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TOTAL SYNTHESES OF THE ALKALOIDS HAEMANTHIDINE AND TAZETTINE

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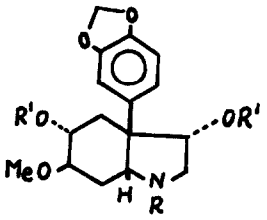
Recently stereospecific synthesis of the hydroindole derivative (1) and its successful conversion to the alkaloid haemanthamine were reported[1]. In this communication we report the transformations of this intermediate diol (1) to haemanthidine and tazettine, the alkaloids of the family Amaryllidaceae, via a novel type of Bischler-Napieralski reaction in which bridge-head nitrogen is concerned.

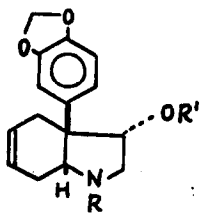
First the model compound (2) was converted to the O-acetyl-N-formyl derivative (3)[2,3], m.p. 125-126°, IR: 1735, 1660 cm^{-1}, NMR: δ 8.35 and 8.27 (total 1H, 3:1, N-CHO), 2.10 and 2.05 (total 3H, 1:3, OAc), by formylation (HCOOAc), partial hydrolysis ($NaHCO_3$-MeOH), and then by acetylation (Ac_2O-pyridine). When (3) was treated successively with $POCl_3$ in xylene (100°, 15 min.) and aqueous base (NH_3 or Na_2CO_3), it gave a tricyclic hydroxy-compound (5), m.p. 257-260° (81%). The structure of the product was proved from its NMR spectrum ($CDCl_3$) which indicated that the hydroxy-group at C_6 of (5) is in equilibration ($5_a \rightleftarrows 5_b$) as that in haemanthidine since the aromatic and benzylic proton signals appeared at δ 6.98, 6.80, and 6.73 (total 2H, 1:2:3) and at 5.35 and 5.11 (total 1H, 1:2) respectively, the pattern of which being almost identical with that of haemanthidine and of 6-hydroxy-crinamine[4]. This structural assignment was further confirmed by converting (5) on treatment with CH_3I then with 2% NaOH to the rearranged compound (7), m.p. 216-218°, NMR: δ 4.80 (2H, AB_q, δ=28 Hz, J=14 Hz, benzylic protons). However, on standing of the solid derived from $POCl_3$ reaction with methanol prior to base treatment, a single methoxy-compound (6), m.p. 200-201° (72%), NMR: δ 3.62 (3H, s., OMe), 4.42 (1H, s., benzylic proton), was



1 R = R' = H

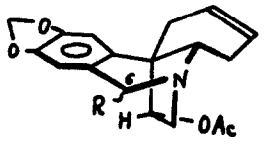
8 R = R' = CHO

9 R = CHO, R' = Ac



2 R = R' = H

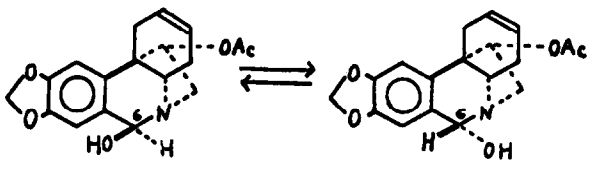
3 R = CHO, R' = Ac



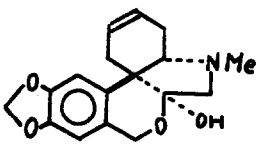
4 R = Cl

5 R = OH

6 R = OMe



5a 5b



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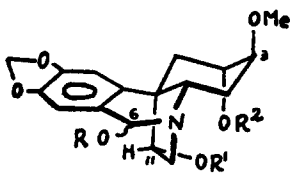


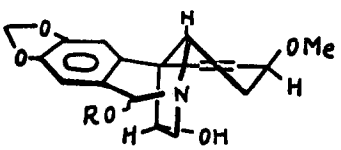
10 R = H, R¹ = R² = CHO

11 R = H, R¹ = R² = Ac

12 R = Me, R¹ = R² = Ac

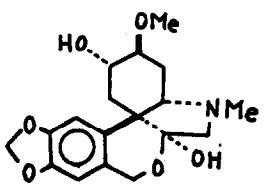
13 R = Me, R¹ = R² = H

14 R = Me, R¹ = H, R² = p-CH₃C₆H₄SO₂-



15 R = Me

16 R = H



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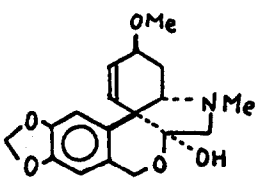

