The Synthesis of 4-Ethyl-3,3a,10,11,12,12a-hexahydro-12-methyl-2*H*-furo[3',2':5,6]pyrido[3,4-*a*]carbazol-2-yl Methyl Ketone. Structure of Subincanine

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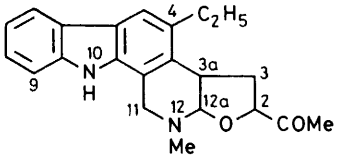
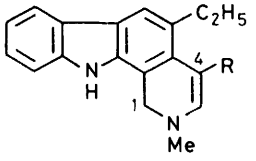
The synthesis of the two 12a,3a-*cis*-stereoisomers of the title ketone (6b) is described; it is shown that none of the stereoisomers corresponds to subincanine, an alkaloid which had earlier been preliminarily assigned this structure. The differences between natural alkaloid and synthetic material are discussed.

SOME while ago we isolated a small quantity of an alkaloid, subincanine, from *Aspidosperma subincanum* and on the basis of the limited spectral information obtained on the base and a couple of degradation products, assigned [1] the novel structure (1), without stereochemistry, as a working hypothesis. In the absence of a further quantity of the alkaloid for a fuller investigation we have now synthesised two of the four possible stereoisomers of structure (1). Neither is the same as the



(1)



(2)
a ; R = H
b ; R ≠ H

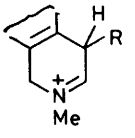
natural alkaloid. As is argued later, the other stereoisomers of this structure are also very unlikely to correspond to the alkaloid and it must therefore be concluded that the structure suggested [1] is incorrect.

RESULTS AND DISCUSSION

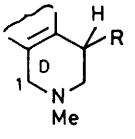
The unstable enamine (2a) [2] has the appropriate reactivity for the electrophilic introduction of a suitable substituent at C-4, with anticipated formation of a substituted enamine (2b). It was our aim to choose an R-group such that the acetyl-substituted tetrahydrofuran ring could be formed subsequently,[3] by cyclisation *via* the enamine-protonated form (3) of the anticipated alkylation product. In the event, this plan had to be modified, for no substituted enamine products (2b) could be obtained. For example, when the enamine (2a) was reacted [3] with methyl vinyl ketone, as a model, only the reduced form (4a) of the immediate alkylation product was obtained. We interpret this as the very rapid reductive trapping of alkylated immonium salt (3) by hydride donation from C-1 of unreacted enamine. This process parallels the disproportionation [2,4] of (2a) which co-occurs with the alkylation process; the reduced derivative (4b) was the major extractable product of the alkylation reaction.

The construction of the fifth ring of the target structure required the presence of an alcohol function on the introduced side-chain. Accordingly the enamine (2a) was treated with 3-acetoxybut-3-en-2-one; [5] again the major product isolated was the reduced tetracycle (4b), but in addition 19% of a stereoisomeric mixture of acetoxyketones (4c) could be obtained. These were difficult to separate, partial equilibration occurring on t.l.c. on silica, but sufficient of one of the isomers could be obtained free from the other for a full characterisation, apart from relative stereochemistry, while the mixture was utilised in subsequent steps of the synthesis.

Since the alkylations were not giving products at the enamine oxidation level in ring D, essential for the formation of the tetrahydrofuran ring, it was necessary to seek ways of re-introducing unsaturation regioselectively. However, as was feared, reagents which are normally used for the conversion of tertiary amines into immonium derivatives, *e.g.* iodine or mercuric acetate, oxidised selectively at the undesired, benzylic carbon, C-1. Attempts to involve the alcohol group to force regioselective oxidation [6] also failed. It was accordingly decided to attempt the re-aromatisation of ring D, with the idea that then the type of N^b-methylation and partial



(3)

