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SYNTHESIS OF POLYFUNCTIONALLY SUBSTITUTED BENZOTHIAZINES BASED ON VINYLTHIOHALOBENZENES AND 2-MERCAPTOETHYLAMINE

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Regioselective nucleophilic substitution of the fluorine atoms in positions 2 and 5 of the benzene ring takes place in the reaction of 3,6-bis(vinylthio)-1,2,4,5-tetrafluoro- and 3-vinylthio-6-chloro-1,2,4,5-tetrafluorobenzenes with 2-mercaptoethylamine in isopropyl alcohol–water–dimethylformamide mixture at 40-45°C in the presence of KOH. The products of disubstitution obtained are converted into 1,4-benzothiazines on heating to 100°C in dimethylformamide in the presence of K_2CO_3 as a result of intramolecular substitution.

The present study is a continuation of research to investigate the reactivity of previously synthesized vinylthiopolyhalobenzenes [1-3] and is dedicated to obtaining polyfunctionally substituted heterocyclic compounds with reactions of nucleophilic substitution of 3,6-bis(vinylthio)-1,2,4,5-tetrafluoro- (I) and 3-vinylthio-6-chloro-1,2,4,5-tetrafluorobenzene (II) with 2-mercaptoethylamine. The last compound was selected because many compounds containing an $S-CH_2-CH_2-N$ fragment exhibit physiological activity. In addition, we previously conducted similar reactions of vinylthiohalobenzenes with 2-aminoethanol [2, 3] and showed that as a function of the conditions (basicity of the medium, temperature), this amino alcohol forms products of monosubstitution with vinylthiohalobenzenes I, II, and 2,3,5,6-tetrakis(vinylthio)-1,4-difluorobenzene with the participation of either a hydroxyl or an amino group, as well as cyclic compounds: 5,8-bis(vinylthio)-6,7-difluoro-2,3,-dihydro-1,4-benzoxazine (in the reaction with vinylthiotetrafluorobenzene I) and 5-vinylthio-6,7-difluoro-8-chloro-2,3-dihydro-1,4-benzoxazine (in the reaction with vinylthiofluorochlorobenzene II). In the reaction of compounds I and II with 2-aminoethanol, even with a large excess of the latter, it was not possible to synthesize the product of disubstitution even in the presence of a base [2, 3].

It was shown in the present study that vinylthiohalobenzenes I and II with 2-mercaptoethylamine can yield products of substitution and/or cyclization with the participation of both the SH and NH_2 function of the indicated aminothiol.

2-Mercaptoethylamine was introduced in the reaction in the form of the hydrochloride; 50% aqueous isopropyl alcohol and KOH, whose amounts varied from equimolar to five-fold with respect to the starting hydrochloride, were used to generate it. Vinylthiohalobenzenes I and II were added to the reaction mixture in the form of solutions in dimethylformamide. At 40-45°C and with a ratio of the reagents vinylthiotetrafluorobenzene I (vinylfluorochlorobenzene II)-2-mercaptoethylamine hydrochloride–KOH equal to 1:2:10, 2,5-bis(2-aminoethylthio)-3,6-bis(vinylthio)-1,4-difluorobenzene (III) with a yield of 57% or 2,5-bis(2-aminoethylthio)-3-(vinylthio)-1,4-difluoro-6-chlorobenzene (IV) with a yield of 51% was formed (the yields were calculated for compounds I or II entering into the reaction).

In the case of compound III, there was only one singlet in the region of −96.46 ppm in the ^{19}F NMR spectrum, indicating the equivalence of all fluorine atoms, which takes place for any variant of substitution on the two aminothiol residues (2,4-, 4,5-, and 2,5-). The signals of the protons of both vinylthio groups in the PMR spectra coincide, which is least probable for 2,4-disubstitution. The variant of 4,5-substitution is excluded due to the capacity of compound III for intramolecular cyclization (see below), i.e., the indicated structure of product III is the most realistic. There are two doublets in the region of −104.39 and −95.63 ppm in the ^{19}F NMR spectrum of compound IV. This nonequivalence of the fluorine atoms allows eliminating the possibility of 2,4-disubstitution. The absence of the latter is also confirmed by splitting of the α-proton of the

