Bromothiophene Reactions. II. A Novel Rearrangement in the Zinc and Acetic Acid Reduction

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The elimination of the α-bromine atoms of the bromothienylethanolamine derivatives **2a,b,c,d** with zinc and acetic acid unexpectedly involved a migration of the ethanolamine side chain from the 3 to the 2 position in the thiophene ring. Experiments carried out with simpler analogous compounds **3**, **4** and **6** seem to indicate that this rearrangement takes place only in those cases in which the carbon atom of the side chain next to the ring supports an oxygen atom capable of being protonated in the reaction medium. A tentative mechanism is proposed to explain the experimental results.

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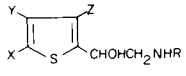
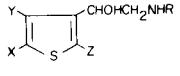
In previous work (1,2) all possible thienylethanolamine derivatives of general formula **1** were synthesized and their β-adrenergic blocking properties tested. In order to complete the study of the structure-activity relationships, the synthesis of the isomeric compounds of general formula **2** was subsequently undertaken. Compounds **2** directly accessible by initial chloroacetylation of 2,5-dihalo and 2,3,5-trihalothiophenes, were obtained (3) without any major difficulties (*cf.* 4). However, when the preparation of other compounds of this series, through elimination of the α-bromine atoms from previously prepared bromothiophene derivatives, was attempted, an anomalous course of the reaction took place.



1

R = a iso-C_3H_7; b t-C_4H_9



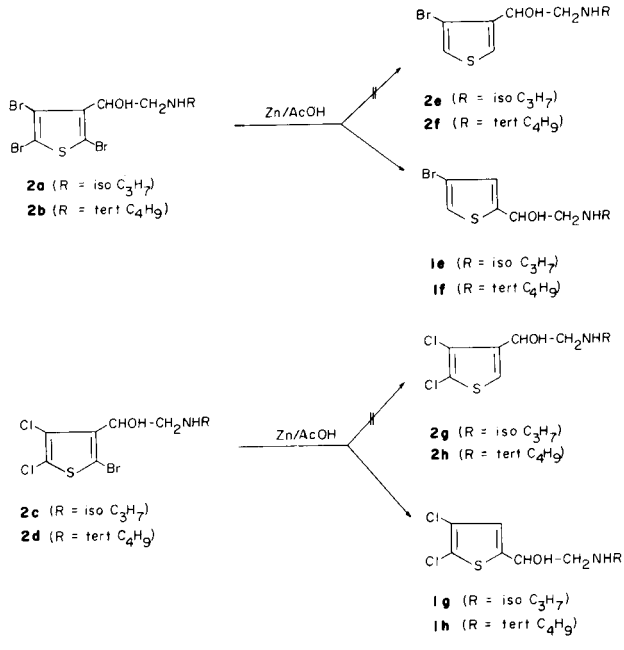
2

X, Y, Z = Cl, H or Br, H

Thus, when compounds **2a** and **2b** (3) and **2c** and **2d** (for synthesis see Experimental) were boiled with zinc and aqueous acetic acid, following a standard procedure for α-debromination in thiophenic compounds (5), previously described compounds **1e** and **1f** (2) and **1g** and **1h** (1) were respectively obtained instead of the expected compounds **2e**, **2f**, **2g** and **2h** (Scheme I). Therefore, treatment with zinc and acetic acid produced not only elimination of the α-bromine atoms, but also the migration of the ethanolamine side chain from 3 to 2 position in the thiophene ring.

The unexpected results in the reduction of the ethanolamines **2**, encouraged us to further study the behaviour of more simple compounds capable of being debrominated under these conditions. It was also considered of interest to change the substitution in the 3-side chain, in order to elucidate the scope of the reaction, and to obtain additional data to propose a possible mechanism. Acetyl and α-hydroxyethyl groups, with capability of protonation in the reaction medium, and also the ethyl group was chosen. Starting materials and the expected compounds after