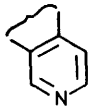


(4) R
a ; R = CH_2CH_2COMe
b ; R = H
c ; R = $CH_2CH(OAc)COMe$
d ; R = $CH_2CH(OH)C(O_2)Me$

reduction with lithium aluminium hydride sequence which had been successful [2] in producing the enamine (2a) in the first place could be utilised. Firstly it was demonstrated that the unsubstituted tetracycle (4b) *could* be efficiently dehydrogenated with loss of the N^b-methyl to the aromatic pyridocarbazole (5) with Pd–C in refluxing decalin. However, application of these conditions to keto-acetates (4c) led not to an alkyl

substituted pyridocarbazole but only to (5), cleavage of both N^b-methyl *and* side-chain having occurred.

This unexpected and (at first sight) unhelpful result actually gave us the clue necessary for completion of the synthesis. The cleavage of the side-chain can be most readily rationalised as meaning that, whatever the exact

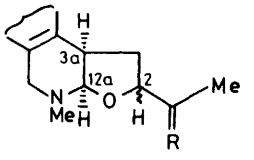


(5)

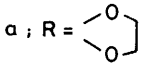
mechanistic details of the dehydrogenation process, regioselective partial dehydrogenation to a species (3) [or (2b)] must occur *first*, and that it is (3) which loses the side-chain by a reverse Michael process, the exact reverse counterpart of that by which the alkyl side-chain was introduced in the first place. With this rationalisation it became clear that we had, fortuitously, discovered exactly the regioselective oxidising agent we had sought.

In order to remove the reverse Michael option, the acetoxy-ketones (4c) were converted to ethylene acetals and then, because this produced a mixture in which partial de-acetylation had occurred, to the separable, stereoisomeric hydroxy-acetals (4d) by subsequent treatment with lithium aluminium hydride.

On reaction of *either* of the alcohols with palladium–charcoal in refluxing decalin, by carefully monitoring the progress of the reaction, it was possible to isolate in 21% yield the product (6a) of regioselective partial dehydrogenation, trapped as the desired tetrahydrofuran.



(6)

a ; R = 

b ; R = O

In all the many t.l.c. solvent systems tried, the ether-acetal (6a) [prepared starting from *either* of the stereoisomeric precursor alcohol-acetals (4d)] *appeared* to be the same, single, compound. However, there was alternative evidence that it was in fact a mixture of stereoisomers. Thus mild room-temperature sodium borohydride cleavage of the NCO linkage gave a mixture of the open alcohol-acetals (4d). Further, the n.m.r. spectrum clearly showed *pairs* of signals corresponding to several of the features of the molecule, for example the C-6 hydrogen as two doublets at τ 1.91 and 1.97 and the *N*-methyl as two singlets at τ 7.29 and 7.32. Of particular relevance structurally were the two signals for the C-12a hydrogen at τ 5.09 and 5.11. Both signals were doublets and both had J values of 5 Hz. From the values of the chemical shifts [7] and the values of the coupling constants [8] and an examination of molecular models it can be concluded first that the C-12a hydrogen in each isomer is equatorial to ring D, and secondly that *each isomer* has *cis*-stereochemistry at the C-12a/C-3a ring junction. It follows that the difference between the two isomers lay only in the relative stereochemistry at C-2, the acetyl-bearing carbon.

The formation of *two* cyclised isomers from *either* of the precursor alcohols is entirely consistent with the postulated initial regioselective dehydrogenation of ring D to enamine oxidation level, as in (2b) where, with the formation of a trigonal C-4, the stereochemical difference between the alcohols would be lost.

The very easy borohydride re-opening, implying the presence of an equilibrium concentration [9] of immonium salt of the form (3) in protic solvent, means that *cis*-stereochemistry at the D/E ring junction is the thermodynamically preferred situation.

