PREPARATION AND STUDY OF GEOMETRIC ISOMERS OF METHYL 2-NITRO-3-[2-(5-X-FURYL)]ACRYLATES*

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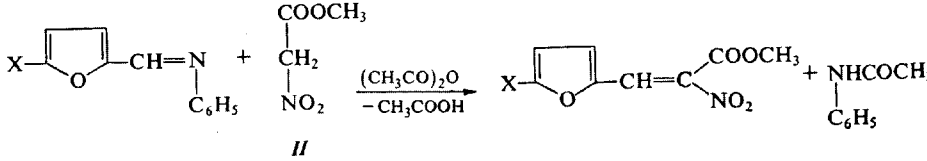
Methyl 2-nitro-3-[2-(5-X-furyl)]acrylates (X = H, Br, I, CH_3, $COOCH_3$, NO_2) were prepared by condensation of methyl nitroacetate with azomethines of 5-substituted 2-furancarbaldehydes or from 5-substituted 2-furancarbaldehydes by a modified Knoevenagel condensation catalysed with $TiCl_4$ and pyridine in tetrahydrofuran. Crystallisation from aprotic non-polar solvents afforded in all cases one of the isomers in a pure state. The geometric isomers of the synthesized compounds were studied by IR, UV and ^{1}H-NMR spectroscopy.

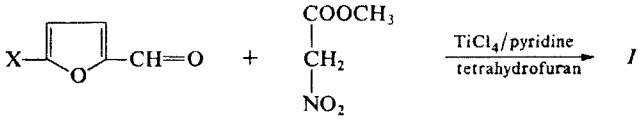
Esters of 2-nitro-3-[2-(5-X-furyl)]acrylic acids (*I*) are of interest as starting compounds in further syntheses and also as possible intermediates in the nitration of esters of furylacrylic acids. Several methods of preparation of α,β-unsaturated α-nitro esters are described in the literature[1-6]. Of furan derivatives, ethyl 2-nitro-3-(2-furyl)-acrylate was prepared by a modified Knoevenagel condensation of furancarbaldehyde with ethyl nitroacetate in the presence of $TiCl_4$ and pyridine in tetrahydrofuran[6].

We prepared esters of 2-nitro-3-[2-(5-X-furyl)]acrylic acid, where X = H, Br, I, CH_3, $COOCH_3$ and NO_2, either by condensation of methyl nitroacetate with azomethines of 5-substituted 2-furancarbaldehydes (Scheme 1) or by a modified Knoevenagel reaction (Scheme 2). Anilides of 5-substituted 2-furancarbaldehydes react with methyl nitroacetate at 40–50°C. The reaction was carried out using a 10%



SCHEME 1

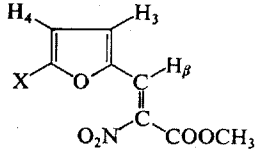
* Part LXXII in the series Furan Derivatives; Part LXXI: This Journal 41, 1692 (1976).



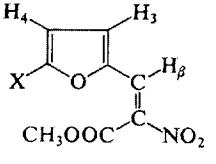
SCHEME 2

molar excess of azomethine in a tenfold excess of acetic anhydride. The desired 2-nitro-3-[2-(5-X-furyl)]acrylates were obtained in 20–50% yields. Application of the Lehnert modification of the Knoevenagel condensation[6] resulted in substantially higher yields of the reaction. The synthesized compounds, their physical constants and analyses are given in Table I.

According to the IR and ^{1}H-NMR spectra (Table II and III), the products obtained by the both methods are identical and they represent mixtures of *Z* and *E* isomers. Crystallisation of these mixtures from aprotic non-polar solvents afforded one of the isomers in a pure state. Infrared and ^{1}H-NMR spectra have shown that the crystallisation afforded *Z*-isomer in the case of the compounds *I* with X = H, Br, I, CH_3, $COOCH_3$, whereas when X = NO_2 the obtained isomer had *E*-configuration. Compounds *I* with the *Z*-configuration are of interest because the NO_2 group is *cis* to the furan ring whereas in the hitherto prepared 2-nitrovinyl-1-[2-(5-X-furyl)]-derivatives the nitro group was always in the *trans*-position[8]. Literature data[9] show that the *Z*-arrangement is possible only when the furan nucleus and the nitro group overlap each other.



