Some Substitution Reactions of 2-(2'-Thienyl)pyrimidine and 2-(3'-Thienyl)pyrimidine

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Dedicated to Professor K. A. Jensen on his 70th birthday

2-(2'-Thienyl)pyrimidine (**1**) and 2-(3'-thienyl)pyrimidine (**2**) have been prepared from the corresponding thiopheneamidines hydrochlorides through reaction with 3-(dimethylamino)propenal. Isomer distributions in nitration of **1** and **2** under different conditions and in bromination with bromine in acetic acid have been determined. The isomeric nitro and bromo derivatives were separated and their structures determined by NMR spectroscopy.

The directing properties of the 2-pyrimidyl group as a substituent on thiophene in electrophilic substitution are discussed.

In connection with a study of the chemistry of biaryls of heterocyclic type ¹ we have synthesized 2-(2'-thienyl)pyrimidine **1** and 2-(3'-thienyl)pyrimidine **2** and have investigated some nitration and bromination reactions with the purpose of evaluating the directing effects of a 2-pyrimidyl group on electrophilic substitution in the thiophene series. The synthesis, nitration with mixed acids, and lithiation of **1** and **2** have been the subject of a short communication published when the major part of this work was finished.²

RESULTS

Synthesis and spectral properties. Our synthesis of **1** and **2** followed the usual pathway for the preparation of 2-arylpyrimidines,³ as outlined in Scheme 1.

2-Cyanothiophene (**3**) was obtained in a convenient one-pot procedure through reaction of thiophene with chlorosulfonyl isocyanate,⁴ giving

Scheme 1.

2-thiophenecarboxamido-*N*-sulfochloride (**4**) which was then treated with dimethylformamide⁵ — a simpler method than the usual three step procedure.⁶ 3-Cyanothiophene (**5**) was prepared by refluxing 3-bromothiophene (**6**) and copper(I) cyanide in dimethylformamide.⁷ By reaction with ethanol and hydrogen chloride in ether, **3** and **5** were converted to the thiophenecarboximidic acid ethyl ester hydrochlorides (**7** and **8**), which after treatment with ammonia in ethanol gave the thiopheneamidines hydrochlorides (**9**) and (**10**). In the final step, **9** and **10** were reacted with 3-(dimethylamino)propenal⁸ to give **1** and **2**, respectively.

The ¹H NMR spectra of **1** and **2** (see experimental part) are well resolved, and from the

known coupling constants of thiophene⁹ and pyrimidine,¹⁰ each band can be assigned to a definite hydrogen, thus facilitating the structure determination of the substitution products. In the mass spectrometer, *1* and *2* show a small tendency to fragmentation (see experimental part) with the molecular ion giving the base peak and, in addition to *M* - 1 in the case of *2*, the only peak with an intensity higher than 12 % is *m/e* = 109. This is probably the thiophenenitrile ion, in analogy with the dominance of benzonitrile ion in spectra of 2-phenylpyrimidines.¹¹

The intensity of *M* - 1 is 8 % in spectrum of *1*, but 19 % in the spectrum from *2*. The greater tendency to hydrogen abstraction in the 3-substituted thiophene may, as in the case of 2- and 3-(2'-pyridyl)thiophene,¹² be due to the presence of a reactive α -thienyl centre near one of the nitrogen atoms (cf. Scheme 2).

Scheme 2.

Reactions of *1* and *2*. 2- and 3-Nitrothiophene and other deactivated thiophenes undergo nitration with nitric acid in trifluoroacetic acid at 25 °C.¹³ Under the same conditions, *1* reacted rather slowly. After reaction for 48 h at 25 °C between equimolar amounts of substrate and reagent, NMR analysis showed the reaction mixture to contain about 90 % of starting material. The reaction was considered not to have preparative value, but was used for a comparison of the reactivity of *1* and *2* with 2-nitrothiophene on a semiquantitative basis.

However, *1* and *2* were shown to be stable towards 98 % sulfuric acid, as neither decomposition nor sulfonation could be detected by NMR analysis after reaction for 24 h at 25 °C. Thus, 100 % nitric acid in 98 % sulfuric acid was chosen as the reagent for nitration of *1* and *2*. In order to study the nitration under essentially non-acidic conditions, *1* and *2* were also treated with an excess of acetyl nitrate in acetic anhydride. Brominations of *1* and *2* were performed with molecular bromine in acetic acid containing sodium acetate to neutralize the hydrogen bromide formed in order to prevent

the precipitation of the hydrobromides of the pyrimidines involved.

The results of these reactions are summarized in Table 1. In all cases but one, mixtures of products were obtained. Efforts to separate these products by GLC were without success. (The isomers of 4-(nitrophenyl)pyrimidine separate on SE-30.¹⁴) However, mainly by PTLC all compounds but one (*11*) could be isolated in pure form. The structures of the compounds were determined by MS and ¹H NMR (see experimental part). The quantitative analysis of the mixtures obtained after work-up was performed by integration of the ¹H NMR spectra of the crude products.

Nitration with mixed acids (entries 1 and 3) gave mononitro isomers in high yield. The 2-isomer *1* gave a mixture of 2-(4'-nitro-2'-thienyl)pyrimidine (*12*) and 2-(5'-nitro-2'-thienyl)pyrimidine (*13*) in about equal amounts. The assignments of *12* and *13* were based on the presence in the ¹H NMR spectra of thiophene doublets with coupling constants of 1.5 and 4.4 Hz, respectively. Nitration of *2* was much more selective, and gave predominantly 2-(5'-nitro-3'-thienyl)pyrimidine (*16*), *J*_{2,4'} = 1.7 Hz. Small amounts of 2-(4'-nitro-3'-thienyl)pyrimidine (*15*), *J*_{4,6'} = 3.8 Hz and 2-(2'-nitro-3'-thienyl)pyrimidine (*14*), *J*_{4,6'} = 5.5 Hz, were also isolated.

