Synthetic Entry into N(5)-Ergolines

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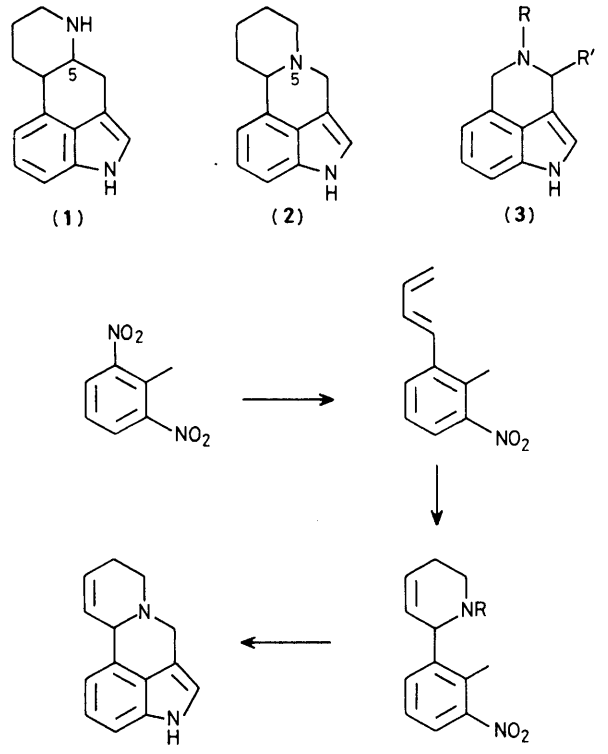
The first synthesis of the N(5)-ergoline system has been achieved *via* a hetero Diels–Alder reaction on a readily accessible substituted phenyl butadiene.

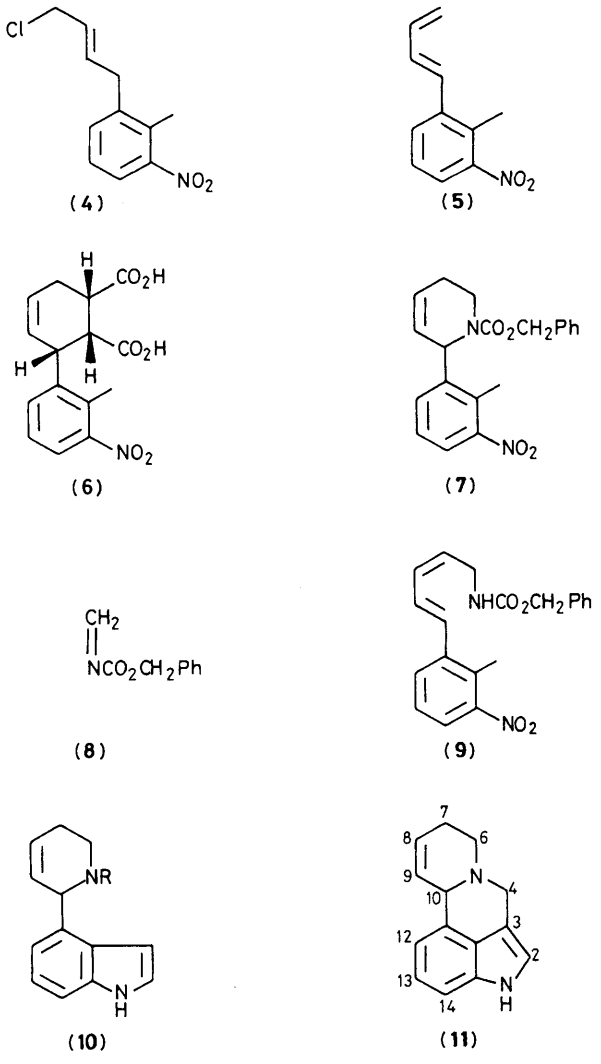
Powerful biological effects of alkaloids based on the ergoline system (**1**) have stimulated much synthetic activity,[1] although thus far N(5)-ergolines (**2**) have not been reported, in spite of the known biological activity of the simple tricycle (**3**)[2] and of descarboxy lysergic acid.[3] We now report the first synthetic entry into this system (**2**). In order to provide rapid access to C-4 substituted indoles, from cheap starting materials, we employed the synthetic design shown in Scheme 1. Our strategy was based on the application of the relatively unused Meerwein arylation procedure[4] to provide a substituted phenyl butadiene as a component for a hetero Diels–Alder reaction. This has been realised as follows. Thus 2-methyl-3-nitroaniline, readily available from 2,6-dinitrotoluene, was diazotised and allowed to react with butadiene ($CuCl_2$ catalysis) to give the adduct (**4**)† (88%, after flash chromatography on silica gel) followed by dehydrochlorination {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 2 equiv., tetrahydro-

† Satisfactory spectroscopic and analytical data have been obtained for all new compounds.



