Stereoselective Total Synthesis of the Alkaloid Haemanthamine

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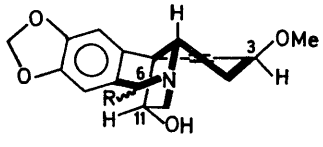
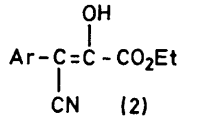
Summary The total synthesis of haemanthamine, an alkaloid of family Amaryllidaceae is reported.

THE Amaryllidaceae alkaloids contain the 5,10-ethanophenanthridine group; haemanthine (**1a**) is of particular interest since this group is then convertible into the 5,11-methanomorphanthridine group such as is found in manthine.[1] Haemanthamine itself has not yet been synthesized, although its hydroxy-analogue, haemanthidine (**1b**), has recently been synthesized by Hendrickson *et al.*[2] Since their route *via* a quasi-lactam is not applicable to this alkaloid and since removal of the extra hydroxy-group from haemanthidine while the rest of the molecule remains intact has failed so far,[3] we have used a synthetic approach based on the tetrahydro-indole synthesis described in the preceeding communication;[4] the total synthesis of this alkaloid is reported.

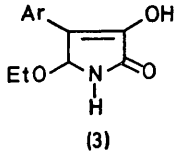
Condensation of 3,4-methylenedioxybenzyl cyanide with ethyl oxalate in the presence of NaOEt yielded the pyruvate (**2**),† m.p. 131—132° (90—95%). Catalytic hydrogenation of (**2**) over Raney Ni in ether containing a small amount of ethanol (40 kg cm^{-2}; 70°), which caused cyclization of an intermediate imine, afforded the ethanol-adduct (**3**) (turned red at *ca.* 185° and decomposed at 253—255° (25—30%). Diels–Alder reaction of (**3**) with butadiene in $HCONMe_2$ (or in Me_2SO) at 160—180° furnished the expected indole (**4a**), m.p. 203—205° (70%). The methoxy-



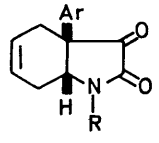
(1a); R = H
(1b); R = OH



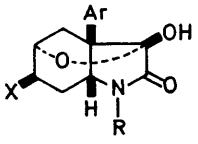
Ar = 3,4-$CH_2O_2C_6H_3$



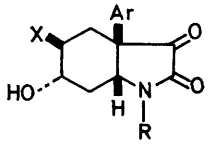
(3)



(4a); R = H
(4b); R = Me

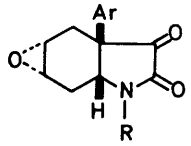


(5a); X = Br, R = H
(5b); X = OMe, R = H
(5c); X = OMe, R = Me

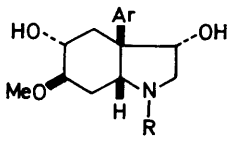


(6a); X = Br, R = H
(6b); X = OMe, R = H
(6c); X = OMe, R = Me

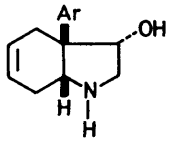
† Satisfactory elementary analyses were obtained for all crystalline compounds; all compounds reported had spectroscopic properties in accord with their assigned structures.



(7a); R = H
(7b); R = Me



(8a); R = H
(8b); R = Me



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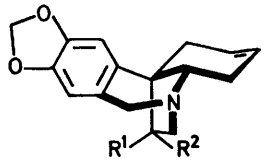
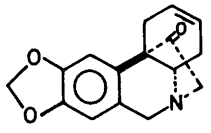
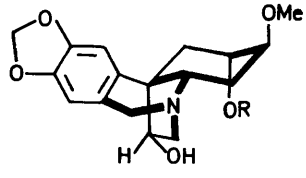


(10a); R^1 = H, R^2 = OH
(10b); R^1 = OH, R^2 = H



(11)



(12a); R = H
(12b); R = *p*-Me·C_6H_4

group at C-3 in haemanthamine (**1a**) which is axial and *cis* to the aromatic group was introduced as follows. Treatment of (**4a**) with *N*-bromoacetamide in dioxan containing a catalytic amount of $HClO_4$ gave a mixture (*ca.* 2:1) of a bromoacetal (**5a**), m.p. 212—214° and a bromohydrine (**6a**), both of which when kept, in MeONa–MeOH (5%) changed into the same epoxy-ketone (**7a**), m.p. 223—225° (i.r. 1710 and 1770 cm^{-1}). Treatment with BF_3–Et_2O in methanol caused opening of the epoxide of (**7a**) to a 7–8:1 mixture of (**5b**), m.p. 250—255°, and an isomer (**6b**). The overall yield of (**5b**) from (**4a**) was *ca.* 50% and of (**6b**) was *ca.* 5%. An interesting reversion of stereoselectivity was observed when the epoxide was opened under basic conditions; *e.g.*, (**7b**) gave a 6:1 mixture on treatment with BF_3–MeOH, but gave a *ca.* 1:2 mixture of (**5c**) and (**6c**) when heated with MeONa in MeOH.

Reduction of the methoxy-acetal (**5b**) with $LiAlH_4$ gave a single diol (**8a**), m.p. 80—90°, whose stereochemistry was the same as that of natural alkaloid, no epimeric compound being found in the product. The correctness of the stereochemistry assigned to the hydroxy-group was confirmed by a model experiment with (**9**) and also by the transformation of (**8a**) into (±)-haemanthamine. Compound (**9**), m.p. 140—143°, obtained by reduction of (**4a**) with $LiAlH_4$ gave (**10a**), m.p. 230—231° in excellent yield when heated with HCHO–HCl. Oxidation of (**10a**) and reduction of the product (**11**), m.p. 160—162°, i.r. 1740 cm^{-1}, with $NaBH_4$ gave a *ca.* 1:2 mixture of (**10a**) and an epimer (**10b**) as shown by t.l.c. Since reduction of haemanthaminone by hydride yields predominantly the unwanted 11-epimer,[5] (**11a**) should have the stereochemistry as assigned.

Pictet–Spengler cyclization of crude (**8a**) by treatment with HCHO–MeOH followed by AcOH yielded an ethanophenanthridine (**12a**), m.p. 263° (50%), and the unwanted *N*-methyl derivative (**8b**) (gum; *ca.* 40%); the structure of the latter was proved by an alternative synthesis from (**4b**), m.p. 154—155°. Tosylation of (**12a**) at room temperature afforded the monotosylate (**12b**), m.p. 183—184° (60—70%), which on heating with excess of 1,5-diazabicyclo[5,4,0]-undec-5-ene in Me_2SO quantitatively yielded (±)-haemanthamine (**1a**), m.p. 225°. The identity of this with the natural specimen‡ was confirmed by t.l.c., and i.r. ($CHCl_3$) and n.m.r. spectroscopy.

The conversion the intermediate (**8a**) into (±)-tazettine and (±)-haemanthidine will be reported elsewhere.

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[2] J. B. Henderickson, T. L. Bogard, and M. E. Fisch, *J. Amer. Chem. Soc.*, 1970, **92**, 5538.
[3] *Cf.* S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, 1958, **80**, 2590.
[4] Y. Tsuda, K. Isobe, and A. Ukai, preceding communication.
[5] H. M. Fales and W. C. Wildman, *J. Amer. Chem. Soc.*, 1960, **82**, 197; W. C. Wildman and D. T. Bailey, *ibid.*, 1969, **91**, 150.