

Preparation of Some Brominated Thieno[2,3-b]thiophenes and Thieno[3,2-b]thiophenes*

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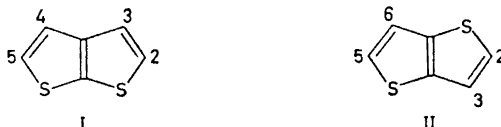
The introduction of bromine and its subsequent replacement by other substituents in the isomeric thieno[2,3-b]thiophene (I) and thieno[3,2-b]thiophene (II) have been investigated. By the reaction between 2,3,5-tribromothieno[2,3-b]thiophene and butyllithium a novel ring-opening reaction was discovered.

Only a few brominated thienothiophenes have been described in the literature even though the first recorded example, tetrabromothieno[2,3-b]thiophene, m.p. 172°, was synthesized in 1886 by Biedermann and Jacobson.¹ A dibromothienothiophene with m.p. 122.5° was mentioned by Capelle.² Challenger and Harrison³ pointed out, however, that the reported melting point was very close to the reported melting point 123-124° of 2,3,5-tribromothieno[2,3-b]thiophene. Another bromo-compound, m.p. 223°, was also described by Capelle² which may be identical with the tetrabromothienothiophene, m.p. 229-230°, prepared by Meyer and Wesche⁴ and shown by Challenger and Harrison³ to be tetrabromothieno[3,2-b]thiophene. In an attempt to prepare a monobrominated thieno[3,2-b]thiophene by treatment of thieno[3,2-b]thiophene with one equivalent of bromine in glacial acetic acid Challenger *et al.*⁵ obtained only the dibromo-compound along with polymers. Similar polymers were obtained from both the isomeric thienothiophenes when they were treated with hydrogen bromide in glacial acetic acid. Electrophilic substitutions in both the thienothiophenes were found by Challenger⁶ to occur preferentially in the 2- or α -positions while the normal position for substitution in benzo[b]thiophene is the 3- or β -position. Pariser-Parr-Pople SCF-MO calculations by Clark⁷ on thieno[2,3-b]thiophene and thieno[3,2-b]thiophene shows high electron density at the positions adjacent to the sulphur atoms, which is consistent with the predominance of electrophilic substitution at these sites. Similar calculations by Momicchioli and Rastelli⁸ and Trinajstić and Hinchliffe⁹ on benzo[b]thiophene shows high

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electron density in the 3-position, which may account for the predominance of electrophilic substitution in this site.

This paper reports studies on the introduction of bromine and its subsequent replacement by other substituents in the isomeric thieno[2,3-*b*]thiophene and thieno[3,2-*b*]thiophene compounds. A survey of the importance of brominated thiophenes for the synthesis of substituted thiophenes can be found in Ref. 10.



The fact that hydrogen bromide tends to polymerize the thienothiophenes⁵ indicated that a bromination process where hydrogen bromide is not evolved might be more successful and this proved to be the case. The instability of the 2-bromo-compounds and the fact that the polybrominated thienothiophenes can be prepared by direct bromination indicates, however, that the polymerisation may also have other causes than the evolved hydrogen bromide. Treatment of the thienothiophenes, prepared according to Ref. 11, with equivalent amounts of *N*-bromosuccinimide (NBS) in glacial acetic acid gave the monobrominated compounds as the major products in both series. The structure of 2-bromothieno[2,3-*b*]thiophene was verified by halogen-metal interconversion with butyllithium at -70° . The resulting reaction mixture was poured onto solid carbon dioxide and the IR-spectrum showed the acid to be thieno[2,3-*b*]thiophene-2-carboxylic acid.¹¹ In order to prove the structure of 2-bromothieno[3,2-*b*]thiophene the compound was synthesized *via* 2-lithiothieno[3,2-*b*]thiophene.¹¹ The metalated thieno[3,2-*b*]thiophene in ether was cooled to -70° , one equivalent of bromine in dry hexane was added, and the reaction mixture was poured into water. Both the solid 2-bromothieno[2,3-*b*]thiophene and the solid 2-bromothieno[3,2-*b*]thiophene are unstable compounds which decompose in a few hours at room temperature but can be stored for weeks at -15° .

