A SIMPLE SYNTHESIS OF AMPHIMEDINE

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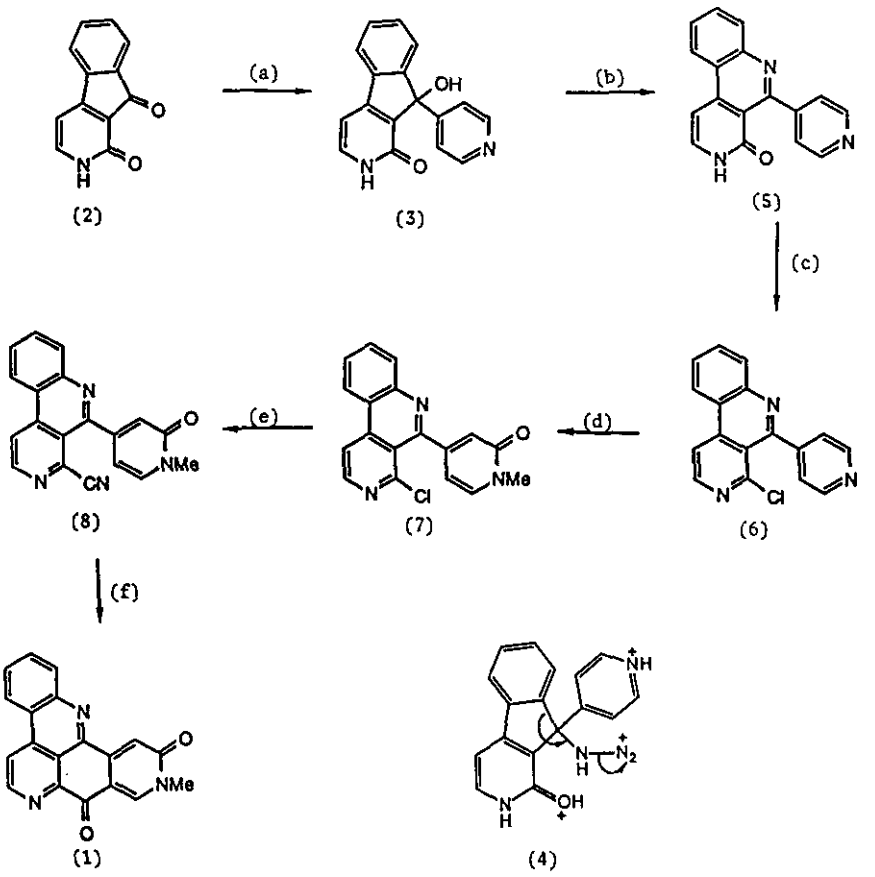
Abstract - Amphimedine may be synthesised in six simple steps from the readily available azafluorenone (2).

Amphimedine (1) is one of a number of pentacyclic alkaloids recently isolated from marine sources[1-3]. Because of its general cytotoxicity[1], we were interested in devising a synthesis that would generate intermediates that might possess more specific anti-tumor properties. We have communicated our synthesis at a Conference[4], and recently reported syntheses of amphimedine by Echavarren and Stille[5] and Kubo and Nakahara[5] prompt us to report our quite different approach.

The fluorenone (2)[6-7] was silylated and treated with 4-pyridyllithium at -20°C to give the fluorenol (3)[8] in 87% yield. By analogy with our previous work[7], we were confident that reaction of (3) with hydrazoic acid would result in migration only of the most electron-rich benzene ring (cf 4), to give the desired diazaphenanthrene (5), mp 327-328°C, which was isolated in 69% yield. Conversion of (5) to the chloropyridine (6), mp 227-228°C was achieved (90%) with phosphorus oxychloride and dimethylformamide in phosphorus trichloride. Of the three nitrogen atoms in (6) that on the pyridine ring was methylated exclusively with one equivalent of methyl fluorosulfonate, and alkaline ferricyanide oxidation then led cleanly to (7), mp 280-282°C (decomp), which was converted to the nitrile (8) by reaction with cuprous cyanide in hot dimethyl sulfoxide. Finally, reaction of (8) with hot PPA gave amphimedine (1), mp > 340°C, with identical spectroscopic properties (ir, uv, nmr) as those kindly provided by Professor F.J. Schmitz. Prior hydrolysis of the nitrile to the acid, followed by cyclisation proved to be more efficient.[6] The route described herein is short and efficient, using readily available reagents. A number of analogues of (2) and (5) have been subjected to cytotoxicity and mutagenic activity studies[9]. The compounds showed little mutagenicity activity using the hypoxanthine-guanine phosphoribosyl transferase or cytokinesis-block micronucleus assays. Analogues of (2) showed cytotoxicity, as measured by the frequency of clone-forming cells or blocking of ^{3}H-thymidine uptake.



(a) (i) Me_3SiCl, Et_3N, THF 60°C, 60 min (ii) 4-bromopyridine, BuLi, -40°C~20°C, 2 h, 87%.

(b) NaN_3, PPA, 45°C, 20 h, 69%. (c) PCl_5, DMF (cat.) in $POCl_3$, 180°C, 20 h, 90%.

(d) (i) $MeOSO_2F$, 1.3 equiv., 20°C, 40 min (ii) KOH, $K_3Fe(CN)_6$, 2 equiv., 20°C, 10 h, 61%.

(e) CuCN, DMSO, 150°C, 4 h, 70%. (f) PPA, 90°C, 5 h, 35%.

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8. All new compounds, except the unstable (3), gave satisfactory microanalytical or high resolution mass spectral figures.

9. Carried out by Professor A. Morley and D.B. Tran in the Flinders Medical Centre.

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