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REACTIONS OF SOME DICARBONYL COMPOUNDS

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Abstract—The reactions of some halogeno keto-esters and the sodio derivatives of β-dicarbonyl compounds have been investigated.

IN a recent publication[1] we discussed some aspects of the chemistry of furan tetracarboxylic acid (F.T.C.A.; I; R = H), and in particular the preparation of F.T.C.A. by the hydrolysis of its tetraester, (I; R = Et.). The latter compound may be obtained in very satisfactory yield by the dehydration of the tetraester, variously described as II,[2] III,[3] and IV.[4] Further structures, V and VI, have been suggested as reasonable possibilities.[1,4] We have now shown that the tetraester is V.

The tetraester (V), which gives no ferric reaction, may be conveniently prepared[2] by the addition of bromine to a stirred suspension of ethyl sodio-oxaloacetate in an inert solvent. This is a base catalysed reaction of ethyl bromo-oxaloacetate with ethyl oxaloacetate since we have shown that preformed bromo ester will react with ethyl oxaloacetate in presence of sodium acetate or pyridine to give V.

Structures II and III cannot be seriously entertained since both possess an enolizable keto group and would give a ferric reaction. The tetraester (V) shows strong absorption at 3500 cm^{-1}, typical of a single bridge bonded hydroxyl group, but not of an enol. Moreover it is difficult to see how III could cyclize to give I (R = Et), though this reaction has been suggested,[3] and indeed a recent text book[5] draws special attention to it.

Ethyl bromopyruvate condenses with ethyl sodio-oxaloacetate to give a tricarboxylic ester which has been formulated as VII or VIII. Its formation must proceed by a similar mechanism to that which gives V. Structure VIII and not VII must however represent the triester since on hydrolysis it affords furan 2,3,4-tricarboxylic acid (IX; R = H) and not its 2,3,5-isomer (X). By analogy we assign V and not IV to the tetraester. Furthermore both IV and VII are hemiketals which with acid would undergo ring cleavage to give furan 2,5-dicarboxylic acid.

Structure VI is a possible alternative to V for the tetraester, but spectroscopic data given in Tables 1 and 2 show that the tetraester (and the triester) cannot possess the ethylene oxide structure of VI.

In Table 1 only the bands in the 3500 and 1800–1500 cm^{-1} ranges are given. Below 1500 cm^{-1} and particularly in the 1350–1000 cm^{-1} region the spectra are very complex and it is difficult to distinguish between the C–O stretching absorptions of alcohols and esters.

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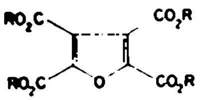
[1] W. Cocker, W. J. Davis, T. B. H. McMurry and P. A. Start, *Tetrahedron* **7**, 299 (1959).

[2] H. Sutter, *Liebigs Ann.* **499**, 56 (1932).

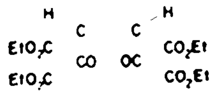
[3] T. Reichstein, A. Grussner, K. Schindler and E. Hardmeyer, *Helv. Chim. Acta* **16**, 276 (1933).

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

[5] A. R. Katritsky and J. M. Lagowski, *Heterocyclic Chemistry* p. 154. Methuen, London (1960).



I



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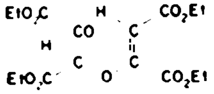
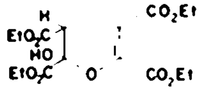
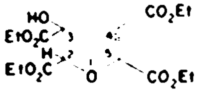


III

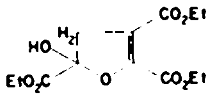


IV

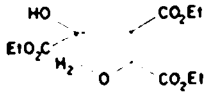


V

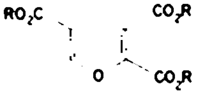
VI



VII

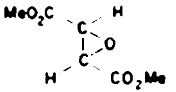


VIII



IX

X



XI

$EtO \quad C(R) \quad C(R')(R'')$

XII

XIII

TABLE 1. INFRA-RED MEASUREMENTS WERE MADE IN NUJOL (n), LIQUID FILM (l) OR CHLOROFORM (c)

