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The Reaction of Ethyl Alkylchloropyruvate with Sodiomalonate and Sodioacetoacetate[1]

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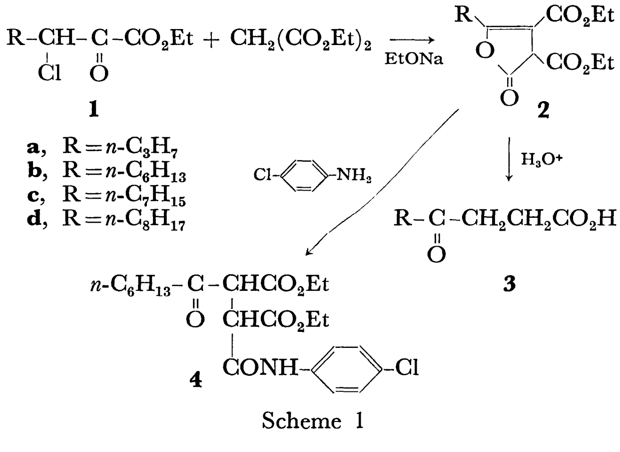
The reaction of alkylchloropyruvate (**1**) with sodiomalonate gave γ-alkyl-α,β-dialkoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolide (**2**), which led to γ-ketocarboxylic acid (**3**). The reaction of **1** with sodioacetoacetate gave 2-alkyl-5-methylfuran-3,4-dicarboxylate (**6**) *via* the intermediate 2-alkyl-3-hydroxy-5-methyl-2,3-dihydrofuran-3,4-dicarboxylate (**5**). It has been shown unambiguously that the carbanions of both sodiomalonate and sodioacetoacetate attack the carbonyl carbon of **1** predominantly.

Reichstein *et al.* disclosed in 1933 that bromopyruvic ester reacted with sodiooxaloacetate to yield 2,3,4-furantricarboxylic ester.[2] Dunlop and Hurd[3] assumed that the cyclization process involved the formation of 3-hydroxy-2,3-dihydrofurantricaboxylate as the intermediate. Cantlon *et. al.* later discussed and confirmed its structure by means of NMR data.[4] We reported that the reaction of ethyl chlorophenylpyruvate with diethyl sodiomalonate gave γ-phenyl-α,β-diethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolide, which on hydrolysis and subsequent decarboxylation afforded γ-benzoylpropionic acid.[5]

Since the mode of reactions of carbanions such as sodiomalonate and sodioacetoacetate with alkylhalopyruvate has not been investigated, it appears to us worthwhile to elucidate the structures of intermediates as well as products in reactions, which lead to 2,5-dialkyl-3,4-dialkoxycarbonylfurans, or to γ-alkyl-α,β-dialkoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolides. The facility of



Scheme 1

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[1] Presented in part at the Annual Meetings of the Chemical Society of Japan, April 1, 1967 (Tokyo) and April 4, 1969 (Tokyo).

[2] T. Reichstein, A. Grussner, K. Schindler, and E. Hardmeyer, *Helv. Chim. Acta*, **16**, 276 (1933).

[3] A. P. Dunlop and C. D. Hurd, *J. Org. Chem.*, **15**, 1160 (1950).

[4] I. J. Cantlon, W. Cocker, and T. B. H. McMurry, *Tetrahedron*, **15**, 46 (1961).

[5] A. Takeda, S. Wada, and T. Uno, *Mem. School Eng., Okayama Univ.*, **2**, 80 (1967).

Table 1. γ-Alkyl-α,β-diethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolides (**2**)

Compound	R	Yield %	Bp °C/mmHg	n_D^{25}	Found, % C	Found, % H	Calcd, % C	Calcd, % H
2a	n-C_3H_7	43	133—135/3	1.4564	57.83	6.93	57.77	6.71
2b	n-C_6H_{13}	46	155—157/3	1.4551	61.26	8.05	61.52	7.74
2c	n-C_7H_{15}	42	164—168/3	1.4571	62.35	8.29	62.56	8.03
2d	n-C_8H_{17}	32	160—163/1	1.4565	63.62	8.40	63.51	8.29

obtaining alkylchloropyruvic esters (**1**)[6] also prompted us to study these reactions in order to find new synthetic routes to 2,5-dialkylfurans and γ-oxoalkanecarboxylic acids.