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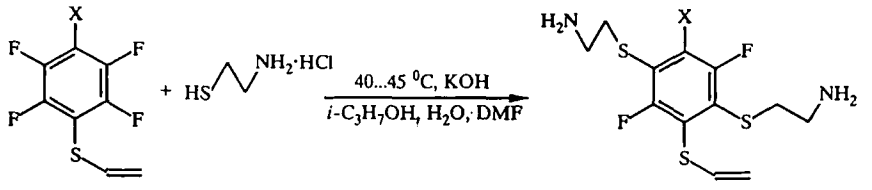
vinylthio group on the fluorine atom, noted previously in [1], observed in the PMR spectrum. In view of the capacity of compound IV for intramolecular cyclization, as in the case of compound III, it is possible to consider the *para* position of the entering substituents as most probable.

When the reagents are used in equimolar amounts, products of disubstitution are also formed. Substitution of isopropyl alcohol by ethyl alcohol in the mixture of solvents decreases the yield of target product III to 38%.

The process examined thus takes place regioselectively with substitution of two fluorine atoms in the *para* position relative to each other. This direction is confirmed by the data from the ^{19}F and ^{1}H NMR spectra of products III and IV, and the results of their intramolecular cyclization.



I, II

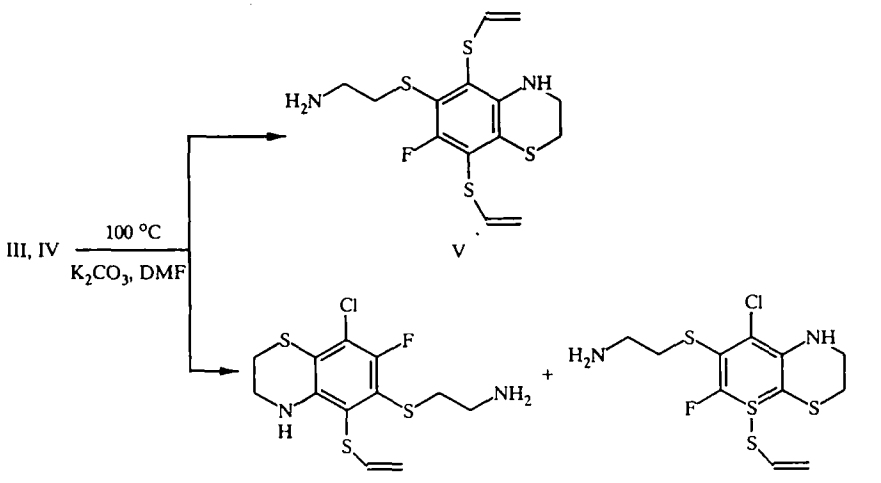
I, III X = SCH = CH_2; II, IV X = Cl

III, IV

When the temperature of a reaction mixture consisting of vinylthiotetrafluorobenzene I, 2-mercaptoethylamine hydrochloride, and KOH in the ratio of 1:4:4 (KOH is only used for generation of 2-mercaptoethylamine) is increased to 85°C (the boiling point of the mixture of solvents), in addition to formation of product of disubstitution III (yield of ~19%), its cyclization also takes place, resulting in 6-(2-aminoethylthio)-5,8-bis(vinylthio)-7-fluoro-2,3-dihydro-1,4-benzothiazine (V) with a yield of ~6.5%, i.e., both the SH group and the NH_2 group participate in the reaction. 2-Mercaptoethylamine probably exists in the free state in the form of a zwitterion in which the sulfur atom bears a negative charge, which facilitates its attack on the fluorine atoms and formation of product of disubstitution III. Increasing the temperature of the reaction to 85°C favors its intramolecular cyclization with the participation of the NH_2 group.

A singlet in the region of −108.10 ppm, assigned to cyclic compound V, appears in the ^{19}F NMR spectrum of a mixture of compounds III and V together with a singlet in the region of −96.51 ppm characteristic of product of disubstitution III. In addition to the signals corresponding to compound II, the PMR spectrum contains a multiplet of a fragment of the 1,4-thiazine ring, SCH_2CH_2NH, at 3.59 ppm, and the chemical shifts in the region of 4.86, 5.20, 6.21 and 5.05, 5.24, and 6.39 ppm can be assigned to protons of the vinylthio groups of cyclic compound V.

