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PROTOLYTIC CLEAVAGE OF DERIVATIVES OF 2,5-DIMETHOXY-2,5-DIHYDROFURAN

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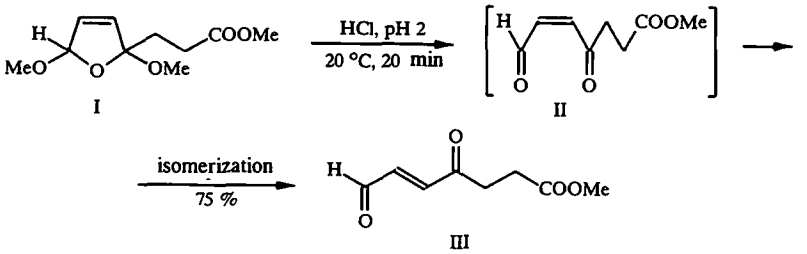
By analysis of the products from the protolytic cleavage of methyl 3-(2,5-dialkoxy-2,5-dihydro-2-furyl)propionate (I) in the presence of mixed nucleophiles and investigation of their mutual transformations the main paths in the dissociation of the protonated molecule of (I), with the formation of both linear cleavage products (derivatives of 1,4-diketones and 4-ketopimelic acid) and furylcarbinol derivatives, were determined.

The acid cleavage of 2,5-dialkoxy-2,5-dihydrofuran derivatives is used in organic chemistry for the production of such valuable starting materials for the synthesis of complex natural compounds as malealdehyde [1-4], fumaraldehyde [3, 4], 3-acetylacrolein [1, 2], 3-acetylacrylic acid and its derivatives [5, 6], levulinic acid and its derivatives [5, 7, 8], and also a large number of 1,4-diketones [9-11]. The latter are widely used in the synthesis of hydroxycyclopentene derivatives [12-18].

The hydrolytic cleavage of the ring in 2,5-dialkoxy-2,5-dihydrofurans is a complex process, leading to the formation of a multicomponent mixture of unstable reaction products [4-8], the detailed mechanism of which is not yet clear. In the present work we investigated the protolytic cleavage of methyl 3-(2,5-dimethoxy-2,5-dihydro-2-furyl)propionate (I) in the presence of both individual and mixed nucleophiles (water, methanol).

Earlier we investigated the use of compound (I) as a readily obtainable starting material in the synthesis of 4-hydroxy-2-methoxycarbonylmethyl-2-cyclopenten-1-one (an intermediate for the production of prostaglandins [19]) and also its thermal stability [20]. In addition, we suppose that the linear products of the cleavage of the investigated compound, i.e., derivatives of 1,4-dienes containing seven carbon atoms, may find independent use in organic synthesis.

The cleavage of compound (I) at pH 2 in dilute hydrochloric acid leads to the formation of the unstable *cis*-enedione (II). In a weakly alkaline medium it readily undergoes cyclization to 3-hydroxy-2-methoxycarbonylmethyl-4-cyclopenten-1-one [19]. In the presence of a catalytic amount of iodine it isomerizes with a high yield to methyl *trans*-4,7-dioxohept-5-enoate (III).



During treatment of the initial compound (I) with anhydrous hydrogen chloride in methanol at room temperature for 2 h the main cleavage product was methyl 4-oxo-6,7,7-trimethoxyheptanoate (IV), formed with a yield of 48-50%. In addition, the reaction mixture contained 11-12% of methyl 4-oxo-7,7-dimethoxy-5-heptenoate (V), 1-6% of methyl 4,7-dioxo-6-methoxyheptanoate (VI), 21-26% of methyl 3-methoxy-3-(2-furyl)propionate (VII), and 4-6% of dimethyl 4-oxo-1,7-heptanedicarboxylate (VIII).