The cyclic acetal mixture (6a) was easily hydrolysed by reaction with 1N hydrochloric acid at reflux. Two ketones (6b) were formed. Although the two ketones could be clearly seen as distinct spots on t.l.c. analysis, attempted preparative separation by chromatography failed, the same mixture of isomers always being obtained. It was inferred that equilibration α to the ketonic carbonyl was taking place. An n.m.r. spectrum of the mixture showed that, as with their precursors, both isomers had *cis*-stereochemistry at the C-12a/C-3a ring junction, as shown by signals for the C-12a hydrogen at τ 4.93 and 5.19 with identical J values of 5 Hz. A comparison of integrals showed there to be an approximately 2 : 1 mixture of the two ketones.

A direct t.l.c. comparison of the mixture of ketones with our remaining very small sample of subincanine clearly showed, by a large difference between R_F values of alkaloid and synthetic ketones, that neither synthetic ketone corresponded with the natural material. It can be further argued that since the isolation of the natural alkaloid involved acidic conditions, such as would have allowed equilibration *via* NCO cleavage and reclosure, that neither of the stereoisomeric possibilities for structure (1) with a *trans*-D/E ring junction could represent the alkaloid either. To add further weight to this conclusion a sample of subincanine was refluxed in 1N HCl for 1 h. The recovered base was totally unchanged: whatever the structure of the alkaloid it would seem to represent a thermodynamically favourable situation at the NCO carbon and also at the carbon carrying the acetyl group.

Three further features which distinguish natural subincanine from the synthetic ketones (6b) are worthy of comment. All the synthetic intermediates and final products were air-sensitive, turning yellow easily by oxidation at the benzylic carbon C-1 (C-11). Such sensitivity was not noted for subincanine. Secondly, one of the aromatic protons of the alkaloid resonated at τ 3.01. Since this was a doublet (J 7 Hz) it must correspond to the C-9 proton [numbering on (1)]. None of the synthetic intermediates nor final ketones had an

aromatic proton signal above τ 2.9. The conclusion to be drawn from this last is that some feature of rings D or E or acetyl substituent in the alkaloid must be influencing the magnetic environment of the proton in question.

When the mass spectra of subincanine and synthetic ketone mixture were run consecutively and under exactly the same conditions, significant differences in intensity were noted (Table). As one would expect from

	Percentage of base peak	
m/e	Subincanine	Synthetic (6b)
348 (M^+)	18	42
305	100	54
287	16	
275		21
262	25	63
261	12	100

the known structure of the synthetic material, the base peak corresponds to loss of the entire ring E unit together with a hydrogen. The base peak from the alkaloid corresponds to loss of acetyl. Further, a mass measurement of the *m/e* 262 peak from synthetic material showed no trace of $C_{18}H_{16}NO$, the result of loss of acetyl radical and CH_2NMe, such as was displayed [1] by the alkaloid. This seems to suggest that subincanine contains an unsubstituted CH_2NMe unit available for retro-Diels–Alder loss, in the way shown by the synthetic materials in this paper which do not have a fused ring E [*i.e.* (4a) and (4c)].

EXPERIMENTAL

4-(3-*Oxobutyl*)-5-*ethyl*-1,2-3,4-*tetrahydro*-2-*methyl*-11H-*pyrido*[3,4-a]*carbazole* (4a).—The enamine (2a) prepared in ether solution by the addition of lithium aluminium hydride (10 mg) to 5-ethyl-2-methyl-11H-pyrido[3,4-*a*]carbazolium iodide (120 mg) at 20 °C was treated with methyl vinyl ketone (63 mg) at −78 °C and then at room temperature for 6 h. The mixture was filtered and the precipitate thoroughly washed with ether, which after evaporation gave a crude product purified by chromatography (silica, Et_2O) to give the ketone (4a) (12 mg) as a gum, $\lambda_{max.}$ (MeOH) 263, 285 infl., 298, 325, and 337 nm; $\nu_{max.}$ ($CHCl_3$) 1 720s cm^{-1}; τ ($CDCl_3$) 2.05 (1 H, d, *J* 7 Hz, C-7-H), 2.2 (1 H, s, NH), 2.3 (1 H, s, C-6-H), 2.7—2.9 (3 H, m, Ar-H), 5.9 (1 H, d, *J* 10 Hz, C-1-H_A), 6.7 (1 H, d, *J* 10 Hz, C-1-H_B), 7.6 (3 H, s, NMe), 7.9 (3 H, s, COMe), and 8.7 (3 H, t, *J* 8 Hz, *Me*CH_2); *m/e* 334 (M^+, 52%), 305 (45), 262 (20), and 261 (100) (Found: M^+ 334.204 4; *m/e* 305.165 3. $C_{22}H_{26}N_2O$ requires *M*, 334.206 1; $C_{20}H_{21}N_2O$ requires *m/e* 305.166 3).

