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Cyclisation of Arylnitrenium Ions to the Aporphine Ring System: Remarkable Formation of a Sixteen-membered Ring by an Intramolecular Electrophilic Aromatic Substitution

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The delocalised π-cations from 1-(*m*-nitreniobenzyl)-1,2,3,4-tetrahydroisoquinolines cyclise to 9- and 11-aminoaporphines, but the *p*-nitrenium isomers do not form a 5-membered ring unless the ring undergoing attack is strongly activated; on the other hand, 1-(*p*-nitreniobenzyl)-7-benzyloxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline undergoes a remarkable intramolecular electrophilic substitution to give (**8**) (confirmed by an *X*-ray study) containing a 16-membered ring.

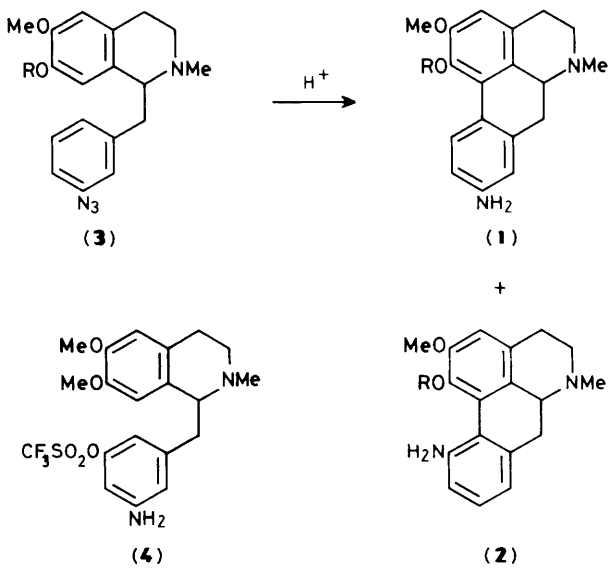
Intramolecular remote functionalisation of arylnitrenium ions is proving to be a useful and versatile method of forming homo- and hetero-cyclic rings,[1] *e.g.* six-[2a] and seven-membered[2b] rings, lactones,[2a,c] dihydrophenanthridines and benzo[*c*]chromens.[2d] *ipso*-Substitution[2c] has also been demonstrated, and has been applied[2e] to the synthesis of prostaglandin photoaffinity probes. On the other hand, no aminofluorene is obtained from the nitrenium ion from 3-azidodiphenylmethane,[3a] or with the corresponding oxenium ion intermediate.[3b] Clearly, the transition state for 5-membered ring formation (attack by a π-cation upon the π-cloud of the adjacent ring) is very strained and, in solution, competing processes are more favourable.[1b,3] In contrast, 5-membered lactones are formed readily.[2a,c]

The aporphine ring system is synthesised readily in this way. Reduction of 1-(3-nitrobenzyl-1,2,3,4-tetrahydro)-*N*-substituted isoquinolines with Zn and CF_3SO_3H (TFMSA)/CF_3CO_2H (TFA) (1:1) gives the corresponding 9-aminoaporphine.[4]† We now show that, not unexpectedly, the azide route leads to both 9- (**1**) and 11-aminoaporphines (**2**).

Thus, (**3**; R = Me) (oil)‡ in TFA was treated at 0 °C under N_2 with a few drops of TFMSA to give (**1**; R = Me) (13.6%), m.p. 182 °C,‡ and (**2**; R = Me) (26.2%), m.p. 203 °C,‡ together with compound (**4**) (16.5%), m.p. 134 °C.‡ Similar treatment of (**3**; R = $PhCH_2$) (oil) led to cyclisation and benzyl–O cleavage to give (**1**; R = H) (26.7%) (picrate, m.p. 190 °C) and (**2**; R = H) (17.8%) (picrate, m.p. 113 °C).