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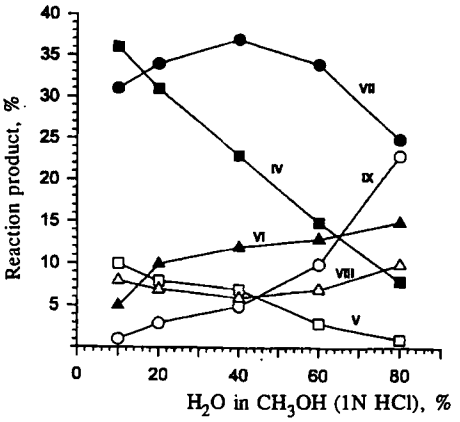
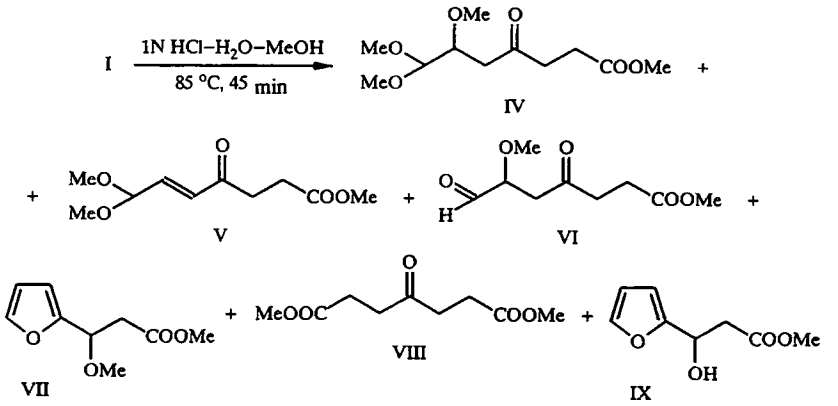


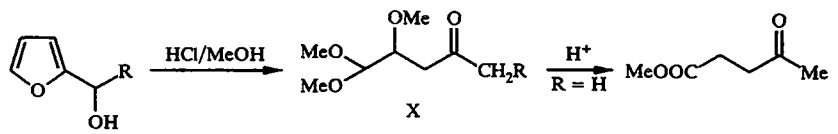
Fig. 1. Effect of the water—methanol ratio on the yield of the products from the cleavage of methyl 3-(2,5-dimethoxy-2,5-dihydro-2-furyl)propionate (I).

The cleavage of dimethoxydihydrofuran (I) with an aqueous 0.1 N solution of.hydrochloric acid in the presence of methanol gave a reaction mixture consisting of six compounds. Their ratios depended on the amount of the competing nucleophile methanol in the reaction mixture (Fig. 1).

. Among the cleavage products we identified the acetals (IV, V), the aldehyde (VI), the furylcarbinol derivatives (VII, IX), and dimethyl 4-oxopimelate (VIII). All the reaction mixtures were analyzed by TLC, GLC, and chromato-mass spectrometry. The individual compounds were isolated by column chromatography on silica gel, and their structures were confirmed by their ^1H PMR spectra.



Great similarity was observed during comparison of the products from the cleavage of the furylcarbinols and 2,5-dialkoxy-2,5-dihydrofurans in an acidic medium. In the literature the acyclic acetals (X) were isolated from the products from the cleavage of furylcarbinols in an acidic medium [21, 22]. The further reaction of the acetal (X) (R = H) with hydrogen chloride in methanol led to the formation of methyl levulinate with a yield of 70-75% [22].



