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# A NEW SYNTHESIS OF INDOLO[2,3-*a*]QUINOLIZIDINE DERIVATIVES: A FORMAL TOTAL SYNTHESIS OF (±)-GEISSOSCHIZINE

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*A stereospecific elimination process has been developed for introducing the* E*-ethylidene group in a transformation of tryptamine into methyl (±)-geissoschizoate.*

Syntheses of corynantheine-type indole alkaloids have usually involved closure of either the 2,3- or the 4,21-bonds in the reactions used to complete the tetracyclic nucleus (see diagram (*4*)). We now describe an approach to this system based on the disconnection of the 15,20-bond, permitting the incorporation of a (1-methoxy)ethyl C-20 substituent.[1] The base-catalysed elimination of methanol from four tetracyclic intermediates carrying this sidechain has been shown to generate exclusively an *E*-configurated exocyclic double bond, irrespective of the initial C-20 configuration. Advantage of this was then taken in establishing a new synthesis of the racemate of the ethylidene-bearing alkaloid geissoschizine[2] (*11b*) and the first total syntheses of alkaloids of the related C-mavacurine group[3] from common intermediates.

Diethyl malonate was alkylated (NaH, THF) with *tert*-butyl bromoacetate to give the triester (*1a*) which with *p*-TsOH in benzene heated under reflux gave the acid (*1b*). This was condensed with tryptamine (1 equivalent) using 1,1'-carbonyldiimidazole in THF to give the tryptamide (*2*)[4] (mp 78°) in 95% yield. Construction of ring C was achieved under Bischler-Napieralski conditions ($POCl_3$, benzene, reflux) to give an imine salt which was reduced ($NaBH_4$, EtOH, 0°) to the unstable amine (*3*). Condensation of the crude product with (racemic) *erythro*-2-bromo-3-methoxybutyryl chloride[5] in pyridine at -20° gave the bromo-amide (*6*) (mp 158-160°), a chromatographically homogeneous mixture of (C-3) diastereoisomers, in 80% overall yield from *2*. Treatment of the mixture of amides (*6*) with NaH (1 equivalent, THF, room temperature) resulted in reaction occurring in only one of the diastereoisomers,[6] giving (49% yield after separation of unreacted *6*) the lactam-diester (*5*)[7] (mp 248-250°). When the amine (*3*) was condensed under Schotten-Baumann conditions with 2-chloroacetyl chloride, a chloro-amide (mp 164-165°) was produced which underwent the expected complete cyclisation under the conditions used above, to give the C-20 unsubstituted analogue of *5*, whose structure was confirmed by direct comparison with material prepared by the method of Sakai *et al.*[8] Partial hydrolysis of *5* (NaOH, aqueous

EtOH, room temperature) followed by decarboxylation (DMF, 100°) gave an approximately equal mixture of the lactam-esters (*4*), found (*vide supra*) to be epimeric only at *C-20*.[9]

Reduction of the mixture of esters (*4*) using $NaBH_4$ in methanol heated under reflux gave a 4:1 mixture of the alcohols (*7a,b*).[9,10] Conversion of the major isomer (*7a*) (obtained in 71% yield from *5*) to the *O*-mesylate (MsCl-pyridine) followed by treatment with NaCN in DMF at 70° gave the nitrile (*7c*), from which an entirely stereospecific elimination of methanol was then induced by heating with NaOMe in MeOH, giving the *E*-ethylidene-bearing nitrile (*8b*) (60% yield from *7a*). The spectroscopic data obtained for this compound were identical to those reported by Müller and Winterfeldt[11] for material prepared independently. The use of the minor isomer (*7b*) in this sequence was shown to give the same final product (*8b*), although in addition to the expected mesylate, the reaction with MsCl gave the tetrahydrofuran derivative (*9*), incidently establishing the relative C-20 configurations in the two series. Elimination of MeOH (NaOEt, EtOH, reflux) from the *mixture* of alcohols (*7a,b*) gave (79% yield from *5*) the ethylidene-bearing alcohol (*8a*) (*O*-acetate, mp 231°) (again each C-20 epimer was separately found to give only this product),[12] the structure of which was confirmed by its transformation[3] to (±)-*epi*-pleiocarpamine. However, the alcohol (*8a*) could not be converted efficiently to the nitrile (*8b*).

