Formation of a 12-Aza Steroid by 1-Aza Triene Cyclisation

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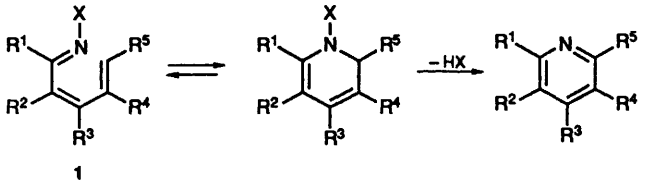
An approach to 12-aza analogues of estrone is described in which ring *C* is formed by electrocyclic ring closure of a dienone *N,N*-dimethylhydrazone

The pyridine ring system can be formed by the thermal six-π-electron electrocyclic ring closure of 1-aza trienes. There have been several examples of the synthesis of fused pyridines by cyclisation of dienone oximes or oxime ethers **1** (X = OH or OR) (Scheme 1) and we have described analogous reactions of



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Scheme 1

dienone *N,N*-dimethylhydrazones **1** (X = NMe_2).[1] There are also examples of the isolation or trapping of 1,2-dihydropyridines after thermal electrocyclic ring closure of 1-aza trienes.[2] As an extension of earlier work in which electrocyclic ring closure has been used to produce ring *C* of aromatic steroids related to estrone[3] we have investigated the application of the same methods to the synthesis of 12-aza steroids. Relatively few 12-aza steroids are known.[4] The aim was to prepare an aza analogue of estrone such as **2** bearing a bridgehead methyl group at C-13, no estrone analogues of this type having been reported so far.

The dimethylhydrazone **3** of the known[3] 2-bromo-6-methoxy-3,4-dihydronaphthalene-1-carbaldehyde was prepared (78%) from the aldehyde and *N,N*-dimethylhydrazine in dichloromethane containing a catalytic amount of toluene-*p*-sulfonic acid. The dimethylhydrazone, a waxy yellow solid m.p. 42–44 °C, was then used in a number of palladium(0)-catalysed coupling experiments with 3-bromo-2-methylcyclopent-2-enone as the electrophilic partner. In the most successful of these the dimethylhydrazone **3** was converted into the chlorozinc intermediate **4** by reaction with butyllithium at −78 °C for 0.5 h followed by the addition of zinc chloride at −20 °C. The chlorozinc species **4** was then heated with the bromocyclopentenone and 5 mol% $[Pd(PPh_3)_4]$ in THF for 16 h to give the coupling product **5** in 45% yield. Many variations in these conditions were explored in attempts to improve the yield of the coupling product **5**; these included the use of different palladium catalysts, the use of trifurylphosphine as a ligand in place of triphenylphosphine[5] and different temperatures and reaction times, but the dimethylhydrazone **5** was never isolated in a yield higher than 45%. The compound, a viscous yellow oil, proved to be unstable, even when stored in the dark below 0 °C, but it was characterised by mass spectrometry and by NMR spectroscopy.

It was cyclised by heating in bromobenzene (156 °C) for 1 h. The solution developed a bright blue colour during the initial stages of heating and a blue reaction product could be detected by TLC. The major product was, however, a pale yellow solid, m.p. 183–184 °C, which had an elemental analysis consistent with the aza steroid structure **2** but which clearly did not have this structure on the basis of its IR and NMR spectra. It showed

