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THE THIOLATE ANION AS A NUCLEOPHILE

PART VII*. REACTIONS OF SOME FLUORINATED ANILINES AND PHENYLHYDRAZINES

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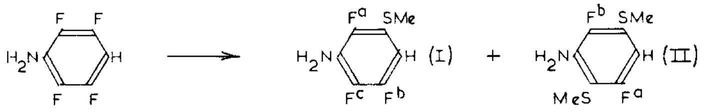
SUMMARY

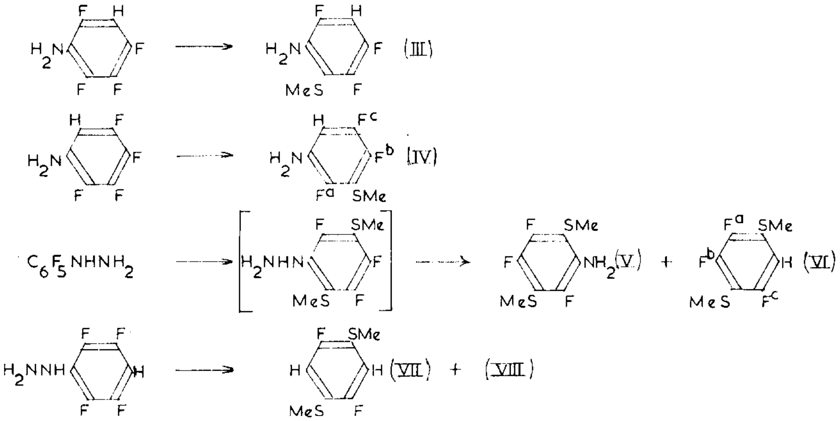
Direct nucleophilic substitution with sodium methanethiolate of the fluorinated anilines and phenylhydrazines, pentafluorophenylaniline, the three isomeric tetrafluoroanilines, pentafluorophenylhydrazine, and 2,3,5,6-tetrafluorophenylhydrazine, gave replacement of one or two fluorine atoms. The new compounds isolated have been characterised by elemental analysis, infrared and mass spectra and their stereochemistries have been deduced from their NMR spectra (^{1}H, ^{19}F and, in one instance, ^{13}C).

INTRODUCTION

Nucleophilic substitution of various pentafluorophenyl derivatives, C_6F_5X, with the methanethiolate anion usually gave initial replacement of the fluorine atom para to the group X [2], however with pentafluoroaniline no monosubstituted product could be isolated and only 2,5-di(methylthio)-trifluoroaniline was obtained [2]. In order to study further the effects of the nitrogen containing group on the position of substitution the nucleophilic substitution of the tetrafluoroanilines, 2,4,6-trifluoroaniline, pentafluorophenylhydrazine, 2,3,5,6-tetrafluorophenylhydrazine, p-diaminotetrafluorobenzene and p-di(methylamino)tetrafluorobenzene with the methanethiolate anion has been investigated. The reactions observed are summarized below, only the major products being shown.

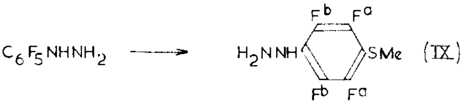


For Part VI, see ref.1



No reaction: *p*-$(H_2N)_2C_6F_4$, *p*-$(MeHN)_2C_6F_4$, 2,4,6-$F_3C_6H_2NH_2$.

The reaction conditions such as solvent system (ethylene glycol-pyridine) were the same as used previously [2]. In ethylene glycol alone as solvent monosubstitution of pentafluorophenylhydrazine,



and disubstitution of pentafluoroaniline forming V, analogous to the reaction in ethylene glycol-pyridine [2], occurred.

RESULTS AND DISCUSSION

The deactivating effect of the nitrogen containing groups on the aromatic ring in the nucleophilic substitution reactions is noticeable in the relative slowness of the reactions, as well as the considerable recovery of starting materials, when compared with the reactions of the corresponding fluorobenzenes [3]. This is well illustrated in the non reaction of *para*-diaminotetrafluorobenzene and *para*-di(methylamino)tetrafluorobenzene.