Scheme I

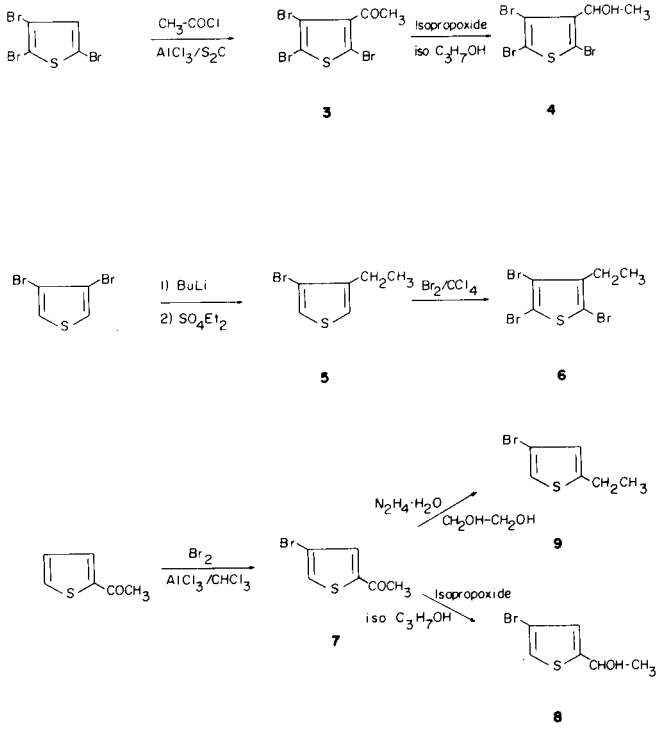


debromination, with or without transposition, were synthesized according to Scheme II.

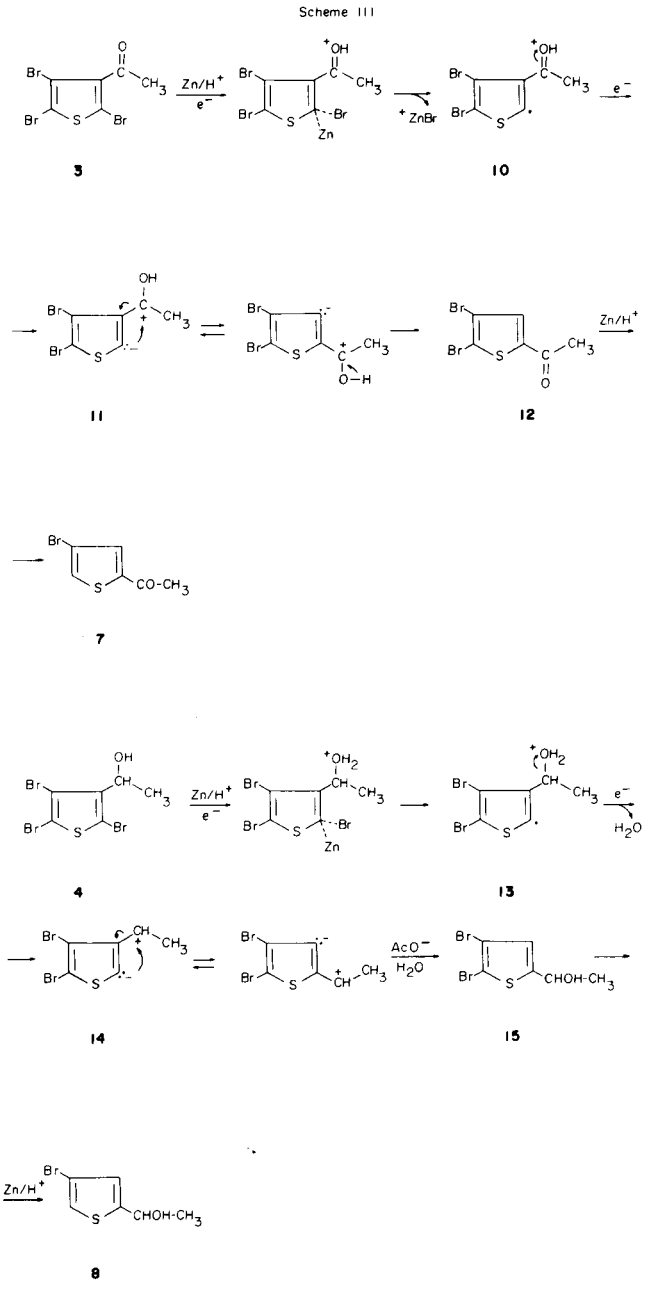
When 3-acetyl-2,4,5-tribromothiophene **3** was reduced under the indicated debromination conditions, the compound obtained was identical to 2-acetyl-4-bromothiophene **7**. In a similar manner, treatment of 3-(1-hydroxyethyl)-2,4,5-tribromothiophene **4** with zinc and acetic acid, afforded 2-(1-hydroxyethyl)-4-bromothiophene **8**. On the other hand, reduction of 3-ethyl-2,4,5-tribromothiophene **6** under the same conditions, yielded 3-ethyl-4-bromothiophene **5**. Identification of the reduced compounds was easily achieved by comparison with samples obtained via Scheme II (ir and nmr spectra).

