NITRATION OF 5-FORMYL-SUBSTITUTED 2-CYCLOPROPYLFURANS AND 2-METHYLFURANS AND THE CORRESPONDING THIOPHENES

S. S. Mochalov, F. M. Abdel'razek, T. P. Surikova, and Yu. S. Shabarov

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In the nitration of 5-formyl-substituted 2-cyclopropylfurans and the corresponding thiophenes, in addition to the formation of the corresponding 3-nitro derivative the replacement of the formyl group by a nitro group takes place. For a thiophene derivative the latter direction of the reaction is observed to a substantially smaller degree. Under nitration conditions, 5-formylsylvane is converted only into 5-nitrosylvane, while the corresponding formylmethylthiophene is nitrated exclusively in position 3. The difference observed in the behavior on nitration of the furans and thiophenes studied is explained by the different degrees of participation of the heteroatom in the delocalization of the charges in the heterocyclic ipso-ions formed as intermediates.

The nitration of cyclopropylfurans and cyclopropylthiophenes substituted to different degrees has scarcely been studied. It has been reported only that the nitration of 2- and 3-cyclopropylthiophenes takes place with the retention of the tricyclic ring and is unselective [1]. There is no information whatever on the nitration of furylcyclopropanes. At the same time, it is known that in the nitration of both 2-substituted and 2,5-disubstituted furans in addition to the entry of nitro groups into the free positions of the furan ring, there is also replacement by the nitro group of such substituents as halogen atoms and carboxy, sulfo, or acetyl groups [2]. The presence of electron-donating substituents in the furan ring facilitates this replacement [2]. For thiophene derivatives, these side reactions are less pronounced [3].

In an examination of the mechanism of ipso-nitration (the entry of a nitro group into the position of a departing substituent) of furan and thiophene systems it was established that for 2,5-disubstituted heterocycles this reaction may take place through the formation of stable adducts of the substrate with acetyl nitrate [2, 4, 5] which on re-aromatization are capable of being converted into the corresponding nitro derivatives.

In the present work we have studied the behavior in the nitration reaction of 2-cyclopropyl- and 2-formyl-5-methyl-substituted furans and thiophenes. We set ourselves two tasks: in the first place to study the relationship of the formyl group to ipso-substitution on the nitration of formylfurans and formylthiophenes containing electron-donating hydrocarbon substituents — a cyclopropyl or a methyl radical — and, in the second place, to obtain the corresponding 2-cyclopropyl-3-nitro derivatives which were required as objects of the investigation of the possibility of their isomerization into 3-nitroso-2-propionylfurans and — thiophenes (similarly to the corresponding benzenes [6]).

The formyl derivatives necessary for the study were obtained from the corresponding cyclopropylfurans and methylfurans and -thiophenes by the Vilsmeier reaction.

The initial 2-cyclopropylfuran (I) and 2-cyclopropylthiophene (II) were synthesized by methods differing somewhat from those described in the literature [1, 7]. Thus, cyclopropylfuran (I) was obtained by the catalytic decomposition of 5-furylpyrazoline by the scheme used in the synthesis of phenylcyclopropane [8].

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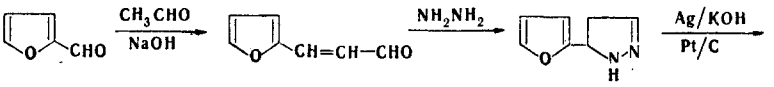
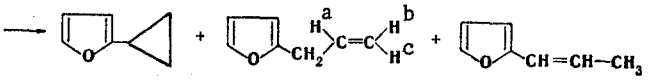


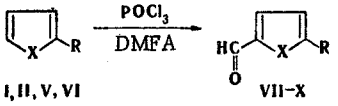


I 69% III 16% IV 15%

After fractionation of the catalysate, compound (I) was isolated with a yield of 48% in a purity of 98% (according to GLC).*

2-Cyclopropylthiophene (II) was obtained from N,N-dimethylaminoethyl thienylketone by the method of Zefirova and Karakhanov [9].

The formylation of the cyclopropyl- and methylfurans and cyclopropyl- and methylthiophenes was carried out in a similar manner to that described by Karakhanov et al. [10].



