NUCLEOPHILIC REPLACEMENT OF FLUORINE IN TETRAFLUORODIBENZ[b,f]-[1,4]OXAZEPINES

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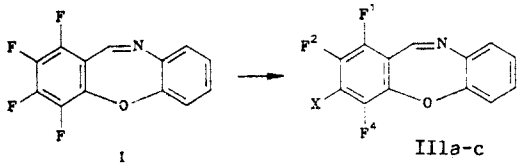
Tetrafluorodibenz[b,f][1,4]oxazepines react with piperidine, ammonia, and sodium methoxide with replacement of the fluorine atom in the para-position to the azomethine group.

Interest in dibenz[b,f][1,4]oxazepines arises from their broad spectrum of biological activity [1, 2], which can be modified by introducing substituents into the aromatic rings of the dibenzoxazepine system [3].

We have previously described a method for the synthesis of novel fluorinated dibenz[b, f][1,4]oxazepines [4, 5] in which the polyfluorinated aromatic ring may be attached to the carbon or nitrogen atom of the azomethine bond. Since the principal method used to introduce functional groups into polyfluoroaromatic compounds is by nucleophilic replacement of fluorine [6], we have now examined the reactions of 1,2,3,4-tetrafluoro- and 6,7,8,9-tetrafluorodibenz[b,f][1,4]-oxazepines (I) and (II) with nucleophiles, namely sodium methoxide, aqueous ammonia, and piperidine.



I IIIa-c

IIIa X=OMe b X=NC_5H_{10}, c X=NH_2

The reaction of (I) with sodium methoxide in methanol proceeds readily at room temperature, with replacement of one fluorine atom by methoxy to give a high yield of 3-methoxy-1,2,-4-trifluorodibenz[b,f][1,4]oxazepine (IIIa). Analogous reactions of (I) with piperidine in ethanol at 20°C and with 25% aqueous ammonia at 100°C afforded the 3-substituted compounds (IIIb, c).

The structures of (IIIa-c) were confirmed by their elemental analyses, ^1H and ^{19}F NMR spectra, and the close correspondence between the observed values of the ^{19}F chemical shifts and those calculated by the additive method (Table 1). The entry of the nucleophile into the position para- to the azomethine group is in accordance with accepted views regarding the orientation of nucleophilic replacement in the polyfluoroaromatic series [7].

The oxazepine (II), which bears fluorine atoms in the ring attached to nitrogen, in which the electron acceptor influence of the azomethine group is less pronounced, does not react with sodium methoxide at ambient temperatures. On boiling, a product was obtained which, from its elemental analysis and ^1H and ^{19}N NMR spectra was 7-methoxy-6,8,9-trifluorobenz[b,f][1,4]oxazepine (IVa).

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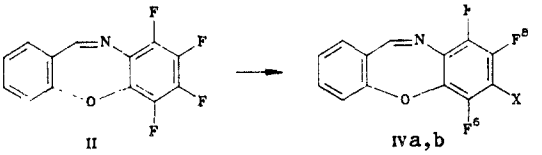
TABLE 1. Properties of Compounds Obtained

Compound	Empirical formula	mp, °C (ethanol)	PMR spectrum, σ, ppm ($CDCl_3$)
IIIa	$C_{14}H_8F_3NO_2$	81...83	4,10 (3H, s, CH_3); 7,24 (4H, br.s, Harom); 8,60 (1H, s, CH=N),
IVa	$C_{14}H_8F_3NO_2$	165...167	4,04 (3H, s, CH_3); 7,34 (4H, m, H arom); 8,50 (1H, s, CH=N)
IIIb	$C_{18}H_{15}F_3N_2O$	89...90 †	1,60 (6H, br.s, $3CH_2$); 3,27 (4H, br. s, $2CH_2$); 6,97...7,37 (4H, m, H arom); 8,57 (1H, s, CH=N)
IVb	$C_{18}H_{15}F_3N_2O$	71...72 †	1,67 (6H, br.s, $3CH_2$); 3,20 (4H, arom $2CH_2$); 7,10...7,50 (4H, m, H arom); 8,50 (1H, s, C=N)
IIIc	$C_{13}H_7F_3N_2O$	135...137	4,57 (2H, br. s, NH_2); 7,24 (4H, br. s, H arom); 8,54 (1H, s, CH=N)

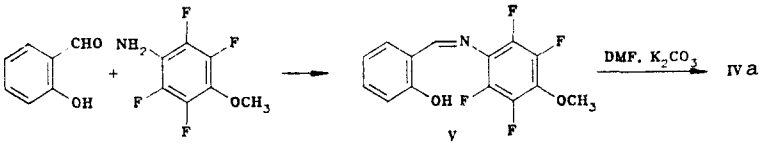
*Using the values of the substituent increments reported in [9, pentafluoro-2'-hydroxybenzylideneanilines [5].
†From n-hexane.



