SYNTHESIS AND TRANSFORMATIONS OF SULFIDES OF THE THIOPHENE SERIES.

33.* STRUCTURES OF THE PRODUCTS OF FORMYLATION OF 2-METHOXY-5-METHYLTHIOTHIOPHENE

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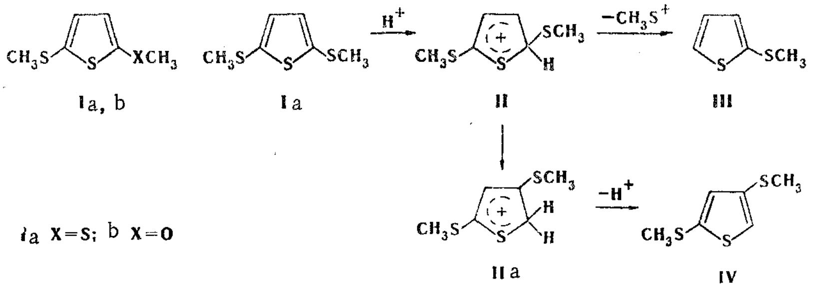
Isomeric alkoxy(alkylthio)formylthiophenes were synthesized from 4-iodo-2-methoxythiophene, and the structures of the products of Vilsmeier formylation of 2-methoxy-5-methylthiothiophene were confirmed.

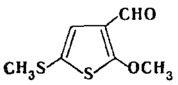
In the course of our study of methods for the synthesis of polyfunctional derivatives of thiophene, particularly substituted sulfides of the I type, and their reactivities, we demonstrated that in the formylation of 2,5-bis(methylthio)thiophene (Ia) under the conditions of the Vilsmeier reaction up to 20% 5-methylthio-2-formylthiophene and a small amount (∿5%) of 3,5-bis(methylthio)-2-formylthiophene are formed in addition to the principal reaction product, viz., 2,5-bis(methylthio)-3-formylthiophene [2]. As pointed out previously, the formation of these side products may be associated with conversion of an intermediate σ complex of the II type, which develops under the conditions of C-protonation of thiophene Ia [3], to monosulfide III or the isomeric bissulfide IV, which then undergoes formylation.



Ia X=S; b X=O

A different picture was observed in the formylation of 2-methoxy-5-methylthiothiophene (Ib). In this case, a complex mixture of the formyl derivatives was formed in which analogs of the aldehyde corresponding to sulfide III, viz., 5-methylthio- or 5-methoxy-2-formyl thiophenes were not detected. The principal product was 2-methoxy-5-methylthio-3-formylthiophene (V) in a mixture with isomeric aldehydes, the structures of which we did not establish definitively [4].

The aim of the present research was to obtain, starting from thiophene derivatives with prefixed positions of the substituents, isomeric aldehydes VI and VII, the presence of which in the mixture seemed most likely. By a comparison of their properties with the properties of the aldehydes detected in the mixture, we might be able to solve the problem of the nature of the products of formylation of methoxy sulfide Ib and thereby ascertain



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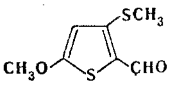

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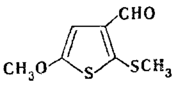

VII

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*See [1] for Communication 32.