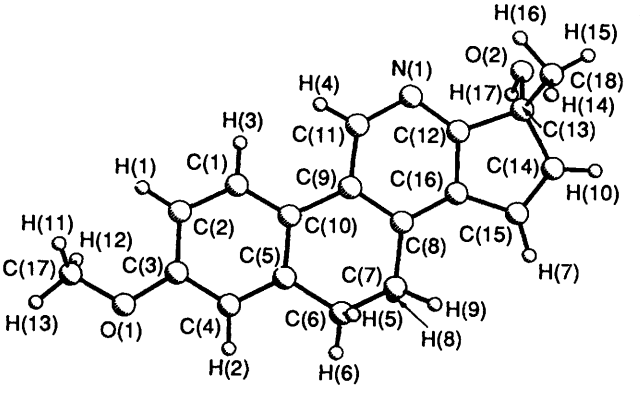


Fig. 1

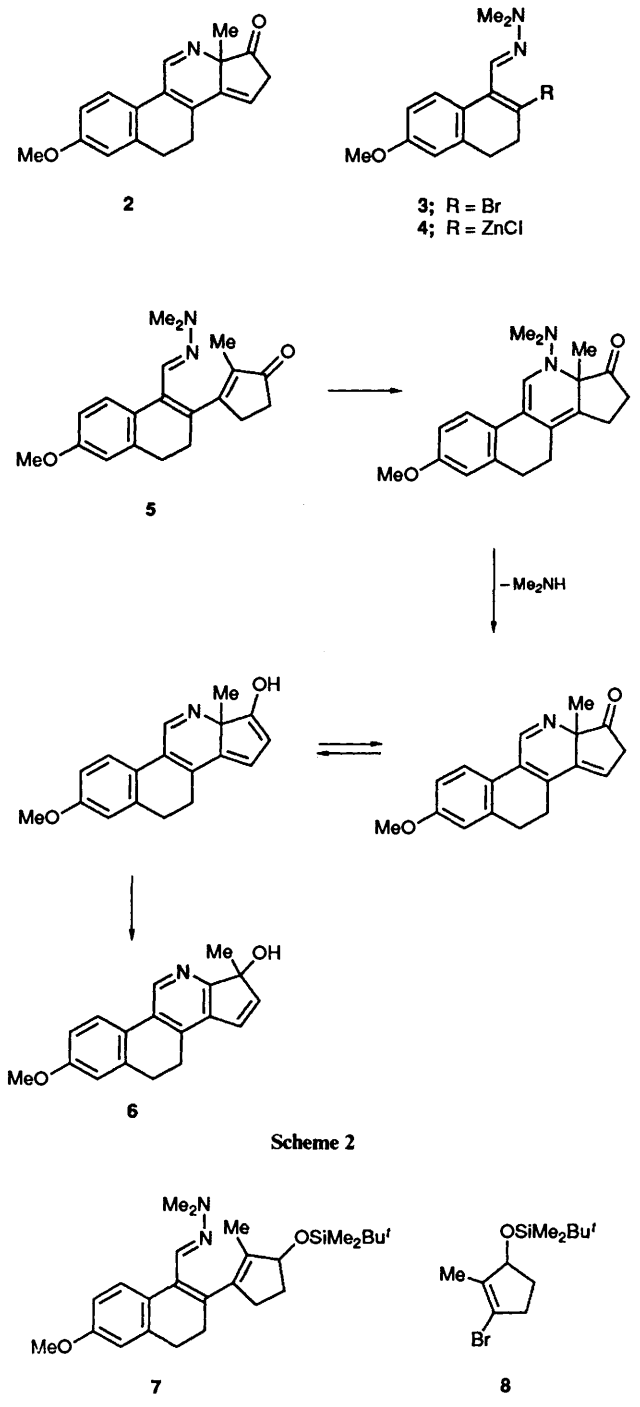
no carbonyl absorption in the IR spectrum and the ^1H NMR spectrum showed a pair of doublets (*J* 6.1 Hz) at δ 6.51 and 6.78 consistent with the presence of a C-15 to C-16 double bond in the 5-membered ring. This indicated that a series of hydrogen atom or proton shifts had occurred during the cyclisation process. The presence of a fully aromatic pyridine ring was also suggested by the presence of a singlet at δ 8.53 for 11-H. The structure was established as the fused pyridine **6** by an X-ray crystal structure determination (Fig. 1).†

Scheme 2 shows a series of intermediates through which compound **6** could be produced from the aza triene **5**. The reactions are represented as thermal processes but it is possible that some steps are acid catalysed (bromobenzene can contain traces of acid but attempts to catalyse the formation of **6** by adding acids resulted in the production of tars). A precedent for the thermal methyl shift shown in Scheme 2 exists in the rearrangement of 3-methoxy-3a-methyl-3a*H*-indene to 1-methoxy-1-methyl-1*H*-indene when heated in hexane.[6] It proved impossible to isolate a product of cyclisation from the aza triene **5** under milder conditions.

In an attempt to produce an intermediate which might cyclise more easily the silyl ether **7** was prepared from compound **3** by coupling to the cyclopentenyl ether **8**. The product was an unstable oil which was characterised by mass and NMR spectrometry but which did not cyclise cleanly when heated in solution. Other intermediates having this oxidation level are

† *Crystal data for* $C_{18}H_{17}NO_2$, **6**. *M* = 279.34, orthorhombic, space group *Pbca* (#61), *a* = 25.612(7), *b* = 15.77(1), *c* = 7.20(1), *V* = 2908(7) Å^3, *Z* = 8, D_c = 1.276 g cm^{-3}, F_{000} = 1184, μ(Mo-Kα) = 0.78 cm^{-1}, *T* = 297 *K*. Number of independent intensities = 2231 from yellow prism, 0.300 × 0.150 × 0.400 mm. *R* = 0.054, *Rw* = 0.067 for 816 observed reflections [$I > 3.00\sigma(I)$] and 190 variable parameters.

