1,4-BENZODIAZEPINES AND THEIR CYCLIC HOMOLOGS AND ANALOGS.

XX.* SYNTHESIS AND PROPERTIES OF 1,4-BENZODIAZEPINES WITH FLUORINE-CONTAINING SUBSTITUENTS

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5-Difluoromethylsulfonyl-2-aminobenzophenone was synthesized by condensation of p-difluoromethylsulfonylaniline with benzoyl chloride. 5-Difluoromethoxy- and 5-difluoromethylthio-2-aminobenzophenones were obtained by condensation of phenylacetonitrile with the appropriate p-substituted nitrobenzenes and subsequent reduction of the resulting anthranils. 7-Difluoromethoxy-, 7-difluoromethylthio-, and 7-difluoromethylsulfonyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones were obtained by the successive action of bromoacetyl bromide and ammonia on the 2-aminobenzophenone derivatives or by reaction of 2-aminobenzophenones with aminoacetyl chloride hydrochloride. The structure of the 1,4-benzodiazepines was confirmed by a study of the UV, IR, PMR, and mass spectra.

It has been shown that the replacement of a hydrogen atom by a nitro group or by halogen atoms in 1,2-dihydro-3H-1,4-benzodiazepines gives effective tranquilizers [2]. 7-Fluoro-, 7-trifluoromethyl-, 7-trifluoromethoxy-, and 7 trifluoromethylithio-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones have high activity [3-5]. The correlations found between the structure and the psychotropic activity of dihydro-1,4-benzodiazepinones [6] have made it possible to assume that the introduction of various substituents that approach the halogens and the nitro group with respect to the electron-shift effects induced by them may lead to the preparation of new effective preparations.

We therefore undertook the synthesis of 1,4-benzodiazepines with difluoromethoxy, difluoromethylthio, and difluoromethylsulfonyl groups in the 7 position. In attempting this, we took into account the fact that difluoromethoxy and difluoromethylthio groups can be considered to be "pseudohalogens" (the Hammett σ_m and σ_p constants of these substituents are 0.31 and 0.18 for the $OCHF_2$ group and 0.33 and 0.36 for the $SCHF_2$ group) [7, 8]. The electronic nature of the difluoromethylsulfonyl group is close to that of the NO_2 group (the Hammett σ_m and σ_p constants are, respectively, 0.75 and 0.86 [8, 9]).

We found it necessary to obtain substituted 2-aminobenzophenones (Ia-c) as intermediates. Compound Ic was obtained by condensation of p-difluoromethylsulfonylaniline with benzoyl chloride in the presence of anhydrous zinc chloride by a known method [6]. However, we were unable to synthesize Ia and Ib by this method. Condensation of p-difluoromethoxy- and difluoromethylthioacetanilides with benzoyl chloride under various conditions of the Friedel–Crafts reaction also did not give satisfactory results. A method [10] previously used for the synthesis of chloro, methoxy, trifluoromethoxy, and trifluoromethylthio derivatives of 2-aminobenzophenone [5] proved to be more successful. More precisely, anthranils (IIa, b, see Table 1), the reduction of which with iron in acetic acid gives aminobenzophenones Ia and Ib, were obtained by condensation of p-substituted nitrobenzenes with phenylacetonitrile.

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*See [1] for communication XIX.

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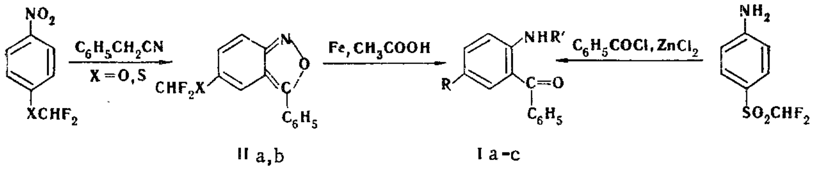
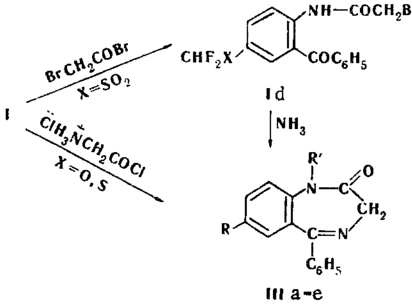
TABLE 1. Difluoromethoxy- Difluoromethylthio-, and Difluoromethylsulfonylanthranils, Aminobenzophenones, and 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones

