REACTIONS OF AROMATIC AND HETEROAROMATIC COMPOUNDS CARRYING ELECTRON-ACCEPTOR SUBSTITUENTS. 26.* ACYLAMINOMETHYLATION OF 2-ACYLTHIOPHENES, 2-THIOPHENECARBOXYLIC ACID, AND ITS ESTERS.

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The reaction of 2-thiophene aldehyde, 2-acetylthiophene, 2-thiophene carboxylic acid, and its methyl ester with N-(hydroxymethyl)chloroacetamide in concentrated sulfuric acid yields a mixture of 4- and 5-(N-chloroacetylamino)methyl derivatives, the former being preferred.

As early as 1935 a paper [2] had appeared in which it was reported that when 2-thiophene carboxylic acid (I) reacts with the N-(hydroxymethyl)amides of acetic and benzoic acids in concentrated sulfuric acid the products are N-acylaminomethylated in position 4 of the thiophene ring. When one considers the powerful α-orientating effect of the hetero-atom, which is clearly displayed in thiophene carrying acceptor substituents in position 2, such a direction of the oxidation is surprising. Hence in a well-known monograph on the chemistry of thiophene [3] the quoted results of [2] were regarded with doubt and it was suggested that the compounds obtained were in fact 2,5-disubstituted. This doubt was also shared by the authors of a review on N-acylaminoalkylation reactions [4].

In a series of papers emanating from our laboratory (see the reviews [5] and [6]) it was shown that conversion of certain thiophene carbonyl compounds into nv-complexes with $AlCl_3$ or protonation at the carbonyl group markedly accentuated the electron-accepting ability of the substituent and directed electrophilic attack onto the 4-position of the thiophene ring. At the same time, while carrying out various electrophilic substitution reactions of 2-thiophene aldehyde (II), 2-acetylthiophene (III) and the methyl ester of 2-thiophene carboxylic acid (IV) in concentrated sulfuric acid, that is, in conditions close to those of [2] for the acylaminomethylation of the acid (I), the α-orientating effect of the heteroatom was not completely overcome and in addition to the 2,4-substituted thiophenes considerable quantities (10 to 50%) of the 2,5-isomers were obtained [7-11]. It should be noted that, in distinction from true protonation which is attained, for example, by the action of HCl and $SbCl_5$ in 1,2-dichloroethane and permits one to obtain, in the case of bromination of the aldehyde II and the ketone III, 4-bromoderivatives containing respectively 2 and 4% of the 5-isomers [12], in sulfuric acid it seems that hydrogen bonded complexes are formed [11]. Thus the formation of 4-acylamino-methyl derivatives as the sole products when carrying out the reaction in concentrated sulfuric acid [2] gives rise to doubt, the more so since the carboxyl group as a substituent has a lower electron-accepting ability than formyl or acetyl.

The object of the present work was an investigation of the direction of acylaminomethylation of a series of thiophene derivatives carrying electron-acceptor substituents: the acid I and compounds II-IV. Because of the reactivity of the reagent and the possibility of determining the ratio of the isomers formed by PMR we used the example of N-chloroacetylaminomethylation by the action of N-(hydroxymethyl)chloroacetamide in sulfuric acid.

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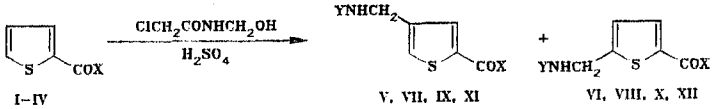
TABLE 1. PMR Spectra of (N-Chloroacetylamino)methyl-Substituted 2-Thiophenecarboxylic Acid, Its Ester, 2-Thiophenealdehyde, and 2-Acetylthiophene

