REACTION OF SUBSTITUTED γ-CROTONOLACTONES UNDER THE CONDITIONS OF THE MICHAEL ADDITION

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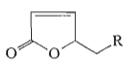
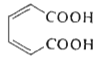
Under the conditions of the Michael addition γ-lactone of ethyl 4-hydroxy-6-oxo-2-octenedioate (*II*) isomerizes to γ-lactone of ethyl 4-hydroxy-6-oxo-4-octenedioate (*VIII*). The addition of an excess of ethyl acetate anion to γ-lactone of ethyl 4-hydroxy-2-hexenedioate (*I*) affords γ-lactone of ethyl 3-ethoxycarbonylmethyl-4-hydroxy-6-oxo-octanedioate (*XI*). The dimers *IX* and *X* are formed during the usual performance of the same addition. The mechanism of isomerization of *II* and the factors affecting the addition of the ethyl acetate anion are discussed.

In connection with the synthesis of prostaglandin derivatives[1-3] from catechol it was necessary to investigate the behaviour of 4-substituted γ-crotonolactones under the conditions of the Michael addition. For the study of the Michael addition of ethyl acetate anion we used γ-lactone of ethyl 4-hydroxy-2-hexenedioate (*I*): γ-lactone of ethyl 4-hydroxy-6-oxo-2-octenedioate (*II*) was used for the study of the possibility of intramolecular Michael addition.

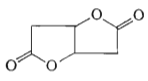
The preparation of compounds *I* and *II* starts with catechol which can be converted by oxidation to *cis,cis*-2,4-hexadienedioic acid (*III*). After checking the described methods[4,7] we obtained the best results by oxidation of catechol with commercial 40% peracetic acid, during which acid *III* is formed in a 40% yield. Using a known procedure[4], based on the use of sulfuric acid, we converted *III* to acid *IV* in a 70% yield. In several cases we isolated the described[7,8] bis-lactone *V* as a by-product. On esterification of acid *IV* we prepared compound *I* in a 89% yield.

We converted acid *IV* using thionyl chloride to the unstable chloride *VI* which we used immediately, without isolation, for the acylation of dilithium ethyl hydrogen





III



V

I, R = $COOC_2H_5$
II, R = $COCH_2COOC_2H_5$
IV, R = COOH
VI, R = COCl
VII, R = $COCH(COOC_2H_5)COOtertC_4H_9$

malonate. We isolated keto ester *II* by a described procedure[9] in 30% yield. Ethyl tert-butyl malonate[10] afforded γ-lactone of tert-butyl 7-ethoxycarbonyl-4-hydroxy--6-oxo-2-octenedioate (*VII*), from which compound *II* was formed on reaction with trifluoroacetic acid in a 28% total yield. In our effort to optimize this reaction we used magnesium salt of ethyl hydrogen malonate, but when the described procedure[11] was used, keto ester *II* was obtained in a substantially worse yield and purity.

The intramolecular addition of keto ester *II* was carried out according to described procedures gradually with sodium hydride in tetrahydrofuran[12], sodium ethoxide[13], pyridine[14], sodium ethoxide in benzene[15], sodium hydride in methanol[16], but seemingly the best result was obtained when a trace amount of tetrabutylammonium hydroxide in benzene was used[17]. γ-Lactone of ethyl 4-hydroxy-6-oxo-4-octenedioate (*VIII*) was formed in 68% yield.

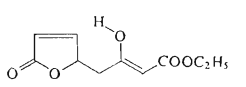
When comparing ^{1}H NMR spectra of compounds *II* and *VIII* the disappearance of the characteristic AB system of two olefinic hydrogens of the γ-crotonolactone grouping at 6·22 and 7·72δ in *II* becomes evident. This system is substituted by the multiplet of the proton in the position 5 of compound *VIII* the resonance of which is at 6·26δ. For γ-crotonolactones the multiplet of the proton in the position 4, at 5·53δ in *II*, is also characteristic. Unlike this the methylene protons in positions 2 and 3 of *VIII* are characterized by multiplets at 2·80 and 3·45δ.

