THE STRUCTURE OF NITRARINE

A. A. Ibragimov, S. -M. Nasirov,
V. T. Andrianov, S. Kh. Maekh,
Yu. T. Struchkov, and S. Yu. Yunusov

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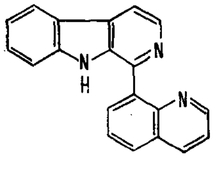
The alkaloid nitrarine (I) has been isolated from the epigeal part of Nitraria schoberi L. [1]. Nitrarine is a white crystalline, optically inactive compound with the composition $C_{20}H_{25}N_3$, mp 256-257°C (ethanol–chloroform). Molecular weight 307 (mass spectrometrically). The UV spectrum of the base has two main maxima at 226 (log ε 4.52) and between 280 and 292 nm (log ε 4.01), these being characteristic for tetrahydro-β-carboline systems [2]. The mass spectrum shows the following peaks of ions with m/e: 307 (M^+, 100%), 306, 279, 278, 224 (85%), 223 (85), 197, 196, 195, 184, 183, 182, 171, 170, 169, 156, 144, 83. As can be seen, here we are dealing with all the peaks characteristic for the decomposition of alkaloids of the yohimban series [3]. The NMR spectrum of (I) shows two one-proton signals in the 7.8-8.2 δ region due to the protons of two NH groups. These signals are absent from the NMR spectrum of the N-acetate of (I). Consequently, in addition to the indole and quinolizidine nitrogen atoms the molecule of (I) has a secondary amino group which must apparently be in a piperidine ring (peak with m/e 83 in the mass spectrum). The presence of intense peaks of ions with m/e 223 and 224 in the mass spectra both of nitrarine itself and of its N-Me and N-Ac derivatives due to a tetramethylenetetrahydro-β-carboline fragment shows the position of the third nitrogen atom in ring E of yohimban.

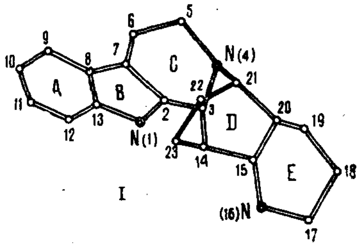
Adams hydrogenation did not lead to the absorption of hydrogen. It follows from this, and also from the interrelationship of the molecular form and the total number of rings and double bonds [4], that a sixth ring must be formed in (I) in addition to the heteroyohimban dimethylene group.

The dehydrogenation of (I) with selenium formed a series of compounds, including compounds with masses of 299 (II) and 295 (III), the latter being product of complete dehydrogenation. The absence of fragmentation in the mass spectrum of (III) shows the absence of branching in it. The loss of 12 protons with the retention of all the carbon and nitrogen atoms is possible if the dimethylene group is present between C_{14} and C_{21}, C_{14} and C_{16}, or C_{21} and C_{19}.

The UV spectrum of (II) has distinct absorption bands of a 5,6,7,8-tetrahydroquinoline (214 and 271 nm), and in an acid medium the absorption of a β-carbolinium ion is observed (256, 309, and 375 nm), showing the cleavage of the N_4-C_{21} bond in the dehydrogenation reaction, which is characteristic for alkaloids of the yohimban series [5]. This indicates that the dimethylene bridge is attached in positions C_{14} and C_{21}, and product (II) is 3-(5,6,7,8-tetrahydroquinolinyl)-β-carboline. Consequently, compound (III) must have the structure of 3-quinolinyl-β-carboline. The ease of formation of ions with masses of 223 and 224 in the mass spectrum of (I) shows the location of a nitrogen atom in position 16 of the skeleton of the molecule.



III



I

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For an unambiguous determination of the structure of (I) we performed an x-ray structural investigation of its hydrochloride, which proved to be the monohydrate in the crystalline state. The crystals, $C_{20}H_{25}N_3 \cdot 2\ HCl \cdot H_2O$, are monoclinic, $a = 13.057(1)$, $b = 14.420(1)$, $c = 7.709(1)$ Å, $\gamma = 103.3(3)°$, $V = 1955$ Å^3, mol. wt. = 369.4, $d_{meas} = 1.33$, $d_{calc.} = 1.36$ g/cm^3, $Z = 4$, space group $P2_1/b$. The structure was interpreted by the direct method from 2200 reflections with $[F]^2 \geq 3\sigma$ measured on a diffractometer (λCuK_α), and was refined in the anisotropic approximation to $P = 0.085$.

The carbon–nitrogen skeleton of the molecule of (I) is close to that found in yohimban (IV) [6] and reserpine (V) [7] (A–B indole system condensed with a C–D quinolizidine system which, in its turn, is condensed with the six-membered ring E). Differences consist in the fact that ring E in (IV) and (V) is a cyclohexane ring and in (I) it is a piperidine ring, and the presence in (I) of a dimethylene bridge between C(14) and C(21), leading to an azatriptycene system of rings D–F–G (ring D is formed by atoms 3, 4, 21, 20, 15, and 14; ring F by atoms 3, 4, 21, 22, 23, and 14; and ring G by atoms 14, 15, 20, 21, 22, and 23).

The length of the bonds and the valence angles are normal. There is a remarkable difference in the lengths of the C–N bonds at the indole nitrogen atom, N(1) (1.37 and 1.38 Å) and at the N(4) and N(16) atoms, which are quaternary in this structure (1.52-1.55, mean 1.54 Å). The A–B indole system is planar and the conformations of the other rings are as follows: C – distorted half-chair $^6H_5$ or boat $^{4,5}B$, or envelope ^5E; D, F, and G are of a somewhat twisted boat conformation $^{14,21}B$; and E is boat $^{16,19}B$. The linkages of the rings are: C/D – cis; D/E – cis.

All six active hydrogen atoms participate in the formation of hydrogen bonds in the crystal: N(1)–H... Cl 3.22, N(4)–H...Cl 3.06, N(16)–H...Cl 3.06 and 3.15 (two bonds), HO–H...Cl 3.12, HO–H...OH_2 3.09, and HO–H...Cl 3.39 Å (one bifurcate bond).

The centrosymmetry of the crystals shows the racemic nature of the substance under investigation, which is in agreement with the absence of optical activity.

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