I, II, V, VI VII–X

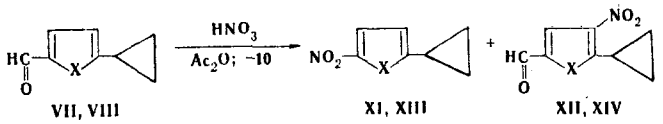
I, V, VII, IX X=O; II, VI, VIII, X X=S;
I, II, VII, VIII R=C_3H_5-cyclo V, VI, IX, X R=CH_3

The nitration of the formyl-substituted furans and thiophenes (VII-X) was carried out by the action of acetyl nitrate in acetic anhydride solution at −10°C. After the usual working up of the reaction mixture (see experimental part), in the case of 2-cyclopropyl-5-formylfuran (VII) a viscous oil was obtained which liberated oxides of nitrogen on standing at room temperature. On distillation with steam or during chromatography on plates coated with alumina of activity grade II [eluent: ether–hexane (1:3)], a considerable part of the reaction mixture was lost, but two compounds were isolated with a yield of 55% — 2-cyclopropyl-5-nitrofuran (XI) and 2-cyclopropyl-5-formyl-3-nitrofuran (XII).

The structures of compounds (XI) and (XII), as of all the compounds obtained for the first time in the present work, were shown by IR and PMR spectroscopy (see the experimental part).

Under the conditions studied, 2-cyclopropyl-5-formylthiophene (VIII) gave reaction products with a similar structure (XIII and XIV) but without the preliminary formation of a viscous unstable intermediate, and the combined yield of the end-products was higher (~75%) than the yield of the corresponding furan derivatives.

Attention is attracted by the fact that on nitration, the furan (VII) and the thiophene (VIII) gave deformylation products (XI and XIII) and nitration products (XII and XIV) in different ratios. Thus, the ratio of substances (XI) to (XII) was 1:1, and of (XIII) to (XIV) 1:15.



VII, VIII XI, XIII XII, XIV

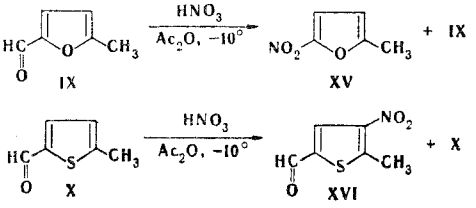
VII, XI, XII X=O; VIII, XIII, XIV X=S

Under the nitration conditions adopted, followed by the standard working-up, like cyclopropylfuran (VII), 5-formylsylvane formed a viscous oil which decomposed on standing, while

*Compounds (III) and (IV) were not isolated in the individual form. Their structures were confirmed by PMR spectroscopy [the presence in the spectrum of the catalysate of the corresponding signals of the protons of the allyl group (δ, ppm: d (2 H) 3.31; m (H^b) 4.91; m (H^c) 5.12; m (H^a) 5.50-6.02) and of the protons of a propenyl group (d (3 H) 1.83) (the signals of the olefinic protons of this group were superposed on the signals of the furan ring and cannot be assigned strictly)] and by the elementary analysis of the mixture.

2-formyl-5-methylthiophene (X), like the cyclopropylthiophene (VIII), gave no similar unstable intermediate.

A fundamental difference in the behavior of methyl derivatives of furan (IX) and of thiophene (X) on nitration was that the first gave only 5-nitrosylvane (XI), while the second gave a trisubstituted reaction product 5-formyl-2-methyl-3-nitrothiophene (XVI), although in both cases about 15% of the starting compounds was recovered from the reaction.



Thus, deformylation on nitration takes place readily for cyclopropylformylfurans and formylmethylfurans but is practically uncharacteristic for the corresponding substituted thiophenes.

The explanation of this difference must obviously be sought in the method of stabilization of the intermediates formed from them and in the influence of the nature of the heteroatom on this stabilization.

It is known that aromatic systems (particularly disubstituted benzenes) bearing methyl or cyclopropyl radicals as substituents, together with direction nitration at the free positions of benzene rings, readily undergo ipso-attack (attack of an electrophile on a carbon atom bearing a substituent) by the nitryl cation, giving the corresponding ipso-phenonium ions [11, 12]. The further transformations of the latter under the reaction conditions depend both on the nature of the substituents and on the acidity or basicity of the medium [11].

