SYNTHESIS AND REACTIONS OF TRIMETHYLAMMONIUM SALTS OF 5-NITRO-2-FURAN AND 5-NITRO-2-THIOPHENE. THE PREPARATION OF 5-NITRO-2-FURYL- AND 5-NITRO-2-THIENYL AZIDE*

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Preparation of new water-soluble derivatives of 5-nitro-2-furan and 5-nitro-2-thiophene from 2-bromo-5-nitrofuran (*Ia*) or 2-bromo-5-nitrothiophene (*Ib*) and trimethylamine is described. The trimethylammonium derivatives *IIa*, *IIb* react with the azide or cyanide anion in water to afford azides *IVa*, *IVb* or nitriles *Va*, *Vb* of 5-nitro-2-furan or 5-nitro-2-thiophene. The reactivity of these azides with dimethyl 2-butinedioate and triphenyl phosphine was studied.

A trimethylammonium grouping[1-4] is quite advantageous in organic synthesis for these compounds are often water soluble. So far, it has not been succeded to prepare and isolate trimethylammonium derivatives of 5-membered heterocycles with the exception of those reported in[5]. Nevertheless, these authors failed to quaternize directly the five-membered heterocyclic ring by the Menshutkin reaction[6,7] and obtained the by-product, the transalkylated tertiary amine *IIIb*. They prepared the quaternary salt of *IIb*-type (perchlorate) by a three-step reaction starting from 2-N,N--dimethylaminothiophene[5].

We ascertained that 5-nitro-2-bromofuran (*Ia*) and 5-nitro-2-bromothiophene react in aprotic nonpolar solvents with trimethylamine to yield trimethylammonium salts *IIa*, *IIb* at room temperature. The quaternary ammonium salts *IIa* and *IIb* undergo decomposition at temperatures above 35°C and at a great excess of trimethylamine to give 2-N,N-dimethylamino-5-nitrofuran (*IIIa*) or 2-N,N-dimethylamino-5-nitrothiophene (*IIIb*). The decomposition of samples dissolved was monitored by ^{1}H NMR spectrometry in hexadeuteriodimethyl sulfoxide within the 25–100°C interval.

The 5-trimethylammonium salts *IIa*, *IIb* form a group of water-soluble derivatives of 5-nitro-2-furan and 5-nitro-2-thiophene of a considerable biologic and synthetic importance; they belong to a class of labile quaternary ammonium salts[8] possessing

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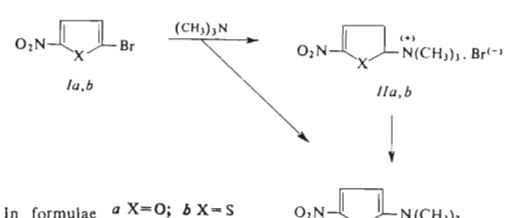


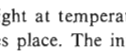
Ia,b *IIa,b* *IIIa,b*

SCHEME I

antibacterial, coccidiostatic, antifungal *etc.* activities. Their synthetic importance is in introduction of 5-nitro-2-furan and 5-nitro-2-thiophene grouping into various molecules. The reaction with an azide and cyanide anions exemplifies their reactivity.

The azide group is, in addition to the trimethylammonium group, an advantageous grouping, too. Heterocyclic azides can be obtained by a nucleophilic replacement of substituents at the heterocycle by an azide anion[9] (*e.g.* nitro[10], diazonium[11], halide in a phase transfer catalysis[12], organometallic with *para*-toluenesulfonyl azide[13] groups). These methods failed for substitutions into position 2 of the furan or thiophene rings in the presence of strong electron withdrawing substituents in position 5, the exceptions[10,14] being rather rare.