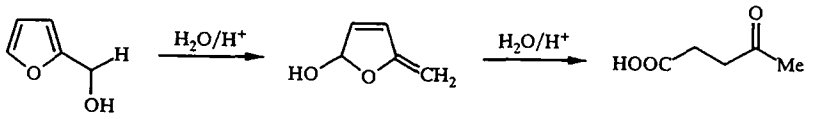
R = H, alkyl

TABLE 1. Chromatographic Characteristics of Compounds (I-IX, XI)

Compound	GLC analysis, t_R, min	TLC		
		R_f (1:1 hexane–ethyl acetate)	Development	
			UV lamp	color (vanillin)
I	7,32 ± 0,05	0,68; 0,60*	-	bl
II	—	0...0,30	+	o
III	6,73 ± 0,10	0,43	+	br
IV	10,14 ± 0,07	0,28	-	bl
V	9.41 ± 0,02	0,50	±	bl
VI	7,88 ± 0,05	0,14	-	bl
VII	4,98 ± 0,07	0,06	±	y
VIII	8,24 ± 0,05	0,38	-	(o)
IX	5,43 ± 0,06	0,76	±	bl
XI	6,84 ± 0,05	0,64; 0.70*	+	bl

*The *cis* and *trans* isomers, bl = blue, o = orange, br = brown, y = yellow.

In addition, the ^{13}C NMR spectra support the suggestion [23, 24] about the formation of 2-hydroxy-5-methylene-2,5-dihydrofuran as the main intermediate compound in the synthesis of levulinic acid from furylmethanol [25, 26].



For detailed investigation of the cleavage of compound (I) the aldehydes (II, III) were used as models and were treated with three reaction solutions: A) anhydrous HCl/MeOH/$CHCl_3$; B) anhydrous HCl/MeOH/$CHCl_3$ with a catalytic amount of trimethyl formate; C) HCl/MeOH/$CHCl_3$ with a catalytic amount of water. All the mixtures were heated at 60°C for 20 min and investigated by TLC, GLC, and chromato-mass spectrometry. The results of chromatographic analysis are given in Table 2.

The simultaneous formation of derivatives of the aldehydes (IV-VI), the furan derivative (VII), and dimethyl oxopimelate (VIII) indicates competing reactions in the protonated molecule of the dihydrofuran (I) (expts. 1-3). During treatment of the *cis*-aldehyde (II) with solutions A, B, and C (expts. 4-6) the reaction products and their ratios hardly differed at all from the previous series.

There is clearly an equilibrium between the *cis*-aldehyde and the dihydrofuran (I). At the same time the equilibrium between the *trans*-aldehyde (III) and the dihydrofuran (I) is observed to lesser degree (expt. 9).

The main reactions in the protolytic cleavage of the dihydrofuran (I) are presented in the scheme. Initial protonation of the oxygen atom of the 2-methoxy group in the cyclic acetal and the elimination of the CH_3OH molecule lead to the formation of the carbonium ion *C-I*, which secures the formation of the ring opening products (II-VI) by breaking the ring bond $C_{(2)}$—O, according to path A, through the intermediate carbonium ion *C-II* and by reacting with the nucleophiles (methanol, water). The *cis*-aldehyde (II) is formed exclusively during the reaction of compound (I) with hydrochloric acid in the absence of methanol, but the reaction in the presence of the mixed nucleophiles gives both aldehydes (II) and (III) (expts. 3, 6). (The *cis*-aldehyde in the reaction mixture is only determined by TLC.) This can clearly be explained by solvolytic stabilization of the intermediate ion *C-II* by the methanol. This gives rise to *E/Z* isomerization and/or addition of the methanol to the double bond in the Michael reaction, securing the formation of compounds (IV-VI).

