11-SUBSTITUTED POLYFLUORODIBENZ[b,f][1,4]OXAZEPINES

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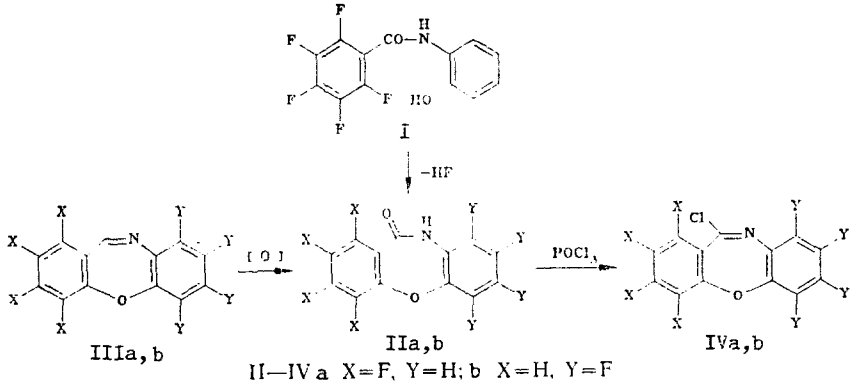
Tetrafluorodibenz[b,f][1,4]oxazepin-11-(10H)-ones have been synthesized and converted to 11-chloro and 11-piperidino substituted polyfluorodibenz[b,f][1,4]oxazepines.

Dibenz[b,f][1,4]oxazepines containing a substituted amino group in position 11 find use in medicine as neuroleptics and tranquillizers [1]. Their synthesis included intermediate 11-chlorodibenz[b,f][1,4]oxazepines obtained from the corresponding dibenz[b,f][1,4]oxazepin-11-(10H)-ones [2].

In this work we have studied the preparation of polyfluorodibenz[b,f][1,4]oxazepinones and their 11-substituted derivatives. In the nonfluorinated series of dibenzoxazepinones the most widely used synthetic method is the intramolecular cyclization of 2-hydroxybenzanilides containing a halogen in the 2' position [3]. We have previously shown [4, 5] that polyfluoro-2-hydroxybenzylidene anilines readily form dibenz[b,f][1,4]oxazepines upon heating in DMF through intramolecular nucleophilic substitution of the ortho fluorine atom. On this basis we hoped to obtain polyfluorodibenz[b,f][1,4]oxazepinones from polyfluoro-2-hydroxybenzanilides. However, it turns out that o-hydroxy-N-(pentafluorobenzoyl)aniline (I) (obtained from pentafluorobenzoyl chloride and o-aminophenol) was unchanged when refluxed in DMF or heated at 100°C in DMF with anhydrous KF. When carried out in the presence of anhydrous potash the reaction led to an unidentified high melting product, insoluble in polar organic solvents. Cyclization of I succeeded when sodium hydride was used as the condensing agent. The low yield of 1,2,3,4-tetrafluorodibenz[b,f][1,4]oxazepin-11-(10H)-one (IIa) and the formation of a side product insoluble in DMF may, in this case, be due to a preferred intermolecular nucleophilic substitution reaction leading to oligomers.

Oxidation of the previously synthesized tetrafluorodibenz[b,f][1,4]oxazepines IIIa,b [4, 5] proved more successful. It is known that ambiguous oxidation of their nonfluorinated analogs can take place [6] but use of six valent chromium compounds as oxidant opens the possibility of preparing dibenzoxazepinones [7]. We have found that refluxing IIIa,b with sodium bichromate in acetic acid [7] gives high yields of the oxazepinones IIa,b. In their IR spectra intense C=O and N–H absorptions are seen at 1695-1705 and 2980-3230 cm^{-1} respectively.

Tetrafluoro-11-chlorodibenz[b,f][1,4]oxazepines IVa, b were obtained from oxazepinones IIa, b by refluxing with phosphorus oxychloride in the presence of PCl_5 [7]. In the case of IIa the slower reaction is evidently due to the lowering of the reactivity of the carbonyl group by the adjacent fluorinated ring [8]. Use of N,N-dimethylaniline as catalyst (cf. [2]) leads to lower yields of 11-chloro compounds IVa, b.



