NITRATION OF FURAN DERIVATIVES

WITH ACETYL NITRATE

I. INVESTIGATION OF THE PRODUCT'S OF NITRATION

OF METHYL FURAN-2-CARBOXYLATE

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The mixture of products formed in the nitration of methyl furan-2-carboxylate in acetic anhydride was separated by means of thin-layer and column chromatography. It was found that products of cis and trans addition of acetyl nitrate to the furan ring – methyl 5-nitro-2-acetoxy-2,5-dihydrofuran-2-carboxylate and 5-nitro-4-acetoxy-4,5-dihydrofuran-2-carboxylate – and methyl 5-nitrofuran-2-carboxylate are formed in the nitration.

Methyl furan-2-carboxylate (I) is included among furan compounds that form readily isolable and sufficiently stable "intermediates" during nitration in acetic anhydride.

The nitration of ester I in acetic anhydride was first carried out by Marquis [1, 2], who obtained methyl 5-nitrofuran-2-carboxylate (II) by treatment of the "intermediate" nitration product with pyridine. Subsequent studies [3] showed that the "intermediate" nitration product is a mixture of substances, from which Freure and Johnson [3] were able to isolate a crystalline compound with mp 96.3°C, which, with respect to its composition, corresponded to an adduct of acetyl nitrate and the starting compound and for which the methyl 5-nitro-2-acetoxy-2,5-dihydrofuran-2-carboxylate structure (III) was confirmed [3-7].

 $R = H; II R = NO_{2}$

In the present research we investigated the composition of the products of nitration of ester I under the conditions in [3] by means of column chromatography and thin-layer chromatography (TLC). In addition to the previously known adduct (III), we were able to isolate from the ether extract of the mother liquor an oily fraction of the "intermediate" that was first mentioned in [3]. Analysis by TLC on silica gel showed that the isolated oily product of nitration of ester I is a mixture of five compounds: A, B, C, D, and E (Table 1).

This mixture was separated into individual substances by means of successive column chromatography and TLC.

According to the IR and UV spectroscopic data [5, 8, 9] and the R_f values and the change in the color of the spots, substance A proved to be identical to III (Table 1). The results of an analysis of the PMR spectrum of substance A (III) are presented in Table 2; they are close to the literature data for the analogous 2,5-dihydrofuran derivative [10, 11].

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	Brand of	t.	Rf of nitration products						Rf of model substances			
	silica g e l		A	В	С	D	E	x†	111	II	I	
Chromatography	From KSK G Merck H Ferak H Ferak Silufol UV-254 Silufol UV-254	1 1 1 2 2 3	0,31 0,16 0,20 0,29 0,14 0,47	0,36 0,22 0,25 0,33 0,21 0,55	0,43 0,29 0,32 0,38 0,25 0,66	0,54 0,41 0,44 0,45 0,36 0,76	0,66 0,53 0,56 0,48 0,41 0,81	 0,23 0,19 0,06 0,27	0,31 0,16 0,20 0,29 0,14 0,47	0,56 0,41 0,44 0,45 0,36 0,76	 0,55 0,50 0,45 0,84	
	Exposure to NH ₃ vapors		У (s)	·v	v	y (s)	у (s)	ь	у (s)	y (s)		
Detection#	Spraying with 0,1 KMnO ₄ — 2 CH ₃ COOH (1: Color on violet background UV light Spraying with 0,5 soln, of 2,4-DNP in 2 N HC1	N N 1) - 3% H	w or (s)	y or (s)	y or (s)	d		w or (s)	w or (s)	d	w d or (S)	

TABLE 1. TLC of Model Substances and Products of Nitration of I

*System 1 was carbon tetrachloride -ether (7:3), system II was benzene -heptane -ethyl acetate (8.25:1.00:0.75), and system 3 was benzene -ether (9:1).

