

SYNTHESIS AND SOME TRANSFORMATIONS OF SULFIDES OF THE THIOPHENE SERIES. X. PREPARATION OF THIENOISOTHIAZOLES FROM MERCAPTOALDIMINES

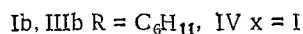
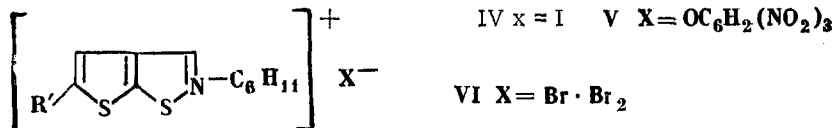
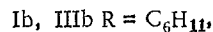
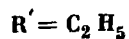
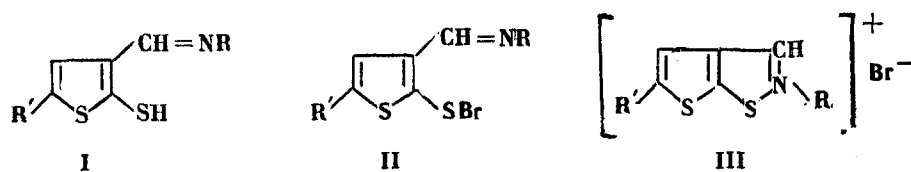
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The action of bromine on 2-mercapto-5-alkyl-3-thienylideneimines gives thieno[3, 2-d]isothiazole bromides. 5-Ethylthieno[3, 2-d]isothiazole bromide readily splits off HBr to give 5-ethylthieno[3, 2-d]isothiazole. Lithium aluminum hydride reduces mercaptothienylideneimines to aminomethyl derivatives.

2-Mercapto-5-ethyl-3-thienylideneimine and its N-substituted derivatives I, which have previously been described [1, 2], constitute a new type of bifunctional compound, without analogs in the benzene series. Hence it was of interest to investigate their chemical properties as widely as possible. The present paper gives the results of experiments on brominating these thiophene derivatives.

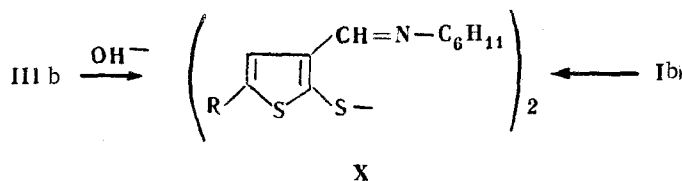
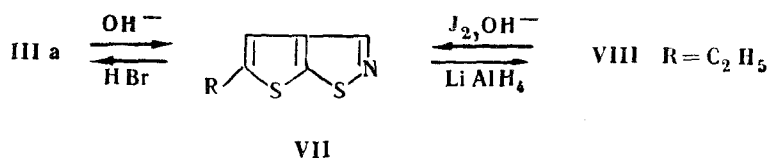
The action of bromine on compounds of structure I may be directed at at least two reaction centers in the molecule, the sulfhydryl