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obtained, which was able to hydrolyse by AcOH-H_2O to the hydroxy-compound (5), thus confirming the structure. While (5) did not give any methoxy-compound on heating with methanol and acid (p-TsOH), it gave (6) on treatment with $POCl_3$ and subsequently with methanol. These facts suggest that the products (5) and (6) were produced by the solvolysis of the intermediate (4) respectively. This unusual type of Bischler-Napieralski reaction is undoubtly due to bridge-head character of the nitrogen in (4) where usual dehydrochlorination is prohibited by Bredt's rule, instead the chlorine is activated for solvolytic replacement since it is at benzylic position and at α-position of amino group. Since the methoxy-group in (6) was stable to base (NaOH) and easily hydrolysed to the hydroxy-compound (5) as indicated above, C_6-methoxylation should be a suitable protection of C_6-hydroxy group from basic rearrangement of the hydroxy-compound to nortazettine type alkaloid[5].

Based on above model experiments, the diol (1) was converted to O-acetyl-N-formyl derivative (9), gum, IR: 1730 (OAc), 1660 cm^{-1} (N-CHO), NMR: δ 8.52 and 8.42 (total 1H, 2:1, N-CHO), by formylation, hydrolysis, then by acetylation. Successive treatment of (9) with $POCl_3$ in xylene (100°, 15 min.) and methanol gave the methoxy-compound (12), m.p. 178-182° (35%), NMR: δ 4.40 (1H, s., benzylic proton), 3.58 (3H, s., C_6-OMe), 3.38 (3H, s., C_3-OMe). Alkaline hydrolysis (NaOH) of (12) and tosylation (p-TsCl-pyridine) of the resulting diol gave (14), m.p. 199-201° (40%), NMR: δ 7.64 (2H, AB_q, δ=29 Hz, J=8 Hz) and 2.48 (3H, s., CH_3), which on treatment with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU) in dimethylsulfoxide (DMSO) afforded the compound corresponding to hitherto unknown methyl-haemanthidine (15). Heating of (15) in 50% AcOH furnished (±)-haemanthidine (16), m.p. 221-223°[6], in excellent yield (60% from 14).

On the other hand, successive treatment of (9) with $POCl_3$ and aqueous base gave the hydroxy-compound (11), m.p. 238-240° (67%), IR: 1742 cm^{-1}. The methiodide obtained by CH_3I-MeOH treatment was rearranged to (17), gum, in contrast to model experiment, by 20% NaOH in 50% yield. The NMR pattern of its benzylic hydrogens (δ 4.80, 2H, AB_q, δ=28 Hz, J=14 Hz) was almost identical with that of tazettine. Tosylation (p-TsCl-pyridine) of (17) and detoluenesulfonic acid (DBU-DMSO) of the resulting tosylate afforded (±)-tazettine (18), m.p. 237-238°.

The identities of the synthetic alkaloids with natural specimens were confirmed by t.l.c., NMR, and IR in $CHCl_3$ comparisons.

Acknowledgement. We are grateful to Dr. K. Kotera, Shionogi Research Lab. for providing us the natural alkaloids.

References and Footnotes

1. Y. Tsuda and K. Isobe, Chem. Comm., 1555 (1971).
2. All compounds reported had spectroscopic properties in accord with their assigned structures.
3. Satisfactory elementary analyses were obtained for all crystalline compounds.
4. R.W. King, C.F. Murphy, and W.C. Wildman, J. Am. Chem. Soc., 87, 4912 (1965).
5. H. Irie, Y. Tsuda, and S. Uyeo, J. Chem. Soc., 1446 (1959).
6. The m.p. of our (±)-haemanthidine is higher than that reported by Hendrickson et al.[7] (m.p. 195°). But we observed during crystallizations that the compound in undefined crystalline forms showed m.p. ca 195°.
7. J.B. Hendrickson, T.L. Bogard, and M.E. Fisch, J. Am. Chem. Soc., 92, 5538 (1970).