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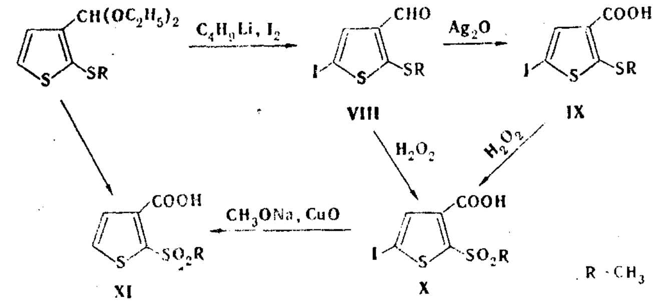
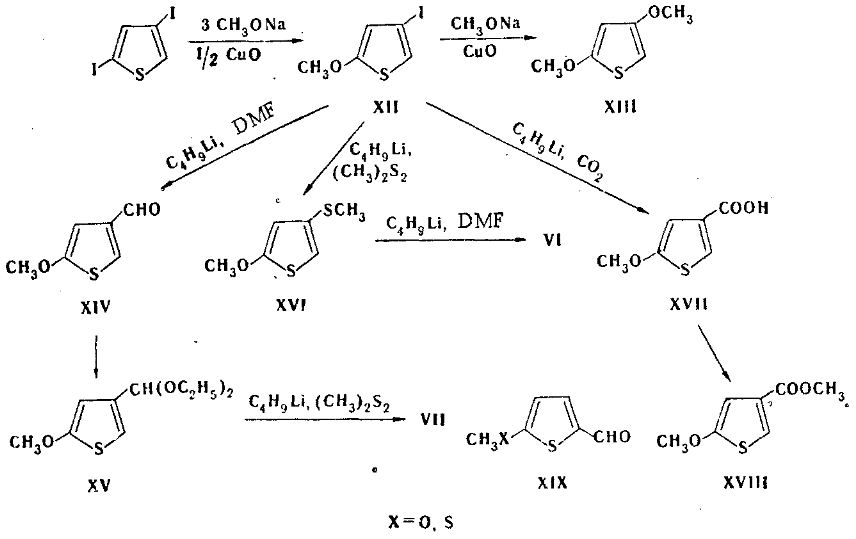
the effect of replacement of the methylthio group in bissulfide Ia by a methoxy group on the formation of compounds of the I type under the conditions of the Vilsmeier reaction.

In addition, let us note that such aldehydes, particularly those that contain a formyl group in the β position of the ring, may be starting compounds for the synthesis of valuable physiologically active compounds (see [5]); in addition, aldehyde VII seemed of interest with respect to our research on the preparation of new ligands of the thiophene series.

The corresponding iodo derivatives of thiophene served as the starting compounds in all of the syntheses that we undertook. Our attempt to obtain aldehyde VII or the corresponding acid from 5-iodo-2-methylthio-3-formylthiophene (VIII) diethylacetal and, respectively, iodo acid IX by replacement of the halogen atom by a methoxy group by the method in [6] was unsuccessful — the starting compound was recovered unchanged. We were unable to realize replacement of the iodine atom by a methoxy group by this method, and only a dehalogenation product, viz., 2-methylsulfonylthiophene-3-carboxylic acid (XI), was isolated from the resulting mixture in the case of iodo sulfone X. We also obtained acid XI by an independent method by oxidation of 2-methylthio-3-formylthiophene.



We synthesized isomeric aldehydes VI and VII from 4-iodo-2-methoxythiophene (XII) obtained from 2,4-diiodothiophene. Replacement of the α-iodo atom by a methoxy group was achieved by heating 2,4-diiodothiophene with sodium methoxide in the presence of CuO by the method previously described for the synthesis of 2-methoxythiophene [6]. The optimum yield of XII [60-70% according to data obtained by gas—liquid chromatography (GLC)] is achieved when 3 moles of MeONa and 0.5 mole of CuO per mole of 2,4-diiodothiophene are used in the case of a reaction time of 3 h. In addition to iodomethoxythiophene XII, 3-iodothiophene (10-15%), 2,4-dimethoxythiophene* (5-10%), and a small amount of diiodothiophenes were detected in the mixture by GLC. An increase in the amount of sodium methoxide (to 6 moles) and the heating time (to 6-30 h) leads to a decrease in the yield of iodomethoxythiophene



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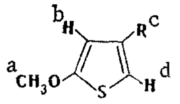
*We obtained 2,4-dimethoxythiophene (XIII) from XII by replacement of the iodine atom by a methoxy group. The data from the PMR spectrum confirm its structure; however, we were unable to obtain this compound in the analytically pure state, since it proved to be extremely unstable and decomposed rapidly upon distillation and during storage.

