New Biogenetic-type Approach to *Cephalotaxus* Alkaloids

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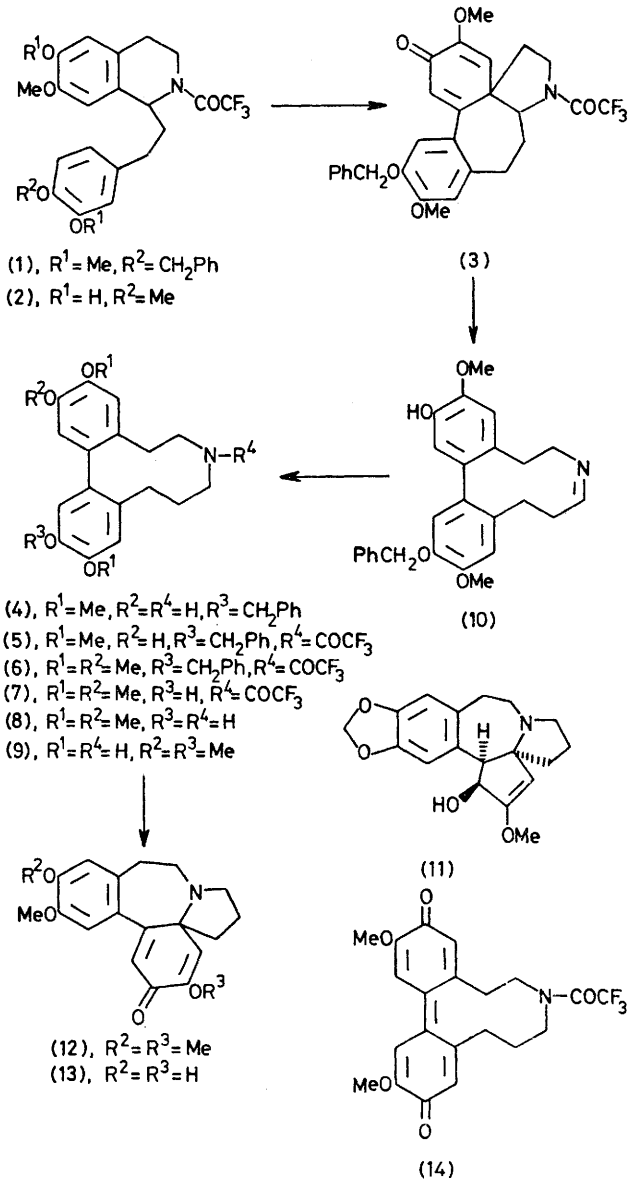
Summary A cephalotaxine-type skeleton (**12**) has been synthesized starting from the substituted phenethyltetrahydroisoquinoline (**1**) *via* the monophenolic dibenz[*d*,*f*]azocine (**8**).

THE total synthesis of cephalotaxine (**11**),[1] the alkaloidal portion of the antitumour esters[2] of *Cephalotaxus harringtonia*, has been an attractive goal in recent years. The presence of *Schelhammera*-type alkaloids[3] in *Cephalotaxus* species[4] has led[4a,5] to the proposal that both the *Schelhammera*-type and *Cephalotaxus* alkaloids are biogenetically related and may be classified as homoerythrina alkaloids. It has been reported[5] that a unified approach to homoerythrina skeletons *via* the substituted phenethylisoquinoline (**2**) and the pivotal diphenolic dibenz[*d*,*f*]azocine (**9**) has produced the *Schelhammera*-type compound and homoerysodienone, but not the cephalotaxine-type skeleton. An earlier attempt to oxidize (**9**) using a variety of oxidizing agents to the corresponding diphenoquinone (**14**) which could then be transformed into the cephalotaxine precursor (**13**) *via* an intramolecular Michael addition of the nitrogen[4] has been unsuccessful.[5] We report herein the synthesis of the monophenolic dibenz[*d*,*f*]azocine (**8**) and its oxidative transformation into the cephalotaxine-type skeleton (**12**).