The nitrile (*8b*) was converted to the oxazoline (*8c*) ($NH_2CMe_2CH_2OH$, $ZnCl_2$, 140°) which was reduced to the amine (*10a*) with $Bu^i_2AlH$ in THF at -20°. Acid methanolysis of *10a* gave the known[11,13] methyl (±)-*epi*-geissoschizoate (*10b*) (46% yield from *8b*), which has been converted,[13] *via* its C-3 epimer (*11a*), to (±)-geissoschizine (*11b*). In an attempt to find a superior epimerisation sequence for this transformation, the amine (*10b*) was subjected to the reductive C/D ring cleavage reaction[14] with $PhO_2CCl$ and $NaBH_3CN$ at -70° to give (76%) the urethane derivative (*12*). Treatment of *12* with 1-chlorobenzotriazole (1 equivalent) in MeOH followed by heating the mixture of C-3 methoxylated derivatives in AcOH at 90°[15] returned *10b* (49%) together with the required methyl (±)-geissoschizoate[2] (*11a*) (14%). This product was identical to a sample prepared from *10b* by the $Hg(OAc)_2$ oxidation - Zn reduction sequence,[13] which in turn had been identified by direct comparison (TLC and MS) with material obtained by degradation[16] of akuammicine, but it is apparent that the new sequence offers no advantage, and an efficient process for the conversion of *10b* to *11a* has yet to be found.

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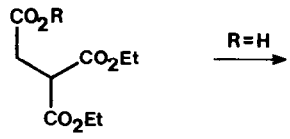
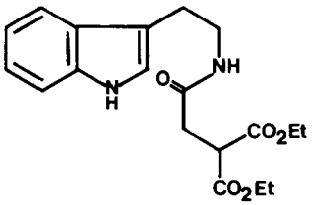


**1a** R = Bu$^t$

**1b** R = H

R=H



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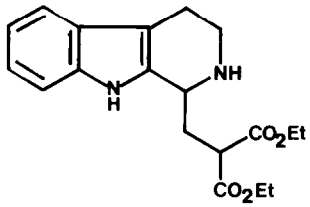

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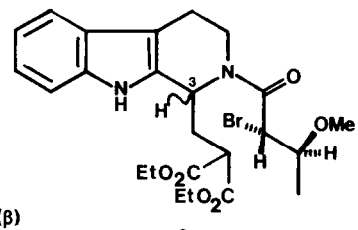
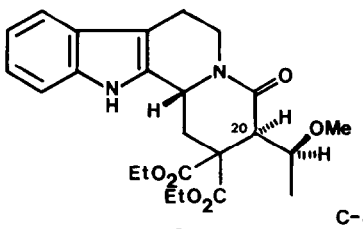
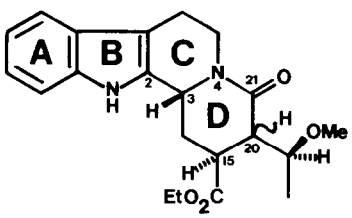


**6**

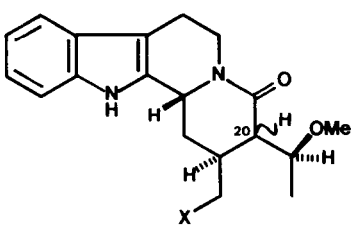
C-3 H(β)



