CONDENSATION OF PENTAFLUOROBENZALDEHYDE WITH o-AMINOTHIOPHENOL

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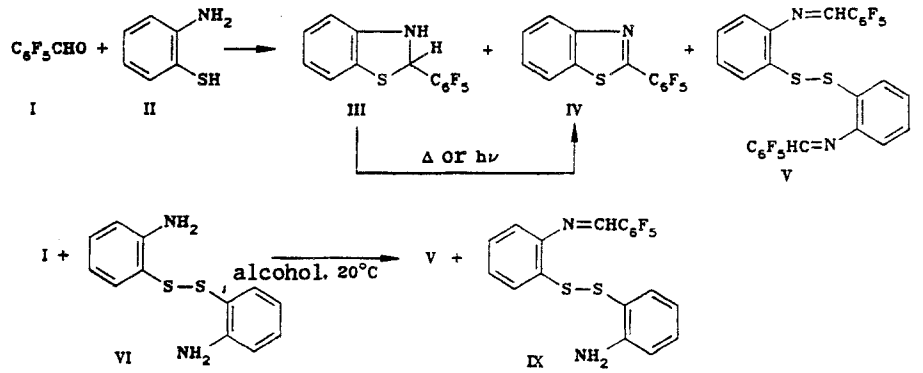
The condensation reaction of pentafluorobenzaldehyde with o-aminothiophenol is shown to lead, depending on the conditions used, to the formation of 2-pentafluorophenylbenzthiazoline or a fluorine-substituted derivative of cyclophane and cannot serve as a method for preparing 1,2,3,4-tetrafluorodibenz-[b,f][1,4]thiazepine.

At the present time there is great interest in dibenz[b,f][1,4]oxazepine and -thiazepine systems, derivatives of which possess various biological activities. Some of them are used in medicinal practice as antidepressants and tranquilizers [1, 2].

Earlier, we proposed a method for obtaining polyfluorinated dibenz[b,f][1,4]oxazepines, including the synthesis of polyfluoro-o-hydroxybenzylideneanilines and their intramolecular dehydrofluorination [3, 4]. In the present work we have investigated the applicability of an analogous approach to obtaining polyfluorinated dibenz[b,f][1,4]thiazepines beginning with pentafluorobenzaldehyde (I) and o-aminothiophenol (II).

It is known that the result of condensing compound II with aldehydes, RCHO (R = Alk, Ar), is the formation not of the corresponding Schiff's base, but of its isomer, 2-R-benzthiazoline [5-8]. However, an equilibrium exists between the cyclic and open forms which can be shifted to the open form by the action of bases [5, 8, 9]. Recently, the intermediate formation of the azomethine derivative has been proposed as an alternate route to obtaining the thiazepine structure in the condensation of 2-chloro-3-formylquinoline with thiophenol II in DMF in the presence of potassium carbonate [10].



We have found that the reaction of benzaldehyde I with compound II goes readily on mixing without a solvent or in alcohol. However, unlike the reaction of compound I with o-aminophenol [3], the reaction product is not the corresponding Schiff's base, but 2-(pentafluorophenyl)benzthiazoline (III). According to the ^{19}F-NMR spectroscopic data, the reaction mixture contains 2-(pentafluorophenyl)benzthiazole (IV) and bis(2-pentafluorobenzylideneaminophenyl)disulfide (V). Benzthiazole IV is identical in melting point and spectroscopic data to the sample described in [11]. The structure of benzthiazoline III was confirmed by its dehydrogenation to compound IV, which agrees with the data in [5, 6]. The structure of compound V is shown by its alternate synthesis from aldehyde I and bis(o-aminophenyl)disulfide (VI) according to [5, 12].