II—IV a X=F, Y=H; b X=H, Y=F

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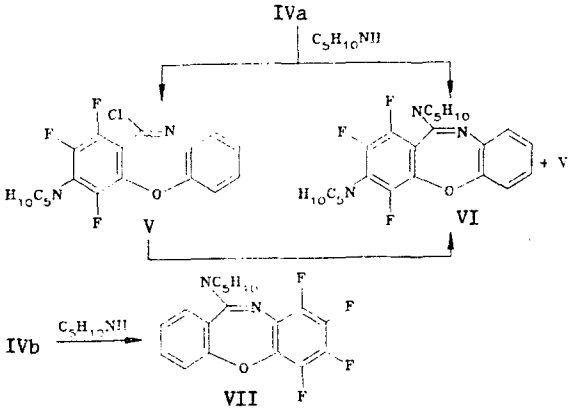
We have explored the possibility of forming 11-amino substituted derivatives by a study of the reaction of IVa,b with piperidine. In this case it is necessary to consider the presence of two nucleophilically mobile atoms in the molecules, i.e., the chlorine and the fluorine atoms in the aromatic ring. Compound IVa contains the fluorine atoms in the ring connected to the carbon of the C=N bond and reacts with piperidine in alcohol at room temperature to form 3-piperidino-11-chloro-1,2,4-trifluorodibenz[b,f][1,4]oxazepine (V) in quantitative yield. Its structure was proved by elemental analytical data and by IR and ^1H and ^{19}F NMR spectroscopy. The ^{19}F NMR spectrum showed three signals of equal intensity confirming substitution of one fluorine atom. Introduction of the piperidine ring in the position para to the electron acceptor group agrees with general orientation concepts in nucleophilic aromatic substitution [9] and is supported by comparison of the ^{19}F NMR chemical shifts with those calculated by an additive scheme.



Refluxing oxazepine IVa with piperidine in alcohol leads to substitution of both the 3-fluoro atom and the chlorine atom to form the bis(piperidino) product VI.

In oxazepine IVb the nucleophilic mobility of the fluorine atom is lower than in IVa and the reaction with piperidine in alcohol at 20°C gives 11-piperidino-6,7,8,9-tetrafluorodibenz-[b,f][1,4]oxazepine (VII).

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as KBr tablets. NMR spectra were taken on a Varian A-56/60A (60 and 56.4 MHz) in $CDCl_3$ and THF with HMDS and C_6F_6, respectively, as internal standards. Elemental analytical data for C, H, F, Cl, and N agreed with that calculated.

o-Hydroxy-N-(pentafluorobenzoyl)aniline (I, $C_{13}H_6F_5NO_2$). A solution of pentafluorobenzoyl chloride (5.5 g, 0.02 mole) in absolute ether (10 ml) was added dropwise at room temperature to o-aminophenol (5.0 g, 0.05 mole) in absolute ether (40 ml). After 10 min the reaction mixture was poured into water and the precipitated solid filtered off, washed with hot water and petroleum ether (40-70°C) to give I (5.2 g, 72%) with mp 216-217°C (from alcohol). IR spectrum: 1680 (C=O), 3310 cm^{-1} (N–H). ^1H NMR spectrum (DMSO-d_6): 6.54-7.04 (3H, m, H arom); 7.74-8.07 (1H, m, H arom); 9.97 and 10.14 ppm (1H, s, OH and 1H, s, NH). ^{19}F NMR spectrum: 1.0, 9.5, and 22.0 ppm; intensity ratio 2:1:2.

1,2,3-4-Tetrafluoro- and 6,7,8,9-Tetrafluorodibenz[b,f][1,4]-oxazepin-11-(10H)-ones (IIa, b). A. IIIa or IIIb (5.0 g) was added to a solution of sodium bichromate (5.0 g) in acetic acid (100 ml). The mixture was refluxed with stirring for 3 h, cooled, poured into water, and the precipitate filtered off, washed with water, and dried in air. It was then dissolved in chloroform and chromatographed on Al_2O_3 (activity grade II) to give IIa ($C_{13}H_5F_4NO_2$) in 72% yield with mp 245-247°C and ^{19}F NMR spectrum (DMF): 2.5, 0.0, 12.1, and 22.9 ppm. Compound IIb ($C_{13}H_5F_4NO_2$) (82%) had mp 247-249°C and ^{19}F NMR spectrum (DMF): 0.3, 4.4, and 12.2 ppm (peaks in the ration 2:1:1).

B. A solution of I (3.0 g, 0.01 mole) in DMF (30 ml) was added dropwise over 1 h and in an argon stream to sodium hydride (0.45 g, 0.02 mole) in DMF (70 ml). The reaction mixture was held for 3 h at 100°C, cooled, poured into water, and neutralized with hydrochloric acid. The precipitate was filtered off, dried (3.5 g), and Soxhlet extracted with benzene. Evaporation of solvent gave IIa (0.92 g, 32%). The residue after extraction (2.1 g) was insoluble in organic solvents and did not melt below 360°C.

