NUCLEOPHILIC VINYLIC SUBSTITUTION ON α-TOSYLOXYMETHYLENE LACTONES

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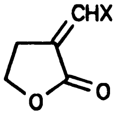
Sodium salt of 3-hydroxymethylenetetrahydro-2*H*-pyran-2-one (*V*), obtained by Claisen condensation of δ-valerolactone with ethyl formate, was converted into its sulfonates and carboxylates *IV*, *VII* – *X*, which were obtained either as pure *E*-isomers or as mixtures of *E*- and *Z*-isomers; the mixtures were chromatographically separated. Substitution reaction of α-tosyloxymethylene lactones *II*, *III* and *IV* with aromatic thiols, azide anion, secondary amines and sodium enolates *XI*, *XII* and *V* was studied. The stereochemical outcome of this substitution is discussed from the viewpoint of mechanism of nucleophilic vinylic substitution (S_NV).

α-Methylene lactones bearing an easily leaving group at the exocyclic double bond were already studied in connection with their potential antitumor effects[1,2] which are ascribed to the sensitivity of the double bond to nucleophilic attack. The easy accessibility of pure geometric isomers of α-tosyloxymethylene derivatives of butyrolactone[3], γ-valerolactone[4] and *trans*-hexahydro-2(3*H*)-benzofuranone[5] turned our attention to stereochemical studies of nucleophilic vinylic substitution (S_NV) on such substrates. The substitution on 3-(4-toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanone (*I*) was already investigated[6] by us; in our present paper we have studied this reaction using 3-(4-toluenesulfonyloxymethylene)-5-methyldihydro-2(3*H*)-furanone (*II*), 3-(4-toluenesulfonyloxymethylene)-*trans*-hexahydro-2(3*H*)-benzofuranone (*III*) and 3-(4-toluenesulfonyloxymethylene)tetrahydro-2*H*-pyran-2-one (*IV*). Similar to the previous cases[3 – 6], the prepared *E*- and *Z*-isomers of these derivatives can be easily distinguished by ^{1}H NMR spectra in which the olefinic proton signal of the *E*-isomers is shifted downfield due to magnetic anisotropy of conjugated bonds in the lactone system.

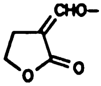
EXPERIMENTAL

The temperature data are uncorrected. The melting points were determined on a Kofler block. IR spectra ($\tilde{\nu}$, cm^{-1}) were measured on a Pye Unicam SP 1000 instrument, ^{1}H NMR and ^{13}C NMR spectra (δ, ppm; *J*, Hz) on Tesla 567 (100 MHz) and Bruker AM 400 (400 MHz) instruments. The chemical shifts were referenced to tetramethylsilane as internal standard. For ^{1}H NMR spectra of *XIIIg* with lanthanide shift reagents (LSR) we used Eu(fod)$_3$ (H(fod) = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione) and

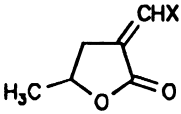


I, $X = OSO_2C_6H_4\text{-}p\text{-}CH_3$

XVII, $X =$



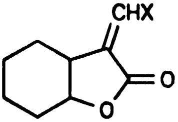
XIX, $X = N_3$



II, $X = OSO_2C_6H_4\text{-}p\text{-}CH_3$

XI, $X = ONa$

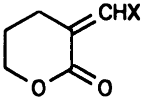
XIIIa – *XIIIg*



III, $X = OSO_2C_6H_4\text{-}p\text{-}CH_3$

XII, $X = ONa$

XIVa – *XIVf*, *XIVh*



IV, $X = OSO_2C_6H_4\text{-}p\text{-}CH_3$

V, $X = ONa$

VI, $X = OH$

VII, $X = OSO_2C_6H_5$

VIII, $X = OSO_2CH_3$

IX, $X = OCOCH_3$

X, $X = OCOC_6H_5$

XVa – *XVf*, *XVi*

In formulae *XIII*, *XIV* and *XV* :

a, $X = SC_6H_4\text{-}p\text{-}CH_3$

b, $X = SC_{10}H_7$

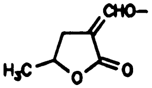
c, $X = N_3$

d, X = 1-piperidino

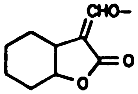
e, X = 1-pyrrolidino

f, X = 1-morfolino

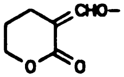
g, $X =$

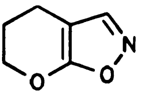


h, $X =$



i, $X =$





XVI

$Eu(tfc)_3$ (H(tfc) = 3-(trifluoromethylhydroxymethylene)-(+)-camphor). The shift parameter S was calculated as the slope of relationship

$$\delta_i = \delta + S\,[\mathrm{LSR}]/[XIIIg],$$

where δ is chemical shift of the given proton in the absence of LSR and δ_i is chemical shift of the same proton at the molar ratio [LSR]/[*XIIIg*].

The attempted separation of diastereoisomeric ethers *XIII* by HPLC was carried out on a 200 × 4 mm column packed with Silasorb 600; the samples were eluted with dichloromethane and a dichloromethane–heptane mixture (3 : 1) and detected by UV at 254 nm. Thin-layer chromatography was performed on SiO_2 (Silufol UV 254 Kavalier, Votice) in chloroform or diethyl ether. Flash chromatography was carried out on silica gel 40 – 100 μm (Lachema, Brno). For the photochemical preparation of *E,Z*-ethers we used a low-pressure Original Hanau TNN-15 mercury lamp. Tosylates *II* and *III* were prepared according to refs[4,5], ethers *XVII* according to ref.[6].

^{13}C NMR spectral data of compounds *IV*, *VII* – *X* are given in Table I, elemental analyses for compounds *XIII*, *XIV* and *XV* in Table II and physicochemical characteristics in Tables III – V.

Sodium 3-(Hydroxymethylene)tetrahydro-2*H*-pyran-2-one (*V*)

A solution of tetrahydro-2*H*-pyran-2-one (10 g, 0.1 mol) and ethyl formate (9 ml, 0.11 mol) in anhydrous diethyl ether (100 ml) was added dropwise to a suspension of sodium (2.3 g, 0.1 mol) in diethyl ether (100 ml). After stirring at 0 – 5 °C for 6 h, the yellow solid was filtered, washed with diethyl ether and dried in vacuo; yield 93% of sodium salt *V*. IR spectrum (KBr): 665, 760, 1 540, 1 640, 1 720. ^1H NMR spectrum (D_2O): 8.76 t, 1 H, J = 1.3 (=CH); 4.20 t, 2 H, J = 5 (CH_2O); 2.29 dt, 2 H, J = 6.3 and 1.3 (CH_2C=); 1.82 m, 2 H (CH_2CH_2O).

