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AZAFLUORANTHENE ALKALOIDS: A REINVESTIGATION OF THE SYNTHESIS OF 5,6-DIMETHOXYINDENO[1,2,3-ij]ISOQUINOLINE

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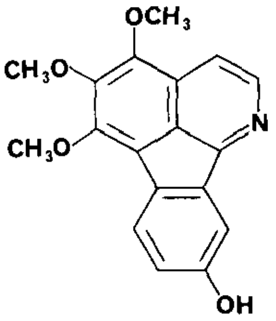
Abstract - The title alkaloid has been synthesized *via* thermolysis of an isolated triazinium salt. The resulting dihydro alkaloid is described for the first time. The reported synthesis of the alkaloid was reinvestigated, with isolation of two products not previously obtained during its preparation.

A limited number of syntheses of the indeno[1,2,3-i,j]isoquinoline ("azafluoranthene") alkaloids and analogs have been described.[1] Of these, only one, that of norrufescine (1)[2] involved isolation of an intermediate triazinium salt (2), and the scope of this procedure remained to be investigated.



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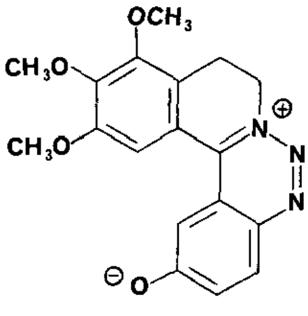

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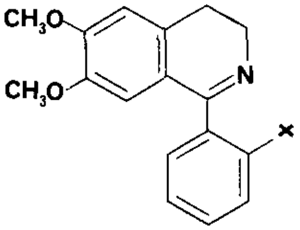
We now report the extension of this method to the synthesis of the alkaloid 5,6-dimethoxyindeno-[1,2,3-i,j]isoquinoline[3] ("triclisine"[4]) by a procedure that resulted in the isolation of the intermediate previously uncharacterized dihydro base 5 (Scheme 1). Diazotization of 3a[3,5] with $NaNO_2$ in 1 N H_2SO_4 and adjustment of the pH to 6.5 gave material which crystallized from $CH_3OH/CHCl_3$ containing a few drops of conc. HCl, affording 89% yield of orange crystals of the triazinium salt 4, mp 161-164°C (decomp.) (no ir band at 2200 cm^{-1}).

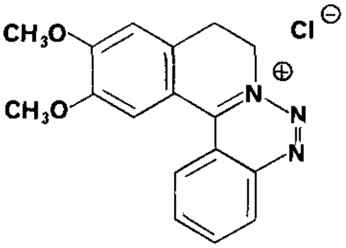
The nmr spectrum ($CDCl_3$) of 4 showed two methoxyls (δ 4.07, 4.13) and the B-ring protons of the isoquinoline system as triplets centered at δ 5.24 and δ 3.67. In the aromatic region, two singlets appeared at δ 7.77 and 7.31 (H-8 and H-5). The rest of the aromatics formed multiplets at δ 8.47 (2H), 8.67 (1H) and 8.87 (1H). The uv spectrum (95% EtOH) showed absorption maxima at 218 (log ε 4.30), 220 (4.27), 233 (4.27), 235 (4.26), 284 (4.08), 288 (4.06), 312 (3.95) and 428 nm (2.67).

Thermolysis of the benzotriazinium salt 4 in refluxing chlorobenzene gave the hydrochloride of the dihydro compound 5 (12%), accompanied principally by the deaminated material 3b. The hydrochloride of 5 formed yellow crystals ($CH_3OH/CHCl_3$), mp 212-214°C; high-resolution MS 265.1086 (calcd. for $C_{17}H_{15}NO_2$ 265.1098); uv (95% EtOH) λ_{max} 222 (log ε 3.78), 243 (4.08), 255 (4.09), 274 (3.91), 306 (3.22), 352 nm (3.54). The free base 5 had nmr [$CDCl_3$] δ 2.81 (2H, t, J = 8.1 Hz, H-3), 3.93, 3.96 (2x 3H, s), 4.23 (2H, t, J = 8.1 Hz, H-2), 6.58 (H-4, s), 7.82, 7.87 (2x 1H, split doublets, J_o = 7.5 Hz, J_m = ~1 Hz, H-7 and H-10), 7.32 and 7.44 (2x 1H, doublet of doublets, J_{8-9} = 7.5 Hz).

Dehydrogenation of 5 with 10% Pd/C in refluxing p-cymene afforded 6 (52%), light yellow needles ($CHCl_3$), mp 153-155°C, identical'(ir, uv, nmr) to the natural product.



3a. X = NH_2
3b. X = H



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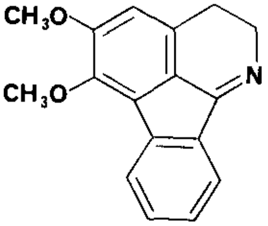

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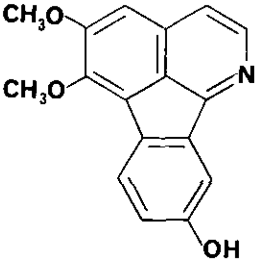

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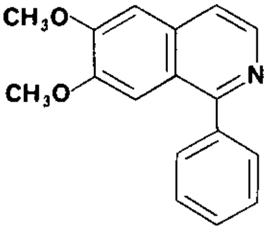

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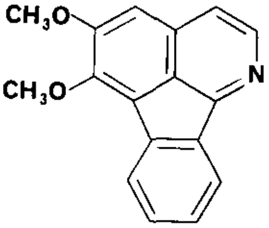

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A reinvestigation of the synthesis of 6 by direct aqueous decomposition of the diazonium sulfate from 3a in presence of Cu[3] afforded the following products: 6 (4%), 5 (11%), 3b (15%) and 7 (4%). It therefore appears that our procedure, although not offering an overall yield advantage over the literature preparation, is more specific. We are currently extending this approach to the synthesis of telitoxine (8)[4].

REFERENCES

1. K. T. Buck, 'Azafluoranthene and Tropoloisoquinoline Alkaloids', in '<u>The Alkaloids</u>', ed. by A. Brossi, Academic Press, New York, 1984, p. 301.
2. M. D. Menachery, M. P. Cava, K. T. Buck and W. J. Prinz, <u>Heterocycles</u>, 1982, <u>19</u>, 2253.
3. R. *Huls*, J. *Gaspers and* R. *Warin*, <u>Bull. Soc. R. Sci. Liege.</u>, 1976, <u>45</u>, 40. These workers prepared <u>6</u> by aqueous diazotization of <u>3a</u>, followed by heating with Cu, basification with NaOH, extraction and column chromatography.
4. This alkaloid has been referred to as "triclisine" (M. D. Menachery and M. P. *Cava*, <u>J. Nat. Prods.</u>, 1980, <u>44</u>, 320). However, it was pointed out that this name had been used for an alkaloid of unknown structure. (H. Guinaudeau, M. Leboeuf and A. Cavé, <u>J. Nat. Prods.</u>, 1983, <u>46</u>, 761).
5. S. Rajagopalan, <u>Proc. Indian Acad. Sci.</u>, 1941, <u>14A</u>, 126.

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