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THE TOTAL SYNTHESIS OF (±)-C-MAVACURINE

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The processes of reductive opening and oxidative reclosing of the 3,4-bond have been applied to effect overall epimerisation at C-3 in the transformation of synthetic epi-*geissoschizine analogues into mavacurine-type alkaloids.*

The mavacurine-type indole alkaloids[1] form a small subgroup of the *Corynanthe* series distinguished by the presence of a 6-membered ring (E) formed by bonding *N*(a) to C-16. C-Mavacurine, the parent member, first isolated[2] from calabash curare, was shown to have the structure (*1*),[3] to be transformed[4] into C-alkaloid Y (2α,7α-dihydroxy-2,7-dihydro-(*1*)) by catalytic oxidation in aqueous solution and thence into C-fluorocurine (the pseudoindoxyl resulting from pinacol-type rearrangement) by treatment with acid, and was converted[3,5] to ε_2-dihydromavacurine (*2*)[6] by hydrogenolysis over Pt in alkaline solution. Furthermore, the triad of calabash curare alkaloids has been correlated[3] with the tertiary alkaloid (+)-pleiocarpamine (*3*): Heating *3* with methoxide in methanol quantitatively produced its C-16 epimer, *9c*, reduction of which gave normavacurine (*epi*-pleiocarpaminol[7]) (*9d*), a compound previously derived[8] from C-fluorocurine. Methylation of *9d* gave C-mavacurine (*1*).

A partial synthesis[9a,c] of 19,20β-dihydro-(*9c*) and -(*9d*)[10] from dihydrocorynantheine or hirsutine and the analogous transformation[9b,c] of (+)-geissoschizine into (+)-*epi*-pleiocarpamine (*9c*) itself were achieved by Sakai and Shinma using as key reactions[11,12] the *solvolytic* C/D ring cleavage of indoloquinolizidines (BrCN-EtOH) and an acetolytic C/D ring regeneration.

We now report the first *total* synthesis of (±)-C-mavacurine (*1*), *via* (±)-*epi*-pleiocarpamine (*9c*) and (±)-normavacurine (*9d*), together with a total synthesis of (±)-ε_2-dihydromavacurine (*2*) from a common intermediate. Our established route[13] to indolo[2,3-*a*]quinolizidines bearing both a C-15 substituent and a C-20 *E*-ethylidene group only permits the synthesis of intermediates initially having the *wrong* relative configurations of the dependent chiral centres, C-3 and C-15, of C-mavacurine (*1*). For the projected elaboration of such an intermediate into alkaloids of the mavacurine group an efficient epimerisation at C-3 was therefore sought. The use of the *solvolytic* C/D ring cleavage reaction by analogy with the work in the 19,20-dihydro series[9a,c] was found *not* to effect the anticipated[9a] overall epimerisation (see appendix to Note 16). However, we have now circumvented this problem by first synthesising ε_2-dihydromavacurine (*2*) derivatives (for which a novel *reductive* C/D ring cleavage reaction has been developed[14]) and then establishing *dependently* the correct C-3 configuration in reconstituting the 3,4-bond of the mavacurine system.

The alcohol (*4a*)[13] was oxidised using dimethyl sulphoxide (DMSO) activated with dicyclohexylcarbodiimide in the presence of H_3PO_4 to give the aldehyde (*4b*)[15] which was converted to the dithiolane (*4c*) (60% yield from *4a*) by treatment at 0° with ethane-1,2-dithiol and $BF_3{\cdot}Et_2O$ in dichloromethane. Reductive removal of the C-21 oxo function was accomplished using Bu^i_2AlH in 1,2-dimethoxyethane at -55° to give the amine (*5*).[16] This was subjected to the chloroformate ester induced *reductive* C/D ring cleavage reaction[14] with PhO_2CCl and $NaBH_3CN$ in tetrahydrofuran (THF) at -70° to room temperature to give the urethane derivative (*6a*) (71% yield from *4c*).

