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2-CYANO Δ^3 PIPERIDINES[1] II : TOTAL SYNTHESIS IN THE (±) ERVITSINE α-ACYLINDOLE ALKALOID SERIES

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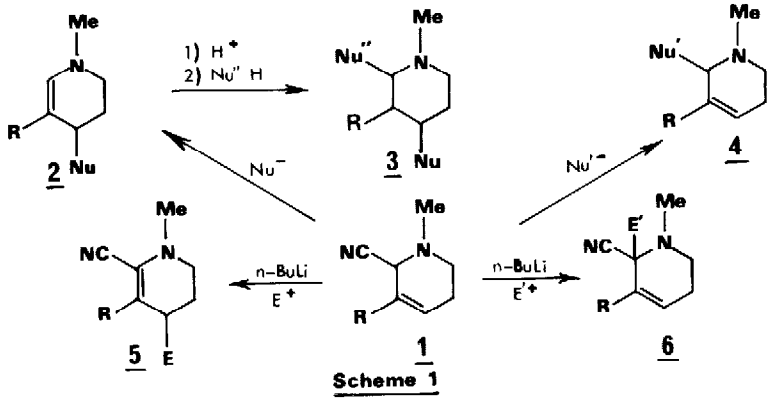
Summary : The first total synthesis in the ervitsine α-acylindole alkaloid series was achieved via two successive nucleophilic substitutions on the relevant 2-cyano Δ^3 piperidine by an indole moiety.

Ervitsine 16 an α-acylindole alkaloid of a novel type was isolated in these laboratories[2] from the root barks of Pandaca boiteaui (Apocynaceae). The known biological activity of related α-acylindole alkaloids coupled with the low abundance of 16 in the plant (0.006 g/kg) prompted us to undertake synthetic investigations in the ervitsine series. We describe herein the preparation of the α-acylindole 15, representing the first synthesis of the ervitsine skeleton.



Scheme 1

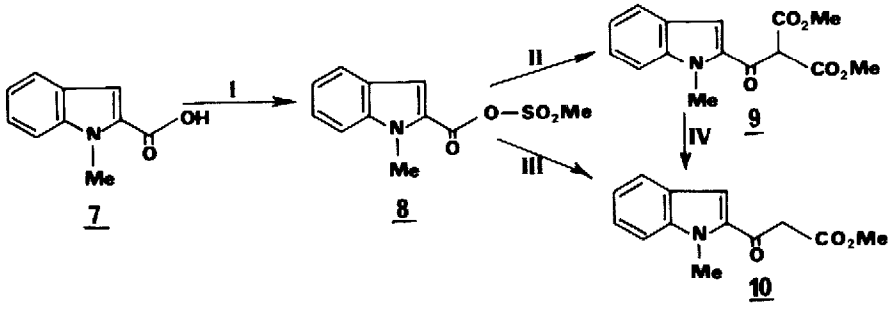
We have recently discussed[1] the preparation and the synthetic potential of 2-cyan Δ^3 piperidines of type 1 and their ability to act as potential and masked dihydropyridinium salts. These compounds react with high regioselectivity with nucleophiles at the C-2 (4) or C-4 (2) positions depending on the nature of the nucleophile. On the other hand formation of an ambident anion by treatment of 1 with n-BuLi generates a species in which "umpolung" of the normal reactivity is achieved and which reacts with electrophiles at the C-2 (6) or C-4 (5) positions (scheme 1).

One of the many features of the versatile synthons 1 is their ability to undergo successive functionalisation at C-4 followed by 1,2 nucleophilic addition to give intermediates of type 3 (scheme 1). This type of reactivity suggested an approach to the skeleton of ervitsine 16, which can be regarded as a piperidine bearing indolyl substituents at the C-2 and C-4 positions *.

* C-5 and C-15 positions using the ervitsine 16 numbering which will be used for the synthetic intermediates throughout this paper.

The extrapolation of the reaction of sodium methylacetoacetate with 1[1] (R=Et) in the presence of silver salt[1] to that of the sodium salt of the β-ketoester 10 with 1 (R=Me) under similar conditions offered an attractive possibility for the formation of the C-14, C-15 bond of the required skeleton, at the same time generating an electrophilic carbon necessary for subsequent cyclisation onto the β carbon (C-7) of the indole nucleus.

