New Syntheses of 3-Bromothiophene and 3,4-Dibromothiophene

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3-Bromothiophene is a key intermediate in the preparation of 3-substituted thiophenes[1]. It has been obtained from 2,3,5-tribromothiophene by removal of the α-bromines through the Grignard, entrainment method[2] with ethyl bromide as the auxiliary halide or through halogen metal interconversion with n-butyllithium[3]. In both cases the metal-organic compounds were hydrolyzed with water. It has also been obtained from 4,5-dibromo-2-thiophenecarboxylic acid through simultaneous debromination and decarboxylation with copper powder in quinoline[4].

Zinc-dust in acid media is a classical reagent for the removal of halogen and has been used for the preparation of alkanes from alkyl halides[5]. It appears however, that this reagent has been considered rather unspecific and therefore has not been used for selective dehalogenation of polyhalogen compounds. The effectiveness of this reagent is evident from the results of Bak *et al.*[6] They reduced 3-iodo- and 3,4-diiodothiophene to the corresponding deuterated thiophenes in 75 min at 100°C using Zn-dust in CH_3COOD and D_2O.

For other investigations 2,3- and 2,4-dideuterothiophene were needed[7]. It was, however, found that when the corresponding bromine compounds were subjected to dehalogenation with Zn-dust in acetic acid under conditions similar to Bak's only small yields of the desired dideuterated compounds were obtained[7]. The main products (70–80 %) were the corresponding deuterated 3-bromothiophenes. With ordinary acetic acid 3-bromothiophene free from the 2-isomer was obtained.

This prompted the present author to investigate the possibility of obtaining isomer-free 3-bromothiophene from 2,3,5-tribromothiophene and 3,4-dibromothiophene from tetrabromothiophene. It was also found that refluxing 2,3,5-tribromothiophene with Zn-dust in acetic acid gave an 80 % yield of 3-bromothiophene free from the 2-isomer ($<$ 0.5 %). This fact was established by the absence in the product's IR-spectrum of the very strong 2-bromothiophene absorption band[2] at 10.25 μ.

It is interesting to note that in the dehalogenation of tetrabromothiophene under similar conditions a 65 % yield of 3-bromothiophene and only 10 % of 3,4-dibromothiophene was obtained. The IR-analysis proved the absence of other isomeric bromothiophenes. These results indicate that one β-bromine facilitates the removal of another. By changing the experimental conditions it was, however, possible to obtain 3,4-dibromothiophene in 68 % yield.

This preparation of 3-bromothiophene is more convenient and gives better yield than earlier methods.

Experimental. 3-Bromothiophene. To a mixture of 55 g of 2,3,5-tribromothiophene, 32 ml of acetic acid and 100 ml water, 65 g of Zn-dust was added. The mixture which grew hot was frequently shaken during the first half hour and then refluxed for 16 h. Thiophene 3-bromothiophene and water were directly distilled off until the temperature of the vapour had risen to 103°. The organic layer was separated, dried with anhydrous sodium carbonate and fractionated. After a small forerun consisting of mainly thiophene (1.2 g), 22.4 g of 3-bromothiophene, b.p. 159–161° $n_D^{20} = 1.5919$, was obtained, which had the same IR-spectrum as authentic 3-bromothiophene[2].

3,4-Dibromothiophene. In a two-necked flask fitted with a refluxcondenser and a dropping-funnel was placed 65 g of tetrabromothiophene 65 ml of acetic acid 200 ml of water and 65 g of Zn-dust. The mixture was heated until a vigorous reaction started. The heating mantle was removed and when the reaction had somewhat subsided the flask was arranged for distillation. The reaction mixture was rapidly distilled. After each 50 ml of distillate the heavier organic layer was separated and the aqueous layer returned to the reaction mixture through the dropping-funnel. After 3 h 35 g of organic phase had been obtained and no more distilled with the water. The organic phase was dried with sodium carbonate and fractionated *in vacuo.* After a forerun of 3.2 g, b.p. 45–94°/12 mm Hg, consisting of 3-bromo- and 3,4-dibromothiophene, 26,5 g (68 %) of pure 3,4-dibromothiophene, b.p. 94–95°/12 mm Hg, $n_D^{20} = 1.6380$ was obtained. The IR-spectrum was identical to that of the authentic 3,4-dibromothiophene[8] and the strong characteristic lines of 2,3-, 2,4- and 2,5-dibromothiophene in the 10.0–10.3 μ region were absent in its spectrum.