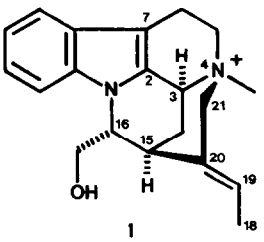
Successive modifications of the C-15 substituent of *6a* were performed as follows:- Hydrolysis of the dithiolane function (excess MeI in aqueous acetone containing suspended $CaCO_3$ at room temperature) gave the aldehyde (*6b*). Treatment with HCN in aqueous THF gave the cyanohydrins (*6c*) (approximately equal mixture of diastereoisomers) which were converted to the mesylates (*6d*) by reaction with $MeSO_2Cl$ in pyridine-dichloromethane. Displacement of the mesyloxy groups using excess LiCl in *N*,*N*-dimethylformamide at 110° gave the cyano-chlorides (*6e*) in an overall 76% yield from *6a*.

Treatment of the mixture of chlorides (*6e*) with NaH in DMSO at room temperature gave (64%) the ε_2-dihydromavacurine-type derivative (*7a*)[18] (mp 207-208°; anal C,H,N) together with an unavoidable β-elimination product (*8*) (13%). Establishment of the full mavacurine ring system was accomplished by refunctionalisation of C-3 in *7a* with *concomitant* removal of the urethane group using a remarkable *oxidative* C/D ring regeneration reaction. Treatment with one equivalent of 1-chlorobenzotriazole[19] in the presence of excess Et_3N in dichloromethane at room temperature rapidly gave the *epi*-pleiocarpamine-nitrile (*9a*)[20] as the only acid-extractable indolic product, in 54% yield. The mechanism of this reaction has been examined with model (C-16 and C-20 unsubstituted) systems, where deuteration studies have shown that exclusively the C-3 α-proton is lost from the ε_2-dihydromavacurine system. The details will be presented elsewhere.[14]

The nitrile (*9a*) was readily hydrolysed (aq-ethanolic KOH) to the amide (*9b*) which was methanolised by heating under reflux in methanol containing 14% BF_3 to give (±)-*epi*-pleiocarpamine (*9c*) as the only detectable product (65% yield from *9a* after purification by preparative TLC).[21] The identity of this product was demonstrated by spectroscopic comparison with material derived from (+)-pleiocarpamine (*3*)[22] and by its $LiAlH_4$ reduction to (±)-normavacurine (*9d*), which was in turn identified by direct comparison (MS and TLC) with a small sample of the naturally-derived base kindly supplied by Prof. M. Hesse. Quaternisation of *9d* with MeI in methanol gave (±)-C-mavacurine (*1*) iodide (mp 224-227° decomp.), the NMR- and UV-spectra of which closely corresponded with those recorded[3] for the alkaloid.

A total synthesis of (±)-ε_2-dihydromavacurine (*2*) was achieved *via* selective methanolysis of the cyano function of *7a* (by reaction with ethanolic KOH and then methanolic BF_3) to give the ester (*7b*) (C-16 configuration assigned by analogy with the formation of *9c* from *9a*, and therefore not requiring the assumed[18] stereochemistries of *7a* and *9a* to be correct), which was reduced with $LiAlH_4$ at room temperature. The product showed the same remarkable indolic-indolinic pH-dependent UV-spectrum reported[3] (see Note 6) for the naturally-derived base and gave a mass spectrum[23] which closely corresponded with that published for *2*.

This work was supported by the Science Research Council.



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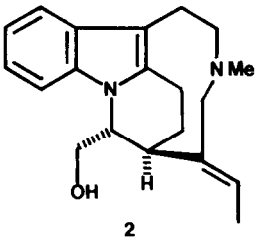

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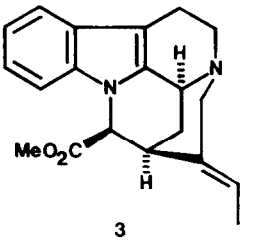

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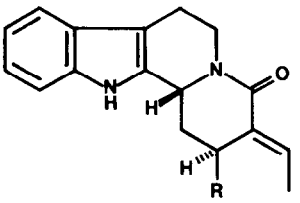
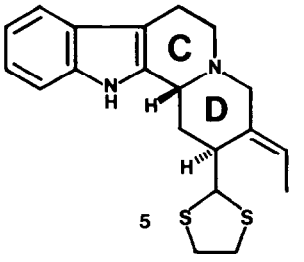


