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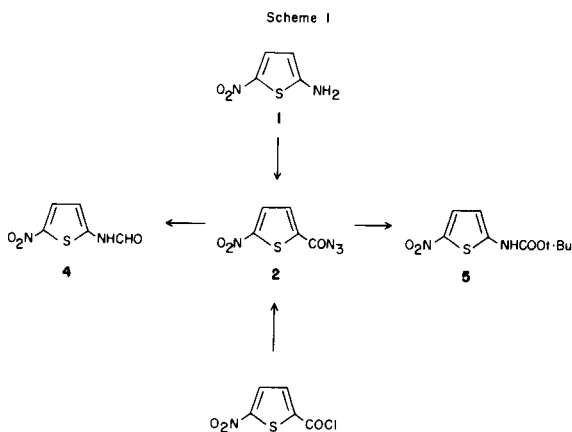
The preparation of 2-amino-5-nitrothiophene, 2-formamido-5-nitrothiophene, 2-acetamido-5-nitrothiophene and 2-*t*-butyloxycarbonylamino-5-nitrothiophene are described. Abnormal values of the coupling constants $J_{3,4}$ had been observed in the $^1\text{H-nmr}$ spectra of compounds obtained.

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Aminothiophenes have become important intermediates for the synthesis of condensed thiophene derivatives. In connection with a general program directed to the study of such systems, we have prepared 2-amino-5-nitrothiophene (**1**). It is known that 2-aminothiophenes tend to be unstable in the absence of electron-withdrawing groups in the 3- or 5-position. However, 2-amino-5-nitrothiophene (**1**) has not been previously described in the literature. In the present work we wish to report the preparation and the nmr spectra of **1** and related compounds.

Of the different synthetic methods for the preparation of 2-aminothiophenes (**1**), the rearrangement of acyl azides to formamido derivatives is a widely used method. Thus, we attempted the synthesis of compound **1** from the acyl azide **2** as a precursor (*cf.* Scheme 1).

Compound **2** was prepared from the acid chloride **3** (**2**). By the action of sodium azide on compound **3**, a yellow solid was obtained in almost quantitative yield. This product was identified as the acyl azide **2** (**3**).



The formamido derivative **4** was prepared according to the method of Stevenson and Johnson (4) by the reaction of compound **2** with formic acid. The formyl proton was readily identifiable in the nmr spectrum appearing as a doublet at 8.8 ppm. This splitting is due to the restricted rotation of the formyl group. The coupling constant showed a value of 1.5 Hz (5). Several methods for cleaving the formyl group in **4** were tested (6). Under mild conditions

(dilute acid or alkali, room temperature) the formamido compound **4** was recovered unchanged. Under drastic conditions desulfurization resulted giving tarry products.

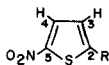
In view of these results we tested the preparation of compound **1** from its *t*-butyloxycarbonyl derivative **5**, according to Binder, *et al.*, (7). By reaction of compound **2** with *t*-butyl alcohol in dry dioxane, compound **5** was obtained in 70% yield. When **5** was treated with anhydrous hydrogen bromide in an aprotic solvent (methylene chloride) a crystalline product was obtained. The melting point of this solid changed with time. This fact can be explained by the loss of hydrogen bromide from the salt (**1**·HBr), due to the weak basicity of the amino compound **1**. Drying this crystalline substance in a desiccator under vacuum with potassium hydroxide allowed us to isolate the free base **1**. This product proved to be stable for 48 hours; after this time compound **1** darkens and polymerizes to a tar in contact with air. When it is stored under a vacuum or under a nitrogen atmosphere, the amine is stable for several days.

By reaction of compound **1** with acetic anhydride, the *N*-acetyl derivative **6** was obtained in 60% yield (8). Spectral data and analyses were consistent with the structures of compounds **1**, **2**, **3**, **4**, **5** and **6**.

Investigations concerning the $^1\text{H-nmr}$ spectra of thiophenes (9,10) have shown that the coupling constants fall in four distinct regions: $J_{3,5} = 1.25\text{--}1.70$ Hz, $J_{2,5} = 3.20\text{--}3.65$ Hz, $J_{3,4} = 3.40\text{--}4.35$ Hz and $J_{4,5} = 4.95\text{--}5.80$ Hz, and that the dependence upon substituents is small. Due to importance of these couplings constants as a diagnostic tool for structure determination of disubstituted thiophenes, we wish to report the abnormal values of the coupling constants $J_{3,4}$ measured in the $^1\text{H-nmr}$ spectra of the compounds obtained by us. The positions of the $\text{C}_3\text{-H}$ and $\text{C}_4\text{-H}$ proton signals and the $J_{3,4}$ of such compounds are shown in the Table.

Compounds **2**, **3** and **6** are described in the literature, but the ir and nmr spectra of these compounds have not been reported. Compound **7**, precursor of **3**, has been prepared in our laboratory (2) and the chemical shifts of the 3- and 4-hydrogens are shown in the Table. The $J_{3,4}$ is

Table

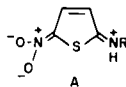
Physical and ¹H-Nmr Spectra of 2-Substituted 5-Nitrothiophenes

Compound No.	R	M.p. °C	Yield %	Chemical Shifts (ppm) (a)		J _{3,4} (Hz) (b)	Solvent
				C ₃ -H	C ₄ -H		
1	NH ₂	182	90	6.05 d	7.75 d	6.0	methanol-d ₄
2	CON ₃	62	97	7.75 d	7.95 d	5.0	deuteriochloroform
3	COCl	52	95	8 s	8 s	0	deuteriochloroform
4	NHCHO	174	68	6.7 d	7.9 (c)	6.0	methanol-d ₄
5	NHCOO- <i>t</i> -Bu	146	70	6.4 d	7.8 d	6.0	deuteriochloroform
6	NHCOCH ₃	227-228	60	6.72 d	7.95 d	5.4	methanol-d ₄
7	COOH	157	85	7.8 d	8.05 d	4.5	methanol-d ₄

(a) Abbreviations: d = doublet, s = singlet. (b) Obtained by reading the scales of spectra (at 60 MHz). (c) Complex signal.