Compound	Chemical shift, δ, ppm								
	$ClCH_2$	NCH_2	NH	proton groups X			protons of thiophene ring		
				CHO	CH_3CO	$COOCH_3$	3-H	4-H	5-H
V	4,10 s	4,45d	8,10 broad	—	—	—	7,73d	—	7,60d
VI	4,10s	4,63d	8,10 broad	—	—	—	7,60 overlap	7,05d	—
VII	4,08s	4,47d	7,15 broad	—	—	3,88s	7,71d	—	7,41 broad
VIII	4,08 s	4,66d	7,26 broad	—	—	3,86s	7,64d	6,98 d	—
IX	4,08s	4,50d	7,55 broad	9,83dt	—	—	7,74d	—	7,63 broad
X	4,08s	4,68d	7,55 broad	9,80s	—	—	7,80d	7,10d	—
XI	4,13s	4,46d	8,10 broad	—	2,48s	—	7,79d	—	7,68d
XII	4,13s	4,62d	8,24 broad	—	2,46 s	—	7,65d	7,04d	—

*Spectra of compounds V, VI, XI, XII, run in $(CD_3)_2CO$, VII-X in $CDCl_3$.
†J(5-H, CHO) = 1 Hz (spectrum run on Bruker WM-250).

When we repeated the experiments described in [2], we obtained a mixture of 4- and 5-(N-chloroacetylamino)methyl-2-thiophenecarboxylic acids (V and VI respectively) in the ratio of 75:25 (by PMR). Oxidation of this mixture and subsequent treatment with diazomethane led to a mixture of the methyl esters of 2,4- and 2,5-thiophenedicarboxylic acids in 75:25 ratio (by GLC). This mixture of acids melted over a wide range of temperature (120-140°C) and was isolated in 83% yield. The substance described in [2] as the acid V had mp 153-156°C and was obtained in 53% yield. Evidently a change in the ratio of the isomers in the mixture took place on recrystallization but it is impossible to judge the purity of the acid isolated in [2] without further information.

On amidoalkylation of the methyl ester IV we obtained a mixture of esters VII and VIII, 70:30 (by PMR). An attempt to increase the proportion of the 2,4-isomer VII by carrying out the reaction not in sulfuric acid but in the presence of an excess of $AlCl_3$ (about 4 moles) was unsuccessful: around 75% of the initial ester was recovered unchanged and around 10% of a 50:50 mixture of esters VII and VIII was formed. Assuming that in reacting with N-(hydroxymethyl)-chloroacetamide aluminum chloride can be partially irreversibly converted to hydrolysis products, incapable of activating an electrophilic agent and of forming a complex with the ester IV, we carried out the reaction of the same ester IV with N-(chloromethyl)chloroacetamide in the presence of 4 moles $AlCl_3$. A mixture of esters VII and VIII was isolated in the ratio 85:15 and in 10% yield but there was considerable tar formation and recovery of the initial ester IV amounted to 20% in all. Because of this result we used only N-(hydroxymethyl)chloroacetamide in sulfuric acid for subsequent amidomethylations.



I–IV V, VII, IX, XI VI, VIII, X, XII

Y=$ClCH_2CO$; I, V, VI X=OH; II, IX, X X=H; III, XI, XII X=CH_3; IV, VII, VIII X=OCH_3

The aldehyde II, reacted with N-(hydroxymethyl)chloroacetamide over a period of 3 h, gave a 20% yield of a mixture of 4- and 5-(N-chloroacetylamino)methyl-2-thiophenealdehydes (IX and X) in the ratio 93:7; around 50% of the aldehyde II was recovered. When the reaction time was increased to 24 h, the same mixture was obtained in 32% yield but only 7% of the aldehyde II was recovered. From the ketone III a mixture of the 4- and 5-derivatives (XI and XII) in 90:10 ratio was obtained in 25% yield after 3 h reaction, 45% of the ketone III being recovered. Increasing the reaction time to 28 h gave the same mixture in 46% yield but the recovery of the ketone III was only 5%.

The proportions of the 2,4- and 2,5-isomers was determined in each case from the proton PMR spectrum. The signals were assigned on the basis of the values of their coupling constants: For the 2,4-disubstituted derivatives J_{35} = 1.5 Hz and for 2,5-disubstituted, J_{34} = 4 Hz. Values of the chemical shift of the protons for compounds V-XII are given in Table 1. In all cases, $J(NHCH_2)$ = 6 Hz. Recrystallization of the mixtures of N-(chloroacetylamino)-derivatives increased the concentration of the 2,4-isomer but isolation of this compound free from the 2,5-derivative was successful only in the case of the aldehyde II. An individual sample of 5-(N-chloroacetylamino)methyl-2-acetylthiophene (XII) was prepared by the action of chloroacetyl chloride on 5-aminomethyl-2-acetylthiophene which we had prepared earlier [13].

