CONFIGURATION OF SODIUM SALT AND PREPARATION OF SULPHONATES AND CARBOXYLATES OF (*E*)- AND (*Z*)-3-(HYDROXYMETHYLENE)DIHYDRO-2(3*H*)-FURANONE

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Dedicated to Dr M. Kratochvil on the occasion of his 60th birthday.

The sodium salt of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone (*I*) can be obtained in solid state in the form of (*Z*)-isomer, (*E*)-isomer, or their mixture, whereas in solutions it only exists in the form of (*E*)-isomer. Reactions of these sodium salts with sulphonyl or acyl chlorides or sulphonic acid anhydrides give the respective (*E*)- and (*Z*)-sulphonates or carboxylates of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone in high yields and purity. Configuration of the sodium salt isomers has been confirmed by their IR and ^{12}C NMR spectra in solid state, that of the isomeric sulphonates and carboxylates has been confirmed by their ^{1}H and ^{13}C NMR spectra in solution.

The sodium salt of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone (*I*) was prepared for the first time by Korte and Machleidt[1] and was used in reactions with sulphonic acid chlorides[2-4], trifluoromethanesulphonic acid anhydride[4], and acyl chlorides[4,5]. In this way it was possible to prepare (*E*)-3-(*p*-toluenesulphonyloxymethylene)dihydro-2(3*H*)-furanone[2,3] (*E*)–(*II*), a 5 : 1 mixture of (*Z*)- and (*E*)-3-(methanesulphonyloxymethylene)dihydro-2(3*H*)-furanones[4] (*Z*)–(*III*) and (*E*)–(*III*), and a 1 : 5 mixture of (*Z*)- and (*E*)-3-(trifluoromethanesulphonyloxymethylene)dihydro-2(3*H*)-furanones[4], from which the individual isomers were separated by column chromatography, a 1 : 20 mixture of (*Z*)- and (*E*)-3-(acetoxymethylene)dihydro-2(3*H*)-furanones[5] (*Z*)–(*IV*) and (*E*)–(*IV*), and (*E*)-3-(benzoyloxymethylene)dihydro-2(3*H*)-furanone[3] (*E*)–(*V*). The sulphonates and carboxylates derived from compound *I* are interesting with respect to the role of α-methylene-γ-butyrolactone grouping presumed in the cancerostatic effects of both natural[6] and synthetic products[3,4], and they serve as suitable substrates in studies of the addition-elimination reactions at the activated double bond[7]. Therefore, we have investigated properties of the salt *I* with the aim of preparation of pure (*E*)- and (*Z*)-isomers of the said sulphonates and carboxylates.

The solid salt *I* was found to be a polymorphous substance. Two crystalline modifications, (*E*) and (*E* + *Z*), were proved, and the existence of the third, (*Z*), is presumed.

The modification (*Z*) is obtained when the salt *I* is prepared at −15 to −20°C; it is considerably unstable, being rapidly converted (the half-life in minutes) to the stable modification (*E*) at about 0°C. The modification (*E* + *Z*) with varying admixture of the (*E*) modification is formed at toom temperature and transformed slowly (the half-life of several weeks) to the (*E*) modification. The phase transitions (*Z*) → (*E*) and (*E* + *Z*) → (*E*) can be accelerated considerably by heating up to 100°C,

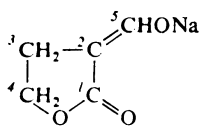
TABLE I

The diffraction angles (ϑ), distances (*d*) between the planes, and intensities (*I*) obtained from the powder diagrams of the sodium salt of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone (*I*)

