TRANSFORMATIONS OF 3-(METHYLENE)DIHYDRO--2(3H)-FURANONE DERIVATIVES

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Dedicated to Assoc. Prof. Dr M. Kratochvíl on the occasion of his 60th birthday.

(*E*)- and (*Z*)-3-(4-toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanones ((*E*)-*I*) and ((*Z*)-*I*) react with piperidine, pyrrolidine, morpholine, butanethiol, 4-toluenethiol, and 2-naphthalenethiol to give (*E*)-isomers of the corresponding enamines *II*—*IV* and thiomethylene derivatives *V*— *VII* in high yields. As has been shown, the reactions proceed with retention of configuration; the initially formed (*Z*)-*II*, (*Z*)-*III*, (*Z*)-*IV*, and (*Z*)-*V* isomerize rapidly to the thermodynamically more stable (*E*)-isomers. Ether *IX* was obtained by reaction of (*E*)-*I* with the (*E*)-isomer of sodium salt of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone ((*E*)-*VIII*) and a mixture of ethers *IX* and *X* resulted from reaction of (*Z*)-*I* with sodium salt of (*E*)-*VIII*. Compounds (*E*)-*I* and (*Z*)-*I* afforded the corresponding azides (*E*)-*XI* and (*Z*)-*XI* upon treatment with sodium azide, and hydroxybutanoic acids (*E*)-*XII* and (*Z*)-*XII* with sodium hydroxide in aqueous acetone. Chloride (*E*)-*XIII*, prepared by reacting (*E*)-*I* with methanolic hydrogen chloride, furnished with piperidine, pyrrolidine, morpholine, or 2-naphthalenethiol the corresponding (*E*)-*II*, (*E*)-*III*, (*E*)-*IV*, and (*E*)-*VII*. Potassium cyanide reacted with (*E*)-*I* in dimethyl sulfoxide to yield nitrile (*E*)-*XIV*. Cycloaddition of the azide (*E*)-*XI* to isobutyl vinyl ether or cyclohexyl vinyl ether proceeds quantitatively to give the respective triazolines (*E*)-*XV* and (*E*)-*XVI*. Alkaline hydrolysis of *IX* afforded the acid *XVII*. Reduction of (*E*)-*I*, (Z)-*I*, and (*E*)-*VII* with chloralane gave the respective butanediols (*E*)-*XVIII*, (*Z*)-*XVIII*, and (*E*)-*XIX*, respectively. Configurations of these substances were elucidated by ^{1}H NMR spectrometry.

Preparation of pure sulfonates and carboxylates of (*E*)- and (*Z*)-3-(hydroxymethylene)dihydro-2(3*H*)-furanones has already been described[1]. Considering the availability of the starting compounds, it seemed useful to investigate nucleophilic substitution of (*E*)- and (*Z*)-3-(4-toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanones ((*E*)-*I*, (*Z*)-*I*) with respect to both the more general problem of steric course of nucleophilic substitutions at an activated double bond[2], and the presumed importance of α-methylene-γ-butyrolactone grouping associated with the cancerostatic effect of natural[3], as well as synthetic[4] compounds.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H NMR spectra were recorded with Tesla BS 567 and Tesla BS 467 apparatuses at 100 and 60 MHz, respectively; measured were deuteriochloroform

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solutions containing hexamethyldisiloxane as internal reference unless stated otherwise. The chemical shift values were converted to tetramethylsilane as the standard. Tosylates (*E*)-*I* and (*Z*)-*I* were prepared according to[1].

(*E*)-3-(Piperidinomethylene)-, (*E*)-3-(Pyrrolidinomethylene)-, and (*E*)-3-(Morpholinomethylene)dihydro-2(3*H*)-furanones ((*E*)-*II*, (*E*)-*III*, and (*E*)-*IV*)

A) From tosylate (*E*)-*I*: piperidine (2 ml, 20 mmol), or pyrrolidine (1·7 ml, 20 mmol), or morpholine (1·75 ml, 20 mmol) in acetone (10 ml) was added to a stirred solution of (*E*)-*I* (2·7 g, 10 mmol) in acetone (50 ml). The mixture was stirred for 2 h, the solvent was evaporated under diminished pressure and the residue dissolved in benzene (50 ml) was extracted with water (4 × 50 ml). The benzene solution was dried with magnesium sulfate and the solvent was evaporated *in vacuo* to give 90—95% of the corresponding enamines, which were crystallized from cyclohexane ((*E*)-*II* and (*E*)-*III*) or ethyl acetate ((*E*)-*IV*).

