SYNTHESIS OF NORRUFESCINE

Mary D. Menachery and Michael P. Cava*
Department of Chemistry, University of Pennsylvania
Philadelphia, PA 19104
and
Keith T. Buck and William J. Prinz
Fries and Fries Division
Mallinckrodt, Inc.
Cincinnati, OH 45216

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

The azafuroanthenes 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)⁶. The three non-phenolic bases have been synthesized²,⁵ using a classical Pechmann 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 Pechmann-type cyclization of a condensed benzotriazine intermediate.

1. R = H; R¹ = H
2. R = CH₃; R¹ = H
3. R = CH₃; R¹ = OCH₃
4. R = H
5. R = OH
Reaction of 6-(2,3,4-trimethoxyphenyl)ethylamine with the acid chloride of 2-nitro-5-benzylxybenzoic acid gave the corresponding crystalline amide, mp 121-122°C, which was converted by phosphorus oxychloride in acetonitrile into the dihydroisoquinoline, mp 128-130°C (58% from amine).

Reduction of 7 with hydrazine and 5% palladium/charcoal in ethanol gave the aminophenol in 70% yield. Diazotization of 8 in 1N H₂SO₄, basification of the solution to pH 8 and extraction into chloroform gave the amorphous permanganate-colored benzotriazine dipole 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 CHCl₃-ether, gave yellow-orange crystals of the triazinium chloride, mp 187-190°C dec (no band 2200 cm⁻¹).

The nmr spectra of 10 (CDCl₃) 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 in refluxing chlorobenzene gave dihydronorrufescine (24%) and the deaminated product (17%). Dihydronorrufescine crystallized from methanol/ether as yellow crystals, mp 240-242°C; nmr spectrum (CDCl₃-CD3OD) 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.
REFERENCES


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