According to these results, side chain transposition takes place only in those cases in which there is a group, ketone or hydroxyalkyl, attached to thiophene ring which is capable of being protonated in the reaction medium.

Scheme II



Scheme III



With these data and the few references found in the literature about the mechanism of reductive debromination with zinc/acetic acid, it is only possible to suggest a tentative course of the reaction to explain the experimental results.

These results can be interpreted supposing that protonation of the side chain ketone or alcoholic group in the reaction medium followed by attack of the metal surface at the C-Br bond would give rise to a thiophenic radical **10** or **13** by one-electron transfer. This radical would be converted to a thiophenic anion **11** or **14** by another one-electron transfer, in a similar manner to the mechanism suggested for the reduction with zinc of halogenated compounds in the allycyclic (6,7) and alkyl (8) series. The mechanism might also involve a cyclic intermediate instead of zwitter-ions **11** and **14**. In the "normal" reduction this anion is protonated to afford the debrominated compound, but in this case rapid attack by the side chain carbocation can product **12** or **15**. A new reduction of the C-Br bond at the 5 position finally produces compounds **7** or **8** (Scheme III).

No observed transposition in the 3-alkyl side chain case excludes the possibility of a rearrangement of the intermediate thiophenic radical, in a similar manner to that observed by Pedulli in the 3,3'- and 2,3'-bithienyl radical anions (9).

EXPERIMENTAL

Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained on a spectrophotometer Perkin-Elmer Model 457. ^{1}H nmr spectra were determined on a Perkin-Elmer R-10 Spectrometer, using TMS as an internal standard.

Halo and Acetylthiophenes.

5-Bromo-2,3-dichloro (10), 3,4-dibromo (11), 2,3,5-tribromo (12), 2-acetyl (13), and 3-acetyl-2,4,5-tribromothiophenes **3** (4) were prepared according to literature procedures.

N-Isopropyl- and *N*-*t*-Butyl-2-amino-1-(2 or 3-thienyl)ethanols.

Compounds **1e** and **1f** (2), **1g** and **1h** (1) and **2a** and **2b** (3) were prepared and described in the course of previous work.

Compounds **2c** and **2d** were synthesized by the following procedure:

To a stirred suspension of anhydrous aluminium trichloride (38.5 g, 0.29 mole) in dry carbon disulfide (250 ml) chloroacetyl chloride (32.6 g, 0.29 mole) was added, and then dropwise 5-bromo-2,3-dichlorothiophene (58.0 g, 0.25 mole). The mixture was stirred at room temperature overnight and then refluxed for 1 hour. The reaction mixture was poured into 500 ml of ice-water, the organic layer separated, washed with water, dried (magnesium sulfate) and the solvent evaporated. The residue was distilled *in vacuo* yielding 58.6 g of a mixture of two compounds bp 120-126°/2.5 mm.

A part of the mixture was separated by preparative tlc (ethyl acetate-hexane 1:10) and the compounds identified as 2-bromo-3-chloroacetyl-4,5-dichlorothiophene (63% in the mixture) mp 85-86° (petroleum ether); nmr (deuteriochloroform): δ 4.68 (s, 2H, CH_2Cl).

Anal. Calcd. for $C_6H_2BrCl_3OS$: C, 23.30; H, 0.65; S, 10.30. Found: C, 23.04; H, 0.68; S, 10.18.

2-Chloroacetyl-4,5-dichlorothiophene.

This compound was obtained in a yield of 37% mp 60-61° (petroleum ether) [lit (14) 61-62)]; nmr (deuteriochloroform): δ 4.66 (s, 2H, CH_2Cl) and 7.49 (s, 1H, thiophene 3H). This result is in agreement with those reported in reference (4).

The rest of the mixture (42.5 g) was reduced with aluminium isopropoxide (31.6 g, 0.155 mole) and anhydrous 2-propanol (300 ml) following a standard procedure (15). The mixture of thienylchloroethanols was separated by fractional distillation *in vacuo*. 2-Chloro-1-[2-(4,5-dichloroethienyl)]ethanol (8.8 g) bp 115-120°/1 mm [lit (1) 113°/0.25 mm] distills in the first place, and then 2-chloro-1-[3-(2-bromo-4,5-dichloroethienyl)]-ethanol (19.4 g) bp 145-150°/1 mm; nmr (deuteriochloroform): δ 3.76 (d, 2H, CH_2Cl) 5.15 (t, 1H, CHOH) J = 14.0 Hz and 4.25 wide band.

