Tetrahedron Letters No. 47, pp 4161 - 4164, 1975. Pergamon Press. Printed in Great Britain.

ASPIDOSPERMA ALKALOIDS: THE TOTAL SYNTHESIS OF (±)-N,O-DIACETYLCYLINDROCARPINOL, (±)-CYLINDROCARINE, (±)-CYLINDROCARPINE, AND (±)-CYLINDROCARPIDINE

J. E. Saxton*, A. J. Smith, and (in part) G. Lawton

Department of Organic Chemistry, The University, Leeds LS2 9JT

(Received in UK 26 September 1975; accepted for publication 9 October 1975)

The recent communication by Ban *et al.*,[1] in which the synthesis of 1,2-deoxylimapodine and N_a-acetylaspidoalbidine is described, prompts us to report our synthetic work in this area, which has so far resulted in the synthesis of N,O-diacetylcylindrocarpinol (1), cylindrocarine (2), cylindrocarpine (3), and cylindrocarpidine (4).

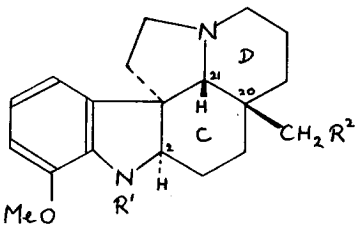
The synthesis[2] of both aspidospermine (5) and a stereoisomer containing a *trans* C/D ring junction from a common intermediate indicates that the two stereo-chemical series probably differ little in stability; in the aspidospermine group the *cis* C/D series appears to be favoured, but the order of stabilities may well be reversed in compounds containing a bulky substituent at C-20. The construction of the aspidospermine ring system by the Fischer indole reaction would then afford an opportunity for the formation of the undesired *trans* C/D isomer by a reversible Mannich fission on the intermediate indolenine. For this reason we considered that the most viable route to alkaloids of the cylindrocarpine group was that *via* a tricyclic aminoketone such as (6a) which contains at the angular position the least sterically-demanding substituent, i.e. the allyl group, that can subsequently be converted into the desired functionalised two-carbon unit. Our first objective was thus the synthesis of the pentacyclic base (7) by appropriate modification of Stork's approach[3].

The pyrrolidine enamine of pent-4-enal[4] was successively alkylated with methyl acrylate and methyl vinyl ketone to give, after cyclisation with acetic acid, 4-(2-methoxycarbonylethyl)-4-allylcyclohex-2-enone (8), b.p. 154-156°/0.4 mm., which was converted into the bicyclic keto-lactam (9), m.p. 109-110°, by reaction with ammonia in ethanol, and thence into the ethylene ketals (10) (cis isomer, m.p. 126·5-127·5°; trans isomer, m.p. 162-163°)[5]. Reduction ($LiAlH_4$) of these ketals afforded the corresponding aminoketals (11) (cis isomer, m.p. 194·5°; trans isomer, m.p. 235-237°), acid hydrolysis of which gave the oily aminoketones (12a and b). The cis aminoketone (12a) was identical with that independently (and more conveniently) synthesised by cyanoethylation of the ketone (13),[6] followed by reduction ($LiAlH_4$), acid hydrolysis, and cyclisation.

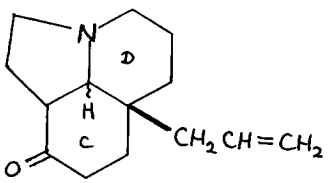
Chloroacetylation of the aminoketals (11), followed by acid hydrolysis and cyclisation ($KOBu^t$-Bu^tOH), afforded the two tricyclic aminoketones (6a) (m.p. 127·5-129°) and (6b) (m.p. 124-125°). Further elaboration of (6a) by Stork's method eventually gave the pentacyclic base (7), m.p. 189·5-190°, $\nu_{max.}$ 2780, 2720 (Bohlmann bands), 1640 cm^{-1}; τ ($CDCl_3$), 5·45 (1H, bq, aspidospermine "fingerprint", C-2 H), 6.1 (3H, s, OMe), 7.78 (3H, s, NCOMe); $\lambda_{max.}$ (ε): 218 (33,900), 256 (11,000), 290sh (2700) nm; m/e 366 (15), 324 (60), 323 (55), 136 (100). Oxidative fission of the allyl group (OsO_4-$Na_2H_3IO_6$) gave the aldehyde (14), m.p. 214-216°, which on reduction afforded (±)-N-acetylcylindrocarpinol (15), m.p. 200-201°, identical with authentic material in its I.R. spectrum and t.l.c. behaviour in three solvent systems. Acetylation of (15) gave (±)-N,O-diacetylcylindrocarpinol (1), also identical with authentic material[7,8].

