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RESEARCHES IN THE THIOPHENE SERIES
IX. 3, 4-Bis (chloromethyl)-2, 5-diethylthieno [2, 3-b] Thiophene and Some of its Reactions*

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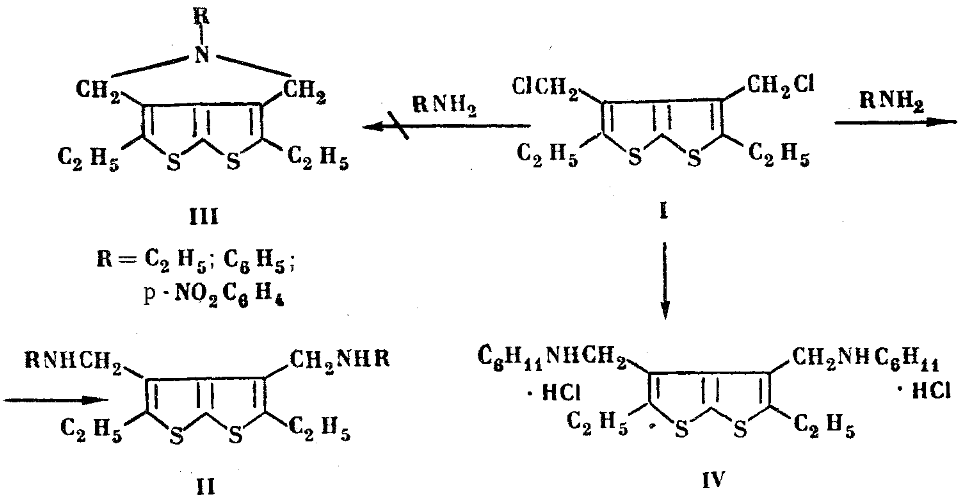
A method is devised for preparing some bifunctional derivatives of 2, 5-diethylthieno [2, 3-b] thiophene. Unlike the analogous naphthalene derivatives, 3, 4-bis-(chloromethyl)-2, 5-diethylthieno [2, 3-b] thiophene when treated with amines does not give the corresponding tricyclic system. Apparently this is due to differences between the geometries of the thienothiophene and naphthalene rings.

In the years which have elapsed since the discovery of thiophene, the view has arisen that it is the closest analog of benzene, not only chemically, but also with respect to physical properties. Considerations of relative similarity between benzene and thiophene based on formal indications could be extended to condensed benzene and thiophene systems, viz. naphthalene and isomeric thienothiophenes. Hence it was of interest to investigate the possibility of building a condensed tricyclic system based on thieno [2, 3-b] thiophene. With that end in view, the present authors studied the reaction of 3, 4-bis(chloromethyl)-2, 5-diethylthieno [2, 3-b] thiophene (I) with primary amines, viz. ethylamine, aniline, p-nitroaniline, and cyclohexylamine, under the conditions given in a previous paper [2]. The reaction medium used was dry benzene, and the ratio of dichloromethyl compound to amine was varied (1 : 1, 1 : 2, 1 : 3, and 1 : 4). Symmetrical diamines II were found to be formed in every case. Here it is necessary to note that the reaction of I with amines does not take place in one way only. Apparently, polycondensation also occurs. Type III compounds could not be detected in the reaction products. The symmetrical diamine IV, the starting compound I (47.3% of the initial amount), and cyclohexylamine hydrochloride were isolated from the mixture formed by reacting 3, 4-bis(chloromethyl) 2, 5-diethylthieno [2, 3-b] thiophene (I) with cyclohexylamine in the ratio 1 : 1.



The fact that under the given conditions formation of a six-membered ring is not observed, while analogous naphthalene compounds give the corresponding tricyclic derivatives, can be ascribed to the fact that the CH_2 groups in 3, 4-bis(chloromethyl)-2, 5-diethylthieno [2, 3-b] thiophene (I) are a greater distance apart than in the naphthalene. Obviously this is due to the difference in valence angles between naphthalene and thieno [2, 3-b] thiophene.

These results [3] are in agreement with findings that reaction of dimethyl 3, 4-diaminothieno [2, 3-b] thiophene-2, 5-dicarboxylate with ethyl orthoformate or acetic anhydride gives, respectively, dimethyl 3, 4-bis(ethoxymethyleneimino) and dimethyl 3, 4-bis(acetamido)-thieno [2, 3-b] thiophene-2, 5-dicarboxylate. Similarly dimethyl 3, 4-dihydroxythieno [2, 3-b] thiophene-2, 5-dicarboxylate and ethyl orthoformate give only dimethyl 3, 4-bis(acetoxy) thieno [2, 3-b] thiophene-2, 5-dicarboxylate. Thus other authors too could not obtain the tricyclic compound, starting from compounds with two functional groups at positions 3 and 4 in the thiophene system.