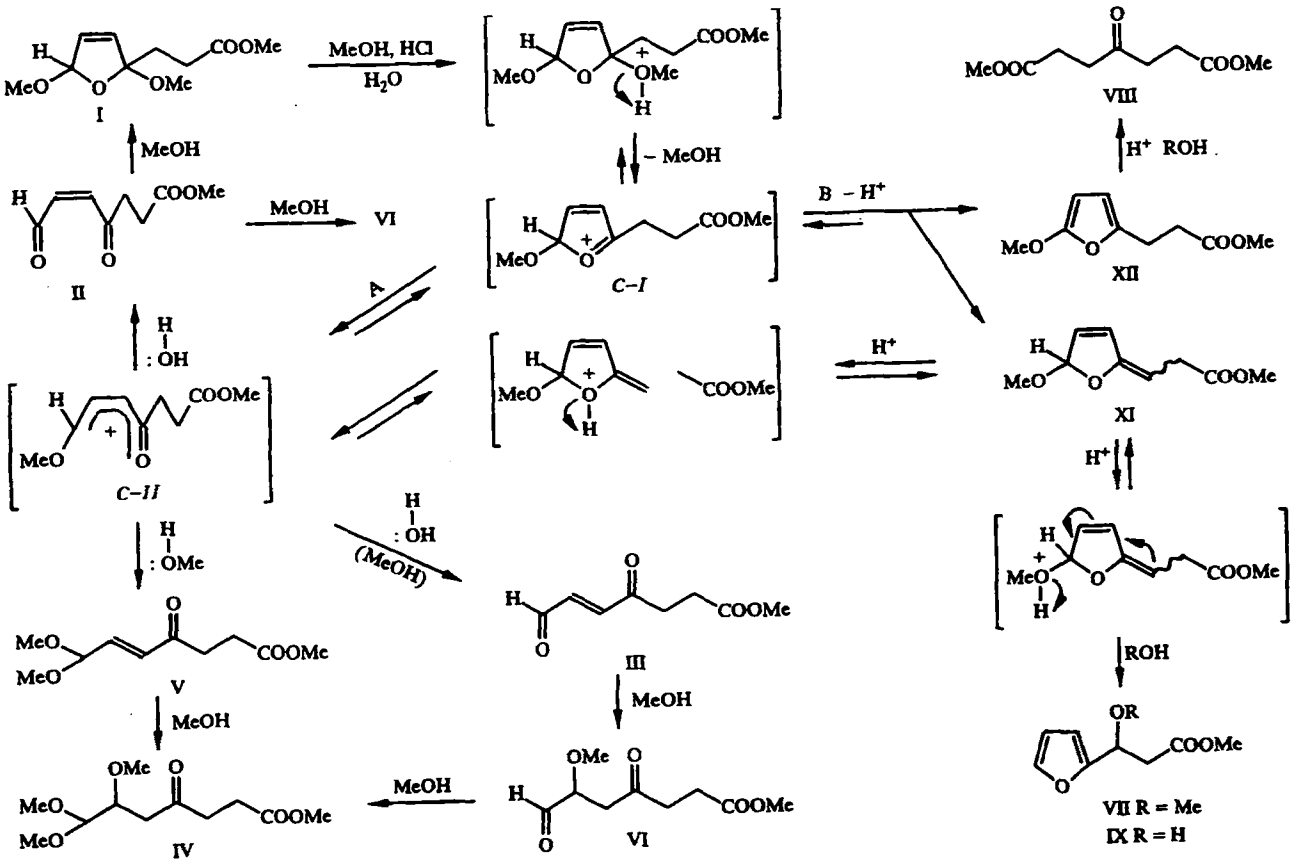
It could be supposed that like the formation of levulinic acid from the acetal (X) (R = H) [22] compound (IV) could be transformed into methyl 4-oxopimelate (VIII). In the model reaction, however, when compound (IV) was boiled in anhydrous HCl/MeOH solution for 1 h, 60.5% of the unreacted acetal (IV), 4.35% of the aldehyde (VI), 16.9% of compound (VII), and only 7.8% of compound (VIII) were found in the reaction mixture. This result shows that the bulk of compound (VII) was formed not from the trimethoxy compound (IV) but in a different way.