The aldehyde (14) also furnished an oxime, m.p. 230-232°, which with acetic anhydride gave the corresponding nitrile (16), m.p. 245-247°. Methanolysis of (16) with $MeOH/H_2SO_4$ produced amorphous (±)-cylindrocarine (2)[9], which on acetylation gave (±)-cylindrocarpidine (4)[7,10], m.p. 178-179°, and on cinnamoylation gave amorphous (±)-cylindrocarpine (3)[7,11].

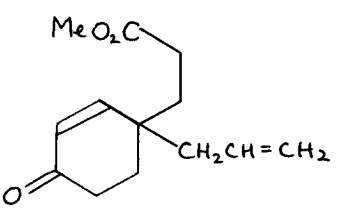
For comparison purposes the trans tricyclic aminoketone (6b) was converted into (17) by cyclisation of its o-methoxyphenylhydrazone with anhydrous formic acid, and replacement of the formyl group in the product (18) by an acetyl group. As expected, Fischer cyclisation by the Stork method, followed by reduction and acetylation, gave a mixture of (7) and (17). Neither (17) nor (18) contains the aspidospermine "fingerprint" at ~5.45 τ (C-2 proton); in (17) the C-2 proton absorbs at 5.13 τ, and in (18) at 5.20 τ.



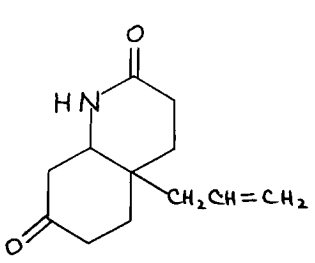
(1) R' = Ac, R^2 = CH_2OAc
(2) R' = H, R^2 = CO_2Me
(3) R' = COCH = CHPh, R^2 = CO_2Me
(4) R' = Ac, R^2 = CO_2Me
(5) R' = Ac, R^2 = Me
(7) R' = Ac, R^2 = $CH = CH_2$
(14) R' = Ac, R^2 = CHO
(15) R' = Ac, R^2 = CH_2OH
(16) R' = Ac, R^2 = CN



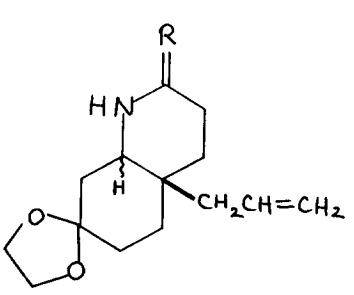
(6) a; cis C/D junction
b; trans C/D junction



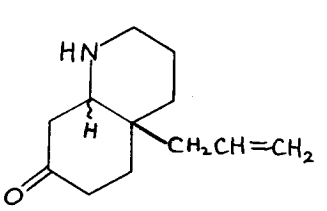
(8)



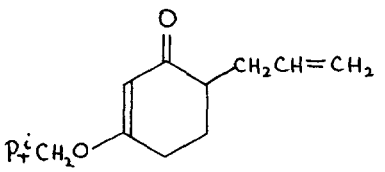
(9)



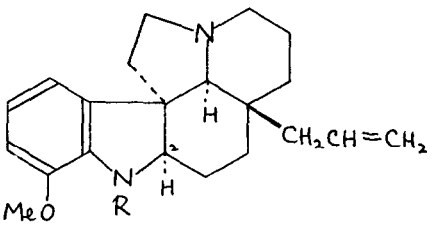
(10) R = O
(11) $R = H_2$



(12) a; cis
b; trans



(13)



(17) R = Ac
(18) R = CHO

References

1. Y. Ban, T. Ohnuma, K. Seki, and T. Oishi, Tetrahedron Letters, 1975, 727.

2. Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, Tetrahedron Letters, 1965, 2261; Y. Ban and I. Iijima, ibid., 1969, 2523.

3. G. Stork and J. E. Dolfini, J. Amer. Chem. Soc., 1963, 85, 2872.

4. R. F. Webb, A. J. Duke, and J. A. Parsons, J. Chem. Soc., 1961, 4092.

5. Satisfactory analytical data have been obtained for all the intermediates isolated in this work.

6. G. Stork and R. L. Danheiser, J. Org. Chem., 1973, 1775.

7. Identical with authentic material on t.l.c. in 3 solvent systems, U.V., I.R., and mass spectra.

8. A critical n.m.r. comparison could not be carried out owing to lack of authentic material, but the spectra obtained (Fourier transform, 1000 scans) although poorly resolved, appeared to be identical.

9. Authentic material was not available for comparison, but R_f values were identical with those recorded in the literature.

10. Identity with authentic material also established by comparison of n.m.r. spectra.

11. Comparisons with authentic N-acetylcylindrocarpinol, N,O-diacetylcylindrocarpinol, cylindrocarpine and cylindrocarpidine were performed on specimens kindly supplied by Prof. C. Djerassi, to whom we express our grateful thanks.