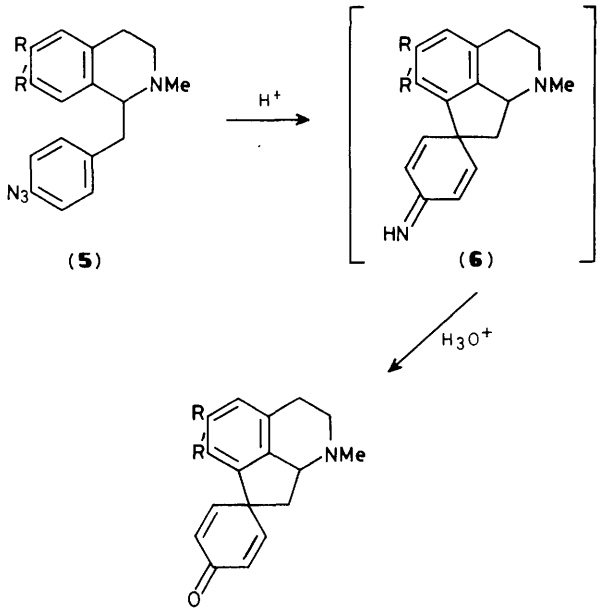
The results also highlight the fact that, in contrast to the behaviour of aryl σ-cations (*e.g.* as generated in the cationic version of the Pschorr cyclisation[5]) steric effects by substituents *ortho* to the position of attack do not appear to be important with π-aryl cations; *e.g.* 2′-aminopapaverine diazonium salt cyclises to an imidazole and an indenoquinoline rather than a dihydroaporphine.[6]

As expected on the basis of the strain in the transition state (*vide supra*) no five-membered ring [(**6**); R = R′ = H] or (**7**) was formed by *ipso*-attack from (**5**; R = R′ = H) and TFMSA. If the ring being attacked were made more nucleophilic *ipso*-substitution could begin to compete with other intermolecular processes. This was found to be the case. Thus,

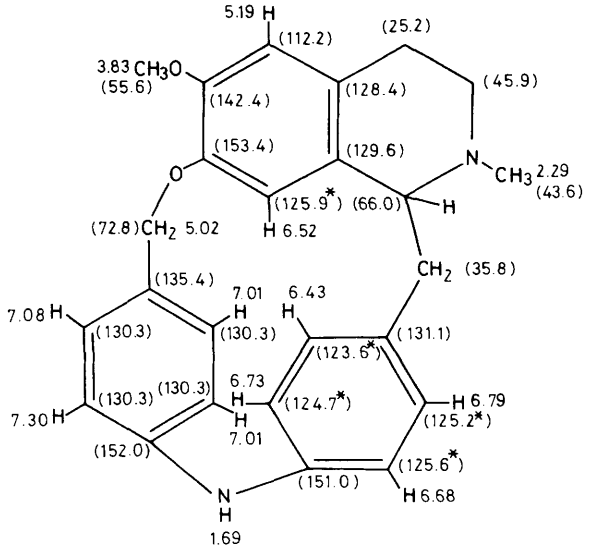


† The reaction probably involves initial reduction to the hydroxylamine which, with strong acid, yields the nitrenium ion. Alternatively, a concerted cyclisation–water elimination could account for the formation of only one isomer.

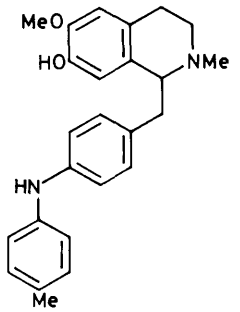
‡ All new compounds gave the expected microanalytical, i.r., n.m.r., and mass spectral data.