3-(Hydroxymethylene)tetrahydro-2*H*-pyran-2-one (*VI*)

Sodium salt *V* (3.0 g, 0.02 mol) was dissolved with stirring in glacial acetic acid (20 ml). After stirring for 10 h, the excess acid was evaporated in vacuo and the solid residue was extracted with chloroform (4 × 30 ml). The chloroform extracts were dried over anhydrous sodium carbonate, filtered and concentra-

TABLE I
^{13}C NMR spectra of compounds *IV*, *VII* – *X* (0.5 M solutions; signals of atoms of methylene lactone skeleton, δ, ppm)

Compound	C-2	C-3	C-4	C-5	C-6	C-7
(*E*)-*IV*	164.69	114.71	21.50	21.17	69.02	146.10
(*Z*)-*IV*	161.52	113.18	24.41	22.73	68.72	141.89
(*E*)-*VII*	164.62	114.64	21.40	21.20	68.98	146.18
(*Z*)-*VII*	161.45	113.37	24.41	22.70	68.69	141.66
(*E*)-*VIII*	165.63	112.21	21.88	21.69	68.87	145.69
(*Z*)-*VIII*	162.91	109.39	24.87	23.14	68.81	142.71
(*E*)-*IX*	164.81	114.30	21.46	21.20	69.13	145.81
(*Z*)-*IX*	162.80	113.93	24.38	22.73	68.80	141.36
(*E*)-*X*	165.96	111.34	21.73	21.42	69.17	145.77
(*Z*)-*X*	162.98	109.13	24.67	23.11	68.91	142.67

TABLE II
Analytical data for compounds *XIII*, *XIV* and *XV*

Compound	Formula	M. w.	Calculated/Found		
			% C	% H	% N
XIIIa	$C_{13}H_{14}O_2S$	234.4	66.64	6.02	–
E			66.81	6.24	–
Z			66.78	6.18	–
XIIIb	$C_{16}H_{14}O_2S$	270.3	71.08	5.22	–
E			71.21	5.31	–
Z			71.30	5.15	–
XIIIc	$C_6H_7N_3O_2$	153.2	47.05	4.61	27.44
E			47.16	4.58	27.32
Z			47.22	4.46	27.51
XIIId	$C_{11}H_{17}NO_2$	195.3	67.66	8.78	7.18
			67.48	8.92	6.97
XIIIe	$C_{10}H_{15}NO_2$	181.2	66.27	8.34	7.73
			66.18	8.42	7.91
XIIIf	$C_{10}H_{15}NO_3$	197.2	60.89	7.67	7.10
			60.67	7.81	7.23
XIIIg	$C_{12}H_{14}O_5$	238.2	60.50	5.92	–
E			60.64	6.07	–
Z			60.72	5.83	–
XIVa	$C_{16}H_{18}O_2S$	274.4	70.04	6.61	–
E			70.27	6.73	–
Z			70.19	6.49	–
XIVb	$C_{19}H_{18}O_2S$	310.4	73.52	5.85	–
E			73.46	5.68	–
Z			73.78	5.73	–
XIVc	$C_9H_{11}N_3O_2$	193.2	55.94	5.74	21.75
E			56.06	5.90	21.92
Z			55.62	5.66	21.99
XIVd	$C_{14}H_{21}NO_2$	235.3	71.45	9.00	5.95
			71.63	8.87	6.07
XIVe	$C_{13}H_{19}NO_2$	221.3	70.55	8.65	6.33
			70.72	8.48	6.33
XIVf	$C_{13}H_{19}NO_3$	237.3	65.80	8.07	5.90
			66.07	8.15	5.72

TABLE II
(*Continued*)

Compound	Formula	M. w.	Calculated/Found		
			% C	% H	% N
XIVh	$C_{18}H_{22}O_5$	318.4	67.91	6.97	–
E			68.11	6.74	–
Z			68.19	6.81	–
XVa	$C_{13}H_{14}O_2S$	234.3	66.64	6.02	–
E			66.53	5.87	–
Z			66.86	5.94	–
XVb	$C_{16}H_{14}O_2S$	270.3	71.08	5.22	–
E			70.87	5.36	–
Z			71.26	5.18	–
XVc	$C_6H_7N_3O_2$	153.2	47.05	4.61	27.44
			47.31	4.56	27.26
XVd	$C_{11}H_{17}NO_2$	195.3	67.66	8.78	7.18
			67.42	8.56	6.99
XVe	$C_{10}H_{15}NO_2$	181.2	66.27	8.34	7.73
			66.43	8.50	7.91
XVf	$C_{10}H_{15}NO_3$	197.2	60.89	7.67	7.10
			61.03	7.48	6.95
XVi	$C_{12}H_{14}O_5$	238.2	60.50	5.92	–
E			60.72	5.81	–
Z			60.62	6.03	–

ted in vacuo to give an oil which crystallized (2.4 g, 94%), m.p. 80 – 87 °C (benzene). IR spectrum (KBr): 775, 1 550, 1 610, 1 670, 1 720, 2 700. IR spectrum ($CHBr_3$): 1 610, 1 650, 1 710. ^1H NMR spectrum ($CDCl_3$): 7.15 t, 1 H, J = 1.1 (=CH); 4.33 t, 2 H, J = 5.3 (CH_2O); 2.43 dt, 2 H, J = 1.1 and 6.0 (CH_2C=); 1.90 m, 2 H (CH_2CH_2O). For $C_6H_8O_3$ (128.1) calculated: 56.24% C, 6.29% H; found: 56.48% C, 6.50% H.

(*E*)-3-Hydroxymethylenetetrahydro-2*H*-pyran-2-one Sulfonates and Carboxylates (*E*)-*IV* and (*E*)-*VII* – (*E*)-*X*

A solution of sodium salt *V* (3.0 g, 0.02 mol) and triethylamine (2.0 g, 0.02 mol) in tetrahydrofuran–water (2 : 1; 90 ml) was added during 45 min to a solution of the corresponding sulfonyl or acyl chloride (0.02 mol) in the same solvent system (90 ml). The mixture was stirred at room temperature for 24 h and then the tetrahydrofuran was evaporated in vacuo. Solid products were filtered, washed with water, dried and crystallized, liquids were extracted with chloroform (5 × 20 ml) from the aqueous residue, the extracts were

TABLE III
Physicochemical characteristics of α-methylene-γ-valerolactone derivatives *XIIIa* – *XIIIg*

Compound	Yield, %	M. p., °C Solvent	^{1}H NMR				
			CH_3[a]	$CH_2C=$[b]	CHO[c]	=CH[d]	Other signals
(*E*)-*XIIIa*	70	51 – 53 cyclohexane	1.38(6.1)	3.06, 2.54	4.67	7.58(2.8)	7.84, 7.42 AA'BB'q, 4 H, *J* = 8.5 (H-arom.); 2.49 s, 3 H (CH_3)
(*Z*)-*XIIIa*	72	95 – 103 PE[e]–benzene	1.42(6.3)	3.10, 2.54	4.70	7.03(2.1)	7.38, 7.17 AA'BB'q, 4 H , *J* = 8.5 (H-arom.); 2.36 s, 3 H (CH_3)
(*E*)-*XIIIb*	71	79 – 82 PE[e]–ethanol	1.47(6.1)	3.07, 2.48	4.76	7.76(2.8)	7.30 – 7.95 m, 7 H (H-arom.)
(*Z*)-*XIIIb*	70	99 – 107 PE[e]–ethanol	1.43(6.3)	3.12, 2.57	4.72	7.15(2.2)	7.38 – 8.05 m, 7 H (H-arom.)
(*E*)-*XIIIc*	82	59 – 62 diethyl ether	1.42(6.3)	3.03, 2.41	4.69	7.38(2.8)	
(*Z*)-*XIIIc*	79	44 – 46 cyclohexane	1.41(6.3)	3.10, 2.55	4.69	6.74(2.1)	
(*E*)-*XIIId*	90	48 – 49 hexane	1.31(6.3)	3.04, 2.51	4.50	7.07(1.6)	3.17 – 3.42 m, 4 H (2 × CH_2N); 1.37 – 1.75 m, 6 H (3 × CH_2)
(*Z*)-*XIIId*[f]						6.43(1.1)	
(*E*)-*XIIIe*	92	55 – 57 hexane	1.30(6.1)	3.25, 2.62	4.48	7.29(1.6)	3.32 – 3.56 m, 4 H (2 × CH_2N); 1.72 – 1.96 m, 4 H (2 × CH_2)
(*Z*)-*XIIIe*[f]						6.58[g]	
(*E*)-*XIIIf*	90	79 – 80 cyclohexane	1.32(6.1)	3.10, 2.50	4.51	7.05(1.9)	3.24 – 3.54 m, 4 H (2 × CH_2N); 3.52 – 3.76 m, 4 H (2 × CH_2O)
(*Z*)-*XIIIf*[f]						6.23(1.4)	
(*E,E*)-*XIIIg*	82	127 – 129 ethanol	1.31(6.3)	3.12, 2.48	4.66	7.74(2.8)	
(*E,Z*)-*XIIIg*	33	155 – 156 ethanol	1.43(6.3)	2.95, 3.45[h] 2.40, 2.80[i]	4.75	6.82(2.1)[h] 7.46(2.7)[i]	

