Methylation of 1,3-cyclopentanedione, 1,3-cyclohexanedione, and 1,3-cycloheptanedione with iodomethane in aprotic solvents in the absence and in the presence of 18-crown-6

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Anions of 1,3-cyclopentanedione, 1,3-cyclohexanedione, and 1,3-cycloheptanedione were methylated with iodomethane in aprotic solvents. It was found that the highest amount of *O*-derivative was formed in nonpolar solvents (diethyl ether, tetrahydrofuran). The presence of 18-crown-6 did not affect the C/O ratio of methylation of the investigated 1,3-cycloalkanedione anions significantly. The reasons for different solvent effects on the C/O ratio of alkylation of cyclic and acyclic 1,3-dicarbonyl compounds are discussed.

Было осуществлено метилирование анионов 1,3-циклопентандиона, 1,3-циклогександиона и 1,3-циклогептандиона иодистым метилом в апротических растворителях и было обнаружено, что больше всего *O*-производного образуется в неполярных растворителях (диэтиловый эфир, тетрагидрофуран). Было найдено, что присутствие 18-краун-6 не влияет существенно на отношение C/O метилирования анионов изученных 1,3-циклоалкандионов. Обсуждаются причины различного влияния полярности растворителя на отношение C/O алкилирования в случае циклических и ациклических 1,3-дикарбонильных соединений.

At alkylations of acyclic β-dicarbonyl compounds the change from nonpolar solvents of low solvation ability to polar aprotic solvents of higher solvation ability results in relative increase of the *O*-alkylation product, *i.e.* the C/O ratio decreases [1, 2]. In the case of alkylation of 2-aryl-1,3-indandiones, 2-phenyl-2,3-dihydro-1,3-phenalenedione, and 5,7-dioxo-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptane the reverse is true; more *O*-derivative is formed in less polar solvents [3—6].

The different solvent effects on the C/O ratio of alkylation of 2,4-pentanedione anions and ethyl acetoacetate on one hand and of the polycyclic β-diketone anions on the other hand led us to the investigation of this effect on simpler type of cyclic β-diketones, namely, 1,3-cycloalkanediones with five to seven carbon atoms in the cycle. The results of these reactions should simultaneously answer the question whether the mentioned different solvent effect is of a general nature and is connected with conformation arrangement of the anions of cyclic and acyclic

β-dicarbonyl compounds, respectively, or it is connected with the stability of the ketoenol and the diketo forms of these compounds.

The effect of the solvent on the C/O ratio of alkylation of 1,3-cycloalkanediones has not been studied yet. Only alkylations of 1,3-cyclohexanedione were carried out in water and alcohol where products of alkylation on the carbon atom were predominantly formed [7]. In the case of 1,3-cyclopentanedione, alkylations of its thallium(I) salts were carried out [8]. Reactions of 1,3-cyclopentanedione and 1,3-cyclohexanedione with diazomethane resulted exclusively in products of *O* alkylation [9]. Based on this knowledge we prepared the *C*- and the *O*-methyl derivatives of 1,3-cycloalkanediones as standards for gas chromatographic determination of the C/O ratio of methylation. Such derivatives of 1,3-cycloheptanedione, except 2-methyl-1,3-cycloheptanedione, have not been described yet [10].

Experimental

Melting points were determined on a Kofler block. Infrared spectra were measured in chloroform solutions on a Perkin—Elmer 567 spectrometer in the region of 400—2000 cm^{-1} in NaCl cells. ^{1}H-N.m.r. spectra were measured in deuterated chloroform on a Tesla BS 487 apparatus at 80 MHz working frequency using tetramethylsilane as internal standard.

2-Methyl-1,3-cycloalkanediones

To the solution of 1,3-cycloalkanedione (0.10 mol) and sodium hydroxide (0.10 mol) in water (12.5 ml) and dioxan (7.5 ml) iodomethane (0.12 mol) was added and the mixture was refluxed until neutral reaction mixture. After cooling the reaction mixture to 0°C, the product was sucked and crystallized from ethanol. In the case of 2-methyl-1,3-cycloheptanedione the reaction mixture was after cooling to laboratory temperature extracted with chloroform (5 × 10 ml) and the extract was dried with magnesium sulfate. The solvent was distilled off and the residue was rectified on a column (10 cm).

2-Methyl-1,3-cyclopentanedione: Yield 35%, m.p. 210—212°C in accordance with the literature [11].

2-Methyl-1,3-cyclohexanedione: Yield 50%, m.p. 207—209°C; Ref. [12] gives m.p. 208—210°C.

2-Methyl-1,3-cycloheptanedione: Yield 54%, b.p. 107—108°C/1066 Pa.

