STUDY OF KETO-ENOL TAUTOMERISM AND ALKYLATION REACTIONS OF β-KETOSULPHONES OF 5-NITROFURAN SERIES*

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Received September 15th, 1980

2-(5-Nitro-2-furyl)-2-oxoethyl 3-X-phenyl sulphones *I* react with diazomethane in tetrahydrofuran or dioxane to give trisubstituted ethylenes *II*, *i.e.* 1-(5-nitro-2-furyl)-1-methoxy-2-(4-X-phenylsulphonyl)ethylenes (X = H, CH_3, OCH_3, $N(CH_3)_2$, Cl, NO_2) which have *Z* configuration. From results of spectral and chemical investigation it follows that β-ketosulphones of 5-nitrofuran series only exist in ketoform and are very strong CH-acids (pK_a 7·82—5·23). Alkylation of the sulphones *I* (X = H, CH_3) with methyl iodide under conditions of extraction alkylation gives the corresponding C-methyl derivatives *III*. Interpretation is given of IR, UV, ^{13}C-NMR, and ^1H-NMR spectra of the sulphones *I* and *II*.

In our previous papers we studied some properties and synthetic application of sulphones od 5-nitrofurfuryl type which represent relatively strong CH-acids[1]. Carbanions of these compounds undergo stereospecific condensation reactions with aromatic and heterocyclic aldehydes to give trisubstituted ethylenes[2-6] which are non-planar, having the 5-nitrofuran nucleus deviated from the plane of the ethylene bond. These compounds have *E* configuration[2,7]. 5-Nitrofurfuryl trichloromethyl sulphone reacts also with aliphatic aldehydes to give the corresponding cyclopropanes of 5-nitrofuran series[8,9]. In our previous papers[10-12] we dealt with study of transmission of substituent polar effects in various types of sulphones of 5-nitrofuran series inclusive of the starting 2-(5-nitro-2-furyl)-2-oxoethyl 4-X-phenyl sulphones. Alkylation reactions of some CH-acids of 5-nitrofuran type are described in ref.[13].

The present paper deals with alkylation reactions of β-ketosulphones of 5-nitrofuran series (general formula *I*, Scheme 1) with diazomethane or methyl iodide.

The starting sulphones *I* were synthetized by alkylation of salts of sulphinic acids with 2-bromoacetyl-5-nitrofuran in ethanol[14]. Reaction of the sulphones *I* with diazomethane in tetrahydrofuran or dioxane only gives the unsaturated methoxy derivatives *II*, which was confirmed by analysis of the ^1H NMR spectra of the raw reaction mixtures. Uniform course of this reaction indicated that the compounds *I* could

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* Part CLXII in the series Furan Derivatives; Part CLXI: This Journal *46*, 3110 (1981).

exist in keto–enol tautomeric equilibrium ($A \rightleftharpoons B$), the reaction with CH_2N_2 (accompanied by nitrogen gas evolution) involving the enolform. The latter could be considerably stabilized by formation of intramolecular hydrogen bond (Scheme 1). The enolform could explain also the observed very high acidity of these compounds (pK_a 7·82 – 5·23) as compared with other 5-nitrofuran derivatives containing active methylene group[10–14]. Inclusion of CO group between 5-nitrofuran nucleus and sulphonyl group increases acidity of hydrogen atoms in CH_2 group by more than three orders of magnitude as compared with the reference compounds without CO group[11]. Usual application of IR spectroscopy for study of keto–enol tautomerism[15] is prevented in our case by very low solubility of the compounds in non-polar solvents, which makes it impossible to measure the concentration dependences. Spectra of these compounds, therefore, were measured in tetrahydrofuran or dioxane. However, in these solvents hydrogen bonds are formed between acid hydrogen atoms of methylene group in the sulphones and ether oxygen atom of solvent, which makes itself felt by a broad band in the region 3 575 and 3 508 cm^{-1}. The same band is also observed with the sulphones lacking carbonyl groups. IR spectra obtained by other techniques (*e.g.* in saturated chloroform solutions, Nujol, as well as in KBr disc) involve intensive unsplit carbonyl band in the region 1 693 – 1 684 cm^{-1} and lack the vibrations corresponding to $\nu(C{=}C)$ and $\nu(OH)$. Intramolecular and/or intermolecular hydrogen bonds of the possible OH isomer were also studied with the use of far IR spectroscopy (400 to 60 cm^{-1})[16]. The spectra are complicated due to possible internal rotation about two different axes, but it is possible to assign unambiguously the absorption bands of SO_2 vibrations (325 – 315 cm^{-1}) and to C—S—C groupings (230 – 218 cm^{-1}). The spectra contain regularly repeating bands of equal intensities which are due to deformation vibrations of the whole system. Substituents cause the deformation motion of the molecules to be divided into two parts, which results in broadening of the bands (marked especially in the case of electron-donor substituents OCH_3 and $N(CH_3)_2$). Spectrum of the basic sulphone *I* (X = H) does not change within a broad temperature range (25°C to −183°C), which shows that the compound is symmetrical ketoform.