(7)



(8)



(9)

decomposition of [(5); R = R′ = OMe]‡ in TFA/TFMSA at 0—5 °C afforded pronuciferine [(7; R = R′ = OMe),[7] *via* hydrolysis of the imine (6) in low yield (5%), together with

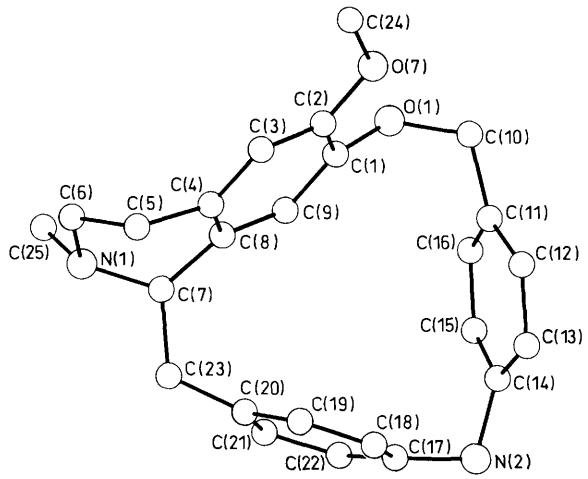


Figure 1. Crystal structure of (8).

uncyclised amine (16.3%), m.p. 118 °C,[8] [precursor to (5)], resulting from hydrogen-abstraction by the reactive intermediate.

In contrast, acid-catalysed (TFA; room temp.) decomposition of [(5); R = OMe, R′ = OCH_2Ph] did not yield [(7); R = OMe, R′ = OH] as expected by analogy with the above results. Instead, a product (8) (30%) was isolated having a single NH group (3310 cm^{-1}), whose ^1H n.m.r. and mass spectra (*m/z* 386, $M^{\cdot+}$) showed that it still contained the benzyl group. Hydrogenolysis of (8) (H_2/Pd–C) gave a somewhat unstable product (9) (65%) [OH and NH functions (i.r.), a new 3H singlet at δ 2.23 ($ArCH_3$), a symmetrical 4H multiplet centred at δ 6.93; chemical ionisation mass spectrum, *m/z* 389 (*M* + 1)].

On that basis, we assigned the 16-membered ring structure (8) to the cyclised product, and structure (9) to the hydrogenolysis product. The structure of (8) was confirmed by a single crystal *X*-ray structure determination. Figure 1 shows an ORTEP plot of (8).§ Dreiding molecular models suggest a very strained 16-membered ring, and the C(4)–N(2)–C(17) bond angle is 102.7°. The faces of the benzene rings are oriented towards the centre of the macrocycle. Tentative assignments [^1H, (^{13}C)] based on analysis of proton decoupled and undecoupled n.m.r. spectra are shown in (8). Starred values are interchangeable.

Formation of this 16-membered macrocycle appears to be the first such moderately large ring formation observed which results from intramolecular electrophilic attack by a nitrenium ion (or any other cation, as far as we can tell) upon an aromatic nucleus. Though the yield is not high, it is nevertheless spectacular when one considers the size of the ring formed, the obvious strain in the system, and the fact that there are no other known methods for the synthesis of such compounds at present. Possible factors which could facilitate such a cyclisation include (i) the presence of the 6-methoxy group in (5), forcing the benzyloxy group into the conformation ($PhCH_2$

§ White crystals: m.p. 227 °C (from acetonitrile). *Crystal data*: $C_{25}H_{26}N_2O_2$, *M* = 386.5, monoclinic, $P2_1/c$ (No. 14), *a* = 8.650(1), *b* = 6.556(3), *c* = 35.660(32) Å, β = 96.18(8)°, *V* = 2010.5(3) Å^3, *Z* = 4, D_c = 1.277 g cm^{-3}, *R*(F) = 0.077, R_w(F) = 0.074 for 2210 observed unique reflections [I > 2σ(I)] collected at 234 K with Mo-K_α radiation (λ = 0.71073 Å) to 2 ≤ 2θ ≤ 48°. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue 1.

away from OMe) necessary for ring-closure; (ii) the *p*-azidobenzyl group may be in a *pseudo*-axial conformation relative to the tetrahydropyridine ring, as it needs to be in the product, and (iii) an attractive interaction (*e.g.* π-complexing) between the highly electron-deficient arylnitrenium ion (or the protonated azide precursor) and the 7-benzyloxy group, such that the two rings are pre-oriented favourably. One could anticipate a number of other reactive intermediates, *e.g.* carbenium ions, behaving similarly, suggesting the synthesis of a variety of novel, moderately large ring systems.

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