SYNTHESIS OF FLUOROSUBSTITUTED 10,11-DIHYDRODIBENZ[b,f][1,4]OXAZEPINES

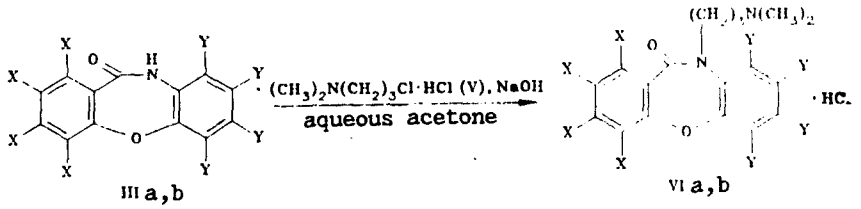
A. V. Konstantinova, O. D. Zbrovskaya, and T. N. Gerasimova

UDC 547.892'539.1.07

The synthesis of a series of polyfluorinated derivatives of 10,11-dihydrodibenz[b,f][1,4]oxazepine and dibenz[b,f][1,4]oxazepine-11(10 H)-one has been effected.

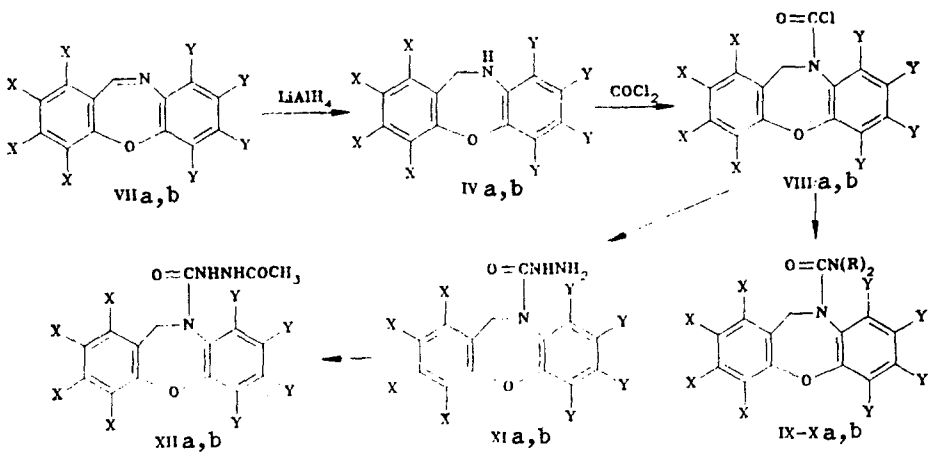
Compounds of the dibenz[b,f][1,4]oxazepine series display psychotropic properties [1]. Their 10,11-dihydro derivatives, in particular 10-[3-(dimethylamino)propyl]-2-nitrodibenz[b,f][1,4]oxazepine oxazepine-11(10H)-one (I) and 10-carbamoyl-3-chloro-10,11-dihydrodibenz[b,f][1,4]oxazepine oxazepine (II), are used in medicine [2-4].

Previously, we described a method of synthesizing 1,2,3,4- and 6,7,8,9-tetrafluorodibenz[b,f][1,4]oxazepine oxazepine-11(10H)-ones (IIIa, b) [5], and also 10,11-dihydro-1,2,3,4-tetrafluorodibenz[b,f][1,4]oxazepine (IVa) [6, 7]. In the present work we have investigated the possibility of obtaining polyfluorinated derivatives of a number of 10,11-dihydrodibenz[b,f][1,4]oxazepine oxazepines of the type I and II.



III, VI a X=F, Y=H; b X=H, Y=F

Fluorine-containing analogs of compound I were obtained by boiling tetrafluorodibenzoxazepine IIIa, b with the hydrochloride of 3-(dimethylamino)propyl chloride (V) in acetone in the presence of an aqueous solution of base according to the procedure in [2]. The low yields of end products VIa, b are due to the considerable reduction of the basicity of the amide NH



IV, VII—XII a X=F, Y=H; b X=H, Y=F; IX R=H; X R=CH_3

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1679-1682, December, 1990. Original article submitted April 24, 1989; revision submitted September 19, 1989.

0009-3122/90/2612-1396$12.50

group in the starting polyfluorodibenzoxazepinones, IIIa, b, caused by the acceptor action of the four fluorine atoms. Lengthening the reaction time does not increase the yield. Compound IIIb shows this effect to the greatest extent; it has a fluorinated ring directly attached to the nitrogen atom.