Anal. Calcd. for $C_6H_4BrCl_3OS$: C, 23.22; H, 1.30; S, 10.30. Found: C, 23.52; H, 1.28; S, 10.27.

The last compound (9.6, 0.03 mole) and isopropyl or *t*-butylamine (0.075 mole) was heated at 100° for 24 hours in a sealed tube. The cooled mixture was treated with ether and water. Drying (magnesium sulfate) and concentration of the ethereal extracts gave the crude product which was purified in a neutral alumina chromatography column (ethyl acetate-hexane 1:1).

Compound **2c** (4.7 g, 46%) was obtained as a syrup; nmr (deuteriochloroform): δ 1.08 (d, 6H, $2CH_3$), 2.84 (d, 2H, CH_2N) 3.10 (m, 1H, CHN) and 3.08 wide band.

Anal. Calcd. for $C_9H_{12}BrCl_2NOS$: C, 32.43; H, 3.60; N, 4.20. Found: C, 32.66; H, 3.72; N, 4.37.

Compound **2d** (5.0 g, 48%) was also obtained as a syrup; nmr (deuteriochloroform): δ 1.10 (s, 9H, $3CH_3$) 2.82 (d, 2H, CH_2N) 4.78 (t, 1H, CH), and 3.24 wide band.

Anal. Calcd. for $C_{10}H_{14}BrCl_2NOS$: C, 34.58; H, 4.03; N, 4.03. Found: C, 34.70; H, 4.14; N, 4.10.

2-Acetyl-4-bromothiophene (**7**).

To a stirred mixture of 2-acetylthiophene (42.7 g, 0.338 mole) and anhydrous aluminium trichloride (101.3 g, 0.760 mole) in dry chloroform (225 ml) a solution of bromine (57.5 g, 0.360 mole) in dry carbon tetrachloride (375 ml) was added dropwise. The mixture was stirred at room temperature overnight and then poured into ice-water. The organic layer was separated, washed with water, dried (magnesium sulfate) and evaporated. The residue was distilled *in vacuo*, yield 52.2 g (75%), bp 110-115°/3 mm; n_D^{31} = 1.6057 [lit (16) 117-119°/7 mm (16) n_D^{20} = 1.6080]; nmr (deuteriochloroform): δ 2.52 (s, 3H, CH_3); 7.49 (d, 1H) and 7.52 (d, 1H) J = 1.3 Hz, AB system thiophenic protons.

2,4,5-Tribromo-1-(3-thienyl)ethanol (**4**) and 4-Bromo-1-(2-thienyl)ethanol (**8**).

These compounds were prepared by treatment of 3-acetyl-2,4,5-tribromothiophene **3** and 2-acetyl-4-bromothiophene **7** (0.06 mole) with aluminium isopropoxide (4.12 g, 0.022 mole) in anhydrous 2-propanol (50 ml) following a standard procedure (15).

2,4,5-Tribromo-1-(3-thienyl)ethanol (**4**) was obtained in 65% yield, bp 135-137°/1.6 mm; nmr (deuteriochloroform): δ 1.56 (d, 3H, CH_3) and 5.28 (q, 1H, CH) J = 6.6 Hz, and 2.40 (wide band, 1H, OH).

Anal. Calcd. for $C_6H_5Br_3OS$: C, 19.73; H, 1.37; S, 8.77. Found: C, 19.81; H, 1.40; S, 8.69.

4-Bromo-1-(2-thienyl)ethanol (**8**) was obtained in 72% yield, bp 105-108°/1.1 mm; nmr (carbon tetrachloride): δ 7.09 (d, 1H, thiophene 5H) and 6.82 (d, 1H, thiophene-3H) J = 1.3 Hz; 4.94 (q, 1H, CH) and 1.36 (d, 3H, CH_3) J = 6.7 Hz, and 3.39 (wide band, 1H, OH).

Anal. Calcd. for C_6H_7BrOS: C, 34.79; H, 3.40; S, 15.44. Found: C, 34.50; H, 3.63; S, 15.28.

4-Bromo-3-ethylthiophene (**5**).

This compound was prepared according to the method described by Gronowitz for the synthesis of the 3-ethylthiophene (17).