This paper deals with the preparation of four γ-alkyl-α,β-diethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolides (**2a**—**d**), which were readily converted to γ-ketocarboxylic acids (**3a**—**d**), together with the preparation of three 2-alkyl-5-methylfuran-3,4-dicarboxylates (**6b**—**d**), which were converted to 2-alkyl-5-methylfurans (**8b**—**d**). These furans were finally transformed to the corresponding 1,4-diketones (**9b**—**d**). The intermediate 2-alkyl-3-hydroxy-5-methyl-2,3-dihydrofuran-3,4-dicarboxylates (**5b**—**d**) also were isolated and characterized.

The reaction of **1** with sodiomalonate gave the product (**2**) in a 40—50% yield, which was separated as a colorless oil and purified by vacuum distillation. The structure of **2** was confirmed by elemental analyses and IR spectra (lactone C=O 1835, 1820 cm^{-1}; ester C=O 1750, and conjugated ester C=O 1725 cm^{-1}; C=C 1665 cm^{-1}). Further evidence to support the $\Delta^{\beta,\gamma}$-butenolide structure of **2** was provided by the fact that the treatment of **2b** with *p*-chloroaniline gave *N*-(*p*-chlorophenyl)-2,3-diethoxycarbonyl-4-oxocapramide (**4**) in 95% yield. The acid hydrolysis of **2** and the subsequent decarboxylation yielded γ-ketocarboxylic acids (**3a**—**d**) in good yield (Scheme 1). IR spectra of **3** exhibited a characteristic band at 1695 cm^{-1} due to C=O and were identical with those of the authentic sample.[7] A series of γ-alkyl-α,β-diethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolides (**2a**—**d**) and γ-keto acids (**3a**—**d**) derived in this way are listed in Tables 1 and 2, respectively.

Table 2. Preparation of γ-keto acids (**3**) from $\Delta^{\beta,\gamma}$-butenolides (**2**)

Compound	R	Yield, %	Mp, °C
3a	n-C_3H_7	51	48—49[a]
3b	n-C_6H_{13}	59	66—67[b]
3c	n-C_7H_{15}	74	78—78.5[c]
3d	n-C_8H_{17}	55	78—79[d]

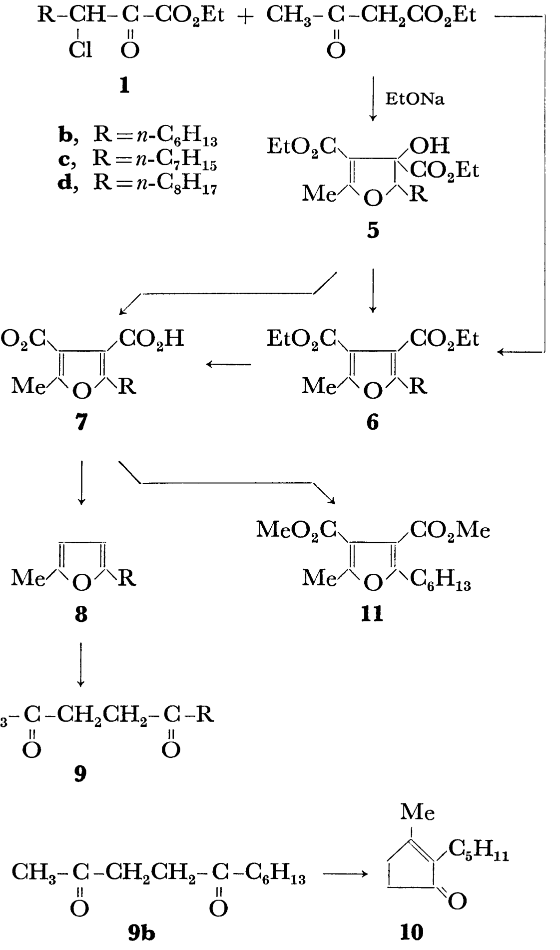
a) Mp 48.5—49.5°C: A. S. Perlin and C. B. Purves, *Can. J. Chem.*, **31**, 227 (1953).