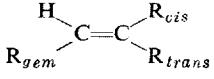
I(*Z*), X = H, Br, I, CH_3



I(*E*), X = NO_2

The configuration of the prepared compounds was determined from their infrared (Table II) and ^{1}H-NMR spectra (Table III) according to the literature[3,10,11]. The two geometric isomers *Z* and *E* in compounds *I* were distinguished on the basis of stretching vibrations $\nu_s(NO_2)$ and $\nu_{as}(NO_2)$ of the α-nitro group. The bands due to the stretching vibrations $\nu_s(NO_2)$ and $\nu_{as}(NO_2)$ of α-nitro group in the *E*-isomer (X = NO_2) with the *trans*-β-nitrovinylfuran structure are situated at lower wavenumbers than in the *Z* isomers (X = H, Br, I, CH_3, $COOCH_3$) with *cis*-β-nitrovinylfuran structure. The ratio of intensities of these absorption bands in the two isomers is reversed. The IR spectral data of the geometric isomers are given in Table II.

The obtained data are compared with the values published by Watarai and collaborators[10] for analogous *Z* and *E* isomers of ethyl 2-nitro-3-phenylacrylate. The *Z* and *E* isomers were also distinguished on the basis of different chemical shifts of the β-carbon protons and the methoxy group in the ^{1}H-NMR spectra[3]. The signal of the vinyl proton H_β in the spectra of the *E* isomers is situated at lower fields than in the spectra of *Z* isomers. This considerable shift of the vinyl proton signal is caused by a greater magnetic anisotropy of the nitro group as compared with the carbonyl group. Chemical shifts of the olefinic protons in the *E* and *Z* isomers were calculated using additive increments for substituents R in a *gem*, *cis* and *trans* position relative to the proton[12].



$$\delta_{CH=C} = 5{\cdot}25 + Z_{gem} + Z_{cis} + Z_{trans}$$

The experimental and calculated values differ by about 1 p.p.m.; this indicates a deviation of the system from planarity. The size of all of the three groups leads necessarily to the conclusion that both *E* and *Z* isomers of the obtained compounds *I* are not planar. This is confirmed also by stretching vibrations $\nu_{(C=C)}$ (Table II), UV spectra (Table II) and ^{1}H-NMR spectra (Table III).

TABLE I

Methyl 2-Nitro-3-[2-(5-X-furyl)]acrylates *I*

X	Formula (mol. wt.)	M.p., °C yield, % (A; B)[a]	Calculated/Found		
			% N	% C	% H
H	$C_8H_7NO_5$	*Z* 70—72	7·10	48·70	3·55
	(197)	(45; 88)	6·97	48·85	3·53
Br	$C_8H_6BrNO_5$	*Z* 95—97	4·34	34·78	2·17
	(275—277)	(39; 85)	4·20	34·85	2·10
I	$C_8H_6INO_5$	*Z* 86—90	4·33	29·73	1·85
	(323)	(30; 65)	4·07	29·88	1·97
CH_3	$C_9H_9NO_5$	*Z* 95—97	6·63	51·18	4·27
	(211)	(30; 74)	6·40	51·20	4·32
$COOCH_3$	$C_{10}H_9NO_7$	*Z* 125—127	5·49	47·06	3·53
	(255,)	(—; 70)	5·22	47·15	3·25
NO_2	$C_8H_6N_2O_7$	*E* 101—103	11·57	39·68	2·50
	(242)	(30; 70)	11·41	39·74	2·40

[a] A and B are yields of the reactions according to Scheme 1, and Scheme 2, respectively.

The biological activity of the synthesized group of compounds was hitherto not investigated. Benzene analogues, *i.e.* esters of α-nitrocinnamic acids, were shown to exhibit cancerostatic activity which is ascribed to the activity of the double bond[13]. Antibacterial screening of selected compounds *I* has shown that methyl 2-nitro-3-[2-(5-nitrofuryl)]acrylate exhibits an unusually high activity against a resistent kind of *Pseudomonas aeruginosa*. The other derivatives showed no remarkable activity against the microorganisms used in the screening (Table IV).

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. IR spectral measurements were performed on a UR-20 Zeiss Jena spectrophotometer, ^{1}H-NMR spectra were taken on a Tesla BS 487C 80 MHz spectrometer in $CDCl_3$ at 25°C using tetramethylsilane as the internal standard. The mass spectra were measured on a MS 902S AEI instrument.

The azomethines were prepared using the method described in ref.[14] and their physical constants agreed with those given in the literature[15–17]. Methyl nitroacetate was prepared according

TABLE II

Infrared (wavenumbers in cm^{-1}) and Ultraviolet (wavelengths in nm) Spectral Data for the Compounds *I*

X		$\nu_s(NO_2)$		$\nu_{as}(NO_2)$		ν(C=C)	λ_{max}	log ε
		$\tilde{\nu}$	ε	$\tilde{\nu}$	ε			
H	*Z*	1 370	176	1 549	365	1 652	313	4·204
	E	1 325		1 540		1 653		
Br	*Z*	1 375	140	1 549	512	1 659	321	4·315
	E	1 322		1 540		1 650		
I	*Z*	1 375	113	1 549	299	1 648	333	4·214
	E	1 323		1 541		1 648		
CH_3	*Z*	1 373	176	1 549	395	1 645	325	4·311
	E	1 321		1 540		1 645		
$COOCH_3$	*Z*	1 375	170	1 552	390	1 655	320	4·371
	E	1 330		1 542		1 657		
NO_2	*Z*	1 375		1 555		1 652	355	4·313
	E	1 330	811	1 540	300	1 653		
		1 348	674					
[a]	*Z*	1 370	170	1 538	700	—	—	—
	E	1 330	420	1 530	400			

[a] Ref.[10] for $C_6H_5CH{=}C(NO_2)COOC_2H_5$.