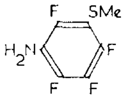
In the relatively basic solvent system employed some ionization of the nitrogenous bases forming anions may have occurred. In experiments with pentafluoroaniline no polymerization due to possible reaction of the anion with the nonionized species was observed.

Compounds containing the hydrazine group are thermally unstable and pentafluorophenylhydrazine decomposes at greater then 180°C to pentafluorobenzene and pentafluoroaniline [4].

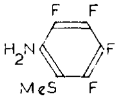
$$2C_6F_5NHNH_2 \rightarrow C_6F_5NH_2 + C_6F_5H + NH_3 + N_2$$

As the compound VI cannot be obtained from pentafluorobenzene and the methanethiolate anion [3], initial substitution of the pentafluorophenylhydrazine must have occurred forming an unstable intermediate which then decomposed in the work up to V and VI.

The position on initial substitution cannot be totally rationalized. There are two different effects, the activating influence of the fluorines and the deactivating effect of the nitrogen. In most nucleophilic substitution reactions the effect of the fluorine atoms is predominant and the position of attack relative to the fluorine atoms is *meta* > *ortho* > *para*. However when a strongly electron donating group, such as NH_2, is present electron pair repulsion predominates and substitution occurs mainly *meta* to the electron pair donating group [5]. The effect of the nitrogen may be enhanced in the basic medium used, ethylene glycol-pyridine, which could cause ionization of the weak bases forming the corresponding anion. For example $C_6F_5NH^-$ could be produced from pentafluoroaniline. In the reaction of pentafluoroaniline with the methanethiolate anion two intermediates X or XI are possible which then react further to give V [2]. Attempts to



(X)



(XI)

isolate a monosubstituted product using the hydrogen sulfide anion, which usually only gives monosubstitution, as a nucleophile failed and no reaction was observed. The formation of an unstable intermediate analogous to V in the reaction of pentafluorophenylhydrazine can account for the observed products V and VI. The intermediate XI is unlikely as *ortho* substitution occurs in solvents of low dielectric constant [6] and has not been observed previously in ethylene glycol-pyridine solvent. In the formation of X the effect of the NH_2 group predominates, but in the reaction of X to V the effects of the fluorine atoms predominate. In other reactions reported here the effect of the nitrogen containing group determined the position of substitution observed in I and the fluorine atoms the substitution found in II, III and IX. Only in the formation of IV do the effects of both the nitrogen group and the fluorine atoms reinforce each other. It is noteworthy that wherever possible substitution occurred *para* to either hydrogen or a methylthio group. The formation of IX from pentafluorophenylhydrazine in ethylene glycol is not readily rationalized as V is formed in a similar reaction from pentafluoroaniline. In the pentafluorophenylhydrazine reaction the effect of the nitrogen is less than the effect of the fluorine atoms, whereas in pentafluoroaniline the effect of the nitrogen