Product V is also formed with a yield of 89% as a result of holding compound III in dimethylformamide at 100°C in the presence of K_2CO_3 (III:K_2CO_3, 1:2). A difficult to separate mixture of cyclic regioisomers VI and VII in the ratio of ~4:1 (according to PMR data) is obtained from compound IV in the same conditions.



V

VI

VII

In the PMR spectrum of products of cyclization VI and VII, the signals in the region of 4.83 (d), 5.17 (d), and 6.18 (q) ppm are assigned to protons of the vinylthio group in compound VI, while the signals at 5.01 (d), 5.21 (d), and 6.25 (q) ppm perhaps belong to protons of the vinylthio group of compound VII. This assignment was based on a comparison of the PMR spectra of compounds V and VII, which only differ by the substituents in position 5.

The predominant formation of cyclic compound VI confirms the previously observed [3] effect of the vinylthio group on the mobility of the fluorine atoms in the *ortho* position with respect to it. They are substituted more easily than the fluorine atoms in the *ortho* position relative to the chlorine atom. An overall activating effect of the vinylthio groups on the capacity of fluorine atoms in vinylthiopolyfluorobenzenes for nucleophilic substitution can perhaps be observed, since according to the data in [4], the reaction of hexafluorobenzene with bifunctional nucleophiles takes place at high temperatures. However, it is also not possible to exclude the effect of the solvents on these reactions. As demonstrated previously in [5], hexafluorobenzene easily reacts with these reagents in liquid ammonia.

EXPERIMENTAL

The IR spectra were made on a Bruker IFS-25 spectrometer in a thin layer or in KBr pellets. The ^1H and ^{19}F NMR spectra were recorded on a JEOL FX 90Q instrument.

2,5-Bis(2-aminoethylthio)-3,6-bis(vinylthio)-1,4-difluorobenzene (III). A solution of 2.6 g (9.8 mmole) of compound I in 30 ml of dimethylformamide was added to a mixture of 2.3 g (19.6 mmole) of 2-mercaptoethylamine hydrochloride and 5.5 g (98 mmole) of KOH in 100 ml of 50% aqueous isopropanol at 30°C; it was held for 5 h at 40-45°C, then ~16 h at room temperature, and then poured into a large amount of water. The mass obtained was extracted with diethyl ether, and the extract was washed with water and dried with $MgSO_4$. The finely crystalline residue after elimination of the ether was washed with hexane, and 0.72 g of compound I was separated on cooling. The washed residue was recrystallized from hot hexane and 1.54 g (57%) of product II was obtained in the form of white crystals. Mp = 78-79°C. IR spectrum: 1590 ($SCH=CH_2$), 1390 cm^{-1} (C–F). ^1H NMR spectrum ($CDCl_3$): 1.42 (4H, s, $2NH_2$); 2.78 (4H, t, $2CH_2S$); 3.01 (4H, t, $2CH_2N$); 5.16, 5.31 (4H, two d, $2CH_2=$); 6.43 ppm (2H, q, 2CH=), $^3J_{HHcis}$ = 9.5, $^3J_{HHtrans}$ = 16.6 Hz. ^{19}F NMR spectrum: −96.46 ppm (s). Found, %: C 43.73; H 4.84; F 9.54; N 7.18; S 33.71. $C_{14}H_{18}F_2N_2S_4$. Calculated, %: C 44.19; H 4.77; F 9.99; N 7.36; S 33.69.

2,5-Bis(2-aminoethylthio)-3-vinylthio-1,4-difluoro-6-chlorobenzene (IV). Compound IV was synthesized by the method described above. Yield of 51%. Mp = 40-41°C. IR spectrum: 1585 ($SCH=CH_2$), 1395 cm^{-1} (C–F). ^1H NMR spectrum ($CDCl_3$): 1.69 (4H, s, $2NH_2$); 2.78 (4H, m, $2CH_2S$); 3.01 (4H, m, $2CH_2N$); 5.07 and 5.29 (2H, two d $=CH_2$), 6.34 ppm (1H, q. d, =CH), $^3J_{HHtrans}$ = 16.5, $^5J_{FH}$ = 1.5 Hz. ^{19}F PMR spectrum: −95.63 (d, 4-F); −104.39 ppm (d, 1-F), $^5J_{1F\text{-}4F}$ = 14.6 Hz. Found, %: C 40.83; H 4.80; Cl 10.05; F 10.23; N 7.68; S 26.94. $C_{12}H_{15}ClF_2N_2S_3$. Found, %: C 40.38; H 4.24; Cl 9.94; F 10.65; N 7.85; S 26.95.