TABLE III

^{1}H-NMR Data for the Compounds *I*

(Chemical shifts in values δ (p.p.m.); calculated values[1,2] $\delta_{CH=C}$ for *E* 8·75 p.p.m., for *Z* 8·10 p.p.m.).

X	Isomer	Hβ	ΔHβ	OCH_3	ΔOCH_3
H	*Z*	7·25	0·50	3·81	0·06
	E	7·75		3·87	
Br	*Z*	7·20	0·55	3·81	0·09
	E	7·75		3·90	
I	*Z*	7·20	0·50	3·81	0·14
	E	7·70		3·95	
CH_3	*Z*	7·22	0·53	3·80	0·10
	E	7·75		3·90	
$COOCH_3$	*Z*	7·37	0·40	3·86	0·14
	E	7·77		4·00	
NO_2	*Z*	7·28	0·49	3·86	0·15
	E	7·77		4·01	

TABLE IV

Antibacterial Activity of the Compounds *I*

The tests No 1—5 were carried out by standard methods using solid media, 200, 50, 12, 5 μg/ml; tests No 6—9 were performed in liquid media, 800, 200, 50 μg/ml.

Organism	X = H	X = Br	X = NO_2
1 *Staphylococcus pyogenes*	50	200	12·5
2 *Bacillus subtilis*	200	—	12·5
3 *Escherichia coli*	—	—	12·5
4 *Pseudomonas aeruginosa*	—	—	50
5 *Candida pseudotropicalis*	200	200	12·5
6 *Euglena gracilis* (min. IC)	200	50	200
7 *E. gracilis*[a]	50	12·5	50
8 *Trichomonas foetus*	200	200	50
9 *Trypanozoma cruzi*	200	200	50

[a] Concentration, indicating the highest percentage of mutants.

to Matthews and Kubler[18], b.p. 50–55°C/1 Torr (ref.[18] reports b.p. 46–47°C/0·8 Torr, n_D^{20} 1·426).

Methyl 2-Nitro-3-[2-(5-X-furyl)]acrylates *I* (Scheme 1)

A mixture of the corresponding azomethine (0·11 mol) and methyl nitroacetate (0·10 mol) in acetic anhydride (50 ml) was kept at 40–50°C for 10 hours. The compounds *I* were isolated using one of the following methods: *A*) The reaction mixture was poured into 1 000 ml of warm (80°C) water, the aqueous layer was decanted and the residue dissolved in tetrachloromethane (100 ml). The solution was washed rapidly with water (50 ml), dried over $MgSO_4$, taken down and the residue was crystallised from heptane. *B*) The acetic anhydride and acetic acid were removed from the reaction mixture by evaporation *in vacuo* on a rotatory evaporater and the residue was dissolved in tetrachloromethane. Chromatography on a silica gel column afforded the compound *I*, the yields being 10–20% higher than in the method *A*. The yields and melting points are given in Table I. Crystallisation of the compounds *I* from heptane afforded in all cases one of the stereoisomers in the pure state. The mother liquors contained a mixture of *Z* and *E* isomers.

Methyl 2-Nitro-3-[2-(5-X-furyl)]acrylates *I* (Scheme 2)

Titanium tetrachloride (0·1 mol) in tetrachloromethane (50 ml) was added to dry tetrahydrofuran (250 ml) at −5°C under efficient stirring. The arising yellow flaky precipitate was stirred for 20 minutes. A solution of 5-X-furan-2-carbaldehyde (0·05 mol) in tetrachloromethane (20 ml), followed by methyl nitroacetate (0·05 mol), was added and the mixture was stirred for 30 minutes. Pyridine (0·2 mol) was added to the stirred mixture at 0°C and the stirring was continued for 24 hours. The mixture was diluted with water (25 ml) and ether (400 ml), the aqueous layer was washed twice with ether (100 ml) and the combined ethereal extracts were dried over magnesium sulphate and taken down. The residue was distilled or chromatographed on a silica gel column using aprotic non-polar solvents as eluants. Crystallisation of the mixture of *Z* and *E* isomers from hexane, heptane or light petroleum afforded one of the isomers in the pure state. The yields and melting points are given in Table I.

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