B) From tosylate (*Z*)-*I*: the same procedure was applied to prepare (*E*)-*II*, (*E*)-*III* and (*E*)-*IV* in 90—95% yields.

(*E*)-3-(Butylthiomethylene)dihydro-2(3*H*)-furanone ((*E*)-*V*)

A) From tosylate (*E*)-*I*: butanethiol (3 ml, 40 mmol) and (*E*)-*I* (8·1 g, 30 mmol) were successively added to a solution of sodium metal (0·9 g, 40 mmol) in methanol (150 ml) with stirring. After 24 h the solution was evaporated under reduced pressure, the residue was diluted with water (100 ml) and extracted with chloroform (5 × 50 ml). The combined extracts were dried with sodium sulfate, filtered, and the solvent was removed under diminished pressure. The residue was column-distilled *in vacuo*, to obtain (*E*)-*V* in a 48% yield.

B) From tosylate (*Z*)-*I*: in the same manner, the compound (*E*)-*V* was obtained in a 52% yield.

(*E*)-3-(4-Tolylthiomethylene)- and (*E*)-3-(2-Naphthylthiomethylene)dihydro-2(3*H*)-furanones ((*E*)-*VI*) and ((*E*)-*VII*)

A) From tosylate (*E*)-*I*: a suspension of sodium hydride (40%) in mull oil (0·27 g, 11 mmol) was gradually added to a stirred mixture of 4-toluenethiol (1·25 g, 10 mmol), or 2-naphthalenethiol (1·6 g, 10 mmol), benzene (100 ml), (*E*)-*I* (2·7 g, 10 mmol), and 2-propanol (5 drops). Sodium 4-toluenesulfonate separated during reaction; after *c.* 1 h, when the starting compound has been consumed, the mixture was filtered, evaporated *in vacuo* and the crude product was crystallized from benzene. The yield of (*E*)-*VI* and (*E*)-*VII* was 84 and 75%, respectively.

B) From tosylate (*Z*)-*I*: applying the same procedure, compounds (*E*)-*VI* and (*E*)-*VII* were obtained in the same yields.

Monitoring the Reaction between (*Z*)-3-(4-Toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanone ((*Z*)-*I*) and Piperidine, Pyrrolidine, Morpholine, or Butanethiol by NMR Spectrometer

Piperidine, pyrrolidine, morpholine, or butanethiol ($2{\cdot}5 \cdot 10^{-5}$ mol) was added to a solution of (*Z*)-*I* (0·5 ml, 0·1 mol l^{-1}) in hexadeuterioacetone containing a minimal amount of hexamethyldisiloxane in an NMR-tube, the solution was shaken and the ^{1}H FT NMR spectra with a minimum number (12) of pulses required were immediately measured in pre-set time intervals.

The reaction with butanethiol did not observingly proceed and it was therefore catalyzed by addition of sodium hydride. Attention was primarily paid to the vinylic proton absorption as its chemical shift makes it best possible to discern configurations both of the starting compound and products. The results are as follows: *1*) isomerization of (*Z*)-*I* to (*E*)-*I* did not take place, *2*) (*Z*)-isomers of *II*, *III*, *IV*, and *V* were primarily formed; they were characterized by chemical shift values and coupling constants of typical ^{1}H NMR absorptions, *3*) isomerization of the originaly formed (*Z*)-isomers to thermodynamically more stable (*E*)-isomers of *II*, *III*, *IV*, and *V* was so rapid as to make their preparation impossible.

Di((*E*)-2(3*H*)-dihydrofuranone-3-methine) Ether (*IX*)

A mixture of (*E*)-*I* (2·7 g, 10 mmol) and sodium 3-(hydroxymethylene)dihydro-2(3*H*)-furanone (*VIII*, 1·7 g, 12 mmol), dissolved in aqueous acetone (70%, v/v, 100 ml) was stirred at room temperature for 4 days, concentrated under reduced pressure and filtered off. The precipitate was washed with water and crystallized from a great volume of ethanol to give *IX* in a 90% yield.

(*E*)-2(3*H*)-Dihydrofuranone-3-methine (*Z*)-2(3*H*)-Dihydrofuranone-3-methine Ether (*X*)

A solution of sodium 3-(hydroxymethylene)dihydro-2(3*H*)-furanone (*VIII*, 0·9 g, 7 mmol) in water (15 ml) was treated with a solution of (*Z*)-3-(4-toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanone (*Z*)-*I*, (1·35 g, 5 mmol) in acetone (35 ml) with stirring at room temperature for 24 h. The solution was concentrated under diminished pressure, the precipitate was filtered off, washed with water and dried. The product, obtained in a 95% yield, was a 1 : 2 mixture of *IX* and *X*; it was separated by chromatography on silica gel column (30 cm in length, particle size 40/100) chloroform being the eluent and ether *IX* eluting as the first.