group with formation of sulfenebromide [3] and the azomethine group, which may lead to products of addition at the C=N bond [4]. The mercaptoaldimines I give crystalline compounds containing one atom of bromine, by reaction with an equimolecular quantity of bromine in chloroform solution. The reaction is accompanied by separation of hydrogen bromide, showing that it proceeds through a stage of substitution of an hydrogen atom by bromine. Of two possible structures for the bromination products, sulfenebromide II and thienothiazole bromide III, the latter is undoubtedly preferable, since it is very problematical whether a reactive sulfenebromide group can function, when the molecule contains a powerful basic center. In this connection, it should be mentioned that sulfene halides are usually colored, quite soluble in ether, and react readily with amines [5], whereas the crystalline compounds obtained by bromination have a clearly defined salt-like character. This is especially true of compound IIIa, as it does not melt up to 400°, and is insoluble in ether and hydrocarbons. The compound to which structure IIIb can be ascribed is salt-like, but not as markedly so; it melts (mp 169°), is soluble in hot benzene, but not in hot pentane. However, its capacity, on the one hand, to exchange its bromine atom for an iodine or picric acid ion, compounds IV and V, and, on the other, to react directly with p-nitroaniline, is in complete accord with the ionic character of the bromide. Here it should be noted that the uv spectra of bromides IIIa and IIIb differ (Fig. 1), possibly because IIIa bromide in dilute solution undergoes alcoholysis, and what is involved is the spectrum of the base. IIIb bromide can add a further two bromine atoms in chloroform solution, to give an intensely colored crystalline substance, which simply by treatment with ether in alcohol solution loses two bromine atoms, reverting to the starting bromide IIIb. Evidently what is involved here is formation and decomposition of a perbromide VI. The complete identity of the uv spectra of the two bromides is in complete agreement with this. As is known, a like property of readily giving perbromides is characteristic of the closely related systems thiazole and benzothiazole [6].

That compound IIIa is an isothiazole compound is further confirmed by its loss of HBr through hydrolysis or the action of soda, whereupon it changes into a base whose composition and properties correspond completely with 5-ethylthieno[3, 2-d]isothiazole VII. With hydrogen bromide in acetic acid the latter re-forms bromide IIIa. In character the above-described synthesis of a thienoisothiazole is close to the reaction for obtaining benzisothiazoles by the action of amines of ammonia on formylated arylsulfene bromides [7, 8]. When o-mercaptopehnylaldoximes [9, 10] is used as the

starting material, closure can be preceded by introduction of a nitrogen atom into the molecule. Further evidence that the resultant base has formula VII is the fact that it is formed when 2-mercapto-5-ethyl-3-thienylamine VIII is oxidized by iodine under the conditions described for synthesis of benzoisothiazoles from o-mercaptobenzylamines [11].



Aminomercaptan VIII, required for this reaction, was obtained by lithium aluminum hydride reduction of the mercaptoaldimine Ia. The free base from this compound is unstable; it is readily reduced to the mercaptoaldimine Ib under the conditions employed. The specimens of thienoisothiazole, obtained by the methods indicated, were identical, and their

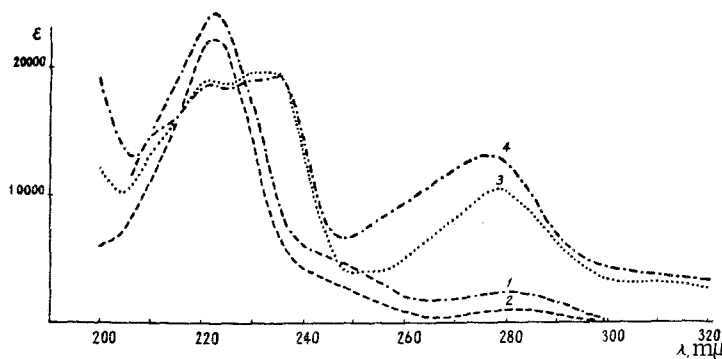


Fig. 1. Uv spectrum in alcohol: 1) thienoisothiazole VII; 2) thienoisothiazole bromide IIIa; 3) thienoisithiazole bromide IIIb; 4) perbromide VI.

uv spectra coincided completely: λ_{max} 2225 Å, $\epsilon = 24\,450$ (in alcohol), 21 400 (in heptane). For the isothiazole λ_{max} 2420 Å $\log \epsilon$ 3.818 [12]. It is of interest that the uv spectra of thienoisothiazole VII and thieno[2,3-b]thiophene [13] are almost identical, so that substitution of nitrogen for double-bonded carbon in the latter does not show up in the spectrum. Figure 2 gives the ir spectrum of the thienoisothiazole.

