52. The Methyl Enol Ethers of Ethyl 2,4-Dioxopentanoate

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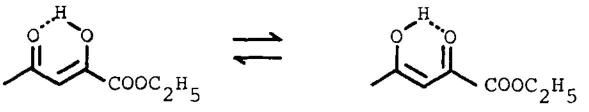
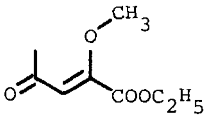
Summary

Methylation of ethyl 2,4-dioxopentanoate with diazomethane gives a mixture of two enol ethers, the 2-methoxy and the 4-methoxy isomer, with a product ratio which depends upon reaction temperature. Both enol ethers, initially (*Z*)-configurated, isomerize to the corresponding (*E*)-conformers, the 4-methoxy compound with particular ease.

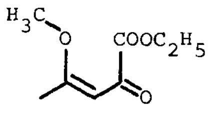
Introduction. – The highly enolic properties of ethyl 2,4-dioxopentanoate (**1**) were already recognized before 1900 and discussed by *Michael* [1] together with other cases of known *β*-diketones. The preparation of isomeric enol ethers of **1** by various methods led to controversial interpretation of the results. Thus *Claisen*'s provisional '*α*-enol ether' (=2-ethoxy isomer) obtained with ethyl orthoformate and NH_4Cl [2] turned out to be the 4-ethoxy isomer as shown by *Rossi & Lauchenauer* 40 years later [3] who prepared the 4-ethoxy compound from the 4-diethyl acetal



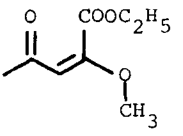
1



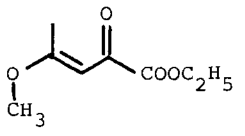
2a (*Z*),s-*trans*



3a (*Z*),s-*trans*



2b (*E*),s-*cis*



3b (*E*),s-*cis*

by elimination of ethanol. The 2-methoxy derivative **2** prepared by *v. Auwers & Cauer* [4] by treatment of the Na-salt of **1** with CH_3I or $(CH_3)_2SO_4$ was earlier assumed to be the C-methylated ketone by *Kötz & Lemien* [5]. Unambiguous proof for the structure of this enol ether **2** was achieved by *Rossi & Schinz* [6] who obtained it from the reaction of **1** with diazomethane.

The formation of isomeric enol ethers by the reaction of β-diketones with diazomethane was later demonstrated by *Eistert et al.* [7]. Obviously, the 4-methoxy isomer **3** had not been noticed by the earlier authors, and three is no further mention of this particular compound in the literature since.

Results and discussion. – The reaction of the completely enolized ethyl 2,4-dioxopentanoate (**1**) with diazomethane in ether leads to a mixture of isomeric methyl enol ethers **2a** and **3a**, their proportion in the mixture depends upon the reaction temperature. At 0°, 68–69% of **2a** and 31–32% of **3a** is obtained; this product ratio was determined by the signal intensities of the olefinic and the $H_3C(5)$ protons in the ^1H-NMR. spectrum of the mixture. The product ratio changes at lower reaction temperatures in favor of the already prevailing **2a**; at −30 and −78°, its proportion in the mixture increases to 70 and 77%, respectively (*Table 1*). The overall reaction at low temperatures proceeds considerably slower.

The primary methylation products of **1**, exclusively in (*Z*)-conformation, are of limited stability, particularly the 4-methoxy isomer **3a**. Observable only in solution, **3a** isomerizes easily with rising temperature to the (*E*)-conformer **3b**. At 0°, the isomerization of **3a** in $CDCl_3$ takes some days, at room temperature 20 hours, but at 40°, it is complete within one hour (^1H- and ^{13}C-NMR. measurements). The (*Z*)-2-methoxy isomer **2a** is stable under these conditions; traces of acid, however, which may be present in aged $CDCl_3$ promote the slow conversion into a (1:1)-mixture of (*Z*)- and (*E*)-isomers **2a** and **2b**. Thus, without paying attention to these factors a methylation mixture obtained from **1** may turn out to be rather puzzling at first inspection by spectroscopy.

It is possible to separate the (*Z*)-2-methoxy, (*E*)-2-methoxy and (*E*)-4-methoxy isomers **2a**, **2b** and **3b**, respectively, by chromatography on silica gel, but not the unstable (*Z*)-4-methoxy compound **3a**. Some isomerization of **2a** occurs on prolonged contact with silica gel.