1. Gronowitz, S. *Arkiv Kemi* **13** (1959) 295.
2. Gronowitz, S. *Arkiv Kemi* **7** (1954) 267.
3. Lawesson, S. O. *Arkiv Kemi* **11** (1957) 373.
4. Motoyama, R., Nishimura, S., Imoto, E., Murakami, Y., Hari, K. and Ogawa, J. *J. Chem. Soc. Japan* **78** (1957) 950.
5. Wislicenus, J., *Ann.* **219** (1883) 312.
6. Bak, B., Christensen, P., Rastrup-Andersen, J. and Tannenbaum, E. *J. Chem. Phys.* **25** (1956) 892.
7. Hoffman, R. A. and Gronowitz, S. *Arkiv Kemi. In print.*
8. Steinkopf, W., Jacob, H. and Penz, M. *Ann.* **512** (1934) 136.

Received June 9, 1959.

The Identification of Drugs

VI. Nitration of Acetarsol *

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In order to obtain a suitable derivative of acetarsol (3-acetamido-4-hydroxyphenylarsonic acid) as an identity test in the Scandinavian Pharmacopoeia nitration was tried. Burschkies and Rothermundt [1] state that acetarsol treated with a mixture of concentrated nitric acid and concentrated sulphuric acid at a temperature below 0°C yields 5-nitroacetarsol (m.p. 218–220°C).

In the present work 2 M nitric acid was added to acetarsol and the solution was boiled for 15 sec and then cooled. A yellow derivative immediately crystallised and it did not contain arsenic.

We have now proved that the derivative is identical with 2-acetamido-4,6-dinitrophenol which means that besides the expected introduction of a nitro group *ortho* to the hydroxyl group another nitro group has replaced the arsonic group to give a dinitro derivative. The identity was confirmed by quantitative titration with titanous chloride and mixed melting point determination with an authentic sample prepared by nitration of 2-acetamidophenol. Furthermore, the free phenol group of the derivative was acetylated and the resulting product was found to be identical with O,N-diacetylpicramic acid. This compound was prepared by acetylation of picramic acid.

The proposed derivative is specific for acetarsol as none of the other arsenicals used as drugs will give this derivative.

Experimental. 2-Acetamido-4,6-dinitrophenol from acetarsol. 0.1 g acetarsol is added 5 ml of 2 M nitric acid and the solution is boiled about 15 sec. and then immediately cooled with tapwater. The yellow precipitate is recrystallised from 10 ml of water. M.p. (corr.) 206–207°C (lit.[2] 205–206°C). Titanometric equiv. weight, found: 20.2, 20.1. Calc. for $C_8H_7O_6N_3$: 20.1. If the mixture is boiled for 5 min no precipitate is formed, probably due to an oxidation.

Acetylation of picramic acid and 2-acetamido-4,6-dinitrophenol. The substance is refluxed for 30 min with acetic anhydride and a few drops of pyridine. After cooling water is added and the precipitate is recrystallised from glacial acetic acid. Nearly colourless crystals, m.p. (corr.) 191°C (lit.[2] 190–191°C).

1. Burschkies, K. and Rothermundt, M. *Arch. Pharm.* **276** (1938) 226.
2. King, H. *J. Chem. Soc.* **1927** 1049.

Received June 11, 1959.

* Part V. *Dansk Tidsskr. Farm.* **32** (1958) 81.

Correction to "Least Square Method for Computor Calculations of Stability Constants" *

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P. 187, right column, first line from above,

for $L = 35$ *read* $L = 46$.

* Acta Chem. Scand. **13** (1959) 186.

Received March 11, 1959.