Acetyl nitrate (entries 2, 4, and 5) gave a less selective reaction and a lower yield of nitrated products. Thus *1* now yielded *13* as the main product and the amount of *12* formed is even less than that of 2-(3'-nitro-2'-thienyl)pyrimidine (*11*). The nitration of *2* under these conditions was even more complex; *14* now became the main isomer, and the amount of *15* was approximately the same as in the nitration with mixed acids, while much less of *16* was formed. This is partly due to further nitration of *16* to a dinitro derivative (cf. entries 4 and 5). ¹H NMR and MS show that this compound contains two nitro groups bonded to the thiophene nucleus and the ¹³C spectrum demonstrates that the dinitro derivative is 2-(2',5'-dinitro-3'-thienyl)pyrimidine (*17*). In ¹³C NMR the unsubstituted thiophene carbon shows a direct C-H coupling constant of 184 Hz. In a series of monosubstituted thiophenes, *J*(C5H5) was found to vary between 184 and 199 Hz and *J*(C4H4) between 164 and 177 Hz (the highest

Table 1. Some substitution reactions and their products. R = 2-pyrimidyl.

 11	 12	 13	 14	 15	 16	 17	
 18	 19		 20	 21			
Entry	Reaction ^a	Composition of isolated material/ mol %					Yield
1	1 + HNO ₃ , H ₂ SO ₄ , 0 °C, 1 h	11	12	13			93
2	1 + AcONO ₂ , 25 °C, 3 h	11	5	84			70
3	2 + HNO ₃ , H ₂ SO ₄ , 0 °C, 1 h	14	15	16	17	2	93
4	2 + AcONO ₂ , 25 °C, 48 h	39	5	19	19	18	59
5	2 + AcONO ₂ , 25 °C, 96 h	45	5	7	43	—	62
6	1 + Br ₂ , AcOH, NaOAc, 25 °C, 0.5 h			18	100		93
7	2 + Br ₂ , AcOH, NaOAc, 25 °C, 18 h	19		20	21	2	59
8	2 + Br ₂ , AcOH, NaOAc, 25 °C, 18 h	24		36	12	28	59
		39		32	29	—	73

^a Acetyl nitrate was used in 12-fold excess, nitric acid and bromine in equimolar amounts, except in entry 8 where 1.7 equiv. of bromine were used.

values are observed when the substituent is a nitro group).¹⁵ The coupling constant obtained from 17 is at first sight not typical for a C₄—H₄ coupling, but that assignment seems to be reasonable considering the electronegative character of the substituents (cf. also ¹³C NMR of compound 21, see below). Further proof of the structure is obtained from the fact that 2, which at 0 °C gives 16 mainly, upon nitration with mixed acids, first at room temperature and then at 100 °C, produces 17, exclusively. The nitro group in 16 is also expected to deactivate position 4 (*ortho*) more than position 2 of the thiophene nucleus. Our results also indicate that 14 is more deactivated towards further nitration than 16, and that 1 is more reactive than 2 towards nitration with acetyl nitrate.

Also in the bromination 1 was more reactive than 2, and gave 2-(5'-bromo-2'-thienyl)pyrimidine (18) selectively and in high yield. As in the

case of nitration with acetyl nitrate, 2 also gave a more complex product mixture than 1 upon bromination, and the reaction was further complicated by a bromine-consuming side reaction giving some unstable by-products. 2-(2'-Bromo-3'-thienyl)pyrimidine (19), $J_{4'5'} = 5.7$ Hz, 2-(5'-bromo-3'-thienyl)pyrimidine (20), $J_{2'4'} = 1.2$ Hz, and 2-(2',5'-dibromo-3'-thienyl)pyrimidine (21), were the products isolated. The structures of the two monobromo derivatives are obvious from the characteristic coupling between the two remaining thiophenic protons. The structure of 21 seems reasonable from those of the monobromo derivatives, and was confirmed by its ¹³C NMR spectra, which showed a direct coupling constant from the unsubstituted thiophene carbon of 178 Hz, assigned as $J(\text{C4H4})$. The value is somewhat larger than usually observed but the assignment is justified by a comparison with ¹³C-parameters^{15b} of 2,3-

dibromo-4-formylthiophene, $J(\text{C5H5})$ 194 Hz, and 2,5-dibromo-3-formylthiophene, $J(\text{C4H4})$ 178 Hz.

Our results (*cf.* entries 1 and 3), differ somewhat from those reported in Ref. 2, according to which **1** reacts with mixed acids (conditions not specified) to give **12** and **13** in the ratio 65:35 (*cf.* entry 1). From the same reaction with **2** as substrate, only 2-(5'-nitro-3'-thienyl)pyrimidine **16** was observed as product by the French workers (*cf.* entry 3).

Scheme 3.

DISCUSSION

According to classic electronic theory the 2-pyrimidyl group with its amidine-like structure can be expected to be a $-I$ -substituent. For the resonance hybrid of **1** in the ground state, structures **1a**–**1f** (Scheme 3) may contribute. However, structures **1e** and **1f**, with a positive charge on the nitrogen, are of less importance, indicating that the $-M$ -effect of the 2-pyrimidyl group is of greater importance than its $+M$ -effect.

A comparison of the ^1H NMR shifts (CDCl_3) of **H5** (δ 7.00) and **H5'** (7.45) in **1** with the corresponding protons in unsubstituted pyrimidine (7.36)¹⁰ and thiophene (7.30),¹⁶ respectively, indicates the operation of a $-M$ -effect of the pyrimidine ring in the ground state. The same conclusion can be drawn in the case of **2**, where the ^1H NMR (CDCl_3) shows the signal from **H5** at 7.08.

On the other hand, it seems reasonable to consider the possibility that the 2-pyrimidyl group of **1**, through a $+M$ -effect, could stabilize transition states following attacks of electrophiles in the 5- (or 3-) position of the thiophene nucleus. In **2** the same $+M$ -effect should favour

electrophilic attack in the 2-position (*cf.* Scheme 4).

Scheme 4.

In protonated **1** and **2** such stabilization is much less likely as the pyrimidinic moiety will be doubly charged.