The mass spectra of both compounds, *II* and *VIII*, are very similar. The fundamental difference consists in the ions with maximum intensity. While in ester *II* this is the ion $m/z = 83$, formed by the usual α-cleavage with respect to the lactone ring oxygen, in the spectrum of keto ester *VIII* the ion $m/z = 125$ is found, corresponding to the splitting off of the $CH_2COOC_2H_5$ group, which is characteristic of the keto ester grouping conjugated with the double bond. Then this ion splits off the carbonyl group twice, forming the ions $m/z = 97$ and $m/z = 61$. All these splittings were confirmed by corresponding metastable ions. The infrared spectra are also in agreement with the structure *VIII*.

In order to explain the isomerization of *II* to *VIII* we submitted to an analogous reaction both the ester *I* alone, and also its mixture with one equivalent of ethyl acetoacetate. In all instances ester *I* was recovered from the reaction mixture. We explain the isomerization by the process shown in Scheme 1.

The hydroxyl group of the enol form attacks the α,β-unsaturated system of the lactone, and the cyclic intermediate formed then isomerizes *via* β,γ-unsaturated lactone to *VIII*.

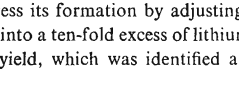
In the study of the addition mechanism of the ethyl acetate anion to ester *I* we found that the γ-lactone system opens irreversibly at about 20°C in alkaline medium, and therefore we carried out the reaction according to the described method[18] so, that the ethyl acetate anion was formed *in situ* from lithium diisopropylamide and ethyl acetate in tetrahydrofuran at −78°C. The reaction afforded various products, depending on the ratio of the reacting components. When a mild excess of li-



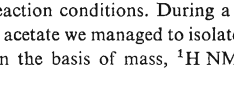
II

VIII

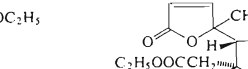
thium ethyl acetate was used, we could prove in the reaction mixture the presence of three products of which the structures of two were determined. They are isomeric dimers *IX* and *X* the formation of which is similar to the behaviour of β-angelicalactone in the presence of potassium carbonate[19]. The assignment of the structures *IX* and *X* is based on the different hydrogen shift in the α-position to the lactone ring oxygen in the ^{1}H NMR spectra of both substances. Since the formation of the dimers is undesirable from the point of view of synthetic exploitation, we endeavoured to suppress its formation by adjusting the reaction conditions. During a slow addition of *I* into a ten-fold excess of lithium ethyl acetate we managed to isolate a product in 28% yield, which was identified as *XI* on the basis of mass, ^{1}H NMR and IR spectra.



IX



X



XI

Hence, in the reaction Claisen condensation also takes place in addition to the Michael addition. In view of the structure of the dimers formed it may be said that in this case too the course of the Michael addition is affected adversely by the

presence of the acid hydrogen in the position 4 of the γ-crotonolactone grouping, because its splitting off affords an anion which is capable of undergoing addition in the sense of the Michael addition.

EXPERIMENTAL

The melting points and the boiling points are not corrected. Before analysis the samples were dried in a vacuum of 76 Pa for 12 h. The ^{1}H NMR spectra were measured on a Varian XL-100 instrument in deuteriochloroform, using tetramethylsilane as internal reference. The chemical shifts are given in δ-units. The IR spectra were measured on a Perkin Elmer 325 spectrophotometer. The mass spectra were recorded with a Gas Chromatograph-Mass Spectrometer 9000.

cis,cis-2,4-Hexadienedioic Acid (*III*)

A saturated solution of 140 g of catechol in acetic acid was added over 15 h into 800 ml of 40% peracetic acid (Persteril, Chemical Works Sokolov, Czechoslovakia) at 35—40°C. On cooling (10°C) the acid crystallized out which was recrystallized from 1 100 ml of ethanol. Yield, 70 g (40%) of *III*, m.p. 182—185°C, lit.[4] gives 187°C.