According to path B, the competing stabilization of the intermediate ion *C-I* can be realized by deprotonation of either the 5-H of the ring or a hydrogen atom in the side chain. In this case highly reactive compounds are formed, i.e., methyl 3-(5-

TABLE 2. Chromatographic Analysis of the Reaction Mixture of Products from Cleavage of Compound (I) and Model Compounds

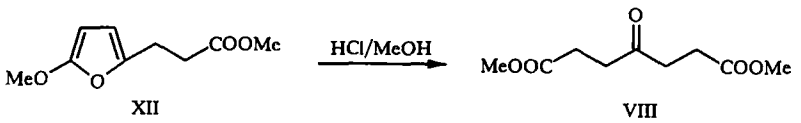
Expt. No.	Compound	Solvent	Reaction products						
			I	III	IV	V	VI	VII	VIII
1	I	A	—	—	31,75	1,91	8,96	23,19	28,38
2		B	—	—	35,03	4,46	6,11	26,54	21,84
3		C	7,01	30,30	9,44	5,68	14,31	18,48	7,41
4	II	A	0,98	—	14,84	—	24,49	28,91	21,17
5		B	—	—	36,65	2,28	13,03	22,80	16,68
6		C	21,11	21,51	6,18	4,06	11,87	18,48	6,23
7	III	A	—	8,55	30,67	16,17	18,95	6,34	9,53
8		B	0,50	—	54,89	2,32	21,21	4,93	7,61
9		C	4,26	31,12	0,07	49,21	4,43	2,70	—
10	XI	A	—	—	19,87	—	15,94	29,25	33,41
11		B	—	—	4,41	—	16,94	30,01	47,23
12		C	—	16,79	3,71	—	12,54	40,14	24,93

methoxy-2,5-dihydro-2-furfurylidene)propionate (XI) and methyl 3-(5-methoxy-2-furyl)propionate (XII) respectively. In order to prove this suggestion experiments were carried out with the individual compounds (XI) and (XII), obtained by the pyrolysis of compound (I) at 200°C [20].



During the treatment of compound (XI) with mixtures A, B, and C the furan (VII) and the ketopimelate (VIII) were isolated as the main products (Table 2, expts. 10-12). This experiment confirms that compounds (VII) and (VIII) are mainly formed by path B; compound (XI) is the true intermediate compound in this process. It was not possible to detect compound (XI) in the reaction mixture since it quickly reacts with the nucleophiles in the presence of acids.

With an anhydrous HCl/MeOH solution compound (XII) instantly forms the ketopimelate (VIII) with an 88.6% yield.



XII VIII

EXPERIMENTAL

The PMR spectra were obtained on WH-90/DS and WM-360 spectrometers at room temperature in solutions in chloroform with TMS as internal standard. The chromato-mass spectra were recorded on a Kratos MS-25 instrument at 70 eV. A Carlo Erba EA-1108 instrument was used for elemental analysis. The melting points were determined on a Boëtius heater bench and were not corrected. Thin-layer chromatography was conducted on Silufol UV-254 plates. The plates were sprayed with vanillin reagent, prepared from 3 g of vanillin, 100 ml of ethanol, and 1 ml of concentrated sulfuric acid. They were then heated at 130°C until the colored spots appeared. Silasorb 600 (LC) (30 μ) was used for preparative column chromatography with 2:1 hexane—ethyl acetate as eluant. All the solvents were purified by routine methods. Gas-liquid chromatography was performed on a Varian 3700 chromatograph with a quartz capillary column; 5 m × 0.53 mm, thickness of stationary phase 2.5 μ, 60-200°C (10°C/min), nitrogen, 0.18 atm. The sample was introduced without stream splitting. The beginning of stream splitting was 0.5 min. The reaction mixtures were evaporated under vacuum in a water bath at $\leq$30°C.

Synthesis of Model Compounds. Compounds (I, VII, XI, XII) were obtained according to [20]. (For the chromatographic characteristics, see Table 1.) The synthesis of compound (IX) was described in [27].

