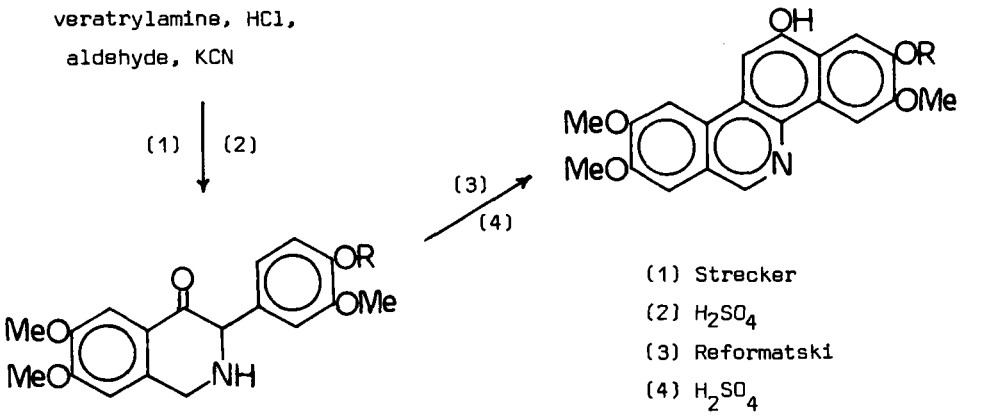
A SIMPLE SYNTHESIS OF POTENTIAL ANTILEUKAEMIC BENZO(c) PHENANTHRIDINES

T.A. Olugbade, R.D. Waigh, Department of Pharmacy, Manchester University, Manchester M13 9PL.

Naturally occurring benzo(c)phenanthridine alkaloids are restricted in structural type and distribution (Cordell & Farnsworth, 1976; Santavy, 1979; Zee-Cheng & Cheng, 1973). They may have a protective role in the plant and in accord with this several have been shown to exhibit antibacterial and antifungal activity (Stermitz et al, 1975). Two compounds, nitidine and fagaronine, show instead marked antileukaemic activity in animals (Wessmer et al 1972; Zee-Cheng & Cheng 1973). Both possess the 2,3,8,9 oxygenation pattern, with methoxy groups at the 8,9 positions. Various synthetic routes to the natural products and their analogues have been developed , but without exception these are long syntheses with low overall yields (Minomiya et al 1977; Stermitz et al 1975; Zee-Cheng & Cheng 1975). The number of analogues which have been prepared is therefore quite small.

We have examined a potentially advantageous route to related compounds with the desired 8,9-dimethoxy substitution pattern, and have found a method which achieves the synthesis in four steps, with quaternisation as a final fifth step, starting from readily available materials:



The overall yield where R = Me, which we have examined in greatest detail so far, is 20-25%. The synthesis of analogues of the antileukaemic natural products thus promises to be considerably easier and cheaper than hitherto.

Cordell, G.A., Farnsworth, N.R. (1976) Heterocycles 4: 393-420.
Minomiya, I., Yamamoto, O., Kiguchi, T., Maito, T., Ishi, H. (1977) Heterocycles 6: 1730-1734.
Santavy, F. (1979) in :Manske, R.H.F., Rodrigo, R.G.A. (eds) The Alkaloids, Acedmic Press, New York, XVII: 493-500.
Stermitz, F.R., Gillespie, J.P., Amoros, L.G., Romero, R., Stermitz, T.A., Larson, K.A., Earl, S., Ogg, J.E. (1975) J. Med. Chem. 18: 708-713.
Wessmer, W.M., Tin-Wa, M., Fong, H.H.S., Bellvelle, C. Farnsworth, M.R., Abraham, D.J., Trojanek, J. (1972) J. Pharm. Sci. 16: 1858-1859.
Zee-Chneg, K.Y., Cheng, C.C. (1973) J. Heterocyclic Chem. 10: 85-88.
Zee-Cheng, K.Y., Cheng, C.C. (1975) J. Med. Chem. 18: 66-71.

0022-3573/81/120081P-01$02.50/0