Scheme 1

furan (THF), room temperature} to diene (**5**) [91%, δ_H ($CDCl_3$) 6.80—6.50 (3H, m), 5.45 (1H, d, *J* 17 Hz), 5.25 (1H, d, *J* 10 Hz), and 2.40 (3H, s)], which reacted satisfactorily with a variety of dienophiles, *e.g.* with maleic anhydride ($AlCl_3$ catalysis, benzene, 80 °C, 3 h) to give the *endo*-adduct isolated as the diacid (**6**) (89%, m.p. 198 °C). The piperidine ring was now introduced by a hetero Diels–Alder reaction of (**5**) with dienophile (**8**), produced *in situ* from the corresponding methylene bisurethane[5] with $BF_3{\cdot}OEt_2$ (benzene, 80 °C, 25 min), to yield the bicycle (**7**) as an oil, chromatographed on silica gel {52%, δ_H ([$^2H_6$]Me_2SO, 120 °C‡) 6.06 (1H, m), 5.78 (1H, m), 2.40 (3H, s)}. Longer reaction times resulted in formation of the acyclic isomer (**9**), presumably resulting from ring opening of (**7**). The indole construction was achieved by reaction of (**7**) with tris(dimethylamino)methane in dimethylformamide (DMF)[6] (130 °C, 14 h under argon) followed immediately by reductive cyclisation of the intermediate enamine with iron(II) chloride according to the method of Velluz[7] (ethanol–acetic acid, 90 °C, 90 min) to the indole (**10**; R = CO_2CH_2Ph) {35% from flash silica gel chromatography, δ_H ([$^2H_6$]Me_2SO, 120 °C) 7.24 (1H, m), 6.69 (1H, m), purple colour with van Urk's reagent}. The benzyloxycarbonyl group was removed quantitatively with sodium in liquid NH_3 to afford (**10**; R = H). The final Mannich type cyclisation proved difficult, no doubt a result of the strain imposed by the 3,4-bridged indole structure, but was finally achieved using formaldehyde in acetic acid–methanol (72 h, room temperature).[8] The N(5)-ergoline (**11**) was obtained as an unstable oil and purified by preparative layer chromatography on silica gel [14%, δ_H ($CDCl_3$), 8.00 (1H, br., NH), 7.20 (2H, m, H-2 and H-14), 6.93 (1H, m, H-13), 6.90 (1H, m, H-12), 6.36 and 5.97 (each 1H, m, H-8 and H-9), 4.57 (1H, br., H-10), 4.13 (2H, m, H-4), 3.05 and 2.86 (each 1H, M, H-6), and 2.37 (2H, m, H-7);



$\nu_{max.}$ ($CHCl_3$), 3490 cm^{-1}; $\lambda_{max.}$ (EtOH) 222 (10 400), 281 nm (6 800), *m/z* 210.1157, calc. 210.1152].

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‡ N.m.r. spectra on compounds showing rotameric forms were simplified by running at 120 °C.

References

1 Reviewed by D. C. Horwell, *Tetrahedron*, 1980, 3123. See also R. Ramage, V. W. Armstrong, and S. Coulton, *Tetrahedron*, 1981, 157; W. Oppolzer, E. Francotte, and K. Bättig, *Helv. Chim. Acta*, 1981, **64**, 478; J. Rebek, D. F. Tai, and Y-K. Shue, *J. Am. Chem. Soc.*, 1984, **106**, 1813; W. F. Haefliger, *Helv. Chim. Acta*, 1984, **67**, 1942.
2 C. A. Demerson, A. H. Phillipp, and L. G. Humber, *J. Med. Chem.*, 1974, **17**, 1140.
3 N. J. Bach, D. A. Hall, and E. C. Kornfeld, *J. Med. Chem.*, 1974, **17**, 312.
4 C. S. Rondestvedt, Jr., *Org. React.*, 1976, **24**, 225.
5 B. S. Thyagarajan and K. C. Majundar, *J. Heterocycl. Chem.*, 1974, **11**, 937.
6 L. I. Kruse, *Heterocycles*, 1981, **16**, 1119.
7 L. Velluz, G. Muller, A. Allais, and J. Enezian, US Pat 2 985 659, 1961; *Chem. Abstr.*, 1961, **55**, 23576c.
8 M. Somei, F. Yamada, and C. Kaneko, *Fokusokan Kagaku Toronkai Koen Yoshishu 12th*, 1979, 91.