The results in entries 1 and 3 indicate that the pyrimidine ring acts as a *meta*-directing substituent¹⁷ in the nitration in mixed acids. However, the results from entries 2 and 4 imply that the pyrimidine ring in nitration with acetyl nitrate in neutral medium acts more as an *ortho-para*-directing group. These differences may be due to differences in the nitration process. Thus, it could be possible that acetyl nitrate reacts via an addition-elimination reaction. (Furan and furan derivatives carrying electronegative substituents undergo this type of nitration¹⁸ and in the case of 4-phenylpyrimidine acetyl nitrate adds to the pyrimidine ring to give 2,4-diacetoxy-6-phenyl-1,3,5-trinitro-1,2,3,4-tetrahydropyrimidine in high yield.¹⁴) However, to our knowledge, no examples of such addition-elimination nitration are known from the thiophene series and no acetoxy compounds were observed in the reaction mixtures from entries 2, 4 and 5. Further, acetyl nitrate in acetic anhydride or *N*-nitropicolinium salts in acetonitrile give almost identical results in nitration of 2-acetylthiophene,¹⁹ indicating that acetyl nitrate gives a normal electrophilic nitration with this deactivated thiophene.

A more plausible explanation for the difference in directing power is that the substrate in concentrated sulfuric acid reacts in a protonated form, *i.e.* the orientational pattern in entries 1 and 3 is caused by a protonated pyrimidine ring, while that in entries 2 and 4 is caused by an unprotonated ring.

Protonation on a pyrimidine nitrogen must increase the $-I$ -effect of the 2-pyrimidyl group, but can also, as mentioned above, be expected to inhibit an eventual $+M$ -effect of the substituent, both phenomena favouring substitution in the 4-position of **1** and the 5-position of **2**.

Selective bromination in the 5-position, as in entry 6, is observed for thiophenes substituted in position 2 by for example halogens ($-I, +M$) and carbonyl-containing groups ($-I, -M$). Strong $+M$ -substituents also give reaction in the 3-position, whereas strong $-M$ -substituents, such as complexed carbonyl groups, lead to 4- and 5-substitution.¹⁷

Our results then exclude strong $+M$ or strong $-M$ as a characterization of the 2-pyrimidyl group, and this together with the *ortho-para* pattern obtained in entry 2, justifies the above assumption of a $+M$ -character of the 2-pyrimidyl group.

The orientation in the acetyl nitrate nitration (entries 4 and 5) and bromination (entries 7 and 8) of **2** differs from most 3-substituted thiophenes in giving approximately equal amounts of 2- and 5-substitution, but seems to be reasonable for strong $-I$, weak $+M$ -substituent.

The facile dibromination and especially dinitration of **2** is quite interesting but somewhat difficult to explain at present.

An isomer distribution similar to that in entries 7 and 8 is obtained by the bromination of 3-phenylthiophene with bromine in acetic acid. This reaction was shown to be reversible due to the presence of the hydrogen bromide formed, and the isomer distribution was explained as the result of thermodynamic product control.²⁰ However, in our brominations, the hydrogen bromide was neutralized by sodium acetate, and hence thermodynamic control is less likely.

The relatively large amount of *ortho*-substitution (cf. entries 2, 4, and 5) could also, tentatively, be explained by the assumption that the 2-pyrimidine group has a $-M$ character but also coordinates the electrophile to one of its nitrogens before an intramolecular substitution process occurs. In such a case, the orientational consequences of an eventual $-M$ -effect of the substituent could be masked. However, it is known that thiophenes substituted in the 2-position by $-I, -M$ groups react more slowly than the corresponding 3-isomers.¹³ A comparison of entries 2 and 4 or 6 and 7 makes it clear that in the cases of **1** and **2** the 2-substituted isomer reacts faster than the 3-substituted, indicating that the 2-pyrimidyl group can hardly be a $-M$ -substituent. The discussion above leads to the conclusion that the 2-

pyrimidyl group in **1** and **2** acts as $-I, -M$ -substituent in strongly acidic medium, but as a $-I, +M$ -substituent under neutral conditions.

Comparison with literature data confirms these assumptions. In mixed acids, **1** and 2-nitrothiophene give a similar substitution pattern,²¹ whereas the latter does not react with acetyl nitrate in acetic anhydride.²²

To obtain more detailed data on the reactivity of 2-nitrothiophene towards bromine,²³ we tested the conditions used in entry 6, but after reacting for 3 h only starting material could be found by GLC.

A semiquantitative comparison of the nitration with nitric acid of 2-nitrothiophene, **1** and **2** in strongly acidic medium (trifluoroacetic acid¹³) was made by following the disappearance of starting material by ¹H NMR and the following order of reactivity was obtained: 2-nitrothiophene > **2** > **1**. Here **2** is more reactive than **1** (cf. above) confirming the $-I, -M$ -character in strongly acidic medium.

In comparison with the corresponding 4-pyrimidyl derivatives,^{1b} **1** and **2** appear to be more reactive under non-acidic conditions. The 4-pyrimidyl derivatives do not react with acetyl nitrate, and 4-(3'-thienyl)pyrimidine gives no bromination products with bromine in acetic acid at room temperature, but reacts sluggishly at 50 °C.

EXPERIMENTAL

Melting points are uncorrected. The ¹H NMR spectra were recorded with Varian A60, JEOL PMX-60, or JEOL MH-100 spectrometers; data given below refer to recordings at 60 MHz in CDCl₃ solution if not otherwise stated. ¹³C NMR spectra were obtained in (CD₃)₂CO solution on a JEOL-FX60 NMR spectrometer. The shifts were determined from proton decoupled spectra with TMS as internal standard. The MS were recorded on an LKB A 9000 spectrometer. GLC analyses were carried out on a Varian aerograph 1400 gas chromatograph equipped with a flame ionization detector.

Separations by preparative thin layer chromatography (PTLC) were performed on silica gel plates, 20 × 20 cm, layer thickness 2 mm (Merck Fertigplatten, Kieselgel 60 F₂₅₄). The fractions were isolated by methanol extraction of the silica gel. 3-Bromothiophene,²⁴ 3-(dimethylamino)propen-2-yl⁸ and 100 % nitric acid²⁵ were prepared according to methods described in the literature.

2-Cyanothiophene **3**. Chlorosulfonyl isocyanate (85.0 g, 0.60 mol, 52.1 ml) was rapidly added

to a stirred solution of thiophene (168.2 g, 2.00 mol) in dry ether (100 ml) and dry benzene (150 ml). The reaction mixture was kept at 35 °C until crystals began to precipitate. More chlorosulfonyl isocyanate (198.2 g, 1.40 mol, 122.0 ml) in dry benzene (250 ml) was then added over a period of 1 h, during which time the temperature rose but was kept at 50 °C with a water bath. After complete addition, the mixture was stirred at 50 °C for another h and was then left at room temperature over night.