11-Chloro-1,2,3,4- and 11-chloro-6,7,8,9-tetrafluorodibenz[b,f][1,4]oxazepines (IVa,b). A. Phosphorus pentachloride (1.5 g) was added to a solution of IIa or IIb (1.0 g) in phosphorus oxychloride (10 ml). The mixture was stirred at reflux for 6 and 2 h, respectively. The excess oxychloride was removed under vacuum (water pump) and the residue treated with a mixture of ice and ammonia solution. The precipitated solid was filtered off, washed with water and dried to give IVa and IVb in 85 and 95% yields, respectively.

B. A mixture of IIa (0.5 g), phosphorus oxychloride (7 ml), and dimethylaniline (0.2 ml) was refluxed for 6 h. Excess oxychloride was distilled off (water pump) and the residue treated with a mixture of ice and dilute ammonia. The solid was filtered off, washed with water, dried, dissolved in benzene, and chromatographed on SiO_2 (L 40-100 micron). Evaporation of solvent gave IVa with mp 74-75°C (from petroleum ether). ^{19}F NMR spectrum: 3.2 (2-F, dd, J_{21} = 22 Hz, J_{23} = 21 Hz); 6.2 (4-F, dd, J_{43} = 21 Hz, J_{41} = 10 Hz), 13.8 (3-F, td, $J_{34}=J_{32}$ = 21 Hz, J_{31} = 6 Hz) and 28.9 ppm (1-F, ddd, J_{12} = 22 Hz, J_{14} = 10 Hz, J_{13} = 6 Hz).

C. A mixture of IIb (0.20 g), phosphorus oxychloride (20 ml), and dimethylaniline (0.6 ml) was refluxed for 6 h and worked up as in experiment B to give IVb ($C_{13}H_4ClF_4NO$) (1.42 g, 67%) with mp 104-106°C (ethanol). ^{19}F NMR spectrum: 0.7, 3.7, 50.0, and 15.0 ppm.

Reaction of Oxazepines IVa,b with Piperidine. A. Piperidine (0.16 ml, 1.6 mmole) was added to a solution of oxazepine IVa (0.11 g, 0.4 mmole) in ethanol (10 ml). The mixture was stirred for 3 h at room temperature, poured into water, and extracted with ether. The ether layer was washed with dilute hydrochloric acid and water and dried over $CaCl_2$. Evaporation of the ether gave 11-chloro-3-piperidino-1,2,4-trifluorodibenz[b,f][1,4]oxazepine (V, 0.15 g, ~100%) with mp 131-133°C (ethanol.). IR spectrum: 2860, 2940 cm^{-1} (CH_2). ^{19}F NMR spectrum: 13.5 (15.6)* (2-F, d, J_{21} = 21 Hz); 16.3 (18.6)* (4-F, d, J_{41} = 10 Hz) and 26.2 (26.4)* ppm (1-F, dd, J_{12} = 21 Hz, J_{14} = 10 Hz). ^1H NMR spectrum: 1.56 (6H, br.s, 3 CH_2); 3.23 (4H, br. s, 2 CH_2) and 7.20 ppm (4H, br. s, H_{arom}).

B. Piperidine (0.45 ml, 4 mmole) was added to a solution of IVa (0.30 g, 1 mmole) in ethanol (10 ml) and refluxed for 2 h. The alcohol was distilled off and the residue washed with dilute hydrochloric acid, water, dried, and chromatographed on an SiO_2 column (L 40-100 micron) using benzene as eluent. The first fraction gave V (0.13 g, 35%) and the second gave 3,11-bispiperidino-1,2,4-trifluorodibenz[b,f][1,4]oxazepine (VI, $C_{23}H_{24}F_3N_3O$, 0.16 g, 40%) with mp 205-207°C (ethanol). IR spectrum: 2860, 2950 cm^{-1} (CH_2). ^{19}F NMR spectrum: 12.9, 17.6, and 22.2 ppm. ^1H NMR spectrum: 1.66 (12H, br. s, 6 CH_2), 3.26 (4H, br. s, 2 CH_2), 3.60 (4H, br. s, 2 CH_2), and 7.13 ppm (4H, m, H_{arom}).

