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SYNTHESIS OF NORRUFESCINE

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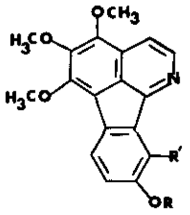
Abstract - The phenolic azafluoranthene alkaloid norrufescine 1 has been synthesized. The key step in the synthesis involved the formation of the tetracyclic azafluoranthene nucleus by a novel aprotic thermolysis of a condensed triazine precursor.

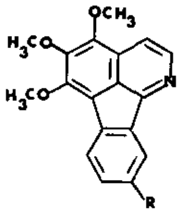
The azafluoranthenes constitute a small group of isoquinoline-derived alkaloids consisting of the non-phenolic bases rufescine (2)[1], imeluteine (3)[1] and triclisine (4)[2], and the phenolic bases norrufescine (1)[1,3] and telitoxine (5)[4]. The three non-phenolic bases have been synthesized[2,5] using a classical Pschorr approach, although no synthesis of either phenolic base has yet appeared. We now report a total synthesis of norrufescine (1) by a route which involves, as the key step, an unusual aprotic Pschorr-type cyclization of a condensed benzotriazine intermediate.



1. R = H; R^1 = H

2. R = CH_3; R^1 = H

3. R = CH_3; R^1 = OCH_3

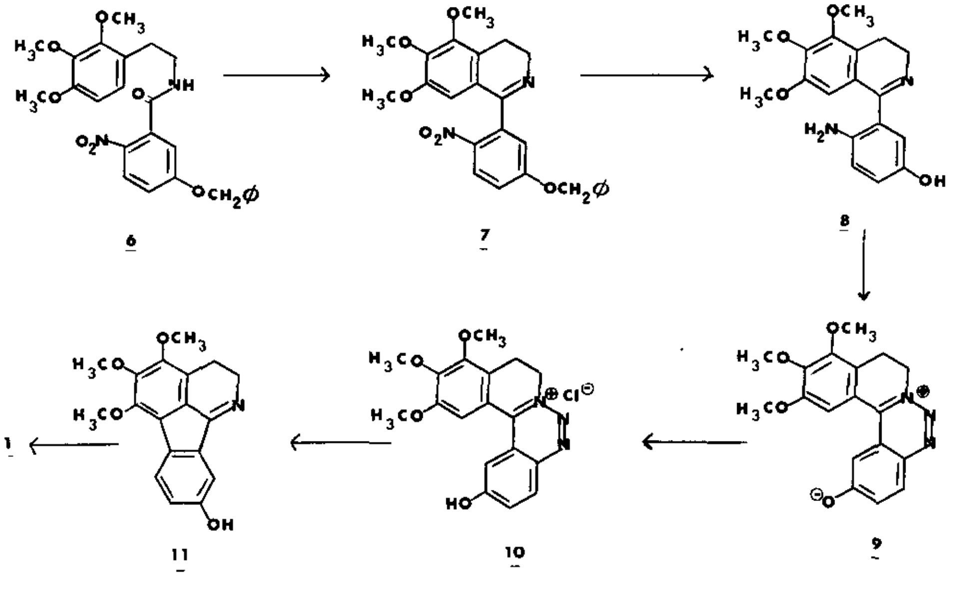


4. R = H

5. R = OH

Reaction of β-(2,3,4-trimethoxyphenyl)ethylamine[6] with the acid chloride of 2-nitro-5-benzyloxybenzoic acid[7] gave the corresponding crystalline amide 6, mp 121-122°C, which was converted by phosphorus oxychloride in acetonitrile into the dihydroisoquinoline 7, mp 128-130°C (58% from amine).

Reduction of 7 with hydrazine and 5% palladium/charcoal in ethanol gave the aminophenol 8 in 70% yield. Diazotization of 8 in 1N H_2SO_4, basification of the solution to pH 8 and extraction into chloroform gave the amorphous permanganate-colored benzotriazine dipole 9 in 90% yield; in accord with structure 9, this material showed no infrared diazo band in the 2200 cm^{-1} region. Treatment of dipole 9 with a little conc. HCl, followed by crystallization from $CHCl_3$-ether, gave yellow-orange crystals of the triazinium chloride 10, mp 187-190°C dec (no band 2200 cm^{-1}). The nmr spectra of 10 ($CDCl_3$) showed three methoxyls at δ 3.98, 4.14 and 4.25 (3H each) and the B-ring protons of the isoquinoline system as triplets centered at δ 3.38 and δ 4.97. In the aromatic region, four protons appeared, a singlet at δ 7.63, doublet of a doublet at δ 7.97, doublet at δ 8.42 (J=9Hz) and a doublet at δ 8.83 (J=2Hz). The uv absorption spectrum showed maxima at 230 (log ε 4.26), 273(4.20), 326(3.86), 375(3.99), 440(3.60) and 498 nm (3.58).



Thermolysis of the benzotriazinium salt 10 in refluxing chlorobenzene gave dihydronorrufescine 11 (24%) and the deaminated product (17%). Dihydronorrufescine crystallized from methanol/ether as yellow crystals, mp 240-242°C; nmr spectrum ($CDCl_3$-CD_3OD) δ 2.81 and 4.13 (2H each, t), 3.89, 3.97 and 3.96 (3H each, s) 6.87 (1H, dd, J=8Hz and 2Hz), 7.20 (1H, d, J=2 Hz), 7.56 (1H, d, J=8Hz). Dehydrogenation of 11 by 10% palladium/charcoal in refluxing p-cymene afforded norrufescine (1), mp 234-236°C (46%), identical (ir, nmr) with the natural base.

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