NITRO DERIVATIVES OF THE THIOPHENE SERIES.

3.* STUDY OF THE NITRATION OF THIOPHENE α,β-UNSATURATED KETONES IN THE PRESENCE OF PROTIC AND APROTIC ACIDS

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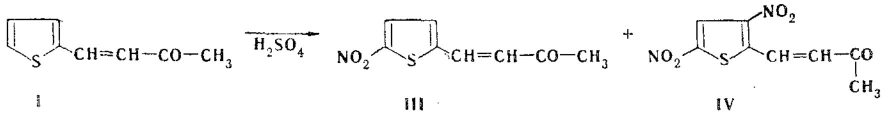
The nitration of 4-(5-R-2-thienyl)but-3-en-2-ones (R = H, CH_3, C_2H_5) with a nitrating mixture and group I and III metal nitrates in concentrated sulfuric and trifluoroacetic acids, as well as in the presence of aluminum chloride, was investigated. Nitration with a nitrating mixture and potassium, sodium, lithium, copper, and aluminum nitrates in sulfuric acid takes place in the heterocyclic ring to give a mixture of nitro ketones. Nitration in trifluoroacetic acid and in the presence of aluminum chloride proceeds with the formation of a single α-nitro ketone. The structures of the substances obtained were proved by means of the IR and PMR spectra. A possible mechanism of the reaction is discussed.

In a previous paper [1] we reported the results of a study of the nitration of thiophene ketones with concentrated nitric acid and group I and III metal nitrates in organic solvents. It was noted that unsaturated ketones react in the protonated form to give a single α-nitro compound under the influence of nitric acid or lithium, copper, and aluminum nitrates in carbon tetrachloride, 1,2-dichloroethane, and acetonitrile.

In this connection, it was of interest to study the nitration of unsaturated methyl ketones in the presence of protic and aprotic acids, which, as is well known, may display a protonating capacity with respect to the carbonyl group or form complexes with it [2, 3]. In analogy with [1], one might have assumed that the first step in the process would be protonation of the starting unsaturated ketone at the carbonyl group, as a result of which, substitution would take place in the aliphatic chain to give a single α-nitro ketone. In particular, we investigated the action of a nitrating mixture and potassium, sodium, copper, and aluminum nitrates in concentrated sulfuric acid (sp. gr. 1.84) at −15 to −10°C.

The data from the PMR spectra of the crude mixtures demonstrated that our assumptions were incorrect — the nitration of ketones I and IIa, b in sulfuric acid takes place exclusively in the heterocyclic ring without involvement of the aliphatic ring. Thus two isomers, viz., 5-nitro- and 3,5-dinitro-substituted ketones, are formed in a ratio of 4:1 in the nitration of ketone I with a nitrating mixture and potassium, sodium, and lithium nitrates (the ratio of nitric acid to the unsaturated ketone was 1.2:1). The use of copper and aluminum nitrates leads to a mixture of the same nitro ketones. However, the ratio between III and IV changes in favor of the preponderant formation of the dinitro ketone and amounts to 1:3.3. The dependence of the ratio of the mono- (III) and dinitro-substituted (IV) ketones on the molar ratio of nitric acid to the substance undergoing nitration is presented in Fig. 1.



A mixture of nitro ketones is formed by the action of potassium, sodium, lithium, copper, and aluminum nitrates on ketones IIa, b, which contain electron-donor substituents in

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*See [1] for Communication 2.

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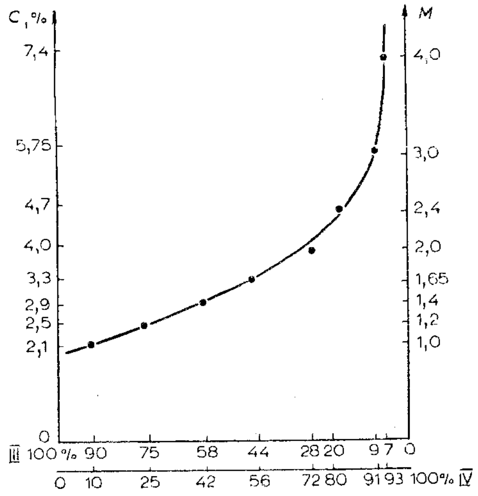


Fig. 1

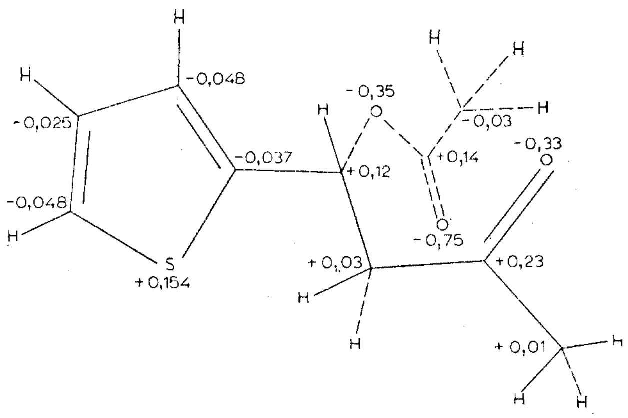
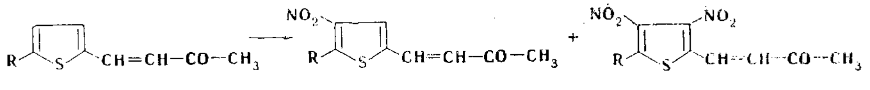


