The Cyclization of Diethyl 3, 6-Dioxo-azelate

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1, 4, 7-Cyclononanetrione (XIX) has many active methylenes and seems to be structurally interesting compound, but its convenient synthesis cannot be found in the literature. It has only obtained in the form of trioxime in a poor yield.[1] In this paper the synthesis of XIX will be attempted through the acyloin condensation[2,3] of the bisethylene ketal derivative (XI) of diethyl 3, 6-dioxo-azelate (I).

It is well-known that diesters of aliphatic dicarboxylic acids afford the corresponding cyclic acyloin by the action of sodium. However, when XI was subjected to this reaction, the reaction product was not the expected acyloin (XVIII). This anomalous result stimulated the present authors to examine these reactions further. Though the ultimate synthesis of XIX was unsuccessful, the synthesis of I and its anomalous cyclization reactions will be reported in this paper.

Results and Discussion

I was obtained through two synthetic routes. In one route, furyl-acrylic acid (VII) was changed into diethyl 4-oxo-pimelate (II),[4] which was then partially hydrolyzed[5] and converted to an ester chloride (IV). IV was derived into I through malonic ester synthesis.[6] However, it was difficult to obtain pure I by this method. Even after repeated distillation, the product showed infrared absorptions at 1780 ($\nu_{C=O}$, γ-lactone), 1740 ($\nu_{C=O}$, ester), 1720 ($\nu_{C=O}$, ketone) and 1600 cm^{-1} ($\nu_{C=C}$), indicating the presence of an unsaturated γ-lactone (X).[7]

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[1] S. Kawai, S. Tanaka, K. Terai. M. Tezuka and T. Nishiwaki, This Bulletin, **33**, 251 (1960).

[2] V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947); M. Stoll, J. Hulstkamp and A. Rouvé, ibid., **31**, 543 (1948); A. T. Blomquist, L. H. Liu and J. C. Bohrer, *J. Am. Chem. Soc.*, **74**, 3643 (1952); P. D. Gardner, G. R. Haynes and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957); N. L. Allinger, "Organic Syntheses," Vol. 36, 79 (1956).

[3] J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, *J. Am. Chem. Soc.*, **75**, 6231 (1953).

[4] W. S. Emerson and R. I. Longley, Jr., "Organic Synthese," Vol. 33, 25 (1953).

[5] W. Marckwald, *Ber.*, **21**, 1402 (1888).

[6] D. S. Breslow, E. Baumgarten and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944).

[7] F. A. Kuehl, Jr., R. P. Linstead and B. A. Orkin, *J. Chem. Soc.*, **1950**, 2213.

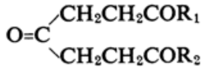
In the other route, I was obtained by the ring opening of ethyl furyl-acryloyl-acetate (IX),[8] which was synthesized from VII by malonic ester synthesis.[6] It was shown by gas chromatography that the reaction product of IX with hydrogen chloride in ethanol consisted of I and ethyl 4, 7-dioxo-octanoate (VI),[9] and that I and VI were separated by distillation. I showed strong infrared absorptions at 1740 ($\nu_{C=O}$, ester) and 1720 cm^{-1} ($\nu_{C=O}$, ketone) and produced the corresponding dibasic acid (V) on hydrolysis with an aqueous sodium hydroxide solution.

Before the acyloin cyclization of I is carried out, its keto groups must be protected.[10] Therefore, I was changed into the bis-ethylene ketal derivative (XI). XI showed no infrared absorption at 1720 ($\nu_{C=O}$, ketone), but it did show one at 1740 cm^{-1} ($\nu_{C=O}$, ester).

A dilute xylene solution of XI was added very slowly, through a capillary tube and with vigorous stirring, to xylene in which sodium had been dispersed. After 24 hr. the reaction mixture was then neutralized by acetic acid. The isolated product was proved to be not an acyloin (XVIIII), but 2-ethoxycarbonyl-4, 4-ethylenedioxy-1, 7-cyclooctanedione (XXII), a partially hydrolyzed compound of a Dieckmann condensation product (XXII).