b) Mp 66—67°C: H. Reinheckel, K. Haage, and R. Gensike, *Angew. Chem.*, **77**, 810 (1965).

c) Mp 77—79°C: I. Ernest, H. Jelinkova, *Collect. Czech. Chem. Commun.*, **24**, 3341 (1959); *Chem. Abstr.*, **54**, 4375 (1958).

d) Mp 78°C: H. Reinheckel *et. al, loc. cit.*

The reaction of **1** with ethyl sodioacetoacetate was carried out in dry ethanol. Ethyl 3-chloro-2-oxononanoate (**1b**) gave ethyl 2-*n*-hexyl-3-hydroxy-5-methyl-2,3-dihydrofuran-3,4-dicarboxylate (**5b**) as the condensation product in 73% yield. Treatment of **5b** with sulfuric acid effected the dehydration to afford ethyl 2-*n*-hexyl-5-methylfuran-3,4-dicarboxylate (**6b**) in quantitative yield. The structural assignment of **5b** was based on IR spectra (OH 3490 cm^{-1}; ester C=O 1735, 1706 cm^{-1}; C=C 1640 cm^{-1}) and NMR spectra (CDCl$_3$) (τ 7.74, s, 3H, $^{-C}_{-O}{>}C{-}CH_3$; τ 7.58, s, 1H, OH). When treated with alcoholic potassium hydroxide solution, **5b** underwent both dehydration and hydrolysis to give 2-*n*-hexyl-5-methylfuran-3,4-dicarboxylic acid (**7b**) in good yield. **7b** was transformed into dimethyl ester (**11**) with diazomethane and identified. While **1b** (R=n-C_6H_{13}) gave only **5b** as the major product, **1c**(R=n-C_7H_{15}) and **1d** (R=n-C_8H_{17}) afforded



Scheme 2

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[6] A. Takeda, S. Wada, M. Fujii, and H. Tanaka, This Bulletin, **43**, 2997 (1970).

[7] A. Takeda, K. Takahasi, S. Torii, and T. Moriwake, *J. Org. Chem.*, **31**, 616 (1966).

TABLE 3. 1,4-DIKETONES (**9**) AND THE INTERMEDIATES (**5**,**6**,**7**,**8**)

Compound	R	Yield %	Bp °C/mmHg (Mp, °C)	n_D^{25}	Found, % C	Found, % H	Calcd, % C	Calcd, % H
5b	n-C_6H_{13}	73	158—161/3	1.4649[a]	62.16	8.59	62.18	8.59
5c	n-C_7H_{15}	b)	183—185/6[c]	1.4639	63.07	8.78	63.14	8.83
5d	n-C_8H_{17}	b)	180—182/2.5[c]	1.4659	64.43	9.05	64.02	9.05
6b	n-C_6H_{13}	99	150—152/2	1.4705[a]	66.18	8.56	65.78	8.44
6c	n-C_7H_{15}	b)	183—185/6[c]	1.4680	66.70	8.83	66.64	8.70
6d	n-C_8H_{17}	b)	180—182/2.5[c]	1.4688	67.69	9.10	67.43	8.93
7b	n-C_6H_{13}	99[d]	(120—121)		61.62	7.14	61.41	7.14
7c	n-C_7H_{15}	e)	(105)		62.87	7.64	62.67	7.51
7d	n-C_8H_{17}	e)	(112.5)		64.01	7.89	63.81	7.85
8b	n-C_6H_{13}	77	101—103/29[f]	1.4538	79.83	10.71	79.46	10.91
8c	n-C_7H_{15}	46	113—114/22[g]	1.4522	80.05	10.98	79.94	11.18
8d	n-C_8H_{17}	55	128—129/21[h]	1.4538	80.07	11.64	80.35	11.41
9b	n-C_6H_{13}	79	(34)[i]		72.04	10.77	71.70	10.94
9c	n-C_7H_{15}	54	(43)[j]		72.47	11.36	72.68	11.18
9d	n-C_8H_{17}	57	(48—49)		73.17	11.49	73.54	11.39