Compound	R	R′	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	F	N	C	H	F	N	
Ia	F_2CHO	H	97—98 (benzene)	$C_{14}H_{11}F_2NO_2$	64,1	4,1	14,6	5,2	64,0	4,2	14,4	5,1	79
Ib	F_2CHS	H	67—68 (benzene)	$C_{14}H_{11}F_2NOS$	60,2	3,9	13,7	4,9	60,0	3,9	13,6	5,0	81
Ic	F_2CHSO_2	H	174—175 (benzene)	$C_{14}H_{11}F_2NO_3S$	53,7	3,6	12,1	4,4	53,8	3,6	12,2	4,5	40
Id	F_2CHSO_2	$COCH_2Br$	127—128 (benzene)	$C_{16}H_{12}BrF_2NO_4S$	44,0	2,8	8,7	3,2	44,2	2,7	8,8	3,1	80
IIa	F_2CHO	—	76—78 (ethanol)	$C_{14}H_9F_2NO_2$	64,4	3,3	14,5	5,0	64,5	3,4	14,6	5,3	50
IIb	F_2CHS	—	130—131 (methanol)	$C_{14}H_9F_2NOS$	60,4	3,1	13,8	5,1	60,6	3,2	13,7	5,0	37
IIIa	F_2CHO	H	182—183 (toluene)	$C_{16}H_{12}F_2N_2O_2$	63,5	3,9	12,6	9,2	63,6	4,0	12,6	9,2	70
IIIb	F_2CHS	H	174—175 (toluene)	$C_{16}H_{12}F_2N_2OS$	60,5	3,7	12,0	8,7	60,5	3,8	11,9	8,8	84
IIIc	F_2CHSO_2	H	247—248 (ethanol)	$C_{16}H_{12}F_2N_2O_3S$	54,8	3,5	10,7	8,0	54,8	3,4	10,8	8,0	46
IIId	F_2CHS	CH_3	123—124 (ether—petroleum ether)	$C_{17}H_{14}F_2N_2OS$	61,5	4,3	11,4	8,4	61,5	4,2	11,5	8,4	69
IIIe	F_2CHSO_2	CH_3	140 (ether—petroleum ether)	$C_{17}H_{14}F_2N_2O_3S$	56,2	3,6	10,4	7,7	56,1	3,8	10,5	7,7	70



The structure of I was confirmed by the IR spectra. Thus the the band at 1645 cm^{-1} in the spectrum of Ia corresponds to the stretching vibrations of the carbonyl group, and the two bands at 3490 and 3333 cm^{-1} correspond to the asymmetrical and symmetrical vibrations of a primary amino group.

5-Difluoromethylsulfonyl-2-bromacetamidobenzophenone (Id) was obtained by reaction of aminobenzophenone Ic with bromoacetyl bromide. Treatment of Id with a methanol solution of ammonia under the conditions in [11] gave benzodiazepinone IIIc (Table 1). Compounds IIIa and IIIb (Table 1) were obtained by condensation of aminobenzophenones Ia and Ib with aminoacetyl chloride hydrochloride under conditions close to those described in [12].



The reaction of sodium salts of IIIa and IIIb with dimethyl sulfate gave their 1-methyl derivatives IIId and IIIe (Table 1).

The IR spectra of III contain the absorption band of a lactam carbonyl group at 1695-1705 cm^{-1}. The bands of NH groups that are usual for such systems are observed in the spectra of 1-unsubstituted IIIa-c at 3175-3390 cm^{-1}.

The UV spectra of solutions of III in ethanol (Fig. 1) contain two absorption bands at λ_{max} 315-317 nm (log ε 3.4) and 225-228 nm (log ε 4.5). Changes similar to those previously described for 1,2-dihydro-3H-1,4-benzodiazepin-2-ones [11] are observed in the spectra as the pH changes.

A singlet band of protons of a methylene group is observed in the PMR spectra of IIIa-c, and this constitutes evidence for rapid inversion of the diazepine ring. The signal of the methylene protons in the spectra of IIId and IIIe is a quartet because of slowed down inversion.

Ion peaks with m/e 350 (85.4%) (M^+), 349 (86.6%) ($M^+ - H$), 322 (100%) ($M^+ - CO$), 323 (39.7%) ($M^+ - HCN$), 234 (72.2%) ($M^+ - H$) − SO_2CHF_2 etc. are noted in the mass spectrum of benzodiazepine IIIc, and this also confirms the structure of this substance. The structure of IIa, b, d, e was similarly confirmed.

EXPERIMENTAL

The UV spectra were recorded under the conditions in [11]. The mass spectra were obtained in the laboratory of nitrogen bases of Moscow State University with an MKh-1303 spectrometer at an

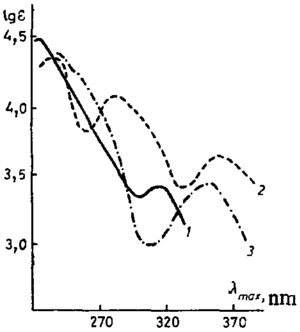


Fig. 1. UV spectra of IIIa at: 1) pH 6.5; 2) pH 1.5; 3) pH 13.5.

ionizing electron energy of 50 eV. The authors thank Professor A. N. Kost and his co-workers for recording the spectra and for their assistance in their interpretation. The IR spectra of CCl_4 solutions of the compounds were recorded with an IKS-14A spectrometer.