6-(2-Aminoethylthio)-5,8-bis(vinylthio)-7-fluoro-2,3-dihydro-1,4-benzothiazine (V). Here 0.4 g (1.05 mmole) of compound III and 0.3 g (2.1 mmole) of K_2CO_3 in 40 ml of dimethylformamide were stirred for 6 h at 100°C. The cooled reaction mass was poured into cold water and extracted with CH_2Cl_2. The extract was washed with water and dried with $MgSO_4$. Methylene chloride was distilled off at reduced pressure, the residue (0.34 g) was recrystallized from hot hexane, and 0.33 g of compound V was obtained. Yield of 89%, mp = 74°C. IR spectrum: 1583 ($SCH=CH_2$), 1473 cm^{-1} (C–F). ^1H NMR spectrum (acetone-D_6): 2.95 (2H, m, CH_2S); 3.07 (2H, m, CH_2NH_2); 3.32 (2H, m, CH_2S in ring); 3.62 (2H, m, CH_2N in ring); 4.83, 5.18, and 6.30 (3H, two d and q, 5-$SCH=CH_2$); 5.02, 5.23, and 6.41 ppm (3H, two d and q, 8-$SCH=CH_2$). ^{19}F NMR spectrum: −104.39 ppm (s). Found, %: C 47.10; H 4.45; F 4.89; N 7.38; S 36.03. $C_{14}H_{17}FN_2S_4$. Calculated, %: C 46.69; 4.75*; F 5.26; N 7.76; S 35.53.

6-(2-Aminoethylthio)-5-(vinylthio)-7-fluoro-8-chloro-2,3-dihydro-1,4-Benzothiazine (VI) and 6-(2-Aminoethylthio)-8-(vinylthio)-7-fluoro-5-chloro-2,3-Dihydro-1,4-benzothiazine (VII). Similar to synthesis of dihydrobenzothiazine V, 0.5 g of a crystalline mixture of regioisomers VI and VII in the ratio of 4:1 (according to PMR data) was obtained from 1 g (2.8 mmole) of compound IV. Yield of 53%. IR spectrum: 1583 ($SCH=CH_2$), 1487 cm^{-1} (C–F). ^1H NMR spectrum ($CDCl_3$): compounds VI and VII: 1.58 (2H, s, NH_2); 2.75 (2H, m, CH_2S); 2.92 (2H, m, CH_2NH_2); 3.05 (2H, m, CH_2S in ring); 3.64 (2H, m, CH_2N in ring); 5.45 (1H, br. s, NH); compound VI: 4.83, 5.17, and 6.18 (~2.4H, two d and q, 5-$SCH=CH_2$); compound VII: 5.01, 5.21, and 6.25 ppm (~0.6 H, two d and q, 8-$CH=CH_2$). ^{19}F NMR spectrum: −116.96 (s) (compound

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VI) and −108.04 ppm (s) (compound VII). Found, %: C 42.55; H 3.90; F 5.02; Cl 10.32; N 7.98; S 28.0. $C_{12}H_{14}FClN_2S_3$. Calculated, %: C 42.78; H 4.19; F 5.64; Cl 10.52; N 8.31; S 28.55.

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REFERENCES

1. S. V. Amosova, V. I. Gostevskaya, G. M. Gavrilova, A. V. Afonin, L. S. Romanenko, and L. Stefanik, Zh. Org. Khim., **28**, 1463 (1992).
2. S. V. Amosova, V. I. Gostevskaya, G. M. Gavrilova, A. V. Afonin, and D. S. D. Toryashinova, Zh. Org. Khim., **29**, 2416 (1993).
3. S. V. Amosova, V. I. Gostevskaya, G. M. Gavrilova, A. V. Afonin, and B. A. Gostevskii, Zh. Org. Khim., **33**, 1169 (1997).
4. J. Burdon, V. A. Damodaran, and J. C. Tatlow, J. Chem. Soc., No. 2, 763 (1964).
5. T. A. Kizner and V. D. Shteingarts, Zh. Org. Khim., **25**, 2424 (1989).