a) Measured at 27°C. b) Obtained as a mixture. Separation into the components was by tlc (Experimental). c) Temperature range at which the mixture distilled. d) Yield from **6b**. e) The mixture of **5** and **6** was used as the starting material (Experimental). f) Bp 102—105°C/30 mmHg.[8] g) Bp 107—110°C/16 mmHg.[8] h) Bp 95—97°C/11 mmHg.[8] i) Mp 33°C.[9] j) Mp 40.5°C.[9]

the mixtures of the corresponding intermediate (**5c**, **5d**) and the dehydrated product (**6c**, **6d**). These mixtures were used without fractionation for the preparation of **7c** as well as **7d** by means of alkaline hydrolysis. Decarboxylation of acids **7b**—**d** carried out in quinoline by heating with copper powder, afforded 2-alkyl-5-methylfurans (**8b**—**d**). IR spectra and the boiling point of the furans (**8b**—**d**) were identical with those of the authentic samples, which were obtained in the alternative way.[8] The ring-opening of **8b**—**d** to give the 1,4-diketones (**9b**—**d**) was effected by heating with aqueous acetic acid containing a small amount of sulfuric acid. The sequence of these reactions is shown in Scheme 2. Table 3 shows the yields, physical properties, and analytical data of three 1,4-diketones obtained in this experiment and their intermediates. Diketone **9b** was converted to 2-n-pentyl-3-methyl-2-cyclopenten-1-one (**10**) by the usual method.

Since substrate (**1**) has two reactive positions, α and β, in the molecule, there are possibilities of forming two kinds of ring skeleton for both reactions described in Schemes 1 and 2. The formation of **3** from **2** and that of **8** from **5** unambiguously indicate that the carbanions of sodiomalonate and sodioacetoacetate have attacked the carbonyl carbon of **1** predominantly.

Experimental[10]

All boiling points and melting points are uncorrected. Thin layer chromatography was carried out on silica gel G (E. Merck AG, Darmstadt), where the spots of materials were detected by spraying with sulfuric acid solution of potassium permanganate (7: 3 in wt.). Infrared spectra were determined on a Hitachi IR EPI-S2 spectrophotometer.

Ethyl alkylchloropyruvates (**1**) other than **1a** used in this experiment were prepared by the Darzens type condensation of the appropriate aldehydes and ethyl dichloroacetate.[6] Ethyl 3-chloro-2-oxohexanoate (**1a**) was obtained as a pure product by direct chlorination of ethyl 2-oxohexanoate[11] with sulfuryl chloride.

The followings are typical of the experiments to derive **2**, **3**, **5**, **6**, **7**, **8**, and **9**.

*Ethyl 3-Chloro-2-oxohexanoate (**1a**).* To a stirred solution of ethyl 2-oxohexanoate (7.9 g, 0.05 mol) was added dropwise 7.0 g (0.052 mol) of sulfuryl chloride at 25—30°C. The reaction mixture was stirred at room temperature for additional 60 hr. Distillation of the crude product gave 7.3 g (76%) of **1a**: bp 98—100°C/16 mmHg; n_D^{25} 1.4387; IR (cm^{-1}, liquid) 1755 (ketone C=O) and 1735 (ester C=O).

