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INDOLOQUINOLIZIDINE SYNTHESIS
STEREOCHEMISTRY AND MECHANISM OF CYCLISATION

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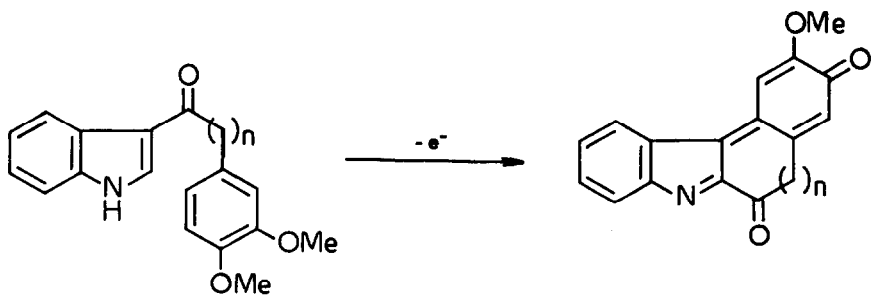
Summary: *A stereocontrolled cyclisation of suitably substituted indole derivatives can be explained by the revised Pictet-Spengler reaction mechanism.*

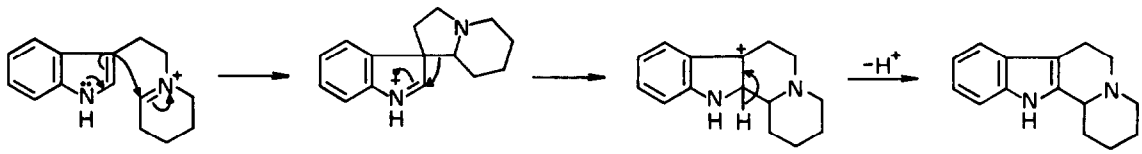
The recent observations[1] that the enaminoketone 1a failed to cyclise to the tetracycle 2a on electrochemical oxidation but that in the case where n=2 (1b to 2b) the cyclisation proceeded almost quantitatively[2] were explained with the Baldwin rules for cyclisation[3] which state that 5-*endo-trig* processes (e.g. 1a to 2a) are disfavoured while 6-*endo-trig* processes (e.g. 1b to 2b) are favoured.



1a n=1
1b n=2

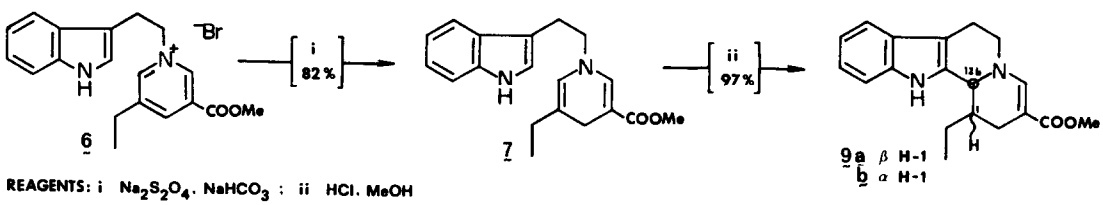
2a n=1
2b n=2

These findings led us to take a closer look at the mechanism of the widely used Pictet-Spengler type cyclisation of indole derivatives. Investigations by Jackson and Smith[4-7] have suggested that in 3-substituted indole derivatives 3, initial attack occurs at the 3-position[8] and the resultant 3,3-spirocyclic indolenine 4 undergoes a Wagner-Meerwein type rearrangement to the 2,3-disubstituted system 5[9,10].



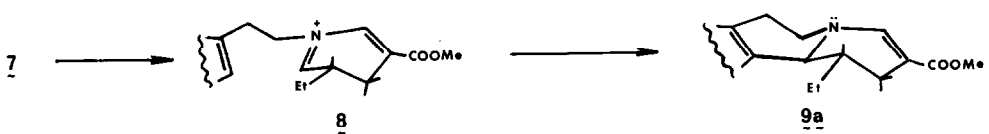
3 4 5

According to this mechanism, the cyclisation of the dihydropyridine 7[11] in acid should produce the iminium 8. Nucleophilic attack of the indole nucleus to the iminium should occur from the less hindered side thus rendering the product 9a in which the hydrogens at C-12b and C-1 are *trans*-oriented to each other.