For $C_8H_{12}O_2$ (140.2) calculated: 68.54% C, 8.63% H; found: 68.42% C, 8.59% H. IR: ν(C=O) 1703, 1730 cm^{-1}. ^{1}H-NMR (δ, p.p.m.): 1.18 (3H, d, J = 7 Hz, —CH_3), 1.95 (4H, m, —CH_2—CO—), 2.52 (4H, m, —CH_2—), 3.75 (1H, d, J = 8 Hz, —C<u>H</u>(CH_3)—).

2,2-Dimethyl-1,3-cycloalkanediones

To the solution of 1,3-cycloalkanedione (0.10 mol) and sodium hydroxide (0.10 mol) in water (25 ml) and dioxan (15 ml) iodomethane (0.10 ml) was added and the mixture was

refluxed to neutral reaction. Sodium hydroxide (0.10 mol) and iodomethane (0.50 ml) were added under cooling and the mixture was refluxed again to neutral reaction. After cooling and extraction with chloroform (5 × 15 ml), the extracts were washed with sodium hydrogen carbonate and water and dried with magnesium sulfate. The solvent was distilled off and the residue was rectified on a column (10 cm). 2,2-Dimethyl-1,3-cyclopentanedione was crystallized from petroleum ether instead of distillation.

2,2-Dimethyl-1,3-cyclopentanedione: Yield 20%, m.p. 46—47°C; Ref. [13] gives m.p. 46—47°C.

2,2-Dimethyl-1,3-cyclohexanedione: Yield 45%, b.p. 103—105°C/1066 Pa, m.p. 36—38°C; Ref. [14] gives m.p. 38—39°C.

2,2-Dimethyl-1,3-cycloheptanedione: Yield 49%, b.p. 91—93°C/1066 Pa, m.p. 41—43°C.

For $C_9H_{14}O_2$ (154.2) calculated: 70.10% C, 9.15% H; found: 69.96% C, 9.12% H. IR: ν(C=O) 1703, 1730 cm^{-1}. ^{1}H-NMR (δ, p.p.m.): 1.20 (6H, s, —CH_3), 1.88 (4H, m, —CH_2—CO—), 2.45 (4H, m, —CH_2—).

3-Methoxy-2-cycloalken-1-ones

Dry ether solution of diazomethane, prepared from nitrosomethylurea (0.20 mol), was added to 1,3-cycloalkanedione (0.10 mol) in methanol (20 ml) under cooling. When the evolution of nitrogen stopped, the solvents were distilled off and the residue was rectified on a column (10 cm). At the preparation of 3-methoxy-2-cyclopenten-1-one the solid residue was sublimed at 40°C/1333 Pa.

3-Methoxy-2-cyclopenten-1-one: Yield 90%, m.p. 49—51°C; Ref. [15] gives m.p. 52—53°C.

3-Methoxy-2-cyclohexen-1-one: Yield 85%, b.p. 122—123°C/2000 Pa; Ref. [16] gives b.p. 65°C/133 Pa.

3-Methoxy-2-cyclohepten-1-one: Yield 80%, b.p. 119—120°C/1066 Pa.

For $C_8H_{14}O_2$ (140.2) calculated: 68.54% C, 8.63% H; found: 68.51% C, 8.60% H. IR: ν(C=C) 1615 cm^{-1}, ν(C=O) 1652 cm^{-1}. ^{1}H-NMR (δ, p.p.m.): 1.80 (4H, m, —CH_2—CO—), 2.55 (4H, m, —CH_2—), 5.40 (1H, s, —CH=).

3-Methoxy-2-methyl-2-cycloalken-1-ones

The procedure is identical with the preparation of 3-methoxy-2-cycloalken-1-ones. As starting compounds 2-methyl-1,3-cycloalkanediones were used.

3-Methoxy-2-methyl-2-cyclopenten-1-one: Yield 90%, m.p. 63—65°C; Ref. [17] gives m.p. 65—68°C.

3-Methoxy-2-methyl-2-cyclohexen-1-one: Yield 85%, b.p. 126—128°C/1066 Pa, m.p. 43—45°C; Ref. [18] gives m.p. 40°C.

3-Methoxy-2-methyl-2-cyclohepten-1-one: Yield 70%, b.p. 101—103°C/1066 Pa.

For $C_9H_{14}O_2$ (154.2) calculated: 70.10% C, 9.15% H; found: 70.02% C, 9.11% H. IR: ν(C=C) 1620 cm^{-1}, ν(C=O) 1646 cm^{-1}. ^{1}H-NMR (δ, p.p.m.): 1.33 (3H, s, —CH_3), 1.90 (4H, m, —CH_2—CO—), 2.50 (4H, m, —CH_2—), 3.68 (3H, s, —OCH_3).