(*E*)-3-(Azidomethylene)dihydro-2(3*H*)-furanone ((*E*)-*XI*)

Water (*c.* 50 ml) was dropwise added to a stirred mixture of (*E*)-*I*, (13·5 g, 50 ml) and sodium azide (6·5 g, 0·1 mol) in acetone (500 ml) till a solution resulted; stirring was continued at an ambient temperature for 48 h. Acetone was distilled off under reduced pressure and the remaining suspension was extracted with chloroform (5 × 50 ml). The combined extracts were dried with sodium sulfate, filtered, and evaporated *in vacuo* to furnish the sufficiently pure (*E*)-*XI* in a 85% yield.

(*Z*)-3-(Azidomethylene(dihydro-2(3*H*)-furanone ((*Z*)-*XI*)

This compound was analogously prepared from (*Z*)-*I*, (2·7 g, 10 mmol), sodium azide (2·1 g, 30 mmol), in acetone (100 ml) with the exception that water (*c.* 20 ml) was added and the mixture was kept at 10°C, since an increased temperature caused a partial or total isomerization of (*Z*)-*XI* to (*E*)-*XI*. Yield of a sufficiently pure (*Z*)-*XI* was 80%.

(*E*)- and (*Z*)-2-(4-Toluenesulfonyloxymethylene)-4-hydroxybutanoic Acids ((*E*)-*XII*) and ((*Z*)-*XII*)

The respective compound (*E*)-*I*, or (*Z*)-*I* (2·7 g, 10 mmol) in acetone (40 ml) was added to a solution of potassium hydroxide (0·60 g, 15 mmol) in water (10 ml) and the solution formed was left standing at room temperature for 48 h. Acetone was distilled off under diminished pressure, the residue was diluted with 0·1M-HCl (100 ml), the precipitate was suction-filtered and crystallized from water to afford the title acids in a 90—95% yield.

(*E*)-3-(Chloromethylene)dihydro-2(3*H*)-furanone ((*E*)-*XIII*)

Compound (*E*)-*I* (30 g, 0·11 mol) was added to methanolic hydrogen chloride (2M, 300 ml) and the solution was refluxed till the starting compound disappeared, as checked by thin-layer chromatography (*c.* 30 h). The mixture was cooled, washed with ice-cold water saturated with potassium carbonate (300 ml), the organic layer was separated, the aqueous-methanolic one was extracted with chloroform (4 × 40 ml), the combined extracts were dried with magnesium sulfate, filtrated, concentrated under reduced pressure and the residue was distilled *in vacuo* employing a Vigreux column to furnish (*E*)-*XIII* in a 34% yield.

Reaction of (*E*)-3-(Chloromethylene)dihydro-2(3*H*)-furanone ((*E*)-*XIII*) with Piperidine, Pyrrolidine or Morpholine

Compound (*E*)-*XIII* (0·24 g, 0·18 mmol) was added to the respective solution of morpholine (0·032 g, 0·46 mmol), or pyrrolidine (0·026 g, 0·36 mmol), or piperidine (0·031 g, 0·36 mmol) in dry tetrahydrofuran (2 ml), the solution was refluxed for a short time, cooled, diluted with water (10 ml) and extracted with benzene (2 × 5 ml). The organic layer was dried with sodium sulfate, filtered and removed under reduced pressure. The remaining solid was suspended in a little amount of diethyl ether and filtered off. Yield of enamines (*E*)-*II*, (*E*)-*III* and (*E*)-*IV* varied within 60—70%.

Reaction of (*E*)-3-(Chloromethylene)dihydro-2(3*H*)-furanone ((*E*)-*XIII*) with 2-Naphthalenethiol

2-Naphthalenethiol (0·031 g, 0·2 mmol) in tetrahydrofuran (5 ml) was reacted with sodium metal (0·1 g), the solution was filtered, refluxed with (*E*)-*XIII* (0·024 g, 0·13 mmol) for a short time, cooled and filtered; the solvent was removed *in vacuo* and the residue was crystallized from ethyl acetate to give (*E*)-*VII* in a 86% yield.

(*E*)-3-(Cyanomethylene)dihydro-2(3*H*)-furanone ((*E*)-*XIV*)

Potassium cyanide (0·78 g, 12 mmol) in dimethyl sulfoxide (30 ml) was added to a stirred solution of (*E*)-*I* (2·7 g, 10 mmol) in dimethyl sulfoxide (20 ml) at room temperature. The solution, which shortly after addition turned dark, was stirred for 3 h, diluted with water (500 ml), and extracted with chloroform (5 × 50 ml); the combined extracts were dried with sodium sulfate, concentrated under reduced pressure and diluted with ether. The separated product was filtered off and crystallized from ethanol. Yield 15%.

