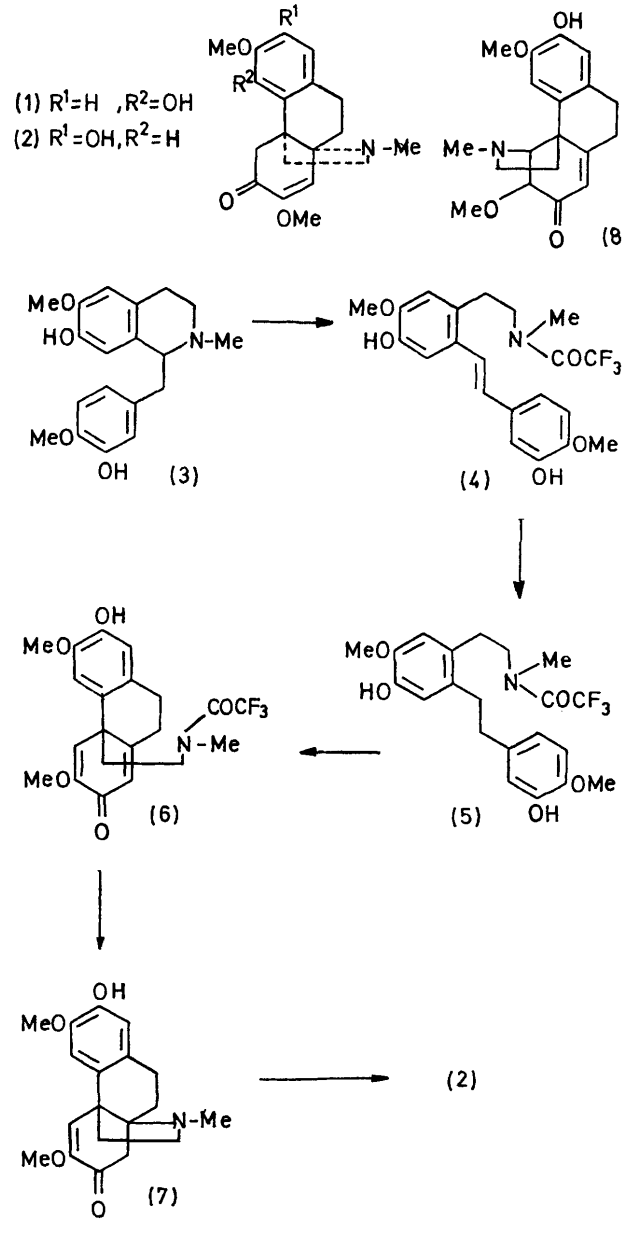
Synthesis of the Hasubanan Ring System from the Alkaloid Reticuline

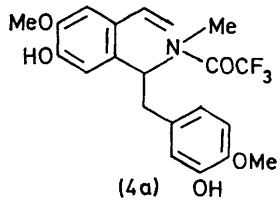
By T. KAMETANI,* T. KOBARI, and K. FUKUMOTO
(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan*)

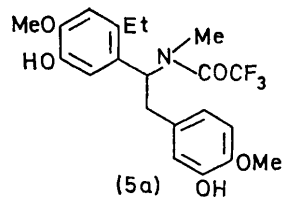
Summary The synthesis of a cepharamine-type compound from reticuline by phenolic oxidation is reported.

CEPHARAMINE, an alkaloid from *Stephania cepharantha*,[1] has been assigned the benzindolizine structure (**1**) by chemical and spectroscopic methods,[1] and bases having this ring system are called hasubanan aklaloids.[2] Rearrangement of the phenolic oxidative product from a diphenolic isoquinoline[3] should provide a biosynthetic pathway to these alkaloids. We have been investigating the synthesis of hasubanan ring systems from benzylisoquinolines,[4] and here report a simple synthesis of the cepharamine analogue (**2**) from reticuline (**3**).

Reticuline was treated with trifluoroacetic anhydride to give the methine base (**4**), showing a *trans*-stilbene absorption in its u.v. spectrum, which was reduced by Adam's catalyst to the dihydromethine base (**5**) which had no Et n.m.r. absorption, thus fact excluding a possible product (**5a**) derived from (**4a**). Phenolic oxidation of (**5**) ($VOCl_3$) gave the dienone (**6**) (20%), which showed a typical α-methoxylated cross-conjugated dienone system in its i.r. [ν_{max} ($CHCl_3$), 1665, 1640, and 1625 cm^{-1}] and u.v. spectra [λ_{max} (MeOH) 239 and 280 nm; log ε 4·16 and 3·84]. The n.m.r. spectrum revealed two aromatic (δ 6·88 and 6·68 p.p.m.) and two olefinic protons (6·38 and 6·27 p.p.m.) with the expected three methyl resonances (3·93, 3·80, and 3·06 p.p.m.). Hydrolysis of the dienone (**6**) with aqueous K_2CO_3 yielded the enone (**7**), $C_{19}H_{23}NO_4$ (M^+ 329), ν_{max} ($CHCl_3$) 1679 and 1625 cm^{-1}, λ_{max} (MeOH) 257 and 283sh nm; log ε 3·74 and 3·505, the picrate of which gave yellow neeedles (from EtOH), m.p. 213—215°. Its structure was assigned on the basis of its n.m.r. spectrum which showed three methyl (δ 2·24, 3·58, and 3·80 p.p.m.), two aromatic (6·80 and 6·58 p.p.m.) and one olefinic resonance (5·80 p.p.m.). These data are similar to those of dihydro-orientalinone[5] and dihydrokreysiginone,[6] and eliminate the alternative structure (**8**). Treatment of (**7**) with methanolic







HCl[7] gave the cepharamine analogue (**2**) [ν_{max} ($CHCl_3$) 3460, 1678, and 1625 cm^{-1}; λ_{max} (MeOH) 255 and 283sh nm; log ϵ 3·87 and 3·775; picrate, m.p. 218—219° (yellow needles from EtOH)]; n.m.r. δ 2·41, (*N*-Me), 3·65 (enolic *O*-Me), 3·84, (*O*-Me), 5·64 (olefinic-H), and 6·65 and 6·56 p.p.m. (each ArH). The *N*-Me, enolic *O*-Me, and olefinic resonances are similar to those of cepharamine (**1**).[1]

(*Received*, 13*th December* 1971; *Com.* 2122.)

[1] M. Tomita and M. Kozuka, *Tetrahedron Letters*, 1966, 6229.
[2] T. Kametani, 'The Chemistry of the Isoquinoline Alkaloids', Hirokawa, Tokyo, 1968, pp. 158, 253.
[3] A. R. Battersby, "Oxidative Coupling of Phenols", eds. W. I. Taylor and A. R. Battersby, Dekker, New York, 1967, p. 119.
[4] T. Kametani, R. Charubala, M. Ihara, M. Koizumi, and K. Fukumoto, *Chem. Comm.*, 1971, 289.
[5] A. R. Battersby and T. H. Brown, *Chem. Comm.*, 1966, 170.
[6] A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 934.
[7] D. H. R. Barton, A. J. Kirby, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1968, 929.