The synthesis of tetrafluorosubstituted 10-carbamoyl-10,11-dihydrodibenz[b,f][1,4]oxazepines includes the subsequent reduction of tetrafluorodibenz[b,f][1,4]oxazepines VIIIa, b [6] in absolute ether by the procedure in [7], the reaction of the dihydro derivatives formed, IVa, b, with a solution of phosgene in toluene by the procedure in [4], and the reaction of 10-carbonyl chlorides VIIIa, b with ammonia, dimethylamine, and hydrazine hydrate.

The structures of the compounds synthesized were confirmed by elemental analysis, IR, PMR, and ^{19}F-NMR spectroscopy, and mass spectrometry.

Samples of fluorosubstituted 10,11-dihydrodibenz[b,f][1,4]oxazepines have been sent to be tested for biological activity.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument, in KBr pellets. PMR and ^{19}F-NMR spectra were recorded on a Varian A 56/60 A instrument (60 and 56.4 MHz). Solvents were $CDCl_3$ and THF, internal standards were HMDS and C_6F_6, respectively. Molecular weights were determined on a Finnigan MAT 8200 instrument.

The elemental analyses for C, H, Cl, F, and N in compounds IVb, VIa, b, VIIIa, b, IXa, b, Xa, b, XIa, b, and XIIa, b agreed with the calculated values.

10-[3-(Dimethylamino)propyl]-1,2,3,4-tetrafluorodibenz[b,f][1,4]oxazepine-11(10H)-one Hydrochloride (VIa, $C_{18}C_{16}F_4N_2O_2 \cdot HCl$). A solution of 0.71 g (0.25 mmole) of compound IIIa in 7 ml of acetone is treated with 1.2 ml of 2.3 N aqueous NaOH, heated to 60°C, and a solution of 0.40 g (0.25 mmole) of the hydrochloride of compound V in 1.2 ml of 2.3 N NaOH aqueous is added. This is boiled for 5 h with two portions of 0.40 g of compound V in 1.2 ml of 2.3 N aqueous NaOH being added. The acetone is distilled off under vacuum, and the residue treated three times with 20 ml of ether. The ethereal extract is washed with water until the washings test neutral, then dried with $CaCl_2$ and concentrated to a volume of ~20 ml. The initial product that precipitates is filtered off. Dry, gaseous hydrogen chloride is passed through the filtrate, and the sticky precipitate that forms is triturated with absolute ether and recrystallized from ethyl acetate. Yield 0.39 g (39%) of compound VIa. T_{mp} 180-183°C. IR spectrum 1680 cm^{-1} (C=O). PMR spectrum: 2.33 (2H, m, CH_2); 2.70 (6H, b.s, $2CH_3$); 3.30 (2H, m, CH_2); 4.30 (2H, m, CH_2); 7.06-7.70 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: 2.7, 4.4, 12.4, 23.6 ppm. Mass spectrum: 368 (M^+).

10-[3-(Dimethylamino)propyl]-6,7,8,9-tetrafluorodibenz[b,f][1,4]oxazepine-11(10H)-one (VIb, $C_{18}H_{16}F_4N_2O_2 \cdot HCl$) hydrochloride is obtained from compound IIIb in a similar way in 7% yield. T_{mp} 126-129°C. IR spectrum: 1670 cm^{-1} (C=O). PMR spectrum: 2.33-2.40 (6H, $3CH_2$), 2.86 (6H, s, $2CH_3$), 7.06-7.86 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum ($CDCl_3$): 2.7, 5.1, 19.3 ppm. Intensity ratio 1:2:1. Mass spectrum: 368 (M^+).

6,7,8,9-Tetrafluoro-10,11-dihydrodibenz[b,f][1,4]oxazepine (IVb, $C_{13}H_7F_4NO_2$). 0.06 g (15 mmoles) of $LiAlH_4$ is stirred into 150 ml of absolute ether, 4.00 g (15 mmoles) of compound VIIb is added, and the mixture is held for 2 h at room temperature, then poured onto 100 g of ice with 50 ml of 20% HCl and extracted with ether (3 × 50 ml). The ethereal solution is washed with water until the washings test neutral, dried with $CaCl_2$, and evaporated to dryness. Yield 3.0 g (73%) of compound IVb. T_{mp} 97-98°C (from ethanol). IR spectrum: 3430 cm^{-1} (N–H). PMR spectrum: 4.10 (1H, b.s, NH), 4.51 (2H, d, J = 4 Hz, CH_2), 7.16 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: –13.7, –3.9, –0.4, 3.0 ppm.