3-Phenyl-5-difluoromethylthioanthranil (IIb). A 6.5-g (0.056 mole) sample of phenylacetonitrile and a solution of 10.5 g (0.051 mole) of p-nitrodifluoromethylthiobenzene in 80 ml of methanol were added with stirring and cooling (to 0-5°) to a solution of 56 g (1.4 mole) of KOH in 120 ml of methanol, after which the mixture was stirred at 0-5° for 4 h. It was then diluted with 320 ml of water, and the resulting precipitate was removed by filtration, washed with water to neutrality, and dried. Compound IIa was similarly obtained.

2-Amino-5-difluoromethylsulfonylbenzophenone (Ic). A mixture of 14 ml (0.05 mole) of benzoyl chloride, 10.4 g (0.05 mole) of 4-difluoromethylsulfonylaniline, and 8.6 g (0.065 mole) of anhydrous zinc chloride was heated to 195-200° and maintained at this temperature for 2 h, after which it was cooled to 120-130° and washed with 50 ml of water. A mixture of the resulting precipitate and 60 ml of 70% (by weight) sulfuric acid was heated to the boiling point and held at this temperature for 40-45 min. The reaction mixture was then poured over ice, and the resulting precipitate was removed by filtration and washed successively with water to neutrality, 50 ml of 10% NaOH (two to three times), and water to neutrality.

2-Amino-5-difluoromethylthiobenzophenone (Ib). A solution of 2.0 g (0.076 mole) of 3-phenyl-5-difluoromethylthioanthranil in 20 ml of acetic acid was heated on a warm water bath for 2.5 h. During this period, 3 g (0.064 mole) of iron filings and 4.5 ml of water were added. The mixture was then cooled, diluted with water, and extracted with ether. The ether extracts were washed with water, dried, and concentrated in vacuo. Compound Ia was similarly obtained.

5-Difluoromethylsulfonyl-2-bromoacetamidobenzophenone (Id). A 1.3-g (6.42 mmole) sample of bromoacetyl bromide was added dropwise to a solution of 1 g (3.21 mmole) of 5-difluoromethylsulfonyl-2-aminobenzophenone in 15 ml of boiling anhydrous benzene (heating was discontinued). The solution was then refluxed for 3 h, after which it was poured into 20 ml of ice water. The excess bromacetyl bromide was decomposed by the addition of 1 N sodium hydroxide solution until the mixture was weakly alkaline. The grayish precipitate (A) was removed by filtration, washed with water and benzene, and dried. The benzene solution was washed with water, dried over calcined sodium sulfate, and vacuum evaporated. The residue was combined with precipitate A.

7-Difluoromethylsulfonyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IIIc). A total of 15 ml of 13% solution of ammonia in absolute methanol was added to a solution of 1.08 g (2.5 mmole) of 5-difluoromethylsulfonyl-2-bromacetamidobenzophenone in 20 ml of absolute dioxane, and the solution was allowed to stand at room temperature for 16 h. It was then vacuum evaporated to dryness at 20-25°, and the residue was treated with 70 ml of diethyl ether and 70 ml of 0.3 N HCl. The ether layer was separated and washed twice with 70-ml portions of 0.3 N HCl. The acid solutions were combined and filtered, and 10 ml of 12% ammonium hydroxide was added to the filtrate with stirring. The resulting precipitate was removed by filtration and vacuum dried at 20°, after which it was dissolved in boiling absolute ethanol, and the solution was refluxed for 5 h. The solution was then filtered, and the product crystallized from the solution on standing in the cold.

7-Difluoromethylthio-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IIIb). A mixture of 1 g (3.6 mmole) of 2-amino-5-difluoromethylthiobenzophenone, 10 ml of dry chloroform, and 0.46 g (3.6 mmole) of aminoacetyl chloride hydrochloride was refluxed for 3 h (until hydrogen evolution ceased), after which the chloroform was removed by vacuum distillation, 10 ml of dry ethanol was added to the residue, and the mixture was refluxed for 4 h. Water (10 ml) and 1 ml of 25% ammonium hydroxide were added to the reaction mixture, and it was extracted with 25 ml of toluene. The solution was then evaporated, and IIIb crystallized from solution. Compound IIIa was similarly obtained.

7-Difluoromethylsulfonyl-5-phenyl-1-methyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IIIe). A 1.6-g (0.028 mole) sample of freshly prepared sodium methoxide was added with heating on an air bath at 90-100° to a solution of 5.0 g (0.017 mole) of IIIc in 200 ml of absolute benzene, after which 90 ml of benzene was removed by distillation in order to remove the resulting methanol from the reaction sphere. A 1.7-ml (0.017 mole) sample of dimethyl sulfate was then added dropwise to the residual solution of the sodium salt of the benzodiazepinone, and the solution was refluxed for 1 h. It was then cooled to room temperature, washed with water, dried over calcined sodium sulfate, and concentrated in vacuo. The residue was crystallized from diethylether–petroleum ether. Compound IIId was similarly obtained.

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