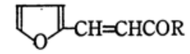
The structure of XXIII was deduced as follows. XXIII gave a positive ferric chloride test, but a negative Fehling test, indicating the absence of the acyloin structure in XXIII. The infrared absorption spectrum of XXIII showed absorptions at 1740 ($\nu_{C=O}$, ester; keto form), 1720 ($\nu_{C=O}$, ketone; keto form), 1660 ($\nu_{C=O}$, ester; enol form) and 1610 cm^{-1} ($\nu_{C=C}$; enol form), the last two being attributed to the enolizable β-ketoester.[11] The ultraviolet absorption spectrum of XXIII showed λ_{max}^{EtOH} 255 (ε, 4500) and $\lambda_{max}^{alkali\ EtOH}$ 287 mμ (ε, 10800).

The NMR spectra[12] of XXIII in carbon tetrachloride were assigned to the ethyl group of the ester at 5.71 (quartet) and 8.68τ (triplet, J 7.0 c. p. s.), to the enolized hydroxyl group at -2.30τ (singlet), to 4 protons of methylene groups neighbor carbonyl groups at 7.46—7.64τ (multiplet), to 4 protons of the other methylenes at 7.81—8.35 τ (multiplet), and to 4 protons of the ethylene ketal group at 6.04τ (singlet).[13] These data indicate that



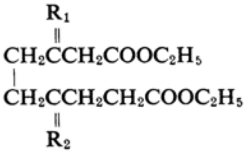
$$O{=}C\begin{cases}CH_2CH_2COR_1\\ CH_2CH_2COR_2\end{cases}$$

I $R_1=CH_2COOC_2H_5$ $R_2=OC_2H_5$
II $R_1=R_2=OC_2H_5$
III $R_1=OH$ $R_2=OC_2H_5$
IV $R_1=Cl$ $R_2=OC_2H_5$
V $R_1=CH_2COOH$ $R_2=OH$
VI $R_1=CH_3$ $R_2=OC_2H_5$



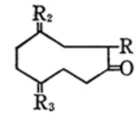
VII $R=OH$
VIII $R=Cl$
IX $R=CH_2COOC_2H_5$

X

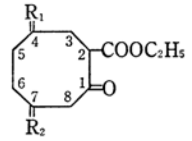


$$\begin{array}{l}\quad R_1\\ \quad \| \\ CH_2CCH_2COOC_2H_5\\ | \\ CH_2CCH_2CH_2COOC_2H_5\\ \quad \| \\ \quad R_2\end{array}$$

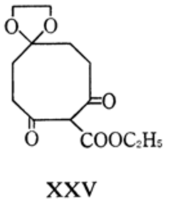
XI $R_1=R_2=OCH_2CH_2O$
XII $R_1=H_2$ $R_2=O$
XIII $R_1=H_2$ $R_2=OCH_2CH_2O$
XIV $R_1=O$ $R_2=H_2$
XV $R_1=OCH_2CH_2O$ $R_2=H_2$
XVI $R_1=O$ $R_2=OCH_2CH_2O$
XVII $R_1=OCH_2CH_2O$ $R_2=O$



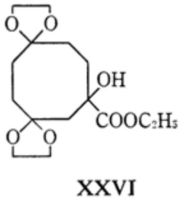
XVIII $R_1=OH$ $R_2=R_3=OCH_2CH_2O$
XIX $R_1=H$ $R_2=R_3=O$
XX $R_1=OH$ $R_2=H_2$ $R_3=OCH_2CH_2O$
XXI $R_1=OH$ $R_2=OCH_2CH_2O$ $R_3=H_2$



XXII $R_1=R_2=OCH_2CH_2O$
XXIII $R_1=OCH_2CH_2O$ $R_2=O$
XXIV $R_1=H_2$ $R_2=OCH_2CH_2O$



XXV



XXVI

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[8] J. English, Jr., and L. J. Lapides, *J. Am. Chem. Soc.*, **65**, 2466 (1943).