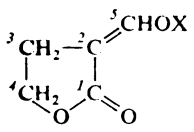
(*E* + *Z*) modification[a]			(*E*) modification[b]		
2ϑ, deg	*d*, Å	*I*	2ϑ, deg	*d*, Å	*I*
7·0	12·63	20	—	—	—
8·0	11·05	4	8·1	10·92	12
13·9	6·371	8	—	—	—
14·6	6·067	16	—	—	—
15·9	5·573	4	16·4	5·405	8
18·05	4·914	12	17·9	4·955	20
21·2	4·191	4	—	—	—
22·1	4·022	4	—	—	—
24·35	3·655	12	24·45	3·641	8
24·95	3·569	12	25·55	3·486	12
25·75	3·460	16	27·25	3·273	4
28·0	3·187	16	27·9	3·198	12
29·7	3·008	12	29·05	3·074	4
30·6	2·921	8	30·25	2·954	8
32·1	2·788	4	32·15	2·784	4
33·3	2·691	12	33·45	2·679	4
34·2	2·622	4	35·8	2·508	8
36·75	2·445	4	38·15	2·359	4
38·0	2·368	16	39·7	2·270	8
39·3	2·292	8	41·75	2·163	8
41·4	2·181	12	—	—	—
44·75	2·025	8	—	—	—
47·6	1·910	4	47·2	1·926	12
50·1	1·820	4	50·1	1·820	8
52·85	1·732	12	54·05	1·697	4

[a] The sample of salt *I* prepared according to ref.[1] at room temperature. [b] The sample sub ([a]) kept at room temperature for 4 months or isomerized by 1 h heating at 100°C.

or by suspending in polar solvent, *e.g.*, acetone. Dissolution of any of the crystalline modifications of the salt *I*, *e.g.* in water or dimethyl sulphoxide, causes immediate formation of the (*E*)-isomer of *I*.



I



II, X = 4-$CH_3C_6H_4SO_2$
III, X = CH_3SO_2
IV, X = CH_3CO
V, X = C_6H_5CO
VI, X = $C_6H_5SO_2$

The (*E*) and (*E* + *Z*) modifications were proved by the powder Debye–Scherrer diagrams (Table I); the proportions of the (*E*)- and (*Z*)-isomers of the salt *I* are proved by the ^{13}C NMR spectrum in solid phase and IR spectra in Nujol (Table II) as well as by the preparation results. A single configuration of the sodium salt *I*

TABLE II

The spectral characteristics of (*E*) and (*Z*) configurations of sodium salt of 3-(hydroxymethylene)-dihydro-2(3*H*)-furanone (*I*)

Configuration	IR spectra[a,b] cm^{-1}	C or H–(C)	^{13}C NMR in solid phase δ, ppm[b]	^{13}C NMR in solution δ, ppm		^{1}H NMR[c] δ, ppm/*J*, Hz
		1	180·9	182·8[c]	173·7[d]	—
	672 s	2	92·2	96·0	84·3	—
(*E*)-*I*	760 s	3	25·1	26·4	23·3	2·80/8·5; 1·7
	1 685 vs	4	66·9	69·4	61·3	4·37/8·5
		5	175·7	174·8	171·0	8·48/1·7
		1	178·9	—	—	—
	713 s	2	86·5	—	—	—
(*Z*)-*I*	782 s	3	28·7	—	—	—
	1 715 vs	4	64·8	—	—	—
		5	174·4			

[a] Suspension in Nujol; [b] measured were both the crystalline (*E* + *Z*) modification prepared according to ref.[1] and kept at room temperature for various periods, and the crystalline (*E*) modification obtained from the (*E* + *Z*) modification either by 4 months keeping or by 1 h heating at 100°C; [c] in $^{2}H_2O$; [d] in hexadeuteriodimethyl sulphoxide.

TABLE III

The prepared sulphonates and carboxylates of (*E*)- and (*Z*)-3-(hydroxymethylene)dihydro-2-(3*H*)-furanone