As might be expected from the properties of N-substituted benzylisothiazole bromides [8], on treatment with alkali bromide IIIb, with a substituent on the nitrogen atom, gives bis [5-ethyl-3-cyclohexyliminothienyl-2]disulfide (X). The structure of the latter is established independently, it being formed by oxidizing (2-mercapto-5-ethyl-3-thienyldene)cyclohexylamine (Ib). The observed fission of the isothiazole ring under the action of alkali also obtains in the lithium aluminum hydride reduction of the thienoisothiazole. Aminomercaptan VIII, formed by oxidizing base VII, is here regenerated. Scission of the isothiazole ring on hydrogenation was also noted previously [14].

EXPERIMENTAL

Bromination of mercaptoaldimines (I).

a) 9.4 g (0.059 mole) bromine in 15 ml chloroform are added gradually to a solution of 10.0 g (0.059 mole) imine in 400 ml dry chloroform at 45-50°C. As the bromine is added, a white crystalline precipitate appears, and evolution of HBr is observed. After 2 hr stirring at about 20°, the precipitate is filtered off, washed with chloroform, and dried. Yield 8.9 g (60.5%) 5-ethylthieno[3,2-d]isothiazole bromide IIIa, which after recrystallization from glacial acetic acid, washing with ether, and vacuum-drying over P_2O_5 , becomes wet at 170-175°, and partly carbonizes, but does not melt on heating to 400°. The bromide is soluble in alcohol and dimethylformamide, insoluble in alcohol, hydrocarbons, chloro-

form, and ethyl acetate. Found: C 33.67; 33.68; H 3.13; 3.21; N 5.56; 5.43%, calculated for $C_7H_8NBrS_2$: C 33.60; H 3.22; N 5.60%.

b) 2.0 g imine Ib is brominated in the way described above, using 1.3 g bromine in 20 ml chloroform. The chloroform is distilled off in a vacuum, the residue dissolved in alcohol, and ethyl acetate or ether used to precipitate 2.1 g (78.5%) of a white crystalline substance melting at 164-165°. After being reprecipitated from anhydrous alcohol with ether, and from chloroform by ethyl acetate, the 2-cyclohexyl-5-ethylthieno[3, 2-d]isothiazole bromide (IIIb) melts at 168-169°. The bromide is soluble in hot benzene, insoluble in water and heptane. Found: C 46.74; 46.89; H 5.33; 5.54; N 4.58; 4.62; Br 23.82; 23.96%, calculated for $C_{13}H_{18}NBrS_2$: C 46.98; H 5.46; N 4.22; Br 24.05%.

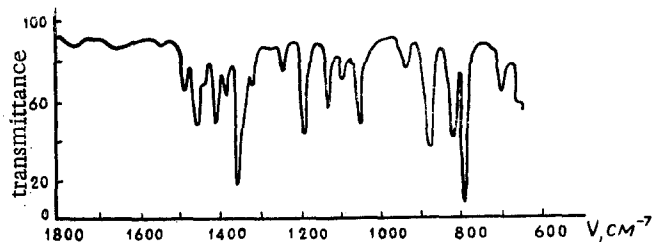


Fig. 2. Ir spectrum of thienoisothiazole (UP)

Reactions of 2-cyclohexyl-5-ethylthieno[3, 2-d]isothiazole bromide (IIIb).

Iodide (IV). Alcohol solutions of 0.3 g bromide IIIb and 0.4 g sodium iodide containing a minimum amount of solvent are mixed and heated for some minutes on a steam bath. The crystals which separate on standing are filtered off, washed with water, and twice recrystallized from alcohol. Yield 0.25 g (71%), mp 169.5-170.5°. Found: C 40.83; 41.05; H 4.66; 4.66%, calculated for $C_{13}H_{18}NIS_2$: C 41.16; H 4.78%.

Picrate (V). Alcohol solutions of 0.3 g bromide IIIb and 0.2 g picric acid are mixed, and next day the yellow precipitate is filtered off, washed with alcohol, and twice crystallized from alcohol. Yield 0.3 g (66.7%) crystals, melting at 185-186°. Found: C 47.40; 47.58; H 4.30; 4.25; N 12.00; 11.86; S 13.27; 13.34%, calculated for $C_{19}H_{20}O_5N_4S_2$: C 47.49; H 4.20; N 11.66; S 13.13%.