1,2,3,4-Tetrafluoro-10-chlorocarbonyl-10,11-dihydrodibenz[b,f][1,4]oxazepine (VIIIa, $C_{14}H_6ClF_4NO_2$). A solution of 4.00 g (15 mmoles) of compound IVa and 1.50 g (15 mmoles) of triethylamine in a mixture of 15 ml of ether and 15 ml of methylene chloride is cooled to 0°C and 13.00 g (20 mmoles) of an 18% solution of phosgene in toluene is added dropwise. The mixture is held at 5°C for 1 h and kept overnight at 20°C. The precipitate is filtered off the filtrate washed with 50 ml of water, and the organic phase separated and evaporated to dryness. Yield is 3.62 g (72%) of compound VIIIa. T_{mp} 151-153°C. IR spectrum: 1720 cm^{-1} (C=O). PMR spectrum: 5.03 (2H, m, CH_2), 7.36 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: –1.8, 5.5, 18.8 ppm. Intensity ratio 1:2:1.

6,7,8,9-Tetrafluoro-10-chlorocarbonyl-10,11-dihydrodibenz[b,f][1,4]oxazepine (VIIIb, $C_{14}H_6ClF_4NO_2$). A solution of 2.96 g (11 mmoles) of compound IVb and 1.10 g of (11 mmoles) triethylamine in 5 ml of ether and 10 ml of methylene chloride is cooled to 0°C, and 12.00 g (15 mmoles) of a 12% solution of phosgene in toluene is added dropwise with stirring. The mixture is held at 5°C for 1 h and kept overnight at 20°C. The reaction mixture is poured into 50 ml of water and extracted with ether (3 × 20 ml). The ethereal extract is washed with water (2 × 50 ml), dried with $CaCl_2$, and the solvent distilled off. Yield is 2.00 g (54%) of compound VIIIb. T_{mp} 69-71°C (from hexane). IR spectrum: 1750 cm^{-1}

(C=O). PMR spectrum: 4.36 (1H, d, J = 18 Hz, CH), 5.50 (1H, d, J = 18 Hz, CH), 6.90-7.33 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: 0.5, 6,7, 8.3, 17.0 ppm.

1,2,3,4-Tetrafluoro-10-carbamoyl-10,11-dihydrodibenz[b,f][1,4]oxazepine (IXa, $C_{14}H_8F_4N_2O_2$). To a solution of 0.70 g (2 mmoles) of compound VIIIa in a mixture of 20 ml of methylene chloride and 10 ml of ether is added 2 ml of 25% aqueous ammonia, and the mixture is held at 20°C for 14 h. The solvent is distilled off, and the precipitate formed is filtered off and washed with water to a pH of 7.0. Yield 0.62 g (94%) of compound IXa. T_{mp} 173-175°C. IR spectrum (in CCl_4): 1690 (C=O), 3420 and 3480 cm^{-1} (NH_2). PMR spectrum: 4.93 (4H, CH_2, and NH_2), 7.36 ppm (4H, H_{arom}). ^{19}F-NMR spectrum: –2.7, 3.5, 5.1, 18.4 ppm. Mass spectrum: 312 (M^+).

6,7,8,9-Tetrafluoro-10-carbamoyl-10,11-dihydrodibenz[b,f][1,4]oxazepine (IXb, $C_{14}H_8F_4N_2O_2$) is obtained similarly to compound IXa from compound VIIIb in a yield of 90%. T_{mp} 200-201°C (from ethanol). IR spectrum: 1680 (C=O), 3330 and 3460 cm^{-1} (NH_2). PMR spectrum (DMSO-d_6): 487 (2H, b.s, CH_2), 6.37 (2H, b.s, NH_2), 7.17 ppm (4H, b.s, H_{arom}). ^{19}F-NMR: –0.7, 4.3, 5.5, 17.0 ppm. Mass spectrum: 312 (M^+).

1,2,3,4-Tetrafluoro-10-N,N-dimethylcarbamoyl-10,11-dihydrodibenz[b,f][1,4]oxazepine (Xa, $C_{16}H_{12}F_4N_2O_2$). To a solution of 0.50 g (1.5 mmoles) of compound VIIIa in 50 ml of methylene chloride is added 3 ml of a 33% aqueous solution of dimethylamine, and the mixture is held for a day at 20°C. The solvent is distilled off and the residue triturated with 20 ml of water, filtered off, washed with water, and dried. Yield 0.40 g (80%) of compound Xa. T_{mp} 99-101°C (from hexane). IR spectrum: 1670 cm^{-1} (C=O). PMR spectrum: 2.67 (6H, s, $2CH_3$), 4.88 (2H, b.s, CH_2), 720 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: –2.8, 3.4, 18.1, 4.4 ppm. Mass spectrum: 340 (M^+).

