

CYCLIZATION OF POLYFLUORO SUBSTITUTED 2-AMINO-
AND 2-ACETYLAMINODIARYL ETHERS INTO DERIVATIVES OF PHENOXAZINE

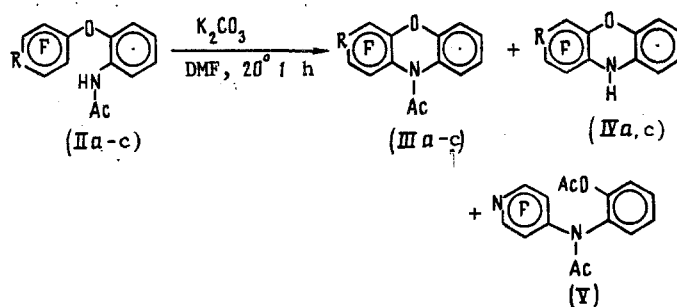
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Cyclization of the diaryl ethers 4-RC₅F₄OC₆H₄NH₂(NHAc)-2' (R = C-NO₂, C-CF₃, N), containing an electron accepting group in the fluorinated ring, proceeds in DMF in the presence of K₂CO₃ following a Smiles rearrangement.

We have shown earlier that heating 4-X-2,3,5,6-tetrafluoro-2'-acetylamino-diphenyl ethers (I, X = Cl, H) in DMF in the presence of K₂CO₃ leads to cyclization due to intramolecular nucleophilic substitution of the F atom. The structure of phenoxazine derivatives so formed indicates that cyclization is preceded by conversion of the starting compounds into isomeric 2-hydroxydiarylamines (Smiles rearrangement) [1]. One can suppose that the absence of the latter in the reaction mixtures is caused by the greater rate of the second step (cyclization). In this case increasing the rate of rearrangement of the starting diphenyl ethers could lead to stabilization of the intermediate 2-hydroxydiarylamines and give direct evidence of a two-step conversion scheme.

It is known that the rate of the Smiles rearrangement can be substantially increased by increasing the amount of activation of the migrating aryl ring [2, 3]. Therefore we have investigated conversion under cyclization conditions (DMF, K₂CO₃) of diaryl ethers 4-RC₆F₄-OC₆H₄NHAc (IIa, b) containing accepting groups (R = NO₂, CF₃) in the fluorinated ring. Previously the possibility was established of rearranging these compounds into isomeric diarylamines in DMF at 60-100°C [4].* The reaction in the presence of K₂CO₃ requires lower conversion temperatures and forms N-acetylphenoxazine derivatives (IIIa, b) as the only or main products



In case of starting ether (IIa) partial cleavage of the acetyl group is observed, which leads to the appearance in the reaction mixture of up to 10% of phenoxazine (IVa).

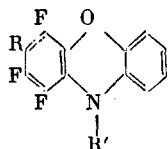
Compound (IIc), a heterocyclic analog of 2-acetylamino-diphenyl ethers, forms under the above conditions a mixture of approximately equal amounts of phenoxazines (IIIc) and (IVc), and diacetyl derivative (V). Formation of the latter, which is apparently the acetylation products of the intermediate 2-hydroxydiarylamines, agrees with the proposed two-step cyclization scheme for polyfluoro-2-acetylamino-diaryl ethers. A direct proof of this scheme is the

*2,3,4,5,6-Pentafluoro-2'-acetylamino-diphenyl ether does not change upon heating in DMF to 100°C.

TABLE 1. Cyclization of Diaryl Ethers (II)

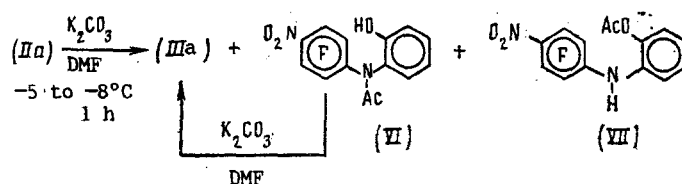
Compound	T, °C	Composition of reaction mixture (from ^{19}F NMR spectrum), %				
		(III)	(IV)	(V)	(VI)	(VII)
(IIa)	20	90	10		—	—
	-5	35	—		50	15
(IIb)	20	100	—		—	—
(IIc)	20	30	40	30	—	—

