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THE SYNTHESIS OF NIGRIFACTIN

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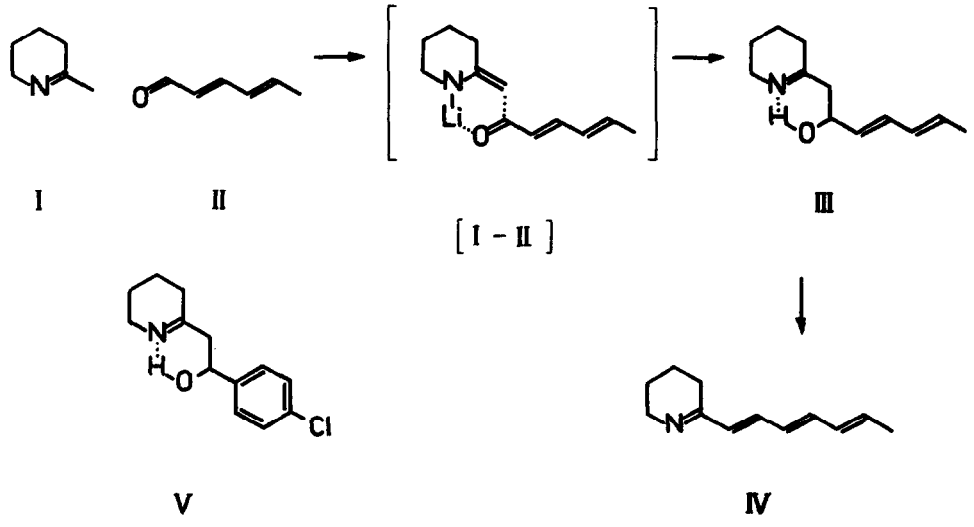
The structure of Nigrifactin (IV), a highly unstable new alkaloid, isolated from Streptomyces strains N^{o} FFD-101 (1) has recently been elucidated by T. Terashima and co-workers (2). We now wish to report a simple and efficient synthesis.

Bearing in mind the reported lability of Nigrifactin as a free base and its stability in acidic solutions, it seemed appropriate to choose a synthetic sequence in which the last step would be carried out in a dilute acidic medium. Our scheme thus envisioned a cyclic version of G. Wittig's "directed aldol-condensation" (3) between I and II, followed by an acidcatalyzed trans-elimination of water.



At the outset it was hoped that a transition state, such as [I-II], would favor condensation at the exocyclic carbon, despite the following two facts: a) the report of G. Wittig (4) that, under identical experimental conditions, in the reaction between 2-butylidenecyclohexylamine and benzophenone condensation occurs predominantly at the secondary carbon. b) the autocatalyzed D-exchange ratio (CH_2/CH_3) in I is 1.5 (after 2 hrs) and 5.5 (after 15 minutes) in DMSO-d_6 / D_2O and CH_3OD respectively (c.f. (5)). However in a model reaction of 2-methyl-Δ^1-piperideine (I) (6) with p-chlorobenzaldehyde (to yield 90% solid V, 58% recrystallized, mp. 79°, NMR ($CDCl_3$) δ = 7.44 (s, 4H); 6.25 (s, 1H exch.); 5.02 (t, J=7, 1H); 3.55 (m, 2H); 2.37 (m, 2H); 2.03 (m, 2H); 1.3 - 1.9 (m, 4H) ppm.) and more importantly in the reaction between I and II the condensation did occur uniquely in the desired sense.

Metalation of I with Li-diisopropylamide in ether at -30° followed by addition of sorbaldehyde (II) (7) at -70° yields 76 % of a crude imine-alcohol, which, according to NMR ($CDCl_3$, δ = 5.2 - 6.5 (m, 5H, incl. 1 exch.); 4.45 (1H, $J_{AM} = J_{AN} = J_{AX} \cong 6$); 3.5 (m, 2H); 2.22 (m, 2H); 2.08 (m, 2H); 1.72 (d, J=6, 3H); 1.4 - 2.3 (m, 4H)) is essentially pure and consists of only one isomer, namely III. Condensation at the alternate carbon would undoubtedly have resulted in a mixture of diastereoisomers. III crystallizes from cold pentane under nitrogen in needles (mp. 42°, IR $\nu_{cm^{-1}}^{CH_2Cl_2}$ 3270 (broad), 1650) decomposing readily upon exposure to air and moisture. Treatment of III with 2 N sulfuric acid at 100° under nitrogen for 30 minutes gave a 71 % yield of a crude picrate (from $CHCl_3$; mp. 175° / reported 175.5° (2)). The picrate can be converted into a nicely crystalline oxalate, mp. 135° ($\lambda_{max.}^{CH_3OH}$: 298 mμ / ε 33460 pH > 9 and 352 mμ / ε 35700 pH < 3). Liberation of the free base with carbonate and immediate recording of the CCl_4-solution gave access to IR ($\nu_{cm^{-1}}^{CCl_4}$ 1605, 995) and NMR spectra (CCl_4 : δ = 5.42 - 6.65 (m, 4H); 3.65 (m, 2H); 2.23 (m, 2H); 1.78 (d, J=6, 3H) and 1.3 - 1.7 (m, 4H)).

Hydrogenation of the stable oxalate IV over PtO_2 in acetic acid produced 2-heptylpiperidine identical in all respects (NMR and HCl-salt: mp., IR, MS, analysis) with the hydrogenation product reported (2) as well as with an unambiguously synthesized sample.

Finally, the synthetic material IV proved to be identical with natural Nigrifactin picrate: mp., mixed mp., TLC (rf = 0.43 Silica Gel G / n-BuOH : AcOH : H_2O = 4 : 1 : 1), NMR (DMSO-d_6, 100 Mc JEOL 4 H-100), IR (KBr) and UV (CH_3OH).

It is believed that Nigrifactin possesses an all-trans configuration. The described synthesis gives further support to this assumption since condensation of I with 2-trans-4-trans-hexadienal

leads to a trans-trans-alcohol III. In all the various examples encountered so far with this type of unsaturated imine-alcohols (8), the elimination leads exclusively to the thermodynamically more stable trans-configuration.

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7. obtained by MnO_2 - oxidation of sorbic alcohol in pentane. Purity according to GLC and NMR: 95 % + 5 % sorbic alcohol
8. Unpublished results in our laboratories.