γ-Lactone of 4-Hydroxy-2-hexenedioic Acid (*IV*) and Di-γ-lactone of 3,4-Dihydroxyhexanedioic Acid (*V*)

32 g (0·23 mol) of *III* were suspended in a mixture of 128 ml of sulfuric acid and 43 ml of water and allowed to stand for 24 h. The mixture was poured into ice (400 g), neutralized with aqueous ammonia to Congo red and extracted with ether for 48 h. The organic phase was dried over magnesium sulfate. Crystallization of 27 g of the crude product from a mixture of benzene (110 ml), toluene (80 ml), and ethanol (20 ml) gave 23 g (70%) of *IV*, m.p. 100—107°C, lit.[4] gives 111°C. ^{1}H NMR spectrum: 2·78 (m, 2 H, CH_2); 5·40 (m, 1 H, H-4); 6·10 (dd, J_{23} = 5 Hz, J_{34} = 2 Hz, 1 H, H-3); 7·75 (dd, J_{23} = 5 Hz, J_{34} = 2 Hz, 1 H, H-2); 1 exchangeable proton (10·15). Further, 4 g (13%) of compound *V* were obtained, m.p. 120—126°C, lit.[8] gives 125 to 126°C. ^{1}H NMR spectrum: 3·51; 3·70; 3·88; 4·07 (4 H, 2 × AB syst., CH_2); 5·35 (d, 2 H, 2 × × CH—O). IR spectrum, cm^{-1}: 835, 925, 1 007, 1 145, 1 188, 1 278, 1 309, 1 340, 1 403, 1 623, 1 795, 2 860, 2 935, 3 025.

γ-Lactone of Ethyl 4-Hydroxy-2-hexenedioate (*I*)

A mixture of 3 g (21·1 mmol) of *III*, 17 g (21·2 ml, 36·9 mmol) of ethanol, 0·5 ml of concentrated sulfuric acid and 21 ml of chloroform was refluxed for 4 h, diluted with 100 ml of chloroform, washed with water and a saturated sodium hydrogen carbonate solution, and dried over $MgSO_4$. The distillation of the product gave 3 g (89%) of *I*, m.p. 94—96°C/6 Pa. For $C_8H_{10}O_4$ (170·2) calculated: 56·47% C, 5·92% H; found: 56·49% C, 6·01% H. ^{1}H NMR spectrum: 1·30 (t, 3 H, CH_3); 2·80 (dd, J = 7 Hz, J = 1·5 Hz, 2 H, CH_2); 4·25 (q, 2 H, CH_2O); 5·45 (m, 1 H, H-4); 6·20 (dd, J_{23} = 6 Hz, J_{34} = 2 Hz, 1 H, H-3); 7·70 (dd, J_{23} = 6 Hz, J_{24} = 1·5 Hz, 1 H, H-2).

γ-Lactone of 4-Hydroxy-2-hexenoic Acid Chloride (*VI*)

1·42 g (10 mmol) of *IV* and 5 ml of thionyl chloride were refluxed for 15 min. The excess of thionyl

chloride was distilled off in a vacuum with two 10 ml portions of benzene and the product was used directly for acylations. For analytical purposes the sample was distilled *in vacuo*, b.p. 125°C/0·27 kPa. For $C_6H_5ClO_3$ (160·6) calculated: 45·17% C, 3·14% H; found: 45·42% C, 3·26% H. ^{1}H NMR spectrum: 3·40 (m, 2 H, CH_2); 5·45 (m, 1 H, H-4); 6·23 (dd, $J_{23} = 6$ Hz, $J_{34} = 2$ Hz, 1 H, H-3); 7·63 (dd, $J_{23} = 6$ Hz, $J_{24} = 2$ Hz, 1 H, H-2).