Furthermore, we used ^{13}C NMR spectroscopy[17] especially for determination of hybridization type at the methylene carbon atom in —CO—CH_2— grouping. From spectra of two derivatives containing strong electron-acceptor (NO_2) or donor ($N(CH_3)_2$) substituents it follows that the compounds exist in ketoform, because resonance signals of carbon atom in CH_2 group are found in strong field corresponding to its sp^3-hybridized state, *i.e.* at 62·8 and 64·3 ppm, respectively, relative to tetramethylsilane. Individual signals of the ^{13}C NMR spectra were assigned on the basis of measurements of singlet frequency off-resonance decoupling spectrum (giving multiplicities of the individual signals, *i.e.* number of directly bound protons at individual carbon atoms) and noise decoupling spectrum (giving number and chemical shifts of the individual carbon atoms).

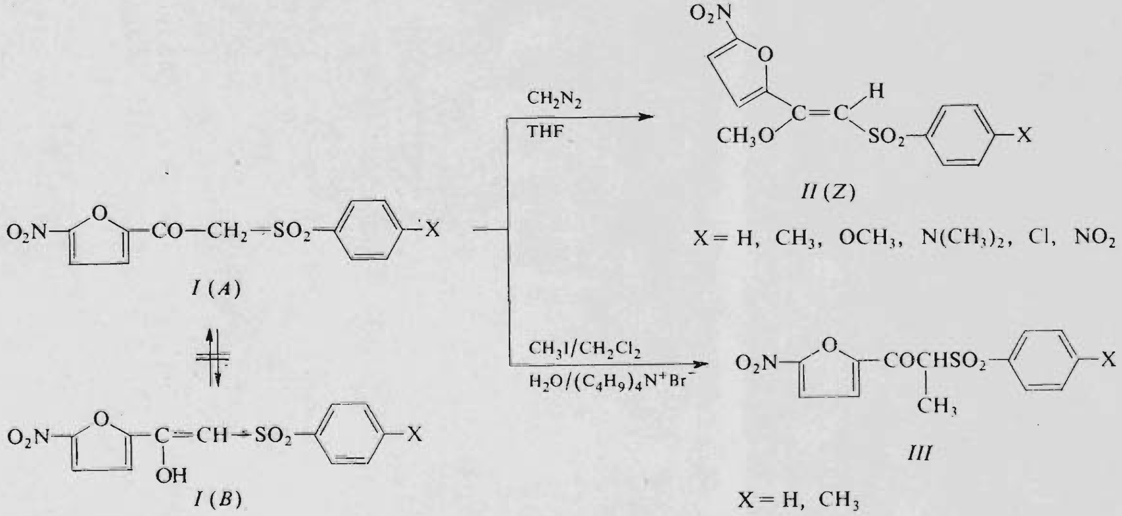
The used spectral methods failed to prove the existence of enolform of β-ketosulphones of 5-nitrofuran series. These compounds give no analytical reactions typical of enols (with $FeCl_3$ or bromine), too. The enolform also could not be detected by reactions of the sulphones *I* with trimethylsilyl chloride or hexamethyldisilazane[18].

For explanation of mechanism of formation of O-methyl derivatives in reactions of the sulphones with CH_2N_2 there exist two possibilities: (*i*) splitting off of acidic hydrogen by the ylide carbon atom of diazomethane to give a methyl cation which would attack the negatively charged oxygen atom of the ambident anion of the sulphone, and (*ii*) through intermediate formation if unstable oxirane. The experiments carried out in the presence of pyridine or furan did not confirm the formation of $CH_3^{(+)}$ cation (no methylation products were detected). The second possibility *via* oxirane derivative seems more probable, although the oxirane could not be isolated. Its formation is supported by the amino alcohol derivative identified by means of ^1H NMR spectra of raw reaction products formed in the presence of dimethylamine. Formation of these derivatives is only possible by reaction of oxiranes with dimethylamine[19]. With respect to this fact, formation of the O-methylated derivatives of β-ketosulphones can be explained by formation of unstable oxirane derivative followed by sigmatropic shift (Scheme 2).

