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

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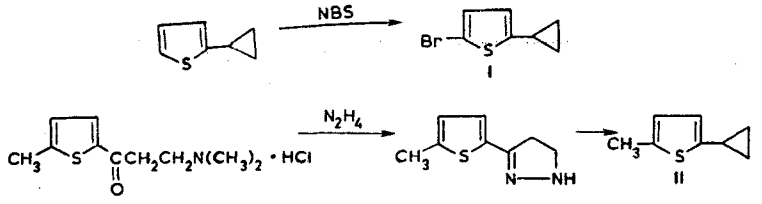
It was established that 5-bromo-2-cyclopropylthiophene and 5-methyl-2-cyclopropylthiophene undergo transformations during nitration with nitric acid in acetic anhydride that are a consequence of ipso attack of the nitryl cation in the 2 or 5 positions of the thiophene rings of the starting compounds.

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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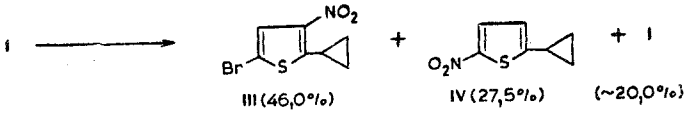
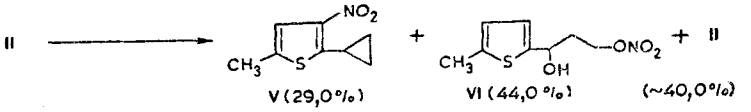
Primarily two products, viz., 4-bromo-3-nitro-2-cyclopropylthiophene (III) and 5-nitro-2-cyclopropylthiophene (IV), were formed in the nitration of 5-bromo-2-cyclopropylthiophene (I):*



Correspondingly, 5-methyl-3-nitro-2-cyclopropylthiophene (V) and 1-(5-methyl-2-thienyl)-propane-1,3-dione 3-nitrate (VI) were obtained under the same conditions but at −55°C.

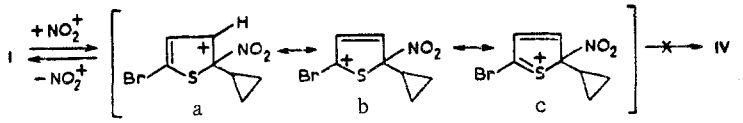


One's attention must be directed to the fact that in both cases significant amounts of the starting compounds (∿20% I, ∿40% II) did not undergo reaction.† This fact, generally speaking, was somewhat unexpected. It is known that the thiophene system is considerably more reactive than the benzene system in electrophilic substitution reactions. One should therefore have expected at least more nearly complete conversion of bromo- and methylcyclopropylthiophenes I and II than one should have observed for the corresponding bromo- and methylcyclopropylbenzenes. However, in contrast to the former, the latter react almost quantitatively [7, 8].

It should be noted that very little study has thus far been devoted to the nitration of 2,5-disubstituted thiophenes with electron-donor substituents. However, it is known that thiophenes that contain electron-acceptor groups in these positions may undergo both nitration with retention of the substituents already present and with ipso substitution of some of them [3, 4, 9]. It is important to emphasize that in contrast to carbocyclic aromatic systems, for which ipso attack of the nitryl cation on the carbon atom of the aromatic ring that is bonded to a strong electron-acceptor substituent is not characteristic, it does occur in the case of thiophene derivatives [3].

In a previous study [4] we demonstrated that replacement of the formyl group by a nitro group occurs along with the formation of the corresponding 3-nitro derivative in the nitration of 2-formyl-5-cyclopropylthiophene, during which the three-membered ring is retained. This result was explained by initial attack by the nitryl cation on the carbon atom of the thiophene ring that is bonded to the cyclopropyl grouping, since a small ring should be retained precisely in this case. However, the data obtained in [3] as well as in the present study compel us to reexamine this point of view.

In fact, if in the nitration of, for example, 5-bromothiophene (I) we assume ipso attack of the nitronium cation only at the carbon atom of the thiophene ring that is bonded to the cyclopropane ring and we examine the pathways of stabilization of the corresponding ipso thiophenonium ions (a-c), it becomes evident that a debromination–nitration product should not be detected in the reaction products.



However, the results of nitration of 5-bromo-2-cyclopropylthiophene (I) show that debromination occurs during the reaction (the product of ipso substitution of the bromine atom by a nitro group, viz., IV, is obtained in 27.5% yield).

