

Stereoselective Total Synthesis of the Alkaloid Haemanthamine

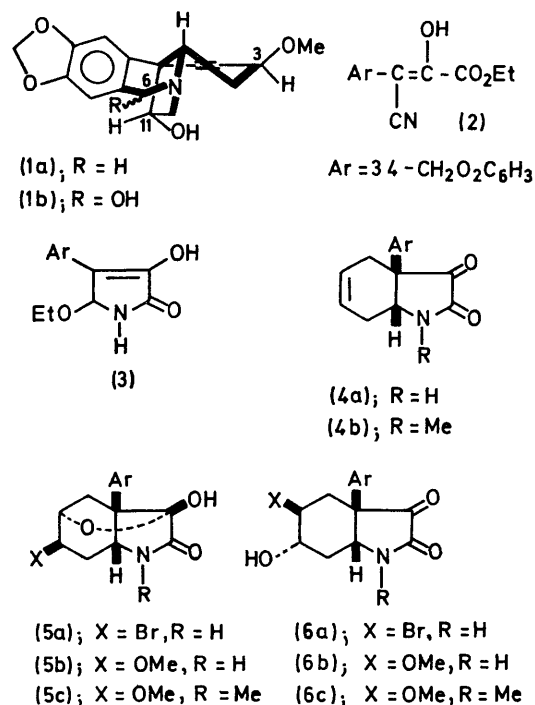
By Y. TSUDA* and K. ISOBE

(Showa College of Pharmaceutical Sciences, Setagaya-ku, Tokyo, Japan)

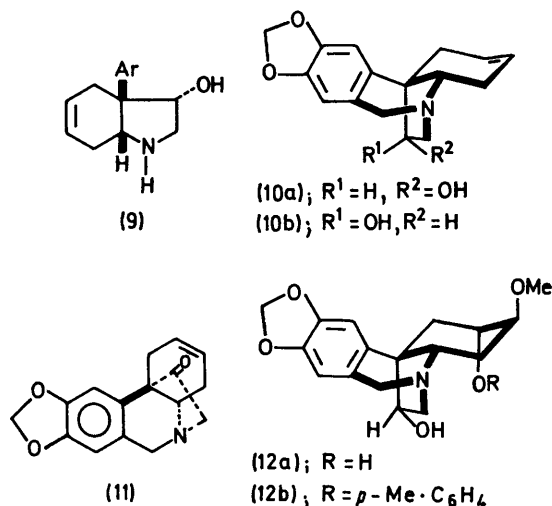
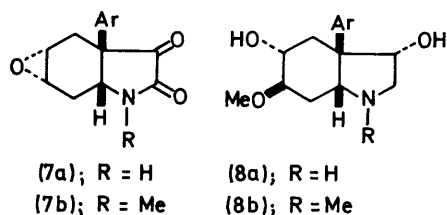
Summary The total synthesis of haemanthamine, an alkaloid of family Amaryllidaceae is reported.

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 HCONMe₂ (or in Me₂SO) at 160—180° furnished the expected indole (**4a**), m.p. 203—205° (70%). The methoxy-



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



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 HClO₄ 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 BF₃–Et₂O 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 BF₃–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 LiAlH₄ 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 LiAlH₄ 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 NaBH₄ 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 Me₂SO quantitatively yielded (±)-haemanthamine (1a), m.p. 225°. The identity of this with the natural specimen[‡] was confirmed by t.l.c., and i.r. (CHCl₃) and n.m.r. spectroscopy.

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

(Received, September 1st, 1971; Com. 1511.)

‡ We thank Dr. K. Kotera, Shionogi Research Laboratory, for a gift of the natural alkaloid.

¹ Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, 1960, **25**, 2153.

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.