[a] Doublet, (*J*); [b] centers of AB part of an ABMX system given; [c] center of X part of ABMX system given; [d] triplet, (*J*); [e] PE light petroleum; [f] olefinic proton signal obtained by measurement of reaction of (*Z*)-*II* with the corresponding amine; [g] singlet; [h] signal of "*Z*-part"; [i] signal of "*E*-part".

TABLE IV

Physicochemical characteristics of 3-methylene-*trans*-hexahydro-2(3*H*)-benzofuran derivatives *XIVa* – *XIVf* and *XIVh*

Compound	Yield, %	M. p., °C Solvent	^{1}H NMR			
			$(CH_2)_4CH^a$	CHO^b	$=CH^c$	Other signals
(*E*)-*XIVa*	80	78 – 80 cyclohexane	1.18 – 2.45	3.68(10.7, 3.5)	7.48(3.3)	7.39, 7.81 AA'BB'q, 4 H, *J* = 8.0 (H-arom.); 2.48 s, 3 H (CH_3)
(*Z*)-*XIVa*	82	118 – 126 PE–ethyl acetate	1.18 – 2.50	3.75(10.7, 3.5)	6.74(2.1)	7.18, 7.38 AA'BB'q, 4 H, *J* = 8.0 (H-arom.); 2.36 s, 3 H (CH_3)
(*E*)-*XIVb*	77	83 – 85 ethanol–PE	1.15 – 2.70	3.70(10.8, 3.5)	^{d}	7.38 – 8.10 m, 8 H (H-arom. and =CH)
(*Z*)-*XIVb*	78	134 – 136 ethanol–PE	1.15 – 2.70	3.70(10.8, 3.5)	6.86(2.8)	7.40 – 8.10 m, 7 H (H-arom.)
(*E*)-*XIVc*	84	oil	1.18 – 2.70	3.63(10.8, 3.8)	7.37(3.0)	
(*Z*)-*XIVc*	78	105 decomp. diethyl ether	1.20 – 2.67	3.70(10.8, 3.8)	6.43(2.6)	
(*E*)-*XIVd*	92	88 – 89 cyclohexane	1.00 – 2.70^d	3.48 – 3.75^e	7.34(1.4)	1.00 – 2.70 m, 6 H ($(CH_2)_3$)^d; 3.20 – 3.64 m, 4 H (2 × CH_2N)
(*Z*)-*XIVd*^{f}					6.01(0.7)	
(*E*)-*XIVe*	94	88 – 90 cyclohexane	1.18 – 2.70^d	3.48 – 3.75^e	7.18(1.3)	1.18 – 2.70 m, 4 H (CH_2CH_2); 3.18 – 3.40 m, 4 H (2 × CH_2N)
(*Z*)-*XIVe*^{f}					6.38(0.7)	
(*E*)-*XIVf*	95	129 – 130 ethyl acetate	1.30 – 2.73	3.30 – 3.80^{d,e}	7.23(2.0)	3.30 – 3.80 m, 8 H (2 × CH_2CH_2N)
(*Z*)-*XIVf*^{f}					5.96(1.3)	
(*E*)-*XIVh*	90	250 – 252 ethanol	1.20 – 2.75	3.75(10.6, 3.5)	7.37(3.0)	
(*Z*)-*XIVh*	32	256.5 – 257 ethanol	1.20 – 2.95	3.76(10.6, 3.5)	7.39(3.1^g) 6.48(2.6^h)	

[a] Multiplet; [b] doublet of triplet, (*J*,*J*); [c] doublet, δ(*J*); [d] signal overlapped with other proton signals; [e] multiplet; [f] reaction of (*Z*)-*III* with the corresponding amine; [g] "*E*-part"; [h] "*Z*-part".

TABLE V
Physicochemical characteristics of α-methylene-δ-valerolactone derivatives *XVa* – *XVf* and *XVi*

Compound	Yield %	M. p., °C Solvent	^{1}H NMR				
			$CH_2CH_2O^a$	$CH_2C=^b$	CH_2O^c	$=CH^c$	other signals
(*E*)-*XVa*	72	81 – 83 ethanol	2.00	2.53(6.7, 2.1)	4.34(5.2)	7.95(2.1)	7.16, 7.36 AA'BB'q, 4 H, *J* = 8.2 (H-arom.); 2.36 s, 3 H (CH_3)
(*Z*)-*XVa*	73	148 – 154 ethanol–PE	1.94	2.63(6.0, 1.6)	4.36(5.3)	7.08(1.6)	7.17, 7.39 AA'BB'q, 4 H, *J* = 8.2 (H-arom.); 2.36 s, 3 H (CH_3)
(*E*)-*XVb*	70	112 – 115 cyclohexane	2.03	2.59(6.7, 2.3)	4.36(5.3)	8.10(2.4)	7.40 – 8.00 m, 7 H (H-arom.)
(*Z*)-*XVb*	69	145 – 148 ethanol–diethyl ether	1.96	2.61(6.5, 1.6)	4.38(5.4)	7.21(1.6)	7.40 – 8.00 m, 7 H (H-arom.)
(*E*)-*XVc*	99	70 decomp. PE–benzene	1.90	2.47(6.7, 2.2)	4.32(5.3)	7.67(2.2)	
(*Z*)-*XVc*	81	oil	1.95	2.57(6.8, 1.6)	4.31(5.5)	6.70(1.6)	
(*E*)-*XVd*	98	oil	1.86	2.61(6.3)	4.20(5.2)	7.57^d	1.52 – 1.73 m, 6 H ($(CH_2)_3$); 3.30 – 3.50 m, 4 H (2 × CH_2N)
(*E*)-*XVe*	98	oil	^{e}	2.76(6.4)	4.22(5.1)	7.77^d	1.80 – 2.00 m, 4 H (CH_2CH_2); 3.48 – 3.60 m, 4 H (2 × CH_2N)
(*Z*)-*XVe*^{f}						6.68^d	
(*E*)-*XVf*	98	oil	1.93	2.61(6.3)	4.22(5.2)	7.51^d	3.35 – 3.84 m, 8 H (2 × CH_2CH_2N)
(*Z*)-*XVf*^{f}						6.39^d	
(*E,E*)-*XVi*	47	195 – 196 ethanol	1.96	2.61(6.5, 2.1)	4.35(5.3)	7.74(2.1)	
(*E,Z*)-*XVi*	21	180 – 181 ethanol	1.95	2.72(6.5, 1.9)^g 2.55(6.7, 1.4)^i	4.33^h	7.64(1.9) 6.77(1.4)^i	

[a] Multiplet; [b] doublet or triplet, (*J,J*); [c] triplet, (*J*); [d] singlet; [e] signal overlapped with other proton signals; [f] reaction of (*Z*)-*IV* with the corresponding amine; [g] "*E*-part"; [h] multiplet; [i] "*Z*-part"

dried over magnesium sulfate, filtered, the solvent was evaporated and the solid residue crystallized from an appropriate solvent.