In quantitative studies of the bromination with equivalent amounts of NBS the reactions were allowed to proceed for two hours at 25° . The composition of the reaction mixture from the bromination of thieno[2,3-*b*]thiophene was determined by comparing the extinction coefficients of pertinent bands in the IR-spectra in carbon disulphide with the extinction coefficients of the same bands from the spectra of known concentrations of the pure components in the same solvent. In the same manner, using chloroform as solvent, the reaction mixture from the bromination of thieno[3,2-*b*]thiophene was determined. Bromination of thieno[2,3-*b*]thiophene gave 8 mole % of thieno[2,3-*b*]thiophene 83 mole % of 2-bromothieno[2,3-*b*]thiophene and 9 mole % of 2,5-dibromothieno[2,3-*b*]thiophene. Bromination of thieno[3,2-*b*]thiophene gave 15 mole % of thieno[3,2-*b*]thiophene, 70 mole % of 2-bromothieno[3,2-*b*]thiophene and 15 mole % of 2,5-dibromothieno[3,2-*b*]thiophene. The IR-spectra showed only the above mentioned components present in the reaction

mixture. Additional experiments, run for 30 min under the above experimental conditions, showed the same compositions of the reaction mixtures as found after the longer reaction times.

Gjøes and Gronowitz¹² have reported that acid catalyzed rearrangement of 3-phenyl-2-bromothiophene in glacial acetic acid leads to 3-phenyl-5-bromothiophene, 3-phenyl-2,5-dibromothiophene and 3-phenylthiophene. It would thus seem that hydrogen bromide liberation during the bromination of 3-phenylthiophene with bromine in glacial acetic acid makes the bromination reversible, and that the product mixture ultimately formed is thermodynamically controlled. The same authors also report that the bromination of 3-phenylthiophene with NBS in glacial acetic acid gives a mixture of reaction products. In order to check whether the bromination of the thienothiophenes is in fact reversible, each brominated component was separately treated for two hours at 25° with small amounts of hydrogen bromide in glacial acetic acid. However, no spectral change took place, indicating that the bromination of the thienothiophenes under the above conditions is not reversible.

2,5-Dibromothieno[2,3-b]thiophene and 2,5-dibromothieno[3,2-b]thiophene were both obtained in good yields by bromination with two equivalents of NBS in glacial acetic acid at room temperature. The assigned structures were confirmed by their NMR-spectra, which show singlets in the aromatic region. Both tribromothienothiophenes were synthesized by bromination of the respective thienothiophenes in carbon disulphide with three equivalents of bromine following the procedure of Challenger and Harrison.³ Treatment of 2,3,5-tribromothieno[3,2-b]thiophene with butyllithium at -70° followed by hydrolysis gave 2,6-dibromothieno[3,2-b]thiophene. It was evident from the presence of two singlets with equal intensities at τ 2.33 and τ 2.40 in the NMR-spectrum that the halogen-metal interconversion had occurred in the 2-position. In order to obtain 3-bromothieno[3,2-b]thiophene 2,3,5-tribromothieno[3,2-b]thiophene was treated with an excess of zinc in glacial acetic acid. The reaction product was shown by gas chromatography to contain 70–80 % of a main product, whose structure was shown to be 3-bromothieno[3,2-b]thiophene, together with thieno[3,2-b]thiophene and 2,6-dibromothieno[3,2-b]thiophene identified from their IR-spectra. Preparative gas chromatography gave the pure 3-bromothieno[3,2-b]thiophene as an oily liquid. Treatment of 2,3,5-tribromothieno[2,3-b]thiophene with excess zinc in glacial acetic acid similarly gave the crystalline 3-bromothieno[2,3-b]thiophene, whereas the use of a smaller amount of zinc gave 2,4-dibromothieno[2,3-b]thiophene. The NMR-spectrum of 2,4-dibromothieno[2,3-b]thiophene showed two singlets with equal intensities in the aromatic region.

In an attempt to prepare 2,4-dibromothieno[2,3-b]thiophene through halogen-metal interconversion at -70° an unexpected compound was isolated together with the starting material. This compound is believed to be 2-(5-bromo-3-ethynyl-2-thienylthio)-3,5-dibromothieno[2,3-b]thiophene (III), though the structures (IV) or (V) are not excluded. The elementary analysis indicates a compound with the composition $C_{12}H_3Br_3S_4$ (515.2). This is confirmed by the mass spectrum which shows molecular ions at m/e 512, 514, 516, and 518 in the approximate ratio of 1/3/3/1 indicating three bromine atoms in the molecule. The NMR-spectrum shows three singlets