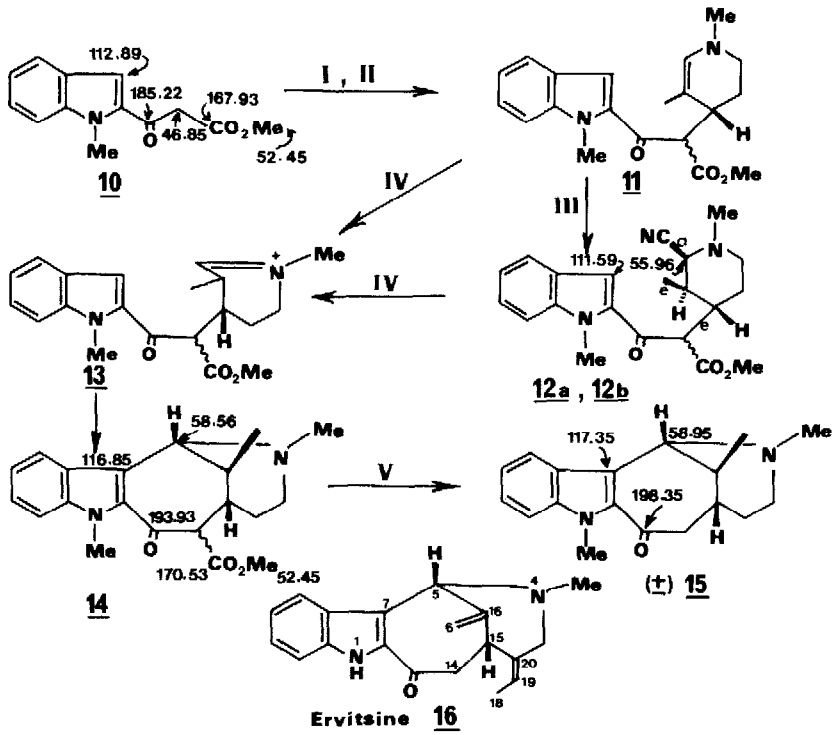
The β-ketoester 10 was prepared efficiently via the routes shown in scheme 2. The mixed anhydride 8, prepared from the reaction of 1-methylindole 2-carboxylic acid 7 with mesylchloride in the presence of triethylamine, was reacted with sodium dimethylmalonate or methyllithioacetate in THF[4] to afford the products 9 (81 %) and 10 (72 %) respectively. Clean monodecarboxylation of 9 into 10 was achieved on its refluxing in 1.5 % aqueous THF with basic alumina[7] (Y : 87 %).



Reagents : I, $MeSO_2Cl$, $(Et)_3N$, THF, -50°, 2 h ; II, sodium dimethylmalonate, THF 20°, 1 h ; III, methyl lithioacetate, THF -50°→0°, 1 h ; IV, 8 g basic alumina Merck per mmole product, 1.5 % aq. THF, 4 h, Δ.

Scheme 2

Addition of the sodium salt of 10 to 1 (R=Me) in the presence of $AgBF_4$ led to formation, in 91 % yield, of the enamines 11 as an approximately I : I mixture of isomers[8]. The unstable enamines 11 could be transformed into a crystalline derivative 12a[9] on reaction with NaCN at pH_4 in a two phase system[1]. It was observed that on attempted isolation of the minor isomer 12b by preparative tlc a mixture of 12a and 12b was always obtained. Under these conditions it is unlikely that epimerisation α to the nitrile occurs thus 12a and 12b are likely to be epimers at C-14. The fact that one α-amino nitrile isomer predominates indicates that epimerisation must occur at C-14 during the preparation of 12 and that the cyanide ion is introduced in a stereoselective manner into the iminium salt 13 . Cyclisation of 11 or 12 to give 14 was achieved on their refluxing in toluene in the presence of TsOH (Y: 65 % from 11, 75 % from 12). The assignment of the structure of 14 to the product was made unequivocally on the basis of its spectral properties[10,12]. Decarboxylation of 14 afforded 15 cleanly (95 % yield)[11] . The small coupling constant between the protons borne by C-5 and C-16 observed for 14 and 15 evidences their equatorial-equatorial relationship. Moreover the bridged system implies the substituents at C-5 and C-15 should be cis diaxial. The unexpected axial position for the methyl group at C-16 can be explained by a necessary ring flip at the stage of the iminium salt 13 (axial protonation of 11) in order to allow the approach of the C-7 and C-5 centers.

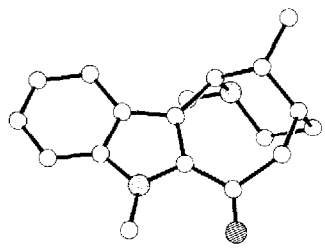


Reagents : I, NaH, THF, 20°, 1 h ; II, 1,3-dimethyl 2-cyano Δ^3piperidine, $AgBF_4$ THF, 1 h ; III, NaCN, CH_2Cl_2, H_2O, citric acid, 1 h ; IV, TsOH, toluene, Δ 22 h ; V, H_2O, AcOH, H_2SO_4(10, 10, 1), 5 h.

Significant ^{13}C NMR shifts are given in the scheme.