Found: C, 50.18; H, 6.83%. Calcd for $C_8H_{13}ClO_3$: C, 49.88; H, 6.80%.

*γ-n-Hexyl-α,β-diethoxycarbonyl-$\Delta^{\beta,\gamma}$-butenolide (**2b**).* Diethyl malonate (20.0 g, 0.125 mol) and ethyl 3-chloro-2-oxononanoate (**1b**)[6] (11.7 g, 0.05 mol) were added to 60 m*l* of anhydrous ethanol in which 2.3 g (0.1 g-atom) of sodium was dissolved. The mixture was heated for 7 hr at 65—70°C with stirring and allowed to stand overnight. The reaction mixture was acidified with 10% aqueous sulfuric acid and taken up in ether. The ethereal extract was washed with aqueous sodium bicarbonate and then with water, dried over anhydrous magnesium sulfate, and concentrated. Distillation of the residual oil afforded 7.2 g (46%) of **2b**; bp 155—157°C/3 mmHg; IR (cm^{-1}, liquid) 1835, 1820 (lactone C=O), 1750 (ester C=O), 1725 (conjugated ester C=O), and 1665 (C=C).

*4-Oxodecanoic Acid (**3b**).* A mixture of 3.0 g (0.01 mol) of **2b**, 60 m*l* of sulfuric acid, and 90 m*l* of water was stirred for 10 hr at 170°C in an oil bath. The reaction mixture was cooled, extracted with ether. The ethereal layer was shaken with 5% aqueous sodium hydroxide. The aqueous layer was acidified and then taken up in ether. The extract was

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[8] Office de Recherches Industrielles de Laboratoire, French 1186346 (1959); *Chem. Abstr.*, **56**, 455 (1962).

[9] H. Hunsdiecker, *Ber.*, **75**, 452 (1942).

[10] Elementary analyses were carried out by Mr. Eiichiro Amano of our laboratory. We are indebted to Dr. Akira Suzuki and Mr. Sigezo Simokawa, both of Hokkaido University, Sapporo, for NMR measurements.

[11] M. Igarasi and H. Midorikawa, *J. Org. Chem.*, **29**, 2082 (1964).

dried over anhydrous magnesium sulfate and the solvent was removed. The residual solid was recrystallized from *n*-hexane to give 1.1 g (59%) of **3b**: mp 66—67°C.

N-(p-*Chlorophenyl)-2,3-diethoxycarbonyl-4-oxodecanamide (4).* A mixed solution of **2b** (0.6 g, 0.002 mol) and *p*-chloroaniline (0.25 g, 0.002 mol) in 2 m*l* of chloroform was stirred at room temperature for 1 hr. After evaporation of the solvent 0.6 g (95%) of **4** was obtained: mp 80—81°C; IR (cm^{-1}, Nujol) 3300 (amide NH), 1730 (ester C=O), 1715 (ketone C=O), and 1665 (amide C=O).

Found: C, 59.94; H, 7.11; N, 3.33%. Calcd for $C_{22}H_{30}ClNO_6$: C, 60.06; H, 6.87; N, 3.18%.

*Ethyl 2-*n*-Hexyl-3-hydroxy-5-methyl-2,3-dihydrofuran-3,4-dicarboxylate (5b).* To a solution of ethyl sodioacetoacetate, prepared from sodium (2.3 g, 0.1 g-atom), anhydrous ethanol (100 m*l*), and ethyl acetoacetate (26.0 g, 0.2 mol), was added 23.5 g (0.1 mol) of **1b**. The mixture was heated at 60—65°C with stirring for 7 hr. After being kept standing overnight at room temperature, the reaction mixture was acidified with 20% aqueous sulfuric acid and taken up in ether. The ethereal extract was washed with water, dried over anhydrous sodium sulfate, and concentrated. Distillation of the residue yielded 24.4 g (73%) of **5b**: bp 158—161°C/3 mmHg; R_f 0.54.[12]