[9] F. L. Breush and E. Ulusay, *Rev. faculté sci. univ. Istanbul*, **13A**, 51 (1948); *Chem. Abstr.*, **42**, 5850h (1948).

[10] E. J. Salmi, *Ber.*, **71**, 1805 (1938).

[11] S. J. Rhoads, J. C. Gilbert, A. W. Decora, L. R. Garland, R. J. Spangler and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

[12] NMR spectra were measured on a Varian A-60 megacycle spectrometer by courtesy of Dr. S. Yoshida of Sankyo Co. Ltd.

[13] E. Capsi, Th. A. Wittstruck and D. M. Piatak, *J. Org. Chem.*, **27**, 3183 (1962).

one of the ethylene ketal groups at C-7 was hydrolysed to a ketone.

In order to find a reasonable explanation why only the Dieckmann condensation reaction occurred in this case, diethyl azelate was subjected to the same treatment as above; 2-hydroxy-cyclononanone (azeloin)[2] was obtained in about a 25% yield. Even in the presence of ethanol, azeloin was obtained, but in this case, the product was contaminated with a small amount of a Dieckmann condensation product, 2-ethoxycarbonyl-cyclooctanone.

The different behavior of XI and diethyl azelate could be attributed to the presence of two ethylene ketal groups in the former. It is suspected that the relative position of the ketal group and the ethoxycarbonyl group might influence their behavior. In fact, this was proved by the reaction of the ethylene ketal of 4-oxo-azelate (XII)[14] and 3-oxo-azelate (XIV) under the same conditions.

From XIII, the ethylene ketal of XII, acyloin (XX) was obtained. XX gave a positive Fehling test. Its infrared absorption spectrum showed absorptions at 3400 (ν_{OH}) and 1705 cm^{-1} ($\nu_{C=O}$, ketone). Its ultraviolet absorption spectrum showed λ_{max}^{EtOH} 260 mμ (ε, 2600), which shifted to $\lambda_{max}^{alkali\ EtOH}$ 310 mμ (ε, 3800).

On the other hand, from XV, the ethylene ketal of XIV, a Dieckmann condensation product (XXIV) was obtained instead of the corresponding acyloin (XXI). The structure of XXIV was deduced from the following facts. The product obtained gave a positive ferric chloride test, but a negative Fehling test. Its infrared absorption spectrum showed absorptions at 1705 ($\nu_{C=O}$, ketone) and 1730 cm^{-1} ($\nu_{C=O}$, ester).

Now let us discuss when and why one of the ethylene ketal groups was hydrolyzed in the reaction of XI to XXIII. In the first place, the hydrolysis may be presumed to occur after the ring closure. If it had occurred before the ring closure, the intermediate compound, XVI or XVII, must be subjected to the condensation reaction. Of these two intermediates, only XVI can produce XXIII. However, methylene at C-2 in XVI would be more reactive than methylene at C-8, and the reaction from XVI to XXV must be predominant over the reaction from XVI to XXIII. As the experimental results were not in accord with this reasoning, the formation of the cyclic intermediate (XXII) must precede the hydrolysis of one member of the ethylene ketal group.

Next, let us consider the partial hydrolysis of XXII. The ethylene ketal group at C-7 seems to be less stable than that at C-4, because of the effect of the β-carbonyl group at C-1 or because of the steric effect of the other ethylene ketal group at C-4 in the medium-size ring. As a model compound of ethylene ketal with a β-carbonyl group, 4,4-ethylenedioxy-2-pentanone[15] was prepared, and the hydrolysis of the ketal with acetic acid was studied. It was found that only a small amount of 2,4-pentanedione was produced. Therefore, the partial hydrolysis of XXII during the neutralization of the reaction mixture with acetic acid, seems to be effected mainly by the steric hindrance, not by the electron displacement.