Hydrolysis of Methyl 3-(2,5-dimethoxy-2,5-dihydro-2-furyl)propionate (I). A. To 3.0 ml of a buffer solution (0.18 ml of concentrated hydrochloric acid and 0.54 g of sodium chloride diluted to 200 ml with water, pH 2) we added 0.22 g (1 mmole) of the dihydrofuran (I). The mixture was stirred at room temperature for 15 min, extracted with 2 ml of deuterochloroform, and quickly filtered through a small layer of anhydrous sodium sulfate. The solution of methyl *cis*-4,7-dioxo-5-heptenoate (II) was analyzed by PMR (360 MHz): 2.70 (2H, t, J = 6.3 Hz, H^2), 2.95 (2H, t, J = 6.3 Hz, H^3), 3.67 (3H, s, $COOCH_3$), 6.21 (1H, dd, J = 7.0, J = 11.9 Hz, H^6), 6.95 (1H, d, J = 11.9 Hz, H^5), 7.86 (1H, d, J = 7.0 Hz, H^7). For analysis by TLC and GLC the solution was kept at −20°C. Compound (II) decomposes during evaporation.

B. To 1.08 g (5 mmole) of the dihydrofuran (I) we added 11.0 ml of the buffer solution. The mixture was stirred at room temperature for 15 min and extracted with chloroform (3 × 10 ml). The extract was dried over anhydrous sodium sulfate for 30 min, and a catalytic amount (~5 mg) of iodine was added. After 5 min the solvent was evaporated under vacuum, and 0.64 g (75%) of methyl *trans*-4,7-dioxo-5-heptenoate (III), sufficiently pure for spectroscopic analysis, was obtained. PMR spectrum (360 MHz): 2.71 (2H, t, J = 6.3 Hz, H^2), 3.03 (2H, t, J = 6.3 Hz, H^3), 3.49 (3H, s, $COOCH_3$), 6.83 (1H, dd, J = 16.8, J = 7.0 Hz, H^6), 6.93 (1H, d, J = 16.8 Hz, H^5), 8.26 (1H, d, J = 7.0 Hz, H^7). Mass spectrum, m/z (I_{rel}, %): 139 ($M-OCH_3$, 11)$^+$, 138 ($M - CH_3OH$, 20)$^{+\cdot}$, 115 (8), 111 (10), 97 (7), 87 (7), 83 (62), 59 (30), 55 (100). For TLC and GLC the solution was kept at −20°C. Compound (III) decomposes in the presence of air.

C. To 1.08 g (5 mmole) of the dihydrofuran (I) we added 25 ml of methanol—water solution, containing 0.1 M of hydrochloric acid ($MeOH/H_2O$, see Fig. 1). The mixture was heated at 80°C (oil bath temperature) for 45 min and cooled, and 5 ml of a saturated solution of sodium carbonate was added. The methanol was evaporated under vacuum, and the product was extracted with benzene (3 × 10 ml). The extract was washed with a saturated solution of sodium chloride (2 × 10 ml), dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The product was analyzed by GLC, TLC, and chromato-mass spectrometry. Mass spectrum, m/z (I_{rel}, %): Compound (IV), 217 ($M - OCH_3$, 0.04)$^+$, 216 ($M - CH_3OH$, 0.1)$^{+\cdot}$, 185 (0.1), 173 (0.1), 167 (0.1), 161 (0.07), 153 (3), 115 (13), 101 (5), 75 (100), 59 (8), 55 (12); compound (V), 185 ($M - OCH_3$, 8), 169 (5), 153 (40), 143 (4), 141 (28), 129 (11), 125 (23), 115 (7), 111 (28), 97 (38), 83 (22), 75 (100), 69 (18), 59 (50), 55 (70); compound (VI), 173 ($M - CHO$, 12)$^+$, 143 (4), 141 (5), 139 (10), 115 (85), 111 (9), 87 (28), 73 (12), 59 (51), 55 (100). The PMR spectra and mass-spectrometric characteristics of (VII) are given in [17]; compound (VIII), 171 ($M - OCH_3$, 1.7)$^+$, 143 (14), 115 (100), 111 (38), 87 (12), 73 (5), 59 (49), 55 (88).