Fig. 2

Fig. 1. Dependence of the ratio of the mono- (III) and dinitro-substituted (IV) ketones on the molar ratio of nitric acid to the substance undergoing nitration (M) and the HNO_3 concentration in the reaction mixture (C, %) in the nitration of ketone I.

Fig. 2. Residual π-electron density on the atoms of 4-(2-thienyl)-4-acetoxy-2-butanone (VIII).

the 5 position. It is interesting that, as in the case of ketone I, the action of sodium, potassium, and lithium nitrates in sulfuric acid on IIa, b leads to the preponderant formation of mononitro ketones (60% of the overall yield of products). However, the use of copper and aluminum nitrates in equimolar amounts leads to the preponderance of the 3,4-dinitro-5-alkylthienyl ketones (75%) in the mixture.



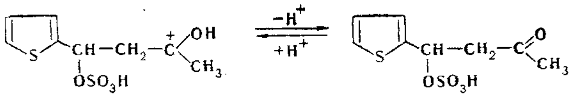
II a, b

V a, b

VI a, b

II, V, VI a $R=CH_3$; b $R=C_2H_5$

This nitration pathway in concentrated sulfuric acid cannot be explained starting from the calculated indexes of reactivity of both the neutral molecule and the protonated form of the starting ketones [1]; it also does not agree with the pathway of nitration of the simplest carbonyl compounds of the thiophene series, viz., 2-formylthiophene and 2-acetylthienone, in concentrated sulfuric acid [4, 5]. To explain the results it was assumed that sulfuric acid adds initially to the activated C=C bond of ketone I to give adduct VIIa or VIIb, which then undergoes nitration exclusively in the thiophene ring; as a consequence of redistribution of the electron density as compared with ketone I, the 3 and 5 positions of the heteroring should be activated. This is confirmed by quantum-chemical calculation of the electron structure of the adduct of acetic acid and the starting ketone (VIII), the structure of which is similar to the structure of ester VIIa. The calculation gave the following values of the residual π-electron density on the atoms of the thiophene ring (Fig. 2). In this case the overall charge of the heteroring has a negative value of −0.0156, in contrast to the neutral and protonated molecules of ketone I (+0.0215 and +0.1315, respectively [1]), while the aliphatic chain has an overall positive charge (+0.0159). In the thiophene ring itself the 3 and 5 positions of the thiophene ring are actually the most nucleophilic positions; the values of the residual π-electron densities on them are identical and are twice the value of the 4 position. The calculated data are in complete agreement with the experimental results.



VIIa

VIIb

TABLE 1. Physicochemical Characteristics of Nitrothiophene α,β-Unsaturated Ketones

Compound	mp, °C	IR spectra, cm^{-1}				Found, %				Empirical formula	Calculated, %				Yield, %
		C=C	C=O	NO_2^{as}	NO_2^{s}	C	H	N	S		C	H	N	S	
III	131—132,5	1615	1705	1550	1340	48,4	3,3	7,3	16,7	$C_8H_7NO_3S$	48,7	3,6	7,1	16,3	75
IV	121—122	1595	1687	1555	1340	39,9	2,1	11,3	13,4	$C_8H_6N_2O_5S$	39,7	2,5	11,6	13,2	58
Va	117—118	1622	1675	1545	1342	51,6	4,5	16,2	15,6	$C_9H_9NO_3S$	51,2	4,3	6,6	15,2	95
Vb	71—72,5	1597	1690	1538	1335	52,9	4,7	6,0	13,8	$C_{10}H_{11}NO_3S$	53,3	4,9	6,2	14,2	56
VIa	149—150	1615	1665	1545	1330	42,3	3,3	10,4	12,7	$C_9H_8N_2O_5S$	42,2	3,1	10,9	12,5	68
VIb	98—99	1600	1696	1540	1328	44,1	3,7	10,1	11,4	$C_{10}H_{10}N_2O_5S$	44,4	3,7	10,4	11,9	42