Dehydrogenations of 5-*Ethyl*-1,2,3,4-*tetrahydro*-2-*methyl*-11H-*pyrido*[3,4-a]*carbazole* (4b) *and* 4-(2-*Acetoxy*-3-*oxobutyl*)-5-*ethyl*-1,2,3,4-*tetrahydro*-2-*methyl*-11H-*pyrido*[3,4-a]*carbazole* (4c).—The substrate (4b) (24 mg) or (4c) (36 mg) was heated in decalin (6 ml and 7 ml, respectively) with Pd–C (10%, 6 mg and 9 mg, respectively) at reflux for 15 h. The catalyst was removed by filtration through Hyflo and the solvent evaporated under reduced pressure. In each case, after purification [1] 5-ethyl-11*H*-pyrido[3,4-*a*]carbazole [20 mg and 23 mg from (4b) and (4c), respectively] was isolated and identified by comparison with authentic material.

4-(2-*Acetoxy*-3-*oxobutyl*)-5-*ethyl*-1,2,3,4-*tetrahydro*-2-*methyl*-11H-*pyrido*[3,4-a]*carbazoles* (4c).—The enamine (2a) was prepared in solution (600 ml) by the addition of lithium aluminium hydride (224 mg) to a suspension of 5-ethyl-2-methyl-11*H*-pyrido[3,4-*a*]carbazolium iodide (2.24 g) under nitrogen at room temperature, during 0.5 h. 3-Acetoxybut-3-en-2-one (2 ml) was then added dropwise during 1 h at −78 °C. After 12 h at room temperature the mixture was filtered, the precipitate throughly washed with ether, and the extracts evaporated to give a crude product (1.94 g) containing (4c) and (4b), which was purified by chromatography over silica; ether eluted a mixture of the diastereoisomers (4c) (425 mg) as a foam. A sample of one of the isomers was obtained free from the other by preparative t.l.c. on silica eluting with Et_3N–EtOAc (1 : 9). It had $\lambda_{max.}$ (EtOH) 250, 262, 286 infl., 298, 326, and 339 nm; $\nu_{max.}$ ($CHCl_3$) 1 740s cm^{-1}, τ ($CDCl_3$) 2.05 (1 H, d, *J* 7 Hz, C-7-H), 2.25 (1 H, s, C-6-H), 2.2 (1 H, s, NH), 2.6—2.8 (3 H, m, Ar-H), 4.8 (1 H, dd, *J* 11 Hz and 2 Hz, AcOC*H*), 5.8 (1 H, d, *J* 10 Hz, C-1-H_A), 6.6 (1 H, d, 10 Hz, C-1-H_B), 7.6 (3 H, s, NMe), 7.8 (3 H, s, OCOMe), 7.9 (3 H, s, CCOMe), and 8.7 (3 H, 7, *J* 8 Hz, CH_2Me); *m/e* 392 (M^+, 13%), 391 (17), 349 (13), 332 (12), 264 (55), 263 (33), 262 (100), 261 (75), and 246 (24) (Found: M^+, 392.206 2; *m/e* 394.167 8 and 261.139 1. $C_{24}H_{28}N_2O_3$ requires *M*, 392.210 0; $C_{22}H_{23}NO_3$, 349.178 3; and $C_{18}H_{17}N_2$, 261.140 2).