The lability of the (*Z*)-conformers has been demonstrated for the first time by *Eistert et al.* [7] who could separate the two conformers of 4-methoxy-3-penten-2-one. Precise assignments were achieved by spectroscopic methods for the same

Table 1. *The ratios of the products obtained from methylation of ethyl 2,4-dioxopentanoate with diazomethane at various temperatures*

Bath temp.	(*Z*)-2-Methoxy isomer **2a** [%][a])	(*Z*)-4-Methoxy isomer **3a** [%][a])
0°	68–69	31–32
−30°	69–71	29–31
−78°	76–77	23–24

[a]) Accuracy: ±1%.

case by *Awang* [8]. Other examples were reported later by *Castels et al.* [9]. The temperature dependence of the formation of the isomeric enol ethers has not been recognized before.

The constitutional isomers **2** and **3** are readily distinguished by their spectroscopic properties and the conformations are assigned by means of IR. data and ^{1}H-NMR. techniques.

In the ^{13}C-NMR. spectra, the terminal CH_3-C-atoms (C(5)) appear at *ca.* 30 ppm for **2** (methyl ketone) and *ca.* 20 ppm for **3** (allylic C-atom; s. *Table 2*). The (*Z*)- and (*E*)-configurations follow from ^{1}H-NMR. nuclear *Overhauser* experiments. The observed shifts of the ^{1}H-NMR. signals of the $H_3C(5)$ group and of the olefinic H–C(3) in going from the (*Z*)- to the (*E*)-forms correspond to the 'ene-one cross shielding' rules, formulated by *Dabrowski & Tencer* [10] as a consequence of anisotropy effects in the preferred conformations: the s-*trans*-conformation of the ether **2a** is documented by the deshielding of its methyl keton protons (3 H–C(5) at 2.37 ppm) caused by the neighboring enol ether O-atom; s-*cis*-conformation suits to the isomerized ether **2b** (3 H–C(5) at 2.19 ppm). Similarly, (*E*),s-*cis*-conformation is attributed to **3b** where these CH_3-protons are deshielded due to the vicinity of the carbonyl group; **3a** in return has no such effect (3 H–C(5) at 2.11 ppm) being prevalent in (*Z*),s-*trans*-conformation. The deshielding of the olefinic H–C(3) by 0.5 ppm in **2a** and **3b** as compared to those in **2b** and **3a** is explained by an additional effect of the neighboring ester group.

Confirmation of these assignments is provided by the IR. spectra, again according to the investigations of *Dabrowsky & Tencer* [10]: s-*trans*-conformation of **2a** is indicated by strong 'inner bands' at 1669 and 1622 cm^{-1}, the shoulders at 1690 and 1600 cm^{-1} (so called 'outer bands') arising from small amounts of the corresponding s-*cis*-conformer; the s-*cis*-conformation of **2b** is manifested by strong 'outer bands' at 1695 and 1597 cm^{-1}.

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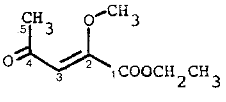
Experimental Part

1. *General.* The solvents were devoid of acid traces: ether and CCl_4 were washed with $NaHCO_3$-solution, dried and distilled; $CDCl_3$ was filtered through alumina. Diazomethane was freshly prepared from nitrosomethylurea according to [11]. Ethyl 2,4-dioxo pentanoate *(Fluka)* was distilled before use (60-65°/0.01 Torr). TLC. was performed on silica gel plates *Whatman K5F* for analytical, and *PLK5F* for preparative separations. UV. spectra ($\lambda_{max}(\varepsilon)$ in nm): *Unicam SP 1800.* IR. spectra (cm^{-1}): *Beckman IR-20A*. NMR. spectra: *Bruker WP 80, WP 60 FT* and *WH 360.* Mass spectra (MS.) (*m/z*, intensities in % of base peak): *Hewlett-Packard HP 5980 A.*