4a R = CH_2OH
4b R = CHO
4c R = ·CH·SCH_2CH_2S



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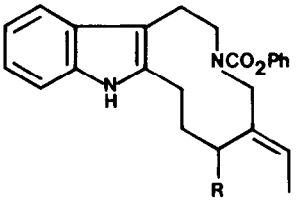
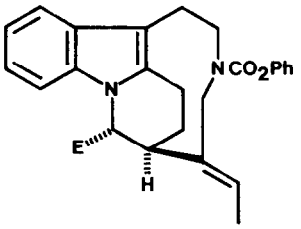
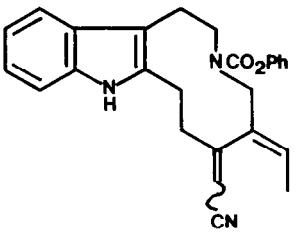


6a R = ·CH·SCH_2CH_2S
6b R = CHO
6c R = CH(OH)CN
6d R = $CH(OSO_2Me)CN$
6e R = CH(Cl)CN



7a E = CN
7b E = CO_2Me



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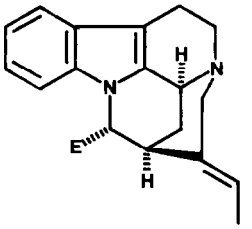
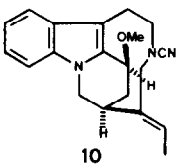


9a E = CN
9b E = $CONH_2$
9c E = CO_2Me
9d E = CH_2OH

REFERENCES AND NOTES

1. M. Hesse,"Indolalkaloide in Tabellen," Springer, Berlin, Heidelberg, New York, 1968, 117.
2. Th. Wieland and H. Merz, *Chem. Ber.*, 1952, 85, 731.
3. M. Hesse, W.v. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller-Friedmann, W.I. Taylor, H. Schmid and P. Karrer, *Helv. Chim. Acta*, 1964, 47, 878.
4. H. Fritz, Th. Wieland and E. Besch, *Ann.*, 1958, 611, 268.
5. H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, 1955, 38, 649.
6. The chemical reactions[3] of *2* show the effect of a strong transannular interaction between C-2 and *N*(b). Thus, protonation and methylation occur at *C-7* with concomitant closure of a 2,4-bond. These reactions have been mimicked in a model system (D.D. O'Rell, F.G.H. Lee and V. Boekelheide, *J. Amer. Chem. Soc.*, 1972, 94, 3205).
7. Direct $LiAlH_4$ reduction of *3* correspondingly gave[3] pleiocarpaminol, distinguishable from *9d*.
8. H. Bickel, E. Giesbrecht, J. Kebrle, H. Schmid and P. Karrer, *Helv. Chim. Acta*, 1954, 37, 553.
9. (a) S. Sakai and N. Shinma, *Chem. Pharm. Bull.* (Tokyo), 1974, 22, 3013; (b) *Idem.*, *Heterocycles*, 1976, 4, 985; (c) *Idem.*, *Yakugaku Zasshi*, 1978, 98, 950.
10. The 19,20β-dihydro derivatives of mavacurine-type alkaloids were previously unknown. Note that a total synthesis of 19,20α-dihydronormavacurine has been reported (ref cited in Note 6).
11. S. Sakai, A. Kubo, K. Katano, N. Shinma and K. Sasazo, *Yakugaku Zasshi*, 1973, 93, 1165.