γ-Lactone of Tert-Butyl 7-Ethoxycarbonyl-4-hydroxy-6-oxo-2-octenedioate (*VII*)

0·25 g of Mg, 0·2 ml of abs. ethanol and 0·02 ml of CCl_4 were mixed and when the exothermic reaction started the mixture was cooled and 3·3 ml of ether were added. Tert-butyl malonate (1·85 g) in ethanol (1 ml) was added dropwise to the suspension, followed by 2 ml of ether and the mixture was refluxed for 3 h. After dropwise addition of 1·6 g (0·01 mol) of chloride *VI* in 2 ml of ether the mixture was refluxed for 30 min, then acidified with sulfuric acid (1 : 1) and the organic layer was separated. The aqueous layer was extracted with ether and the combined ethereal extracts were dried over $MgSO_4$, filtered and evaporated. Yield, 2·3 g of a crude mixture, from which 1·2 g (40%) of compound *VII* were isolated by column chromatography (40 × 2·5 cm, silica gel, CCl_4 with 10% of acetone). For $C_{15}H_{20}O_7$ (312·3) calculated: 57·69% C, 6·45% H; found: 57·82% C, 6·48% H. ^{1}H NMR spectrum: 1·30 (m, 3 H, CH_3—CH_2); 1·45 (s, 9 H, CH_3—$\overset{|}{\underset{|}{C}}$—); 3·20 (m, 2 H, —$CH_2$—CO); 4·20 (m, 2 H, CH_2—O); 4·50 (s, 1 H, —CH(COOR)$_2$; 5·42 (m, 1 H, H-4); 6·10 (bd, $J = 6$ Hz, 1 H, H-3); 7·70 (bd, $J = 6$ Hz, 1 H, H-2).

γ-Lactone of Ethyl 4-Hydroxy-6-oxo-2-octenedioate (*II*)

A) n-Butyllithium (40—45 ml of a 1 mol l^{-1} concentration) in hexane was added dropwise over 5 min and under stirring to 4·21 g of ethyl hydrogen malonate (31·2 mmol) in 78 ml of cooled tetrahydrofuran containing a trace of 2,2′-bipyridyl. The reaction was carried out under nitrogen, taking care that the temperature should rise from −78°C to −5°C and the mixture have a permanently pink colour. The suspension of dilithium ethylmalonate was again cooled to −78°C and a solution of crude chloride *VI* (2·5 g; 15·6 mmol) in 20 ml of tetrahydrofuran was added to it. After 2 min standing the mixture was poured into 150 ml of ether and 78 ml of 1M-HCl. The organic phase was separated, neutralized with a saturated solution of sodium hydrogen carbonate, washed with water and dried over $MgSO_4$. After evaporation of the solvents 2 g (60%) of a crude product were obtained from which 1 g (30%) of compound *II* were obtained by column chromatography on silica gel (2·5 × 35 cm column, 5% acetone in benzene). R_F (benzene with 10% of acetone): 0·40. For $C_{10}H_{12}O_5$ (212·2) calculated: 56·60% C, 5·70% H; found: 57·02% C, 5·80% H. ^{1}H NMR spectrum: 1·30 (t, 3 H, CH_3); 3·06 (m, 2 H, CH_2); 3·60 (s, 2 H, —CH_2—COO); 4·23 (q, 2 H, CH_2—O); 5·53 (m, 1 H, H-4); 6·22 (dd, $J_{23} = 5·5$ Hz, $J_{34} = 2$ Hz, 1 H, H-3); 7·72 (dd, $J_{23} = 5·5$ Hz, $J_{24} = 1·5$ Hz, 1 H, H-2). Mass spectrum, *m/z* (%): 83 (100); 97 (48); 125 (43); 55 (36); 43 (32); 167 (3P); 42 (27); 98 (26); 138 (23); 166 (23); 115 (18); 79(15); 82 (14); 124 (12); 84 (11). IR spectrum, cm^{-1}: 625, 660, 720, 815, 903, 925, 995, 1 025, 1 070, 1 110, 1 160, 1 220, 1 318, 1 370, 1 410, 1 445, 1 465, 1 475, 1 602, 1 655, 1 720, 1 760, 2 300, 2 360, 2 420, 2 420, 2 860, 2 900, 2 930, 2 980, 3 020, 3 500, 3 680.

