristallography, see: L. Dupont, O. Dideberg and L. Angenot : Acta Cryst. (to be published in 1975).
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