Rearrangements of Substituents in Highly Substituted Fluorinated Heterocyclic Compounds

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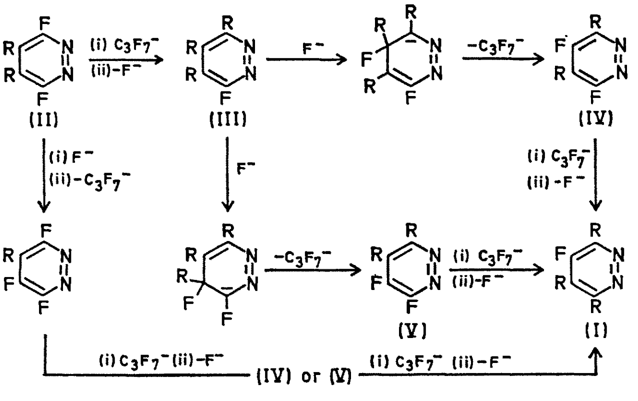
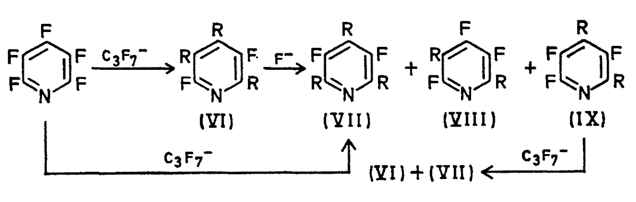
Summary Examples of the fluoride-catalysed migration of a heptafluoroisopropyl group in a substituted pyridazine and a substituted pyridine are reported.

THE controlled reaction at 70° in a suitable dipolar aprotic solvent (MeCN) between tetrafluoropyridazine and heptafluoroisopropyl anion, prepared from an excess of hexafluoropropene and caesium fluoride, gives only one trisubstituted compound, the 3,4,6-derivative [(I); 35% yield]. This compound is also formed (57% yield) by the attack of $C_3F_7^-$ on the unambiguously-characterised 4,5-disubstituted compound (II), and the thus established novel rearrangement of the C_3F_7 group from positions 4 or 5 is considered to involve fluoride ion attack to give a carbanion from which $C_3F_7^-$ is displaced. This is the first rearrangement of a pyridazine of this type to be reported. It is probable that the 3,4,5-substituted compound (III) is formed by the attacking $C_3F_7^-$ ion entering at the expected position 3, and that steric interaction in (III) then facilitates its rearrangement into (I) *via* (IV) or (V).



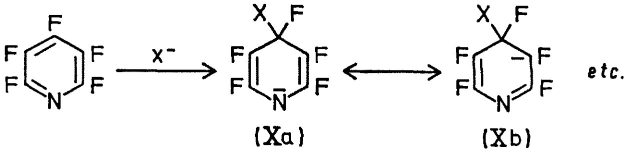
[R = $(CF_3)_2CF$-]

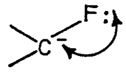
This rearrangement is related to one[1] based upon information presented verbally,[2] which showed that the 2,4,5-trisubstituted pyridine (VI) was the predominant product under certain conditions (favouring kinetic control) from a $C_3F_7^-$ attack on pentafluoropyridine, rather than the thermodynamically-stable 2,4,6-isomer (VII). 2,4,6-Substitution is expected by analogy with most other anionic attack on pentafluoropyridine. The authors correctly attribute[1] to one of us a verbal statement that steric factors are important in considering the formation of (VI) and (VII), but apparently misunderstood our considered view of the reaction by implying that *only* steric factors were important or that they *encouraged* the formation of (VI). Our investigation has in fact shown that (VI) rearranges into (VII) in presence of fluoride ion, but under conditions much more vigorous than for the rearrangement of (III). The rearrangement is in accord with one of the results reported by Chambers *et al.* who failed to notice,[1,3] however, that considerable amounts of the 2,5- as well as the 2,4-disubstituted compounds [(VIII); 40%, (IX); 38% yield] were also formed under the conditions described [R = $(CF_3)_2CF$]:

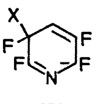


Thus in (VI) *both* the 4- and the 5-heptafluoroisopropyl groups are susceptible to nucleophilic displacement by fluoride ion, and not just the 5-group as had been assumed earlier.[1]

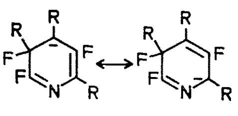
The usual pattern of nucleophilic attack on pentafluoropyridine, position 4 followed by 2 then 6, has been interpreted in terms of the stabilisation of the intermediate carbanion with (a) structures of type (Xa) with negative charge accommodated on nitrogen of particular importance, and (b) structures which involve location of the negative



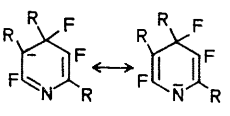
charge on carbon carrying α-fluorine *e.g.*, (Xb) or (XI) less-preferred since the stabilising effect of α-fluorine is offset by a destabilising effect involving repulsion of the delocalised *p*-electrons in the π-system of the carbanion by *p*-electrons on fluorine . The further attack of $C_3F_7^-$ on the 2,4-compound (IX), the main product from disubstitution, thus yields (VI) as well as (VII) despite the steric interaction in (VI), and this is attributed to the much more powerful effect of an α-perfluoroalkyl group compared



(XI)



(XII)



(XIII)

with α-fluorine in stabilising the intermediate carbanion (XII); the α-perfluoroalkyl group does not exhibit the destabilising *p*-electron repulsion effect. Related studies on fluorocarbanion stability have been reported.[4] Loss of the 5-substituent from (VI) is thus the reverse of its introduction into (IX). Competitive loss of the 4-substituent is attributed to the stabilisation of (XIII) by the anion-stabilising substituents at positions 1 (ring-nitrogen) and 5 (perfluoroalkyl). It should be pointed out that the relative stabilising effects of a sterically-crowded polyfluoroalkyl group or a sterically-crowded ring fluorine compared with a corresponding non-crowded polyfluoroalkyl group or ring fluorine cannot yet be assessed, but may not be unimportant in these highly-substituted heterocyclic compounds.

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[1] R. D. Chambers, R. P. Corbally, J. A. Jackson, and W. K. R. Musgrave, *Chem. Comm.*, 1969, 127.

[2] R. N. Haszeldine, S.C.I. Fluorine Chemistry Symposium, University of Birmingham, March 1968; Tilden Lecture, University College, London, November 1968.

[3] R. D. Chambers, J. A. Jackson, W. K. R. Musgrave, and R. A. Storey, *J. Chem. Soc.* (*C*), 1968, 2221.

[4] L. A. Kaplan and H. B. Pickard, *Chem. Comm.*, 1969, 1500, where references to earlier work are given.