(*E*)-3-(Isobutoxy-1-triazolinomethylene)- and (*E*)-3-(Cyclohexyloxy-1-triazolinomethylene)-dihydro-2(3*H*)-furanones ((*E*)-*XV*) and ((*E*)-*XVI*)

Isobutyl vinyl ether (4 ml, 30 mmol), or cyclohexyl vinyl ether (4·5 ml, 30 mmol) was added to (*E*)-*XI* (2·25 g, 15 mmol) in dichloromethane (10 ml) and the solution was allowed to stand at room temperature in the dark till the starting material disappeared, which lasted approximately 14 days (checked by thin-layer chromatography). The residue, obtained by removing the solvent under diminished pressure, was suspended in ether, suction-filtered and crystallized from tetrachloromethane–pentane to afford (*E*)-*XV*, or (*E*)-*XVI* in a 90—95% yield.

1,1′-Oxydi((*E*)-1-butene-4-hydroxy-2-carboxylic) Acid (*XVII*)

Potassium hydroxide (2·5 g, 45 mmol) in water (40 ml) was added into a solution of *IX* (3·4 g,

16 mmol) in acetone (200 ml); the mixture was stirred at an ambient temperature for 24 h, acetone was removed under reduced pressure and the residue was acidified with dilute hydrochloric acid. The separated precipitate was filtered off and crystallized from a little amount of water to give *XVII* in a 95% yield.

(*E*)- and (*Z*)-2-(4-Toluenesulfonyloxymethylene)-1,4-butanediols ((*E*)-*XVIII*) and ((*Z*)-*XVIII*)

To a solution, prepared by a 1 h-stirring of lithium hydridoaluminate (2·13 g, 56 mmol) in ether (100 ml) with aluminum chloride (7·48 g, 56 mmol) in ether (100 ml), a suspension of (*E*)-*I*, or (*Z*)-*I* (20 g, 74 mmol) in ether (100 ml) was added at room temperature. Stirring was continued till the starting compound disappeared (monitored by thin-layer chromatography, *c.* 48 h), the unreacted reagent was decomposed by a successive addition of aqueous ether and water and the product was extracted with ether for 15 h. The extract was dried with magnesium sulfate, filtered and the solvent was evaporated under diminished pressure. The crystalline diol (*E*)-*XVIII* was recrystallized from dioxane–tetrachloromethane 1 : 4, the oily (*Z*)-*XVIII* was not further purified. Yield of (*E*)-*XVIII* was 66%, that of (*Z*)-*XVIII* 49%; heating of the former with acetic anhydride afforded the diacetate (*E*)-*XX* in a 80% yield.

(*E*)-2-(2-Naphthylthiomethylene)-1,4-butanediol ((*E*)-*XIX*)

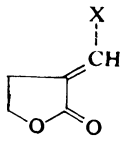
A suspension of (*E*)-*VII* (2·5 g, 10 mmol) in ether (50 ml) was gradually added to a mixture obtained by reacting lithium hydridoaluminate (0·4 g, 11 mmol) in ether (25 ml) with aluminium chloride (1·3 g, 10 mmol) in ether (25 ml) under nitrogen for 30 min. Stirring was continued till the starting product was consumed (3 days, monitored by thin-layer chromatography). The excess of the reagent was decomposed as with (*E*)-*XVIII* and the product was extracted with ether for 48 h and worked up in a routine way. The yield of (*E*)-*XIX*, which was crystallized from tetrachloromethane, was 60%.

RESULTS AND DISCUSSION

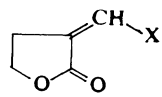
As reported[5–7], addition-elimination routes of nucleophilic substitutions at an activated double bond proceed mostly with retention of configuration of the starting double bond. Vinylic substitutions with amines[8,9], excluding ethyleneimine, where a stereoconvergence due to post-isomerization of the enamine formed has been reported[10], are the exceptions. The first stereoconvergences under conditions of kinetic control were described[6] in reactions of (*E*)- and (*Z*)-α-iodo-β-nitrostyrenes with sulfur-containing nucleophiles.