stirring during 5 min. The reaction mixture was stirred for an additional 15 min before it was poured into water, the organic layer collected, and the water layer extracted once with ether. The combined ether phases were washed with 2 N sodium hydroxide solution, and then with water, dried over calcium chloride together with some decolorizing carbon. Evaporation of the ether left 9.9 g of a green oil which was distilled at reduced pressure. The main fraction, 5.9 g, b.p._{0.1} 62.0–72.0°, gave after treatment with ethanol a partially crystalline oil. Recrystallisation of this oil gave 2.8 g (26 %) of 2-bromothieno[3,2-*b*]thiophene. The analytic sample was recrystallized from ethanol to m.p. 36.0–38.0°. NMR (CDCl₃): τ_3 2.89; τ_5 2.77; τ_4 3.02. J_{56} 5.2 c/s; J_{36} 0.6 c/s. (Found: C 32.7; H 1.44; Br 36.6; S 28.9. Calc. for C₆H₃BrS₂ (219.1): C 32.89; H 1.38; Br 36.47; S 29.27).

*Thieno[2,3-*b*]thiophene-2-carboxylic acid.* In the usual nitrogen swept Grignard apparatus, a solution of 1.10 g (0.005 mole) of 2-bromothieno[2,3-*b*]thiophene in 20 ml of dry ether was cooled to –70°, and a solution of 5.1 ml of 1.09 N ethereal butyllithium added with stirring over 5 min. The reaction mixture was stirred for another 5 min and poured onto dry ice covered with dry ether. When the reaction mixture had reached room temperature water was added and the ethereal phase washed once with water. The combined water phases were acidified with dilute hydrochloric acid precipitating 0.7 g (77 %) of thieno[2,3-*b*]thiophene-2-carboxylic acid,¹¹ identified by its IR-spectrum.

*3-Bromothieno[3,2-*b*]thiophene.* A mixture of 3.77 g (0.01 mole) of 2,3,5-tribromothieno[3,2-*b*]thiophene, 2.6 g (0.04 mole) of zinc dust and 75 ml of glacial acetic acid was slowly heated with stirring to boiling and refluxed for 5 h. The reaction mixture was poured into water, extracted with chloroform, and the chloroform phase washed with water and saturated sodium bicarbonate solution before it was dried over calcium chloride. Evaporation of the chloroform left 2.2 g of the crude reaction product containing 70–80 % 3-bromothieno[3,2-*b*]thiophene together with thieno[3,2-*b*]thiophene and 2,6-dibromothieno[3,2-*b*]thiophene, determined by gas chromatography. The pure 3-bromothieno[3,2-*b*]thiophene was obtained by means of preparative gas chromatography. B.p.₀ 126°, n_D^{20} 1.6879. NMR (CDCl₃): τ_2 2.85; τ_5 2.70; τ_6 2.88. J_{56} 5.3 c/s; J_{25} 1.4 c/s. (Found: C 32.95; H 1.31, Br 36.26; S 29.19. Calc. for C₆H₃BrS₂ (219.1): C 32.89; H 1.38; Br 36.47; S 29.27).

*3-Bromothieno[2,3-*b*]thiophene* was prepared from 3.5 g (0.009 mole) of 2,3,5-tribromothieno[2,3-*b*]thiophene and 3.6 g (0.055 mole) of zinc dust in glacial acetic acid as described above. This gave 1.7 g of an oily reaction product which crystallized on standing. Recrystallisation from ethanol gave 1.3 g (63 %) of 3-bromothieno[2,3-*b*]thiophene. The analytic sample was recrystallized from ethanol to m.p. 36.5–37.0°. NMR (CDCl₃): τ_2 2.83; τ_4 2.89; τ_5 2.70. J_{45} 5.3 c/s; J_{25} 1.2 c/s. (Found: C 32.79; H 1.54; Br 36.45; S 28.96. Calc. for C₆H₃BrS₂ (219.1): C 32.89; H 1.38; Br 36.47; S 29.27).

*2,4-Dibromothieno[2,3-*b*]thiophene.* 0.98 g (0.015 mole) of zinc dust was added all at once to a stirred slurry of 3.77 g (0.01 mole) of 2,3,5-tribromothieno[2,3-*b*]thiophene in 75 ml of glacial acetic acid at 60°. The reaction mixture was heated to boiling and refluxed for 30 min, poured into water and the reaction product was extracted with chloroform. The chloroform phase was treated with water and saturated sodium bicarbonate solution before it was dried over calcium chloride. Evaporation of the chloroform gave 2.9 g of the crude reaction product which after recrystallisation from ethanol gave 2.1 g (71 %) of 2,4-dibromothieno[2,3-*b*]thiophene. The analytic sample was recrystallized from ethanol to constant m.p. 70.0–76.0°. NMR (CDCl₃): τ 2.69; τ 2.75. (Found: C 24.11; H 0.72; Br 53.70; S 21.52. Calc. for C₆H₄Br₂S₂ (298.0): C 24.18; H 0.68; Br 53.63; S 21.52).