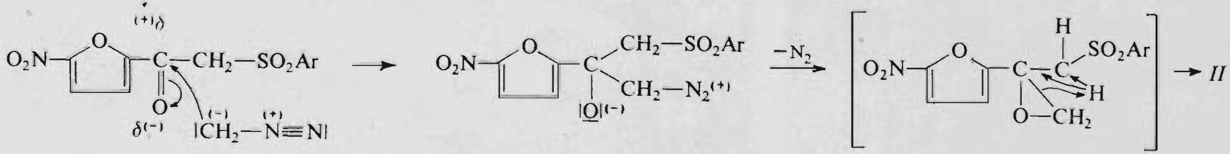
TABLE I

Properties of the unsaturated sulphones *IIa*—*IIf*

Compound X	Formula (mol. mass)	M.p., °C (yield, %)	Calculated/Found		
			% C	% H	% N
IIa H	$C_{13}H_{11}NO_6S$ (309·3)	137—138 (36)	50·58 50·61	3·58 3·63	4·53 4·28
IIf CH_3	$C_{14}H_{13}NO_6S$ (323·3)	145—146 (40)	52·00 51·75	4·05 3·98	4·33 4·27
IIc CH_3O	$C_{14}H_{13}NO_7S$ (339·3)	151—153 (42)	49·55 49·18	3·86 3·74	4·12 4·07
IId $N(CH_3)_2$	$C_{15}H_{16}N_2O_6S$ (352·4)	138—139 (38)	51·13 51·37	4·58 4·80	7·95 7·66
IIe Cl	$C_{13}H_{10}ClNO_6S$ (343·1)	156—158 (45)	45·50 45·22	2·94 2·76	4·08 3·93
IIf NO_2	$C_{13}H_{10}N_2O_6S$ (354·3)	142—143 (40)	44·07 44·21	2·84 2·90	7·91 7·75



SCHEME 1



SCHEME 2

Tables I and II give results of elemental analyses and spectral characteristics of the methoxy derivatives obtained. From ^{1}H NMR analysis of raw reaction mixtures it was found that one isomer only is present and has *Z* configuration which follows from additive increments[20] (Scheme 1). The Z configuration follows from comparison of the calculated and the measured chemical shifts of the ethylene protons of these substances: for the basic sulphone *IIa* calculated δ(C=C—H) for *Z* 6·16 ppm, for *E* 5·66 ppm; the values found for sulphones *IIa*–*IIf* 6·65–6·71 ppm. Chemical shifts of methyl protons in OCH_3 group are observed as singlets in the region 2·86 to 3·92 ppm.

UV spectra of the sulphones *II* contain four absorption bands in the regions 209 to 212 nm, 221–226 nm, 236–243 nm, and 301 nm. The intensive band with constant position at 301 nm corresponds to electronic transitions in 5-nitrofuran nucleus (λ_{max} of 5-nitrofuran 302 nm, $\log \varepsilon = 3{\cdot}95$) (ref.[21]) and indicates that this nucleus is deviated from the plane of ethylene bond, which is similar to other trisubstituted ethylenes of 5-nitrofuran series[1–7] containing two bulky substituents at the same carbon atom.

The C-methyl derivatives *III* which served as standards were synthetized by alkylation of the sulphones *IIa* and *IIb* with methyl iodide under the conditions of extrac-

TABLE II

Spectral data of the unsaturated sulphones *IIa*—*IIf*

Compound	λ_{max}, nm (log ε)				$\nu_s(CH_3)$ cm^{-1}	$\nu_{as}(CH_3)$ cm^{-1}	ν(C=C) cm^{-1}	OCH_3 δ(ppm)	$_s$C=CH δ(ppm)
IIa H	211 (4·20)	221 (4·25)	238 (4·21)	301 (4·12)	2 945	2 855	1 618	3·86	6·70
IIb CH_3	209 (4·27)	222 (4·20)	240 (4·19)	301 (4·19)	2 944	2 853	1 623	3·89	6·68
IIc OCH_3	212 (4·25)	225 (4·23)	238 (4·15)	301 (4·20)	2 944	2 860	1 624	3·90	6·65
IId $N(CH_3)_2$	210 (4·29)	223 (4·18)	236 (4·15)	301[a] (4·39)	2 940	2 860	1 615	3·92	6·64
IIe Cl	211 (4·33)	226 (4·42)	243 (4·20)	301 (4·20)	2 945	2 852	1 620	3·88	6·71
IIf NO_2	211 (4·25)	225 (4·30)	240 (4·18)	301 (4·20)	2 946	2 850	1 622	3·89	6·72