12. We have employed similar reactions in a total synthesis of desethylidene-*9c* and -*9d* (M.J. Calverley, Ph.D. Thesis, Cambridge, 1979).
13. B.J. Banks, M.J. Calverley, P.D. Edwards and J. Harley-Mason, preceding communication.
14. M.J. Calverley, papers in preparation.
15. A low temperature $LiAlH_4$ reduction of *4b* back to *4a* demonstrated that neither an isomerisation of the exocyclic double bond nor an epimerisation at C-15 had occurred.
16. The *trans* relative disposition of the C-3 and C-15 hydrogens in *5*, inferred from the correlation[13] of *4a* with known C-3 -*epi* geissoschizine analogues, was confirmed by independent spectroscopic and chemical evidence: Thus, (a) the presence of significant absorptions in the 2705-2850 cm^{-1} region in the solution IR-spectrum and the absence of a relatively low-field signal for the C-3 proton in the NMR-spectrum of *5* readily established a *trans* C/D ring fusion, known to be the preferred mode only in the (3,15-) *trans*-series (ie *epi*-series) for *E*-ethylidene-bearing systems (see G. Rackur and E. Winterfeldt, *Chem. Ber.*, 1976, 109, 3837, and refs cited therein); and (b) the *solvolytic* C/D ring cleavage reaction[17] of *5*, with BrCN and excess MeOH, was found to be entirely stereospecific, a result expected[17] for a *trans*-quinolizidine derivative, and furthermore, invoking the known[17] stereochemical consequence of inversion at C-3 during this reaction, the assigned C-3 configuration in *5* is consistent with the low-field proton resonance for the methoxyl group (δ 3·57), indicating its β-configuration,[17] in the derived *seco*-mavacurine-type cyanamide (*10*). [The conversion of *5* to *10* required successive (i) ring cleavage (BrCN-MeOH-Na_2CO_3), (ii) deprotection (MeI-H_2O-MeCN-$CaCO_3$) and (iii) reduction ($NaBH_4$) of the aldehyde function, (iv) mesylation ($MeSO_2Cl$-py), and (v) cyclisation (NaH-DMSO).] *Note* that submitting *trans*-series[17] *seco*-mavacurine-type derivatives (eg *10*) to the acetolytic C/D ring regeneration reaction[9] was found *not* to give the corresponding mavacurine-type compound (eg *9*,*E-H*), in contrast to the reaction undergone by the corresponding C-3 epimers, and hence using this approach the correction of the stereochemical information at C-3 must be made *before* closing ring E (M.J. Calverley, Ph.D. Thesis, Cambridge, 1979).



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17. M.J. Calverley, J. Harley-Mason, S.A. Quarrie and P.D. Edwards, *Tetrahedron*, 1980, 36, 0000.
18. The definition of the α-configuration to the C-16 substituent in *7a* and consequently in *9a* (only a single diastereoisomer was produced in each case) is assumed from their epimeric stability to base by analogy with studies[3,9] on C-16 methoxycarbonyl-bearing systems.
19. This reagent (C.W. Rees and R.C. Storr, *J. Chem. Soc.*, 1969, 1474) had been introduced by our group as a convenient alternative to Bu^tOCl for preparing chloroindolenine derivatives of indole alkaloids (K.V. Lichman, Ph.D. Thesis, Cambridge, 1970).
20. *9a*: ν_{max} (no significant features), δ ($CDCl_3$) 1·10 (1H, br d, *J* 14Hz, C-21 H(β)), 1·62 (3H, dd, *J* 7,2, C-18 H), 3·94 (1H, m, C-3 H), 4·85 (1H, br s, C-16 H), 5·28 (1H, qd, *J* 7,2, C-19 H), and 7·01-7·57 (4H, m, Ar-H) ppm, *m/e* (rel intensity) 289·1585 (M^+, 100; $C_{19}H_{19}N_3$ requires 289·1579), 288 (37), 205 (34) and 180 (26), λ_{max} (EtOH) 230 and 288 nm.
21. Treatment of (±)-*9c* with *m*-CPBA (1 eq, in dichloromethane at 0°) gave (±)-*epi*-pleiocarpamine-*N*(b)-oxide, the racemate of a new alkaloid reported to occur in *Vinca minor* (Z. Voticky, L. Dolejs and E. Grossmann, *Coll. Czech. Chem. Comm.*, 1979, 44, 123).
22. The UV-spectra and photographic reproductions of the NMR-spectra of *3* and *9c* are recorded in ref 3. We thank Prof. S. Sakai for copies of the IR-, NMR- and mass spectra he obtained for *9c*. Compared spectra were submitted for refereeing with this communication.
23. Accurate mass measurements have confirmed the identity of all seven fragment ions postulated in the interpretation[3] of the mass spectrum of *2*. In addition, the ion *m/e* 155 was shown to correspond to the formula $C_9H_{17}NO^+$.

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