X-Ray intensity measurements were made using the omega scan technique to a maximum 2Θ value of 45.0° on a Rigaku AFC6S diffractometer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre [see 'Instructions for Authors (1992),' *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1].



being prepared in the hope of obtaining cyclisation products in which the 13-methyl group is retained.

Experimental

2-Bromo-3,4-dihydro-6-methoxynaphthalene-1-carbaldehyde N,N-Dimethylhydrazone **3**.—2-Bromo-3,4-dihydro-6-methoxynaphthalene-1-carbaldehyde[3] (0.93 g, 3.47 mmol) and 1,1-dimethylhydrazine (0.40 cm^3, 5.26 mmol) were heated in dichloromethane (15 cm^3) containing toluene-*p*-sulfonic acid (50 mg) for 3.5 h to give the *hydrazone* **3** (0.84 g, 78%) as a yellow solid, m.p. 42–44 °C (Found: C, 54.6; H, 5.5; N, 9.05. $C_{14}H_{17}BrN_2O$ requires C, 54.4; H, 5.5; N, 9.1%); δ(400 MHz; $CDCl_3$) * 2.83 (4 H, 3-H and 4-H), 2.97 (6 H, NMe_2), 3.80 (3 H, OMe), 6.67 (1 H, br, 5-H), 6.72 (1 H, d, br, *J* 8.5, 7-H), 7.41 (1 H, CH=N) and 7.88 (1 H, d, *J* 8.5, 8-H).

3,4-Dihydro-6-methoxy-2-(2-methyl-1-oxocyclopent-2-enyl)-naphthalene-1-carbaldehyde N,N-Dimethylhydrazone **5**.—To a solution of the hydrazone **3** (1.07 g, 3.46 mmol) in THF (25 cm^3) at −78 °C under argon was added butyllithium (3.79 mmol) in hexane. After 0.5 h zinc chloride (1.0 mol dm^3 solution in ether; 5.20 mmol) was added and the reaction mixture was stirred at −20 °C for 1 h. 3-Bromo-2-methylcyclopent-2-enone (0.61 g, 3.48 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.76 g, 5 mol %) in THF (20 cm^3) were then added. The mixture was allowed to warm to room temperature and then heated under reflux for 16 h. Flash column chromatography gave [with ethyl acetate–cyclohexane (2:5)] the *hydrazone* **5** (0.50 g, 45%) as a bright yellow oil [Found: *m/z* 324.1837 (M^+). $C_{20}H_{24}N_2O_2$ requires *M*, 324.1838]; $\nu_{max}(CH_2Cl_2)$ 1693 (C=O) and 1608 (C=N) cm^{-1}; δ(400 MHz; $CDCl_3$) 1.65 (3 H), 2.41 (2 H, t, *J* 7.4), 2.47–2.49 (2 H, m), 2.69–2.75 (2 H, m), 2.78 (2 H, t, *J* 7.4), 2.86 (6 H), 3.82 (3 H), 6.75–6.77 (2 H, m, 5-H and 7-H), 6.90 (1 H) and 7.85 (1 H, d, *J* 8.3, 8-H).

10,11-Dihydro-2-methoxy-7-methyl-7H-benzo[h]cyclopent-[c]isoquinolin-7-ol **6**.—The hydrazone **5** (0.30 g, 0.93 mmol) was dissolved in bromobenzene (20 cm^3) and the solution heated under reflux in an argon atmosphere for 1.5 h. The solvent was removed on the rotary evaporator and the residue subjected to flash column chromatography. This gave [with ethyl acetate–cyclohexane (7:3)] the *title compound* **6** (0.098 g, 38%), as buff crystals, m.p. 183–184 °C (from ethyl acetate–cyclohexane) (Found: C, 77.45; H, 6.1; N, 5.0. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%); ν_{max}(KBr)/cm^{-1} 3478, 3414 (OH) and 1616 (C=N); δ(400 MHz; $CDCl_3$) 1.67 (3 H, 7-Me), 2.80–2.91 (4 H, m, 10-H and 11-H), 3.84 (3 H, OMe), 6.51 (1 H, d, *J* 6.1, 8-H or 9-H), 6.78 (1 H, d, *J* 6.1, 8-H or 9-H), 6.79 (1 H, d, *J* 2.2, 1-H), 6.84 (1 H, dd, *J* 8.5 and 2.6, 3-H), 7.69 (1 H, d, *J* 8.5, 1-H) and 8.53 (1 H, 5-H).

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* *J* Values in Hz.