Scheme 3

The proposed relative configurations for 15 were confirmed by X-Ray diffraction as shown on the figure. Crystals are monoclinic, space group $P2_1/n$, a = 13.862 (5), b = 7.097 (4), c = 15.326 (6) Å, β = 92.3° (1), Z = 4. The final R value is 0.99 for 734 observed reflexions.



The high yield stereoselective synthesis described underlines the utility of the 2-cyano Δ^3 piperidine synthons.

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References and Notes

1. Part I see :
D.S. GRIERSON, M. HARRIS and H.-P. HUSSON, J. Am. Chem. Soc., 1980, 102, 1064.

2. M. ANDRIANTSIFERANA, R. BESSELIÈVRE, C. RICHE and H.-P. HUSSON, Tetrahedron Lett., 1977, 2587.

3. Y. PICHON and M.-P. SAUVIAT, J. Physiol. London, 1978, 280, 29.

4. The reaction of mixed sulphonic anhydrides with anions will be published independently : M. HARRIS and H.-P. HUSSON.

5. 9 : mp 137° (EtOAc) ; MS m/e (relative intensity) : $M^{+\cdot}$ 289 (25) 175 (100) 158 (100) ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 3.8 (6H, s, CH_3O), 4.05 (3H, s, CH_3N), 5.37 (1H, s, CH) ; Y = 81 % from the acid 7.

6. 10 : mp 106-106.5°(EtOAc) ; MS m/e (relative intensity) : $M^{+\cdot}$ 231 (30), 158 (100) ; ^1H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 3.7 (3H, s, CH_3O), 3.9 (2H, s, CH_2), 4.05 (3H, s, CH_3N), 7.35 (1H, s, indole β proton) ; Y = 72 % from acid 7.

7. Cf. A.E. GREEN, A. GRUZ and P. CRABBÉ, Tetrahedron Lett., 1976, 2707. Using THF instead of dioxane as solvent avoided bis-decarboxylation. We wish to thank Dr. Y. TROUIN for his help on this reaction.

8. 11 : sensitive amorphous product ; MS m/e (relative intensity) : $M^{+\cdot}$ 340 (30), 110 (100) ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 2.52, 2.54 (3H, 2s, CH_3N-4), 3.65 (3H, s, CH_3O), 4.05 (3H, s, CH_3-N-1), 4.35, 4.5 (1H, 2d, J = 4 Hz, CH-CO), 5.6, 5.7 (1H, 2s, N-4-CH =).

9. 12a : mp 161-162°(EtOAc) ; MS m/e (relative intensity) : $M^{+\cdot}$ 367 (5) 110 (100) ; ^1H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 1.2 (3H, d, J = 7 Hz, CH_3-CH), 2.4 (3H, s, CH_3N-4), 3.73 (3H, s, CH_3O), 3.77 (1H, d, J = 4 Hz, CHCO), 4.1 (3H, s, CH_3N-1) ; Y = 80 %.
The stereochemistry as depicted for 12a is inferred from the observation of an axial-equatorial coupling constant (J = 4 Hz) between the C-5 and C-16 protons and the knowledge that the substituents at C-15 and C-16 are trans (by extrapolation from 15). This implies axial protonation of 11 (usual in cyclic enamines) followed by attack of nitrile on the face opposite that of protonation.

10. 14 : mp 160-162°(MeOH) ; MS m/e (relative intensity) : $M^{+\cdot}$ 340 (100) ; ^1H NMR ($CDCl_3$, 400 MHz, TMS δ = 0) : 1.53 (3H, d, J = 7 Hz, CH_3CH), 2.0 (3H, s, CH_3-N-4), 3.7 (3H, s, CH_3O), 3.8 (1H, d, J = 4 Hz, CHCO), 3.98 (3H, s, CH_3-N-1), 4.3 (1H, s, C-5 H), no C-7 H.

11. 15 : mp 179-180°(MeOH) ; MS m/e (relative intensity) : $M^{+\cdot}$ 282 (100), IR ($CHCl_3$) 1 630 cm^{-1} ; UV λ_{max}^{EtOH} (qualitative) 236, 318 nm ; ^1H NMR ($CDCl_3$, 240 MHz, TMS, δ = 0) 1.55 (3H, d, J = 7 Hz, CH_3CH), 2.0 (3H, s, CH_3-N-4), 2.95 (H_A, dd, J_{AB} = 12 Hz, J_{AX} = 4 Hz, CH_2-C = 0), 3.15 (H_B, dd, J_{AB} = 12 Hz, J_{BX} = 4 Hz, CH_2-C = 0), 3.95 (3H, s, N-1-CH_3), 4.35 (1H, s, H-5).

12. In particular, the absence of an indole β proton (^1H NMR) and the quaternisation of the indole β carbon during the reaction (^{13}C NMR) evidenced cyclisation onto the indole nucleus. An alternative cyclisation possibility was attack of the oxygen of the enol form of the α-acylindole onto the iminium salt cf Ref. 1.

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