† Compound X was isolated from the products of reaction of C with sodium acetate and also from the mother liquor in the synthesis of II. ‡ Colors of the spots on the chromatograms: y is yellow, v is violet, b is blue, w is white, o is orange, d indicates a dark spot, and (s) indictates the color forms slowly.

Additional low-intensity signals of methyl groups at δ 3.81 and 2.13 ppm (~10 mole %) are observed in the PMR spectrum of some of the samples of III. The resonance signals corresponding to the protons of the 2,5-dihydrofuran framework are hidden under the multiplet of the principal product. This splitting of the peaks indicates the presence of two diastereomers in III (substance A). Inasmuch as 2,5-dihydrofurans have a half-envelope conformation with an oxygen bridge projecting from the $C_2-C_3-C_4-C_5$ plane [12], the probability of finding one of the substituents attached to the C_2 atom in the plane of the double bond is higher. The effect of the magnetic anisotropy of the $C_3 = C_4$ double bond on this substituent will be greater, i.e., the resonance absorption of the protons of the latter should be found at weaker field as compared with the second diastereomer. The principal component of substance A (III) should therefore be assigned to the isomer with a cis orientation of the NO₂ and CH₃-CO-O- groups (IIIa), and the IIIb structure corresponds to the minor component (Table 2). The C¹³ NMR spectrum also confirms the 2,5-dihydrofuran structure of III.

It must be noted that deacetoxylation of III and conversion of it to II is observed on several sorts of silica gels (for example, Merck H and G, Ferak H and G, and Chemapol L) during chromatography; this was proved by means of two-dimensional chromatography. Deacetoxylation of substance A and of the corresponding model compound III is not observed on acidic KSK silica gel. The deacetoxylating action of the indicated brands of silica gels can be avoided by prior washing of the plates with a 1% solution of acetic acid in ether.

Substance D proved to be identical to II (Table 1) with respect to its chromatographic mobility and spectroscopic characteristics [5, 6, 8, 13].

Substance B, which was isolated as a white crystalline compound (mp 76-77°), proved with respect to its elementary composition, to be the previously unknown adduct of a molecule of acetyl nitrate and a molecule of I. The IR spectrum of substance B indicates the presence in the molecule of an unconjugated nitro group $(\nu_{NO_2}^{as} 1580 \text{ and } \nu_{NO_2}^{s} 1370 \text{ cm}^{-1})$; the absorption at 1030 cm⁻¹ attests to retention of the ether grouping of the furan ring (ν_{C-O-C}^{s}) . The low-intensity absorption at 1625 cm⁻¹ indicates the presence of a vinyl grouping in the molecule [9, 14]. According to the UV spectroscopic data [$\lambda_{max} 280 \text{ nm}$ (log $\varepsilon 2.34$) in glacial acetic acid] a conjugated system of double bonds is absent in system B.

Com-	Struc-	0.1.	Che	mical shi	SSCC, Hz					
pound ture		Solvent	COOCH ₃	OCOCH ₃	3-H	4-H	5-H	J _{3,4}	J _{4.5}	J _{5.3}
A*.	III a III b	(CD ₃) ₂ CO (CD ₃) ₂ CO	3,77 3,81	2,16 2,13	6,54	6.78	6.68	5.8 —	1,2	1.2
В	IV a	(CD ₃) ₂ CO C ₅ D ₅ N	3,88 3,80	$2.20 \\ 2.12$	7.11 7.42	6,71 6,75	6,71 7.02	1,2	 5,9	 0.8
С	IVb	(CD₃)₂CO C₅D₅N	3.92 3,79	2,17 2,06	7.34 7 .6 5	6.74 6.80	6.74 6.98	0.8		 1.2
Х	V a Vb	CDCl ₂ CDCl ₃	3,79 3,81	2.10 2.13	6.35 † 6.33 †	6.22 † 6.20 †	6.90 7.05	5.9 5.9	0.8 0,8	0.8 0,8

TABLE 2. PMR Spectra of the Products of Nitration of I

* The PMR spectrum of substance A was described in [7], but it was impossible to analyze the multiplet of protons of the dihydrofuran framework with a spectrometer with an operating frequency of 40 MHz.