(E)-3-(4-Toluenesulfonyloxymethylene)tetrahydro-2H-pyran-2-one ((*E*)-V): yield 69%, m.p. 93 – 94 °C (diethyl ether). ^{1}H NMR spectrum: 7.74 t, 1 H, *J* = 2.5 (=C–H); 4.29 t, 2 H, *J* = 5.3 (CH_2O); 2.52 dt, 2 H, *J* = 6.5 and 2.5 (CH_2C=); 1.85 m, 2 H (CH_2CH_2O); 7.83, 7.39 q AA'BB', 4 H, *J* = 8.3 (H-arom.); 2.48 s, 3 H (CH_3). For $C_{13}H_{14}O_5S$ (282.3) calculated: 55.31% C, 5.00% H; found: 55.36% C, 4.48% H.

(E)-3-(Benzenesulfonyloxymethylene)tetrahydro-2H-pyran-2-one ((*E*)-VII): yield 60%, m.p. 47 – 48.5 °C (diethyl ether–cyclohexane). ^{1}H NMR spectrum: 7.76 t, 1 H, *J* = 2.4 (=C–H); 4.29 t, 2 H, *J* = 5.3 (CH_2O); 2.51 dt, 2 H, *J* = 6.4 and 2.4 (CH_2C=); 1.86 m, 2 H, (CH_2CH_2O); 7.50 – 8.05 m, 5 H (H-arom.). For $C_{12}H_{12}O_5S$ (268.3) calculated: 53.72% C, 4.51% H; found: 53.80% C, 4.55% H.

(E)-3-(Methanesulfonyloxymethylene)tetrahydro-2H-pyran-2-one ((*E*)-VIII): yield 62%, m.p. 82 – 83 °C (diethyl ether–toluene). ^{1}H NMR spectrum: 7.85 t, 1 H, *J* = 2.4 (=CH); 4.37 t, 2 H, *J* = 5.3 (CH_2O); 2.62 dt, 2 H, *J* = 6.6 and 2.4 (CH_2C=); 1.95 m, 2 H, (CH_2CH_2O); 3.21 s, 3 H (CH_3). For $C_7H_{10}O_5S$ (206.2) calculated: 40.77%C, 4.89% H; found: 40.82% C, 4.91% H.

(E)-3-(Acetoxymethylene)tetrahydro-2H-pyran-2-one ((*E*)-IX): yield 58%, m.p. 74 – 75.5 °C (diethyl ether). ^{1}H NMR spectrum: 8.37 t, 1 H, *J* = 2.4 (=CH); 4.34 t, 2 H, *J* = 5.3 (CH_2O); 2.62 dt, 2 H, *J* = 6.5 and 2.4 (CH_2C=); 1.93 m, 2 H (CH_2CH_2O); 2.25 s, 3 H (CH_3). For $C_8H_{10}O_4$ (170.2) calculated: 56.46% C, 5.92% H; found: 56.55% C, 6.00% H.

(E)-3-(Benzoyloxymethylene)tetrahydro-2H-pyran-2-one ((*E*)-X): yield 45%, m.p. 113 – 115 °C (diethyl ether–light petroleum). ^{1}H NMR spectrum: 8.64 t, 1 H, *J* = 2.4 (=CH); 4.39 t, 2 H, *J* = 5.3 (CH_2O); 2.80 dt, 2 H, *J* = 6.8 and 2.4 (CH_2C=); 2.00 m, 2 H (CH_2CH_2O); 8.06 – 8.20 m, 2 H (H-*ortho*); 7.40 – 7.68 m, 3 H (2 × H-*meta*, H-*para*). For $C_{13}H_{12}O_4$ (232.2) calculated: 72.45% C, 5.21% H; found: 72.41% C, 5.15% H.

(*E*)- and (*Z*)-3-Hydroxymethylenetetrahydro-2*H*-pyran-2-one Sulfonates and Carboxylates ((*E*)- and (*Z*)-*IV*, *VII* – *X*)

The corresponding sulfonyl or acyl chloride (0.02 mol; 4-toluenesulfonyl chloride in 20 ml of diethyl ether) was added to a stirred suspension of sodium salt *V* (3.0 g, 0.02 mol) in anhydrous diethyl ether (50 ml) at temperature lower than 15 °C. After stirring and cooling for 6 to 10 h, the mixture was washed with water (20 ml), the ethereal layer was separated and the aqueous one extracted with dichloromethane (2 × 10 ml). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated to give crude mixtures of *E*- and *Z*-isomers (50 – 80%) of the corresponding sulfonates and carboxylates *IV*, *VII* – *X* which were separated by flash chromatography.

(Z)-3-(4-Toluenesulfonyloxymethylene)tetrahydro-2H-pyran-2-one ((*Z*)-IV): yield 36%, eluted with dichloromethane–ethyl acetate (25 : 1) as the second fraction; m.p. 96 – 96.5 °C (diethyl ether–ethyl acetate). ^{1}H NMR spectrum: 6.89 t, 1 H, *J* = 1.7 (=CH); 4.22 t, 2 H, *J* = 5.5 (CH_2O); 2.48 dt, 2 H, *J* = 5.4 and 1.7 (CH_2C=); 1.92 m, 2 H (CH_2CH_2O); 7.86, 7.35 AA'BB', 4 H, *J* = 8.6 (H-arom.); 2.45 s, 3 H (CH_3). For $C_{13}H_{14}O_5S$ (282.3) calculated: 55.31% C, 5.00% H; found: 55.24% C, 4.96% H.

(Z)-3-(Benzenesulfonyloxymethylene)tetrahydro-2H-pyran-2-one ((*Z*)-VII): yield 32%, eluted with diethyl ether as the second fraction; m.p. 86 – 87 °C (diethyl ether). ^{1}H NMR spectrum: 6.89 t, 1 H, *J* = 1.7 (=CH); 4.22 t, 2 H, *J* = 5.5 (CH_2O); 2.50 dt, 2 H, *J* = 6.8 and 1.7 (CH_2C=); 1.92 m, 2 H (CH_2CH_2O); 8.00 – 7.50 m, 5 H (H-arom.). For $C_{12}H_{12}O_5S$ (268.3) calculated: 53.72% C, 4.51% H; found: 53.83% C, 4.56% H.