Compound	M.p., °C (solvent) yield, %	^{1}H NMR in C^2HCl_3 σ (ppm)/J (Hz) H–(C)	^{13}C NMR in C^2HCl_3[a] δ (ppm) C	Formula (m.wt.)	Calculated/Found	
					% C	% H
(*E*)-*II*	116·5—117·5[b] (ethanol) 83	(3) 2·84/7·2; 3·0 (4) 4·30/7·2 (5) 7·58/3·0	(1) 168·21 (2) 111·62 (5) 141·15			
(*Z*)-*II*	145—146·5 (ethanol) 68	(3) 2·88/7·4; 2·3[c] (4) 4·23/7·4 (5) 6·98/2·3	(1) 164·14 (2) 110·65 (5) 137·49	$C_{12}H_{12}O_5S$ (268·3)	53·73 53·68	4·51 4·62
(*E*)-*III*	119·5—120·5 (ethanol) 75	(3) 3·01/7·2; 2·9[d] (4) 4·43/7·2 (5) 7·74/2·9 (X) 3·22	(1) 168·16 (2) 111·46 (5) 140·72	$C_6H_8O_5S$ (192·2)	37·49 37·18	4·19 4·24
(*Z*)-*III*	92—93 (ethanol) 73	(3) 3·01/7·2; 2·24[d] (4) 4·42/7·2 (5) 7·07/2·4 (X) 3·23	(1) 164·58 (2) 111·61 (5) 137·18	$C_6H_8O_5S$ (192·2)	37·49 37·23	4·19 4·41
(*E*)-*IV*	40·5—41·5 (diethyl ether) 52	(3) 3·00/7·4; 3·0[e] (4) 4·42/7·4 (5) 8·25/3·0 (X) 2·26	(1) 169·41 (2) 108·30 (5) 140·29	$C_7H_8O_4$ (156·1)	53·85 54·07	5·16 5·07

(*Z*)-*IV*	92—93·5 (ethyl acetate) 48	(3) 3·00/7·4; 2·2[c] (4) 4·38/7·4 (5) 7·62/2·2 (X) 2·28	(1) 165·57 (2) 107·63 (5) 137·28	$C_7H_8O_4$ (156·1)	53·85 54·18	5·16 5·37
(*E*)-*V*	151—152[f] (ethyl acetate) 67	(3) 3·12/7·4; 3·0[f] (4) 4·13/7·4 (5) 8·53/3·0	(1) 169·24 (2) 109·00 (5) 140·50			
(*Z*)-*V*	142—143 (ethyl acetate) 65	(3) 3·02/7·6; 2·2 (4) 4·40/7·6 (5) 7·90/2·2	(1) 165·66 (2) 107·39 (5) 137·63	$C_{12}H_{10}O_4$ (218·2)	66·05 66·21	4·62 4·75
(*E*)-*VI*	82·5—83·5 (ethanol) 86	(3) 2·88/7·2; 2·9 (4) 4·34/7·2 (5) 7·62/2·9	(1) 168·13 (2) 111·84 (5) 141·04	$C_{11}H_{10}O_5S$ (254·3)	51·96 52·09	3·96 4·11
(*Z*)-*VI*	133—134 (ethanol) 71	(3) 2·91 7·6; 2·4 (4) 4·32/7·6 (5) 7·04/2·4	(1) 164·06 (2) 110·87 (5) 137·30	$C_{11}H_{10}O_5S$ (254·3)	51·96 52·27	3·96 4·09

[a] With respect to hexamethyldisiloxane as the internal standard; [b] ref.[2] m.p. 118—119°C; [c] in C^2HCl_3–hexadeuterioacetone; [d] *cf.* ref.[4]; [e] *cf.* ref.[5]; [f] *cf.* ref. [3].

in solutions is confirmed by ^{1}H and ^{13}C NMR spectra (Table II), and it is identified as the (*E*) configuration by the preparation results.

The findings were used for developing methods of preparation of pure sulphonates and carboxylates of (*E*)- and (*Z*)-3-(hydroxymethylene)dihydro-2(3*H*)-furanone. The reactions of suspensions of the salt *I*, prepared according to ref.[1] except for the temperature used (−15 to −20°C), with acetone solutions of sulphonic acid chlorides or anhydrides or acyl chlorides at −75°C give pure (*Z*) sulphonates or carboxylates of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone, whereas the reactions of the salt *I* with sulphonic acid chlorides or anhydrides or acyl chlorides in aqueous-acetone solutions give pure (*E*) sulphonates or carboxylates of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone. A study of behaviour of the salt *I* in aqueous-acetone solutions of various pH by means of ^{1}H NMR spectroscopy showed that the decomposition takes the course suggested by Korte and Büchel[8]; the starting substrate of the decomposition is 3-(hydroxymethylene)dihydro-2(3*H*)-furanone, and the decomposition rate depends directly on the proton concentration in the medium. That is why the presence of triethylamine in the reactions of the solutions of the salt *I* with sulphonic acid chlorides, anhydrides, or acyl chlorides increases the yields and, in addition, diminishes substantially the reaction time. The configurations of the prepared sulphonates and carboxylates derived from the salt *I* were determined with the help of the ^{1}H and ^{13}C NMR spectra. Our findings agree with those of Treptow[9] who applied both the relation derived by Pascual and coworkers[10] and a study of the Overhauser effect. In the ^{13}C NMR spectra of the compounds prepared, most valuable for determination of the configuration are the differences in the chemical shifts of $C_{(1)}$ and $C_{(5)}$ carbon atoms which show a down-field shift with the (*E*)-isomers by 3−5 ppm. The preparation of (*Z*)−*II* tosylate also solves definitively the problem of configuration of the tosylate *II* prepared by Arjungi and coworkers[2]: the (*Z*) configuration suggested by these authors and made doubtful in ref.[3] is not correct.