As a modified acyloin condensation, liquid ammonia has been used[3] instead of xylene. The acyloin condensation reaction of XI in the presence of sodium in liquid ammonia gave a product different from XXIII. On the basis of infrared spectra at 3400 (ν_{OH}) and 1740 cm^{-1} ($\nu_{C=O}$, ester), a negative Fehling test, and a positive ferric chloride test, the structure of the product was tentatively proposed to be 1-ethoxycarbonyl-3,3,6,6-bisethylenedioxy-1-cyclooctanol (XXVI). The details of this reaction will be reported elsewhere.

Experimental

All melting points are uncorrected.

6-Ethoxycarbonyl-4-oxo-hexanoic Acid (III).—A solution of 120 g. of diethyl 4-oxo-pimelate and 26 g. of potassium hydroxide in 2 l. of ethanol was allowed to stand overnight at room temperature. After the reaction mixture had been concentrated under reduced pressure, it was poured into cold water, acidified with hydrochloric acid, and extracted with benzene. The benzene solution was then dried over anhydrous sodium sulfate. After the benzene had been removed, 10 g. of crude III was obtained. This was recrystallized from benzene-petroleum ether as colorless plates; m. p. 70.5°C. IR: ν 1730, 1700 cm^{-1}.

6-Ethoxycarbonyl-4-oxo-hexanoyl Chloride (IV).—A mixture of 10 g. of III and 15 g. of thionyl chloride was allowed to stand overnight at room temperature. After the excess thionyl chloride had been removed, IV was obtained as a colorless oil; b. p. 171—176°C/17 mmHg, yield 6.5 g.

Ethyl Furyl-acryloyl-acetate (IX).—To 0.56 g. of magnesium were added 0.5 ml. of absolute ethanol, a few drops of carbon tetrachloride, and 10 ml. of anhydrous ether. After a few minutes, 4.3 g. of ethyl *t*-butyl malonate, 2 ml. of absolute ethanol, and 18 ml. of anhydrous ether were added, and the mixture was refluxed for 4 hr. with stirring. To the mixture, 3.7 g. of furylacryloyl chloride (b. p.

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[14] S. Hünig and W. Lendle, *Chem. Ber.*, **93**, 913 (1960).

[15] P. C. Dutta, P. K. Dutta and K. N. S. Sastry, *J. Indian Chem.*, **31**, 881 (1954); *Chem. Abstr.*, **50**, 838h (1956).

119—120°C/19 mmHg)[8] in 15 ml. of anhydrous ether was then added slowly and the solution refluxed for one hour. The mixture was acidified with 1.8 N sulfuric acid and washed with water. After the ether had been removed, the residue was dissolved in benzene and refluxed for 4 hr. with 100 mg. of *p*-toluenesulfonic acid. The benzenene solution was washed with water, and the solvent was removed. IX was obtained as pale yellow oil; b. p. 77—107°C/3.5 mmHg, IR: ν 3080, 1730, 1640, 1540 cm^{-1}; UV: λ_{max}^{EtOH} 342 mμ.

2, 4-Dinitrophenylhydrazone was prepared and recrystallized from ethanol - ethyl acetate; m. p. 179°C.

Found: C, 52.17, 52.26; H, 3.91, 3.97; N, 13.90, Calcd. for $C_{17}H_{16}N_4O_7$: C, 52.58; H, 4.15; N, 14.43%.

Diethyl 3, 6-Dioxo-azelate (I).—1) I was obtained from IV in about a 35% yield by a procedure similar to the one described for IX.