(*E*)- and (*Z*)-3-(4-toluenesulfonyloxymethylene)dihydro-2(3*H*)-furanones ((*E*)-*I*) and ((*Z*-*I*) react with piperidine, pyrrolidine, morpholine, butanethiol, 4-toluenethiol, and 2-naphthalenethiol at 20°C to give pure corresponding (*E*)-3-(piperidinomethylene)dihydro-2(3*H*)-furanone ((*E*)-*II*), (*E*)-3-(pyrrolidinomethylene)dihydro-2(3*H*)-furanone ((*E*)-*III*), (*E*)-3-(morpholinomethylene) dihydro-2-(3*H*)-furanone ((*E*)-*IV*), (*E*)-3-(butylthiomethylene)dihydro-2-(3*H*)-furanone ((*E*)-*V*), (*E*)-3-(4-tolylthio-methyl ene)dihydro-2-(3*H*)-furanone ((*E*)-*VI*), and (*E*)-3-(2-naphthylthiomethylene)dihydro-2(3*H*)-furanone ((*E*)-*VII*). Investigation of the reaction of tosylates (*E*)-*I* and (*Z*)-*I*

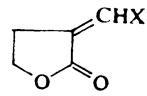
with 0·5 equivalent of the above-mentioned nucleophiles in an NMR tube showed that primarily, products having the configuration of the starting olefin were formed; a rapid isomerization to the more stable (*E*)-isomer is taking place with (*Z*)-isomers of *II*, *III*, *IV*, and *V*. Compounds (*Z*)-*II*–(*Z*)-*V* were characterized by ^{1}H NMR spectra, and it was shown that no isomerization of tosylate (*Z*)-*I* to (*E*)-*I* takes place under conditions applied. Experimental conditions prevented to prove the formation of products of the same configuration as the starting substrate upon treatment of tosylate (*Z*)-*I* with 4-toluenethiol or 2-naphthalenethiol; the course of these reactions remains so far open. Tosylates (*E*)-*I* and (*Z*)-*I* react with sodium azide to afford pure (*E*)- and (*Z*)-3-(azidomethylene)dihydro-2(3*H*)-furanones ((*E*)-*XI*) and ((*Z*)-*XI*), the latter, however, slowly isomerizes even at only a little



(*E*)

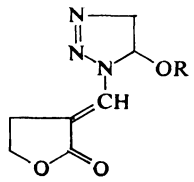


(*Z*)



I, X = 4-$CH_3C_6H_4SO_3$
II, X = piperidino
III, X = pyrrolidino
IV, X = morpholino
V, X = C_4H_9S
VI, X = 4-$CH_3C_6H_4S$

VII, X = 2-$C_{10}H_7S$
IX and *X*, X = $CH_2CH_2OCOC{=}CHO$
XI, X = N_3
XIII, X = Cl
XIV, X = CN



XV, R = C_4H_9
XVI, R = cyclo-C_6H_{11}

$ZOCH_2CH_2C(Y){=}CHX$

XII, X = 4-$CH_3C_6H_4SO_3$; Y = CO_2H; Z = H
XVII, X = $CH_2(OH)CH_2C(CO_2H){=}CHO$; Y = CO_2H; Z = H
XVIII, X = 4-$CH_3C_6H_4SO_3$; Y = CH_2OH; Z = H
XIX, X = 2-$C_{10}H_7S$; Y = CH_2OH; Z = H
XX, X = 4-$CH_3C_6H_4SO_3$; Y = CH_2OCOCH_3; Z = $COCH_3$

elevated temperature (*c.* 30°C), or on longer standing in solution at a temperature around 20°C to give the azide (*E*)-*XI*; this has to be considered when preparing the azide (*Z*)-*XI*, the preparative exploitation of which is therefore somehow limited.

The (*E*)-isomer of sodium 3-(hydroxymethylene)dihydro-2(3*H*)-furanone[1] ((*E*)-*VIII*) reacts with tosylate (*E*)-*I* to furnish pure di((*E*)-2(3*H*)-dihydrofuranone--3-methine) ether (*IX*), with tosylate (*Z*)-*I* it yields a 1 : 2 mixture of ether *IX* and ((*E*)-2(3*H*)-dihydrofuranone-3-methine) ((*Z*)-2(3*H*)-dihydrofuranone-3-methine) ether (*X*); neither isomerization of the ether *IX* to ether *X*, nor isomerization of tosylate (*Z*)-*I* to (*E*)-*I* was observed under these reaction conditions. It could be therefore presumed that stereoconvergence during reaction of the activated double bond with the bulky oxygen-containing nucleophile was involved.