There are papers [2, 4-6] giving rather detailed studies of chloromethylation in the thiophene series and various

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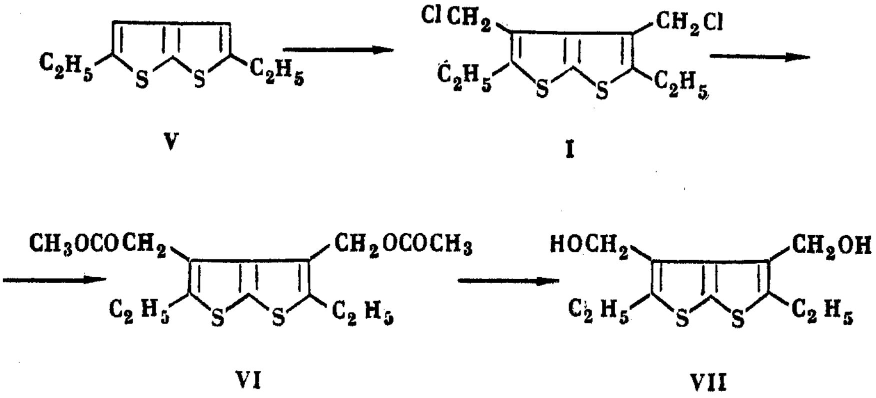
* For Part VIII see [1].

transformations of the resultant chloromethyl derivatives. In particular it was shown that reaction of paraformaldehyde and HCl at 50° with 2, 5-dimethyl- and 2, 5-di-tert-butylthiophene gives, respectively, 3, 4-bis(chloromethyl)-2, 5-dimethylthiophene (65% yield) and 3, 4-bis(chloromethyl)-2, 5-di-tert-butylthiophene (55% yield).

Extension of the method to 2, 5-diethylthieno [2, 3-b] thiophene (V) made it possible to obtain an 82.5% yield of the hitherto undescribed 3, 4-bis(chloromethyl)-2, 5-diethylthieno [2, 3-b] thiophene (I). Treatment of that compound with sodium acetate under conditions put forward for the similar conversion of 2, 5-bis(chloromethyl) thiophene [7] and 3, 4-bis-(chloromethyl) 2, 5-dimethylthiophene [5] gave a 97% yield of 3, 4-bis(acetoxymethyl)-2, 5-diethylthieno [2, 3-b]-thiophene (VI). Treatment of the latter with an ethanolic solution of sodium ethoxide gives an 85% yield of 3, 4-bis(hydroxymethyl)-2, 5-diethylthieno [2, 3-b] thiophene (VII).



The compounds I and VII synthesized are characterized by their UV spectra (see Experimental).

Experimental

3, 4-Bis(chloromethyl)-2, 5-diethylthieno [2, 3-b] thiophene (I). This was prepared by a method similar to that used for synthesis of 3, 4-bis-(chloromethyl)-2, 5-dimethylthiophene [4]. A current of HCl was passed into a mixture of 15.2 g paraformaldehyde and 31 ml concentrated hydrochloric acid maintained at 50° until it was completely saturated (the paraformaldehyde dissolved). Continuing to hold the mixture at that temperature, a vigorous stream of HCl was passed, and 9.8 g 2, 5 diethylthieno [2, 3-b] thiophene (V) [8], dropped in, the whole turned green, and was stirred under the same conditions for 2 hr, ice and water were added, and the products extracted thrice with benzene. The extract was washed with water, then with 5% KOH solution, again with water, and then dried over calcium chloride. The benzene was distilled off, and the residue crystallized. Recrystallization from heptane gave 12.1 g (82.5% yield) I mp 106-107°. UV spectrum: λ_{max} 245 mμ, ε 25 900. Found: C 49.00, 49.11; H 4.63, 4.68%. Calculated for $C_{12}H_{14}Cl_2S_2$: C 49.14; H 4.81%.