TABLE 1. Chemical Shifts in CCl_4 of the Protons of Substituted Methoxythiophenes (XII-XVIII) with the General Formula



Compound	R	δ,* ppm				$J_{H^bH^d}$, Hz
		a	b	c	d	
XII	I	3,81	6,07	—	6,55	1,5
XIII	OCH_3	3,78	5,28	3,78	5,78	2
XIV	CHO	3,87	6,42	9,50	7,29	1,5
XV	$CH(OC_2H_5)_2$	3,78	6,05	5,27†	6,41	1,6
XVI	SCH_3	3,80	6,00	2,35	6,07	2
XVII‡	COOH	3,91	6,58	9,55	7,47	1,4
XVIII	$COOCH_3$	3,85	6,47	3,75	7,18	1,3

*The signals of the a and c protons are singlets, while the signals of the b and d protons are doublets.
†Signal of the CH proton.
‡With $CDCl_3$ as the solvent.

and an increase in the amounts of dimethoxy derivative (up to 60% according to GLC) and 3-iodothiophene (up to 30%). Distillation of the mixture yielded virtually pure (according to GLC) iodomethoxythiophene XII (in 35-40% yield), which was subsequently used for the synthesis of various substituted methoxythiophenes, viz., XIV, XVI, and XVII; the structures of the latter as 2,4-disubstituted thiophenes are confirmed by data from the PMR spectra (J_{35} = 1.4-2 Hz, see Table 1). The position of the methoxy group in the thiophene ring of XII was confirmed by its conversion to 2-methoxythiophene under the influence of butyllithium and water.

The successive action of BuLi and DMF on 4-methylthio-2-methoxythiophene (XVI) yielded aldehyde VI, which proved to be identical with respect to its melting point and IR, PMR, and mass spectra, as well as the GLC and TLC data, to one of the aldehydes that we previously isolated [4] in the formylation of methoxy sulfide Ib; structure VII was tentatively proposed for it. The amount of this isomer in the mixture in individual cases reaches 15-25%. This result, in addition to the absence in the reaction mixture of monosubstituted aldehydes of the XIX type, makes it possible to propose that in the case of methoxy sulfide Ib conversion of an intermediate complex of the II type proceeds primarily via a pathway leading to isomerization product XVI (similar to the II → IV transformation for bissulfide Ia). 5-Methoxy-2-methylthio-3-formylthiophene (VII), which we obtained by the action of BuLi and dimethyl disulfide on 5-methoxy-3-formylthiophene diethylacetal (XV), differed with respect to its physical constants and PMR and IR spectra, as well as its retention time under GLC conditions and its R_f value, from isomeric aldehydes V and VI; it should be noted that the chemical shifts of the protons of the thiophene ring in isomers VI and VII are extremely close (the difference is ∿0.14 ppm) but differ considerably from the chemical shifts of the corresponding proton in isomer V (by 0.8-0.9 ppm). Aldehyde VII also proved to be one of the components of the mixture formed in the formylation of methoxy sulfide Ib; however, as we have already noted above, the principal product is isomer V, and this indicates the primary ortho-orienting effect of the methoxy group as compared with the methythio group.

EXPERIMENTAL

The IR spectra were recorded with UR-20 and Specord IR-75 spectrometers. The PMR spectra were obtained with Varian DA-60-IL and Tesla BS-497 spectrometers (100 MHz) with hexamethyldisiloxane as the internal standard. Analysis by GLC was carried out with an LKhM-8MD chromatograph with a flame-ionization detector and a stainless steel column with a length of 2 m and a diameter of 3 mm filled with 5% SE-30 on Chromaton N-AW-DMCS (0.16-0.2 mm) with helium as the carrier gas.

The purity of VI-VIII was monitored by TLC on Silufol UV-254 plates in a hexane—ether system (1:1).