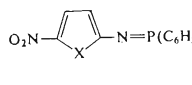
5-Nitro-2-furyltrimethylammonium bromide (*IIa*), Scheme 1 or 5-nitro-2-thienyltrimethylammonium bromide (*IIb*) react in an aqueous medium with azide or cyanide ions at 5 to 25°C to afford the substitution products of azides *IVa* and *IVb* and nitriles *Va* or *Vb* in very good yields. The reactions are indicated by the turbidity of solutions accompanied by evolution of trimethylamine. Azides *IVa*, *IVb* are sufficiently stable in the absence of light at temperatures ranging from −10 to 30°C; at 50 to 90°C decomposition takes place. The infrared spectrum of azides reveals an intense absorption band at 2 100 to 2 190 cm^{-1}. Nitriles *Va,b* obtained in an analogous way were found identical with those already prepared[19,20].



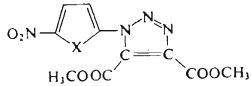
IVa, Nu = N_3, X = O
IVb, Nu = N_3, X = S
Va, Nu = CN, X = O
Vb, Nu = CN, X = S

Azides *IVa,b* react with triphenylphosphine in ethers (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane) to give iminophosphorenes *VIa,b*, suitable synthons for new aminofuran and aminothiophene derivatives[15]. The same azides also react

with 2-butinedioate in the above-mentioned solvents at an ambient temperature to yield cycloadducts *VIIa,b* the structure of which was inferred from ^{1}H NMR data.



VIa, X = O
VIb, X = S



VIIa, X = O
VIIb, X = S

EXPERIMENTAL

Melting points were measured with a Kofler micro hot-stage, IR spectra were taken with a UR-20 Zeiss, Jena spectrophotometer, UV spectra with a UV VIS Zeiss, Jena apparatus. The ^{1}H NMR spectra were recorded with a Tesla BS 487 C instrument operating at 80 MHz with tetramethylsilane as an internal reference. 5-Nitro-2-bromofuran (*Ia*. m.p. 48–49°C, ref.[16]) and 5-nitro-2-bromothiophene (*Ib*, m.p. 46°C, ref.[17]) were freed from haloacids by neutralization with a 10% aqueous Na_2CO_3 in ether and employed after drying with $MgSO_4$.

5-Nitro-2-furyltrimethylammonium Bromide (*IIa*)

Trimethylamine (4 g) in benzene (50 ml) was added to a solution of 5-nitro-2-bromofuran (9·6 g, 50 mmol) in benzene (150 ml), the flask was stoppered and shaken at 10°C for 2 h. The separated substance was filtered off under a nitrogen atmosphere and washed with ether. Yield 9·5 g (75%), m.p. 155–157°C (decomposition). For $C_7H_{11}BrN_2O_3$ (251·1) calculated: 33·38% C, 4·41% H, 31·82% Br; 11·16% N, found: 33·22% C, 4·30% H, 11·22% Br, 11·40% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·70 (s, 9 H, CH_3); 7·35 (d, J = 4·0 Hz, 1 H, $C_{(3)}$—H_{fur}); 7·88 (d, J = 4·0 Hz, 1 H, $C_{(4)}$—H_{fur}).

Picrate prepared according to[2] had m.p. 175–177°C (decomposition). For $C_{13}H_{13}N_5O_{10}$ (399·3) calculated: 39·1% C, 3·3% H, 17·5% N; found: 39·4% C, 3·15% H, 17·95% N.

2-N,N-Dimethylamino-5-nitrofuran (*IIIa*) orange in colour, m.p. 132–134°C (ref.[18] 137°C) was obtained from the ethereal and benzene solutions in a 20% yield (3 g).

2-N,N-Dimethylamino-5-nitrofuran (*IIIa*)

The bromide *IIa* (2·51 g, 10 mmol) was suspended in methanol (50 ml) and refluxed for 1 h. The solvent was removed and the residue chromatographed over a silica gel column (150–250 mesh, eluent benzene). Yield 1·15 g (74%), m.p. 136–137°C (m.p. 137°C ref.[18]). ^{1}H NMR spectrum ($CDCl_3$): 7·50 (d, J = 4·4 Hz, 1 H, $C_{(3)}$—H_{fur}); 5·34 (d, J = 4·4 Hz, 1 H, $C_{(4)}$—H_{fur}); 3·12 (s, 6 H, CH_3).

