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STUDIES ON A NEW ALKALOID OF STREPTOMYCES

STRUCTURE OF NIGRIFACTIN

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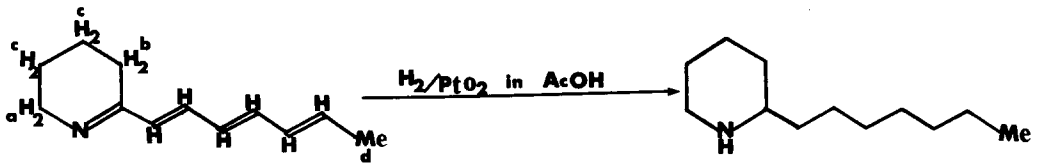
Recently, we reported[1] the successful isolation and pharmacological activities (antihistaminic activity, the influence on blood pressure, etc.) of a new alkaloid, nigrifactin, produced by Streptomyces strain No. FFD-101. Nigrifactin is highly unstable and polymerized promptly on isolation even under the inert gas; however it can be handled in dilute acidic solutions and in the form of its salts such as picrate and flavianate. In this communication we wish to report the structure of nigrifactin.



I. II.

Nigrifactin [picrate: m.p. 175.5-176° (dec.), Anal. Found: C, 53.24; H, 5.05; N, 14.06; O, 28.20. Calcd. for $C_{12}H_{17}N \cdot C_6H_3O_7N_3$: C, 53.46; H, 4.99; N, 13.86; O, 27.70%; Rf: 0.43 (n-BuOH:AcOH:H_2O=4:1:1); $[\alpha]_D$ 0° (C=0.5, methanol) ; pkâ=8.8 (50% ethanol);λmax (ε) 354 mμ (36700, conjugated double bond) in neutral and acidic methanol; positive reactions to Dragendorff (orange), Mandelin (brown) and platinic chloride reagents (greenish blue)] shows in its IR spectrum strong bands at 1610 cm^{-1} and 1000 cm^{-1}, which are attributable to a C=C double bonds. The IR spectrum of the free base shows two characteristic bands at 1645 cm^{-1}(C=N) and 1610 cm^{-1}(C=C). Beyermann et al.[2] stated that the C=N stretching vibration of γ-coniceine occurs at 1663 cm^{-1} and it would

be expected that the C=N stretching vibration of nigrifactin is similar. Examination of the region around 3300 cm^{-1} gives no indication of an N-H vibration. Nigrifactin hydrochloride displays a characteristic UV absorption which shows a considerable hypsochromic shift upon basification (300 mμ above PH 9.2, 354 mμ in neutral and acidic solutions).

Nigrifactin is readily reduced by PtO_2 into a crystalline octahydro compound (II) [HCl salt: m.p. 140.5-141.5°, Anal. Found: C, 65.30; H, 12.33; N, 6.31; Cl, 15.61. Calcd. for $C_{12}H_{25}N \cdot HCl$: C, 65.60; H, 12.30; N, 6.38; Cl, 15.72%; m/e; 183 (M^+); pkâ=10.4 in 50% ethanol], which is a secondary amine. The following IR, UV and mass spectral data clearly show that nigrifactin has four double bonds and one ring. Thus, the octahydro compound (II) shows no bands at 1610 cm^{-1} and 1000 cm^{-1} in its IR spectrum and no UV absorption at 354 mμ. The vinyl proton signals of nigrifactin at the 6–8 ppm region in NMR spectrum were disappeared in the NMR spectrum of the octahydro compound (II). Furthermore similarity of the NMR signals of nigrifactin at 3.67 (a. 2H, multiplet), 2.98 (b. 2H, multiplet), 1.75-2.05 (c. 4H, multiplet) and 1.84 ppm (d. 3H, triplet, J=5.0 cps) to that of 2-(2-propenyl)-Δ^1-piperideine[3] suggests that the octahydro compound (II) has a piperidine ring. A characteristic fragment ion peak at m/e 84 () observed in the mass spectrum of the octahydro compound (II) also supports the presence of a piperidine ring. The octahydro compound (II) contains one active hydrogen atom, whereas nigrifactin is devoid of hydrogen exchangeable for deuterium on dissolving in D_2O. Hence nigrifactin must have a $\rangle C{=}N-$ functional group.

Dehydrogenation of the octahydro compound (II) in boiling p-cymene containing safrol and 30% palladium-on-carbon catalyst afforded a pyridine derivative (III) [platinate: $(C_{12}H_{19}N \cdot HCl)_2PtCl_4$; m.p. 174-175° (dec.); mass spectrum; m/e 177 (M^+ of the free base and the peaks corresponding to the successive loss of CH_2 from the molecular ion); pkâ=5.0 in 50% ethanol; the free base, $C_{12}H_{19}N$: λmax (ε) 257, 263,269 mμ (2860, 3255, 2330 in ethanol); ν_{max}^{neat} 1586 cm^{-1} (C=N)]. These data suggest that the compound (III) is 2-heptyl-pyridine. In order to confirm the suggested structure, 2-heptyl-pyridine was synthesized by condensation of 2-picoline with n-hexyl chloride in the presence of sodium

amide in liquid ammonia[4]. The synthetic 2-heptyl-pyridine (platinate: m.p. 174-175°) was proved to be identical with the pyridine derivative (III) obtained from the natural product (m.p., mixed m.p., IR, Mass and UV spectra, pkâ). The above results suggest that the structure of nigrifactin must be 2-heptatrienyl-Δ^1-piperideine (I).

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