5-Iodo-2-methylthio-3-formylthiophene (VIII). A) An ether solution of 0.33 g (51 mmole) of BuLi was added at −5 to 0°C to 10 g (43 mmole) of 2-methylthio-3-formylthiophene diethylacetal [8] in 60 ml of ether, and the mixture was stirred at 20°C for 30 min. It was then treated with 13 g (51 mmole) of I_2 in 130 ml of ether at −5 to 0°C, and the mixture was stirred at 20°C for 2 h. It was then poured into acidified ice water and the ether layer was separated. The aqueous layer was extracted thoroughly with ether, and the combined ether layer and extract was washed with water, 10% aqueous $Na_2S_2O_3$, and water, and dried with $MgSO_4$. The ether was removed by distillation, and the precipitate was removed by filtration, washed with ether, and dried to give 7.7 g (59%) of iodo aldehyde VIII with mp 111-113°C (from heptane and from ethyl acetate). An additional 3.6 g of iodo aldehyde VIII was isolated from the mother liquor after removal of the ether for an overall yield of 80%. IR spectrum (in $CHCl_3$): 1670 cm^{-1} (CO). PMR spectrum [in $(CD_3)_2CO$]: 2.65 (3H, s, SCH_3), 7.59 (1H, s, 4-H), and 9.85 ppm (1H, s, CHO). Found: C 25.5; H 1.8; I 44.0; S 22.2%. $C_6H_5IOS_2$. Calculated: C 25.4; H 1.8; I 44.6; S 22.5%.

B) An 8.5-g (33 mmole) sample of I_2 and 3.5 g (16 mmole) of HgO were added gradually with shaking to a solution of 6.5 g (28 mmole) of 2-methylthio-3-formylthiophene diethylacetal in 15 ml of dry benzene. After 30 min, the precipitate was removed by filtration and washed with benzene and ether. The filtrate was washed with 10% aqueous $Na_2S_2O_3$ solution and water, dried with $MgSO_4$, and distilled to remove the ether. The residue contained 4.8 g (56%) of iodo aldehyde VIII in the form of a viscous crystallizable oil. The oil was treated with acetone, and the white precipitate was removed by filtration, washed with acetone, and dried to give 1.25 g (15%) of aldehyde VIII with mp 104-105°C. Recrystallization from hexane and from acetone gave a product with mp 108-110°C. No melting-point depression was observed for a mixture of this product with a sample of the aldehyde obtained by method A.

5-Iodo-2-methylthiothiophene-3-carboxylic Acid (IX). A solution of 0.7 g (2.5 mmole) of iodo aldehyde VIII in alcohol was added to 0.6 g (2.6 mmole) of freshly precipitated silver oxide (from 0.86 g of $AgNO_3$ and 0.2 g of NaOH in the minimum amount of water), and the mixture was maintained at 20°C for 12 h. It was then heated to 60°C, filtered in the hot state, and the precipitate was washed with alcohol. The filtrate was evaporated *in vacuo* and the residue was dissolved in water. The solution was filtered and the filtrate was acidified with HCl (1:1). The precipitate was removed by filtration, washed with water, and dried to give 0.5 g (67%) of iodo acid IX with mp 236-237°C (from alcohol and from ethyl acetate with charcoal). IR spectrum (KBr pellet): 1670 (CO) and 2800-3100 cm^{-1} (OH). Found: C 23.9; H 1.7; I 41.9; S 21.1%. $C_6H_5IO_2S_2$. Calculated: C 24.0; H 1.7; I 42.3; S 21.4%.

Methyl Ester of Acid IX. This compound [1 g (88%)] was obtained from a suspension of 1.1 g of acid in ether and an ether solution of diazomethane and had mp 112-114°C (from heptane with charcoal and from MeOH). PMR spectrum (in $CDCl_3$): 2.55 (3H, s, SCH_3), 3.77 (3H, s, CH_3COO), and 7.50 ppm (1H, s, 4-H). Found: C 27.0; H 2.3; S 20.0%. $C_7H_7IO_2S_2$. Calculated: C 26.8; H 2.2, S 20.4%.