Tosylate (*E*)-*I* gave with methanolic hydrogen chloride the reactive (*E*)-3-(chloromethylene)dihydro-2(3*H*)-furanone ((*E*)-*XIII*) which, upon reaction with piperidine, pyrrolidine, morpholine, or 2-naphthalenethiol, afforded the corresponding (*E*)-*II*, (*E*)-*III*, (*E*)-*IV*, and (*E*)-*VII*. Tosylate (*E*)-*I* and potassium cyanide in dimethyl sulfoxide gave the corresponding (*E*)-3-(cyanomethylene)dihydro-2-(3*H*)-furanone ((*E*)-*XIV*) in a low yield only; even a detailed analysis of the reaction mixture failed to separate any other pure compound. Addition of the azide (*E*)-*XI* to isobutyl vinyl ether, or to cyclohexyl vinyl ether is quantitative. So far, we have not succeeded to establish the orientation in addition of vinyl ethers to azide (*E*)-*XI*, and thereby the exact position of the alkoxyl group in (*E*)-3-(5-isobutoxy-1-triazolinomethylene)dihydro-2(3*H*)-furanone ((*E*)-*XV*) and in (*E*)-3-(5-cyclohexyloxy-1-triazolinomethylene)dihydro-2(3*H*)-furanone ((*E*)-*XVI*); they are given in accordance with[11] only.

Alkaline hydrolysis of tosylates (*E*)-*I*, (*Z*)-*I* and the ether *IX* led to the corresponding (*E*)- and (*Z*)-2-(4-toluenesulfonyloxymethylene)-4-hydroxybutanoic acids ((*E*)-*XII*) and ((*Z*)-*XII*), and to 1,1'-oxydi((*E*)-1-butene-4-hydroxy-2-carboxylic) acid (*XVII*). Reduction of (*E*)-*I* and (*Z*)-*I* with chloralane gave the corresponding (*E*)- and (*Z*)-2-(4-toluenesulfonyloxymethylene)-1,4-butanediols ((*E*)-*XVIII*) and ((*Z*)-*XVIII*), reduction of (*E*)-*VII* with the same reagent afforded (*E*)-2-(2-naphthylthiomethylene)-1,4-butanediol ((*E*)-*XIX*). Diols (*E*)-*XVIII* and (*Z*)-*XVIII* are very sensitive towards acid medium due to their allylic and homoallylic hydroxyl groups and therefore, they undergo a deep decomposition. Similarly, a decomposition takes place also in an alkaline medium likely as a result of a primary attack of hydroxyl ions at sulfur. These facts have so far prevented cyclizing the diols into 3-(4-toluenesulfonyloxymethylene)tetrahydrofuran, a potential precursor of the hitherto unknown 3-tetrahydrofuranaldehyde. An excess of acetic anhydride converts the diol (*E*)--*XVIII* to (*E*)-1,4-diacetoxy-2-(4-toluenesulfonyloxymethylene)butane ((*E*)-*XX*).

The (*E*)- and (*Z*)-configurations of substances prepared were assigned on the basis of their ^{1}H NMR spectral data. As reported[4,12,13], vinylic protons of (*E*)-isomers are, like ours, downfield shifted, when compared with the corresponding (*Z*)-isomers (Tables I and II). Our results show that similar signals of vinylic protons of (*E*)-iso-

TABLE I

Physicochemical constants and characteristic ^{1}H NMR signals of 3-(X-methylene)dihydro-2(3*H*)-furanones

Compound	M.p., °C b.p., °C/kPa (n_D^{20})	^{1}H NMR in C^2HCl_3 (δ, ppm)/J (Hz) (1) =CH, (2) CH_2, (3) CH_2O		Formula (M.w.)	Calculated/Found		
					% C	% H	% N
(*E*)-*II*	66—67	(1) 7·13/1·7; (3) 4·24/7·1; (2) 2·95/1·7; 7·1;	(2) 3·00/1·7; 7·1 (1)[a] 6·93/1·7; (3) 4·09/7·1	$C_{10}H_{15}NO_2$ (181·2)	66·28 66·03	8·34 8·27	7·73 7·65
(*Z*)-*II*	—	(1)[a] 6·43/1·0; (3) 4·03/7·1	(2) 7·4/1·0; 7·1	—	—	—	—
(*E*)-*III*	112·5—111·5	(1) 7·30/1·7; (3) 4·18/7·5; (2) 3·09/1·7; 7·5;	(2) 3·08/1·7; 7·5 (1)[a] 7·17/1·7; (3) 4·09/7·5	$C_9H_{13}NO_2$ (167·2)	64·65 64·52	7·84 7·96	8·38 8·44
(*Z*)-*III*	—	(1)[a] 6·43/1·0; (3) 4·09/6·5	(2) 2·78/1·0; 6·5	—	—	—	—
(*E*)-*IV*	102·5—103·5	(1) 7·09/1·9; (3) 4·23/7·5; (2) 3·02/1·9; 7·5;	(2) 2·93/1·9; 7·5 (1)[a] 6·93/1·9; (3) 4·17/7·5	$C_9H_{13}NO_3$ (183·2	59·00 59·13	7·15 7·19	7·65 7·67
(*Z*)-*IV*	—	(1)[a] 6·43/1·2; (3) 4·16/7·5	(2) 2·79/1·2; 7·5	—	—	—	—
(*E*)-*V*	152—156/0·5 (1·5431)	(1) 7·47/2·5; (3) 4·30/7·8; (2) 2·95/2·5; 7·8;	(2) 2·96/2·5; 7·8 (1)[a] 7·45/2·5; (3) 4·34/7·8	$C_9H_{14}O_2S$ (186·3)	58·02 58·21	7·57 7·43	
(*Z*)-*V*	—	(1)[a] 7·14/1·6; (3) 4·04/7·0	(2) 2·93/1·6;7·0	—	—	—	—

