Rearrangement of Benzylaminonitriles to give Cyclohepta[*c*]pyrrol-6(2*H*)-ones

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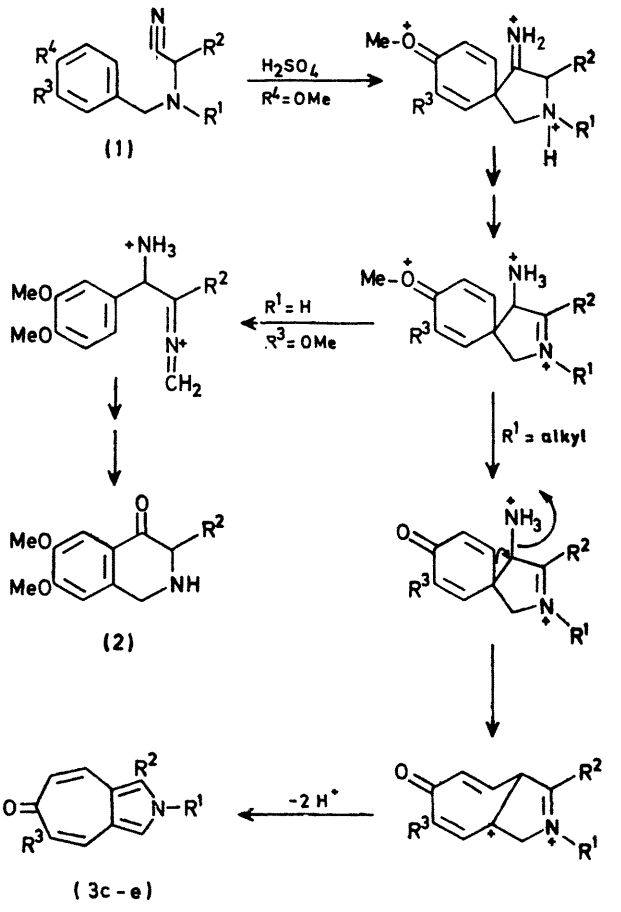
Summary *N*-4-Methoxybenzyl- and *N*-3,4-dimethoxybenzyl-aminoacetonitriles with both 2-aryl and *N*-alkyl substituents undergo *O*-demethylation and rearrangement with elimination of ammonia in concentrated sulphuric acid to give 1-aryl-*N*-alkylcyclohepta[*c*]pyrrol-6(2*H*)-ones.

PREVIOUS work[1] has shown that the benzylaminonitriles (**1a**,**b**) cyclise in concentrated sulphuric acid to give good yields of the isoquinolinones (**2**), and there is good evidence that a major route of cyclisation in many similar examples[2] is through a spiro intermediate (Scheme). It has now been shown that the *N*-alkyl analogues (**1c**,**d**,**e** and **4**) rearrange, probably through a comparable intermediate, to give instead the cyclohepta[*c*]pyrrol-6(2*H*)-ones (**3c**,**d**,**e** and **5**) respectively, in 10—50% yield.‡

The difference in behaviour can be tentatively explained if the spiro intermediate (Scheme) is considered in detail. Under the very strongly acidic conditions protonation would probably occur on both nitrogen atoms, with the possibility of tautomerism to give the most stable conjugated iminium salt. Such a salt could undergo cleavage of the five-membered ring to give the intermediate postulated previously, or a tautomer, when the starting amine is secondary (R^1 = H, Scheme), but when R^1 = alkyl this path is blocked. A longer lifetime of the spiro intermediate might reasonably be expected to lead to *O*-demethylation, apparently followed by a 1,2 shift with elimination of ammonia to give the observed products (Scheme).

All analytical and spectral data (i.r., ^{1}H n.m.r., m.s., C,H,N analysis) support the cyclophepta[*c*]pyrrole structures. The coupling constants for the adjacent protons in the seven-membered ring are 12—13 Hz, in accordance with published data on the parent compound,[3] as are the chemical shifts of these protons and those of the pyrrole ring and the *N*-methyl group. The compounds are bright yellow, changing to deep blue or green in acid.

To test the proposed mechanism, the aminonitrile (**1c**) was prepared with potassium [^{13}C]cyanide and cyclised as usual. The product (**3c**) showed enhancement of a previously low-intensity singlet at 119·1 p.p.m. in the ^{13}C n.m.r. spectrum, with no splitting in the off-resonance decoupled spectrum, in accordance with expectation for a carbon in the ring junction.

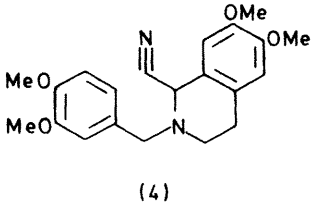


	R^1	R^2	R^3	R^4
a	H	Ph	OMe	OMe
b	H	DMP	OMe	OMe
c	Me	Ph	OMe	OMe
d	Me	DMP	OMe	OMe
e	Me	Ph	H	OMe
f	Me	Ph	OMe	H

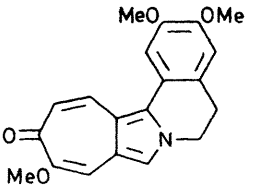
DMP = 3,4-dimethoxyphenyl

SCHEME†

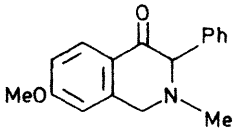
The remaining concern was with the position of the methoxy-group in the seven-membered ring of compounds (**3c**,**d** and **5**). It would be expected on mechanistic grounds that the preferred isomer would be as depicted since only then could the methoxy group stabilise the positive charge developing on the spiro carbon during the 1,2-shift. This supposition is borne out by the large (0·6 p.p.m.) chemical shift difference shown by the proton β to the carbonyl (J 13 Hz) in (**3c**) and (**3d**) compared to (**5**), which would only be expected if this proton could be deshielded by the rigidly held aromatic ring in (**5**).



(4)



(5)



(6)

It has been noted previously that straightforward *ortho*-cyclisation with a single activating methoxy-group is not favoured,[4] and this was borne out by cyclisation of the nitrile (**1f**) which gave 10—12% yields of the isoquinolinone (**6**) and was otherwise largely sulphonated, without cyclisation.

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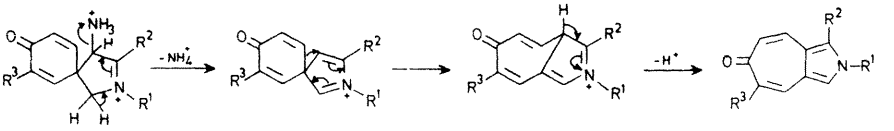
† A referee has suggested that elimination of ammonia could precede ring expansion:



‡ At least 35% of pure recrystallized material except for the product from (**1e**).

[1] D. N. Harcourt and R. D. Waigh, *J. Chem. Soc.* (*C*), 1971, 967.
[2] D. N. Harcourt, N. Taylor, and R. D. Waigh, *J. Chem. Soc.*, *Perkin Trans.* 1, 1978, 1330 and references cited.
[3] J. Duflos, D. Letouzé, G. Queguiner, and P. Pastour, *Tetrahedron Lett.*, 1973, 3453.
[4] D. N. Harcourt, N. Taylor, and R. D. Waigh, *J. Chem. Soc.*, *Perkin Trans.* 1, 1978, 722.