*2,5-Dibromothieno[2,3-*b*]thiophene.* 8.9 g (0.05 mole) of NBS was added in portions during about 20 min to a stirred solution of 3.5 g (0.025 mole) of thieno[2,3-*b*]thiophene in 75 ml of glacial acetic acid at room temperature. The reaction mixture was stirred for about 90 min before it was poured into water and extracted with chloroform. The organic phase was treated with water and saturated sodium bicarbonate solution and dried over calcium chloride together with some decolorizing carbon. Evaporation of the chloroform left 7.0 g of crude reaction product. Recrystallisation from ethanol gave 6.5 g (65 %) of 2,5-dibromothieno[2,3-*b*]thiophene. The analytic sample was recrystallized from ethanol to constant m.p. 95.0–96.0°. NMR (CDCl₃): τ_{34} 2.91. (Found: C 24.08; H 0.98; Br 53.40; S 21.33. Calc. for C₆H₂Br₂S₂ (298.0): C 24.18; H 0.68; Br 53.63; S 21.52).

*2,5-Dibromothieno[3,2-*b*]thiophene* was prepared as described above from 3.5 g (0.025 mole) of thieno[3,2-*b*]thiophene and 8.9 g (0.05 mole) of NBS to give the title compound in a yield of 6.5 g (88 %). The analytic sample was recrystallized from ethanol to constant

m.p. 129.5–131.0° (lit. value⁵ 128.0–129.0°). NMR (CDCl₃): τ_{35} 2.88. (Found: C 24.3; H 0.80; Br 53.8; S 21.3. Calc. for C₈H₂Br₂S₂ (298.0): C 24.18; H 0.68; Br 53.63; S 21.52).

2,3,5-Tribromothieno[2,3-b]thiophene. To a stirred and ice cooled solution of 14.0 g (0.1 mole) of thieno[2,3-b]thiophene in 100 ml of carbon disulphide was added dropwise during about one hour 52.8 g (0.33 mole) of bromine in 50 ml of the same solvent. The reaction mixture was stirred for 48 h at room temperature, washed with 2 N sodium hydroxide solution and then with water and dried over calcium chloride. Evaporation of the carbon disulphide left 35.3 g of the crude reaction product. Recrystallisation from ethanol gave 28.5 g (75 %) of 2,3,5-tribromothieno[2,3-b]thiophene which on one further recrystallisation melted at 122.0–124.0° (lit. value³ 123.0–124.0°). NMR (CDCl₃): τ_4 2.85.

2,3,5-Tribromothieno[3,2-b]thiophene was made as described above from 14.0 g (0.1 mole) of thieno[3,2-b]thiophene and 52.8 g (0.33 mole) of bromine yielding 35.6 g of the crude reaction product. Recrystallisation from chloroform gave 30.5 g (81 %) of 2,3,5-tribromothieno[3,2-b]thiophene. The analytic sample was recrystallized from chloroform to m.p. 140.0–143.5°. NMR (CDCl₃): τ_6 2.80. (Found: C 19.38; H 0.22; Br 63.77; S 16.95. Calc. for C₈HBr₃S₂ (376.9): C 19.12; H 0.27; Br 63.60; S 17.01).

2,6-Dibromothieno[3,2-b]thiophene. 5.8 ml of 1.03 N ethereal butyllithium was cooled to –70° in the usual nitrogen swept Grignard apparatus and a solution of 1.88 g (0.005 mole) of 2,3,5-tribromothieno[3,2-b]thiophene in 25 ml of dry tetrahydrofuran was added dropwise with stirring during 10 min. After stirring for about 5 min, the reaction mixture was poured into water and extracted once with ether. The ethereal phase was washed with water and dried over calcium chloride together with some decolorizing carbon. Evaporation of the ether left 1.3 g of the reaction product which was recrystallized from ethanol to give 1.1 g (74 %) of 2,6-dibromothieno[3,2-b]thiophene. The analytic sample was recrystallized from hexane to m.p. 62.0–64.5°. NMR (CDCl₃): τ_{35} 2.73, (acetone-*d*₆): τ 2.33, τ 2.40. (Found: C 24.12; H 0.65; Br 53.56; S 21.66. Calc. for C₈H₂Br₂S₂(298.0): C 24.18; H 0.68; Br 53.63; S 21.52).