(*E*)-*VI*	97—98	(1)[b] 7·74/3·0; (3) 3·59/7·5	(2) 2·11/3·0; 7·5	$C_{12}H_{12}O_2S$ (220·3)	65·42 65·31	5·49 5·53	
(*E*)-*VII*	150·5—151·5	(1) 7·73/2·7; (3) 4·38/7·5	(2) 2·73/2·7; 7·5	$C_{15}H_{12}O_2S$ (256·3)	70·29 70·68	4·72 5·22	
IX	247—249	(1) 7·54/2·8; (3) 4·41/7·8	(2) 2·99/2·8; 7·8	$C_{10}H_{10}O_5$ (210·2)	57·61 57·52	4·79 4·83	
X	197—198	(1)[c] 7·48/2·8; (3) 4·43/7·4; (2) 2·97/2·1; 7·2;	(2) 3·10/2·8; 7·4 (1)[d] 6·87/2·1; (3) 4·38/7·2	$C_{10}H_{10}O_5$ (210·2)	57·61 57·65	4·79 4·70	
(*E*)-*XI*	96·5—98·5	(1) 7·34/2·8; (3) 4·30/7·5; (2) 2·86/2·8; 7·5;	(2) 2·80/2·8; 7·5 (1)[a] 7·57/2·8 (3) 4·39/7·5	$C_5H_5N_3O_2$ (139·1)	43·17 43·10	3·62 3·51	30·21 29·92
(*Z*)-*XI*	92·5—93·5	(1) 6·76/2·3; (3) 4·34/7·5; (2) 2·96/2·3; 7·5;	(2) 2·95/2·3; 7·5 (1)[a] 7·13/2·3 (3) 4·31/7·5	$C_5H_5N_3O_2$ (139·1)	43·17 42·98	3·62 3·53	30·21 30·11
(*E*)-*XIII*	95/0·6 (1·5056)	(1)[e] 7·13/3·0; (3) 4·33/6·4	(2) 2·95/3·00; 6·4	$C_5H_5O_2Cl$ (132·5)	45·32 45·03	3·80 3·61	
(*E*)-*XIV*	245—247	(1) 7·61/2·8; (3) 4·44/7·4	(2) 2·99/2·8; 7·4	$C_6H_5NO_2$ (123·1)	58·54 58·30	4·09 3·13	11·38 11·29
(*E*)-*XV*	82—83·5	(1) 7·85/2·5; (3) 4·39/7·3;	(2) 3·22/2·5; 7·3	$C_{11}H_{17}N_3O_3$ (239·3)	55·51 55·37	7·18 7·24	17·56 17·18
(*E*)-*XVI*	97—99	(1) 7·63/2·6; (3) 4·38/7·5	(2) 3·24/2·6; 7·5	$C_{13}H_{19}N_3O_3$ (265·3)	58·85 58·61	7·22 7·18	15·84 15·65

[a] In hexadeuterioacetone; [b] in hexadeuteriobenzene; [c] proton signals of the (*E*)-isomer; [d] proton signals of the (*Z*)-isomer; [e] in CCl_4.