The results which we have obtained for the direction of acylaminomethylation of compounds I-IV in sulfuric acid are in agreement with the results for nitration, bromination and chloromethylation under similar conditions [7-11]. The ratio of 2,4- to 2,5-isomers corresponds to the change in electron-acceptor properties in the sequence: CHO > CH_3CO > $COOCH_3$.

EXPERIMENTAL

Tesla BS-467 (60 MHz), Tesla BS-497 (100 MHz) and Bruker WM-250 (250 MHz) instruments were used to obtain the PMR spectra; solvents were deuteroacetone or deuterochloroform and TMS was used as the internal standard. Chromatographic analysis was carried out on a LKhM-8MD chromatograph with a flame-ionization detector, nitrogen carrier gas, pyrex glass capillary column 40 m × 0.25 mm, Carbowax 40M/KF, prepared according to the method of [14].

Chloroacetylaminomethylation of 2-Thiophene Carboxylic Acid (I). To a solution of 6.4 g (50 mmole) acid I in 50 ml 92% H_2SO_4 at 18-22°C, 7.1 g (57 mmole) N-(hydroxymethyl)chloroacetamide [15] was added in portions, stirred 3 h, the reaction mixture poured onto 300 g ice and left to stand at 20°C for 20 h. The thickened oil was rubbed with a glass rod, filtered off and washed on the filter with 2 × 25 ml water; it was dried in vacuum over conc. H_2SO_4. The product (9.8 g, 83%) had mp 120-140°C and, from NMR data, was a mixture of 4- and 5-(N-chloroacetylamino)methyl-2-thiophene carboxylic acids (V and VI) in the ratio 75:25. To 2 g (8.6 mmole) of the mixture of acids was added 8 ml conc. HCl and after boiling for 2.5 h the solution was then evaporated to dryness in vacuum (20 mm). The residue was dried in a vacuum desiccator over KOH, dissolved in 100 ml water, and this solution was then added at 20°C to a solution of 4.75 g (30 mmole) $KMnO_4$ and 2.6 g (40 mmole) KOH in 400 ml water; after 20 h 50 ml alcohol was added to reduce the excess $KMnO_4$ and the ppt. of MnO_2 filtered off. The filtrate was evaporated in vacuum, the residue dissolved in 100 ml water, the solution acidified with conc. HCl and the acid which separated filtered off (0.48 g, 33% yield). By the action of an ether solution of diazomethane (from 1 g nitrosomethylurea), 109 mg of a mixture of the dimethyl esters of 2,4- and 2,5-thiophenedicarboxylic acids (in the ratio 75:25 by GLC, compared with reference compounds [16]) was obtained from 108 mg of the mixed acids.

Chloroacetylaminomethylation of the Methyl Ester of 2-Thiophene Carboxylic Acid (IV) in Sulfuric Acid. To 40 ml conc. H_2SO_4 at 0-5°C was added 5.18 g (36 mmole) of the ester IV, and 5.2 g (42 mmole) N-(hydroxymethyl)chloroacetamide was added in portions. After stirring for 3 h at 20°C the reaction mixture was poured onto ice and extracted out with chloroform. The extract was washed with water, saturated $NaHCO_3$, again with water; distillation yielded 7.1 g (80%) of a product with bp 195-198°C at 0.2 mm, mp 80-86°C which was shown by PMR to be a mixture of 4- and 5-N-(chloroacetylamino)methyl-2-methoxycarbonylthiophenes (VII and VIII) in the ratio 70:30. Recrystallized from methanol, the product had mp 86-97°C, the ratio of VII:VIII was 92:8 and elemental analysis gave the following results. Found: C 43.6, H 4.2, Cl 14.3. S 12.9%. Calculated, %: for $C_9H_{10}ClNO_3S$. C 43.6, H 4.1, Cl 14.3, S 12.9%. In an analogous experiment, it was found that increasing the reaction time to 3 days at 20°C reduced the yield to 54%.

