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THE STRUCTURE OF THE PRINCIPAL ALKALOID FROM VALERIANA OFFICINALIS(L.).

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From the dried roots of Valeriana officinalis a crystalline, optically active, quarternary base was isolated as the chloride, $C_{18}H_{22}NOCl$, $[\alpha]_D^{22}$ +50.5° (CH_3OH), dec. 201-203°. It was converted to a trifluoroacetate, dec. 201-203°, and to a picrate m.p. 151-152°. The salt is easily soluble in water or alcohol and difficultly soluble in slightly polar organic solvents.

The IR-spectrum shows a strong absorption in the region 3400-2900 cm^{-1} indicating strong hydrogen bonding, two sharp peaks in the olefinic region at 1635 and 1615 cm^{-1} (possibly aromatic) of about the same intensity and aromatic absorption at 1585, 1515 and 1485 cm^{-1}. The strong out of plane bending absorption at 837 cm^{-1} is most probably due to a 1,4 - disubstitution pattern in the aromatic ring. No carbonyl band is present. It was first thought that the absorption at 1635 and 1615 cm^{-1} was due to an olefinic or imine bond but this was excluded by other spectral data. By comparison with the IR-spectra of the hydrochlorides of pyridine and pyridine-4-aldehyde(1) it was found that this pair of peaks is characteristic for the pyridinium structure (in some cases only one peak is visible in the region 1615-1650 cm^{-1}) and is of diagnostic value, cf. Witkop(2). Their relative intensity changes in various pyridinium compounds.

The alkaloid absorbs in the UV-region at λ_{max} = 222 mμ ; ε = 12000 and λ_{max} = 267 mμ ; ε = 5500 in acid and neutral solution

The drug was purchased from Apotekarnes Droghandel, Stockholm.

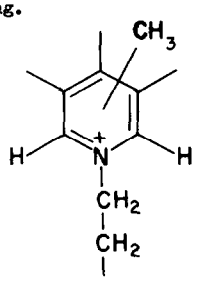
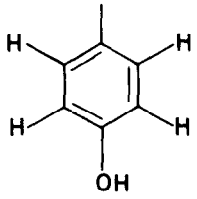
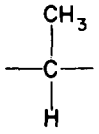
and at λ_{max} = 242 mμ ; ε = 16000 and λ_{max} = 292 mμ ; ε = 3000 in alkaline solution. The shift indicated the presence of a phenolic group which was supported by acetylation that gave a product with an IR-absorption at 1760 cm^{-1}, within the region of phenolic esters. The short-wave absorption of relatively low intensity excludes a longer conjugated system. The calculated UV-curve for the sum of the p-cresol and trimethylpyridinium chromofores is in very good agreement with the absorption curve of the alkaloid.

The NMR-spectra ($(CD_3)_2SO$ solution, Varian A-60 spectrometer) support the earlier assignments and give further important information about the structure. A total of 22 protons was counted, in agreement with the analysis. In the low field part of the spectrum the 2 and 6 protons of pyridine are located at δ = 8.90 and 8.83 ppm and at δ = 7.04 and 6.73 ppm the two pairs of protons of the parasubstituted benzenoid system are centered. They form a typical AB_2-spectrum, J_{AB} = 8.8 c/s, showing that one substituent is a carbon and the other one an oxygen. The triplet at δ = 4.73 ppm is ascribed to a methylene group attached to ammonium and split by another methylene group, J = 7.3 c/s. The alkaloid contains two methyl groups, one aromatic, δ = 2.34 ppm, which must be located on the pyridine ring and one aliphatic at δ = 1.23 ppm split by one hydrogen atom, J = 6.9 c/s. The other aliphatic protons form a broad band at 3.5-1.5 ppm. The NMR-spectrum of the methylated product m.p. 111-113°, (small amounts of the compound remained solid until 123°) showed the presence of two aromatic methoxy groups which was at first puzzling before it was found out that one of them belonged to the monomethylsulphate ion, coincidentally located exactly at the same place as the aromatic methoxy group, δ = 3.71 ppm ($CDCl_3$). The picrate m.p. 143-144° had only one methoxy group at δ = 3.72 ppm ($CDCl_3$).