TABLE 1

Summary of NMR spectral data

Compound	Chemical Shifts		Coupling Constants/Hz						
	^{1}H/ppm	^{19}F/ppm	J(H-F$_o$)	J(H-F$_m$)	J(H-F$_p$)	J(F-F$_o$)	J(F-F$_m$)	J(F-F$_p$)	J(Me-F)
I	2.43S(Me)	135.9M(a)	10.2(H)	6.7,8.2(H)		19.8(b)	9.6(a)	12.0(a)	<0.2
	3.87(NH$_2$)	143.2M(b)	10.1(F)	6.8,8.3(F)		20.1(c)	9.4(c)	11.8(b)	
	6.44(ArH)	159.0M(c)							
	103.57D(ArCH)*		J(C-C-F)	21.2					
	16.05D(SCH$_3$)*		J 2.3						
II	2.42S(Me)	112.3DD(a)	9.0(H)	6.0(H)				14.3(a)	
	2.28S(Me)	137.8DD(b)	9.1(F)	5.9(F)				14.1(b)	
	4.55(NH$_2$)								
	6.25DD(ArH)								
III	2.34S(Me)	136.5†	10.6(H)	7.1(H)					
	4.35(NH$_2$)	149.6†	9.8(H)						
	6.87M(ArH)								
IV	2.47T(Me)	133.9M'(a)	11.0(H)	7.5,8.2(H)		23.7(b)	4.5(a)	12.8(a)	0.8(H)
	3.52(NH$_2$)	145.5M'(b)	11.1(c)	7.8,8.3(F)		23.5(c)	4.2(b)	12.6(c)	0.6(F$_a$)
	6.53M(ArH)	142.1M(c)							1.0(F$_b$)
VI	2.42T(Me)	139.9M(a)	9.2(H)	5.8(H)	2.4(H)	22.8(a)	∿2(c)	12.9(a)	0.7(H)
	2.45S(Me)	128.9D§(b)	∿9(F)	5.8(F)		22.8(b)			0.6(F$_a$)
	6.74(ArH)	110.0Q§(c)						13.0(c)	

S = singlet, D = doublet, T = triplet, Q = quartet, M = 8 line multiplet, M' = 8 line multiplet further split into quartets

* = ^{13}C, † = second order spectrum, § = poorly resolved

TABLE 1 continued

Summary of NMR spectral data

Compound	Chemical Shifts		Coupling Constants
	^{1}H/ppm	^{19}F/ppm	J(Me-F)/ppm
IX	2.43T(Me) 4.02(NH_2) 5.42(NH)	158.5(b) 135.9(a)	0.4(H)

predominate giving initial formation of X. This may be due to differences in acidities, pentafluorophenylhydrazine being presumably somewhat less acidic than pentafluoroaniline, as phenylhydrazine is less acidic than aniline [7], resulting in limited ionization in the weakly basic solvent.

Although the infrared spectra cannot be used for the absolute determinations of the structure they did enable the functional groups present to be detected and a preliminary identification of the products to be made.

The structures of the new products have been deduced from their ^{1}H and ^{19}F NMR spectra and I also from its ^{13}C spectrum. Details of the spectra are shown in Table 1. In most cases first order spectra were observed and the coupling constants deduced from the proton and fluorine spectra for H-F coupling agree reasonably well. In III the spectra of two of the three fluorines overlapped and that of the fluorine was not first order, so values of the coupling constants could not be deduced from the fluorine spectrum.

The product from the reaction of 2,3,5,6-tetrafluoroaniline was found to be I. The fluorine spectrum showed three fluorine atoms <u>ortho</u> and <u>meta</u>, <u>ortho</u> and <u>para</u>, and <u>meta</u> and <u>para</u> to each other. In the proton spectrum of the aromatic hydrogen three different coupling constants were observed that could not unambiguously be assigned to $J(H-F_o)$ and $J(H-F_m)$. These data are consistent with structure I or one involving initial substitution <u>ortho</u> to the NH_2 group. The ^{13}C spectrum, with C-H decoupled, showed an aromatic carbon attached to hydrogen which was split into a doublet by coupling to fluorine. The coupling constant 21.2 Hz is consistent with the literature value of J(C-C-F) 21.0 Hz [8], clearly indicating structure I. The methyl carbon was also split into a doublet, J = 2.3 Hz, probably due to coupling to the <u>ortho</u> fluorine. The methyl protons can be split by coupling to <u>ortho</u> fluorine atoms, the magnitude of the coupling depending on the other group <u>ortho</u> to the SMe group, and similarly the fluorine signals are split into a quartet [2]. When the other group *ortho* to the SMe group is H or NH_2 the methyl protons are not split [2,3]. The non-splitting of the methyl protons further confirmed the structure I.

The spectra of II, III and IV were consistent with the structures shown. In III the fluorine spectrum was second order and the ratio of the peaks at 136.5 and 149.6 ppm was 2:1, indicating that three fluorine atoms were present.