4-(2-*Hydroxy*-3-*oxobutyl*)-5-*ethyl*-1,2,3,4-*tetrahydro*-2-*methyl*-11H-*pyrido*[3,4-a]*carbazole Ethylene Acetals* (4d).—To a solution of the mixture of the diastereoisomers (4c) (425 mg) in dry benzene (300 ml) was added ethane-1,2-diol (22.5 g) and toluene-*p*-sulphonic acid (212 mg) and the whole refluxed for 10 h under a Soxhlet thimble containing molecular sieves (4A). The solution was cooled, diluted with chloroform, washed with water, dried, and evaporated. The residual yellow foam was dissolved in ether and treated with lithium aluminium hydride at room temperature. After treatment with water and drying, the products (4d) (402 mg) were obtained by evaporation as a pale yellow foam. The two isomers could be separated by preparative t.l.c. on silica, eluting with PhMe–EtOAc–MeOH (2 : 2 : 1) to give the two pure isomers as foams, R_F 0.32 and 0.44; each had $\lambda_{max.}$ 262, 286 infl., 293, 324, and 336 nm; τ ($CDCl_3$) 2.0 (1 H, d, *J* 7 Hz, C-7-H), 2.05 (1 H, s, NH), 2.2 (1 H, s, C-6-H), 2.6—1.8 (3 H, m, Ar-H), 6.0—6.4 (6 H, m, OCH_2CH_2O, HO and HOC*H*), 6.65 (1 H, d, *J* 10 Hz, C-1-H_A), 7.8 (1 H, d, *J* 10 Hz, C-1-H_B), 7.55 (3 H, s, NMe), 8.6—8.8 (6 H, m, CH_2Me and CMe); *m/e* 394 (M^+, 43%), 349 (47), 307 (35), 263 (30), 261 (42), and 87 (100) (Found: M^+, 394.224 8. $C_{24}H_{30}N_2O_3$ requires *M*, 394.225 6).

4-*Ethyl*-3,3a,10,11,12,12a-*hexahydro*-12-*methyl*-2H-*furo*-[3′,2′:5,6]*pyrido*[3,4-a]*carbazol*-2-*yl Methyl Ketone Ethylene Acetals* (6a).—Either of the pure alcohols (4d) or the mixture (140 mg) and Pd–C (10%, 35 mg) in dry decalin (35 ml) was heated at reflux for 2 h. The catalyst was filtered off using Hyflo and the solvent removed under reduced pressure. The residue was purified by preparative t.l.c. on silica, eluting with EtOAc to give the pure ether-acetal mixture (6a) (32 mg) as a foam; $\lambda_{max.}$ 260, 294, 325, and 338 nm; τ ($CDCl_3$) (300 MHz) 1.91 and 1.97 (1 H, 2 × d, *J* 8 Hz, C-6-H), 2.06—2.15 (2 H, m, NH and C-5-H), 2.38—2.61 (2 H, m, C-8-H and C-9-H), 2.73 and 2.75 (1 H, 2 × t, *J* 8 Hz, C-7-H), 5.09 and 5.105 (1 H, 2 × d, *J* 5 Hz, C-12a-H) and 8.62 (6 H, m, CH_2Me and CMe); *m/e* 392 (M^+, 23%), 347 (23), 305 (75), 275 (63), 263 (25), 262 (100), and 87 (83) (Found: M^+ 392.209 9, *m/e* 305.165 3, 275.154 8, and 262.147 0. $C_{24}H_{28}N_2O_3$ requires *M*, 392.210 3; $C_{20}H_{21}N_2O$, 305.167 2; $C_{19}H_{19}N_2O$, 275.155 7; and $C_{18}H_{18}N_2$, 262.146 7).