5-Iodo-2-methylsulfonylthiophene-3-carboxylic Acid (X). A mixture of 0.7 g (2.5 mmole) of iodo aldehyde VIII, 30 ml of acetic acid, and 4 ml of 28% H_2O_2 was heated for 3 h on a boiling-water bath, after which the acetic acid was removed by distillation (with the addition of alcohol), and the solid residue was recrystallized from water with charcoal to give 0.64 g (78%) of sulfone X with mp 188-189°C. IR spectrum (KBr pellets): 1710 (CO) and 1135 cm^{-1} (SO_2). PMR spectrum [in $(CD_3)_2CO$]: 3.39 (3H, s, SO_2CH_3) and 7.67 ppm (1H, s, 4-H). Found: C 21.2; H 1.80; I 38.2; S 19.2%. $C_6H_5IO_4S_2$. Calculated: C 21.7; H 1.5; I 38.2; S 19.3%.

2-Methylsulfonylthiophene-3-carboxylic Acid (XI). A) This compound was obtained in quantitative yield as described above for iodo acid X from 0.5 g (3.1 mmole) of 2-methylthio-3-formylthiophene and had mp 182-183°C (from ethyl acetate). Found: C 35.0; H 3.0; S 30.6%. $C_6H_6O_4S_2$. Calculated: C 34.9; H 2.9; S 31.1%.

B) A 0.7-g (2.1 mmole) sample of acid X in MeOH was added to 0.7 g (13 mmole) of MeONa in 40 ml of dry MeOH and 0.08 g of powdered CuO, and the mixture was refluxed with stirring for 30 h. The CuO was removed by filtration and washed with hot MeOH, and the filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in water, and the solution was acidified with HCl. The resulting turbid solution was extracted thoroughly with ether, and the extract was washed with water, dried with $MgSO_4$, and distilled to remove the ether.

The residue contained 0.63 g of an oil, which began to crystallize upon standing. The crystals were removed by filtration, washed with cold ether, and recrystallized from a mixture of ethyl acetate with heptane to give iodine-free acid XI with mp 175-176°C. No melting-point depression was observed for a mixture of this product with a sample of acid XI described in method A. IR spectrum (KBr pellets): 1685 (CO) and 1140 cm^{-1} (SO_2). PMR spectrum [in $(CD_3)_2CO$]: 3.44 (3H, s, SO_2CH_3); 7.67, 7.85 ppm (1H, d, 4-H, 1H, d, 5-H, J_{45} = 5.5 Hz). Found: C 35.0; H 3.0%. $C_6H_6O_4S_2$. Calculated: C 34.9; H 2.9%.

4-Iodo-2-methoxythiophene (XII). A 3.6-g (0.045 mole) sample of finely ground CuO and 30.0 g (0.09 mole) of 2,4-diiodothiophene [9] were added to a solution of sodium methoxide obtained from 6.3 g (0.27 mole) of Na in 90 ml of MeOH, and the mixture was refluxed with stirring for 3 h. The precipitate was removed by filtration, water was added, and the liberated oil was extracted thoroughly with ether. The extract was washed with water, dried with $MgSO_4$, and distilled to remove the ether to give 17.69 g of an oil containing, according to GLC (at 156°C) 66% 4-iodo-2-methoxythiophene (XII), ∿5% 2,4-dimethoxythiophene (XIII) (see below), ∿15% 3-iodothiophene, ∿13% diiodothiophenes, and a small amount of 2-methoxythiophene. Rectification of the mixture with a column filled with a glass packing with a total condensation head gave 9.51 g of a fraction with bp 110-135°C (32 mm) with n_D^{20} 1.6380 containing primarily 4-iodo-2-methoxythiophene (XII) (in 44% yield), from which pure iodomethoxythiophene XII, with bp 132-135°C (32 mm) and n_D^{20} 1.6280, was isolated by column fractionation. Found: C 25.1; H 2.2; I 52.4; S 13.2%. C_5H_5IOS. Calculated: C 25.0; H 2.1; I 52.8; S 13.3%.