II IVa,b

IV a X=OMe, b X=NC_5H_{10}

Comparison of the chemical shifts of the fluorine atoms in the ^{19}F NMR spectrum with those calculated by the additive method (Table 1) did not enable the site of entry of the nucleophile to be established unambiguously, and the structure of (IVa) was therefore established by direct synthesis from 2,3,5,6-tetrafluoro-p-anisidine, as follows:



V IVa

The tetrafluorodibenzoxazepine (II) does not react with piperidine in alcohol at the boil, but heating with piperidine in dimethylformamide at 100°C affords 7-piperidino-6,8,9-tetrafluorodibenz[b,f][1,4]oxazepine (IVb). Compound (II) also fails to react with concentrated aqueous ammonia in a sealed ampul at 120°C, while heating above 150°C results in resinification.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in KBr disks. ^{19}F and ^{1}H NMR spectra were obtained on a Varian A56/60A at frequencies of 56.4 and 60 MHz respectively, internal standards hexafluorobenzene and HMDS. The properties of the products are shown in Table 1. The elemental analyses for C, H, N, and F were in agreement with the calculated values.

Reaction of Tetrafluorodibenz[b,f][1,4]oxazepines (I) and (II) with Sodium Methoxide.

A. To a solution of sodium methoxide, obtained from 0.045 g (2 mmole) of sodium and 9 ml of methanol, was added slowly 0.39 g (1.5 mmole) of (I) at a temperature not exceeding 20°C, and the mixture stirred for 30 min at 20°C. It was then poured into water, and the precipitated (IIIa) filtered off.

B. A mixture of 0.39 g (1.5 mmole) of (II) and a solution of sodium methoxide, prepared from 0.045 g (2 mmole) of sodium and 9 ml of methanol, was boiled for 1.5 h. The cooled mixture was then poured into water, and the precipitated (IVa) filtered off.

^{19}F NMR spectrum, σ, ppm (THF) (J_{FF}, HZ)	Calculated ^{19}F chemical shifts*	Yield, %
5,5 (2-F, d, J_{21}=21); 10,5 (4-F, d, J_{41}=11); 16,8 (1-F, d.d, J_{12}=21, J_{14}=11)	6,5; 12,5; 18,8	92
4,8 (8-F, d, J_{89}=21); 8,6 (6-F, d, J_{69}=9); 13,8 (9-F, d.d, J_{98}=21, J_{96}=9)	6,0; 12,0; 8,7	80
11,3 (2-F, d, J_{21}=20); 15,6 (1-F, d.d, J_{12}=20, J_{14}=10); 16,5 (4-F, d, J_{41}=10)	14,4; 18,2; 20,4	93
11,9 (8-F, d, J_{89}=20); 13,5 (9-F, d.d, J_{93}=20, J_{96}=8); 15,3 (6-F, d, J_{68}=8)	13,9; 8,1; 19,9	60
0,0 (2-F, d.d, J_{21}=21, J_{24}=10); 4,4 (4-F, t, J_{41}=J_{42}=10); 14,5 (1-F, d.d, J_{12}=21, J_{14}=10)	2,0; 8,0; 18,1	86

10] and those calculated from the ^{19}F NMR spectral data for

Direct Synthesis of 7-Methoxy-6,8,9-trifluorodibenz[b,f][1,4]oxazepine (IVa, $C_{14}H_9F_4NO_2$). A mixture of 2.5 g (8 mmole) of 2,3,5,6-tetrafluoro-p-anisidine [8] and 1.56 g (12 mmole) of salicylaldehyde was heated for 5 h at 140°C. The solid mass was extracted with n-hexane, and the solid filtered off, dissolved in benzene, and passed through a layer of silica (L 40-100 μm). Evaporation of the benzene solution gave 2.86 g (74%) of 4-methoxy-2,3,5,6-tetrafluoro-N-(2'-hydroxybenzylidene)aniline (V), mp 78-79°C (from alcohol). ^1H NMR spectrum ($CDCl_3$): 4.0 (3H, s, CH_3), 6.73-7.47 (4H, m, arom. H), 8.77 (1H, s, CH=N), and 12.33 ppm (1H, s, OH). ^{19}F NMR spectrum: 4.4 and 9.8 ppm.

A mixture of 0.6 g (2 mmole) of (V) and 0.6 g of anhydrous potassium carbonate in 4 ml of dry DMF was stirred for 5 h at 100°C, and poured into water. The solid which separated was filtered off, dried, dissolved in benzene, and passed through a layer of silica (L 40-100 μm). The eluent was evaporated to give 0.36 g (66%) of the oxazepine (IVa), identical with that obtained previously (mp, IR and ^{19}F NMR spectra).