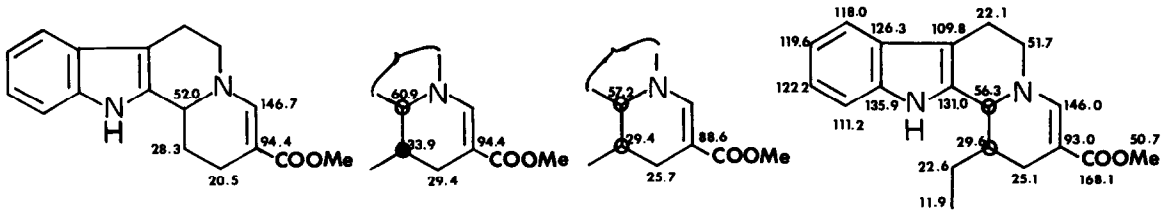
6 7 9a β H-1 b α H-1

REAGENTS: i $Na_2S_2O_4$. $NaHCO_3$; ii HCl. MeOH



7 8 9a

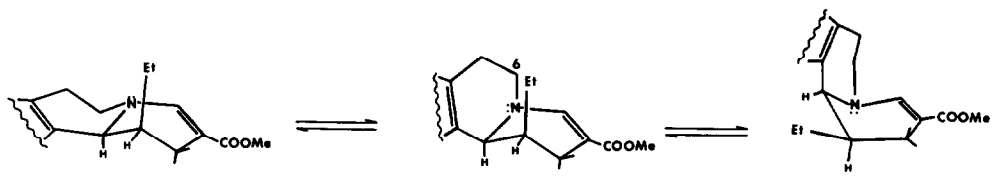
This stereochemical picture could not be substantiated by experimental data. When the dihydropyridine 7[11] was subjected to acid catalysed cyclisation[12-14], the only product formed was the 12b,1 *cis*-product 9b.[15] In fact, 9b could be obtained in excellent yield, what seems to be the general case in these cyclisations.[12,13] The *cis*-relationship of the C-12b, C-1 hydrogens was confirmed on the basis of NMR data. In ^{1}H NMR the coupling constant between the two protons should be about 2 Hz in 9b and about 16 Hz in 9a. The observed coupling constant was 1.2 Hz thus strongly in favour of structure 9b. The ^{13}C NMR data further substantiate this conclusion.



Observed[12] 9a 9b Calculated 9b Observed

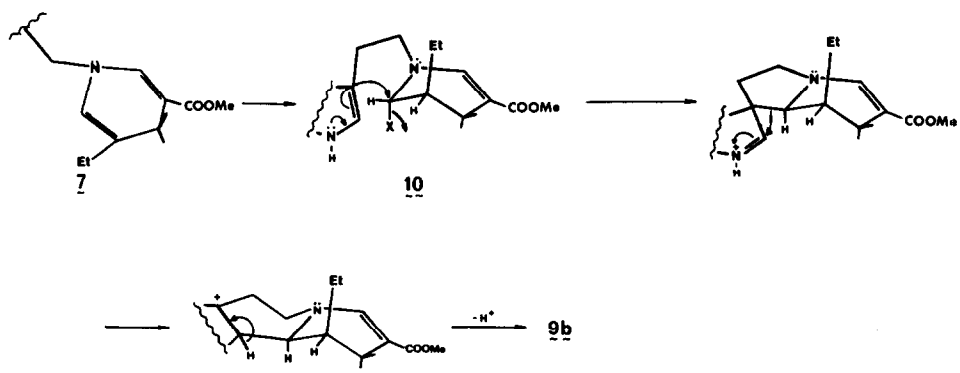
The calculated[12] values for C-12b, C-2 and C-3 are 60.9, 29.4 and 94.4 ppm, respectively, if the C-1 substituent is equatorial while axial substitution gives 57.2, 25.7 and 88.6 ppm, respectively. The observed ^{13}C NMR spectrum verifies axial substitution at C-1.

The compound 9b can exist in conformational equilibrium by nitrogen inversion and ring interconversion. The rings C and D are assumed to be in half-chair conformations.



In conformer **b** the axial ethyl group interacts strongly with the C-6 axial hydrogen and in conformer **c** the N-12 lone-pair and the C-2 pseudoaxial hydrogen become close enough for repulsive interaction. Conformer **b** is further disfavoured by the low possibility of the lone pair of N-5 conjugating with the α,β-unsaturated methoxycarbonyl system. Thus, conformer **a** where no appreciable nonbonded interactions are present would be predominant.

Mechanistically, the formation of 9b can be presented as a favoured 5-*exo*-*tet* process[16] involving the tetrahedral intermediate 10 in which the axial leaving group X (e.g. MeO^- from solvent) is *trans* to the ethyl side chain. A normal S_N2 type displacement then leads to the *cis* substitution pattern.



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11. Prepared from 6 by dithionite reduction[12,13]. IR (KBr): 3350, 1690, ^{1}H NMR ($CDCl_3$,δ, TMS): 0.95 3H t 7 Hz, 1.86 2H q 7 Hz, 2.10 2H t 7 Hz, 3.02 2H s, 3.33 2H t 7 Hz, 3.66 3H s, 5.46 1H m, 6.89 1H d 2.5 Hz, 6.90-7.65 5H m, 8.69 1H s, ^{13}C NMR: 11.0 q ($CH_2\underline{C}H_3$), 25.8 t ($\underline{C}H_2CH_3$), 25.9 t (Ar$\underline{C}H_2$), 27.4 t ($\underline{C}H_2$), 50.6 q (O$\underline{C}H_3$), 54.5 (N-$\underline{C}H_2$), 95.0 s (=$\underline{C}$-COOCH$_3$), 110.5 s (=C-Et), 111.2 s (In C-3), 111.2 d (In C-8), 118.0 d (In C-5), 119.0 d (In C-6), 121.6 d (In C-7), 121.6 d (N-$\underline{C}$H=C-Et), 122.3 d (In C-2), 126.9 s (In C-4), 136.1 s (In C-9), 141.2 d (N-$\underline{C}$H=$\underline{C}$-COOCH$_3$), 169.1 s ($\underline{C}$OOCH$_3$), MS (rel int %): 310 M^+ (19), 165 (19), 144 (55), 130 (100).
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13. M. Lounasmaa, P. Juutinen and P. Kairisalo, Tetrahedron 34, 2529 (1978).
14. M. Lounasmaa and R. Jokela, Tetrahedron Lett., 3609 (1978).
15. Compound 9b, mp. 80-2° (MeOH), IR (KBr): 3350, 1675, 1620, ^{1}H NMR ($CDCl_3$,δ,TMS): 0.98 3H t 7 Hz, 2.05-2.27 5H m, 2.80 2H t 7 Hz, 3.44 2H t 7 Hz, 3.63 3H s, 4.29 1H d 1.2 Hz, 7.00-7.50 4H m, 8.96 1H br s, MS (rel int %): 310 M^+ (42), 281 (100), 279 (30).
16. A recent example of a related process, cf. D.M. Harrison, Tetrahedron Lett. 22, 2501 (1981).

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