Compound	ν_{max} cm^{-1}
Tetraester (V)(n)	3500, 1776, 1764, 1703, 1670, 1650
Triester (VIII)(n)	3500, 1764, 1703, 1650
Furan tetracarboxylic ester (I; R = Me) (n)	1766, 1759, 1747, 1728, 1612
Furan 2,3,4-tricarboxylic ester (IX; R = Me) (n)	1742, 1595m 1545
Methyl furan-3-carboxylate (c)	1726, 1703, 1594, 1581, 1506
trans 1,2-Dimethoxycarbonyl ethylene oxide (XI) (n)[6]	1745
Ethyl β-ethoxyacrylate (XII; R = R' = H; R'' CO$_2$Et) (l)	1724, 1708, 1652, 1632
Ethyl β-ethoxycrotonate (XII; R = CH$_3$; R' = H; R'' = CO$_2$Et) (l)	1742, 1650
Ethyl 2,6-dimethyl-2,3-dihydropyran-5-carboxylate (XIII)[7]	1627
Diethyl maleate (l)	1724, 1639
Dimethyl maleate (l)	1724, 1653
Diethyl fumarate (l)	1724, 1647

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[6] R. Kuhn and F. Ebel, *Ber. Dtsch. Chem. Ges.* **58**, 919 (1925).

[7] F. E. Bader, *Helv. Chim. Acta* **36**, 215 (1953).

TABLE 2. ULTRA-VIOLET LIGHT ABSORPTION MEASUREMENTS WERE MADE IN ETHANOL

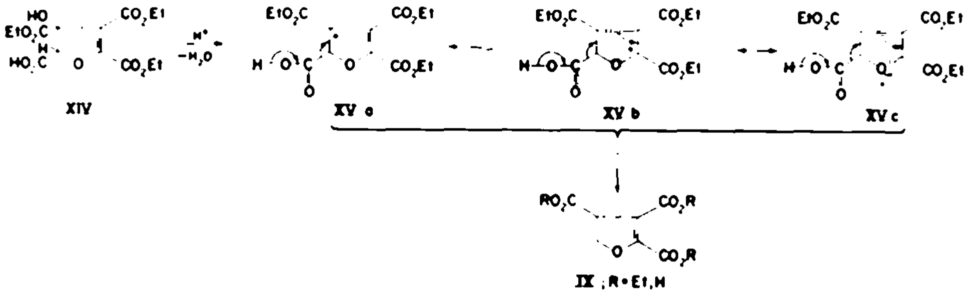
Substance	λ_{max} Å	log ϵ
Tetraester (V)	2470	3·89
Triester (VIII)	2470	3·88
Furan tetracarboxylic ester (I; $R = Me$)	2580	4·09
Furan tricarboxylic ester (IX; $R = Me$)	2450	4·05
trans 1,2-Dimethoxycarbonyl ethylene oxide (XI)	No max	log ϵ 2·09 at 2300 Å
Ethyl β-ethoxyacrylate (XII; $R = R^1 = H$; $R^{11} = CO_2Et$)	2330	4·29
Ethyl β-ethoxycrotonate (XII; $R = CH_3$; $R^1 = H$; $R^{11} = CO_2Et$)	2380	4·09
Diethyl ethoxymethylenesuccinate (XII; $R = H$; $R^1 = CO_2Et$; $R^{11} = CH_2CO_2Et$)	2380	4·02
Ethyl 2,6-dimethyl-2,3-dihydropyran-5-carboxylate (XIII)	2480	4·1
Ethyl oxaloacetate	2650	3·54
Ethyl acetoacetate	2460	3·28
Diethyl maleate	Inf. at 2500	2·95

The carbonyl bands at 1776 and 1764 cm^{-1} shown by V and at 1764 cm^{-1} shown by VIII though at unusually high wave numbers are probably due to the unconjugated ester groups, although furan tetracarboxylic ester shows bands at 1766 and 1759 cm^{-1}. The bands at 1703 cm^{-1} are due to conjugated ester groups and similar bands are found at 1724 cm^{-1} in most of the conjugated esters listed. The strong bands at 1650 cm^{-1} shown by V and VIII are undoubtedly associated with conjugated $C=C$. Similar bands are found at 1632–1653 cm^{-1} in the unsaturated esters listed in Table 1. *trans* 1,2-Dimethoxycarbonyl ethylene oxide (XI) which lacks the ethylenic double bond but contains an oxide structure similar to that of VI shows no absorption save that of the ester groups.