5-Nitro-2-thienyltrimethylammonium Bromide (*IIb*)

5-Nitro-2-bromothiophene (10·5 g, 50 mmol) in benzene (300 ml) was added in one instalment to trimethylamine (4 g) in benzene (100 ml) at 5–10°C, the flask was stoppered and shaken at 10°C for 10 h. The separated substance was filtered off in a nitrogen atmosphere and washed with ether. Yield 9·6 g 72%, m.p. 167–168°C, decomposition. For $C_7H_{11}BrN_2O_2S$ (267·2)

calculated: 31·41% C, 4·15% H, 29·91% Br; found: 32·07% C, 4·41% H, 28·92% Br. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·72 (s, 9 H, CH_3); 7·75 (d, J = 4·4 Hz, 1 H, $C_{(4)}$—$H_{thiophene}$); 7·55 (d, 1 H, J = 4·4 Hz, $C_{(3)}$—$H_{thiophene}$).

Picrate was prepared from *IIb* according to ref.[2]. M.p. 155—157°C. For $C_{13}H_{13}N_5O_9S$ (415·3) calculated: 37·59% C, 3·15% H, 16·86% N; found: 37·89% C, 3·30% H, 17·05% N.

2-N,N-Dimethylamino-5-nitrothiophene (*IIIb*) was obtained from the ethereal washings after removing *IIb*. yield 1·9 g (22%), m.p. 137°C.

2-N,N-Dimethylamino-5-nitrothiophene (*IIIb*)

Bromide *IIb* (2·67% g, 10 mmol) was suspended in methanol (50 ml) and refluxed for 1 h. The solvent was distilled off and the residue purified by chromatography over silica gel column (150—250 mesh, eluent benzene). Yield 1·23 g, 71%, m.p. 137°C. ^{1}H NMR spectrum ($CDCl_3$): 3·13 (s, 6 H, CH_3); 5·82 (d, J = 4·7 Hz, 1 H, $C_{(3)}$—$H_{thiophene}$); 7·76 (d, J = 4·7 Hz, 1 H, $C_{(4)}$—$H_{thiophene}$).

5-Nitro-2-furyl Azide (*IVa*)

Bromide *IIa* (5 g) in water (50 ml) was added into a solution of NaN_3 (2·6 g) in water (10 ml) in a separation funnel containing ether (100 ml). The ethereal layer was separated and the reaction mixture in the separation funnel repeatedly (6 times) extracted in 10 min intervals. The extracts were combined, dried with $MgSO_4$, the solvent removed and the residue purified by chromatography (silica gel column, 150—250 mesh, eluent benzene). Yield 2·7 g (87%) of a yellow; substance, m.p. 41—43°C. For $C_4H_2N_4O_3$ (154·1) calculated: 31·15% C, 1·31% H, 36·36% N, found: 31·55% C, 1·47% H, 36·99% N. ^{1}H NMR spectrum ($CDCl_3$): 6·01 (d, J = 4·0 Hz, 1 H. $C_{(3)}$—H_{fur}), 7·34 (d, J = 4 Hz, 1 H, $C_{(4)}$—H_{fur}). IR spectrum ($CHCl_3$): (N_3) 2 120, 2 190 cm^{-1}

5-Nitro-2-thienyl Azide (*IVb*)

Was obtained as described with *IVa* in a 78% yield in form of an orange-red oil. IR spectrum ($CHCl_3$): (N_3) 2 124, 2 192 cm^{-1}. For $C_4H_2N_4O_2S$ (170·2) calculated: 28·22% C, 1·18% H, 32·92% N; found: 28·55% C, 1·25% H, 32·41% N. ^{1}H NMR spectrum ($CDCl_3$): 5·55 (d, J = = 4·6 Hz, 1 H, $C_{(3)}$—$H_{thiophene}$); 6·97 (d, J = 4·6 Hz, 1 H, $C_{(4)}$—$H_{thiophene}$).

