

Nucleophilic Reactions of Halogen-substituted *N*-Oxides

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As a continuation of our work on this subject¹ we prepared the *N*-oxides of the *N*-pentafluorophenyl heterocycles (I; R = F, X = [CH₂]₃ or CH₂·O·CH₂) by condensation of hexafluorobenzene with the appropriate secondary amine at 70° to give the corresponding *N*-pentafluorophenyl heterocycle. This was then oxidized in a mixture of formic acid and hydrogen peroxide.

Reaction of the *N*-oxides (I; R and X as above) with sodium methoxide in methanol at room temperature caused fluorine replacement within 2 min. and gave the corresponding *p*-methoxy-compounds (I; R = OMe, X as above) in practically quantitative yield. The nature of the products followed from their analysis and from their identity after deoxygenation (aqueous sulphurous acid) with authentic material. The latter was obtained by refluxing the requisite *N*-pentafluorophenyl heterocycle in methanolic sodium methoxide (24 hr.) and orientated by a study of its ¹⁹F n.m.r. spectrum. Thus the reaction of the *N*-oxides (I) with methoxide follows the usual nucleophilic substitution pattern of C₆F₅X-type compounds² but is remarkable for its greatly enhanced rate undoubtedly caused by a powerful inductive effect of the N→O group

However, the morpholino-*N*-oxide (I; R = F, X = CH₂·O·CH₂) reacted exothermically with morpholine and the product after deoxygenation

proved to be the vicinal compound (II; R = CH₂·CH₂·O·CH₂·CH₂, R' = F) (70%). Its constitution was elucidated by analysis and its ¹⁹F

n.m.r. spectrum in chloroform with C₆F₆ as external reference [doublet and triplet at -22.1 and -4.6 p.p.m. and intensities of 2 and 1 respectively with *J* (c./sec.) 20.5 for *ortho*-fluorine coupling]. A similar result was observed for the reaction of the piperidino-compound (I; R = F, X = [CH₂]₃) with piperidine which yielded (after deoxygenation) the *vic*-piperidino-benzene (II; R = C₅H₁₀N, R' = F) and also for the *p*-chlorotetrafluoro-*N*-oxides (I; R = Cl, X = [CH₂]₃ or CH₂·O·CH₂) with piperidine or morpholine respectively. Yields of the triamino-chloro-compounds (II; R' = Cl, R = C₅H₁₀N or CH₂·CH₂·O·CH₂·CH₂) were again *ca.* 70%.

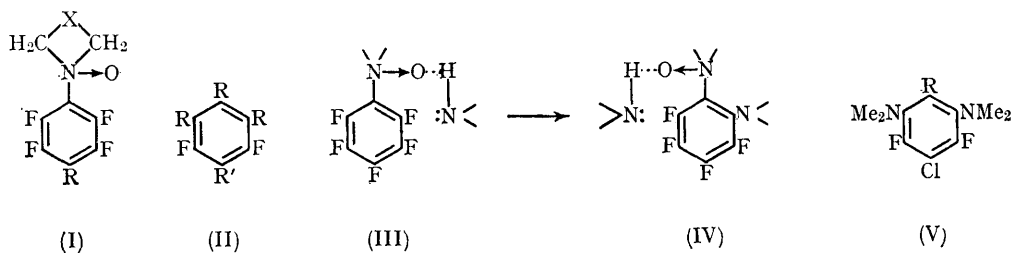
We ascribe this unusual bias for di-*ortho*-substitution mainly to two factors both arising from the presence of the *N*-oxide group. One is the heightened lability of the '*ortho*-fluorines' towards anionic replacement and the other a strong hydrogen-bond between the N→O group and the secondary amine which 'anchors' the approaching reagent twice successively in a favourable position for *ortho*-attack (*cf.* III → IV).

¹ M. Bellas and H. Suschitzky, *J. Chem. Soc.*, 1965, 2096; 1964, 4561; 1963, 4007.

² J. C. Tatlow, *Endeavour*, 1963, 22, 89; L. A. Wall, W. J. Pummer, J. E. Fearn, and J. M. Antonucci, *J. Res. Nat. Bur. Stand.*, 1963 (67,A), 5, 481.

A high proportion of mono-*ortho*-replacement^{3,4} has recently been reported for the reaction of penta-fluoronitrobenzene with ammonia or the methylamines in ether or ethanol and hydrogen-bonding

noteworthy that molecular models (Stuart-Briegleb) of all the triamines mentioned are comfortably assembled and steric hindrance is not apparent.



has been suggested to be one of the controlling agents. With dimethylamine, however, there was a considerable drop in *ortho*-substitution of the fluoronitrobenzene which was attributed to the bulk of the amine coupled with its reduced tendency to form a hydrogen-bond⁴. These limitations did not operate in our *N*-oxides (I) since dimethylamine (in dioxan) at room temperature gave a 90% yield of the trisubstituted amines (V; R = C₅H₁₀N or CH₂·CH₂·O·CH₂·CH₂). It is

The above method of preparing triamino-trihalogenobenzenes has to our knowledge produced the first example of nucleophilic di-*ortho*-substitution in polyfluorobenzenes which occurs readily in one step. The potential use of halogeno-*N*-oxides for making polysubstituted benzenes in general is obvious from these reactions and is under investigation.

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³ G. M. Brooke, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1961, 802.

⁴ J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 1045.