The flask, now containing a precipitate of 2-thiophenecarboxamido-*N*-sulfochloride 4, was placed in a cooling bath (ice/salt). Dimethylformamide (308 g, 4.20 mol) was added at such a rate that the temperature could be kept at 10–12 °C (about 20 min was required). The mixture was stirred at 30 °C for 30 min and was then poured onto 400 g of ice. After separating the organic layer, the water phase was extracted twice with benzene (100 ml). The combined organic layers were washed with water, NaHCO₃ and dried over MgSO₄. Evaporation and distillation yielded 148.6 g (72 %) of the title compound, b.p. 77–78 °C/1.6 kPa; n_D^{20} 1.5619. Lit.²⁶ 72 °C/1.3 kPa; n_D^{20} 1.5612.

3-Cyanothiophene 5. A stirred mixture of 3-bromothiophene (162.6 g, 1.00 mol), copper (I) cyanide (106.0 g, 1.20 mol), and dimethylformamide (150 ml) was refluxed for 3 h. The hot dark reaction mixture was poured into a warm solution of sodium cyanide (200 g) in water (600 ml). The mixture was vigorously shaken and then extracted twice with benzene (200 + 100 ml). The extract was washed with 10 % aqueous sodium cyanide (100 ml) and water. After drying (MgSO₄) and removal of solvent, distillation yielded 69.6 g (64 %) of the title compound, b.p. 82–83 °C/1.6 kPa, n_D^{24} 1.5603. Lit.²⁶ 77 °C/1.3 kPa; n_D^{20} 1.5632.

2-Thiophenecarboximidic acid ethyl ester hydrochloride 7. A stirred solution of 2-cyanothiophene (54.6 g, 0.50 mol) and absolute ethanol (34.5 g, 0.75 mol) in dry ether (300 ml) was cooled to 0 °C (solid CO₂/ethanol) and saturated with dry hydrogen chloride passed into the solution at such a rate that the temperature could be kept between 0–5 °C (about 1 h). The cooling bath was removed and the mixture was stirred for 24 h. The crystalline precipitate formed was then filtered off, rapidly washed with dry ether, and dried *in vacuo* over silica, yielding 86.2 g (91 %) of the title compound, m.p. 126–128 °C (decomposition to amide, m.p. 177–178 °C). Lit.²⁷ 123–126 °C; 176 °C.

The ¹H NMR spectrum of the free imido ester was recorded on a carbon tetrachloride solution (dried over CaCl₂) obtained by shaking CCl₄, 7 and cold 1.0 M NaOH (1.1 equiv.) followed by separation of the aqueous layer: δ 7.43 (s, broad, disappears after addition of D₂O, N=H), 7.39 (3-H, dd, 1 H), 7.30 (5-H, dd, 1 H), 6.95 (4-H, dd, 1 H), 4.28 (CH₂, q, 2 H), 1.37 (CH₃, t, 3 H). J (H3,H4) 3.6 Hz, J (H3,H5) 1.3 Hz, J (H4,H5) 4.9 Hz, J (CH₂–CH₃) 7.0 Hz.

3-Thiophenecarboximidic acid ethyl ester 8 was prepared in 91 % yield from 5 by the same procedure as for 7. The title compound forms white crystals, m.p. 126–129 °C (decomposition to amide, m.p. 180–181 °C). Lit.²⁸ m.p. for amide 179–180 °C. ¹H NMR (CCl₄) of the free imido ester: δ 7.33 (s, broad, disappears after addition of D₂O, N=H), 7.65 (H-2, dd, 1 H), 7.27 (4-H, dd, 1 H), 7.15 (5-H, dd, 1 H), 4.27 (CH₂, q, 2 H), 1.35 (CH₃, t, 3 H). J (H2,H4) 1.6 Hz, J (H2,H5) 2.7 Hz, J (H4,H5) 5.0 Hz, J (CH₂–CH₃) 7.0 Hz.

2-Thiophenecarboxamidine hydrochloride 9. 2-Thiophenecarboximidic acid ester hydrochloride (82.2 g, 0.43 mol) was added in portions to a stirred solution of ammonia (16.3 g, 0.96 mol) in absolute ethanol (200 ml) and the mixture was then stirred at room temperature. Samples of the mixture were made alkaline with dilute NaOH and extracted with ether. The ether phase was analyzed on TLC (Al₂O₃/acetone; R_F amidine 0.05 R_F imido ester 0.90). After 48 h reaction all imido ester was consumed. Eventual ammonium chloride was then filtered off, and after evaporation of the solvent, 67.8 g (97 %) of the title compound was obtained, m.p. 177–178 °C. Lit.²⁷ 176 °C.

To get a sample for ¹H NMR, 9 was treated with cold 2.5 M NaOH (1.5 equiv.). An oil separated which crystallized in the refrigerator. Filtration and drying *in vacuo* yielded 2-thiophenecarboxamidine, m.p. 109–110 °C. ¹H NMR (DMSO-*d*₆): δ 7.63–7.43 (H-3 and H-5, m, 2 H), 7.03 (4-H, dd, 1 H), 6.43 (s, broad, disappeared after addition of D₂O, C(NH)NH₂, 3 H). J (H3,H4) 3.5 Hz, J (H4,H5) 5.0 Hz.

3-Thiophenecarboxamidine hydrochloride 10 was prepared from 8 in 98 % yield by the same procedure as for 9. The title compound forms white crystals, m.p. 177–178 °C. ¹H NMR of the free amidine (m.p. 107–108 °C) in DMSO-*d*₆ gave an AA'X spectrum: δ 7.98 (H-2, t, 1 H), 7.52 (H-4 and H-5, d deformed, 2 H), 6.38 [C(NH)NH₂, s, 3 H disappears after addition of D₂O].