Reaction of 3, 4 bis(chloromethyl)-2, 5-diethylthieno [2, 3-b] thiophene (I) with primary amines. Dry benzene (40-50 ml per 0.02 mole thienothiophene) was the solvent used for carrying out reaction between I and the amines. The reactants were mixed with cooling by ice, or at room temperature, after which the mixture was kept at room temperature for 4-40 hr. In some cases (e.g., with cyclohexylamine) the reaction mixture was heated on a water bath for 2-8 hr. The ratio of dichloromethyl compound I to amine was 1 : 1, 1 : 2, 1 : 3, or 1 : 4. The reaction product usually comprised a benzene solution and a precipitate, which latter was filtered off; it contained hydrochlorides of the starting amine and base formed. The latter was recovered by dissolving these hydrochlorides in water, rendering them alkaline with a strong solution of KOH or potash, and then extracting with benzene and ether. In most cases it was impossible to distil the bases isolated, even in a high vacuum. Attempts to recrystallize them from various solvents were also unsuccessful.

4.16 g (0.041 mole) freshly-distilled cyclohexylamine was added to a solution of 6 g (0.0205 mole) I in 45 ml dry benzene. The mixture was left for 2 hr, then heated on a water bath for 8 hr. The precipitate (4.5 g) which separated after cooling was filtered off. It melted over a wide range (203-236°), and consisted of the hydrochloride of the starting cyclohexylamine with a minor proportion of reaction products. It was carefully washed with benzene, dried (4 g obtained), and then dissolved in alcohol. Ether was added, which precipitated 1.2 g 3, 4-bis(cyclohexylaminomethyl)-2, 5-diethylthieno [2, 3-b] thiophene dihydrochloride (IV), mp 273-274°. Found: C 58.15, 58.12; H 8.46, 8.26; N 6.09, 5.83%. Calculated for $C_{24}H_{40}Cl_2N_2S_2$: C 58.66; H 8.20; N 5.71%.

After evaporating the mother liquor, 2.1 g cyclohexylamine hydrochloride mp 208-209° (206-207.5° [9]) separated. After filtering off the precipitate formed in the reaction, the filtrate was evaporated, the residue dissolved in a small amount of benzene, and petrol ether added. This precipitated 0.6 g light brown powder mp 250-260°, which was IV dihydrochloride (according to the analytical data). The total yield of IV dihydrochloride was 1.8 g. Found: C 58.86, 58.78; H 7.82, 7.77; N 4.82, 5.11%. Calculated for $C_{24}H_{40}Cl_2N_2S_2$: C 58.66; H 8.20; N 5.71%.

1 g IV dihydrochloride was dissolved in hot water, the solution cooled, saturated with potash, and extracted with ether. The ether extracted was dried over potash, the ether distilled off, and the residue vacuum distilled, to give 0.37 g 3, 4-bis(cyclohexylaminomethyl) 2, 5-diethylthieno(2, 3-b) thiophene, bp 220° (0.03 mm). Found: C 69.45. 69.27; H 9.21, 9.34; S 14.63, 14.70%. Calculated for $C_{24}H_{38}N_2S_2$: C 68.84; H 9.14; S 15.07%.

Dipicrate mp 216.5 218° (from alcohol). Found: N 12.85; 13.02%. Calculated for $C_{24}H_{38}N_2S_2 \cdot 2C_6H_3N_3O_7$: N 12.76%.

3, 4-Bis(acetoxymethyl)-2, 5 diethylthieno [2, 3 b] thiophene (VI). 4.1 g (0.014 mole) I, 2.3 g (0.028 mole) sodium acetate, and 15 ml glacial acetic acid were heated together on a water bath for 6 hr, then left for 36 hr at room temperature. The white precipitate of NaCl which separated (1.59 g) was filtered off, the filtrate evaporated, and the residue recrystallized from alcohol, to give 4.66 g VI (97.6%), mp 65.66°. Found: C 57.16, 57.21; H 6.19, 6.14; S 19.35, 19.21%. Calculated for $C_{16}H_{20}O_4S_2$; C 56.44; H 5.92; S 18.83%.

3, 4 Bis(hydroxymethyl) 2, 5 diethylthieno [2, 3 b] thiophene (VIII). 2.7 g (0.008 mole) 3, 4 bis(acetoxymethyl)-2, 5-diethylthieno [2, 3-b]-thiophene (VI) was added dropwise to a solution of sodium ethoxide (prepared from 0.1 g sodium and 30 ml absolute ethanol), the whole left at room temperature for 3 days, and the alcohol then distilled off down to small volume. 3 g ammonium chloride was added to the residue, and the precipitate filtered off and washed a few times with absolute alcohol. The filtrate was evaporated to dryness under reduced pressure, and the residue recrystallized from dilute alcohol. Yield of VII, mp 125-126°, 1.75 g (85%). UV spectrum λ_{max} 235 mμ, ε 28400. Found: C 56.63, 56.67; H 6.56, 6.55; S 24.78, 25.05%. Calculated for $C_{12}H_{16}O_2,S_2$: C 56.18; H 6.29; S 25.01%.

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