[a] λ_{max} 341 nm (log ε 4·10), λ_{max} 381 (log ε 4·00)

tion alkylation with the use of tetrabutylamonium bromide as catalyst. Due to resinification of 5-nitrofuran derivatives in basic media, the yields of the products did not exceed 35%.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus. The ^{1}H-NMR spectra were measured with a Tesla BS 487 B 80 MHz apparatus in deuterated acetone with hexamethyldisiloxane as internal standard (Table II gives the ppm values related to tetramethylsilane). The IR spectra of the starting saturated sulphones *I* were measured with a UR-20 apparatus (Zeiss, Jena). The spectrometer was calibrated with a polystyrene foil; 0·01 to 1 mm NaCl cells were used. The IR spectra in long-wave region were measured with a Grupp-Parson IS 3 Fourier transform far Spectrometer in polyethylene at 25°C (the spectrum of 2-(4-nitro-2-furyl)-2-oxoethyl phenyl sulphone also at —183°C). The IR spectra of the sulphones *II—IIf* were only measured in $CHCl_3$ (saturated solutions); UV spectra of the same compounds were measured with a spectrophotometer UV VIS (Zeiss, Jena) in dioxane in 1 cm cell at the concentration $2·5 . 10^{-5}$ mol l^{-1}; accuracy of readings was ± 1 nm. The ^{13}C-NMR spectra were measured with a JEOL FX-60 spectrometer at 15·03 Hz frequency in dimethyl sulphoxide in 10 mm cells. The chemical shifts were related to tetramethylsilane whose signal in dimethyl sulphoxide was adjusted at 40·4 ppm.

1-Methoxy-1-(5-nitro-2-furyl)-2-(4-X-phenylsulphonyl)ethylenes *IIa—IIf*

Solution of diazomethane (3 to 5 fold molar excess) in ether was gradually added to solution of 0·003 mol 2-(5-nitro-2-furyl)-2-oxoethyl 4-X-phenyl sulphone in 30—50 ml tetrahydrofuran (*IIa—IId*) or dioxane (*IIe, IIf*) with stirring at 0—5°C. The mixture was left to stand at the mentioned temperature 3—5 days. The solvents were distilled off in vacuum, and the solid residue was purified by column chromatography (neutral Al_2O_3, activity III according to Brockmann; benzene–ethyl acetate 3 : 1, or 4 : 1 or 7 : 1) and by crystallization from ethanol.

1-Methyl-2-(5-nitro-2-furyl)-2-oxoethyl 4-X-phenyl Sulphones *III*

Solution of 0·01 mol β-ketosulphone and 0·02 mol (2·84 g) methyl iodide in 10 ml dichloromethane was stirred and treated with 0·1 mol (4·22 g) tetrabutylamonium bromide and 0·02 mol (0·8 g) NaOH in 10 ml water. The stirring was continued 30—50 min until neutral reaction (litmus). Then the organic layer was separated, dried with anhydrous Na_2SO_4, and the solvent was distilled off in vacuum. The solid portion was extracted with ether continually 12 h. After removing ether by distillation the raw C-alkyl derivative was crystallized from a suitable solvent. In the described way we prepared the following substances:

1-*Methyl*-2-(5-*nitro*-2-*furyl*)-2-*oxoethyl phenyl sulphone* (309·3), m.p. 159—161°C (ethanol). For $C_{13}H_{11}NO_6S$ calculated: 50·48% C, 3·58% H, 4·53% N; found: 50·03% C, 3·24% H, 4·17% N. IR spectrum: $\nu_{as}(CH_3)$ 2 955 cm^{-1}, $\nu_s(CH_3)$ 2 860 cm^{-1}, ν(C=O) 1 688 cm^{-1}, $\nu_{as}(CH_3)$ 1 455 cm^{-1}, $\nu_s(CH_3)$ 1 360 cm^{-1}. UV spectrum (λ_{max} (log ε)): 227 nm (4·32), 309 nm (4·12). ^{1}H-NMR spectrum (δ(ppm)): CH_3 d 1·45 (J = 6 Hz), C—H q 5·42 (J = 7 Hz).

1-*Methyl*-2-(5-*nitro*-2-*furyl*)-2-*oxoethyl* 4-*methylphenyl sulphone*, m.p. 160—162°C (ethanol). For $C_{14}H_{13}NO_6S$ (323·3) calculated: 52·00% C, 4·05% H, 4·33% N; found: 51·52% C, 3·68% H, 3·97% N. IR spectrum: $\nu_{a_2}(CH_3)$ 2 952 cm^{-1}, $\nu_s(CH_3)$ 2 863 cm^{-1}, ν(C=O) 1 683 cm^{-1}, $\nu_{as}(CH_3)$ 1 452 cm^{-1}, $\nu_s(CH_3)$ 1 358 cm^{-1}. UV spectrum (λ_{max} (log ε)): 220 nm (4·18), 309 nm (4·12). ^{1}H-NMR spectrum (δ(ppm)): CH_3 d 1·46 (J = 6 Hz), C—H q 5·52 (J = 7 Hz).

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Translated by J. Panchartek.