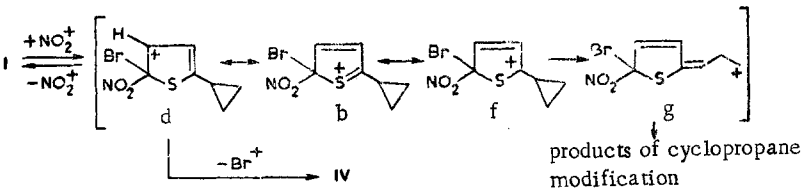
Consequently, whereas the scheme for the conversion of 5-formyl-2-cyclopropylthiophene to a deformylation–nitration product that was proposed in [4] seemed plausible, the forma-

*The yields of III and IV, as well as V and VI, were calculated on the basis of the converted starting compounds.

†According to data from the PMR spectra of the reaction mixtures. We were unable to quantitatively isolate the unchanged I and II by, for example, chromatography on Al_2O_3 or silica gel, since considerable amounts of the substances underwent modification in this case.

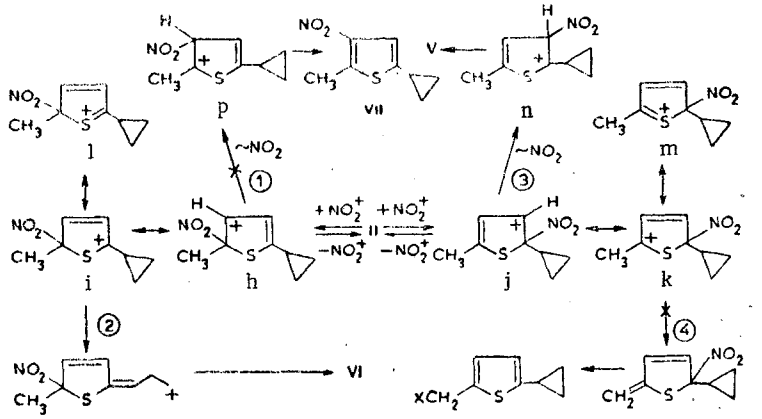
tion from bromide I of a debromination–nitration product through preliminary attack of the nitrating particle on the atom of the thiophene ring that is bonded to the three-membered ring seems doubtful.

At the same time, if it is assumed that the nitryl cation attacks the carbon atom of the thiophene ring that is bonded to the halogen atom, as in the case of 4-bromotoluene [6], and that cleavage of the C–Br bond in the intermediate ion (of the d type) takes place more rapidly than conversion of the latter to an ion with structure f, which then undergoes opening of the three-membered ring, the formation of nitro derivative IV will be completely natural.



The data obtained in the nitration of 5-methyl-2-cyclopropylthiophene (II) serve as indirect evidence that cleavage of the C–Br bond occurs in a step preceding conversion of ion d to ion f.

There are two possibilities of ipso attack of the nitryl cation in the nitration of II; it follows from literature analogies [2], that both possibilities should have led either to modification of the alkyl or cycloalkyl group or to ordinary nitration products (the possibility that this occurs in both cases through 1,2 migration of the nitro group in ipso thiophenonium ions h and j is not excluded).



Since the principal products of nitration of II were V and VI, one should speak of the preferred transformations of ipso thiophenonium ions h–i via pathway 2 and of ion j via pathway 3.*

The absence of a product of ipso substitution of an alkyl or cycloalkyl group in the nitration of II can be explained by the fact that the splitting out of an alkyl group in the form of a cation (as in the splitting out of a bromine cation from ion d) that is necessary for the formation of an ipso substitution product is less favorable than splitting out of a nitryl cation [1]. For this reason, ipso thiophenonium ion h may undergo either reversible conversion to starting II or may be converted to resonance ipso ions l and i. The conversion of the latter also leads to a product of modification of the three-membered ring (VI).

The preference of a process taking place via pathway 3 rather than pathway 4 is evidently due to facile migration of the nitro group in ion j, which leads to the formation of isomeric ion n, the delocalization of the positive charge in which is more favorable due

*It should be noted that completely analogous preference of similar transformations was also observed in the nitration of p-tolylcyclopropane: 2-nitro-4-methylphenylcyclopropane and 1-(4-methylphenyl)propane-1,3-dione derivatives were detected in the products of nitration of the latter; as in the case of a nitro compound with a nitro group in the ortho-position relative to the methyl substituent, substances with a modified methyl group were not detected [7].

to participation in it of the sulfur atom and the cyclopropane grouping; subsequent rapid deprotonation leads to V.