2-(N-Iminotriphenylphosphorano)-5-nitrofuran (*VIa*)

Triphenylphosphine (5·25 g) in ether (50 ml) was dropwise added to a solution of *IVa* (3·1 g, 20 mmol) in ether (50 ml). After addition of c. 20 ml of the solution compound *VIa* (a red substance) becomes to separate. The end of the reaction is indicated by disappearance of the yellow spot of the azide (Silufol sheet, eluent benzene, R_F 0·6) and appearance of triphenylphosphine (visualization with iodine vapours). Yield 7·8 g (98%), m.p. 197°C. For $C_{22}H_{17}N_2O_3P$ (388·4) calculated: 68·03% C, 4·41% H, 7·21% N; found: 67·72% C, 4·30% H, 7·35% N. ^{1}H NMR spectrum ($CDCl_3$): 5·35 (d, J = 4·0 Hz, 1 H, $C_{(3)}$—H_{fur}); 7·36 (d, J = 4·0 Hz, 1 H, $C_{(4)}$—H_{fur}); 7·38—7·75 (m, 15 H, H_{ar}).

2-(N-Iminotriphenylphosphorano)-5-nitrothiophene (*VIb*)

Was prepared by the same procedure as described for *VIa*. Yield 96% of a orange-red compound, m.p. 179—180°C. For $C_{22}H_{17}N_2O_2PS$ (404·5) calculated: 65·32% C, 4·24% H, 6·93% N; found:

65·55% C, 4·05% H, 7·07% N. ^{1}H NMR spectrum ($CDCl_3$): 6·86 (d, J = 4·7 Hz, 1 H, $C_{(3)}$—$H_{thiophene}$); 7·81 (d, J = 4·7 Hz, 1 H, $C_{(4)}$—$H_{thiophene}$); 7·6—7·7 (m, 15 H, H_{ar}).

5-Nitro-2-furonitrile (*Va*)

Bromide *IIa* (5 g, 20 mmol) was treated with NaCN (1·1 g) and worked up as described with *IVa*. Yield 72%, m.p. 64—65°C (ref.[19]). IR spectrum (CCl_4), cm^{-1}: 2 244 (C≡N).

5-Nitro-2-thienyl Cyanide (*Vb*)

Starting from the bromide *IIb* (5·2 g, 20 mmol) and NaCN (1·1 g) and employing procedure as with *IVb*, this product was obtained in a 62% yield. M.p. 43—45°C (ref.[20] 45°C) IR spectrum (CCl_4), cm^{-1}: 2 242 (C≡N).

4,5-Bis(methoxycarbonyl)-1-(5-nitro-2-furyl)-1,2,3-triazole (*VIIa*)

Azide *IVa* (3·1 g, 20 mmol) and dimethyl 2-butinedioate (5·5 g) in ether (100 ml) were homogenized and allowed to stand at room temperature for 100 h. The separated precipitate was filtered off and crystallized from hexane. Yield 2·6 g (44%), m.p. 145—147°C. For $C_{10}H_8N_4O_7$ (196·2) calculated: 40·54% C, 2·72% H, 18·91% N; found: 40·07% C, 2·56% H, 19·33% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·98 (s, 3 H, OCH_3); 4·01 (s, 3 H, OCH_3); 7·41 (d, J = 3·9 Hz, 1 H, $C_{(3)}$—H_{fur}); 7·93 (d, J = 3·9 Hz, 1 H, $C_{(4)}$—H_{fur}).

4,5-Bis(methoxycarbonyl)-1-(5-nitro-2-thienyl)-1,2,3-triazole (*VIIb*)

Was prepared analogously as in the preceding case from the azide *IVb* (3·4 g, 20 mmol). Yield 51%, m.p. 135—137°C. For $C_{10}H_8N_4O_6S$ (312·2) calculated: 38·46% C, 2·58% H, 17·94% N; found: 38·77% C, 2·64% H, 17·22% N. ^{1}H NMR spectrum ($CDCl_3$): 4·00 (s, 3 H, OCH_3); 4·02 (s, 3 H, OCH_3); 7·31 (d, J = 4·6 Hz, 1 H, $C_{(3)}$—$H_{thiophene}$); 7·88 (d, J = 4·6 Hz, 1 H, $C_{(4)}$—$H_{thiophene}$).

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