2,4-Dimethoxythiophene (XIII). A mixture of 5 g (20.8 mmole) of iodomethoxythiophene XII, 3.4 g (63 mmole) of MeONa in 15 ml of MeOH, and 0.83 g (10.5 mmole) of CuO was refluxed with stirring for 12 h, after which it was worked up as described above for iodomethoxythiophene XII to give 1.86 g of an oil containing primarily 2,4-dimethoxythiophene (XIII) and 2-methoxy- and 4-iodo-2-methoxythiophene (GLC at 160°C), from which a fraction with bp 124°C (32 mm) and 117-118°C (22 mm) and n_D^{20} 1.5300 containing 97.5% of dimethoxythiophene XIII was isolated by distillation. The reaction product darkened rapidly and decomposed during storage. We were therefore unable to obtain satisfactory results of elementary analysis for C. Found: C 48.4; H 5.4; S 22.0%. $C_6H_8O_2S_2$. Calculated: C 50.0; H 5.6; S 22.2%.

5-Methoxythiophene-3-carboxylic Acid (XVII). A solution of 0.88 g (13.8 mmole) of BuLi in 10 ml of ether was added gradually at −70°C in a stream of Ar to 3 g (12.5 mmole) of iodomethoxythiophene XII in 10 ml of dry ether. After 15 min, the mixture was poured over dry ice in ether. After evaporation of the CO_2, water was added to the residue, and the ether layer was separated. The aqueous layer was extracted with ether and acidified with dilute HCl (1:1), and the precipitate was removed by filtration, washed with water, and dried to give 1.33 g (67.3%) of acid XVII with mp 133-134°C (from heptane). IR spectrum (KBr pellets): 1680 cm^{-1} (CO). Found: C 45.5; H 3.8; S 20.3%. $C_6H_6O_3S$. Calculated: C 45.6; H 3.8; S 20.3%. Methyl ester XVIII had mp 28-30°C (from heptane). Found: S 18.5%. $C_7H_8O_3S$. Calculated: S 18.6%.

5-Methoxy-3-formylthiophene (XIV). A solution of 8.8 g (0.14 mole) of BuLi in ether was added as described above to 30 g (0.125 mole) of 4-iodo-2-methoxythiophene (XII) in 100 ml of ether. After 15 min, a cooled (to −70°C) solution of 10.3 g (0.14 mole) of DMF in 40 ml of ether was added, and, after 30 min, the mixture was poured into 50 ml of water and 50 ml of HCl (1:1). The organic layer was separated, the aqueous layer was extracted with ether, and the combined organic layer and extract was washed with water, dilute HCl (1:10), and 10% aqueous Na_2CO_3, and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled *in vacuo* to give 11 g (62%) of aldehyde XIV with bp 131-132°C (25 mm) and 115-118°C (13 mm) and n_D^{20} 1.5711. IR spectrum (in $CHCl_3$): 1680-1690 cm^{-1} (CO). Found: C 50.3; H 4.2; S 22.6%. $C_6H_6O_2S$. Calculated: C 50.7; H 4.2; S 22.5%.

The 2,4-dinitrophenylhydrazone had mp 229-231°C (dec., from $CHCl_3$, ethyl acetate). Found: C 44.6; H 3.5; S 10.1%. $C_{12}H_{10}N_4O_5S$. Calculated: C 44.7; H 3.1; S 10.0%.

5-Methoxy-3-formylthiophene Diethylacetal (XV). A mixture of 16.5 g (0.116 mole) of aldehyde XIV, 51.5 g (0.36 mole) of ethyl orthoformate, 60 ml of absolute alcohol, and three drops of concentrated HCl was refluxed for 5.5 h, after which it was neutralized with 10% KOH in MeOH, and the solvents were removed by vacuum distillation. Water was added to the residue and the liberated oil was extracted thoroughly with ether. The extract was washed with water, dried with $MgSO_4$, and distilled to remove the ether. The residue was vacuum distilled to give 18.2 g (73%) of diethylacetal XV with bp 138°C (13 mm) and n_D^{20} 1.4920. Found: C 55.6; H 7.4; S 14.7%. $C_{10}H_{16}O_3S$. Calculated: C 55.5; H 7.4; S 14.8%.

