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2-CYANO Δ^3 PIPERIDINES III[1] :
TOTAL SYNTHESIS OF (±) 20-EPIULEINE

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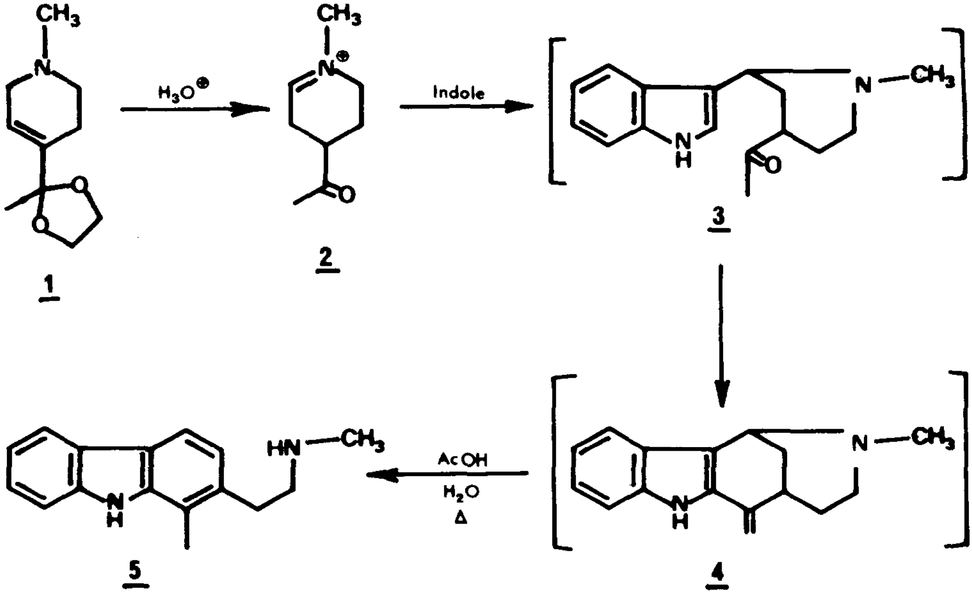
Summary : The total synthesis of the indole alkaloid (±) 20-epiuleine has been achieved starting from indole itself and the appropriate 2-cyano Δ^3 piperidine 7.

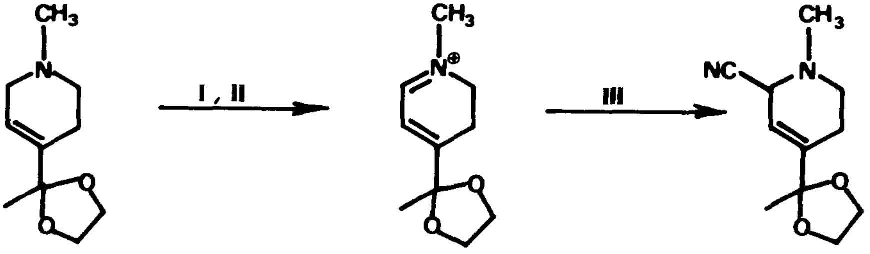
In continuation of our studies on general methods for the synthesis of alkaloids based on 2-cyano Δ^3 piperidine synthons [1,2] we wish to report a short synthesis of (±) 20-epiuleine 10[3].

The strategy employed relates to that of our previous preparation of the carbazole 5 *via* the postulated intermediacy of 3 and desethyluleine 4 [4,5]. In a one pot reaction, condensation of indole with the iminium salt 2 derived from 1, followed by addition-elimination at the keto group, led to desethyluleine which fragmented under the reaction conditions (Scheme 1).



SCHEME 1

For the synthesis in the uleine series, the required intermediate 9 (Scheme 3) analogous to 3 was seen as being derivable by conjugate addition of an ethyl group on the α, β - unsaturated ketone 8. The preparation of 8 itself could be envisaged via the condensation of indole with the conjugated iminium salt 6, followed by hydrolysis. The iminium ion 6 represents a 5,6-dihydropyridinium species and we have demonstrated[2] that 2-cyano Δ^3 piperidines are stable equivalents of this system. Thus we decided to prepare the derivative 7 as a suitable reactive form of the intermediate 6 (Scheme 2).