† The assignment of the signals is ambiguous.

The formation of II, as attested to by the bathochromic shift of the absorption maximum in the UV spectra and a considerable increase in its intensity, is observed after treatment of substance B with a dilute solution of sodium acetate. The formation of II from substance B is also observed on Ferak H silica gel and is confirmed by two-dimensional chromatography. We were unable to obtain substance C, isolated as an unstable oil, in chemically pure form. According to the IR spectroscopic data, substance C contains an unconjugated nitro group ($\nu_{NO_2}^{as}$ 1580 and $\nu_{NO_2}^{s}$ 1370 cm⁻¹), a C-O-C grouping (ν^s 1030 cm⁻¹), and a double bond (1626 cm⁻¹). The UV spectrum of substance C has λ_{max} 277 nm (log ε 2.56) in glacial acetic acid. The splitting out of acetic acid from substance C proceeds with greater difficulty than in the case of substances A and B. For example, substance C remains unchanged when it is chromatographed on those brands of silica gel that deacetoxylate substances A and B. Deacetoxylation of substance C (according to UV spectroscopy, ~15% of starting substance C) is observed under the influence of sodium acetate in aqueous alcohol solution.

On the basis of the above investigations, the structures of two isomeric methyl 5-nitro-4-acetoxy-4,5-dihydrofuran-2-carboxylates (IVa and IVb) were assigned to substances B and C. Inasmuch as the formation of II from substances B proceeds more readily than the formation of II from substance C, the former should apparently be assigned to the cis adduct of acetyl nitrate in the 4,5 position of the furan ring (IVa) (trans elimination of a molecule of acetic acid), whereas the latter should be assigned to the trans adduct of acetyl nitrate (IVb) (cis elimination).



A characteristic feature of the PMR spectra of substances B and C in deuteroacetone is the presence at weak field of two singlets with an intensity ratio of 1:2. This random equivalence of the 4-H and 5-H protons is eliminated in deuteropyridine solutions, in which one observes splitting of the signals because of spin-spin coupling (SSC).* We note that a similar sort of difficulty in the interpretation of the PMR spectra also holds in the case of some other 2,3-dihydrofurans [15, 16]. The identical numerical value of the $J_{5,4}$ constants in both disastereomers B and C are suprising, although the literature data indicate a considerable difference in the magnitudes of this constant in cis and trans isomers [15-17]. This is apparently a consequence of the effect of two electron-acceptor substituents - the NO₂ and CH₃COO groups. The PMR spectra do not provide an unambiguous conclusion relative to the configurations of disastereomers B and C, but inasmuch as the signals of the protons of the trans adducts are usually found at weaker field than those of the cis adducts [7], it may be in agreement with the conclusions drawn on the basis of the chemical properties of these compounds.

^{*} Deacetoxylation of B and C to II is not observed under the experimental conditions. Under similar conditions, III is converted quantitatively to II.

In addition to II, X (mp 85-86°) was detected in the products of reaction of substance C with sodium acetate; the elementary composition of X is $C_{10}H_{12}O_7$, and it is present in appreciable amounts in the products of deacetoxylation of the crude "intermediate" in the nitration of ester I. We used the mother liquor, after removal of II by filtration, for its preparative isolation.

The PMR spectrum of X contains signals from two acetoxy groups and one carbomethoxy group. An analysis of the weak-field region of the spectrum suggests a 2,5-dihydrofuran structure for X (Table 2). The doubling of all of the lines in the spectrum corresponds to two stereomers. The assignments to a definite isomer were made with allowance for the fact that the signals of the acetoxy groups in the spectra of trans-2,5-diacetoxy-2,5-dihydrofurans are found at stronger field than those of the cis isomers [7] and also by analysis of the intensities (Va: Vb=1:0.6). The data from the UV [λ_{max} 217 nm (log ε 2.89), in ethanol] and IR spectra ($\nu_{C=O}$ 1760; $\nu_{C=C}$ 1635; ν_{C-O-C} ^S 1020 cm⁻¹) spectra of X also do not contradict the methyl 2,5-diacetoxy-2,5-dihydrofuran-2-carboxylate structure (V) for this compound. The definitive establishment of the location of the substituents of the dihydrofuran ring by chemical methods is continuing.