2-(2-Thienyl)pyrimidine 1. To a stirred solution made from sodium (2.30 g, 0.100 mol) and methanol (75 ml), 2-thiophenecarboxamidine hydrochloride (16.3 g, 0.100 mol) was added in portions followed by 3-(dimethylamino)propen-2-al (9.91 g, 0.100 mol), after which the mixture was refluxed for 6 h. The sodium chloride formed was filtered off from the hot reaction mixture and washed twice with hot methanol (10 ml). The combined methanol phases were kept at –15 °C overnight. Filtration yielded 9.99 g of the title compound as almost white crystals, m.p. 90–92 °C. The mother liquor was evaporated and the residue recrystallized from aqueous methanol yielding an additional 2.01 g of the title compound, m.p. 89–90 °C, total yield 12.0 g (74 %). To prepare an analytically pure material, the crude product was dissolved in 2 M HCl and the solution was treated with charcoal. After filtration, 5 M NaOH was added

to pH $\approx$ 3, yielding white crystals. m.p. 92–93°C. (Found: C 59.1; H 3.69; N 17.2; S 19.8. Calc. for $C_8H_5N_3S$ (162.22): C 59.27; H 3.73; N 17.27; S 19.73). ^1H NMR: δ 8.63 (H-4 and H-6, d, 2 H), 8.00 (H-3', dd, 1 H), 7.45 (H-5', dd, 1 H), 7.12 (H-4', dd, 1 H), 7.00 (H-5, t, 1 H). $J(H4,H5)$ 4.9 Hz, $J(H3',H4')$ 3.6 Hz, $J(H3',H5')$ 1.3 Hz, $J(H4',H5')$ 4.9 Hz. m/e (%): 162 (100, M^+), 161 (8, $M^+ - H$), 135 (4, $M^+ - HCN$), 109 (52, $M^+ - C_2H_5N$), 82 (9), 45 (12), 39 (11).

2-(3-Thienyl)pyrimidine 2 was prepared from 10 in 76 % yield by the same procedure as for 1. The title compound forms white prisms, m.p. 101–102°C. (Found: C 59.3; H 3.80; N 17.0; S 19.6. Calc. for $C_8H_5N_3S$ (162.22): C 59.27; H 3.73; N 17.27; S 19.73). ^1H NMR: δ 8.73 (H-4 and H-6, d, 2 H), 8.28 (H-2', dd, 1 H), 7.90 (H-4', dd, 1 H), 7.33 (H-5', dd, 1 H), 7.08 (H-5, t, 1 H). $J(H4,H5)$ 4.9 Hz, $J(H2',H4')$ 1.2 Hz, $J(H2',H5')$ 3.1 Hz, $J(H4,H5)$ 5.2 Hz. m/e (%): 162 (100, M^+), 161 (19, $M^+ - H$), 135 (6, $M^+ - HCN$), 109 (50, $M^+ - C_2H_5N$), 81 (8), 45 (2), 39 (8).

Nitration of 2-(2'-thienyl)pyrimidine (1) with nitric and sulfuric acids. 1 (324 mg, 2.00 mmol) was dissolved in 98 % sulfuric acid (3.5 ml). To the yellow solution 100 % nitric acid (83 μ l, 2.0 mmol) was added at 0°C. The mixture was allowed to stand at 0°C for 1 h and was then poured onto ice (ca. 20 g). After collecting the resulting precipitate on a filter, it was stirred with a saturated solution of $NaHCO_3$ at 80°C for 15 min. After cooling, filtration yielded 374 mg (90 %) of yellow crystalline powder, m.p. 160–185°C.

TLC indicated two products and the mixture was chromatographed by PTLC (30 mg/plate, elution 4 times with dichloromethane) which gave two bands. From the band at R_F = 0.40 (356 nm: weak greyish-violet), 2-(4'-nitro-2'-thienyl)pyrimidine (12) was obtained as almost white crystals, m.p. 157–158°C. (Found: C 46.8; H 2.50; N 19.6. Calc. for $C_8H_4N_4O_2S$ (207.2): C 46.4; H 2.43; N 20.3). ^1H NMR: δ 8.77 (H-4 and H-6, d, 2 H), 8.48 (H-3' or H-5', d, 1 H), 8.38 (H-3' or H-5', d, 1 H), 7.25 (H-5, t, 1 H); $J(H4,H5)$ 4.8 Hz, $J(H3',H5')$ 1.5 Hz. m/e (%): 207 (100, M^+), 191 (2, $M^+ - O$), 177 (7, $M^+ - NO$), 162 (7, $M - CHS$), 161 (26, $M^+ - NO_2$), 149 (43, $M^+ - NO - CO$). ν_{max} (KBr): 1515, 1335 cm^{-1} .

From the band at R_F = 0.51 (356 nm: strong dark violet), 2-(5'-nitro-2'-thienyl)pyrimidine (13) was isolated as pale yellow crystals, m.p. 201–202°C. (Found: C 46.6; H 2.48; N 19.5. Calc. for $C_8H_4N_4O_2S$ (207.2): C 46.4; H 2.43; N 19.6). ^1H NMR: δ 8.78 (H-4 and H-6, d, 2 H), 7.93 (H-3' and H-4', s, 2 H, separated in HMPT: δ 8.32, d, and 8.00, d, $J(H3',H4') = 4.4$ Hz), 7.28 (H-5, t, 1 H). $J(H4,H5)$ 4.8 Hz. m/e (%): 207 (100), 191 (2), 177 (20), 161 (20), 149 (28), assignments see for compound 12. ν_{max} (KBr) 1490, 1330 cm^{-1} . Through integration of the ^1H NMR spectrum of the crude product the ratio of 12 to 13 was determined to be 46:54.

The first filtrate above was neutralized to

pH = 7 ($NaOH$, $NaHCO_3$) and was then extracted with dichloromethane (3×10 ml). The combined organic phases were washed (H_2O) and dried ($MgSO_4$). Evaporation of solvent yielded 12 mg of product. TLC together with ^1H NMR showed it to consist of 1 and 12 in ratio 1:3.