1 6 7

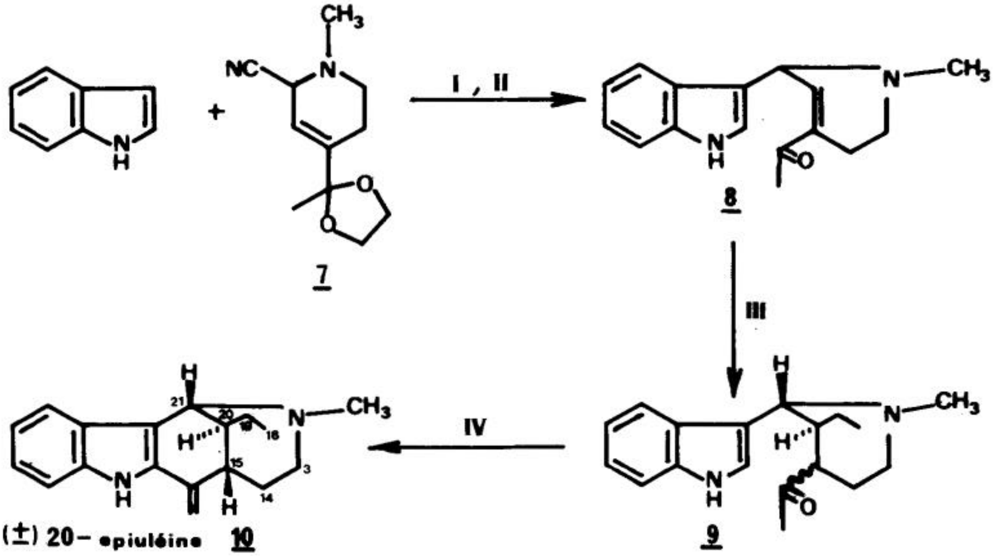
Reagents : I, mCPBA, CH_2Cl_2, 20°, 30 min. ; II, TFAA, CH_2Cl_2, 0°, 1h. ;
III, KCN, H_2O, pH 4.

SCHEME 2

The required compound 7 was synthesized in high yield from 1[4] via the sequence shown in scheme 2. N-oxidation was effected in 95 % yield on the reaction of 1 with m-chloroperbenzoic acid in CH_2Cl_2. Treatment of the resultant N-oxide with trifluoroacetic anhydride and trapping of the intermediate iminium ion 6 with cyanide led to the formation of 7[6] (89 %). No hydrolysis of the ketal function occured under the conditions of the reaction (pH4, two phase system[2]). When 7 was stirred with indole in aqueous acetic acid at room temperature for 16 h, after which time aqueous HCl was added to effect ketal hydrolysis, the required ketone 8[7] was obtained in 95 % yield (Scheme 3). Reaction of 8 with EtMgBr and CuCl in THF, afforded 9[8] in 51 % yield. The trans relationship between the protons at C-20 and C-21 of 9 could be ascertained from their axial-axial coupling constant (J = 11 Hz).

Treatment of 9 in $CHCl_3$ with TsOH (Δ, N_2, 15 h) gave (±) 20-epiuleine 10 in 56 % yield. This last step is the same as that carried out by Natsume and Kitagawa [9/10] in their recent synthesis of the same alkaloid.

The described synthesis of (±) 20-epiuleine is a further example of the utility of 2-cyano Δ^3 piperidines in the total synthesis of alkaloids.



Reagents : I, AcOH-H_2O (1:1), rt, 16h. ; II, HCl 10% ; III, EtMgBr, CuCl, THF, 0°, 5 min. ; IV, TsOH, CH_2Cl_2, Δ, N_2, 15h.

SCHEME 3

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REFERENCES AND NOTES

1. This work was presented for the first time in the course of a lecture at the 12th International Symposium on the Chemistry of Natural Products, September 1980.
   Part II see : M. HARRIS, D.S. GRIERSON, C. RICHE and H.-P. HUSSON, Tetrahedron Lett., 1980, 1957-1960.

2. D.S. GRIERSON, M. HARRIS and H.-P. HUSSON, J. Am. Chem. Soc., 1980, 102, 1064-1082.

3. For the other syntheses in the uleine series, see ref. 9.

4. R. BESSELIÈVRE and H.-P. HUSSON, Tetrahedron Lett., 1976, 1873-1876.

5. R. BESSELIÈVRE and H.-P. HUSSON, *Tetrahedron*, Woodward Memorial Issue, in press.

6. 7 : liquid ; MS m/e (relative intensity) : $M^{+\cdot}$ 208 (10), 180 (15), 121 (17), 87 (100); ^{1}H NMR ($CDCl_3$, 60 MHz, TMS, δ = 0) 1.43 (3H, s, CH_3), 2.49 (3H, s, NCH_3), 3.90 (4H, m, O $(CH_2)_2O$), 4.1 (1H, m, CH CN), 5.9 (1H, m, CH = C).
All yields refer to pure chromatographed products.

7. 8 : amorphous ; MS m/e (relative intensity) : $M^{+\cdot}$ 254 (5), 211 (100), 168 (40), 43 (60) ; ^{1}H NMR ($CDCl_3$, 60 MHz, TMS, δ = 0) 2.20 (3H, s, CH_3CO), 2.25 (3H, s, NCH_3), 4.25 (1H, m, C-21 H), 6.80 (1H, m, CH = C)

8. 9 : amorphous ; MS m/e (relative intensity) : $M^{+\cdot}$ 284 (30), 241 (100), 198 (20), 130 (20) M^{*}162.67 (241 → 198) ; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS, δ = 0), 0.70 (3H, t, J = 6Hz), 2.00 (3H, s, CH_3CO), 2.18 (3H, s, NCH_3), 3.05 (1H, d, J = 11Hz, C-21 H).
The major byproduct (32 %) was the secondary alcohol coming from 1, 2 addition to the α, β -unsaturated ketone.

9. M. NATSUME and Y. KITAGAWA, *Tetrahedron Lett.*, 1980, 839-840.

10. A yield of 36 % for this step is reported by the authors[9] (reagent quantities not specified). We employed 100 ml $CHCl_3$, 700 Mg TsOH for 1 mmole of 9.

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