Compound III, IV or V was prepared in the manner described above from 20.0 ml of 1.09 N ethereal butyllithium and 7.54 g (0.02 mole) of 2,3,5-tribromothieno[2,3-b]thiophene in 30 ml of dry tetrahydrofuran and an addition time of 15 min for this solution. Evaporation of the ether left 4.8 g of a dark oil which partially crystallized on standing. Ethanol extraction of this oil gave 2.5 g of a nearly colourless crystalline product. The IR-spectrum of this product showed that it mainly contained the starting material. Fractional crystallisation of the product from chloroform gave together with the starting material a small amount of a compound which was recrystallized from hexane to m.p. 125.0–130.0° (decomp.). NMR (CDCl₃): τ 2.81, τ 3.00, τ 6.60. IR (CCl₄): 3310 cm⁻¹, 2110 cm⁻¹. The mass spectrum showed molecular ions at *m/e* 512, 514, 516 and 518 and with relative intensities about 1/3/3/1. (Found: C 28.24; H 0.56; Br 46.45; S 25.05. Calc. for C₁₂H₃Br₃S₄ (515.2): C 27.97; H 0.59; Br 46.54; S 24.90).

Bromination of the thienothiophenes with equivalent amounts of NBS. Quantitative measurements. General procedure: 2.23 g (0.0125 mole) of solid NBS was added in portions during 7 min to 1.75 g (0.0125 mole) of the thienothiophene in 75 ml of glacial acetic acid at 25 ± 0.2° and the reaction mixture stirred for 2 h. The reaction mixture was poured into 200 ml of water and extracted once with 20 ml and three times with 10 ml of carbon disulphide or chloroform. The combined organic phases were washed with 10 ml of water, twice with 10 ml of saturated sodium bicarbonate solution and again with 10 ml of water before being dried overnight with calcium chloride. The chloroform used was freed from ethanol by filtering through aluminium oxide (Woelm basic activity grade 1). The dried solutions were diluted to 50 ml with pure solvent. The compositions of the product mixtures were evaluated by comparison of the extinction coefficients in the IR-spectra of some pertinent bands with the extinction coefficients of the same bands in the IR-spectra of the pure components in known concentrations. The thieno[2,3-b]thiophenes were run in carbon disulphide and the thieno[3,2-b]thiophenes in chloroform. The concentrations of the reference spectra and the bands used are as follows: Thieno[2,3-b]thiophene 30.8 mg/ml, 790 cm⁻¹; 2-bromothieno[2,3-b]thiophene 72.2 mg/ml, 1168 cm⁻¹, 929 cm⁻¹; 2,5-dibromothieno[2,3-b]thiophene 64.8 mg/ml, 1154 cm⁻¹, 951 cm⁻¹, 915 cm⁻¹; thieno[3,2-b]thiophene 20.2 mg/ml, 922 cm⁻¹; 2-bromothieno[3,2-b]thiophene 54.6 mg/ml, 882 cm⁻¹ and 2,5-dibromothieno[3,2-b]thiophene 80.3 mg/ml, 1005 cm⁻¹. The average of three parallels gave the compositions: Thieno[2,3-b]thiophene 8 mole %,

2-bromothieno[2,3-b]thiophene 83 mole % and 2,5-dibromothieno[2,3-b]thiophene 9 mole %. Thieno[3,2-b]thiophene 15 mole %, 2-bromothieno[3,2-b]thiophene 70 mole % and 2,5-dibromothieno[3,2-b]thiophene 15 mole %.

A reaction time of 30 min gave spectra which showed the compositions of the product mixtures to be without significant deviations from these averages.

Treatment of some of the brominated thienothiophenes with hydrogen bromide in glacial acetic acid. 2-Bromothieno[2,3-b]thiophene, 2,5-dibromothieno[2,3-b]thiophene, 2-bromothieno[3,2-b]thiophene and 2,5-dibromothieno[3,2-b]thiophene were treated with hydrogen bromide in glacial acetic acid in the following way: 0.003 mole of the brominated thienothiophene was dissolved in 25 ml of glacial acetic acid containing 0.0003 mole of dry hydrogen bromide and stirred for two hours at $25 \pm 0.2^\circ$. The reaction mixture was worked up as described above to give 10 ml of the dry solution. The IR-spectra recorded in the range 1400 cm^{-1} — 700 cm^{-1} were the same as for the starting material.

The IR-spectra for quantitative measurements were recorded with a Perkin-Elmer model 21 spectrophotometer equipped with a sodium chloride prism.

The gas-chromatographic separations were carried out on a Varian Aerograph Series 200 instrument. The column was packed with 20 % silicone gum rubber SE-30 on Chromosorb W (HMDS).

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