Evidently, ions of a similar type (A, see Scheme 1) can also be formed in the nitration of cyclopropyl-substituted (VII, VIII) and methyl-substituted (IX, X) furans and thiophenes, while the different degrees of participation of the heteroatom in the stabilization of the carbonium centers in these ions may be the motive force of the subsequent transformations.*

It may be assumed that in the intermediate (A) the sulfur atom, in the first place, takes a more active part in the delocalization of the positive charge than the oxygen atom, which hinders passage into the corresponding decarbonylated dihydrothiophenonium ion (C) and then into (D) and, in the second place, it favors the formation of the intermediate (B), which can easily be stabilized by splitting out a proton. In its turn, the oxygen-containing ion (A), having a more pronounced positive charge on the carbon atom as compared with the sulfur-containing analog, is, in the first place, more readily deformylated and, in the second place, more readily stabilized by the external nucleophile — the acetate ion. The latter circumstance is probably the reason for the formation of viscous oils — adducts of disubstituted furans with acetyl nitrate.†

In a comparison of the behavior on nitration of cyclopropyl-containing formylfurans and -thiophenes with the behavior of the corresponding methyl derivatives, two fundamental features must be noted. In the first place, the three-membered ring exerts a stabilizing influence on the hetero system, as is shown by the comparatively high yields of reaction products with a retained furan or thiophene nucleus, and, in the second place, position 3 (the β- position) in cyclopropylfuran (VII) and cyclopropylthiophene (VIII) becomes considerably more reactive towards electrophilic reagents under the action of the small ring, than the corresponding positions in the methylfuran (IX) and the methylthiophene (X).

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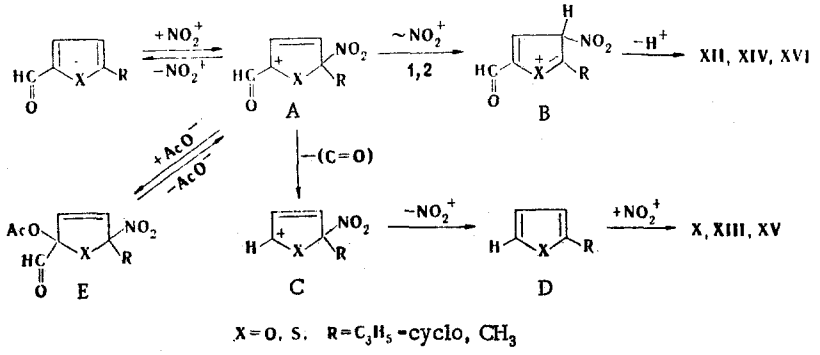
*It is not excluded that the formation of the β-nitro compounds (XII, XIV, XVI) can also take place through direct nitration in the β-positions, but judging from the literature [2, 4], the probability of this is low, at least for the furan derivatives.

†There is information on the quantitative formation of this type of adducts in the nitration or oxidative cleavage of the furan ring by the action of acetyl nitrate on it [2, 4]. The behavior of the adducts obtained in this work resembles the behavior of the oils that we isolated in the primary treatment of the reactions mixtures after the nitration of formyl-substituted cyclopropyl- and methylfurans.



X = O, S. R = C_3H_5-cyclo, CH_3

Scheme 1

As already mentioned, one of the problems posed in this work was to synthesize cyclopropylnitrofurans and cyclopropylnitrothiophenes that could serve as objects for the study of the possibility of their rearrangement into the corresponding nitroso ketones under the action of concentrated sulfuric acid in a similar manner to what has been described for o-nitrophenylcyclopropanes [6].

However, it was found that both 2-cyclopropyl-5-formyl-3-nitro furan (XII) and 2-cyclopropyl-5-formyl-3-nitrothiophene (XIV) are stable to the action of concentrated sulfuric acid even at 30°C — substances (XII and XIV) were recovered from the reaction unchanged.

This unexpected stability of compound (XII) and (XIV) under the action of concentrated sulfuric acid can be explained by the following facts. It is known that the nitro groups can act as an internal nucleophile [13, 14] and provide nucleophilic assistance to the opening of the three-membered ring [15]. However, if the nucleophilicity of the nitro group is weakened by the action of a strong electron-accepting substituent, the nucleophilic assistance may not be shown and the three-membered ring may not be opened even under severe conditions [16]. Thus, 1,4-dicyclopropyl-2,5-dinitro- and -2,3-dinitrobenzenes scarcely isomerize under the action on them of concentrated sulfuric acid at temperatures up to 30°C, while 1,4-dicyclopropyl-2,6-dinitrobenzene smoothly rearranges into the corresponding nitroso ketone even at reduced temperatures (—5 to —10°C), the second three-membered ring being retained in these cases [16]. Obviously, in 2-cyclopropyl-3-nitrofuran (XII) and in the corresponding thiophene compound (XIV) the formyl groups in positions 5 deactivate the nitro group to such an extent that the isomerization process is inhibited.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in paraffin oil and in hexachlorobutadiene, and the PMR spectra on a JNM H-60 instrument with a working frequency of 60 MHz (CCl_4, $CDCl_3$) with HMDS as internal standard. Analysis by the GLC method was carried out on a Tsvet-104 instrument with a steel column 3 m long and 4 mm in diameter containing as the stationary phase 5% of the siloxane elastomer SE-30 on Chromaton N-AW, with helium as the carrier gas.