(Z)-3-(Methanesulfonyloxymethylene)tetrahydro-2H-pyran-2-one ((*Z*)-VIII): yield 36%, eluted with diethyl ether as the second fraction; m.p. 80.5 – 81 °C (diethyl ether–toluene). ^{1}H NMR spectrum: 6.91 t, 1 H, *J* = 1.8 (=C–H); 4.34 t, 2 H, *J* = 5.0 (CH_2O); 2.59 dt, 2 H, *J* = 6.9 and 1.8 (CH_2C=); 2.01 m, 2 H (CH_2CH_2O); 3.22 s, 3 H (CH_3). For $C_7H_{10}O_5S$ (206.2) calculated: 40.77% C, 4.89% H; found: 40.69% C, 4.94% H.

(Z)-3-(Acetoxymethylene)tetrahydro-2H-pyran-2-one ((*Z*)-IX): yield 26%, eluted with diethyl ether as the second fraction; m.p. 26.5 – 28 °C (diethyl ether, cooled with liquid nitrogen). ^{1}H NMR spectrum: 7.48 t, 1 H, *J* = 1.7 (=CH); 4.32 t, 2 H, *J* = 5.4 (CH_2O); 2.57 dt, 2 H, *J* = 6.9 and 1.7 (CH_2C=); 1.98 m, 2 H (CH_2CH_2O); 2.27 s, 3 H (CH_3). For $C_8H_{10}O_4$ (170.2) calculated: 56.46% C, 5.92% H; found: 56.52% C, 5.88% H.

(Z)-3-(Benzoyloxymethylene)tetrahydro-2H-pyran-2-one ((*Z*)-X): yield 20%, eluted with diethyl ether as the first fraction; m.p. 102.5 – 104 °C (diethyl ether). ^{1}H NMR spectrum: 7.79 t, 1 H, *J* = 1.7 (=CH); 4.36 t, 2 H, *J* = 5.5 (CH_2O); 2.66 dt, 2 H, *J* = 7.0 and 1.7 (CH_2C=); 2.01 m, 2 H (CH_2CH_2O); 8.20 – 8.35 m, 2 H (H-*ortho*); 7.65 – 7.40 m, 3 H (2 × H-*meta*, H-*para*). For $C_{13}H_{12}O_4$ (232.2) calculated: 72.45% C, 5.21% H; found: 72.38% C, 5.18% H.

General Procedure for Reaction of Tosylates *II*, *III* and *IV* with 4-Toluenethiol and 2-Naphthalenethiol

Triethylamine (2 ml) was added to a solution of the tosylate (0.0025 mol) and 4-toluenethiol or 2-naphthalenethiol (0.0025 mol) in chloroform (50 ml). After stirring at room temperature for 30 min, the reaction mixture was washed with 5% potassium hydroxide solution (10 ml) and water (2 × 10 ml), dried over magnesium sulfate, filtered, concentrated in vacuo and the solid residue was crystallized. Reaction with *E*-isomers of the tosylates afforded (*E*)-3-(4-tolylthiomethylene)- and (*E*)-3-(2-naphthylthiomethylene)-5-methyldihydro-2(3*H*)-furanones ((*E*)-*XIIIa* and (*E*)-*XIIIb*), (*E*)-3-(4-tolylthiomethylene)- and (*E*)-3-(2-naphthylthiomethylene)-*trans*-hexahydro-2(3*H*)-benzofuranones ((*E*)-*XIVa* and (*E*)-*XIVb*) and (*E*)-3-(4-tolylthiomethylene)- and (*E*)-3-(2-naphthylthiomethylene)tetrahydro-2*H*-pyran-2-ones ((*E*)-*XVa* and (*E*)-*XVb*) in yields 75 – 80%. Reaction with the *Z*-isomers of *II*, *III* and *IV* afforded the sulfides (*Z*)-*XIIIa*, (*Z*)-*XIIIb*, (*Z*)-*XIVa*, (*Z*)-*XIVb*, (*Z*)-*XVa* and (*Z*)-*XVb* in similar yields.

Reaction of Tosylates *II*, *III* and *IV* with Sodium Azide

Water (about 10 ml) was added dropwise to a mixture of the tosylate (0.01 mol), sodium azide (0.8 g, 0.0012 mol) and acetone (60 ml) until the azide dissolved. After stirring for 3 h, the solution was concentrated in vacuo and the aqueous residue was extracted with chloroform (5 × 20 ml). The chloroform extracts were dried over magnesium sulfate, filtered and the solvent was evaporated to give crude azide in about 80% yield. The reaction with *E*-isomers of the tosylates afforded (*E*)-(azidomethylene)-5-methyldihydro-2(3*H*)-furanone ((*E*)-*XIIc*), (*E*)-3-(azidomethylene)-*trans*-hexahydro-2(3*H*)-benzofuranone ((*E*)-*XIVc*) and (*E*)-3-(azidomethylene)tetrahydro-2*H*-pyran-2-one ((*E*)-*XVc*). Reaction of *Z*-tosylates, carried out at 5 °C, led to the corresponding *Z*-azides.

6,7-Dihydro-5*H*-pyrano[2,3-*d*]isoxazole (*XVI*)

The oil obtained from the preparation of (*Z*)-*XVc* (1.25 g, 0.008 mol) was dissolved in chloroform (20 ml) and refluxed for 3 h. The consumption of the starting azide was followed by thin-layer chromatography on Silufol sheets in chloroform. After the reaction had ended, the solvent was evaporated in vacuo, leaving the isoxazole *XVI* as an oil; yield 90%. IR spectrum (film): 675, 703, 715, 820, 975, 1 037, 1 512, 1 650, 2 880, 2 950. ^{1}H NMR spectrum: 7.95 s, 1 H (=CH); 4.39 m, 2 H (CH_2O); 2.48 t, 2 H, *J* = 6.1 (CH_2C=); 1.97 m, 2 H (CH_2CH_2C=). ^{13}C NMR spectrum: 169.38 (C-3a), 151.01 (C-1), 86.47 (C-7a), 70.75 (C-5), 21.52 (C-7), 16.44 (C-6). For $C_6H_7NO_2$ calculated: 57.59% C, 5.64% H, 11.20% N; found: 57.72% C, 5.53% H, 11.37% N.

General Procedure for Reaction of Tosylates *II*, *III* and *IV* with Piperidine, Pyrrolidine and Morpholine

A) A solution of piperidine, pyrrolidine or morpholine (0.1 mol) in acetone (10 ml) was added to a stirred solution of (*E*)-isomer of the corresponding tosylate (0.005 mol) in acetone (30 ml). After stirring at room temperature for 6 – 12 h, the crystalline toluenesulfonate of the ammonium salt (if separated) was filtered, the solvent was evaporated in vacuo and the residue was dissolved in benzene (30 ml). The solution was washed with water (4 x 10 ml), dried over magnesium sulfate, filtered and concentrated in vacuo to afford the enamine in 90 – 95% yield. According to this procedure we prepared (*E*)-3-(piperidinomethylene)-, (*E*)-3-(pyrrolidinomethylene)- and (*E*)-3-(morpholinomethylene)-5-methyldihydro-2(3*H*)-furanone ((*E*)-*XIIId*, (*E*)-*XIIIe* and (*E*)-*XIIIf*; see Table III), (*E*)-3-(piperidinomethylene)-, (*E*)-3-(pyrrolidinomethylene)- and (*E*)-3-(morpholinomethylene)-*trans*-hexahydro-2(3*H*)-benzofuranone ((*E*)-*XIVd*, (*E*)-*XIVe* and (*E*)-*XIVf*; see Table IV) and (*E*)-3-(piperidinomethylene)-, (*E*)-3-(pyrrolidinomethylene)- and (*E*)-3-(morpholinomethylene)tetrahydro-2*H*-pyran-2-one ((*E*)-*XVd*, (*E*)-*XVe* and (*E*)-*XVf*; see Table V) which were crystallized from appropriate solvents.