Methylation of 1,3-cycloalkanedione anions with iodomethane

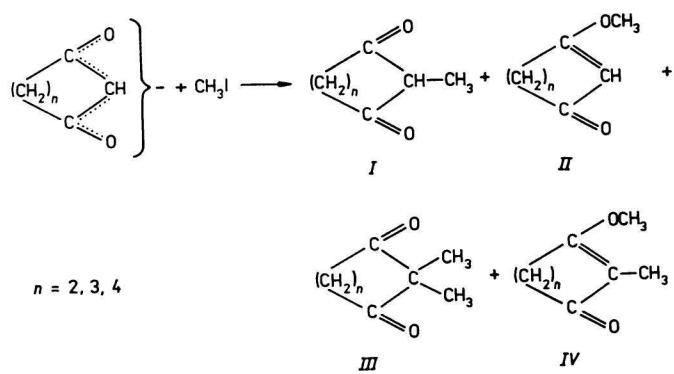
The mixture of 1,3-cycloalkanedione (1 mmol), anhydrous potassium carbonate (5 mmol), and dry solvent (15 ml) was stirred in the atmosphere of nitrogen for 30 min. Then the solution of iodomethane (1 mmol) in dry solvent (10 ml) was added and the reaction mixture was stirred at 25°C under nitrogen for 12 h. The solvent was distilled off under reduced pressure and dry methanol (10 ml) was added to the residue. The solid was filtered off and washed with dry methanol (5 × 1 ml). The supernatant was adjusted to pH 4—5 and the solution was evaporated to 2—3 ml. The individual components were determined by gas-liquid chromatography on the basis of elution times of the prepared standards (column 80 × 0.2 cm, 3% PEG-20-M, 140/220°C, N_2). The results of the reaction are presented in Table 1.

Methylation of 1,3-cycloalkanedione anions with iodomethane in the presence of 18-crown-6

The mixture of 1,3-cycloalkanedione (1 mmol), anhydrous potassium carbonate (1 mmol), 18-crown-6 (1.1 mmol), and dry solvent (15 ml) was stirred in the atmosphere of nitrogen for 30 min. The solution of iodomethane (1 mmol) in dry solvent (10 ml) was added and the reaction mixture was stirred under nitrogen at 25°C for 12 h. Then the mixture was worked up similarly as at the methylation without 18-crown-6. The results of the reactions are presented in Table 1.

Results and discussion

At the methylation of 1,3-cycloalkanedione anions the formation of the following products can be expected: 2-methyl-1,3-cycloalkanediones (*Ia—Ic*), *i.e.* products of *C* methylation, 3-methoxy-2-cycloalken-1-ones (*IIa—IIc*), *i.e.* pro-



Scheme 1

Table 1

Results of the reaction of 1,3-cycloalkanedione anions with iodomethane in different solvents in the presence and in the absence of 18-crown-6

Solvent	1,3-Cyclopentanedione				C/O[a]	Yield %	1,3-Cyclohexanedione				C/O[a]	Yield %	1,3-Cycloheptanedione				C/O[a]	Yield %
	% C	% C,C	% C,O	% O			% C	% C,C	% C,O	% O			% C	% C,C	% C,O	% O		
Diethyl	8	1	4	87	0.15	25	37	6	3	54	0.85	23	31	17	8	44	1.27	60
ether P	2	0	3	95	0.05	10	35	2	3	60	0.67	11	29	17	0	54	0.85	53
THF P	10	5	8	77	0.30	30	25	29	2	44	1.27	28	16	44	20	20	4.00	63
	17	2	7	74	0.35	13	34	14	1	41	1.44	16	20	54	10	16	5.25	57
																	5.25	57
Acetone P	21	8	8	63	0.59	50	27	37	2	34	1.94	67	37	43	8	12	7.33	70
	28	4	10	58	0.72	31	65	20	1	14	6.14	43	38	43	10	9	10.11	65
Aceto-	24	10	13	53	0.89	57	30	28	2	30	2.33	62	31	32	17	20	4.00	60
nitrile P	26	8	6	60	0.67	32	40	19	2	39	1.56	40	29	25	17	29	2.10	48
DMF P	14	8	13	65	0.54	65	5	44	1	50	1.00	73	32	29	25	14	6.14	70
	11	8	13	68	0.47	51	3	45	1	61	0.96	59	25	14	14	47	1.13	65

a) $C/O = \frac{\% C + \% C,C + \% C,O}{\% O}$.