As regards the absence in the reaction products of nitro compound VII, which is isomeric with respect to V, this is once again probably associated with the formation of the most favorable ipso ion i structure (for the reason cited above) as compared with ion p. In explaining the formation of nitro-substituted 2,5-dialkylthiophene V one cannot completely exclude direct nitration of starting II in the free positions of the thiophene ring, especially since their reactivities are intensified substantially by the effect of two electron-donor groups. However, the complete absence in the reaction products of an isomer with a nitro group adjacent to the methyl group may constitute evidence for the preference of nitration that takes place with prior ipso attack.

Another interesting fact that was observed during an analysis of the products of nitration of 2,5-disubstituted thiophene II should be discussed. It is apparent that the product of modification of the three-membered ring is formed in higher yield (by a factor of ~1.5) than the yield of 3-nitro-substituted V. Since opening of the three-membered ring under the investigated conditions is a consequence of ipso attack, it should be stated that the attack of the nitryl cation on the carbon atom of the thiophene ring that is bonded to the methyl group is realized to a greater extent than at the carbon atom bonded to the cyclopropane fragment. On the one hand, this seems completely natural, since the steric limitations created by the cyclopropyl grouping should have a greater effect on the possibility of ipso attack; however, on the other hand, there are data that indicate unambiguously that the steric limitations in this case should not have a decisive effect [10].

In all likelihood, primarily electronic factors show up in the case of ipso attack of similarly substituted thiophenes (and benzenes), and in the case of a concerted orientation of the substituents the attack of the nitryl cation will preferably be realized at the carbon atom on which the excess electron density is concentrated to a greater degree. Since the three-membered ring is capable of activating a fragment bonded to it via both inductive and mesomeric effects, whereas a methyl residue is capable of activating primarily only via an inductive effect, ipso attack at the carbon atom of the thiophene ring that is bonded with a methyl group should predominate. Data on demethylation under the conditions of nitration of 4-methyl- and 4-cyclopropylanisoles also constitute evidence in favor of this assumption [10].

Thus we have obtained evidence that ipso attack of the nitryl cation on the carbon atom of the thiophene ring that is bonded either to a halogen atom or to an alkyl group is realized in the nitration of 5-substituted 2-cyclopropylthiophenes. The fact of ipso attack at the carbon atom of the thiophene ring that is bonded to a small ring requires additional evidence.

EXPERIMENTAL

The IR spectra of thin layers of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CCl_4 and $CDCl_3$ were recorded with JNM-60 and XL-100 spectrometers with hexamethyldisiloxane as the internal standard. Analysis by gas–liquid chromatography (GLC) was carried out with a Tsvet-102 chromatograph with a 3-m long column with a diameter of 4 mm; the stationary phase was 5% SE-30 siloxane elastomer on Chromaton N-AW, and the carrier gas was helium.

2-Cyclopropylthiophene. This compound was obtained by the method described in [4] in 26% yield and had bp 60-61°C (9 mm).

5-Bromo-2-cyclopropylthiophene (I). This compound was synthesized by bromination of 2-cyclopropylthiophene with N-bromosuccinimide (NBS) in an equimolar mixture of chloroform and acetic acid by the method in [11]. The product was obtained in 90% yield and had bp 95-97°C (10 mm).

5-Methyl-2-cyclopropylthiophene (II). A 23.4-g (0.1 mole) sample of 1-(5-methyl-2-thienyl)-3,3-dimethylamino-1-propanol hydrochloride was added with shaking to a mixture of 33 ml of hydrazine hydrate, 150 ml of triethylene glycol, and 11.2 g of KOH, and the mixture was stirred for 30-40 min. It was then heated to 140°C, stirred for another 4 h, allowed to stand for 1 h without heating, and treated with another 11.2 g of KOH. The apparatus was then fitted with a condenser for distillation, and the mixture was heated to 230°C with collection of 5-methyl-2-cyclopropylthiophene (II), water, and excess hydrazine hydrate.