TABLE 2. Polyfluorophenoxazines



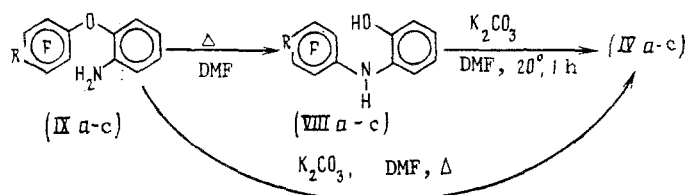
Compound (R, R')	Yield, %	mp, °C (solvent)	Found/Calculated, %				Molecular formula	IR spectrum, ν , cm^{-1}	$\delta^{19}\text{F}$, ppm (ratio of intensities)
			C	H	F	N			
(IIIa) (C—NO ₂ , CH ₃ CO)	56	113—114 petroleum ether	51,82 51,86	2,48 2,47	17,96 17,58	8,52 8,64	C ₁₄ H ₇ F ₃ N ₂ O ₄	1715 (CO)	12,9; 16,3; 23,9 (1:1:1)
(IIIb) (C—CF ₃ , CH ₃ CO)	96	114—116 (alcohol)	51,96 51,88	1,87 2,03	32,81 32,83	3,93 4,03	C ₁₅ H ₇ F ₆ NO ₂	1710 (CO)	19,5; 22,8; 107,2 (1:2:3)
(IIIc) (N, CH ₃ CO)	29	147—148 benzene-petroleum ether	55,59 55,72	2,46 2,52	20,49 20,34	9,94 10,0	C ₁₃ H ₇ F ₃ N ₂ O ₂	1710 (CO)	19,5; 69,5; 72,7 (1:1:1)
(IVa) (C—NO ₂ , H)	Quantitative	164—166 ether	50,73 51,07	1,70 1,79	20,92 20,20	9,88 9,93	C ₁₂ H ₅ F ₃ N ₂ O ₃	3430 (NH)	-0,7; 13,1; 14,7 (1:1:1)
(IVb) (C—CF ₃ , H)	»	194—195 ether	51,13 51,16	1,84 1,65	37,30 37,36	4,26 4,59	C ₁₃ H ₅ F ₆ NO	3440 (NH)	-1,8; 17,2; 20,0; 108,2 (1:1:1:3)
(IVc) (N, H)	»	237—238 ether	54,69 54,47	2,21 2,12	23,99 23,93	11,4 11,7	C ₁₁ H ₅ F ₃ N ₂ O	3440 (NH)	-3,5; 66,4 (1:2)

presence in the reaction mixture obtained from ether (IIa) at -5 to -8°C of its rearrangement products: the N-acetyl derivative of 2-hydroxydiarylamine (VI) and its O-Ac-isomer (VII). The ratio of isomers (VI) and (VII) (Table 1) corresponds with data shown in [4]. As should be expected, compound (VI) easily forms phenoxazine (IIIa) with DMF in the presence of K_2CO_3

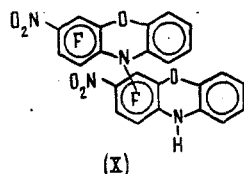


The structures of the initially obtained compounds were established by elemental analysis and physicochemical methods. From acetylphenoxazines (IIIa, b) compounds (IVa, b) were obtained by deacetylation. The structure of the latter is confirmed by independent synthesis from 2-hydroxydiarylamines (VIIIa-c) obtained in [5] by rearrangement of the corresponding diaryl ethers (IXa-c) (see following page for structure).

Phenoxazines (IVa-c) can be obtained directly from compounds (IXa-c) by heating in DMF in the presence of K_2CO_3 , however, the reaction proceeds readily only for ether (IXb). Cyclization of compound (IXc) is accompanied by formation of a product insoluble in organic media and conversion of ether (IXa) by formation of a by-product to which we have assigned the struc-



ture of N,C-biphenoxazine (X) on the basis of its molecular weight, elemental analysis and IR and ^{19}F NMR spectra (see [6])



The ^{19}F NMR spectrum does not allow one to determine unambiguously the position of the phenoxazine fragment on the fluorinated ring. However, the formation of compound (X) from diarylamine (VIIIa) upon cyclization in DMF in the presence of NEt_3 indicates the nitro group to be para to the central nitrogen atom.

EXPERIMENTAL

IR spectra were recorded on an UR-20 instrument in CHCl_3 and ^{19}F NMR spectra on a Varian A 56/60 A (56.4 MHz) and a Varian WP-200 SY (188.28 MHz) instrument. Chemical shifts are shown in ppm from C_6F_6 . Molecular weights were determined on a KV-2091 or a Finnigan MAT 8200 mass spectrometer.

As solvent DMF was used after drying over molecular sieves NaA and NaX and contained 0.3% water.

Cyclization of Polyfluoro-2-acetylaminodiaryl Ethers. Compound (II) in the amount of 0.5 g and 0.5 g of roasted K_2CO_3 in 10 ml of DMF was stirred for 1 h under conditions shown in Table 1. The reaction mixture was poured into water, neutralized with 10% HCl, and extracted with ether. The product, obtained by evaporation of the ether, was analyzed by ^{19}F NMR spectroscopy (Table 1).

Polyfluoro-10-acetylphenoxazines (IIIa) and (IIIc) were isolated from reaction mixtures by TLC on silica gel (L 5/40) in benzene. Yields and properties of compounds (III) are shown in Table 2.