EXPERIMENTAL

The temperature data are not corrected. The ^{1}H NMR spectra were measured with a Tesla BS 567 and a Tesla BS 467 apparatus at 100 and 60 MHz, respectively, using hexamethyldisiloxane or sodium 4,4-dimethyl-4-silapentanesulphonate as internal standards. The ^{13}C NMR spectra of the solutions were measured with a Tesla BS 567 apparatus at 25 MHz using hexamethyldisiloxane as the internal standard. The ^{13}C NMR spectra of the solid samples were measured with a Bruker CXP 200 apparatus at 50·3 MHz with rotation (3·6 kHz) under the magic angle with the crosspolarisation time of 5 ms, using hexamethylbenzene as external standard. All the chemical shifts are given with respect to tetramethylsilane as the internal standard. The infrared spectra were measured with a Zeiss UR 20 apparatus in Nujol suspension. The powder Debye–Scherrer diagrams were obtained with the use of a chamber of 114·6 mm diameter with Cu K_α radiation and at the tube voltage of 40 kV and current of 30 mA with 25 h exposition. The diagrams were evaluated with the accuracy of 0·1 mm using a comparator. The low accuracy of the measurements is due to diffusion of the diffraction lines.

Sulphonates and Carboxylates of (*Z*)-3-(Hydroxymethylene)dihydro-2(3*H*)-furanone (*Z*)-*II*, (*Z*)-*III*, (*Z*)-*IV*, (*Z*)-*V*, and (*Z*)-*VI*

A suspension of 3·5 g (0·15 mol) sodium in 50 ml diethyl ether was stirred at −15 to −20°C, and a solution of 13 g (0·15 mol) γ-butyrolactone and 12 g (0·15 mol) ethyl formiate in 40 ml diethyl ether was added thereto drop by drop during 5 h. The mixture, which separates gradually a cream-coloured precipitate of the sodium salt *I*, was further stirred 1 h and cooled to −75 °C, whereupon a pre-cooled (−75°C) solution of 0·15 mol of the respective sulphonic acid chloride or anhydride or acyl chloride in 400 ml acetone was added at once. After 2 h stirring and cooling, the mixture and the cooling bath were allowed to attain room temperature, and the reaction mixture was concentrated under reduced pressure and washed with 300 ml water. The separated solid was collected by suction, washed with water, dried under reduced pressure and recrystallized. The products prepared and their physico-chemical characteristics are given in Table III.

Sulphonates and Carboxylates of (*E*)-3-(Hydroxymethylene)dihydro-2(3*H*)-furanone (*E*)-*II*, (*E*)-*III*, (*E*)-*IV*, (*E*)-*V*, and (*E*)-*VI*

Sodium salt of 3-(hydroxymethylene)dihydro-2(3*H*)-furanone (*I*) (2·8 g; 0·02 mol) and 2 g (0·02 mol) triethylamine were dissolved in 20 ml water, the solution was diluted with 40 ml acetone, and treated with 0·02 mol (added at once) of the corresponding liquid sulphonic acid chloride or with solution of 0·02 mol of the corresponding solid reagent dissolved in a mixture of 50 ml acetone and 25 ml water. The mixture was stirred 30 min, concentrated under reduced pressure, shaken with 100 ml water, and filtered with suction. The precipitate was dried and recrystallized. The sulphonates and carboxylates prepared and their physico-chemical characteristics are given in Table III.

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