Because of its negligibly small concentration in the mixture of products of nitration of ester I, we were unable to obtain substance E in the quantities necessary for a study of its properties and establishment of its structure.

EXPERIMENTAL

The NMR spectra were recorded with Perkin-Elmer R-12A (60 MHz) and Bruker HX-90 (90 MHz) spectrometers with tetramethylsilane as the internal standard. The IR spectra of mineral oil and hexa-chlorobutadiene suspensions of the compound were recorded with a UR-20 spectrometer. The electronic spectra were recorded with an SF-4A spectrophotometer. Compounds I [18], II [1, 2], and III [3] were obtained by known methods. Compound III had mp 100-101° (from methanol) [mp 99-102° (from methanol) [4]].

Preparation of the Products of Nitration of Methyl Furan-2-carboxylate (I). A 7.7-g (0.122 mole) sample of fuming nitric acid (sp. gr. 1.51) and 0.4 g (0.004 mole) of concentrated H_2SO_4 (sp. gr. 1.83) were added dropwise with stirring at 0-5° under anhydrous conditions to 21.6 g (0.21 mole) of acetic anhydride, after which a solution of 3.15 g (0.025 mole) of ester I in 7.6 (0.074 mole) of acetic anhydride was added with stirring in the course of 1 h at -20° . The molar ratio of I, nitric acid, and acetic anhydride was 1:4.9:11.3. The reaction mixture was maintained at -20° for another 15 min, after which it was poured over 400 g of crushed ice, and the aqueous mixture was stirred at no higher than 10° for 3 h. The resulting white crystallization, washed with water, and air dried. The yield of crude III, with mp 91-94°, was 1.72 g; recrystallization from methanol gave a product with mp 100-101°.

The mother liquor was extracted with five 50-ml portions of ether, after which the ether solution was washed with ice water, dried over anhydrous magnesium sulfate, filtered, and stored at no higher than 5°. The ether solution contained ~1.54 g of a mixture of products of nitration of ester I, which was separated chromatographically.

Method for TLC of the Products of Nitration of I. A variety of silica gels – Merck G and H, Ferak G and H, Woelm DC, Chemapol L and LS_{245} , a sample prepared from KSK by the method in [19], and Silufol UV-254 – were used for TLC. The plates (9 by 12 cm) for the TLC were prepared by the method described in [20] and activated at 110° for 30 min. Practically the same degree of activity of the adsorbent on the plates can be obtained by drying them at 20° for no less than 24 h at an air-relative humidity less than 70%. Where it was necessary to avoid deacetoxylation of the nitration products on the sorbents, a 1% solution of acetic acid in ether was passed through a layer of the adsorbent prior to the experiment, after which the plate was air dried for 1 h.

The results of chromatography of the products of nitration of ester I and the method used to detect the spots are presented in Table 1.

<u>Preparative Separation of the Products of Nitration of I.</u> A 160-g sample of Woelm activity II silica gel for adsorption chromatography was suspended in 750 ml of benzene -heptane -ethyl acetate (8.25:1.00:

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0.75) containing 1% of glacial acetic acid (to avoid the deacetoxylating effect of the adsorbent), and a $100 \times$ 3-cm column was filled with this suspension.

An ether solution containing ~1 g of a mixture of the products of nitration of I was mixed with 5 g of Woelm silica gel, and the powder obtained after evaporation of the solvent was dried in a vacuum desiccator over P_2O_5 for 1 h and added carefully to the previously prepared chromatography column. The components of the mixture were eluted with benzene-heptane-ethyl acetate (8.25:1.00:0.75) at a flow rate of 1.5 ml/min. The compositions and purities of the fractions obtained were monitored by TLC.