B) Trifluoroacetic acid (1 ml; 13·1 mmol) was added to 2·8 g (13·1 mmol) of *VII* and the mixture was allowed to stand overnight. It was evaporated with two 30 ml portions of benzene, diluted with ether, washed with a sodium hydrogen carbonate solution and dried over $MgSO_4$. Chromatography on a silica gel column (2·5 × 40 cm, 5% acetone in benzene) gave 1·9 g (70%) of compound *II*.

γ-Lactone of Ethyl 4-Hydroxy-6-oxo-4-octenedioate (*VIII*)

A mixture of 0·7 g (3·3 mmol) of *II* in 5 ml of benzene and 0·1 ml of tetrabutylammonium hydroxide was refluxed for 6 h, then washed twice with water and the organic phase dried over $MgSO_4$. After evaporation of the solvent the residue was crystallized from CCl_4. Yield, 0·48 g (68%) of *VIII*. M.p. 89–92°C. For $C_{10}H_{12}O_5$ (212·2) calculated: 56·60% C, 5·70% H; found: 56·71% C, 5·78% H. ^{1}H NMR spectrum: 1·30 (t, 3 H, CH_3); 2·80 (m, 2 × H-3); 3·45 (m, 2 H, 2 × H-2); 3·54 (s, 2 H, CH_2COOEt); 4·26 (q, 2 H, CH_3—O); 6·26 (bs, 1 H, =CH—CO). Mass spectrum, m/z (%): 125 (100); 55 (52); 29 (46); 83 (41); 69 (41); 43 (40); 27 (38); 96 (35); 97 (31); 57 (31); 57 (31); 123 (25); 124 (23); 67 (19); 28 (19); 39 (17); 42 (15); 56 (15); 70 (15); 212 (15); 95 (14); 98 (14); 85 (13); 81 (12); 126 (12); 142 (13); 143 (12); 84 (11). IR spectrum, cm^{-1}: 505, 520, 540, 566, 585, 625, 663, 725, 803, 842, 858, 885, 940, 970, 1 030, 1 080, 1 130, 1 155, 1 203, 1 257, 1 280, 1 292, 1 325, 1 375, 1 405, 1 425, 1 445, 1 480, 1 620, 1 680, 1 730, 1 815, 2 915, 2 950, 2 998, 3 430.