D. To 1.08 g (5 mmole) of the dihydrofuran (I) we added 25.0 ml of anhydrous 0.1 N hydrochloric acid in methanol. The mixture was stirred at room temperature for 2 h. The reaction mixture was treated as described above and analyzed by GLC. By column chromatography on 50 g of silica gel we isolated 0.55 g (47%) of compound (IV). PMR spectrum (90 MHz): 2.59 (2H, m, J = 17.0, J = 6.6 and 5.7 Hz, H^2), 2.68 (2H, m, J = 17.0, J = 7.1 and 4.8 Hz, H^5), 2.78 (2H, m, J = 18.0,

J = 6.6 and 5.7 Hz, H^3), 3.42 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 3.435 (3H, s, OCH_3), 3.68 (3H, s, $COOCH_3$), 3.79 (1H, dt, J = 7.1 and 4.8, J = 4.8 Hz, H^6), 4.27 (1H, d, J = 4.8 Hz, H^7). Found, %: C 53.21, H 8.15. $C_{11}H_{20}O_6$. Calculated %: C 53.21, 8.12.

Protolysis of Compounds (I, II, III, XI). We treated 0.2 g (~0.1 mmole) of compound (I) and the aldehydes (II) and (III), produced *in situ* from 0.2 g (~ 0.1 mmole) of the dihydrofuran (I) and 0.18 g (~0.1 mmole) of compound (XI) with three different mixtures of solutions: A) 2.0 ml of chloroform, 2.5 ml of 0.1 N anhydrous HCl/MeOH; B) 2.0 ml of chloroform, 2.5 ml of 0.1 N anhydrous HCl/MeOH, 0.1 ml of $CH(OCH_3)_3$; C) 2.0 ml of chloroform, 2.5 ml of 0.1 N HCl/MeOH, 0.5 ml of water.

The reaction solutions were boiled under a reflux condenser for 20 min, cooled to room temperature, and analyzed by GLC (Table 2) and chromato-mass spectrometry.

Hydrolysis of Compound (IV). While stirring we heated a mixture of 0.166 g (~0.7 mmole) of compound (IV), 50 mg of cation exchanger Dowex 50-W, 3 ml of acetone, and 0.4 ml of water at 60-65°C (water bath temperature) for 30 min. The mixture was filtered and evaporated under vacuum. We obtained 0.12 g (89%) of methyl 4,7-dioxo-6-methoxyheptanoate (VI), sufficiently pure for spectroscopic investigation. PMR spectrum (90 MHz): 2.68-2.95 (6H, m, H^2, H^3, H^5), 3.52 (3H, s, OCH_3), 3.73 (3H, s, $COOCH_3$), 4.10 (1H, t, J = 6.8 Hz, H^6), 9.96 (1H, s, H^7). The product decomposed during preparative column chromatography.

Methanolysis of Compound (IV). To 0.3 g (1.2 mmole) of chromatographically pure (IV) we added 1.5 ml of 0.1 N anhydrous HCl/MeOH. The mixture was boiled under a reflux condenser for 1 h and evaporated under vacuum. We obtained 0.2 g of the product, containing 60.5% of the initial (IV), 4.35% of the aldehyde (VI), 16.9% of compound (VII), and 7.80% of the ketopimelate (VIII).

Methanolysis of Compound (XII). We dissolved 25.6 mg (0.14 mmole) of compound (XII) in 2 ml of anhydrous 0.1 N HCl/MeOH. After 5 min the solution was evaporated under vacuum and chromatographed on 2 g of silica gel (eluant 1:3 hexane—ethyl acetate). We obtained 24.8 mg of dimethyl 4-ketopimelate (VIII). The yield was 88.6% of the theoretical; mp 54.5-55.5°C (mp 56°C [28]).

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