Chloroacetylaminomethylation of the Ester IV in Presence of $AlCl_3$. A. To a complex prepared from 15.3 g (115 mmole) anhydride $AlCl_3$ and 4.1 g (28.8 mmole) of the ester IV, 4.07 g (33 mmole) N-(hydroxymethyl)chloroacetamide was added in portions at 50-60°C with stirring. The mixture was stirred and heated to 70-80°C for 1 h and then, with external cooling, it was decomposed with ice-cold water and extracted with chloroform. The extract was treated as in the preceding example and yielded 3 g (73%) unreacted ester IV and 0.95 g (13%) of a substance shown by PMR to be a mixture of 4- and 5-(N-chloroacetylamino)methyl-2-methoxycarbonylthiophenes (VII and VIII), ~ 50:50. In an analogous experiment, differing in the use of 1,2-dichloroethane as solvent, after boiling the reaction mixture for 6 h and treating it as before, a mixture of the esters VII and VIII in the ratio ~50:50 was obtained in 8% yield together with 76% recovered ester IV.

B. When the ester IV was reacted with N-(chloromethyl)chloracetamide [17] in the presence of 4 moles $AlCl_3$ in dichloroethane (2 days at 20°C, 2 h at bp), considerable tar formation was observed. Chromatographic purification on silica gel using chloroform as eluent resulted in the isolation of the initial ester (~20% recovery) together with a mixture of acylaminomethylation products VII-VIII, 85:15, in ~10% yield.

Chloroacetylaminomethylation of 2-Thiophenealdehyde. To 50 ml conc. H_2SO_4 at 0-5°C, 5.6 g (50 mmole) aldehyde II was added with stirring followed by 7.1 g (57 mmole) N-(hydroxymethyl) chloroacetamide in portions. The mixture was stirred 3 h at 20°C, poured onto ice and extracted with chloroform (3 × 50 ml). The extract was washed with water, saturated $NaHCO_3$, and again with water, after which distillation yielded 2.9 g of the initial aldehyde (52% recovery) and a fraction [2.2 g, bp 200-225°C (0.3-1 mm) (partial decomposition), mp 64-70°C] which was shown by PMR to be a mixture of 4- and 5-(N-chloroacetylamino)methyl-2-thiophenealdehydes (IX and X) in the ratio 93:7, yield 20% on initial II, 42% on II consumed. A sample for analysis was prepared by recrystallization from a mixture of ethyl acetate and hexane, mp 74-75°C; PMR showed this to be the pure 2,4-isomer IX. Found, %: C 43.9, H 3.5, Cl 16.2, S 14.6. Calculated, %: $C_8H_8ClNO_2S$. C 44.1, H 3.7, Cl 16.3, S 14.7. In an analogous experiment in which the reaction mixture was left for 1 day at 20°C a mixture of isomers IX and X was obtained in 32% yield and 7% aldehyde II recovered.

Chloroacetylaminomethylation of 2-Acetylthiophene (III). To 57 ml conc. H_2SO_4 at 5-10°C, 7.3 g (57 mmole) ketone III was added followed by 8.3 g (67 mmole) N-(hydroxymethyl)chloroacetamide in portions. After stirring for 3 h at 20°C the mixture was poured onto 400 g ice and extraced with 4 × 50 ml chloroform. The extract was washed with water, aqueous KOH, and again with water; distillation yielded 3.2 g ketone III (44% recovery) and 3.3 g of a material with bp 200-220°C at 0.2 mm, mp 65-80°C, which was shown by PMR to be a mixture of 4- and 5-(N-chloroacetylamino)methyl-2-acetylthiophenes (XI and XII) in the ratio 90:10. The yield was 25% on the initial ketone III or 45% allowing for that recovered. A sample for analysis was prepared by recrystallization from isopropanol, mp 84-86°C; this proved to be the 2,4-isomer XI with 3% of the 2,5-isomer XII as impurity. Found, %: C 46.3, H 4.5, Cl 15.2, S 13.6. Calculated, %: for $C_9H_{10}ClNO_2S$. C 46.6, H 4.4, Cl 15.3, S 13.8. In an analogous experiment in which the mixture was reacted for 28 h at 20°C the yield of mixed ketones XI and XII was 46%, and 5% of the initial ketone III was recovered.