B) The *E*-isomers of enamines were also obtained by reaction of the corresponding amines with the *Z*-isomers of tosylates *II*, *III* and *IV*.

^{1}H NMR Study of Reaction of Tosylates (*Z*)-*II*, (*Z*)-*III* and (*Z*)-*IV* with Piperidine, Pyrrolidine and Morpholine

^{1}H NMR spectrum of reaction mixture consisting of the corresponding *Z*-tosylate (1.9 . 10^{-5} mol), piperidine, pyrrolidine or morpholine (3.6 . 10^{-5} mol) and hexadeuterioacetone (0.4 ml) was measured. It was shown that the reaction affords *Z*-isomers as the primary products which are further isomerized to the *E*-isomers. The *Z*-enamines were identified by the chemical shift of the vinyl proton.

Reaction of Tosylates *II*, *III* and *IV* with Sodium Salts *V*, *XI* and *XII*

A solution of the tosylate (0.01 mol) and the sodium salt (0.012 mol) in acetone–water (2 : 1; 90 ml) was stirred at room temperature for 24 h. Acetone was then evaporated in vacuo and the aqueous residue was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over magnesium sulfate, filtered, concentrated in vacuo and the solid residue was crystallized. Reaction of *E*-tosylates afforded (*E,E*)-3,3'-(oxydimethylidine)bis(5-methyldihydro-2(3*H*)-furanone) ((*E,E*)-*XIIIg*), (*E,E*)-3,3'-(oxydimethylidine)bis(*trans*-hexahydro-2(3*H*)-benzofuranone) ((*E,E*)-*XIVh*) and (*E,E*)-3,3'-(oxydimethylidine)-bis(tetrahydro-2*H*-pyran-2-one) ((*E,E*)-*XVi*). Reaction of the *Z*-tosylates afforded mixtures of *E,E*- and *E,Z*-isomers of these ethers in ratios 2 : 3 to 1 : 1. The mixtures were separated by flash chromatography on silica gel (100 g) in chloroform–ethyl acetate (4 : 1), the *E,E*-isomers being eluted as the first and the *E,Z*-isomers as the second fraction.

Photoisomerization of Ethers *XIIIg*, *XVi* and *XVII*

A solution of the corresponding ether (0.005 mol) in dichloromethane (100 ml) was irradiated under nitrogen with a low-pressure lamp until the ratio of *E,E*- and *E,Z*-isomers no more changed (TLC in chloroform–ethyl acetate; about 5 h). The solvent was evaporated and the crystalline product, consisting of a 1 : 1 mixture of the *E,E*- and *E,Z*-isomers (^{1}H NMR spectrum), was chromatographically separated as described in the preceding experiment.

RESULTS AND DISCUSSION

The procedure used for the direct preparation of pure *Z*-isomers *I*, *II* and *III*, i.e., Claisen condensation of the lactone with ethyl formate at low temperature followed by tosylation of the formed sodium salt of the corresponding α-hydroxymethylenelactone[3 – 5], was unsuccessful with tosylate *IV* because at temperatures lower than 0 °C δ-valerolactone did not react with ethyl formate in the presence of metallic sodium dispersion. This lower reactivity is probably due to the slower deprotonation in the position α of the lactone. Although direct data for lactones are lacking, this assumption can be supported by the data for α-ethoxycarbonylcycloalkanones showing that the deprotonation rate for the cyclohexanone derivative ($9.7 \cdot 10^{-6}$ s^{-1}) is almost three orders of magnitude lower than that for the cyclopentanone derivative[7] ($2.3 \cdot 10^{-3}$ s^{-1}). At temperatures above 0 °C, the sodium salt of 3-(hydroxymethylene)tetrahydro-2*H*-pyran-2-one (*V*) represented a mixture of *E*- and *Z*-isomers[8]. Reaction of *V* with glacial acetic acid gave smoothly 3-(hydroxymethylene)tetrahydro-2*H*-pyran-2-one (*VI*) which, as shown by ^{1}H NMR spectra, prefers the *Z*-configuration (δ(=CH) = 7.15 ppm in chloroform solution, exists as a mixture of *E*- and *Z*-isomers (δ(=CH) = 7.82 ppm and 7.27 ppm) in acetone, and as the *E*-isomer (δ(=CH) = 7.71 ppm) in dimethyl sulfoxide.

Acylation of the salt *V* in anhydrous diethyl ether at room temperature led to mixtures of *E*- and *Z*-isomers of the corresponding carboxylates and sulfonates. Reaction with *p*-toluenesulfonyl chloride, benzenesulfonyl chloride, methanesulfonyl chloride, acetyl chloride and benzoyl chloride afforded mixtures of *E*- and *Z*-isomers of *IV*, 3-(benzenesulfonyloxymethylene)tetrahydro-2*H*-pyran-2-one (*VII*), 3-(methanesulfonyloxymethylene)tetrahydro-2*H*-pyran-2-one (*VIII*), 3-(acetoxymethylene)tetrahydro-2*H*-pyran-2-one (*IX*), and 3-(benzoyloxymethylene)tetrahydro-2*H*-pyran-2-one (*X*). The corresponding *Z*-isomers were obtained by separation of these mixtures by flash chromatography. Pure *E*-isomers of compounds *IV*, *VII* – *X* can be obtained similarly to (*E*)-*I*, (*E*)-*II* and (*E*)-*III* (refs[3 – 6]) if the reaction of the salt *V* with the sulfonyl or acyl chlorides is conducted in aqueous tetrahydrofuran.

As nucleophiles for mechanistic studies of the S_NV reaction of tosylates *II*, *III* and *IV*, we used thiols (4-toluenethiol, 2-naphthalenethiol), sodium azide, secondary amines (piperidine, pyrrolidine, morpholine) and also sodium salts of hydroxymethylene lactones *XI*, *XII* and *V*.

The reaction with thiols proceeded with retention of configuration: *E*-isomers of tosylates *II*, *III* and *IV* reacted with 4-toluenethiol or 2-naphthalenethiol to give *E*-sulfides *XIIIa*, *XIIIb*, *XIVa*, *XIVb*, *XVa* and *XVb*. Analogously, reaction of (*Z*)-*II*, (*Z*)-*III* and (*Z*)-*IV* led to *Z*-sulfides. The sulfides are stable and do not isomerize at room temperature.