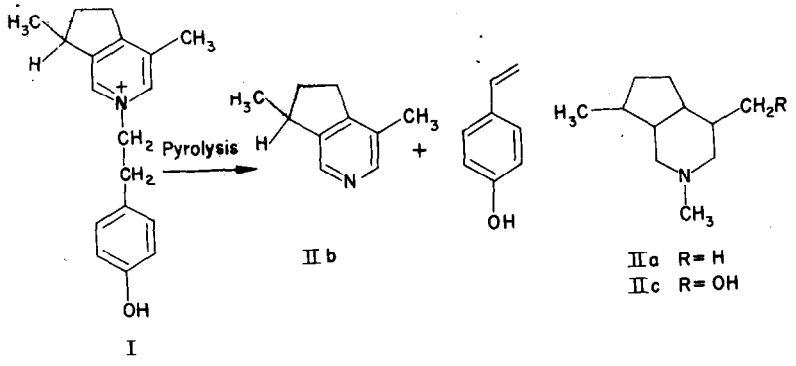
The mass spectrum of the trifluoroacetate (Mw 381) shows no molecular ion peak because the alkaloid is a salt. The highest set of peaks is located at m/e 337 and 336, the origin of which might be a decarboxylation (381-44). Strong peaks are located at 268, 267, 147, 132, 121, 120, 107, 91 and 77. The presence of the trifluoroacetate ion is supported by the peak at m/e 69 = CF_3^+. M/e 268 is the pyridinium ion (381 - CF_3COO^-). The peaks

in the middle part of the spectrum confirm the parasubstituted phenol structure (3).

On basis of these data the following structural elements could be derived,which gives us 16 C, 18 H, N and O. The remaining two methylene groups must be attached to the pyridine nucleus forming a condensed ring.

The alkaloid can thus be represented by the structure I. The aliphatic



I II b II a R= H II c R= OH

methyl group was placed in the α -position due to biogenetic reasons. The β -position is in disagreement with the NMR-data.It is expected that this molecule on pyrolysis would decompose into two fragments: p-hydroxystyrene (Mw 120) and the pyridine derivative (Mw 147).This is nicely confirmed by the strong mass peaks at m/e 120 and m/e 147.The final proof of the structure was obtained by pyrolysis on a larger scale,which afforded the hydrochloride of the pyridine fragment (M^+ = 147).This was identical to a known alkaloid, actinidine, II b, the structure of which was determined by Sakan et al. (4).The melting point of the picrate m.p. 145-147° , agreed with the value reported,

m.p. 146-14[illegible]° (9) and their IR-spectra were identical. The free base was optically active $[\alpha]_D^{22}$ -7.9° ($CHCl_3$). (lit. (4) $[\alpha]_D^{11}$ -7.2° ($CHCl_3$)). The structure of two other closely related alkaloids have recently been elucidated: scytantine (5) (6), II a, tecostanine (7), II c, and tecomanine (8).

It is claimed popularly that Valeriana officinalis excites cats. Now Sakan et al. (4) incidentally report that actinidine, isolated from Actinidia polygama has the same effect. It is therefore quite conceivable that these old statements are justified.

All the compounds reported gave satisfying analytical data.

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REFERENCES

(1) Chiorboli, P., Mirono, P. and Lorenzelli, V., Ann. di. Chim. 48, 358 (1958).

(2) Witkop, B., Experentia 10, 420 (1954).

(3) Budzikiewicz, H., Djerassi, C. and Williams, H. Interpretation of Mass Spectra of Organic Compounds. Holden-Day, San Francisco 1964, Chapter 9.

(4) Sakan, T., Fuyino, A., Murai, F., Butsugan, Y. and Suzui, A., Bull. Chem. Soc. Japan, 32, 315 (1959).

(5) Casinovi, C.G., Garbarino, J.A. and Marini-Bettolo, G.B., Gazz. Chim. Ital., 91, 1037 (1961).

(6) Djerassi, C., Kudney, J.P. and Shamma, M., Tetrahedron, 18, 183 (1962)

(7) Hammouda, Y., Plat, M. and Le Men, J., Bull. Soc. Chim., 2802 (1963).

(8) Jones, G., Fales, H.M. and Wildman, W.C., Tetrahedron Letters, 6, 397 (1963)

(9) Sakan, T., Fuyino, A., Murai, F., Suzui, A. and Butsugan, Y., Bull. Chem. Soc. Japan, 32, 1155 (1959).