4-Methylthio-2-methoxythiophene (XVI). An ether solution of 1.5 g (23.4 mmole) of BuLi was added at −70°C in a stream of Ar to 5 g (20.8 mmole) of iodomethoxythiophene XII in 10 ml of dry ether, 15 min after which a cooled (to −70°C) solution of 2.16 g of dimethyl disulfide in 5 ml of dry ether was added, and the mixture was stirred at −70°C for 30 min. It was then allowed to stand at 20°C for 12 h, after which it was hydrolyzed with water (20 ml) with cooling. The ether layer was separated, and the aqueous layer was extracted with ether. The extract and organic layer were combined and washed with 10% aqueous NaOH and water and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled *in vacuo* to give 2.8 g (83.5%) of sulfide XVI with bp 132-134°C (30 mm) and n_D^{20} 1.5880. Found: C 45.3; H 5.1%. $C_6H_8OS_2$. Calculated: C 45.0; H 5.0%.

5-Methoxy-2-methylthio-3-formylthiophene (VII). An ether solution of 6.6 g (0.1 mole) of BuLi was added dropwise at −40°C in a stream of Ar to a solution of 20 g (0.092 mole) of 5-methoxy-3-formylthiophene diethylacetal in 50 ml of dry ether, and, after 30 min, an ether solution of 9.5 g (0.1 mole) of dimethyl disulfide in 15 ml of ether was added at −40°C. The mixture was allowed to stand at 20°C for 12 h, after which it was hydrolyzed by cooling with 100 ml of water. The ether layer was separated, the aqueous layer was extracted with ether, and the extract and the organic layer were combined and washed with 10% aqueous KOH and water and dried with $MgSO_4$. The ether was removed by distillation, and the residue (22.6 g of a dark oil) was distilled *in vacuo* to give 13.8 g (57%) of 5-methoxy-2-methylthio-3-formylthiophene with bp 132-138°C (4 mm) (with decomposition) and n_D^{20} 1.5333 containing, according to the PMR spectrum, 15-20% aldehyde VII. A 2.2-g sample of the mixture obtained was refluxed in 10 ml of alcohol containing three drops of HCl (1:1), after which the alcohol was removed by distillation, and the residue was dissolved in ether. The ether solution was washed with water, dried with $MgSO_4$, and distilled to remove the ether to give 1.8 g of aldehyde VII with bp 127°C (4 mm) and n_D^{20} 1.6182, which was purified for analysis by column chromatography [silica gel L (100/160 mesh)] by elution with hexane–ether (1:1) (R_f 0.417). IR spectrum in $CHCl_3$: 1670 cm^{-1} (CO). PMR spectrum (in CCl_4): 2.48 (3H, s, SCH_3), 3.87 (3H, s, OCH_3), 6.27 (1H, s, 4-H), and 9.90 ppm (1H, s, CHO). Found: C 45.0; H 4.3; S 33.9%. $C_7H_8O_2S_2$. Calculated: C 44.7; H 4.3; S 34.0%.

The 2,4-dinitrophenylhydrazone had mp 181-182°C (from ethyl acetate and from heptane). Found: C 42.5; H 3.3; N 15.2; S 17.2%. $C_{13}H_{12}N_4O_5S_2$. Calculated: C 42.4; H 3.3; N 15.2; S 17.4%.