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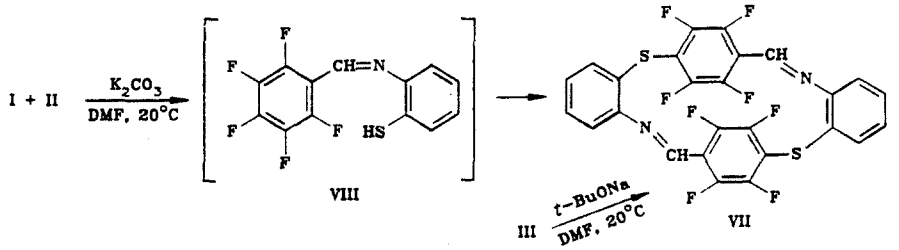
The preparation of disulfide V under the conditions of the reaction of compounds I and II, as well as from benzthiazoline III when it is oxidized with hydrogen peroxide, can indicate the formation in the reaction mixture of an intermediate Schiff's base isomeric to compound III (cf. [5]). The reaction of aldehyde I with compound II in DMF in the presence of anhydrous potassium carbonate takes place readily at room temperature and is accompanied by the splitting out of 1 mole of fluorine per mole of initial aldehyde. The reaction mixture resulting from this does not contain any compounds with four vicinal fluorine atoms in amounts detectable by ^{19}F-NMR spectroscopy. By reprecipitation and recrystallization from organic solvents, a compound was isolated from the mixture to which we ascribe structure VII on the basis of IR, PMR, ^{19}F-NMR, and mass spectroscopic data, as well as elementary analysis. Compound VII was also identified in the reaction product of thiazoline III with t-BuONa in dry DMF.



It can be assumed that the mechanism for the preparation of sulfide VII includes the formation of the intermediate 2-mercapto-N-(pentafluorobenzylidene)aniline (VIII) which, unlike the oxy-substituted analog, does not show a tendency to cyclize via the intramolecular, nucleophilic substitution of the ortho-atom of fluorine. A bimolecular reaction leading to the replacement of the fluorine atom in the para position on the pentafluorophenyl radical proves to be more favorable. The presence in the reaction mixtures of products that are insoluble in organic solvents is obviously evidence of the simultaneous occurrence of intermolecular oligomerization.

EXPERIMENTAL

The IR spectra were taken in KBr tablets on a UR-20 instrument. The PMR and ^{19}F-NMR spectra were recorded on Varian A 56/60 (60 and 56.4 MHz) and Bruker WP-200-SY instruments. As internal standards, HMS and C_6F_6, respectively, were used. The solvent used in recording the ^{19}F-NMR spectra was THF. Mass spectra were recorded on a high-resolution, Finnigan MAT 8200 mass spectrometer.

Reaction of Pentafluorobenzaldehyde (I) with o-Aminothiophenol (II). **A.** Equimolar amounts of compounds I and II are mixed and held for 1 day at room temperature. The mass that has congealed is triturated with alcohol, the residue filtered off and recrystallized from chloroform to obtain 2-(pentafluorophenyl)benzthiazoline (III). $C_{13}H_6F_5N$, mp 164-167°C. IR spectrum: 3360 cm^{-1} (N–H). ^{19}F-NMR spectrum: 303 (M^+). Yield 43%. The filtrate is evaporated at 20°C, the residue washed with hexane, and 2-(pentafluorophenyl)benzthiazole (IV), $C_{13}H_4F_5$, is obtained with the identical melting point and IR spectrum described in [5]. PMR spectrum ($CDCl_3$, 200 MHz): 7.40-7.56 (2H, m, H_{arom}), 7.92 (1H, d, J = 8 Hz), and 8.14 ppm (1H, d, J = 8 Hz). ^{19}F-NMR spectrum: 0.9, 10.8, 24.5 ppm, ratio of intensities 2:1:2. Mass spectrum 301 (M^+). Yield 21%.

B. To a solution of 0.98 g (5 mmoles) of aldehyde I in 10 ml of alcohol cooled to 0°C, 0.62 g (5 mmoles) of freshly distilled compound II is added dropwise. This is stirred for 2 h at 0°C to obtain a product that, according to the ^{19}F-NMR spectrum, contains benzthiazoline III, benzthiazole IV, and bis(2-pentafluorobenzylideneaminophenol)disulfide, V, in the ratio of 7:1:1.