2) Dry hydrogen chloride was passed for 45 min. through a hot solution of 25 g. of ethyl furyl-acryloyl-acetate in 70 ml. of 95% ethanol. After the ethanol had been removed under reduced pressure, the residue was poured into an aqueous solution of sodium carbonate and extracted with benzene, and the benzene layer was dried over sodium sulfate. After the benzene had been removed, the residue was distilled under reduced pressure; b. p. 134—135°C/0.8 mmHg, yield 12 g.

Dibenzylamide, m. p. 177°C.

Found: C, 70.68; H, 6.53. Calcd. for $C_{23}H_{16}N_2O_4$: C, 70.03; H, 6.64%.

3, 6-Dioxo-azelaic Acid (V).—I was added to an aqueous 3 N sodium hydroxide solution, and the mixture was heated until a clear solution was obtained. After it had cooled, the solution was acidified with dilute hydrochloric acid and extracted with ether. The ether layer was separated and dried over sodium sulfate. After the ether had been removed, the free dibasic acid (V) was obtained; it was then recrystallized from benzene-ethanol; m. p. 139°C, IR: ν 3050, 1720, 1700 cm^{-1}.

Found: C, 48.19, 48.09; H, 5.82, 5.47. Calcd. for $C_9H_{12}O_6 \cdot 1/2H_2O$: C, 48.00; H, 5.82%.

Diethyl 3, 3, 6, 6-Bisethylenedioxy-azelate (XI).—The solution of 29.7 g. of I and 15 ml. of ethylene glycol in 200 ml. of benzene was refluxed with 300 mg. of *p*-toluenesulfonic acid under azeotropic distillation for 7 hr. The mixture was washed with water and dried over sodium sulfate. After the benzene had been removed under reduced pressure, XI was obtained as a colorless oil; b. p. 146—154°C/2.5 mmHg, yield 22.4 g.

Found: C, 57.31, 57.09; H, 7.90, 7.98. Calcd. for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83%.

The Acyloin Condensation of Diethyl Azelate.—1) With freshly dispersed sodium: In a 200 ml., three-necked, round-bottom flask equipped with a sealed stirrer, a reflux condenser, and a dropping-funnel, 5.2 g. of sodium and 90 ml. of dry xylene were placed. The mixture was refluxed and stirred (3600 r. p. m.) for 10 min. To the mixture was then added 11 g. of diethyl azelate in 50 ml. of xylene over a 24 hr. period, with sufficient stirring under reflux. After all of the xylene solution of diethyl azelate had been added, the reaction mixture was refluxed for another hour, and cooled with water and then with an ice bath. A mixture of 20 ml. of acetic acid and 20 ml. of xylene was then added. All these procedures were carried out during stirring and under a nitrogen atmosphere. The reaction mixture was washed with water and dried over anhydrous sodium sulfate. After the xylene had been removed under reduced pressure, the residue was distilled. 1.4 g. of 2-hydroxy-cyclononanone (azeloin) was thus obtained; b. p. 124—139°C/17 mmHg; IR: ν 3450, 1700 cm^{-1}; UV: λ_{max}^{EtOH} 262, $\lambda_{max}^{alkali\ EtOH}$ 286 mμ.

2) With commercial dispersed sodium: Into a mixture of 80 ml. of boiling xylene and 12.0 g. of commercial dispersed sodium in toluene (40%), 10.3 g. of diethyl azelate in 45 ml. of xylene was stirred in over a 24 hr. period. After the solution had been treated as has been described above, 700 mg. of azeloin was obtained.

The Reaction of XI with Dispersed Sodium.—The reaction of XI with freshly dispersed sodium was carried out according to the procedure described for azeloin, but no acyloin was detected in the product by a study of its infrared spectrum. The reaction of 11.5 g. of XI and 10 g. of commercial dispersed sodium (40% in toluene) in xylene afforded 1.8 g. of the crude reaction product. By distillation, XXIII was isolated; b. p. 133—137°C/3 mmHg.

Found: C, 58.21, 58.17; H, 6.98, 7.00. Calcd. for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71%.