Nonphenolic oxidative coupling[6] of the phenethyltetrahydroisoquinoline (**1**)‡ with VOF_3 in CH_2Cl_2 and CF_3CO_2H yielded the homoneospirinedienone (**3**), 65%, m.p. 176·5—178 °C (from MeOH), u.v. λ_{max} (EtOH) 342 (log ϵ 3·59), 285 (3·75), 258 (3·93), and 235 (4·15) nm; i.r. ν_{max} ($CHCl_3$) 5·80, 5·88, and 5·97 μm; ^{1}H n.m.r. δ ($CDCl_3$) 7·36 (5H, broad s, OCH_2Ph), 6·66 (2H, s, ArH), 6·34 (1H, s, olefinic H), 5·70 (1H, s, olefinic H), and 3·89 and 3·70 (6H, each s, 2–OMe); mass spectrum *m/e* 513 (M^+) and 423. Treatment of (**3**) with 1 M NaOH in methanol at 0 °C yielded the imine (**10**) which was converted into its hydrochloride salt, m.p. 215—217 °C (decomp.), with anhydrous HCl in MeOH. The imine hydrochloride was reduced with sodium borohydride in ethanol to give the dibenz[*d*,*f*]azocine (**4**) which was treated without purification with trifluoroacetic anhydride and pyridine to yield (**5**) in 70% overall yield from (**3**), m.p. 81—82·5 °C (from EtOH). Methylation of (**5**) with diazomethane gave (**6**), 92%, m.p. 80·5—81·5 °C (from Et_2O). Debenzylation of (**6**) by catalytic hydrogenation (10% Pd/C) gave (**7**) which was treated with K_2CO_3 solution in aqueous MeOH at room temperature to give the monophenolic dibenz[*d*,*f*]azocine (**8**), 78% from (**5**), m.p. 203·5—204 °C (from MeOH), i.r. ν_{max} ($CHCl_3$) 2·76 μm; ^{1}H n.m.r. δ ($CDCl_3$) 6·71, 6·72, 6·58, and 6·54 (4H, each s, ArH), 3·90 (6H, s, 2-OMe), and 3·80 (3H s, 1–OMe); mass spectrum *m/e* 343 (M^+), 328, 311, 298, and 285. Oxidation of the monophenolic dibenz[*d*,*f*]azocine (**8**) with potassium ferricyanide in CH_2Cl_2 and 5% aqueous $NaHCO_3$ solution yielded the cephalotaxine-type compound (**12**), 10% m.p. 149—152 °C (from Et_2O), u.v. λ_{max} (EtOH) 230 (log ϵ 4·16), 260 (3·90), 283 (3·79), and 326 (3·62) nm; i.r. ν_{max} ($CHCl_3$) 5·90, 5·93, and 6·01 μm; ^{1}H n.m.r. δ ($CDCl_3$) 6·68 and 6·59 (2H,



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‡ The phenethyltetrahydroisoquinoline (**1**) was prepared by the Bischler–Napeiralski procedure and subsequent N-acylation with trifluoroacetic anhydride in pyridine. (*Cf.* S. Teitel and A. Brossi, *J. Heterocyclic Chem.*, 1968, **5**, 825; A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J.C.S. Perkin I*, 1972, 1741). All new compounds were characterized by concordant analytical and spectral data. The structural formulae containing asymmetric atoms refer to racemic compounds.

each s, ArH), 6·20 and 5·95 (2H, each s, olefinic H), and 3·89, 3·86, and 3·72 (9H, each s, 3-OMe); high resolution chemical ionization mass spectrum, *m/e* 342·1700 ($M^+ + 1$) (calculated for $C_{20}H_{24}NO_4$ 342·1705).

We thank the National Cancer Institute for financial support.

(*Received, 20th July* 1977; *Com.* 743.)

[1] S. M. Weinreb and J. Auerbach, *J. Amer. Chem. Soc.*, 1975, **97**, 2503; M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *ibid.*, p. 2507; S. M. Weinreb and M. F. Semmelhack, *Accounts Chem. Res.*, 1975, **8**, 158.
[2] K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *Tetrahedron*, 1972, **28**, 1995.
[3] J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 2187; S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *ibid.*, p. 2219; N. Langlois, B. Das, and L. Lacomb, *Bull. Soc. chim. France*, 1970, 3535.
[4] R. G. Powell, *Phytochemistry*, 1972, **11**, 1467; R. G. Powell, and K. L. Mikolajczak, *ibid.*, 1973, **12**, 2987; W. W. Paudler and J. McKay, *J. Org. Chem.*, 1973, **38**, 2210; S. Asada, *Yakugaku Zasshi*, 1973, **93**, 916.
[5] J. P. Marino and J. M. Samanen, *J. Org. Chem.*, 1976, **41**, 179.
[6] S. M. Kupchan, O. P. Dhingra, C.-K. Kim, and V. Kameswaran, *J. Org. Chem.*, 1976, **41**, 4047; S. M. Kupchan, O. P. Dhingra, and C.-K. Kim, *ibid.*, p. 4049.