C. To 1.0 g (5 mmoles) of compound I in 10 ml of anhydrous DMF is added 1.0 g of calcined potassium carbonate, and 0.6 g (5 mmoles) of aminothiophenol II in 7 ml of DMF is added dropwise. This is stirred for 3 h at 20°C in a stream of argon, poured into water, and neutralized with dilute HCl. The residue is filtered off to obtain 1.0 g of product with mp 49-55°C. By reprecipitation with hexane from a benzene solution and recrystallization from a benzene–alcohol mixture, 3,4,6,7,18,19,21,22-octafluoro-1,16-dithia-9,24-diaza[1.2.1.2](p,o,p,o)cyclophane-8,23-diene VII is isolated. $C_{26}H_{10}F_8N_2S_2$, mp 148-151 °C. PMR spectrum ($CDCl_3$): 7.16 and 8.53 ppm, ratio of intensities 4:1. ^{19}F-NMR spectrum: two signals of equal intensity at 21.6 and 30.1 ppm. Found: m/z 566.0105; calculated: m/z 566.0157.

Conversion of 2,3,4,5,6-Pentafluorophenylbenzthiazoline (III). A. A solution of 0.20 g (0.66 mmoles) of compound III in 100 ml of dry benzene is irradiated with light from a DRSh-500 high-pressure mercury lamp for 3 h at room temperature. The solution is evaporated to a volume of 10-15 ml and passed through a column of SiO_2 (0-140 μ) to obtain 0.15 g (75%) of thiazole IV with mp 121-122°C. The IR spectrum is identical to that of a known sample.

B. 0.20 grams (0.66 mmole) of compound III is heated without a solvent for 1 h at 100°C. The reaction mixture is dissolved in benzene and filtered through a layer of SiO_2 to obtain 0.13 g (65%) of thiazole IV.

C. A mixture of 0.50 g (1.65 mmoles) of thiazoline III, 5 ml of methanol, and 0.33 ml of 30% H_2O_2 is heated for 10 min at 80°C, poured into water, and extracted with ether. The ethereal solution is washed with water, dried with $CaCl_2$, and evaporated to obtain 0.36 g of a product containing, according to the ^{19}F-NMR spectrum, thiazole IV and disulfide V in a 1:2 ratio. By chromatography on SiO_2 (0-140 μ) in benzene, 0.14 g (28%) of thiazole IV is isolated.

D. To a solution of 0.75 g (2.5 mmoles) of compound III in 7 ml of dry DMF is added 0.25 g (2.6 mmoles) of t-BuONa and the mixture held for 1 h and 30 min at room temperature. The reaction mixture is poured into water, acidified with dilute HCl, and the precipitate filtered off. The resultant product (0.56 g) is chromatographed on SiO_2 (0-140 μ) in $CHCl_3$ to obtain 0.20 g (29%) of compound VII which is identical in its IR and ^{19}F-NMR spectra to a known sample.

Reaction of Pentafluorobenzaldehyde (I) with Bis(2-aminophenyl)disulfide (VI). A solution of 1.25 g (5 mmoles) of disulfide VI in 30 ml of alcohol is added dropwise to a solution of 2.0 g (10 mmoles) of aldehyde I in 30 ml of alcohol at 0°C in a stream of argon and held for 3 h at 20°C. The precipitate is filtered off, washed with alcohol, and dried to obtain 1.5 g (44%) of 2-(2,3,4,5,6-pentaflurobenzylideneamino)-2'-aminodiphenyldisulfide (IX), $C_{19}H_{11}F_5N_2S_2$, mp 152-155°C (from benzene). IR spectrum: 3310 and 3490 cm^{-1} (NH_2). PMR spectrum (DMSO-d_6, 200 MHz): 5.59 (2H, s, NH_2), 6.43-7.39 (7H, m, H_{arom}), 7.93 (1H, d, J = 8 Hz, H_{arom}), 8.61 ppm (1H, s, HC=N). ^{19}F-NMR spectrum: 0.0, 11.3, 21.6 ppm, ratio of intensities 2:1:2. Mass spectrum 426 (M^+).

The filtrate is evaporated to dryness and the residue recrystallized from chloroform to obtain 1.1 g (23%) of bis[o-(pentafluorobenzylideneamino)phenyl]disulfide (V), $C_{26}H_{10}F_{10}N_2S_2$ with mp 196-199°C. PMR spectrum (DMSO-d_6, 200 MHz): 7.34 (3H) and 7.58 (1H), 8.74 ppm (1H, s, =CH). ^{19}F-NMR spectrum: 0.0, 12.0, 22.0 ppm, ratio of intensities 2:1:2. Mass spectrum: 604 (M^+).

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