3-(2-Furyl)acrolein was obtained by the reaction of furfural with acetaldehyde in the presence of NaOH, yield 75%, mp 54°C [17].

5-(2-Furyl)pyrazoline. With stirring and heating (50-60°C), a hot solution of 20 g of 3-(2-furyl)acrolein in 20 ml of ethanol was slowly added to a solution of 12 ml of 85% hydrazine hydrate in 20 ml of the same solvent. The mixture was boiled for 7 h, the solvent and the excess of hydrazine hydrate were distilled off, and the resulting oily product was distilled in vacuum. This gave 14 g (60%) of 5-(2-furyl)pyrazoline, mp 125°C (12 mm). Found: C 61.5; H 5.7; N 20.2%. $C_7H_8N_2O$. Calculated: C 61.8; H 5.9; N 20.6%.

2-Cyclopropylfuran (I). The decomposition of 68 g of 5-(2-furyl)pyrazoline was carried out in the presence of catalytic amounts of Pt/C and Ag/KOH as described by Kizhner [8], the catalysate was steam distilled, the organic layer was separated off, the aqueous layer was extracted with ether, the ethereal extracts were combined with the separated catalysate, the combined extract was dried with K_2CO_3, and the solvent was evaporated off to give 37.3 g (71%) of a mixture of, according to GLC and PMR spectroscopy, 3-(2-furyl)prop-1-ene (III,

16%), 2-cyclopropylfuran (1.69%), and 1-(2-furyl)prop-1-ene (IV, 15%). Distillation through a column permitted the isolation of 26 g (48%) of 2-furylcyclopropane (I), bp 127°C (761 mm), n_D^{20} 1.4805 [7].

2-Cyclopropylthiopene (II). With stirring, 11 g of 3,3-dimethylamino-1-(2-thienyl)-propan-1-one hydrochloride was added to a mixture of 75 ml of triethyleneglycol, 5.6 g of KOH, and 16.5 ml of hydrazine hydrate (85%), and the mixture was stirred for 30-40 min, heated in the oil bath to 140°C, and stirred for another 4 h. Then it was kept without heating for 1 h and another 5.6 g of KOH was added. The instrument was fitted with a descending condenser, the reaction mixture was heated to 230°C, and 2-cyclopropylthiophene, water, and excess of hydrazine hydrate was collected in the receiver. The organic products were extracted with ether and the extract was washed with water, with dilute HCl solution and then with NaOH, and again with water, and was dried with K_2CO_3. The solvent was evaporated off and the residue was distilled in vacuum to give 1.5 g (25%) of compound(II), bp 59-60°C (8 mm) [1].

The formylation of 2-cyclopropyl- and 2-methylfurans and the corresponding thiophenes was carried out as described by Karakhanov [10].

From 7 g of compound (I) was obtained 6 g (70%) of 2-cyclopropyl-5-formylfuran (VII), bp 115°C (15 mm) [10].

From 7.65 g of compound (II) was synthesized 8.2 g (87.5%) of 2-cyclopropyl-5-formylthiophene (VIII), bp 120°C (8 mm) [1].

From 8.2 g of 2-methylfuran (V) was obtained 7 g (64%) of 2-formyl-5-methylfuran (IX), bp 78-79°C (11 mm) [18].

From 6.9 g of 2-methylthiophene (VI) was isolated 7.7 g (88%) of 2-formyl-5-methylthiophene (X), bp 95-98°C (12 mm) [19].

Nitration of the Disubstituted Furans (VII, IX) and Thiophenes (VIII, X) (Standard Procedure). At −50°C with stirring, 4.15 g (0.1 mole) of fuming nitric acid (d 1.5) was added to 20 ml of acetic anhydride, and then the temperature was raised to −10°C and the mixture was kept at this level for 30 min and, with the temperature again lowered to −50°C, 0.05 mole of the substrate (VII, VIII, IX, or X) in 10 ml of acetic anhydride was slowly added. The temperature was raised to −10°C, the reaction mixture was stirred for 2 h, and it was poured into 200 ml of warm (~30°C) water and was neutralized with sodium carbonate, and the organic products were extracted with chloroform. The chloroform solution was washed with water and dried with $MgSO_4$ and, after the solvent had been evaporated off, an equal volume of ether was added to the residue. The crystals that deposited on standing were separated off, and the mother liquor was evaporated and the residue was chromatographed on plates with alumina of activity grade II in the ether–hexane (1:1) system.