Nitration of 2-(2'-thienyl)pyrimidine (1) with acetyl nitrate. 100 % nitric acid (1.0 ml) was mixed with acetic anhydride (3.0 ml), with cooling. The mixture was kept at room temperature for 15 min, then cooled to 0°C and added to a cold (0°C) solution of 1 (324 mg, 2.00 mmol) in acetic anhydride (3.0 ml). The reaction mixture was then put in a water bath (25°C). White needles (for identification, see below) began to precipitate after some minutes, but were redissolved after about half an hour when a slightly exothermic reaction started. After 3 h, all starting material was consumed (GLC). The yellow precipitate formed was collected on a filter and washed with cold acetic anhydride, which afforded 104 mg (25 %) of 2-(5'-nitro-2'-thienyl)pyrimidine (13) (NMR, IR), m.p. 201–202°C, contaminated with traces of other isomers (TLC). The filtrate was poured onto ice, neutralized (5 M $NaOH$) and the mixture was extracted with dichloromethane (3×15 ml). The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to give 186 mg (45 %) of yellow crystalline material, m.p. 140–170°C. This consisted of a mixture of 2-(3',2'-thienyl)pyrimidine (11), 2-(4'-nitro-2'-thienyl)pyrimidine (12), and 2-(5'-nitro-2'-thienyl)pyrimidine (13) in the proportions 2:1:9, which could be shown as follows. The major product (13) was identified from the ^1H NMR spectrum of the mixture. This spectrum did not allow an unambiguous identification of the other products. Therefore 50 mg of the mixture was chromatographed by PTLC (50 mg/plate, elution 4 times with dichloromethane), which gave two bands. One band (R_F 0.54; 356 nm: strong dark violet) contained 13, and from the other band (R_F 0.43; 356 nm: weak bright violet) 11 mg of crystalline material, m.p. 70–105°C was isolated. The spectroscopical data showed it to be a 2:1 mixture of 11 and 12: ^1H NMR (100 MHz, acetone- d_6) 2-(3'-nitro-2'-thienyl)pyrimidine: δ 8.85 (H-4 and H-6, d, 2 H), 7.82 (H-4' or H-5', d, 1 H), 7.54 (H-4' or H-5', d, 1 H), 7.47 (H-5, t, 1 H). $J(H4,H5)$ 5.0 Hz, $J(H4',H5')$ 5.5 Hz. 2-(4'-Nitro-2'-thienyl)pyrimidine: δ 8.86 (H-4 and H-6, d, 2 H), 8.73 (H-3' or H-5', d, 1 H), 8.37 (H-3' or H-5', d, 1 H), 8.45 (H-5, t, 1 H). $J(H4,H5)$ 5.0 Hz, $J(H3',H5')$ 1.7 Hz. Integration gave the ratio between 11 and 12 = 2:1.

The MS of the mixture showed no other peaks than those expected from 2-(mononitrothienyl)pyrimidines. ν_{max} (KBr) 1518, 1505, 1334 cm^{-1} .

When the NMR parameters of all three isomers in $CDCl_3$ were known, the spectrum of the first isolated mixture could be interpreted, integration giving the product distribution given above.

In one run of the experiment, the precipitate formed in the beginning of the reaction was collected on a filter, giving 210 mg of white needles, m.p. 128°C (decomp. evolution of nitrogen oxides). The product was identical (IR, mixed melting point) with an authentic sample of 2-(2'-thienyl)pyrimidine mononitrate prepared by adding nitric acid to a saturated solution of *1* in acetonitrile. (Found: C 42.4; H 3.14; N 18.6. Calc. for $C_8H_7N_3O_3S$ (225.2) requires C 42.66; H 3.13; N 18.66). ^1H NMR (CH_3CN): The same as (*1*). $\nu(KBr)$ 2500 cm^{-1} (broad, $=NH$).

Nitration of 2-(3'-thienyl)pyrimidine (2) with nitric and sulfuric acids. The same nitration procedure as above was used. Starting from 2.00 mmol of *2*, filtration of the acidic water phase yielded after neutralization of the precipitate 351 mg (85 %) 2-(5'-nitro-3'-thienyl)pyrimidine *16* as a slightly beige powder, m.p. 189–190°. Sublimation (13 Pa, 150°C) gave pale yellow prisms, m.p. 191.0–191.5°. (Found: C 46.5; H 2.25; N 19.8. Calc. for $C_8H_6N_4O_2S$ (207.2): C 46.4; H 2.43; N 20.3). ^1H NMR: δ 8.80 (H-4 and H-6, d, 2 H), 8.72 (H-2' or H-4', d, 1 H), 8.47 (H-2' or H-4', d, 1 H), 7.24 (H-5, t, 1 H). $J(H4,H5)$ 4.9 Hz, $J(H2',H4')$ 1.7 Hz. m/e (%): 207 (100), 191 (2), 177 (12), 161 (11), 149 (29). ν_{max} (KBr) 1498, 1330 cm^{-1} .

After neutralization, the acidic water phase was extracted with dichloromethane, yielding 32 mg of semicrystalline oil. This was chromatographed by PTLC (32 mg/plate; elution 3 times with ether) which gave four bands. Two of these, at R_F 0.63 and 0.56, were of minor magnitude and contained (IR) traces of starting material (*2*) and (*16*), respectively. From the third band (R_F 0.47, 356 nm: pale violet), 2-(4'-nitro-3'-thienyl)pyrimidine *15* was isolated as white prisms, m.p. 93–94°C. ^1H NMR: δ 8.78 (H-4 and H-6, d, 2 H), 8.13 (H-2' or H-5', d, 1 H), 7.88 (H-2' or H-5', d, 1 H), 7.27 (H-5, t, 1 H). $J(H4,H5)$ 4.8 Hz, $J(H2',H5')$ 3.8 Hz. m/e (%): 207 (100), 191 (2), 177 (45), 162 (7), 161 (8), 149 (33). ν_{max} (KBr) 1505, 1348 cm^{-1} .

From the fourth band (R_F 0.38, 356 nm: strong dark violet) 2-(2'-nitro-3'-thienyl)pyrimidine *14* was isolated as yellow needles m.p. 117–118°C. ^1H NMR: δ 8.85 (H-4 and H-6, d, 2 H), 7.52 (H-4' or H-5', d, 1 H), 7.32 (H-4' or H-5', d, 1 H), 7.35 (H-5, t, 1 H). $J(H4,H5)$ 4.8 Hz, $J(H4',H5')$ 5.5 Hz. m/e (%): 207 (100), 191 (2), 177 (40), 161 (16), 149 (79). ν_{max} (KBr) 1495, 1328 cm^{-1} .