The ultra-violet data emphasize the similarity of V and VIII, though it will be noticed that both absorb maximally at 100 to 200 Å higher than the analogous acyclic unsaturated esters. The bathochromic effect is presumably a function of the ring system, and this suggestion finds support in a comparison of the maximum exhibited by ethyl 2,6-dimethyl-2,3-dihydropyran-5-carboxylate (XIII) and its acyclic analogue ethyl β-ethoxycrotonate (XII; $R = CH_3$; $R^1 = H$; $R^{11} = CO_2Et$). The intensity of the maximum absorption of V and VIII is similar to that exhibited by the esters bearing the group $RO_2C-C(R)=C(R)OR$ and is uniformly greater by an order of magnitude than the intensity shown by diethyl maleate which lacks the vinyl ether function. The spectrum of *trans* 1,2-dimethoxycarbonylethylene oxide (XI) shows that the ethylene oxide ring (present in VI) does not behave like an α,β-unsaturated ester or a cyclopropane ring conjugated with an ester group.

The nuclear magnetic resonance spectrum of V also supports its structure. It shows a peak at 4·88 p.p.m. due to a single hydrogen α- to the ether oxygen and to the ester carbonyl. The single hydrogen in IV would be expected to show a peak at 7·5 p.p.m. The methylene groups of the ethyl groups give a complex series of bands around 5·69 p.p.m. A peak at 5·99 p.p.m. is due to the hydroxyl hydrogen. The combined weight of these peaks corresponds to 9 hydrogens. The complex bands around 8·66 p.p.m. are due to the 12 hydrogens of the 4 methyl groups.

When either V or VIII is refluxed with hydrochloric acid, furan-2,3,4-tricarboxylic acid (IX; R; H) is obtained, in the former case admixed with the tetracarboxylic acid. Since furan tetracarboxylic acid, (I; R = H), is unaffected by treatment with hydrochloric acid, the decarboxylation of V must occur before the furan ring is formed. We believe that the secondary 2-ethoxycarbonyl group is the most readily hydrolysed of the four, thus giving XIV, but whether the decarboxylation takes place before or after hydrolysis of the remaining three ester groups is immaterial. The actual decarboxylation is probably preceded by protonation of the 4-hydroxyl group, followed by loss of water, to afford the intermediate XV to which the three canonical forms XVa, XVb and XVc contribute. The intermediate will readily lose a proton and carbon dioxide to afford furan 2,3,4-tricarboxylic acid (IX). A rather similar mechanism has been advanced for the acid catalysed decarboxylation of cinnamic acids.[8]



Since V is prepared under basic conditions the epimerizable centre at C_2 will adjust itself so that the 2- and 3-ethoxycarbonyl groups become *trans* with respect to each other. The loss of water to give furan tetracarboxylic ester (I; R = Et) when V is treated with concentrated sulphuric acid is thus explained. We have also shown that the dehydration can be effected using a mixture of acetic anhydride and pyridine, though dehydration with phosphorus oxychloride and pyridine, or with acetyl chloride or thionyl chloride was not possible.

We were unable to reduce the tetraester V by catalytic methods or by the use of zinc in ethanol, zinc in acetic acid, or the latter reagent containing silver nitrate.[9] Bromination of V could not be effected but a model of V, using space-filling models, shows that the 4- and 5-ester groups are very close together, and that access by bromine to the double bond must be very difficult.