Reaction of Tetrafluorodibenz[b,f][1,4]oxazepines (I) and (II) with Piperidine. A. To a solution of 0.54 g (2 mmole) of (I) in 20 ml of ethanol was added 0.8 ml (8 mmole) of piperidine, and the mixture kept for 48 h at ambient temperature. The mixture was then poured into water, acidified with HCl to pH 7, and the product which separated was extracted with chloroform. The chloroform was distilled off to a volume of 5-10 ml, and the residue passed through a layer of grade II alumina, eluent benzene. Evaporation of the benzene solution gave 0.62 g of (IIIb).

B. To a solution of 0.54 g (2 mmole) of (II) in 10 ml of DMF was added 0.8 ml (8 mmole) of piperidine. The mixture was heated for 3 h at 100°C, cooled, poured into water, acidified with dilute HCl to pH 7, and the solid which separated extracted with ether. The ether extract was dried over $CaCl_2$, the solvent removed, and the residue chromatographed on a column of silica (L 40-100 μm), eluent benzene. The second (yellow) fraction was collected, and evaporated to give 0.41 g of (IVb).

3-Amino-1,2,4-trifluorodibenz[b,f][1,4]oxazepine (IIIc). A mixture of 0.5 g of (I) and 10 ml of concentrated aqueous ammonia was heated for 9 h in a sealed ampul at 100°C. After cooling, the solid was filtered off, washed with water, air-dried, and chromatographed on a column of silica (L 40-100 μm), eluent benzene.

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SYNTHESIS AND STUDY OF 5a,6-DIHYDRO-12H-INDOLO[2,1-b][1,3]-BENZOXAZINES

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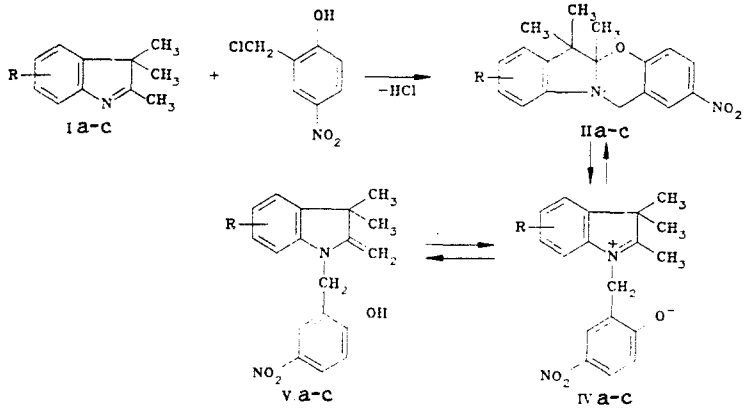
Reaction of 2,3,3-trimethyl-, 2,3,3,5- and 2,3,3,7-tetramethyl-3H-indoles with 4-nitro-2-chloromethylphenol has given the 5a,6-dihydro-12H-indolo-[2,1-b][1,3]-benzoxazines, which have been examined for ring-chain interconversion by NMR spectroscopy. Treatment of 5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazines with either perchloric acid or potassium hydroxide results in opening of the dihydro-oxazine ring with the formation of indole derivatives.

Methods have been reported for the annelation of heterocycles to 3-H-indole, by reacting 2,3,3-trimethyl-3H-indole or its salts with a variety of bifunctional compounds [1-4], and by reacting 2,3-dimethyl-1H-indole with 2-chloromethylphenols to give 2,3-dimethyl-3-(2-hydroxybenzyl)-3H-indolium salts, which undergo ready cyclization to benzypyranol[2,3-b]indoles [5].

We have now examined the reaction of the 3H indoles (Ia-c) with 4-nitro-2-chloromethyl-phenol.

It was found that 2,3,3-trimethyl-3H-indole (Ia) reacts with 4-nitro-2-chloromethylphenol to give the 5a,6-dihydro-12H-indolo[2,1-b][1,3]benzoxazine (IIa) in 60% yield, while the methylated indoles (Ib) and (Ic) gave (IIb) and (IIc) in yields of 27 and 15% respectively.



I IV, V a R=H; b R=5-CH_3; c R=7-CH_3; II a R=H; b R=8-CH_3; c R=10-CH_3

The ^1H NMR spectrum of (IIa) (in CCl_4) showed signals for the diastereotopic geminal methyl groups at 1.13 and 1.47 ppm (Fig. 1a), together with a singlet for the 5a-CH_3 at 1.52 ppm, situated in the cis-position with respect to the lone pair of the nitrogen [6]. When the ^1H NMR spectrum of (IIa) was recorded in $CDCl_3$, the signals for the geminal methyl groups underwent considerable broadening (Fig. 1b), and when 5-10% of methanol was added to the solution, they coalesced. Similar broadening of the signal for the carbon atoms of the geminal methyl groups was seen in the ^{13}C NMR spectrum (in $CDCl_3$), obtained with full

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