*Ethyl 2-*n*-Hexyl-2-methylfuran-3,4-dicarboxylate (6b).* Sulfuric acid (50 m*l*) was added dropwise to 10.0 g (0.03 mol) of **5b** in an ice bath. After being heated for 5 min at 50°C, the reaction mixture was poured into 50 m*l* of ice water and extracted with ether. The ethereal layer was washed with water and subsequently with 10% sodium carbonate solution. After being dried over anhydrous sodium sulfate, the solvent was removed. Distillation of the residue under diminished pressure gave 9.1 g (99%) of **6b**: bp 150—152°C/2 mmHg; R_f 0.73;[12] IR (cm^{-1}, liquid) 1720 (ester C=O) and 1590 (C=C).

*2-*n*-Hexyl-5-methylfuran-3,4-dicarboxylic Acid (7b).* *(a) From 6b:* To a solution of potassium hydroxide (1.0 g, 0.018 mol) in 10 m*l* of 50% aqueous ethanol, 1.0 g (0.003 mol) of **6b** was added. The reaction mixture, after being refluxed for 6 hr, was acidified with 10% aqueous sulfuric acid, and extracted with ether. The ethereal extract, which was treated in the usual manner, gave 0.75 g (99%) of acidic material. The crude product was recrystallized from *n*-hexane - benzene to yield pure sample of **7b**: mp 120—121°C; IR (cm^{-1}, Nujol) 1685, 1630, and 1570.

(b) From 5b: A mixture of **5b** (1.4 g, 0.005 mol) and the solution of potassium hydroxide (5.0 g, 0.09 mol) in 10 m*l* of aqueous 50% ethanol was refluxed for 6 hr. The crude product of **7b** was isolated in the same manner as described in the foregoing experiment. Recrystallization from *n*-hexane - benzene gave 0.8 g (63%) of the prdouct: mp 120—121°C; IR (cm^{-1}, Nujol) 1685, 1630, and 1570.

Reaction of Ethyl 3-Chloro-2-oxodecanoate (1c) with Ethyl Acetoacetate. Ethyl 3-chloro-2-oxodecanoate[6] (37.0 g, 0.15 mol) was added to a solution of ethyl sodioacetoacetate, prepared from 3.4 g (0.15 g-atom) of sodium, 38.7 g (0.3 mol) of ethyl acetoacetate, and 100 m*l* of anhydrous ethanol. The stirred mixture was heated at 60—65°C for 7 hr and allowed to stand overnight at room temperature. After being acidified with 20% aqueous sulfuric acid, the reaction mixture was extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated. Distillation of the resudie yielded 27.3 g of the liquid, which was collected at 183—185°C/6 mmHg. For analysis and spectral determination, the liquid was fractionated to **5c** and **6c** by means of preparative thin layer chromatography. R_f values[13] were 0.30 for **5c** and 0.56 for **6c**. From 0.4 g of the mixture 0.3 g of **5c** and 0.1 g of **6c** were obtained. IR spectra (cm^{-1}, liquid): **5c**, 3490 (OH), 1735(ester C=O), 1705(conjugated ester C=O), and 1640 (C=C); **6c**, 1720 (ester C=O), and 1590 (C=C).

*2-*n*-Heptyl-5-methylfuran-3,4-dicarboxylic Acid (7c).* The liquid mixture (25.0 g) obtained in the foregoing experiment was refluxed with much excess of potassium hydroxide dissolved in 50% aqueous ethanol for 6 hr. It gave 11.0 g of the crude product (**7c**): mp 105°C (from *n*-hexane - benzene); IR (cm^{-1}, Nujol) 1685, 1630, and 1570.