The catalyzate was extracted with ether, and the extract was washed successively with water, 1 N HCl solution, NaOH solution, and water and dried with K_2CO_3. The solvent was removed by distillation, and the residue was vacuum distilled to give 3.45 g (25%) of 5-methyl-2-cyclopropylthiophene (II) with bp 75°C (15 mm). PMR spectrum: 0.48-1.07 (m, methylene protons of the cyclopropane ring), 1.62-2.06 (m, methylidyne proton of a small ring), 2.26 (s, CH_3), and 6.36 ppm (s, β protons of the thiophene ring). Found: C 64.7; H 6.6%. $C_8H_{10}S$. Calculated: C 64.9; H 6.8%.

Nitration of 5-Bromo-2-cyclopropylthiophene (I). A 3.9-ml sample of fuming nitric acid (sp. gr. 1.5) was added with stirring to 15 ml of acetic anhydride at −50°C, and the temperature was raised slowly to 0°C. The nitrating mixture was cooled to −30°C, and 3 g (0.015 mole) of I in 6 ml of acetic anhydride was added slowly. The temperature was raised to −20°C, and the mixture was stirred for 2 h at the same temperature. It was then poured into 150 ml of water, the aqueous mixture was neutralized with sodium carbonate, and the organic compounds were extracted with chloroform. The chloroform solution was washed with water and dried with $MgSO_4$. The solvent was removed by distillation, and the residue (3.5 g) was chromatographed on plates with activity II Al_2O_3 in an ether–hexane system (1:3) to give 0.2 g (∿7%) of starting bromide I,* 0.55 g (27.5%) of 5-nitro-2-cyclopropylthiophene (IV) [viscous oil. PMR spectrum: 0.71-1.39 (m, methylene groups of the cyclopropane ring), 1.83-2.36 (m, methylidyne proton of the cyclopropane ring), 6.70 (d, J_{34} = 4 Hz, 3-H), and 7.68 ppm (d, J_{34} = 4 Hz, 4-H). IR spectrum: 1375, 1530 cm^{-1} (NO_2). Found: C 49.5; H 4.0; N 8.0%. $C_7H_7NO_2S$. Calculated: C 49.7; H 4.1; N 8.3%], 1.35 g (46%) of 5-bromo-3-nitro-2-cyclopropylthiophene (III) [mp 32-33°C. PMR spectrum: 0.72-1.51 (m, methylene protons of the cyclopropane ring), 2.75-3.19 (m, methylidyne proton of a small ring), and 7.58 ppm (s, 4-H). IR spectrum: 1370, 1545 cm^{-1} (NO_2). Found: C 33.6; H 2.3; Br 32.8; S 12.8%. $C_7H_6BrNO_2S$. Calculated: C 33.9; H 2.4; Br 32.7; S 12.9%].

Nitration of 5-Methyl-2-cyclopropylthiophene (II). Nitration was carried out by the method described for I but at −55°C. After decomposition of the reaction mass, the reaction products were extracted with CCl_4. The extract was washed with water and dried with $MgSO_4$, the solvent was evaporated, and the residue was chromatographed as described above. A 3-g (0.021 mole) sample of II yielded 0.36 g (12%) of starting II, 0.79 g (29%) of 5-methyl-3-nitro-2-cyclopropylthiophene (V) [viscous oil. PMR spectrum: 0.56-1.38 (m, methylene protons of the cyclopropane ring), 2.72-3.16 (m, methylidyne proton of a small ring), 2.34 (s, CH_3), and 7.21 ppm (s, 4-H). IR spectrum: 1380, 1540 cm^{-1} (NO_2). Found: C 52.7; H 5.3%. $C_8H_9NO_2S$. Calculated: C 52.4; H 5.0%], and 1.41 g (44%) of 1-(5-methyl-2-thienyl)propane-1,3-diol 3-nitrate (VI) [viscous oil. PMR spectrum: 1.72-2.22 (m, C—CH_2—C), 2.33 (s, CH_3), 3.73 (broad s, OH), 4.86 (t, CH—OH), 4.29-4.78 (m, CH_2—ONO_2), 6.38 (d, J_{34} = 4 Hz, 4-H), and 6.54 ppm (d, J_{34} = 4 Hz, 3-H). IR spectrum: 1285, 1640 (ONO_2); 3420 cm^{-1} (OH). Found: C 44.0; H 4.9; N 6.3%. $C_8H_{11}NO_4S$. Calculated: C 44.2; H 5.1; N 6.4%].

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*Identified by comparison of its PMR spectrum with the spectrum of a genuine sample.