5-Methoxy-3-methylthio-2-formylthiophene (VI). An ether solution of 0.7 g (11 mmole) of BuLi was added at −3-5°C in a stream of Ar to 1.6 g (10 mmole) of 2-methoxy-4-methylthiophene (XVI) in 5 ml of dry ether, 30 min after which a solution of 0.8 g (11 mmole) of DMF in 3 ml of ether was added, and the mixture was stirred without cooling for 2 h and allowed to stand at 20°C for 12 h. It was then hydrolyzed with dilute HCl (1:1), and the precipitate was removed by filtration, washed with water, and dried to give 1.45 g (77%) of aldehyde VI with mp 77.5-78.5°C (from heptane with charcoal and from CCl_4) and R_f 0.167. No melting-point depression was observed for a mixture of this product with a sample of the aldehyde obtained in [4]. IR spectrum (in $CHCl_3$): 1630-1640 cm^{-1} (CO). PMR spectrum (in CCl_4): 2.45 (3H, s, SCH_3), 3.92 (3H, s, OCH_3), 6.13 (1H, s, 4-H), and 9.70 ppm (1H, s, CHO). Found: C 44.6; H 4.3; S 34.1%. $C_7H_8O_2S_2$. Calculated: C 44.6; H 4.3; S 34.0%.

5-Methoxy-3-methylthiothiophene-2-carboxylic Acid. A solution of 0.13 g (0.69 mmole) of aldehyde VI in alcohol was added to 0.15 g (0.65 mmole) of freshly precipitated Ag_2O, and the mixture was stirred with a magnetic stirrer at 50-60°C for 5 h and maintained at 20°C for 12 h. It was then heated and filtered in the hot state, and the precipitate was washed with hot alcohol. The filtrate was evaporated and the residue was dissolved in water. The solution was filtered, the filtrate was acidified with HCl (1:1), and the precipitated acid was removed by filtration and recrystallized from heptane to give a product with mp 162-163°C. PMR spectrum [in $(CD_3)_2CO$]: 2.44 (3H, s, SCH_3), 3.92 (3H, s, OCH_3), and 6.20 ppm (1H, s, 4-H). Found: C 41.3; H 4.1%. $C_7H_8O_3S_2$. Calculated: C 41.2; H 4.0%.

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IPSO ATTACK IN THE NITRATION OF 5-BROMO- AND 5-METHYL-2-CYCLOPROPYLTHIOPHENES

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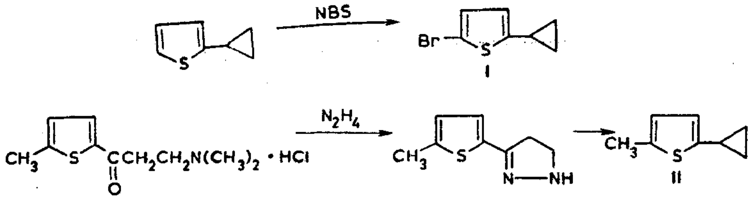
It was established that 5-bromo-2-cyclopropylthiophene and 5-methyl-2-cyclopropylthiophene undergo transformations during nitration with nitric acid in acetic anhydride that are a consequence of ipso attack of the nitryl cation in the 2 or 5 positions of the thiophene rings of the starting compounds.

The concept of ipso attack, which is widely used to explain the results of nitration of benzenoid systems (for example, see [1, 2]), is presently beginning to find application also in the simplest aromatic heterocycles [3, 4]. However, only an extremely small amount of experimental data that reliably confirm the validity of the extension of this concept to heterocyclic compounds are as yet available.

The detection in the ortho- or para-positions to the site of attack of modified alkyl [1] or cycloalkyl [2] groupings, as well as hydroxy groups in the nitration of ethers of phenols [2, 5], and the detection in the reaction mixture of products of ipso substitution of a halogen atom by a nitro group [6] are regarded as convincing evidence for the fact of ipso attack by the nitrating particle in substituted benzenes.

One can assume that it is sufficient to identify compounds with modified alkyl or cycloalkyl groupings or products of ipso substitution of of the corresponding halogen atom in the reaction mixture to establish the fact of ipso attack in the nitration of aromatic heterocyclic systems.

In this connection, in the present research we studied the behavior of 5-bromo- and 5-methyl-2-cyclopropylthiophenes (I, II) in the case of nitration with nitric acid in acetic anhydride. The cyclopropylthiophenes (I and II) necessary for the study were obtained by direct bromination of 2-cyclopropylthiophene with N-bromosuccinimide (NBS) and catalytic decomposition of the corresponding pyrazoline, respectively.



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