A SHORT SYNTHESIS OF 1-PHENYL-3-OXO-OCTAHYDROISOQUINOLINES.

Kai S. Ng, Peter S. Rutledge* and Paul D. Woodgate.
Department of Chemistry, University of Auckland, New Zealand.

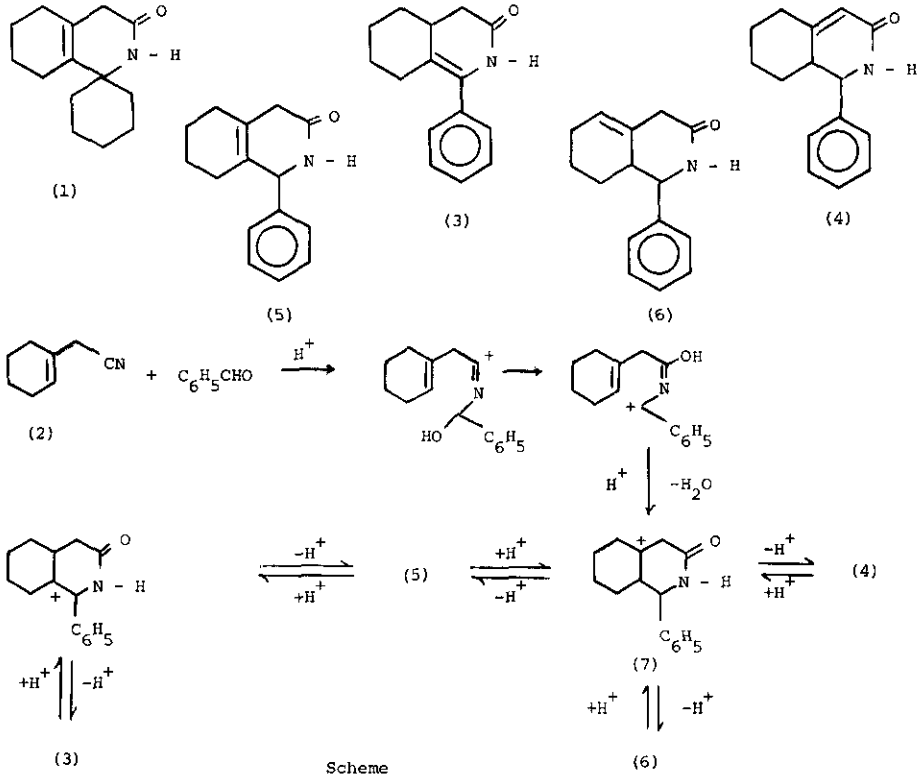
Abstract —— Equimolar amounts of benzaldehyde and 1-cyclohexenylacetonitrile react with P_2O_5 — methanesulfonic acid to give a mixture of isomeric 1-phenyl-3-oxo-octahydroisoquinolines in good yield.

Recently we reported a direct synthesis of the spirolactam (1) from reaction of 1-cyclohexenylacetonitrile (2) with cyclohexanone in polyphosphoric acid (PPA).[1] As part of our programme directed towards syntheses of the opium alkaloids we were interested to see if the analogous reaction of an aryl aldehyde would give a substituted hydroisoquinolone in a process paralleling the classical Pictet-Spengler reaction.[2] We have found that although the nitrile (2) and benzaldehyde do react in PPA the overall yield of the resulting mixture of isomeric hydroisoquinolones is only 8%. In contrast, when the reaction is carried out in methanesulfonic acid containing phosphorus pentoxide a different mixture of isomers is obtained in 67% yield.