6,7,8,9-Tetrafluoro-10-N,N-dimethylcarbamoyl-10,11-dihydrodibenz[b,f][1,4]oxazepine (Xb, $C_{16}H_{12}F_4N_2O_2$) is obtained similarly to compound Xa from compound VIIIb in 95% yield. T_{mp} 143.5-144.5°C (from methanol). IR spectrum (in CCl_4): 1680 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 2.58 (6H, s, $2CH_3$), 4.60 (2H, s, CH_2), 6.50-6.91 ppm (4H, m, H_{arom}). ^{19}F-NMR (CF_3COOH): 1.4, 6.7, 7.9, 12.9 ppm. Mass spectrum: 340 (M^+).

1,2,3,4-Tetrafluoro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-carboxylic Acid Hydrazide (XIa, $C_{14}H_9F_4N_3O_2$). To a solution of 0.32 g (1 mmole) of compound VIIIa in a mixture of 6 ml of methylene chloride and 6 ml of ether is added 0.2 ml (4 mmoles) of 100% hydrazine hydrate, and the mixture is held for 1 h at 20°C. The reaction mixture is diluted with 50 ml of water, acidified with a 10% solution of HCl to the neutral point, and extracted with ether (3 × 20 ml). The ether extract is washed with water (2 × 50 ml), dried with $CaCl_2$, and the ether distilled off. Yield 0.25 g (81%) of compound XIa. T_{mp} 155-157°C. IR spectrum: 1680 (C=O), 3200-3500 cm^{-1} ($NHNH_2$). PMR spectrum: 3.63 (2H, b.s, NH_2), 5.00 (2H, s, CH_2), 5.93 (1H, b.s, NH), 7.33 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: –2.5, 3.7, 5.0, 18.4 ppm. Mass spectrum: 327 (M^+).

6,7,8,9-Tetrafluoro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-carboxylic Acid Hydrazide (XIb, $C_{14}H_9F_4N_3O_2$) is obtained similarly to hydrazide XIa from compound VIIIb. 94% yield. T_{mp} 79-82°C (from hexane). IR spectrum: 1680 (C=O), 3200-3500 cm^{-1} ($NHNH_2$). PMR spectrum: 3.48 (2H, m, NH_2), 4.88 (2H, s, CH_2), 6.30 (1H, m, NH), 7.01-7.25 ppm (4H, m, H_{arom}). ^{19}F-NMR spectrum: –1.2, 3.9, 5.1, 16.3 ppm. Mass spectrum: 327 (M^+).

1,2,3,4-Tetrafluoro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-carboxylic Acid N'-Acetylhydrazide (XIIa, $C_{16}H_{11}F_4N_3O_3$). A suspension of 0.60 g (2 mmoles) of compound XIa in 2 ml of acetic anhydride is heated for 15 min at 90-100°C. The reaction mixture is cooled, and the precipitate filtered off, washed with water until neutral, and dried. Yield 0.40 g (60%) of compound XIIa. T_{mp} 234-235°C. IR spectrum: 1640, 1690 cm^{-1} (C=O). ^{19}F-NMR spectrum (DMSO-d_6): –2.3, 4.3, 18.6 ppm. Intensity ratio 1:2:1. Mass spectrum: 369 (M^+).

1,2,3,4-Tetrafluoro-10,11-dihydrodibenz[b,f][1,4]oxazepine-10-carboxylic Acid N'-Acetylhydrazide (XIIb, $C_{16}H_{11}F_4N_3O_3$) is obtained similarly to compound XIIa from hydrazide XIb in 89% yield. T_{mp} 112-115°C (from ethanol). IR spectrum: 1660 and 1680 cm^{-1} (C=O). PMR spectrum: 1.83 (3H, s, CH_3), 4.86 (2H, s, CH_2), 7.10 (4H, m, H_{arom}), 8.00 (1H, m, NH), 8.60 ppm (1H, m, NH). ^{19}F-NMR spectrum: 0.0, 5.3, 18.1 ppm. Intensity ratio 1:2:1. Mass spectrum: 369 (M^+).

