An Extremely Mild Acetate Pyrolysis Reaction. Novel Synthesis and *X*-Ray Structure Determination of 1-Azaspiro[5.5]undecane Derivatives

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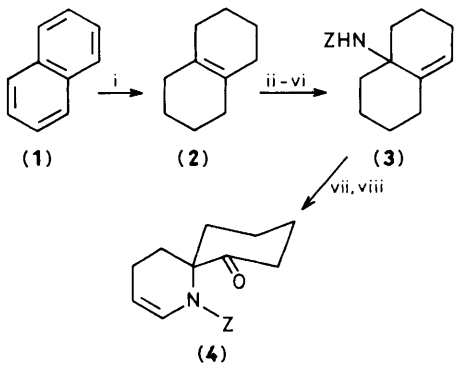
The azaspiro oxo-urethane (**4**), readily available from naphthalene, is reduced to the amino-alcohol (**5**) whose diacetate (**6**), the structure of which was determined by *X*-ray crystallography, undergoes acetate elimination in refluxing toluene to yield the *N*-acetylazaspiroundecene (**7**).

In connection with studies towards the synthesis of histrionicotoxin,[1,2] we have explored various approaches to the azaspiroundecene system. The azaspiro oxo-urethane (**4**)† is readily obtained by the sequence shown in Scheme 1.[3] Reduction of compound (**4**) in the presence of Raney nickel gave the amino-alcohol (**5**)† which was acetylated to give the *N*-acetyl acetoxy compound (**6**)† (Scheme 2).

X-Ray structure determination‡ of (**6**) revealed the structure shown in Figure 1. The interesting features of the structure are the *trans*-relationship of the NAc and OAc substituents and the position of the NAc carbonyl between H(6) and H(10). These protons resonate in the ^{1}H n.m.r. spectrum at δ 6.2 and 2.9 respectively, significantly downfield from the expected positions. Other reactions of the diacetate (**6**) illustrate further aspects of these proximity effects. Thus (**6**) was easily hydrolysed back to the amino-alcohol (**5**) in the presence of potassium carbonate in methanol at room temperature, reflecting the probable intramolecular catalysis by the hydroxy group in the hydrolysis of the hindered tertiary amide.[8] Furthermore, (**6**) was cleanly converted in high yield in refluxing toluene into the corresponding *N*-acetylalkene (**7**)† (Scheme 2). Acetate pyrolytic elimination reactions normally require temperatures in the vicinity of 450 °C and are believed to occur by a *syn*-elimination involving simultaneous breakage of the C–H and C–O bonds.[9] The mild pyrolytic acetate elimination from (**6**) seems unprecedented. The mild conditions are probably a consequence of participation by the neighbouring *N*-acetyl group.

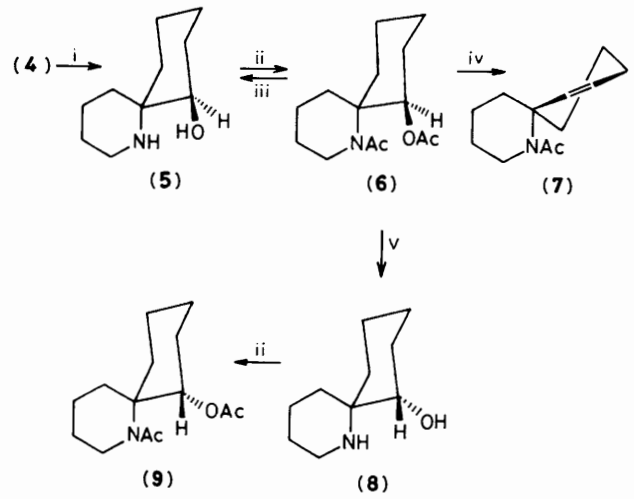
Neighbouring amide group participation in solvolysis reactions has been well studied,[10] but to our knowledge no such



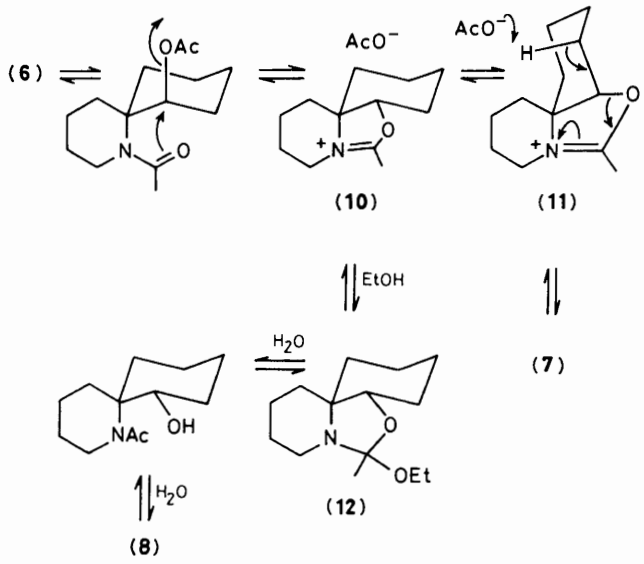
Scheme 1. *Reagents:* i, Li, $EtNH_2$–Me_2NH (63%) (ref. 4); ii, isopentyl nitrite–HCl (70%) (ref. 5); iii, H_2–Pt (98%), (ref. 6); iv, NaOMe–MeOH, room temperature, (90%); v, Al–Hg, tetrahydrofuran–H_2O, reflux (100%), (ref. 7); vi, $PhCH_2OCOCl$ (99%); vii, O_3, CH_2Cl_2, −78 °C; viii, Me_2S (43—72%).