5-(N-Chloroacetylamino)methyl-2-Acetylthiophene (XII). To a solution of 0.3 g of the hydrochloride of 5-aminomethyl-2-acetylthiophene [13] in 20 ml water cooled to 0°C, was added 3 ml chloroacetyl chloride and a solution of 5 g sodium acetate in 7 ml water. This was stirred for 1 h, diluted with water and extracted with chloroform. The extract was washed with 1 N HCl water, 5% KOH, water, and the solvent evaporated off. Recrystallization of the residue (0.3 g, 83%) from isopropanol yielded the ketone XII, mp 95-98°C. Found, %: C 47.1, H 4.6, Cl 15.2, S 13.7. $C_9H_{10}Cl_2NO_2S$. Calculated, %: C 46.7, H 4.4, Cl 15.3, S 13.8.

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IMPROVED METHOD FOR SYNTHESIS OF SUBSTITUTED TETRAPHENYLPORPHINS

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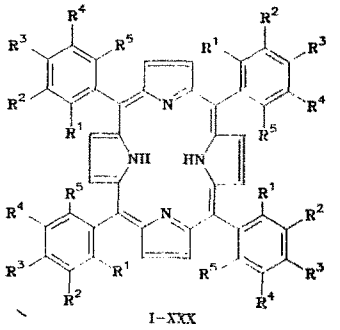
Condensation of pyrrole with benzaldehydes in a mixture of xylene and chloroacetic acid gives a series of substituted tetraphenylporphins with yields exceeding the yields of porphyrins synthesized according to known preparative methods.

The development of practicable methods for the synthesis of porphyrins having the most varied properties and stable to the action of aggressive media and reagents is an urgent necessity [1]. Included among such porphyrins are meso-tetraphenylporphins substituted in the phenyl rings, which are obtained by a one-stage condensation of pyrrole with substituted benzaldehydes.



I–XXX

II $R^1=CH_3$; III $R^2=CH_3$; IV $R^3=CH_3$; V $R^1=OCH_3$; VI $R^2=OCH_3$; VII $R^3=OCH_3$; VIII $R^1=F$; IX $R^2=F$; X $R^3=F$; XI $R^1=Cl$; XII $R^2=Cl$; XIII $R^3=Cl$; XIV $R^1=Br$; XV $R^2=Br$; XVI $R^3=Br$; XVII $R^1=I$; XVIII $R^2=I$, XIX $R^3=I$; XX $R^1=R^2=CH_3$; XXI $R^1=R^3=CH_3$; XXII $R^1=R^4=CH_3$; XXIII $R^1=R^5=CH_3$; XXIV $R^2=R^3=CH_3$; XXV $R^2=R^4=CH_3$; XXVI $R^1=R^2=OCH_3$; XXVII $R^2=R^3=OCH_3$; XXVIII $R^2+R^3=OCH_2O$; XXIX $R^2=R^4=$ = t-Bu; $R^3=OH$; XXX $R^2=R^4=CH_3$, $R^3=OH$; not stated R^1, R^2, R^3, R^4, $R^5=H$

The existing preparative methods for the synthesis of tetraphenylporphins have made it possible for these porphyrins to be obtained with yields not usually exceeding 20-25% [2, 3]. The yield reaches 30-35% only when benzaldehydes with certain electron-seeking substituents are used in the condensation reaction [4, 5]. The best results are achieved when the condensation is carried out in organic solvents containing an acid. A mixture of pyridine and acetic acid (with bp 135°C) [2] and propionic acid (bp 141°C) [3] are the most suitable solvents. The use of acetic acid (bp 118°C) as solvent considerably slows down the rate of reaction in comparison with the reaction in propionic acid (up to 10 h), while in butyric acid (bp 163°C) porphyrins are not formed [6]. The use of mixtures containing strong mineral acids as the medium for conducting the condensation also does not give positive results.

The yield of porphyrins in the condensation reaction decreases if there is water in the reaction medium, whereas the addition to the reaction medium of weak dehydrating agents such as acetic anhydride leads to some increase in yield [6].

The isolation of porphyrins that are very soluble in the reaction mixture and do not crystallize after carrying out the reaction is difficult. Methods of treating the reaction mass under these conditions are protracted and complicated, and are accompanied by considerable losses of porphyrins [2].

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