Bis-2, 4-dinitrophenylhydrazone of XXIII was prepared and recrystallized from ethanol - ethyl acetate; m. p. 167°C.

Found: N, 18.09. Calcd. for $C_{25}H_{26}N_8O_{12}$: N, 17.77%.

Diethyl 4, 4-Ethylenedioxy-azelate (XIII).—By refluxing the mixture of 15.7 g. of ketone (XII), 5 ml. of ethylene glycol, and 100 mg. of *p*-toluenesulfonic acid in 150 ml. of benzene, 13.9 g. of XIII was obtained; b. p. 146—151°C/0.13 mmHg, IR: ν 1740 cm^{-1}.

Found: C, 59.62, 59.45; H, 8.93, 8.87. Calcd. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67%.

The Reaction of XIII with Dispersed Sodium.—By the reaction of 3.2 g. of XIII and 4.5 g. of commercial dispersed sodium (40% in toluene) in 50 ml. of xylene, 200 mg. of the corresponding acyloin (XX) was obtained; b. p. 80—90°C/0.02 mmHg.

6-Ethoxycarbonylhexanoyl Chloride.—From 8.0 g. of 6-ethoxycarbonylhexanoic acid[16] and 6.2 ml. of thionyl chloride, 7.8 g. of the acid chloride was obtained; b. p. 138—141°C/17.5 mmHg, IR: ν 1800, 1740 cm^{-1}.

Diethyl 3-Oxo-azelate (XIV).—The malonic ester synthesis was carried out by a procedure similar to that described for the synthesis of IX. From 650 mg. of magnesium, 0.1 ml. of carbon tetrachloride, 3.6 g. of absolute ethahol, 5 ml. of ethyl *t*-butyl malonate, and 5.4 g. of 6-ethoxy-carbonyl-hexanoyl chloride in 31 ml. of anhydrous

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[16] J. Walker and J. S. Lumsden, *J. Chem. Soc.*, **79**, 1197 (1901).

ether, 1.5 g. of XIV were obtained; b. p. 105—106°C/0.5 mmHg, IR: ν 1740, 1720 cm^{-1}.

Found: C, 60.13, 60.24; H, 9.24, 9.31. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59%.

Diethyl 3, 3-Ethylenedioxy-azelate (XV). — By the same procedure as was used for XI, XV was obtained from 1.3 g. of XIV; b. p. 95—110°C/0.24 mmHg, yield 0.6 g., IR: ν 1740 cm^{-1}.

Found: C, 59.45, 59.49; H, 8.70, 8.75. Calcd. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67%.

The Reaction of XV with Dispersed Sodium.— The reaction of 0.6 g. of XV and 0.5 g. of dispersed sodium (40% in toluene) in xylene afforded only a trace of the product; b. p. 82—87°C/0.05 mmHg; UV: λ_{max}^{EtOH} 250 mμ (ε, 1300).

The Acyloin Condensation of XI in Liqid Ammonia.—0.8 g. of sodium was stirred in a nitrogen atmosphere and thus dissolved into a mixture of 200 ml. of anhydrous ether and about 300 ml. of liquid ammonia cooled in an acetone - dry ice bath. To this solution was then added 1.9 g. of XI in 180 ml. of anhydrous ether over a 2 hr. period. After the ammonia had been removed, 2 ml. of methanol and 75 ml. of 5% hydrochloric acid were added slowly. The ethereal solution was then washed with water and dried over anhydrous sodium sulfate. The ether was removed, and the residue was distilled to give 100 mg. of XXVI; b. p. 70—110°C/2 mmHg. XXVI was treated with 2, 4-dinitrophenylhydrazine acidified with sulfuric acid. Bis-2, 4-dinitrophenylhydrazone was prepared and recrystallized from ethanol - ethyl acetate; m. p. 147°C.

Found: N, 19.81. Calcd. for $C_{23}H_{24}N_8O_{11}$: N, 19.04%.

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