4.5 Hz which is close to the value of 4.3 Hz measured by Gronowitz (9).

As indicated in the Table, none of the coupling constants J_{3,4} for the compounds reported in this study (except 7) fall into the range reported by other authors (9,10) for 2,5-disubstituted thiophenes. On the contrary, these values are in the range of those predicted for 2,3-disubstituted derivatives. The nmr spectra of compounds 1, 4, 5, and 6 were also determined in other solvents and the J_{3,4} values were not altered by contrast with the chemical shifts of the hydrogens. It seems reasonable to assume that the delocalization of the pair of electrons of amino group and the presence of a nitro group at C₅ can lead to a preferential structure such as A in order to explain the abnormal values of J_{3,4}.



EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12B spectrometer using TMS as an internal standard. Chemical shifts are reported as δ values in parts per million (ppm). Infrared spectra were measured on a Pye-Unicam SP 1100 spectrophotometer. Elemental analyses were performed by Instituto de Química Orgánica, Barcelona.

2-Azidocarbonyl-5-nitrothiophene (2).

A solution of 2-chlorocarbonyl-5-nitrothiophene (3) (2) (9.8 mmoles) in chloroform was cooled to 0° and 9.8 mmoles of sodium azide dissolved in water was added dropwise. The reaction was maintained at 0° for 30 minutes, after which time the solution was allowed to warm to room temperature for 1 hour. The organic layer was then separated, dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from benzene giving 18.78 g (97%) of compound 2, mp 62° (3); ir (potassium bromide): 2180 cm⁻¹ (-CON₃).

Anal. Calcd. for C₅H₂N₄O₃S: C, 30.31; H, 1.02; N, 28.28; S, 16.15. Found: C, 30.15; H, 1.09; N, 28.19; S, 16.16.

2-Formamido-5-nitrothiophene (4).

Into a flask was placed 12 ml of formic acid under an atmosphere of nitrogen and the solution was heated to 110°. 2-Azidocarbonyl-5-nitrothiophene 2 (19.8 g) was then added slowly. After completion of the addition, the mixture was maintained at 110° for 1 hour. After this time, water-ethanol was added and the solution was evaporated to dryness. The residue was purified by chromatography on a silica-gel column. On elution with methanol 10 g (68%) of compound 4, mp 174° (recrystallized from water) was obtained; ir (potassium bromide): 3300-3200 cm⁻¹ (NH), 1690 cm⁻¹ (CHO).

Anal. Calcd. for C₅H₄N₂O₃S: C, 34.89; H, 2.34; N, 16.28; S, 18.59. Found: C, 34.57; H, 2.31; N, 16.32; S, 18.46.

2-*t*-Butyloxycarbonylamino-5-nitrothiophene (5).

To a solution of the acylazide 2, (6.076 g, 30 mmoles) in dry dioxane (30 ml) was added 3.215 g (40 mmoles) of *t*-butyl alcohol. The reaction mixture was slowly heated at 150° in an oil-bath and was maintained at this temperature for 1 hour. After this time, the mixture was distilled giving a residue which was recrystallized from benzene to give 4.79 g (70%) of a yellow solid which was identified as compound 5, mp 146°; ir (potassium bromide): 3250 cm⁻¹ (-NH), 1750 cm⁻¹ (-COO-).

Anal. Calcd. for C₉H₁₂N₂O₄S: C, 44.26; H, 4.92; N, 11.48; S, 13.11. Found: C, 44.18; H, 4.91; N, 11.35; S, 13.10.

2-Amino-5-nitrothiophene (1).

A solution of 1.22 g (5 mmoles) of 5 in methylene chloride was saturated with anhydrous hydrogen bromide to give a yellow solid (1·HBr). This solid was dried in a desiccator under vacuum with potassium hydroxide to a constant weight. Recrystallization from benzene gave 670 mg (90%) of the amine 1, mp 182°; ir (potassium bromide): 3300 and 3350 cm⁻¹ (-NH₂).

Anal. Calcd. for C₄H₄N₂O₂S: C, 33.34; H, 2.80; N, 19.44; S, 22.30. Found: C, 33.26; H, 2.73; N, 19.90; S, 22.19.

2-Acetamido-5-nitrothiophene (6) (8).

A solution of 122 mg (0.5 mmoles) of 1 in 10 ml of acetic anhydride was quickly heated under reflux for 15 minutes. The reaction mixture was cooled, poured into 50 ml of cold water and heated again for 15 minutes to decompose the excess of acetic anhydride. Then the solution was extracted with methylene chloride. The organic layer was washed with a solution of sodium carbonate and then with water, dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was recrystallized from chloroform to give 56 mg (60%) of a yellow solid which was characterized as 6, mp, 227-228°; ir (potassium bromide): 3280 cm⁻¹ (-NH), 1690 cm⁻¹ (-CO-); nmr (see Table): 2.25 (s, 3,

CH₃CO).

Anal. Calcd. for C₆H₆O₃N₂S: C, 38.72; H, 3.25; N, 15.05; S, 17.19.
Found: C, 38.70; H, 3.25; N, 15.00; S, 17.17.

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