C. Piperidine (0.27 ml, 3 mmole) was added to a solution of V (0.25 g, 0.7 mmole) in ethanol (10 ml) and refluxed for 6 h. The alcohol was evaporated and the residue washed with water and dried to give VI (0.24 g, 85%).

D. Piperidine (0.21 ml, 2 mmole) was added to a solution of oxazepine IVb (0.30 g, 1 mmole) in ethanol (10 ml) and held for 2 h at room temperature. The mixture was poured into water, extracted with ether, and the ether layer washed with dilute hydrochloric acid and water and dried over $CaCl_2$. Ether was evaporated off to give VII (0.30 g, 72%) with mp 107-109°C (ethanol). IR spectrum: 2860, 2950 cm^{-1} (CH_2). ^{19}F NMR spectrum: −5.3, −2.3, 0.9, and 10.1 ppm.

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*The parenthetic values are ^{19}F chemical shifts for the fluorine atoms calculated by an additive scheme using ^{19}F NMR data for IVa and $C_6F_5NC_5H_{10}$.

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FREE RADICAL CHLORINATION OF METHYL DERIVATIVES OF PYRIDINE, PYRAZINE, AND THIAZOLE BY N-CHLOROSUCCINIMIDE

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When methylazines (2-, 3-, and 4-methylpyridines, methylpyrazine) are treated with N-chlorosuccinimide they undergo successive chlorination of the methyl group to give 2-chloromethylpyridine, 2-dichloromethylpyridine, and dichloromethylpyrazine in preparative yields. 3-Dichloromethylpyridine was synthesized from pyridine-3-aldehyde and PCl_5. The primary chlorination products of 4-methylthiazole are 4-methyl-5-chlorothiazole and 5-chloro-4-chloromethylthiazole.

Dichloromethyl aromatic and heterocyclic compounds are precursors of aryl- and hetaryl-chlorocarbenes and -carbenoids which add to the C=C bond of alkenes to form cyclopropanes [1-3]. Various known methods for introducing halogen into the side chain of methylpyridines have been correlated in a review [4]. Different chlorination methods for picolines, Ia-c [4-7], including use of N-chlorosuccinimide (NCS) [7], lead to only small amounts of the dichloromethylpyridines IIIa-c which are found mixed with their mono- (IIa-c) or trichloromethyl analogs (IVa-c). Hence dichloromethyl derivatives are mainly obtained by indirect routes [8-10].

Dichloromethylpyrazine (IIId) could not be obtained by direct chlorination of methylpyrazine (Id); the product was chlorinated in the ring [11] or was the trichloromethylpyrazine (IVd) [12]. The action of one equivalent of NCS led to the chloromethylpyrazine (IId) [7, 11] but the dichloromethylpyrazine (IIId) necessitated a complex multistage synthesis [13, 14]. 4-Dichloromethylthiazole (IIIe) was obtained in a 1:1 mixture with 4-chloromethylthiazole by treating 4-methylthiazole (Ie) with PCl_3 and Cl_2 in oleum [15]. The reaction of Ie with NCS has not been studied.

Our work concerns the reaction of the available methyl heterocycles Ia-e with N-chlorosuccinimide with a view to preparing the dichloromethyl derivatives IIIa-e. The reaction was carried out in CCl_4 with benzoyl peroxide or UV irradiation for initiation. Methylpyrazine (Id) with excess NCS gave only the products of substituting methyl group hydrogens by chlorine (IId, IIId, IVd):

$$\underset{\text{Ia–d}}{\text{Het–CH}_3} \longrightarrow \underset{\text{IIa,b,d}}{\text{Het–CH}_2\text{Cl}} + \underset{\text{IIIa,b,d}}{\text{Het–CHCl}_2} + \underset{\text{IVa–d}}{\text{Het–CCl}_3}$$

I-IV a Het = 2-pyridyl, b Het = 3-pyridyl, c Het = 4-pyridyl, d Het = 2-pyridyl

Chromatography-mass spectrometry (CMS) and the PMR spectra of the reaction mixtures showed that the principal reaction products of Id with NCS are the monochloro and dichloromethylpyrazines (IId, j/z 128, M^+)* and (IIId, m/z 162, M^+), respectively. Small quantities of the trichloromethylpyrazine (IVd, m/z 196, M^+) were formed. Also present in the mixture (1-5%) were 2-methylchloropyrazine (m/z 128, M^+), isomeric with IId (but with an unidentified position for chlorine in the ring) and two chloro derivatives (m/z 162 M^+) isomeric with IIId which,

*Here, and elsewhere, the mass spectrometric peaks are for the ^{35}Cl isotope.

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