TABLE II

Physicochemical constants and characteristic ^{1}H NMR signals of compounds $ZOCH_2CH_2C(Y)=CHX$

Compound	M.p., °C	^{1}H NMR in C^2HCl_3, (δ, ppm)/J (Hz)M (1) CH_2O; (2) CH_2; (3) =CH, (4), $=CCH_2O$	Formula (m.wt.)	Calculated/ /Found	
				% C	% H
(*E*)-*XII*	131–132	(1) 3·54/7·5; (2) 2·45/7·5; (3) 7·2; (2)[a] 3·48/7·5; (2) 2·45/7·5; (3) 7·57	$C_{12}H_{14}O_6S$ (286·3)	50·34 50·12	4·93 5·11
(*Z*)-*XII*	112–113	(1)[a,b] 3·56/6·6; (2) 2·35/6·6; 1·1; (3) 7·00/1·1 (1)[a,c] 4·28/7·3; (2) 3·07/7·4; 2·3; (3) 7·15/2·3	$C_{12}H_{14}O_6S$ (286·3)	50·34 50·21	4·93 4·86
XVII	201·5–203·5	(1)[d] 3·73/6·9; (2) 2·65/6·9; (3) 7·79	$C_{10}H_{14}O_7$ (246·2)	48·78 48·50	5·73 5·64
(*E*)-*XVIII*	80–82	(1) 3·50/6·0; (2) 2·25/6·0; (3) 6·50; (4) 3·91	$C_{12}H_{16}O_5S$ (172·3)	52·93 52·86	5·92 5·79
(*Z*)-*XVIII*	oil	(1) 3·59/6·0; (2) 2·20/6·0; (3) 6·21; (4) 3·98	$C_{12}H_{16}O_5S$ (172·3)	52·93 42·77	5·92 5·73
(*E*)-*XIX*	132–133	(1) 3·77/5·5; (2) 2·57/5·5; (3) 6·43; (4) 4·13	$C_{15}H_{16}O_2S$ (260·4)	69·19 68·83	6·19 5·91
(*E*)-*XX*	oil	(1) 3·80/6·3; (2) 2·23/6·3; (3) 6·59; (4) 4·39	$C_{16}H_{20}O_7S$ (356·4)	53·92 53·67	5·66 5·50

[a] In hexadeuterioacetone; [b] form of compound (*Z*)-*XIII* predominating in hexadeuterioacetone (2 : 1); [c] the second form of compound (*Z*)-*XII*, representation in deuteriochloroform (1 : 1), [d] in hexadeuterioacetone–^2H_2O.

mers are by 0·30–0·70 ppm downfield shifted (relative to those of their (*Z*)-counterparts). Position of these signals is strongly solvent-dependent and, therefore, it is advantageous to use also the second criterion – the coupling constants of the vinylic protons which are by 0·5–1·0 Hz greater with (*E*)-isomers when compared with (*Z*)--isomers. These differences in a single molecule are well exemplified by the ^{1}H NMR spectrum of ether *X*.

Noteworthy are the ^{1}H NMR spectra of acids (*E*)-*XII* and (*Z*)-*XII*: whereas the former exists in one form only regardless the solvent, the ^{1}H NMR spectrum of the latter indicates the presence of two forms, the ratio of which is a function of the solvent used. Both these forms differ (Table II) not only in chemical shifts of vinylic and methylene protons, but also in coupling constants. We suppose, therefore, that this form, the concentration of which increases with increasing polarity of the medium, is the free acid, and the other one, the concentration of which increases with decreasing polarity of the medium, is the acid (*Z*)-*XII* with a strong intramolecular hydrogen bonding between the carboxyl group and the oxygen atom of the sulfonyloxy group.

The chloro derivative (*E*)-*XIII* exhibited no *in vivo* activity against P 388 lymphocytic leukemia in white mice[14].

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REFERENCES

1. Jonas J.: This Journal *49*, 1907 (1984).
2. Rappoport T.: Accounts Chem. Res. *14*, 7 (1981).
3. Lee J.-H., Huang E.-S., Piantadosi C., Pagano J. A., Geissman T. A.: Cancer Res. *31*, 1649 (1971).
4. Stang P. J., Treptow W. L.: J. Med. Chem. *24*, 468 (1981).
5. Modena G.: Accounts Chem. Res. *4*, 73 (1971).
6. Rappoport Z., Topol A.: J. Amer. Chem. Soc. *102*, 406 (1980).
7. Apeloig Y., Rappoport Z.: J. Amer. Chem. Soc. *101*, 5095 (1979).
8. Rappoport Z.: Advan, Phys. Org. Chem. *7*, 1 (1969).
9. Chalcat J. C., Théron F., Vessiere R.: Bull. Soc. Chim. Fr. *1970*, 4486.
10. Truce W. E., Gorbaty M. L.: J. Org. Chem. *35*, 2113 (1970),
11. Huisgen R.: Angew. Chem. *75*, 618 (1963).
12. Treptow W. L.: *Thesis*. University of Utah, USA, 1980.
13. Howie G. A., Stamos I. K., Cassady J. M.: J. Med. Chem. *19*, 309 (1976).
14. Ujházy V.: Private communication.

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