† All new compounds exhibited spectroscopic and analytical data consistent with their structure.

‡ *Crystal data:* (**6**) $C_{14}H_{23}NO_3$, M = 253.33, orthorhombic, space group $Pna2_1$ (No. 33), a = 15.144(2), b = 14.309(2), c = 6.405(1) Å, U = 1387.9 Å^3, Z = 4, D_c = 1.212 g cm^{-3}, $F(000)$ = 552, λ(Cu-K_α) = 1.5418 Å, μ(Cu-K_α) = 6.01 cm^{-1}, R = 0.075 and R_w = 0.078 for 797 unique diffractometer data with $5 < 2\theta < 120°$ and $F > 3\sigma(F)$; all non-hydrogen atoms were refined anisotropically; H atoms were placed in idealised positions and refined with a common isotropic temperature factor. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.



Scheme 2. *Reagents:* i, H_2–Raney Ni, EtOH (93%); ii, Ac_2O, Et_3N, *N,N*-dimethylaminopyridine, CH_2Cl_2 (94%); iii, K_2CO_3, MeOH (60%); iv, toluene, reflux, 2 days, (96%); v, EtOH (H_2O), reflux [(**6**) → (**9**), 87%].



Scheme 3

participation has previously been reported to lead to elimination products under thermal conditions, probably because the previous studies always involved the use of secondary amides. Further information can be deduced from the observed conversion in refluxing ethanol of (**6**) into the *cis*-amino-alcohol† (**8**) identified as the diacetate (**9**)† which was stable to pyrolysis in boiling toluene. Evidently the ion pair (**10**) arises from *N*-acetyl participation in the ionisation of (**6**), and (**10**) can then collapse in toluene by acetate-assisted elimination to (**7**), or it can be captured by ethanol to give (**12**) which would eventually hydrolyse[10,11] to (**8**) (Scheme 3).

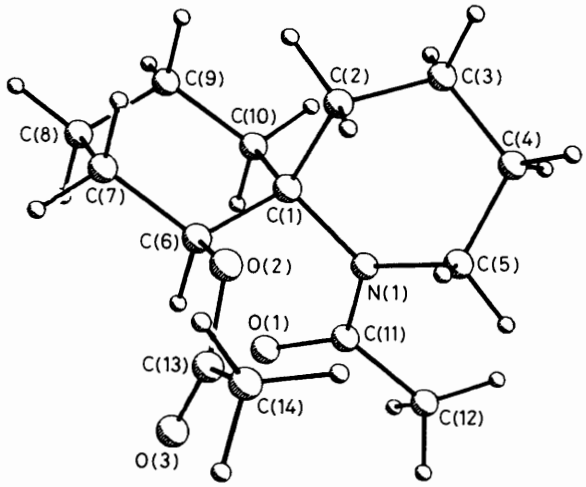


Figure 1. Molecular structure of (**6**) showing the atom numbering scheme; the hydrogen atoms have not been labelled for clarity but follow the numbering of the carbons to which they are bonded. Bond lengths: C(1)–N(1), 1.507(8); C(5)–N(1), 1.468(10); C(11)–N(1), 1.354(10); C(2)–C(1), 1.541(11); C(6)–C(1), 1.522(9); C(10)–C(1), 1.541(10); C(7)–C(6), 1.530(11); O(2)–C(6), 1.457(10); O(1)–C(11), 1.242(9); C(12)–C(11), 1.242(9); C(13)–O(2), 1.333(8); O(3)–C(13), 1.155(12); C(14)–C(13), 1.495(13) Å. Bond angles: C(5)–N(1)–C(1), 116.0(6); C(11)–N(1)–C(1), 121.6(6); C(11)–N(1)–C(5), 121.6(6); C(2)–C(1)–N(1), 107.3(6); C(6)–C(1)–N(1), 109.3(5); C(6)–C(1)–C(2), 112.5(7); C(10)–C(1)–N(1), 108.2(6); C(10)–C(1)–C(2), 109.5(5); C(10)–C(1)–C(6), 109.9(6); O(2)–C(6)–C(1), 108.0(7); O(2)–C(6)–C(7), 107.0(6); C(7)–C(6)–C(1), 112.8(6)°. Torsion angles: C(11)–N(1)–C(1)–C(6), 64.2(7); N(1)–C(1)–C(6)–O(2), 72.8(8); C(1)–N(1)–C(11)–C(12), 173.7(7); C(6)–O(2)–C(13)–C(14), −179.0(8)°.

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