Reaction of tosylates *II*, *III* and *IV* with sodium azide in aqueous acetone afforded azido derivatives *XIIIc*, *XIVc* and *XVc* with retention of configuration of the starting tosylate. However, in the case of compounds (*Z*)-*II* and (*Z*)-*IV* the result may be complicated by the subsequent isomerization of (*Z*)-*XIIIc* and (*Z*)-*XVc* to the corresponding *E*-isomers and decomposition of (*Z*)-*XVc* under formation of isoxazole *XVI*. These reactions can be suppressed by lowering the reaction temperature to 5 °C. Except (*Z*)-*XVc*, the azides *XIIIc* – *XVc* are stable up to 70 °C. Azide (*Z*)-*XVc* liberates nitrogen already at room temperature and is converted into isoxazole *XVI* by reaction analogous to the cyclization of diethyl azidomethylenemalonate[9]. Azides (*Z*)-*XIIIc* and (*Z*)-*XIVc*, as well as (*Z*)-(3-azidomethylene)dihydro-2(3*H*)-furanone (*XIX*), gave no isoxazole derivatives on heating; this may be explained by a greater strain of two fused five-membered rings in the arising isoxazole. The *Z*,*E*-isomerization of azides (*Z*)-*XIIIc* and (*Z*)-*XVc* is catalyzed by azide ion[10]; in solutions containing no azide ions, these compounds are configurationally stable.

Substitution with piperidine, pyrrolidine and morpholine afforded *E*-isomers of the corresponding enamines *XIIId* – *XIIIf*, *XIVd* – *XIVf* and *XVd* – *XVf*, irrespective of the configuration of the starting tosylate. As shown by ^{1}H NMR studies, the substitution leads first to the *Z*-enamine which in the course of the reaction isomerizes to give the *E*-enamine. Thus, we were able to identify by ^{1}H NMR spectroscopy the *Z*-isomers of enamines *XIIId* – *XIIIf*, *XIVd* – *XIVf*, *XVe* and *XVf*. The enamine (*Z*)-*XVd* could not be identified because of faster reaction of (*Z*)-*IV* with piperidine and faster *Z*,*E*-isomerization. At room temperature, the reaction is finished during 2 – 3 minutes and we detected only (*E*)-*XVd* in the product.

In the preparation of tosylates (*E*)-*II*, (*E*)-*III* and (*E*)-*IV*, we reported previously[4 – 6] their substitution with enolate anions of the starting sodium salts *XI*, *XII* or *V*, leading to *E*,*E*-isomers of "divinyl ethers" *XIIIg*, *XIVh* and *XVi*. At low temperatures, in reactions leading to *Z*-isomers of the mentioned tosylates, the formation of analogous ethers was not observed. Now we performed substitutions of *E*- and *Z*-isomers of tosylates *II*, *III* and *IV* with the corresponding enolates in aqueous acetone or tetrahydrofuran at room temperature, i.e., under conditions favouring the *E*-configuration. Thus, starting from (*E*)-*II*, (*E*)-*III* and (*E*)-*IV*, the reaction afforded (*E*,*E*)-3-(oxydimethylidine)bis(5-methyldihydro-2(3*H*)-furanone) ((*E*,*E*)-*XIIIg*), (*E*,*E*)-3-(oxydimethylidine)bis(*trans*-hexahydro-2(3*H*)-benzofuranone) ((*E*,*E*)-*XIVh*) and (*E*,*E*)-3-(oxydimethylidine)bis(tetrahydro-2*H*-pyran-2-one) ((*E*,*E*)-*XVi*). Under these conditions, tosylates (*Z*)-*II*, (*Z*)-*III* and (*Z*)-*IV* gave mixtures of *E*,*E*- and *E*,*Z*-isomers of ethers *XIIIg*, *XIVh* and *XVi* in the ratios 2 : 3 to 1 : 1; these mixtures were then separated by preparative liquid chromatography. We have found that *E*,*Z*-ethers are configurationally stable under conditions of their preparation and their isomerization to *E*,*E*-isomers was observed only at elevated temperature. For compounds (*E*,*Z*)-*XIIIg*, (*E*,*Z*)-*XVi* and (*E*,*Z*)-3-(oxydimethylidine)bis(dihydro-2(3*H*)-furanone) ((*E*,*Z*)-*XVII*), this isomerization in hexadeuteriodimethyl sulfoxide in the range 135 – 170 °C was followed kinetically[11] by the ^{1}H NMR technique.

The *E,Z*-isomers of ethers *XIIIg*, *XIVh*, *XVj* and *XVII* can also be obtained from the preparatively better accessible *E,E*-ethers by separation of mixtures of *E,Z*- and *E,E*-isomers arising on irradiation of the corresponding *E,E*-ethers with low-pressure mercury lamp in acetone, chloroform or dichloromethane. In the photostationary state the ratio of both isomers is approximately 1 : 1. Even in these cases, no formation of *Z,Z*-isomers of the mentioned ethers was observed.

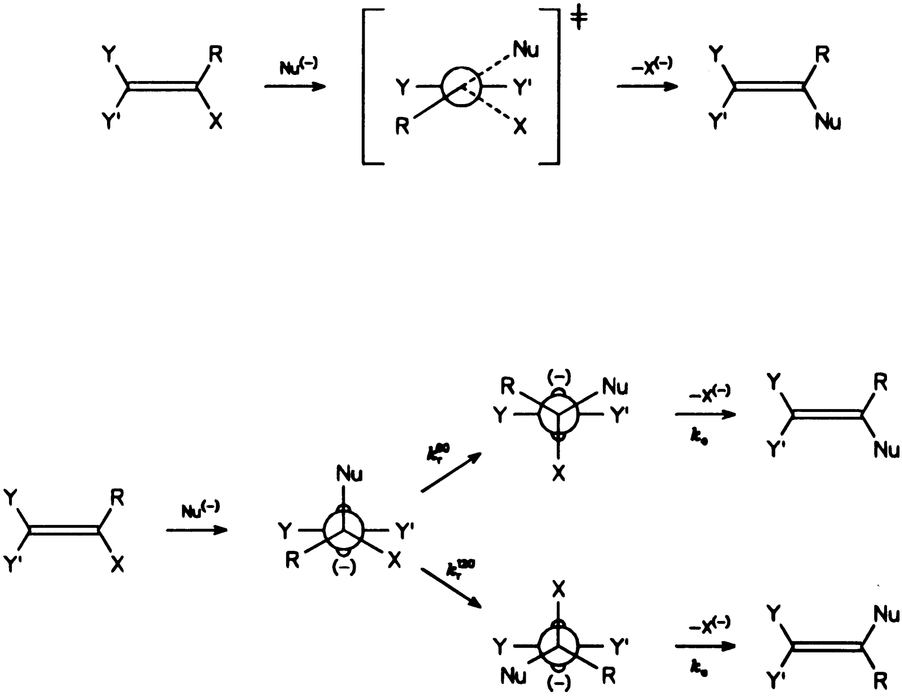
Ethers (*E,E*)-*XIIIg* and (*E,Z*)-*XIIIg*, prepared from racemic γ-valerolactone, must exist as mixtures of stereoisomers: (*E,E*)-*XIIIg* as a mixture of *R,R*-, *S,S*- and *R,S*-stereoisomers in the ratio 1 : 1 : 2 and (*E,Z*)-*XIIIg* as a mixture of *R,R*-, *S,S*-, *R,S*- and *S,R*-isomers in the ratio 1 : 1 : 1 : 1. In both cases, the differences between the corresponding diastereoisomers are so small that they are discernible neither by HPLC nor ^{1}H (100 MHz) nor ^{13}C (25 and 100 MHz) NMR spectra. Only in ^{1}H NMR spectra at 400 MHz there are differences between signals of methylene groups in the R^*,R^*- and R^*,S^*-diastereoisomers of ether (*E,E*)-*XIIIg* and R^*,R^*- and R^*,S^*-isomers of ether (*E,Z*)-*XIIIg*. Instead of the expected two groups of 8 lines of the AB part of the ABMX spin system in the spectrum of (*E,E*)-*XIIIg*, we observed a “doubling” to 32 lines with a shift of 0.8 and 1.0 Hz for the individual groups of lines. In the spectrum of (*E,Z*)-*XIIIg* this effect was apparent only for the signals corresponding to the “*E*-part”, the difference in the shift of lines being more pronounced (3.9 Hz). The individual diastereoisomers were not distinguished in the ^{1}H NMR spectra at 100 MHz even with lanthanide shift reagents (LSR) which form complexes with the studied ethers; as seen from Table VI, the lanthanide atom is coordinated predominantly with the “*E*-part”. Achiral LSR distinguished ligands diastereotopic by internal comparison, chiral LSR ligands enantiotopic and diastereotopic by internal comparison. Ligands diastereotopic by external comparison, i.e., diastereoisomers, remained undistinguished.