Nitration of 2-(3'-thienyl)pyrimidine (2) with acetyl nitrate. The amounts of substrate, nitric acid and acetic anhydride and the way of mixing them were the same as above. After 48 h, the reaction mixture was poured onto ice. The mixture was neutralized to pH=7 with 5 M NaOH and then extracted with dichloromethane (3 $\times$ 10 ml). The extract was washed (H_2O), dried ($MgSO_4$) whereupon evaporation yielded

265 mg of yellow semicrystalline product, m.p. 75–110°C.

Through a combination of PTLC (100 mg/plate, elution 4 times with dichloromethane) and ^1H NMR analysis the product was shown to consist of 12 % starting material *2* together with *14*, *15*, *16* and 2-(2',5'-dinitro-3'-thienyl)pyrimidine *17* in the molar proportions of 48:6:23:23. The dinitro compound *17* was not isolated, but was shown (IR, NMR, TLC) to be identical with authentic *17* (see below).

Repetition of this experiment with prolonged reaction time (96 h) led to 294 mg product which by NMR analysis ($CDCl_3$) was shown to contain no starting material but the same nitrated products as above, now in the molar proportions of 45:5:7:43.

2-(2',5'-Dinitro-3'-thienyl)pyrimidine (17). 100 % nitric acid (0.5 ml) was added to a solution of *2* (162 mg, 1.00 mmol) in 98 % sulfuric acid (2 ml). The mixture was heated to 100°C for one hour, and after cooling the solution was poured onto ice. The precipitate formed was collected on a filter, washed with water, $NaHCO_3$ solution, and water, yielding 113 mg (45 %) of the title compound as a yellow powder, m.p. 125–126°C. Recrystallization from methanol afforded pale yellow prisms, m.p. 126–127°C. (Found: C 38.9; H 1.59; N 22.2. Calc. for $C_8H_4N_6O_4S$ (252.2): C 38.10; H 1.60; N 22.22). ^1H NMR: δ 8.85 (H-4 and H-6, d, 2 H), 8.17 (H-4', s, 1 H), 7.38 (H-5, t, 1 H). $J(H4,H5)$ 5.0 Hz. ^{13}C NMR: δ 129.8 (C4'). $J(C4',H4')$ 183.7 Hz. m/e (%): 252 (76, M^+), 236 (1, $M^+ - O$), 222 (1, $M^+ - NO$), 206 (4, $M^+ - NO_2$), 190 (3, $M^+ - NO_2 - O$), 176 (27, $M^+ - NO_2 - NO$), 164 (32, $M^+ - NO_2 - CNO$), 160 (18, $M - 2NO_2$), 148 (100, $M^+ - NO_2 - NO - CO$). ν_{max} (KBr) 1518, 1322 cm^{-1} .

2 in sulfuric acid as above was also treated with 2 equiv. of nitric acid for 1 h at 40°C. Under these conditions, however, only mononitrated product was obtained.

Bromination of 2-(2'-thienyl)pyrimidine (1). Bromine (320 mg, 102 μ l, 2.0 mmol) was added to a solution of *1* (324 mg, 2.00 mmol) and sodium acetate (330 mg, 4.0 mmol) in acetic acid (10 ml), whereupon the flask was stoppered. After 30 min all starting material was consumed (GLC) and the reaction mixture poured onto ice. The resulting suspension was neutralized with solid sodium carbonate and then extracted with ether (3 $\times$ 20 ml). The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to give 447 mg 93 % of 2-(5'-bromo-2'-thienyl)pyrimidine *18* as a yellow-white solid, m.p. 99–101°C. TLC (silica gel, dichloroethane or ether) showed, in addition to the application spot (polar impurity), only one spot. Sublimation (140°C, 13 Pa) afforded white crystals, m.p. 100–101°C. (Found: C 40.0; H 1.99; Br 34.1. Calc. for $C_8H_5N_2BrS$ (241.2): C 39.85; H 2.10; Br 33.14). ^1H NMR: δ 8.60 (H-4 and H-6, d, 2H), 7.70 (H-3', d, 1 H), 7.07 (H-4', d, 1 H), 7.03 (H-5, t, 1 H). J ($H4,H5$) 4.8 Hz, $J(H3',H4')$

3.9 Hz. m/e (%): 240, 242 (79, 78, M^+), 187, 189 (25, 25, $M^+ - C_3H_3N$), 161 (100, $M^+ - Br$), 108 (7, $M^+ - Br - C_3H_3N$).

Bromination of 2-(3'-thienyl)pyrimidine (2). The same procedure as in the above bromination was used. The reaction was followed by GLC (OV1, 1.9 m, 160°). After 18 h, starting material still remained, but the ratio of products to starting material did not increase further. Work-up as above afforded 324 mg of yellow oil. GLC of this oil showed three peaks which according to MS were caused by starting material, mono- and dibrominated products, respectively. The oil also contained (TLC) some unstable polar, yellow product which slowly decomposed to tars. To remove these impurities, an ether solution of the crude product was filtered through silica gel, which was then washed with ether. After removal of solvent from the combined filtrates a colourless oil (304 mg) was obtained. (GLC of this material was identical with that of the crude product.) When the NMR spectra of the single pure components had been recorded (see below) this mixture could be shown by NMR analysis to consist of starting material 2, 2-(2'-bromo-3'-thienyl)pyrimidine 19, 2-(5'-bromo-3'-thienyl)pyrimidine 20, and 2-(2',5'-dibromo-3'-thienyl)pyrimidine 21 in the molar proportions 28:24:36:12.

To simplify separation work, the experiment was repeated with an excess of bromine in order to eliminate starting material from the product mixture. When 3.4 mmol of bromine (174 μ l) was added in small portions over a period of 18 h, practically all starting material was consumed. Work-up as above yielded a semicrystalline oil (392 mg) which according to NMR analysis consisted of 19, 20, and 21 in the molar proportions 39:32:29. PTLC of this product (75 mg/plate, elution 5 times with dichloroethane) gave 3 bands visible in light of 254 nm. From the first band (R_F 0.73) white crystals, m.p. 85–86°C, were obtained which according to spectral data were identified as 2-(2',5'-dibromo-3'-thienyl)pyrimidine (21). (Found: C 30.8; H 1.85; Br 50.31. Calc. for $C_8H_4N_2Br_2S$ (320.8): C 30.02; H 1.26; Br 49.94). ^1H NMR: δ 8.78 (H-4 and H-6, d, 2 H), 7.65 (H-4', s, 1 H), 7.18 (H-5, t, 1 H). $J(H4,H5)$ 4.8 Hz. ^{13}C NMR: δ 133.4 (C4'). $J(C4'H4')$ 178.2 Hz. m/e (%): 322, 320, 318 (50, 100, 48, M^+), 269, 267, 265 (13, 25, 13, $M^+ - C_3H_3N$), 251, 249 (63, 63, $M^+ - Br$), 160 (29, $M^+ - 2Br$), 107 (33, $M^+ - 2Br - C_3H_3N$).