Perbromide (VI). 0.2 g bromine is added to 0.3 g bromide IIIb in 2 ml chloroform, and the solution heated on a steam bath for a few minutes. The solution is cooled and alcohol added; yellow crystals of perbromide separate (yield 89%) and after recrystallization from alcohol melt at 123-125° (sealed tube). Found: C 32.44; 32.22; H 4.03; 3.97; S 12.87; 13.14%, calculated for $C_{13}H_{18}NBr_3S_2$: C 31.72; H 3.67; S 13.03%. An alcohol solution of the perbromide is poured into ether. After some time a white crystalline substance begins to separate, mp 168.5-169.5° (after reprecipitation from alcohol with ether). Mixed melting point with isothiazole bromide IIb undepressed. Found: C 47.00; 47.04; H 5.30; 5.28%, calculated for $C_{13}H_{18}NBrS_2$: C 46.98; H 5.46%.

Reduction of mercaptoaldimines (I).

a) A suspension of 2.7 g lithium aluminum hydride in 30 ml dry ether is prepared, a stream of nitrogen passed, and 6.0 g mercaptoaldimine Ia added in small portions at such a rate that the ether boils slowly. After stirring for one hr the mixture is treated with 20 ml water and 50 ml hydrochloric acid (1:1) while cooling. The ethereal layer is decanted, and the white precipitate of hydrochloride filtered off, washed with water and ether, dried in a vacuum, and twice reprecipitated with ether from dry methanol. Yield 6.1 g (83.4%) 2-mercapto-5-ethyl-3-thienylamine hydrochloride (VIII), melting at 151-152°. Found: C 39.94; 39.92; H 5.76; 5.63; N 6.68; 6.73%, calculated for $C_7H_{11}NS_2 \cdot HCl$: C 40.08; H 5.77; N 6.68%.

b) 5.0 g mercaptoaldimine Ib and 1.5 g lithium aluminum hydride give, by the method indicated above, an 87% yield of 2-mercapto-5-ethyl-3-thienylcyclohexylamine (IX). After two precipitations from absolute alcohol using dry ether, it forms glistening colorless crystals of hydrochloride (IX) melting at 230-235° (decomp.). Found: C 53.55; 53.50; H 7.74; 7.69; N 5.02; 5.04%, calculated for $C_{13}H_{21}NS_2 \cdot HCl$: C 53.48; H 7.60; N 4.80%.

Addition of a solution of CH_3COOK to an alcohol solution of the hydrochloride precipitates the base as white crystals melting at 121.5-122.5° (from absolute alcohol), rapidly darkening at room temperature, soluble in benzene, and insoluble in ether and heptane. Found: C 61.01; 60.73; H 8.44; 8.31; S 25.02; 25.25%, calculated for $C_{13}H_{21}NS_2$: C 61.12; H 8.29; S 25.10%.

5-Ethylthieno[3, 2-d]isothiazole (VII).

a) From thienoisothiazole bromide (IIIa). A suspension of 10.0 g bromide IIIa in 40 ml ether is shaken with 10% soda solution until solution is complete. The ether layer is separated, the water layer extracted with ether. The ethereal extract is washed with a solution of alkali, then water, and dried over barium oxide. When the ether is evaporated there is obtained 4.5 g (67%) of the thienoisothiazole VII as an oil with n_D^{20} 1.6235. After distillation it boils at 103° (3 mm), d_4^{20} 1.2916, n_D^{20} 1.6255. Found: C 49.60; 49.37; H 4.31; 4.30; S 37.45; 37.58%, M 175.5 (in benzene); MR_D 46.36, calculated for $C_7H_7NS_2$: C 49.67; H 4.17; S 37.96%; M 169.3; MR_D 46.39*. 2 ml of a solution of hydrogen bromide in glacial acetic acid were added to 1.2 g thienoisothiazole VII in 3 ml glacial acetic acid, the precipitate filtered off,