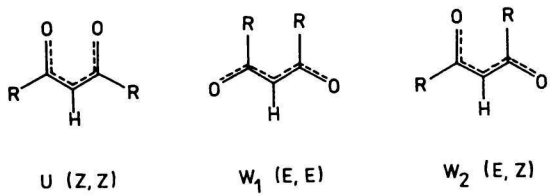
P — in the presence of 18-crown-6.

ducts of *O* methylation, 2,2-dimethyl-1,3-cycloalkanediones (*IIIa—IIIc*) and 3-methoxy-2-methyl-2-cycloalken-1-ones (*IVa—IVc*), *i.e.* products of *C* or *O* methylation of *Ia—Ic* (Scheme 1).

The above-mentioned reaction was carried out in aprotic solvents: diethyl ether, tetrahydrofuran, acetone, acetonitrile, and *N,N*-dimethylformamide. Under the conditions given in Experimental, all four aforesaid products were formed in all solvents. Their percentual composition in the reaction mixture was determined by gas chromatography.

As seen from Table 1, the ratio of C/O increases in all solvents with the increasing number of carbon atoms in the 1,3-cycloalkanedione ring. The highest amount of *O*-derivative with all three investigated 1,3-cycloalkanediones was formed in diethyl ether and tetrahydrofuran. These results are analogous to those obtained in alkylation of polycyclic β-diketones where low polar solvents also prefer the formation of *O*-derivatives [3—6] and are reversed to the results known from the chemistry of acyclic β-dicarbonyl compounds [1, 2]. The different solvent effect on the ratio of C/O in alkylation of acyclic and cyclic β-dicarbonyl compounds can be explained by different conformation arrangement of their anions and by change of the conformation due to the solvent effect.

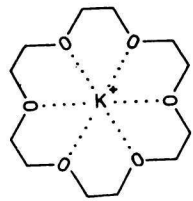
Anions of acyclic β-dicarbonyl compounds can appear in three possible conformations W_1 (E, E), W_2 (Z, E), and U (Z, Z) (Scheme 2). According to the polarity



Scheme 2

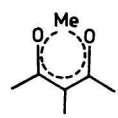
of the solvent, its basicity, and solvation abilities, the anions of β-dicarbonyl compounds appear in the form of associates of ion pairs of different aggregation degree [18, 19]. The degree of association strongly depends on polarity, but first of all on the basicity of the solvent, which plays a significant role in solvation of the cation. In low polar solvents the anions of acyclic β-dicarbonyl compounds appear in U conformation [20, 21] which is stabilized by forming a quasi-aromatic system through the metal cation (Scheme 3).

In such a case almost exclusively *C* alkylation proceeds with haloalkanes in nonpolar solvents (benzene, petroleum ether, dioxan). With the increasing solvation ability of the solvent the amount of the *O*-alkylated product increases because the strength of the bond between the oxygen and the metal atoms weakens,



Scheme 3

consequently, the conformations W_1 and W_2 appear, too. Similar effect, as to the mechanism of action and result, can be achieved by the presence of cyclic polyethers (crowns) which solvate the cations selectively. *Kurts et al.* [22] found that addition of an equimolar amount of dicyclohexyl-18-crown-6 at alkylation of potassium salt of ethyl acetoacetate with ethyl tosylate in benzene results in 100-fold increase of the *O*-alkylated product. The effect of the "crown" is based on the fact that selective solvating of potassium cation leaves the nucleophile free (Scheme 4). The ambident anion becomes "naked" enabling thus its reaction with the atom of higher electron density, *i.e.* the oxygen atom.



Scheme 4

In the case of the cyclic β-diketone anions, regarding the rigidity of the cycle to which belongs the β-dicarbonyl grouping, only the W_1 (E, E) conformation (Scheme 2) is possible where the bond between the metal cation and the anion is not so strong as in the U conformation. The changes in the structure of the cyclic β-diketone anions caused by the solvent effects are not so significant as in acyclic β-dicarbonyl compounds. This conclusion is proved also by the results of reactions carried out in the presence of 18-crown-6. From the results presented in Table 1 it is evident that in ether and tetrahydrofuran the presence of the cyclic polyether does not influence the C/O ratio significantly. As the function of the "crown" is the same at the anions of acyclic as well as cyclic β-dicarbonyl compounds, *i.e.* to solvate the cation, it can be assumed that the bond between the metal cation and the 1,3-cycloalkanedione anion is not so strong and thus its cleavage does not affect the course of alkylation significantly. The C/O ratio was more significantly affected by the presence of 18-crown-6 in acetone only. The highest amount of *C*-derivative was formed in this solvent.

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