LITERATURE CITED

1. K. Nagarajan, *Stud. Org. Chem.* (Amsterdam), **3**, 317 (1979).
2. K. Nagarajan, A. Venkateswarlu, C. L. Kulkarni, A. Goud Nagana, and R. K. Shah, *Ind. J. Chem.*, **12**, 236 (1974).
3. K. Nagarajan, R. K. Maller, and B. Anjaneyulu, *Ind. J. Chem.*, **12**, 270 (1974).
4. K. Nagarajan, J. David, and G. A. Bhat, *Ind. J. Chem.*, **24B**, 840 (1985).

5. A. V. Konstantinova, T. N. Gerasimova, M. M. Kozlova, and N. I. Petrenko, *Khim. Geterotsikl. Soedin.*, No. 4, 539 (1989).
6. N. I. Petrenko and T. N. Gerasimova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 2, 477 (1986).
7. N. I. Petrenko, M. M. Kozlova, and T. N. Gerasimova, *J. Fluor. Chem.*, **36**, 93 (1987).

CRYSTAL, MOLECULAR, AND π-ELECTRONIC STRUCTURE OF 1,3,2-BENZODITHIAZOLIUM CHLORIDE

A. V. Zibarev, I. Yu. Bagryanskaya, Yu. V. Latilov, L. N. Shchegoleva, G. N. Dolenko, and G. G. Furin

UDC 548.737:547.794.3.07

X-Ray diffraction examination and MNDO calculations have shown that 1,3,2-benzodithiazolium chloride (I) is ionic, with a planar heteroaromatic 10π-electron cation. The π–MO of the cation (I) is isolobal with the p-MO of benzo-2,1,3-thiadiazole. In the cation of (I), as in the latter compound, the p-AO of nitrogen and sulfur contribute for the most part to π-MO of differing symmetry (b_1 and a_2, respectively). This has the consequence that although both nitrogen and sulfur participate in the formation of a single π-system in the thiazolium cation of (I), there is virtually no π-bonding between them. Generally speaking, the π-MO of the (I) cation shows a tendency to localization on separate molecular fragments. The charge on the cation is localized at the SNS group, and the five-membered ring is strongly polarized. These features all reduce the heteroaromaticity of the system.

1,3,2-Benzodithiazolium chloride (I), a rational synthesis of which is by reaction of 1,2-bis(chlorosulfenyl)benzene with trimethylsilazane [1], is readily reduced to the 1,3,2-benzodithiazyl radical, which forms with tetracyanoquinodimethane a CTC with the properties of a synthetic metal [1, 2]. Benzobis(1,3,2-dithiazolium) salts (II) behave similarly [3, 4]. Neither the synthetic metals incorporating the benzodithiazolium system, nor the salts (I) and (II) have, however, been examined with respect to structure.

The cation of (I) is isomeric with that of Herz salts (1,2,3-benzothiadiazolium halides [5-7]). Unlike Herz salts, however, which are unstable to atmospheric moisture, light, and heat, (I) is very stable. It is stable on storage under normal conditions for periods of a year, and according to thermogravimetry, it melts at 220°C without decomposition (the maximum for the exothermic decomposition on the DTA plot occurs at 270°C). The most closely related analog of the (I) cation to have been examined, the 4-methyl-1,3,2-dithiazolium hexafluoroarsenate cation (III), has a planar structure [8]. The PMR and ^{13}C NMR spectra of (I) [9] likewise do not conflict with a planar structure for the cation with C_{2v} symmetry; the PMR chemical shifts, which are substantially greater than those for 1,2,3-benzodithiazolium chloride [7] and 1,3-benzodithiolium perchlorate (IV) [10], could indicate considerable charge delocalization in the (I) cation. It my be assumed that the (I) cation, which has ten π-electrons, is heteroaromatic, whereas the cations of Herz salts (which likewise have not been investigated structurally up to the present time) are not heteroaromatic, for example as a result of their nonplanar geometry.

The aim of the present investigation was to examine the crystal, molecular, and π-electronic structure of (I), previously obtained by us [9] by reacting N,N,N',N'-tetrakis(trimethylsilyl)-1,2-bis(sulfenylamino)benzene with selenium tetrachloride.

An x-ray diffraction examination of (I) was carried out (Figs. 1 and 2; Tables 1 and 2). The nonhydrogen atoms in the (I) cation lie in the same plane to within ±0.037 Å. The five- and six-membered rings are individually planar to within ±0.018 Å, the angle between their planes being 1.8°. The mean C–C bond length is 1.396 Å, ranging from 1.366(6) to 1.413(5) Å,

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1683-1688, December, 1990. Original article submitted June 26, 1989.

0009-3122/90/2612-1399$12.50