* The atomic refractions of S and N were taken as 7.26 and 3.776, respectively [15].

washed with ether, and crystallized from acetic acid. Yield of thienoisothiazole bromide (IIIa) 84%. Found: N 5.65; 5.56%, calculated for $C_7H_8NBrS_2$: N 5.50%.

b) From 2-mercapto-5-ethyl-3-thienylamine hydrochloride (VIII). 10.2 g (0.04 mole) iodine in a solution of 25 g potassium iodide in 150 ml water is added to a stirred solution of 4.0 g (0.02 mole) VIII hydrochloride, 400 ml 0.5 N sodium hydroxide solution, and 100 ml ether over a 45 min period. After stirring for an hour the ether layer is separated, and the aqueous layer extracted with ether. The ethereal solution is washed with water, dried over magnesium sulfate, and twice vacuum-distilled. Yield 1.3 g (40%) thienoisothiazole VII boiling at 97° (2 mm), n_D^{20} 1.6260. Found: N 8.34; 8.38%, calculated for $C_7H_7NS_2$: N 8.27%.

The bromide is prepared in the way described above. Found: N 6.03; 5.98%, calculated for $C_7H_8NBrS_2$: N 5.60%. The uv spectrum of this salt was completely identical with the spectrum of bromide IIIa.

Reduction of thienoisothiazole (VII). An ethereal solution of 2.0 g (0.01 mole) thienoisothiazole VII is gradually added to a suspension of 0.5 g (0.01 mole) lithium aluminum hydride in 30 ml dry ether, whereupon the solution starts to boil and turns yellow. The reaction mixture is stirred for 30 min, and hydrolyzed, with cooling, by treating for 1 hr 30 min with 30 ml dilute hydrochloric acid (1:1). The white powder which appears at the water-ether junction is filtered off, washed with water, and dried. Yield 1.8 g (73%) 2-mercapto-5-ethyl-3-thienylamine hydrochloride (VIII), melting at about 150°. This hydrochloride is twice precipitated from alcohol by dry ether, and melts at 152-152.5°. Mixed mp with a specimen made by reducing mercaptoaldimine (Ia) undepressed. Found: C 39.96; 39.87; H 5.84; 5.77%, calculated for $C_7H_{11}NS_2 \cdot HCl$: C 40.08; H 5.77%.

Bis(5-ethyl-3-cyclohexyliminothienyl-2)disulfide (X).

a) From bromide IIIb. A mixture of 1.6 g bromide IIIb, 10 ml water, and 30 ml ether is shaken with 20 ml 10% sodium hydroxide solution until the precipitate no longer wholly passes into the ether layer. The ethereal layer is separated off, washed with water, and dried with potash. The thick yellow oil remaining after removing the ether is treated with alcohol. Yield 0.8 g (63.5%) disulfide X, which, after recrystallization from alcohol and alcohol-ethyl acetate, melts 84.5-85.5°. Found: C 61.82; 61.63; H 7.08; 7.13; S 25.42; 25.22%, calculated for $C_{26}H_{36}N_2S_4$: C 61.85; H 7.19; S 25.41%. Treatment of bromide IIIb with aqueous ammonia gives the disulfide in 26% yield.

b) From (2-mercapto-5-ethyl-3-thienylidene)cyclohexylamine (Ib). A solution of 1.0 g (0.004 mole) imine Ib in a few ml 10% methanolic potassium hydroxide solution is added (with the temperature kept at 0°) to a solution of 1.6 g potassium ferricyanide in 15 ml water. After a few minutes 20 ml water are added. The disulfide formed is extracted with ether, the ether solution washed with water, dried over fused potash, and the ether evaporated. Yield 0.75 g (76%) yellow crystalline disulfide, melting at 84.5-85.5° after two recrystallizations from alcohol. Undepressed mixed melting point with a specimen of disulfide prepared as described in the previous experiment.

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