Thus, equimolar amounts of the βγ-unsaturated nitrile and benzaldehyde were stirred in 83% PPA at 100 °C for 15 min. Work-up, distillation, and then p.l.c. of the fraction of b.p. 200-240 °C at 0.7 mm Hg gave (i) 1-phenyl-3-oxo-2,3,4,4a,5,6,7,8-octahydroisoquinoline[3] (3) (2%) m.p. 125 - 128 °C, m/z 227.1308 ($M^{+\cdot}$, $C_{15}H_{17}NO$, 56%), 198.0952 ($C_{13}H_{12}NO$, 28%), 185.0854 ($C_{12}H_{11}NO$, 100%), $\nu_{max.}$ ($CHCl_3$), 3380, 1680 cm^{-1}, $\lambda_{max.}$ 230 nm (ε, 5500)[4] δ_H ($CDCl_3$) 1.05 - 2.85 (11, m), 6.5 (1, br.s, lost on deuteration, NH), 7.0 - 7.9 (5, m, aryl H), (ii) 1-phenyl-3-oxo-1,2,3,5,6,7,8,8a-octahydroisoquinoline[3] (4) (1%) m.p. 173 - 176 °C, m/z 227.1308 ($M^{+\cdot}$, $C_{15}H_{17}NO$, 61%), 122.0722 ($C_8H_{10}O$, 100%), $\nu_{max.}$ (CCl_4) 1678, (neat) 1675, (KBr)[5] 1658 and 1625 cm^{-1}, $\lambda_{max.}$ 222 nm (ε 9500),[4] δ_H 1.0 - 2.7 (9, m), 4.2 (1, d, J 10 Hz, H1), 5.3 (1, br. s, lost on deuteration, NH), 5.73 (1, s, H4), 7.33 (5, s, aryl H), and (iii) a mixture (5%) of (4) and 1-phenyl-3-oxo-1,2,3,4,5,6,7,8-octahydroisoquinoline (5). Although the desired condensation and cyclisation had been achieved a considerable amount of polymeric material had also formed resulting in low yields of hydroisoquinolones. We felt that a major reason for this was the relatively high reaction temperature used. As an alternative to PPA Eaton has used P_2O_5 in methanesulfonic acid at room temperature.[6] When a mixture of 1-cyclohexenylacetonitrile (0.3 mmol) and benzaldehyde (0.32 mmol) was added over 30 sec to a vigorously stirred mixture of P_2O_5 (9 g) in methanesulfonic acid (10 g) at room temperature an exothermic reaction occurred. After 10 min, work-up and fractional crystallisation from ethanol gave (i) 1-phenyl-3-oxo-1,2,3,5,6,7,8,8a-octahydroisoquinoline[3] (5) (27%) as colourless needles m.p. 159 - 161.5°, m/z 227.1293 ($M^{+\cdot}$, $C_{15}H_{17}NO$, 73%), 226.1210 ($C_{15}H_{16}NO$, 16%), 198.0956 ($C_{13}H_{12}NO$, 32%), 185.0855 ($C_{12}H_{11}NO$, 100%, m* at 150.8 for

formation from $\underline{M}^{+\cdot}$), 122.0738 ($C_8H_{10}O$, 20%), $\nu_{max.}$ (CCl_4) 3200, 1665 cm^{-1}, δ_H ($CDCl_3$) 1.1 - 2.2 (8) 2.9 (2, br. s, H4), 4.7 (1, br. s, H1) 6.1 (1, br. s, NH, lost on deuteration) 7.2 (5, s, aryl H), δ_C[7] 169.7 (C3), 141.9 (C1'), 128.5 (2,C2' and C6'), 127.6 (2C, 4'), 127.3 (2, C3' and C5'), 125.9, 124.67 (C4a and C8a), 62.27 (C1), 35.84[8] (C4), 29.02 (C8), 26.23 (C5), 22.53, 22.14 (C6 and C7, and (iii) a mixture, (40%) m.p. 110 - 135 °C, of (4) (5) and (6) in a ratio of 1.2:3.5:1.[9] Although this mixture was not separable by p.l.c. in ether-chloroform (1:1) the resulting broad band was bisected and the material recovered from the upper half was crystallised from chloroform — acetone to give 1-phenyl-3-oxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (6)[3] m.p. 152 °C, $\underline{m/z}$ 227.1327 ($\underline{M}^{+\cdot}$, $C_{15}H_{17}NO$, 30%), 199.1361 ($C_{14}H_{17}N$, 17%), 122.0733 ($C_8H_{10}O$, 36%), 106.0639 (C_7H_8N, 100%), $\nu_{max.}$ ($CHCl_3$), 3400, 1650 cm^{-1}, δ_H ($CDCl_3$) 3.2 (2, s, H4), 4.10 (1, d, $\underline{J}$ 10 Hz, H1), 5.73 (2, br. s, H5 and NH (lost on deuteration)), 7.36 (5, s, aryl H).

At higher temperature in PPA the unsaturated lactam (6) is presumably converted to the thermodynamically more stable isomers (3), (4), and (5), via the intermediate (7) (Scheme). Under relatively mild conditions however, such reactions clearly have potential for direct syntheses of complex heterocyclic systems from simple starting materials.



Scheme

References

1 K.S. Ng, R.E.S. Sutcliffe, P.S. Rutledge, and P.D. Woodgate Heterocycles in press

2 W.M. Whaley, and T.R. Govindachari, Organic Reactions, 1951, 6, 151.

3 Correct combustion analysis for $C_{15}H_{17}NO$.

4 R.H. Mazur, J. Org. Chem., 1961, 26, 1289; A.I. Scott, "Interpretation of the Ultra-violet spectra of Natural Products", 1964, Pergamon.

5 cf. K. Mitsuhashi, K. Nomura, N. Minami and M. Matsuyama, Chem. Pharm. Bull., 1969, 17, 1578.

6 P.E. Eaton, G.R. Carlson, and J.T. Lee, J. Org. Chem., 1973, 38, 4071.

7 Multiplicities in the SFORD spectrum as required.

8 Irradiation at δ 2.82, the position of resonance of the C4 protons, resulted in a singlet appearing at δ 35.8 in the SFORD spectrum.

9 The mixture was analysed by t.l.c., and i.r. and ^1H n.m.r. spectroscopy.

Received, 24th August, 1981