The proton spectrum of VI showed two methyl groups. The methyl group split into a triplet must be *ortho* to two fluorines and the non-split one *ortho* to a hydrogen and a fluorine. Corresponding splittings were observed in the spectrum of the appropiate fluorine atoms.

The hydrazine group is clearly retained in IX as signals corresponding to NH and NH_2 were found in the proton spectrum. The magnitude of the splitting of the methyl protons into a triplet by two *ortho* fluorine atoms was smaller than expected [9]. Two poorly resolved fluorine signals of equal intensity, probably A_2B_2, were observed clearly indicating a symmetrical structure such as IX. Similar spectra were observed in the *p*-$(MeS)C_6F_4X$ derivatives [2]. The signal at 135.9 ppm can be assigned to the fluorine atoms *ortho* to the MeS group as similar chemical shifts for fluorines *ortho* to the SMe group are found in the compounds *p*-$MeSC_6F_4X$ [2]. The chemical shift of the fluorines *ortho* to the $NHNH_2$ group assigned as 158.5 ppm is similar to that found in *p*-$(H_2NNH)_2C_6F_4$ [10].

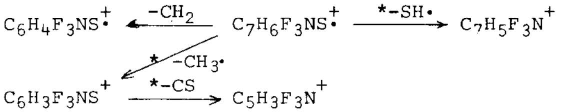
The group of compounds I, III and IV are isomeric and it was of interest to see whether different fragmentation patterns were observed and if these isomers could be distinguished from their mass spectra. The primary ion and ion kinetic energy spectra were recorded.

The primary ion spectra showed that in all cases the principal ions formed were the same, but of somewhat differing intensities. All the spectra showed initial fracture of Ar-S or Me-S bonds. There was no evidence for the loss of H or F from the molecular ion. Similar features were observed in the mass spectra of the isomers of $C_6F_xH_y(SMe)_{6-x-y}$ [3]. The spectra also showed the formation of many doubly charged ions , indicating the formation of relatively stable ions. Rearrangements must have occurred in many of the fragmentations, such as.

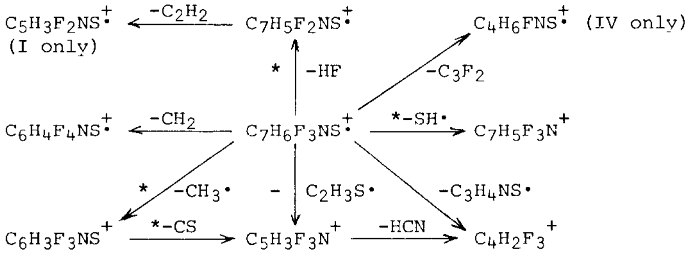
$$C_6H(NH_2)F_3SMe^{+\cdot} \rightarrow C_7H_5F_3N^{+} + SH\cdot$$

$$C_6H(NH_2)F_3SMe^{+\cdot} \rightarrow C_6H_4F_3NS^{+\cdot} + CH_2$$

The same initial fragmentation was observed in all spectra.



In the compounds I and IV a more detailed fragmentation scheme was deduced.



All reactions that have not been confirmed by metastable peaks have been deduced from the ion kinetic energy spectra, except $M^{+\cdot} - CH_2$.

EXPERIMENTAL

All the reagents were available commercially except *p*-$(MeHN)_2C_6F_4$ which was prepared by a literature method [11]. Microanalyses were performed by Mikroanalytisches Laboratorium Beller, Göttingen, West Germany or the Butterworth Microanalytical Consultancy Ltd., Teddington, England. The analytical data and physical properties of the new compounds are shown in Table 2. Mass spectra (70 eV) were recorded on a Du Pont/C.E.C. Model 21-100B mass spectrometer using direct introduction techniques. In cases of ambiguity ion identification was confirmed by high resolution measurements ($R \simeq 15000$) based on spectra recorded photographically. Ion kinetic energy data were obtained as described previously [12]. NMR spectra were recorded in $CDC\ell_3$ solution using TMS or $CFC\ell_3$ as internal standards on a Varian A 56/60, HA 100 or XL 100. Infrared spectra were recorded on a Perkin Elmer model 457 spectrophotometer as thin films, as mulls with Nujol or hexachlorobutadiene, or a KBr discs.