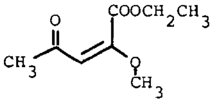
2. *Methylation of ethyl 2,4-dioxopentanoate* (**1**). To 240 mg (1.52 mmol) of **1** in 10 ml of ether at 0° was added a freshly distilled ethereal solution of diazomethane (from 1.5 g of nitrosomethylurea in 20 ml ether and 2.1 g of KOH in 2.1 ml of H_2O). The reaction was followed by TLC. (ether) until the starting material (Rf 0.2) had disappeared (after 4 h, Rf of the product 0.54). The excess of diazomethane was purged with N_2 and the solvent removed at 28°/450 Torr in a rotatory evaporator. The remaining oil (259 mg), analyzed by NMR. ($CDCl_3$), consisted of 65% of **2a**, 30% of **3a** and 5% of **3b** as calculated from integration at 6.12, 5.61 and 6.17 ppm (H–C(3)), and 2.37, 2.11 and 2.37 ppm (3 H–C(5)). The composition remained invariable, when the oil was stored at −20°. – UV. (MeOH): 266 (8100); infl. 270 (8000). – IR. (CH_2Cl_2): 1730*s*, 1668*s*, 1585*s*, 1410-1460*m* br., 1385*m*, 1365*s*, 1345*m*, 1310*m*, 1220*s*, 1175*m*, 1105*s*, 1070*s*, 1105*s*, 1070*m*, 1055*s*, 1040*s*, 1018*s*. – NMR. ($CDCl_3$): s. *Table 2* for the individual components.

3. *Methylation at different temperatures.* Samples of **1** (15-20 mg) in test tubes covered with aluminium foil were dissolved in 1 ml of ether to which 3 ml of ethereal diazomethane solution were added (from 2.5 g of nitrosomethylurea, 1.4 g of KOH and 1.4 of H_2O, 50 ml of ether; dried over KOH and redistilled to give 15 ml of solution) at −78, −30 and 0°. Each experience was performed twice; the reaction was complete after 8, 3 and 1.5 h, respectively. The solvent was removed with a stream of N_2 at ice bath temp. The residues taken in $CDCl_3$ for immediate inspection by

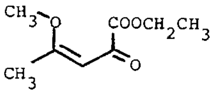
Table 2. *^{1}H- and ^{13}C-NMR. chemical shifts ($CDCl_3$) of the isomeric methyl enol ethers of ethyl 2,4-dioxopentanoate*[a])



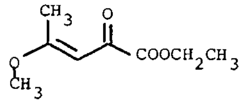
2a



2b



3a



3b

	^{1}H-NMR.				
	3 H–C(5)	CH_3O	H–C(3)	CH_3CH_2O	CH_3CH_2O
2a	2.37	3.88	6.12	4.26	1.33
2b	2.19	3.73	5.50	4.30	1.34
3a	2.11	3.83	5.61	4.24	1.35
3b	2.36	3.76	6.17	4.26	1.35
1	2.25	–	6.34	4.32	1.37

	^{13}C-NMR.							
	C(5)	CH_3O	C(3)	C(4)	C(2)	C(1)	CH_3CH_2O	CH_3CH_2O
2a	31.2	60.0	116.8	197.7	153.7	162.9	61.9	13.8
2b	30.5	56.8	101.1	195.3	161.2	163.8	62.2	13.7
3a	19.0	56.5	102.4	173.3	181.8	164.4	61.4	13.8
3b	20.4	56.1	94.7	179.1	180.7	163.1	61.9	13.8
1	26.8	–	101.5	199.4[b])	166.8[b])	161.5	61.8	13.3

[a]) Chemical shifts in ppm relative to tetramethylsilane (=0 ppm). [b]) Mean values for C(2) and C(4).

^{1}H- and ^{13}C-NMR. contained a mixture of (*Z*)-enol ethers **2a** and **3a** (95–100%; s. *Tab. 1* and *Chap. 4*) and only traces of the (*E*)-ether **3b** (0–5%).

4. *Stability of isomers.* The original product composition remained invariable when the crude mixtures (s. *Chap. 3*) were stored in solution or as oil at –20°; at higher temp. it changed as observed in the ^{1}H- and ^{13}C-NMR. spectra from emerging signals of **3b** at the expense of those of **3a** whereas those of **2a** remained constant.