4-*Ethyl*-3,3a,10,11,12,12a-*hexahydro*-12-*methyl*-2H-*furo*-[3′,2′:5,6]*pyrido*[3,4-a]*carbazole*-2-*yl Methyl Ketones* (6b).—The ether-acetals (6a) (29 mg) were hydrolysed in 1N

hydrochloric acid (10 ml) at reflux in the dark and under nitrogen for 30 min. After cooling and basification with potassium carbonate the product was extracted with ethyl acetate to give the ketones (6b) (18 mg) as a gum which always showed two spots on t.l.c. analysis (silica, EtOAc) even after attempted preparative layer separation, R_F 0.38 and 0.30 (R_F of subincanine in same solvent, 0.1); $\lambda_{max.}$ 251, 261, 285 infl., 295, 326, and 339 nm; $\nu_{max.}$ ($CHCl_3$) 3 460 and 1 718s cm^{-1}; τ ($CDCl_3$) (300 MHz) 1.92 and 1.98 (1 H, 2 × d, *J* 8 Hz, C-6-H), 2.06—2.17 (2 H, 3 × s, NH and C-5-H), 2.46—2.62 (2 H, m, C-8-H and C-9-H), 2.74 (1 H, 2 × t, *J* 8 Hz, C-7-H), 4.93 and 5.19 (1 H, 2 × d, *J* 5 Hz, C-12a-H), 5.5—5.58 (1 H, m, C-2-H), 7.26 and 7.28 (3 H, 2 × s, NMe), 7.74 and 7.82 (3 H, 2 × s, COMe), and 8.64 (3 H, 2 × t, *J* 7 Hz, CH_2Me); *m/e* 348 (M^+, 42%), 305 (54), 275 (21), 262 (63), and 261 (100) (Found: M^+, 348.183 7; *m/e* 305.165 3, 275.154 8, 262.147 0 and 261.139 1. $C_{22}H_{24}N_2O_2$ requires *M*, 348.184 1; $C_{20}H_{21}N_2O$, 305.167 8; $C_{19}H_{19}N_2$, 275.155 4; $C_{18}H_{18}N_2$, 262.148 9; and $C_{18}H_{17}N_2$, 261.138 3).

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REFERENCES

[1] A. J. Gaskell and J. A. Joule, *Tetrahedron Letters*, 1970, 77.
[2] D. Cohylakis, G. J. Hignett, K. V. Lichman, and J. A. Joule, *J.C.S. Perkin I*, 1974, 1518.
[3] *Cf.* J. W. Lewis and P. A. Mayor, *J. Chem. Soc.* (*C*), 1970, 1074.
[4] J. W. Bunting and S. H. Kabir, *J. Org. Chem.*, 1978, **43**, 3662.
[5] P. S. Wharton and B. T. Aw, *J. Org. Chem.*, 1966, **31**, 3787.
[6] V. M. Micovic, R. I. Manuzic, D. Jeremic, and M. Lj. Mihailovic, *Tetrahedron Letters*, 1963, 2091; B. Berkkoj and A. D. Cross, *J. Org. Chem.*, 1963, **28**, 1944; G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jegar, *Helv. Chim. Acta*, 1959, **42**, 1124; G. B. Spero, J. L. Thomson, and W. P. Schneider, *J. Org. Chem.*, 1963, **28**, 2225; A. Goosen and H. A. H. Laue, *J. Chem. Soc.* (*C*), 1969, 383; A. Deluzarche, A. Maillard, P. Rimmelin, F. Schue, and J. M. Sommer, *J.C.S. Chem. Comm.*, 1970, 976; M. L. Mihailovic, Z. Cekovic, and J. Starkovic, *ibid.* 1969, 981.
[7] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 1997.
[8] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon Press, 1969, p. 281.
[9] *Cf.* M. P. Cava, S. K. Talapatra, and D. Douglas, *Chem. and Ind.*, 1963, 1942.