TABLE VI
Shift parameters S (ppm) for signals of selected protons in spectra of (*E,E*)- and (*E,Z*)-*XIIIg*

Compound	LSR	CHO	=CH	CH$_3$
(*E,E*)-*XIIIg*	Eu(fod)$_3$	1.57	3.06	0.96
(*E,Z*)-*XIIIg*[a]	Eu(fod)$_3$	3.68	7.22	2.38
		0.40	0.53	0.20
(*E,E*)-*XIIIg*	Eu(tfc)$_3$	0.23	0.30[b]	0.17[c]
(*E,Z*)-*XIIIg*[a]	Eu(tfc)$_3$	0.46	0.83[b]	0.33[c]
		0	0[c]	0

[a] The upper number refers to the “*E*-part” of the ether, the lower for the “Z-part”; [b] the triplet changes into a broad singlet; [c] the original doublet splits into two doublets in 1 : 1 ratio.

Recently, the nucleophilic substitution at the C=C double bond has been intensively studied and analysis of broad experimental material led to suggestion of many mechanisms for such reaction[12]. For a bimolecular process, initiated by nucleophile attack at the C(α) carbon (bearing a nucleofuge), two variants have been discussed[12]: *a*) a one-step concerted mechanism or *b*) a multistep addition–elimination mechanism: in the first the structure formed after the nuclephile attack is a transition state whereas in the second it is a reaction intermediate (see Scheme 1). For the medium activated system of α-tosyloxymethylene lactones one can reasonably assume an addition–elimination mechanism. The lactone group stabilizes the negative charge of the formed carbanion *XVIII* only so far that the elimination of the nucleofuge is sufficiently fast, faster than the rotation about the $C^{(-)}$–CHXNu bond (k_r^{60}, k_r^{120} < k_e). Under assumption that rotation for 60° about the C–C bond in *XVIII* is faster than for 120° (k_r^{60} > k_r^{120}) this leads to



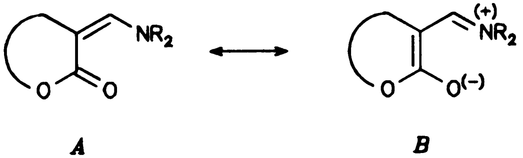
XVIII

SCHEME 1

retention of the starting configuration in the product. An opposite case ($k_r^{60} < k_r^{120}$), leading to configurational inversion, has not been described yet.

The mentioned assumption is apparently fulfilled for reaction of tosylates *II*, *III* and *IV* with thiols, where S_NV proceeeds with retention of configuration, and also for substitution with sodium azide. The subsequent isomerization of (*Z*)-*XIIIc* and (*Z*)-*XVc*, which has been shown[10] to be catalyzed by azide ion, proceeds probably again by an addition–elimination mechanism. Because of the worse leaving ability of the azide group, the anion *XVIII* (X = Nu = N_3), arising by addition of the azide anion to the corresponding *Z*-azide, can rotate about the C–C bond (k_r^{60}, $k_r^{120} \approx k_e$) and the thermodynamically more stable *E*-isomer of the azide is the final product.

As shown by ^{1}H NMR spectra, the substitution with secondary amines proceeds with retention of configuration; however, the *Z*-enamines arising by substitution of *Z*-tosylates are not stable and easily isomerize to give the corresponding *E*-isomers. Since the exchange of the amine substituent (e.g. in the reaction of enamine (*E*)-*XIIIf* with piperidine) does not take place, the isomerization of enamines by subsequent substitution can be excluded. The easy izomerization of *Z*-enamines as compared with sulfides is enabled by a better participation of the nitrogen lone electron pair in the arising "push–pull" system[14] and by enhanced probability of the existence of the mesomeric structure *B* (see Scheme 2) leading to weakening the double bond C=C. These conclusions can be compared with those obtained by Fariña and coworkers[15] on reactions of ethyl ester or nitrile of 3-bromo-4,4-dimethoxy-2-butenoic acid with secondary amines. Whereas the substitution with aziridine led to retention of configuration (the lone electron pair of nitrogen in the formed enamine poorly participates in the conjugation), the reaction with other secondary amines (piperidine, pyrrolidine, diethylamine) proceeded with full or partial stereoconvergence.



SCHEME 2

The sterochemical outcome of substitution with enolates *XI*, *XII* and *V* differs from the results obtained with the nucleophiles mentioned above. In this case we encounter a partial stereoconvergence: the reaction with *E*-tosylates gives *E,E*-isomers of ethers *XIIIg*, *XIVh* and *XVi* whereas reaction with *Z*-tosylates affords mixtures of *E,E*- and *E,Z*-isomers. Because under the given experimental conditions an *E,Z*–*E,E* isomerization has not been observed for these compounds, we assume that in this case there is a lowered barrier to rotation in the intermediate carbanion *XVIII* (X = OTs, Nu = OR). For the *Z*-isomer with expected higher elimination energy, the rate of rotation for 120° about the C–C bond (leading to the *E,E*-isomer) is comparable to the rate of elimination (leading to the *E,Z*-isomer): $k_r^{120} \approx k_e$. The isomerization about the double bond in *E,Z*-ethers requires more energy and, contrary to the *Z*-enamines, the prepared *E,Z*-ethers isomerize only at elevated temperatures. The Arrhenius activation parameters, obtained from the temperature dependence of *E,Z–E,E* isomerization[11] of ethers (*E,Z*)-*XIIIg*, (*E,Z*)-*XVi* and (*E,Z*)-*XVII* (Table VII), suffer from a great error, caused both by slow reaction rates and by the method of measurement employed (^{1}H NMR). As confirmed by control measurement, compound (*E,Z*)-*XVi* isomerizes faster than (*E,Z*)-*XVII* whereas (*E,Z*)-*XIIIg* isomerizes at 137 °C slower and at 168 °C faster than (*E,Z*)-*XVII*. It is thus obvious that introduction of a methyl group into the γ-position in a five-membered lactone ring has a completely different effect on the isomerization than has the transition to a six-membered ring.

TABLE VII
Arrhenius activation parameters of *E,Z–E,E* isomerization of *XIIIg*, *XVi* and *XVII*

Compound	T, K	ln A	E_a, kJ mol^{-1}
XIIIg	410 – 431	13 ± 3	80 ± 13
XVi	410 – 428	33 ± 1	141 ± 4
XVII	411 – 431	28 ± 8	133 ± 28

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