The isomerization of **3a** was slow at 0°; at r.t. complete transformation of **3a** into the (*E*)-isomer **3b** took place within 20 h. Such isomerized solutions were used for the quantitative analysis of the isomers **2** and **3** obtained in the experiments of *Chap. 3*, by integrating (3 times) the 2*s* at 3.88 and 3.76 (CH_3O), respectively, of the remaining **2a** and **3b**. After 6 days at r.t., the mixture contained 45% of **2a**, 21% of **2b** and 34% of **3b**. The isomerization of **3a** (*Z*) to **3b** (*E*) at 40° was complete within 1 h; **2a** remained stable during that period.

On distillation of the original mixture at 110°/11 Torr, a considerable (*Z*)→(*E*)-isomerization **2a**→**2b** took place; composition of the distillate: 66% of **2a**, 13% of **2b** and 21% of **3b**.

The isomerization was rapid in the presence of *p*-toluenesulfonic acid; after 3 min, the initial mixture (69% of **2a**, 1% of **2b**, 23% of **3a** and 7% of **3b**) turned into 55% of **2a**, 15% of **2b** and 30% of **3b**, and after 25 min to 33% of **2a**, 37% of **2b** and 30% of **3b**.

5. *Separation of the stereoisomers.* A mixture **2a**/**2b**/**3b** from isomerization experiments *(Chap. 4)* was separated by prep. TLC. (CH_2Cl_2/ether 98:2); compound **3b** (Rf 0.5) overlapped partially the prevailing **2a** (Rf 0.4), **2b** (Rf 0.25) was well-separated. The unstable **3a** could not be isolated and was characterized only in crude mixtures.

Data of ethyl (Z)-2-methoxy-4-oxo-2-pentenoate (**2a**). Oil, Rf 0.4 (CH_2Cl_2/ether 98:2). – UV. (MeOH): 262 (9300), 270 *S* (8900). – UV. (CH_2Cl_2): 257. – UV. (hexane): 254. – IR. (CH_2Cl_2): 3060-3080*w*, 2990*m* br., 2950*m*, 2910*w*, 1730*s*, 1690*m S*, 1670*s*, 1625*s*, 1600*m S*, 1450*m* br., 1365*s*, 1350*s S*, 1270*m* br. *S*, 1225*s* br., 1180*m*, 1145*m* br., 1040*s*, 1020*m*, 1000*w S*, 965*w* br., 855*w* br. – NMR.: s. *Table 2*. – MS.: 43 (100), 129 (12).

*Data of ethyl (*E*)-2-methoxy-4-oxo-2-pentenoate* (**2b**). Oil, Rf 0.25 (CH_2Cl_2/ether 98:2). - UV. (MeOH): 252 (5730). - UV. (CH_2Cl_2): 250. - UV. (hexane): 246. - IR. (CH_2Cl_2): 2990*m* br., 2950*m*, 2910*w*, 2850*w*, 1745*s* br., 1695*s*, 1665*w*, 1620*w S*, 1595*s*, 1400*m*, 1380*s*, 1355*m*, 1300*m*, 1205*s*, 1182*s*, 1155*s*, 1100*w* br., 1020*m*, 995*m*, 965*w*, 928*m*, 855*w*, 808*m*. - NMR.: s. *Table 2*. - MS.: 43 (51), 129 (25).

*Data of ethyl (*Z*)-4-methoxy-2-oxo-3-pentenoate* (**3a**; only observed in mixtures). - UV. (MeOH): 265 (6500). - IR. (CH_2Cl_2): 1750*s*, 1720*s*, 1675*m*, 1645*s*, 1615*w*, 1590*s*, 1390*s*, 1315*s*, 1180*s*, 1165*s*, 1135*s*, 1075*s*, 1060*s*. - NMR.: s. *Table 2*.

*Data of ethyl (*E*)-4-methoxy-2-oxo-3-pentenoate* (**3b**). Oil, Rf 0.5 (CH_2Cl_2/ether 98:2). - UV. (MeOH): 288 (10500). - UV. (hexane): 280. - IR. (CH_2Cl_2): 3700*m*, 3640*w*, 1745*s S*, 1730*m*, 1680*m* br., 1605*m S*, 1580*s*, 1565*m S*, 1370*w*, 1300*s*, 1250–1280*m* br. *S*, 1105*s*, 1060*m*, 1020*w*, 910–920*w* br., 895*s S*, 860*w*. - MS.: 99 (100), 172 (1). - NMR.: s. *Table 2*.

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