Addition of Ethyl acetate to *I*

A n-butyllithium solution in hexane (12·5 ml, *i.e.* 20 mmol, of a 1·6 molar solution) was added at −78°C and under nitrogen to a solution of 2·02 g (20 mmol) of diisopropylamine in 20 ml of tetrahydrofuran, and after 10 min 17·62 g (19·6 ml, 20 mmol) of ethyl acetate was added to the mixture. After another 20 min a precooled (−78°C) solution of 3·40 g (20 mmol) of *I* in 20 ml of tetrahydrofuran was added dropwise at −78°C to the reaction mixture. After 5 h reaction time an excess of a saturated ammonium chloride solution was added and the mixture was extracted with ether. The etheral layer was dried over $MgSO_4$ and evaporated, to give 3·13 g of a mixture which was chromatographed on a silica gel column (2·5 × 50 cm, chloroform). The main eluted fractions gave 1·06 g (16%) of *IX*, R_F = 0·48 (chloroform with 4% of methanol). ^{1}H NMR spectrum: 1·27 (t, 6 H, CH_3); 2·60–3·20 (m, 7 H, CH_2CO, CH—CH—O); 4·16 (q, 4 H, CJ_2—O); 4·48 (q, 1 H, CH—O); 6·25 (d, J = 7 Hz, 1 H, =HC—C=C—O); 7·64 (d, J = 7 Hz, 1 H, =CH—). Mass spectrum, m/z (%): 97 (100); 170 (50); 143 (48); 109 (37); 123 (17); 127 (16); 249 (13); 295 (13); 295 (13); 276 (12); 248 (11); 253 (10); 221 (10); 126 (10); 110 (10); 340 (2). Further, 0·35 g (5%) of compound *X* were obtained, R_F = 0·55 (chloroform with 4% of methanol). For $C_{16}H_{20}O_8$ (340·3) calculated: 56·46% C, 5·92% H; found: 56·56% C, 6·01% H. ^{1}H NMR spectrum: 1·27 (t, 6 H, CH_3); 2·10–3·10 (m, 7 H, CH_2CO, CH—CH—O); 4·20 (q, 4 H, CH_2—O); 4·80 (q, 1 H, CH—O); 6·30 (d, J = 7 Hz, 1 H, =CH—C=O); 7·68 (d, J = 7 Hz, 1 H, =CH—); Mass spectrum, m/z (%): 97 (100); 170 (52); 143 (45); 109 (37); 123 (15); 127 (15); 249 (13); 295 (13); 276 (12); 248 (12); 253 (11); 221 (11); 248 (11); 126 (10); 240 (3). Finally 0·42 g (6%) of an unidentified product were isolated, with R_F = 0·73 (chloroform with 4% of methanol).

γ-Lactone of Ethyl 3-Ethoxycarbonylmethyl-4-hydroxy-6-oxo-octanedioate (*XI*)

A 1·6 molar solution of n-butyllithium (120 ml; 190 mmol) in hexane was added to a solution of 19·43 g (190 mmol) of diisopropylamine in 200 ml of tetrahydrofuran at −78°C and under nitrogen. After 10 min 16·92 g (19 ml, 190 mmol) of ethyl acetate were added and after 20 min a precooled solution (−78°C) of 3·27 g (19 mmol) of *I* in 20 ml of tetrahydrofuran, at −78°C over 1 h. After 5 h standing the mixture was decomposed with an excess of a saturated ammonium chloride solution, then extracted with ether, the ethereal layer was dried over $MgSO_4$ and evaporated. Yield 6·76 g of a mixture which was submitted to vacuum distillation. After distilling off of the volatile components at a maximum bath temperature of 50°C, the residual product (4·41 g) was chromatographed on silica gel (2·5 × 60 cm, chloroform). Yield, 1·57 g (27%) of *XI*,

R_F = 0·60 (chloroform with 4% of methanol). For $C_{14}H_{20}O_7$ (300·3) calculated: 55·90% C 6·71% H; found: 55·50% C, 6·77% H. ^{1}H NMR spectrum: 1·26 (t, 6 H, CH_3); 2·1—2·9 (m, 5 H, —OC—CH_2—CH—CH_2—CO—); 2·96 (d, J = 5·5 Hz, 2 H, —O—C—CH_2—CO); 3·42 (s, 2 H, —CO—CH_2—CO—); 4·06 (q, 4 H, CH_2—O); 4·45, 4·51, 4·55, 4·61 (AB syst. 1 H, —CH—O). IR spectrum, cm^{-1}: 625, 655, 725, 860, 945, 1 022, 1 095, 1 115, 1 175, 1 230, 1 320, 1 350, 1 375, 1 417, 1 450, 1 470, 1 480, 1 660, 1 730, 1 785, 2 940, 2 990, 3 030. Mass spectrum, m/z (%): 167 (100); 171 (97); 143 (97); 140 (97); 130 (97); 125 (97); 115 (97); 97 (97); 88 (97); 43 (95); 84 (94); 45 (92); 31 (87); 273 (87); 209 (79;) 55 (74); 226 (71); 185 (71); 70 (71); 60 (60); 195 (55); 157· (53); 191 (50); 61 (45); 258 (42); 213 (39); 301 (18); 272 (18); 300 (16).

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