The second band (R_F 0.54) yielded white crystals, m.p. 103–104°C, identified as 2-(5'-bromo-3'-thienyl)pyrimidine (21). (Found: C 40.1; H 2.20; Br 32.7. Calc. for $C_8H_4N_2BrS$ (241.2): C 39.9; H 2.10; Br 33.1). ^1H NMR: δ 8.67 (H-4 and H-6, d, 2 H), 8.13 (H-2', d, 1 H), 7.83 (H-4', 1 H), 7.08 (H-5, t, 1 H). $J(H4,H5)$ 4.8 Hz, $J(H2',H4')$ 1.2 Hz. m/e (%): 242, 240 (100, 97, M^+), 239 (11, $M^+ - H$), 189, 187 (32, 32, $M^+ - C_3H_3N$), 161 (38, $M^+ - Br$), 108 (5, $M^+ - Br - C_3H_3N$).

From the third band (R_F 0.43), white crystals, m.p. 83–85°C, identified as 2-(2'-bromo-3'-thienyl)pyrimidine (19), were isolated. (Found: C 40.2; H 2.20; Br 32.67. Calc. for $C_8H_4N_2BrS$ (241.2): C 39.9; H 2.10; Br 33.1). ^1H NMR: δ 8.77 (H-4 and H-6, d, 2 H), 7.61 (H-4', d, 1 H), 7.25 (H-5', d, 1 H), 7.15 (H-5, t, 1 H). $J(H4,H5)$ 4.8 Hz, $J(H4',H5')$ 5.7 Hz. m/e (%): 242, 240 (79, 79, M^+), 239 (3, $M^+ - H$), 189, 187 (25, 25, $M^+ - C_3H_3N$), 161 (100, $M^+ - Br$), 108 ($M^+ - Br - C_3H_3N$).

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REFERENCES

1. a. Gjös, N. and Gronowitz, S. *Acta Chem. Scand.* 26 (1972) 1851, and references therein; b. Gronowitz, S. and Böler, J. *Ark. Kemi* 28 (1968) 587; c. Gronowitz, S., Hallberg, A. and Liljefors, S. *Acta Pharm. Suec.* 5 (1968) 163; d. Gjös, N. and Gronowitz, S. *Acta Chem. Scand.* 25 (1971) 2596.
2. Pankiewicz, J., Decroix, B. and Morel, J. *C. R. Acad. Sci. Ser. C* 281 (1975) 39.
3. Brown, D. J. *The Pyrimidines*, Interscience, Wiley, New York 1962 and 1970, p. 31 and Supplement p. 20.
4. Graf, R. *Justus Liebigs Ann. Chem.* 661 (1963) 111.
5. Lohaus, G. *Org. Synth.* 50 (1970) 52; *Chem. Ber.* 100 (1967) 2719.
6. Reynaud, P. and Delaby, R. *Bull. Soc. Chim. Fr.* (1955) 1614.
7. Friedman, L. and Shechter, H. *J. Org. Chem.* 26 (1961) 2522.
8. Arnold, Z. and Šorm, F. *Collect. Czech. Chem. Commun.* 23 (1958) 452.
9. Hoffman, R. A. and Gronowitz, S. *Ark. Kemi* 16 (1960) 563.
10. Gronowitz, S., Norrman, B., Gestblom, B., Mathiasson, B. and Hoffman, R. A. *Ark. Kemi* 22 (1964) 65.
11. Kato, T., Yamanaka, H., Abe, H., Sasaki, S. and Ichikawa, H. *Org. Mass Spectrom.* 9 (1974) 981.
12. Wynberg, H., van Bergen, T. J. and Kellog, R. M. *J. Org. Chem.* 34 (1969) 3175.
13. Östman, B. *Acta Chem. Scand.* 22 (1968) 2754.
14. Lynch, B. M. and Poon, L. *Can. J. Chem.* 45 (1967) 1431.
15. a. Gronowitz, S., Johnson, I. and Hörnfeldt, A.-B. *Chem. Scr.* 7 (1975) 76 and 211; b. Gronowitz, S. and Ander, I. *Tetrahedron* 32 (1976) 1403.
16. *NMR Spectra Catalog*, Varian Associates, Palo Alto 1962, No. 52.
17. For reviews of electrophilic substitution in five-membered heterocyclics, see: a. Gronowitz, S. *Adv. Heterocycl. Chem.* 1 (1963) 43ff; b. Marino, G. *Ibid.* 13 (1971) 293.

18. Ref. 17b, p. 254.
19. Belenkii, L. I., Novikova, E. I., Dynchenko, I. A. and Goldfarb, Ya. L. *J. Org. Chem. USSR* 7 (1971) 1803.
20. Gjörs, N. and Gronowitz, S. *Acta Chem. Scand.* 21 (1967) 2893.
21. Blatt, A. H., Bach, S. and Kresch, L. W. *J. Org. Chem.* 22 (1957) 1693; Tirouflet, J. and Fournari, P. *C. R. Acad. Sci. Ser. C* 246 (1958) 2003.
22. Babasinan, V. S. *J. Am. Chem. Soc.* 50 (1928) 2748.
23. Babasinan, V. S. *J. Am. Chem. Soc.* 60 (1938) 2906.
24. Gronowitz, S. and Raznikiewicz, T. *Org. Synth. Coll. Vol. V*, p. 149.
25. Liang, P. *Org. Synth. Coll. Vol. III*, p. 804, note 1.
26. Gronowitz, S. and Hoffman, R. A. *Ark. Kemi* 16 (1960) 515.
27. Freudenberg, K., Eichel, H. and Leutert, F. *Ber. Dtsch. Chem. Ges.* 65 (1932) 1183.
28. Campaigne, E. and LeSuer, W. *J. Am. Chem. Soc.* 70 (1948) 1555.

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