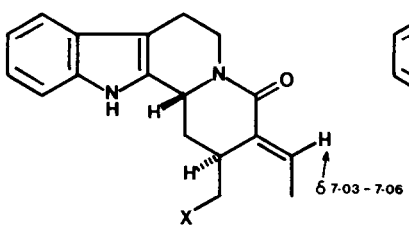
**5**



**4**

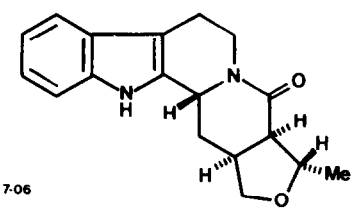


**7a** X=OH, C-20 H(β)
**7b** X=OH, C-20 H(α)
**7c** X=CN, C-20 H(β)
**7d** X=CN, C-20 H(α)

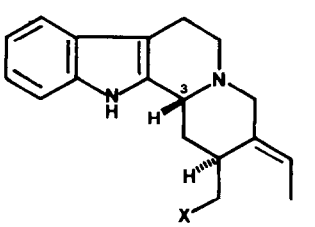


δ 7·03 - 7·06

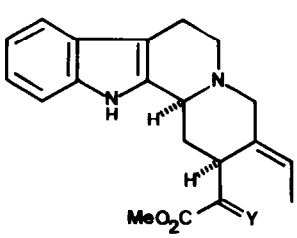
**8a** X = OH
**8b** X = CN
**8c** X = ·C:N·CMe$_2$CH$_2$O



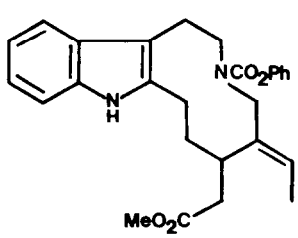
**9**



**10a** X = ·C:N·CMe$_2$CH$_2$O
**10b** X = CO$_2$Me



**11a** Y = H$_2$
**11b** Y = :CH(OH)



**12**

REFERENCES AND NOTES

1. For the use of this strategy in the total synthesis of a Strychnos alkaloid see G.C. Crawley and J. Harley-Mason, Chem. Comm., 1971, 685.
2. For previous total syntheses of 11a and 11b see refs 11, 13 and B. Hachmeister, D. Thielke and E. Winterfeldt, Chem. Ber., 1976, 109, 3825.
3. M.J. Calverley, B.J. Banks and J. Harley-Mason, following communication.
4. All indolic compounds described gave satisfactory elemental analyses (where mp given) or accurate mass spectroscopic data, and IR-, NMR-, Mass and UV-spectra in agreement with the assigned structures.
5. cf O. Brunner and P. Hanke, Monatsh. Chem., 1952, 83, 1485, but using erythro acid (Z. Foldi, Hung. Pat. 139,710; Chem. Abstr., 1950, 44, 6428f).
6. Thus, the NMR-spectrum of the pre-cyclisation material (6) showed two methoxy singlets (at δ3·25 and δ3·46, together integrating for three protons) whereas that of the recovered non-cyclisable material showed only one ( δ3·46). All attempts to epimerise C-3 or C-20 in the recovered product failed, and more vigorous conditions for the cyclisation reaction resulted in lactamisation via attack of N(a) on ester carbonyl.
7. The assigned stereochemistry of 5 follows from the assumption that the diastereoisomer (6) presenting a cyclisable system is the one which can attain the maximum number of pseudo-equatorial substituents on the developing ring D.
8. S. Sakai, A. Kubo, T. Hamamoto and C. Ueda, Yakugaku Zasshi, 1966, 86, 760.
9. cf M.J. Calverley, J. Harley-Mason, S.A. Quarrie and P.D. Edwards, Tetrahedron, 1980, 36, 0000.
10. Stereospecific reduction of each ester (4) to a single, different alcohol (7a,b) was achieved using $NaAlH_4$ in THF at 0°.
11. J. Müller and E. Winterfeldt, Chem. Ber., 1978, 111, 1540.
12. The two (C-3 epimeric) stereoisomers of 8a having the opposite (Z) ethylidene geometry have been synthesised by a stereospecific elimination of MeOH from the diester (5) (p-TsOH, benzene, reflux) and subsequent modification of the C-15 substituents. Comparison of the olefinic proton resonances in the NMR for these alcohols (viz δ5·95 and δ6·05) with that for 8a (viz δ7·05) clearly indicates an E-configurated ethylidene in 8a (cf refs 1, 11 and D. Thielke, J. Wegener and E. Winterfeldt, Chem. Ber., 1975, 108, 1791.
13. K. Yamada, K. Aoki, T. Kato, D. Uemura and E.E. van Tamelen, Chem. Comm., 1974, 908.
14. M.J. Calverley, papers in preparation.
15. cf S. Sakai, A. Kubo, K. Katano, N. Shinma and K. Sasazo, Yakugaku Zasshi, 1973, 93, 1165.
16. W.B. Hinshaw Jr., J. Lévy and J. Le Men, Tetrahedron Letters, 1971, 995.

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