The experimental procedures followed have been described previously [2]. Considerable difficulty was encountered in the separation of the reaction products. Most of the starting materials and products were relatively volatile and absorbed water, presumably due to the presence of an NH_2 group. In some cases the crude products were cleaned up by column chromatography (silica gel) and finally separated by preparative gas chromatography (silicone rubber gum SE 30 column, He carrier gas). The

TABLE 2

Chemical analyses and physical properties of new compounds

Compound	M.p./ °C or b.p./ °C	Calculated (%)				Found (%)			
		C	H	S	N	C	H	S	N
I	50-50.5	43.5	3.13	16.6	--	43.7	3.50	16.7	--
II	52.5-53	43.4	4.10	29.0	6.33	43.1	4.08	28.8	6.43
III	68-69/Atm.	43.5	3.13	16.6	--	44.0	3.22	16.6	--
IV	33-34	43.5	3.13	16.6	7.25	43.3	3.13	16.8	7.44
VI	39-40	42.8	3.15	--	--	42.6	3.15	--	--
IX	101-102	37.2	2.67	--	12.4	37.2	2.61	--	12.4

TABLE 3

Reaction stoichiometry and products

Substrate	Molar ratio MeS^- : substrate	Major product	Yield (%)	Purification
2,3,5,6-TFA	1:1	2,3,5,6-TFA	12	1
		I	10	2,3
		II	8	2,3
2,3,5,6-TFA	4:1	2,3,5,6-TFA	12	1
		I	12	2,3
		II	14	2,3
2,3,4,6-TFA	1:1	2,3,4,6-TFA	21	1
		III	21	2
2,3,4,6-TFA	4:1	III	47	2
2,3,4,5-TFA	1:1	IV	36	4
2,3,4,5-TFA	4:1	IV	63	4,5
$C_6F_5NHNH_2$	1:1	V	4	2,3
		VI	39	2,3
$C_6F_5NHNH_2$*	1:1	IX	54	4
2,3,5,6-TFPH	1:1	VII	10	3
$C_6F_5NH_2$*	1:1	V	34	5

TFA = tetrafluoroaniline; TFPH = tetrafluorophenylhydrazine

* = reaction in ethylene glycol

Purification: 1 = distillation, 2 = column chromatography, 3 = gas chromatography, 4 = recrystallization from hexane, 5 = sublimation latter technique was not suitable for non volatile compounds and thermally sensitive compounds. Details of the reactant stoichiometry and products are shown in Table 3.

Only starting materials were recovered in the reaction of $C_6F_5NH_2$ (10 mmoles) with SH^- (10 mmoles) for 20 mins. at room temp.; p-$(H_2N)_2C_6F_4$ (10 mmoles) with SMe^- (40 mmoles) refluxing for 24 h.; 2,4,6-trifluoroaniline (10 mmoles) with SMe^- (10 or 40 mmoles) with a reaction time up to 23 h.; $C_6F_5NH_2$ (5 mmoles) with NaOH (5 mmoles) omitting the MeSH; an unidentified product, probably polymeric, was obtained from the reaction of p-$(HNMe)_2C_6F_4$ (3.3 mmoles) and SMe^- (20 mmoles) refluxing for 1 h.. The known compounds V and VII were identified from their NMR spectra and m.p.s [2,3]. The compound VIII could not be identified, but was probably a mixture that could not be separated. In the NMR spectra of VIII a methyl proton was observed, but both the aromatic hydrogen and fluorine spectra were unsymmetrical and could not be assigned. No traces of I, II, and NH_2 or $NHNH_2$ group, or p-$H_2C_6F_4$ were found.

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