N-(2,3,5,6-tetrafluoropyridyl)-N-acetyl-(2-acetoxy)aniline (V) was isolated by TLC with 21% yields. IR spectrum (ν , cm^{-1}): 1705 (CO), 1770 (CO). ^{19}F NMR spectrum (δ , ppm): 17.7, 22.7, and 72.2, intensity ratio (1:1:2), m/z (exp.) 342.0631. $\text{C}_{15}\text{H}_{10}\text{F}_4\text{N}_2\text{O}_3$. m/z (calc.) 342.0627.

2,3,4,5,6-Pentafluoro-2'-acetylaminodiphenyl ether (0.2 g) was stirred in 5 ml of DMF at 100°C for 1 h. The reaction mixture was poured into water and extracted with ether. By evaporation of the ether there was obtained 0.18 g of a product which was identical by ^{19}F NMR spectra with the starting compounds.

Cyclization of Compound (VI). a) Compound (VI) (0.10 g) was stirred in 5 ml of DMF in the presence of 0.20 g of roasted K_2CO_3 at 20°C for 1 h. The reaction mixture was poured into water, neutralized with 10% HCl, and extracted with ether. By evaporation of the ether there was obtained 0.08 g (89%) of a product identical by mp, IR spectrum, and ^{19}F NMR spectrum to acetylphenoxazine (IIIa).

b) Analogously at -5 to -8°C there was obtained 0.18 g of a mixture containing, according to ^{19}F NMR spectral data, starting amine (VI), its isomer (VII), and phenoxazine (IIIa) in the ratio 40:48:12.

Deacetylation of 10-acetylphenoxazines (IIIa, b). 1.0 mmole of compounds (IIIa, b) in a mixture with 5 ml of ethanol and 5 ml of concentrated HCl was refluxed for 1 h. The mixture was poured into water, neutralized with Na_2CO_3 , and extracted with ether. By evaporation of the ether phenoxazines (IVa) and (IVb) were obtained with yields of 80 and 96% respectively.

Cyclization of 2-Hydroxydiarylamines (VIII). a) 0.3 g of compound (VIII) and 0.3 g of roasted K_2CO_3 in 7 ml of DMF was stirred at 20°C for 1 h. The reaction mixture was poured into water, the precipitate was filtered, washed with water, and dried in air.

1,2,4-Trifluoro-3-nitrophenoxazine (IVa) was purified by chromatography on a column with silica gel (L 100/160) in benzene. 1,2,4-Trifluoro-3-trifluoromethylphenoxazine (IVb) and 1,3,4-trifluoro-5H-pyrido[3,4-b][1,4]benzoxazine (IVc) were purified by sublimation at 150°C (4 mm). Analytical and spectral characteristics of compounds (IV) are shown in Table 2.

b) 0.2 g of amine (VIIIa) and 0.5 ml of NEt_3 in 5 ml of 20% aqueous DMF was stirred at 20°C for 1 h. The reaction mixture was poured into water, neutralized with 10% HCl, and extracted with ether. By evaporation of the ether there was obtained 0.2 g of a mixture containing (according to ^{19}F NMR spectral data) besides starting amine (VIa) and phenoxazine (IIIa), ~10% of compound (X).

Cyclization of Compound (IX). a) 0.2 g of K_2CO_3 and 0.2 g of compound (IXa) in 5 ml of DMF was stirred at 70°C for 1 h. The reaction mixture was poured into water, neutralized with 10% HCl, and extracted with ether. The product, obtained by evaporation of the ether, contained compounds (IVa) and (X) in the ratio of 70:30 (according to ^{19}F NMR spectral data). By TLC on silica gel (L 5/40) in $CHCl_3$ there was isolated phenoxazine (IVa) with 52% yield and difluoro-3-nitro-(1,2,4-trifluoro-3-nitrophenoxazinyl)phenoxazine (X) with 12% yield, mp of 316-318°C (from DMF). IR spectrum (ν , cm^{-1}): 3440 weak (NH). ^{19}F NMR spectrum in DMF (δ , ppm): 3.4 dd ($J_1 = 22$, $J_2 = 7$ Hz), 14.5 dd ($J_1 = 22$, $J_2 = 10$ Hz), 16.5 dd ($J_1 = 10$, $J_2 = 7$ Hz), 17.2 d ($J = 7$ Hz), 18.2 d ($J = 7$ Hz). Found: C 52.48; H 1.95; F 16.89; N 10.38%; mol. wt. 544. $C_{24}H_9F_5N_4O_6$. Calculated: C 52.95; H 1.67; F 17.45; N 10.29; mol. wt. 544.

b) By heating of 0.2 g of ether (IXb) under the conditions of the preceding experiment at 100°C there was obtained 0.18 g of a product containing compounds (IXb) and (IVb) in the ratio of 25:75 (according to ^{19}F NMR spectral data).

c) 0.2 g of compound (IXc) was stirred under the conditions of experiment (a). There was obtained 0.17 g of a mixture insoluble in organic solvents, from which, by sublimation at 170°C (4 mm) 0.04 g of a product was isolated which was identical by mp and IR spectrum with phenoxazine (IVc).

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