To a stirred solution of 3,4-dibromothiophene (46.0 g, 0.19 mole) in dry ether (1000 ml) in a nitrogen atmosphere at −70°, a 2*M* solution of butyllithium in hexane (100 ml) was added. Stirring was continued for 15 minutes, and then a solution of diethylsulfate (32.5 g, 0.21 mole) in dry ether (100 ml) was added dropwise. The mixture was allowed to reach room temperature and stirred overnight. Then a 12*M* solution of ammonium hydroxide (50 ml) was added and stirring continued for 48 hours. The organic layer was separated, washed with water, dried (magensium sulfate) and evaporated. The residue was steam distilled, and redistilled, yield 25.0 g (69%), bp 105-110°/45 mm, n_D^{20} = 1.5630; nmr (carbon tetrachloride): δ 1.23 (t, 3H, CH_3), 2.63 (q, 2H, CH_2), 6.93 (d, 1H, thiophene 2H) and 7.22 (d, 1H, thiophene 5H), J = 3.4 Hz.

Anal. Calcd. for C_6H_7BrS: C, 37.70; H, 3.69; S, 16.74. Found: C, 37.57; H, 3.42; S, 16.82.

3-Ethyl-2,4,5-tribromothiophene (**6**).

To a stirred solution of 4-bromo-3-ethylthiophene 5 (17.2 g, 0.09 mole) in dry carbon tetrachloride (35 ml), a solution of bromine (32.0 g, 10.2 ml, 0.2 mole) in dry carbon tetrachloride (75 ml) was added dropwise. The mixture was stirred at room temperature overnight and then refluxed for 2 hours. Solid sodium hydroxide (2.0 g) was added and reflux continued for 4 hours. The solid was filtered, and the solution washed with water, dried (magnesium sulfate) and evaporated. The residue was distilled to yield 28.6 g (91%) of a liquid of bp 115-117°/1 mm, n_D^{20} = 1.6359; nmr (carbon tetrachloride): δ 1.1 (t, 3H, CH_3) and 2.7 (q, 2H, CH_2).

Anal. Calcd. for $C_6H_5Br_3S$: C, 20.63; H, 1.43; S, 9.17. Found: C, 20.77; H, 1.52; S, 9.09.

4-Bromo-2-ethylthiophene (**9**).

To a stirred solution of 2-acetyl-4-bromothiophene **7** (10.24 g, 0.05 mole) in ethyleneglycol (40 ml), hydrazine hydrate (85%, 10 ml) was added dropwise, and then heated at 160° for half an hour. To the mixture cooled at room temperature, small portions of solid potassium hydrazide (10.0 g) were added, and the whole heated at 160° for 1 hour. Water (200

Table I

Bromothiophenes Reduction

Starting Compound	Produced Compound	Yield %	mp or bp °C (mm)	Solvent
2a	**1e**	54	88-9 (a)	Petroleum ether
2b	**1f**	52	72-3 (b)	"
2c	**1g**	55	86-7 (c)	"
2d	**1h**	58	96-7 (d)	"
3	**7**	60	100-5 (1.8) (e)	
4	**8**	65	110-3 (1.2)	
6	**5**	62	110-5 (45) (f)	

Literature mp or bp: (a) 87-8 (2). (b) 70-1 (2). (c) 87-9 (1). (d) 98-100 (1). (e) 110-15 (3 mm) (16). (f) Isolated by steam distillation.

ml) was added to room temperature cooled mixture, and the produced 4-bromo-2-ethylthiophene was codistilled with water, the organic phase separated, dried (magesium sulfate) and distilled, yield 6.20 g (65%), bp 88-89°/20 mm, n_D^{22} = 1.5605, [lit (16) 81.5-82.5°/14 mm, n_D^{20} = 1.5617]; nmr (carbon tetrachloride): δ 1.23 (t, 3H, CH_3) and 2.76 (q, 2H, CH_2), J = 7.8 Hz; 6.66 (d, 1H) and 6.93 (d, 1H) J = 1.8 Hz AB system thiophen protons.

Bromothiophenes Reduction. General Procedure.

To a stirred boiling mixture of zinc dust (7.83 g, 0.12 g-atom), water (20 ml) and acetic acid (10 ml), the corresponding compound (0.04 mole) was added slowly. After the addition, the mixture was refluxed for 3 hours. In one case the produced compound was steam distilled and in all other cases extracted with chloroform (100 ml), washed with water, dried (magnesium sulfate), evaporated, and the residue distilled or crystallized (see Table I).

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