Nitration of 2-Cyclopropyl-5-formylfuran (VII). From 6.8 h of compound (VII) by the method described above were obtained: 2.06 g (27%) of 2-cyclopropyl-5-nitrofuran (XI), mp 60-61°C; PMR spectrum, δ, ppm: m (4 H) 0.08-1.33 and m (1 H) 1.72-2.21 (the protons of a cyclopropane ring), d (1 H) 6.17 and d (1 H) 7.11 ($J_{H_\beta H_\beta'}$ = 3 Hz, the protons of the furan nucleus); IR spectrum, cm^{-1}: 1360, 1520 (NO_2). Found: C 55.3; H 4.5%, $C_7H_7NO_3$, Calculated: C 54.9; H 4.6%; and 2.5 g (28%) of 2-cyclopropyl-5-formyl-3-nitrofuran (XII), mp 124-125°C (from ether); PMR spectrum, δ, ppm: m (4 H) 1.21-1.57 and m (1 H) 2.74-3.24 (protons of the cyclopropane ring), s (1 H) 7.59 (protons of the furan nucleus, s (1 H) 9.48 (proton of the CHO group); IR spectrum, cm^{-1}: 1380, 1550 (NO_2), 1680 (C=O). Found: C 53.2, H 4.0%, $C_8H_7NO_4$. Calculated: C 53.0, H 3.9%.

Nitration of 2-Cyclopropyl-5-formylthiophene (VIII). By a similar method, 3 g of compound (VIII) yielded: 2.82 g (71%) of 2-cyclopropyl-5-formyl-3-nitrothiophene (XIV), mp 82-83°C (from ether); PMR spectrum, δ, ppm: m (4 H) 0.79-0.71 and m (1 H) 2.81-3.27 (protons of the three-membered ring), s (1 H) 8.02 (proton of the thiophene nucleus), s (1 H) 9.72 (proton of the aldehyde group); IR spectrum, cm^{-1}: 1365, 1580 (NO_2), 1685 (C = O). Found: C 48.6, H 3.4%. $C_8H_7NO_3S$. Calculated: C 48.7, H 3.6%; and 0.18 g of 2-cyclopropyl-5-nitrothiophene (XIII)*; PMR spectrum, δ, ppm: m (4 H) 0.75-1.42 and m (1 H) 1.93-2.31 (protons of the trimethylene ring), d (1 H) 6.64 and d (1 H) 7.73 ($J_{H_\beta H_\beta'}$ = 4 Hz, protons of the thiophene nucleus).

*It was impossible to isolate compound (XIII) in the pure state. The PMR spectrum was obtained for a sample of this substance having a purity of 88% in CCl_4 solution.

Nitration of 2-formyl-5-methylfuran (IX). On nitration by the standard method, 5.5 g of compound (IX) yielded 9.2 g of a dark red oil which was unstable on standing. Chromatography on plates coated with alumina permitted the isolation from it of 0.77 g (14%) of the starting material (IX) (the parameters of the PMR and IR spectra coincided with those for an authentic sample) and 1.97 g (31%) of 2-methyl-5-nitrofuran (XV), mp 46-47°C; PMR spectrum, δ, ppm: c (3 H) 2.48 (methyl group), d (1 H) 6.31 and d (1 H) 7.18 ($J_{H_\beta H_{\beta'}}$ = 3 Hz, protons of the furan ring); IR spectrum cm^{-1}: 1360, 1520 (NO_2). Found: C 47.3; H 3.9; N 10.6%. $C_5H_5NO_3$. Calculated: C 47.2; H 3.9; N 11.0%.

Nitration of 5-Formyl-2-methylthiophene (X). By the standard method, 6.3 g of compound (X) yielded 0.94 g (15%) of the initial compound (X) (the parameters of the PMR and IR spectra were identical with those of the corresponding spectra of the authentic compound) and 3.3 g (38%) of 5-formyl-2-methyl-3-nitrothiophene (XVI), mp 91-93°C (from ether); PMR spectrum, δ, ppm: s (3 H) 2.93 (methyl group), s (1 H) 8.33 (proton of the thiophene ring), s (1 H) 9.92 (proton of the aldehyde group), IR spectrum, cm^{-1}: 1370, 1540 (NO_2), 1690 (C=O). Found: C 42.4; H 3.0; N 8.4; S 17.9%. $C_6H_5NO_3S$. Calculated: C 42.1; H 2.9; N 8.2; S 18.7%.

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