Reaction of Ethyl 3-Chloro-2-oxoundecanoate (1d) with Ethyl Acetoacetate. Condensation was carried out in the same manner as that of **1c**. The following reactants were used: 23.5 g (0.09 mol) of **1d**; 23.4 g (0.18 mol) of ethyl acetoacetate; 2.1 g (0.09 g-atom) of sodium which was dissolved in 100 m*l* of anhydrous ethanol before use. Distillation afforded 30.5 g of the liquid which was collected at 180—182°C/2.5 mmHg. The liquid was fractionated to **5d** and **6d** by preparative tlc. R_f values[13] were 0.22 for **5d** and 0.43 for **6d**. IR spectra (cm^{-1}, liquid): **5d**, 3490 (OH), 1735 (ester C=O), 1705 (conjugated ester C=O), and 1640 (C=C); **6d**, 1720 (ester C=O) and 1590 (C=C).

*2-*n*-Octyl-5-methylfuran-3,4-dicarboxylic Acid (7d).* The liquid mixture (17.8 g) obtained in the above experiment, gave 8.4 g of the crude product (**7d**) on the alkaline hydrolysis: mp 112.5°C (from benzene); IR (cm^{-1}, Nujol) 1685, 1630, and 1570.

*2-*n*-Hexyl-5-methylfuran (8b).* A mixture of **7b** (10.0 g, 0.039 mol) and quinoline (25 m*l*) was refluxed for 5 hr in the presence of copper powder (5.0 g). After filtration, the mixture was extracted with ether. The extract, washed with water, diluted hydrochloric acid, then with water, was dried over anhydrous sodium sulfate. The fraction distilling at 101—103°C/29 mmHg was collected: yield 5.0 g (77%), IR (cm^{-1}, liquid) 1570.

2,5-Undecanedione (9b). A mixture of **8b** (3.0 g, 0.018 mol), glacial acetic acid (7 m*l*), water (2.5 m*l*), and a few drops of sulfuric acid was refluxed for 2 hr. The mixture was poured into 10 m*l* of water and taken up in ether. The ethereal layer was separated, washed with saturated sodium bicarbonate and water, and dried over anhydrous sodium sulfate. Removal of the solvent yielded crystals. Recrystallization of the crude product from methanol gave 2.6 g (79%) of **9b**: mp 34°C; IR (cm^{-1}, Nujol) 1715 (ketone C=O).

*2-*n*-Pentyl-3-methyl-2-cyclopentene-1-one (10).* Dione **9b** (0.7 g, 0.04 mol) was heated with 3% aqueous sodium hydroxide (7 m*l*) at reflux temperature for 7 hr with vigorous stirring. The mixture was taken up in ether, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave 0.4 g (61%) of **10**. The 2,4-dinitrophenylhydrazone of **10**, mp 119—120°C, was identical with the authentic sample.[14]

*Metyl 2-*n*-Hexyl-5-methylfuran-3,4-dicarboxylate (11).* When treated with diazomethane, **7b** was transformed into its methyl ester **11**: bp 145—148°C (bath)/3 mmHg;[15] n_D^{25} 1.4755; IR (cm^{-1}, liquid) 1720 (ester C=O) and 1590 (C=C); NMR (τ, $CDCl_3$) 7.56 (s, 3H, CH_3), and 6.18 (s, 6H, $2CH_3$-OCO).

Found: C, 64.15; H, 7.59%. Calcd for $C_{15}H_{22}O_5$: C, 63.81, H, 7.85%.

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12) Conditions of tlc: support, silica gel G (E. Merck AG, Darmstadt), 0.3 mm; developer, *n*-hexane - acetone (3:1 v/v).

13) Conditions of preparative tlc: support, silica gel G (E. Merck AG, Darmstadt), 0.8 mm; developer, *n*-hexane - acetone (5:1 v/v); eluent, acetone.

14) C. Rai and S. Dev, *Experientia*, **11**, 114 (1955).

15) The temperature of the oil bath at which **9** was distilled under diminished pressure (3 mmHg).