It was of equal interest to trace the effect on the nitration of ketones I and IIa, b of any other relatively strong acid that theoretically could promote protonation of the starting ketones and add to the olefin bond. We studied the nitration of unsaturated ketones in trifluoroacetic acid under the influence of concentrated nitric acid and potassium and aluminum nitrates. However, we found that trifluoroacetic acid is nevertheless not sufficiently strong to protonate the starting ketones and does not add to the C=C bond, whereas in nitration reactions it serves only as a polar organic solvent that does not have a directing effect on the nitration process. This is confirmed by the fact that nitration with nitric acid at 0-5°C is accompanied by pronounced resinification, and the α-nitro compound is formed in only small amounts (8%). Potassium nitrate in trifluoroacetic acid does not have a nitrating effect, and the starting ketones are isolated. Attempts to carry out nitration in CF_3COOH with potassium and aluminum nitrates and nitric acid at elevated temperatures (>20°C) led to pronounced resinification and evidently to polymerization of the starting unsaturated ketones (according to the data from the PMR spectra).

We also checked the effect of aprotic acids, particularly aluminum chloride, which, according to the literature data, is capable of forming complexes at the carbonyl group [2] but cannot add to the double bond, on the investigated nitration of I. If this ability of aluminum chloride is also manifested in the case of the carbonyl group of unsaturated ketones, one should expect the formation of a single α-nitro ketone, as in the case of true protonation. In fact, nitration of the previously obtained complex of ketone I with aluminum chloride by means of aluminum nitrate in anhydrous 1,2-dichloroethane and glacial acetic acid led to the production in low yield of only the α-nitro ketone. However, in these cases the process was accompanied by significant resinification of the reaction mixture.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $(CD_3)_2CO$ were obtained at 30-50°C with a Tesla BS-497 spectrometer with hexamethyldisiloxane as the internal standard. The signals were assigned by means of the method of selective homonuclear resonance. Ketones I and IIa, b were synthesized by crotonic condensation of acetone with the corresponding thiophene aldehydes by the method in [6]. Nitration with the nitrating mixture was carried out as in [7], while nitration with potassium and sodium nitrates was accomplished by the method in [4]. The properties of the synthesized compounds are presented in Tables 1 and 2.

4-(5-Nitro-2-thienyl)but-3-en-2-one (III). A 1.52-g (0.01 mole) sample of ketone I was added to 15 ml of concentrated sulfuric acid cooled to –15°C, and the mixture was maintained at the same temperature with vigorous stirring while 1.2 g (5 mmole) of copper nitrate (or 1.25 g of aluminum nitrate) was added in small portions. The mixture was then maintained at the same temperature for 2 h, after which it was poured over ice. The resulting precipitate was removed by filtration, washed with water, air dried, and recrystallized from heptane.

4-(3,5-Dinitro-2-thienyl)but-3-en-2-one (IV). A 1.52-g (0.01 mole) sample of ketone I was added to 30 ml of concentrated H_2SO_4 cooled to –15°C, and the mixture was maintained at the same temperature with vigorous stirring while 3.75 g (0.01 mole) of aluminum nitrate (or 2.41 g of copper nitrate) was added in small portions. The reaction product was isolated as in the preparation of III.

TABLE 2. PMR Spectra of Nitro Ketones III-VI

Compound	Chemical shifts, δ, ppm*						
	3-H	4-H	α-H	β-H	CO—CH_3	CH_2	CH_3
III	7,52 d	7,98 d	6,79 d	7,69 d	2,31 s	—	—
IV	—	8,46 s	7,05 d	8,25 d	2,41 s	—	—
Va	7,88 s	—	6,52 d	7,65 d	2,30 s	—	2,81 s
Vb	—	—	6,79 d	7,71 d	2,37 s	—	2,76 s
VIa	7,89 s	—	6,55 d	7,67 d	2,30 s	3,17 q	1,37 t
VIb	—	—	6,84 d	7,74 d	2,37 s	3,17 q	1,40 t

*$J_{\alpha,\beta}$ = 16.0-16.1, $J_{3,4}$ = 4.4, and $J_{CH_2CH_3}$ = 7.5 Hz.

Ketones IIa, b were nitrated similarly by metal nitrates.

Nitration of Ketone I in the Presence of Aluminum Chloride. A 1.3-g (0.01 mole) sample of aluminum chloride was added at 5°C to 1.52 g (0.01 mole) of ketone I in 5 ml of 1,2-dichloroethane, during which the solution turned bright red. The mixture was then heated to 20°C, and 1.25 g (3 mmole) of aluminum nitrate was added slowly with stirring. The resulting mixture was maintained at 20°C for 1.5 h, after which it was poured over ice. The organic layer was extracted with dichloroethane (15 ml), and the extract was washed successively with water, a dilute solution of sodium carbonate, and water, and dried with Na_2SO_4. The solvent was removed by distillation *in vacuo* to give a nitro product that was similar to the previously described α-nitro ketone [1]. The yield of product with mp 146-147°C after recrystallization from heptane was 8%.

The nitration of ketone I in trifluoroacetic acid was carried out in the same way as the nitration in glacial acetic acid [1].

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