The fractions containing substances A, B, C, and D were concentrated to a small volume and rechromatographed preparatively in a layer on 12 by 18-cm plates with Ferak or Chemapol H silica gel,* which were prepared from 10 g of silica gel and 20-30 ml of water by a method similar to that in [20]. Prior to chromatography, a 1% solution of glacial acetic acid in ether was passed through a layer of the adsorbent, and the adsorbent was dried for 1 h. The solvent systems used were benzene - heptane - ethyl acetate (8.25: 1.00:0.75) or benzene - ether (9:1). The time required to develop the chromatograms was 20-40 min. After drying in air for 1 h, the plate was rechromatographed. The substances were eluted from the adsorbent with a small amount of freshly distilled ether. Substances A, B, C, and D were preparatively reseparated until individual compounds, which were characterized by the following data, were obtained.

Substance A, with mp 99-101°, was identical to III. C^{13} NMR spectrum [20% solution in $(CD_3)_2CO$ with tetramethylsilane as the standard]: C_2 108.9, C_3 133.7, C_4 130.6, C_5 110.8, >C=O 165.7 and 168.8, COCH₃ 20.0, and OCH₃ 53.1 ppm.

Substance B had mp 76-77°. Found: C 40.8; H 3.9; N 6.0%. $C_8H_9NO_7$. Calculated: C 41.6; H 3.9; N 6.0%.

Substance C was obtained as an oil that could not be isolated in chemically pure form. Found: C42.9; H 4.4; N 5.2%. $C_8H_9NO_7$. Calculated: C 41.6; H 3.9; N 6.0%.

Substance D, with mp 80-81°, was identical to II.

<u>Deacetoxylation of III (substance A)</u>. A 0.00131-g sample of III was placed in a 25-ml volumetric flask, 1 ml of glacial acetic acid and 4 ml of 1% aqueous sodium acetate solution were added, and the solution was maintained at 50-55° for 1 h, after which it was cooled to 20°, diluted to the mark with ethanol, and its UV spectrum was recorded: $\lambda_{max} 295$ nm ($\varepsilon 1.08 \cdot 10^4$) (III underwent 82% conversion to II). An analysis of the products of deacetoxylation of III by TLC showed that only II was formed in the reaction.

<u>Deacetoxylation of Substance B.</u> Substance B was deacetoxylated by the method used to deacetoxylate substance A. UV spectrum: $\lambda_{max} 295$ nm ($\epsilon 6.55 \cdot 10^3$) (substance B underwent 49% conversion to II). An analysis of the products of deacetoxylation of substance B by TLC showed that the only reaction product was II.

<u>Deacetoxylation of Substance C.</u> A 0.00158-g sample of substance C was dissolved in 2 ml of ethanol in a 25-ml volumetric flask, 4 ml of a 1% aqueous solution of sodium acetate was added, and the mixture was held at 50-55° for 1 h. It was then cooled to 20°, ethanol was added up to the mark, and the UV spectrum of the solution was recorded: λ_{max} 295 nm (ε 2.04 \cdot 10³) (substance C underwent 15% conversion to II). An analysis of the products of deacetoxylation of substance C by TLC showed that X is formed along with II (Table 1).

<u>Substance X.</u> The mother liquor obtained in the synthesis of II [1, 2] was extracted with ether, and the ether extract was dried over anhydrous magnesium sulfate and chromatographed preparatively in a layer of Ferak H silica gel [benzene-ether (9:1)]. Substance X was eluted from the adsorbent with a small amount of ether. Evaporation of the ether gave X with mp 85-86°. Found: C 49.2; H 5.1%. $C_{10}H_{12}O_7$. Calculated: C 49.0; H 5.3%.

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*In order to remove the possible organic impurities, the silica gel was washed prior to use with acetone and specially distilled ether (free of peroxides) and dried.

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