Ozonolysis of V in ethyl acetate afforded a viscous product which gave no ferric reaction. The product showed a maximum at 3500 cm^{-1} in the infra-red, but the peak at 1650 cm^{-1} (C=C) shown by V had disappeared, and a broad band at 1745 cm^{-1} (carbonyl) appeared in place of the four carbonyl peaks exhibited by V. The ozonolysis product reacted rapidly with ammonia to give one molecule of oxamide for molecule of V, and with ethanol it afforded ethyl oxalate. These properties are consistent with an ozonolysis product of structure XVI, but attempts to isolate a

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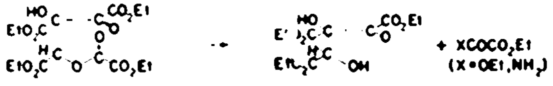
[8] W. S. Johnson and W. E. Heinz, *J. Amer. Chem. Soc.* 71, 2913 (1949).

[9] P. Bladon, *J. Chem. Soc.* 2176 (1955).

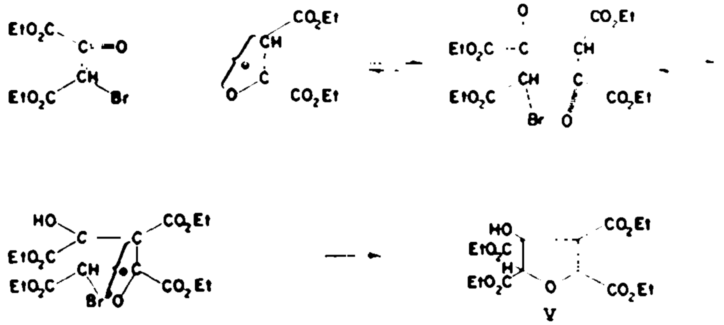
compound of structure XVII from XVI failed. The ozonolysis product of IV would give a ferric reaction.



XVI XVII

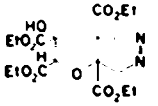
Diazomethane reacted only very slowly with the tetraester (V), to give a viscous liquid which was no longer unsaturated, but it possessed a band at $1540\ \text{cm}^{-1}$ in the infra-red which can be assigned to an imidazoline C=N or N=N (cf. XVIII).

We envisage the formation of the tetraester (V) by the reaction sequence shown below.

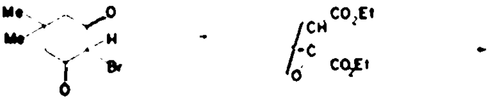


V

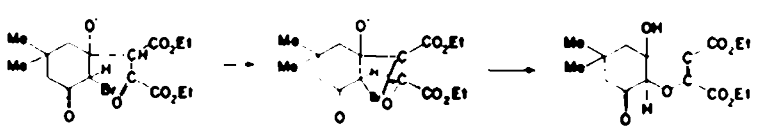
Whilst in the case of the simple ketones the equilibrium of the first stage of the reaction lies to the left[10] the effect of the bromine atom and the carbethoxy groups will be to increase the activity of the carbonyl group. In this connection we should mention that all our attempts to condense ethyl α-bromoacetoacetate with ethyl sodioacetoacetate failed, even when pyridine was used as a solvent. The difference in reactivity between ethyl bromo-oxaloacetate or ethyl bromopyruvate and ethyl bromoacetoacetate is readily explained by the greater reactivity of the keto group in the first two compounds, flanked as it is by $-CO_2Et$ and $-CHBr$-groups.



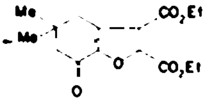
XVIII



XIX



XX



XXI

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[10] J. Hine, *Physical Organic Chemistry* p. 253. McGraw-Hill, New York (1956).

Attempts were also made to condense bromodimedone (XIX) with ethyl sodio-oxaloacetate according to the following reaction sequence—XIX → XX → XXI, but the only product was the tetraester (V) in high yield.

Bromodimedone must thus act as a brominating agent converting part of the ethyl sodio-oxaloacetate to ethyl bromo-oxaloacetate. No reaction occurred when sodiodimedone was shaken with ethyl bromo-oxaloacetate or bromodimedone. This may be due to steric factors, or, as is more likely, to the stability of the enolate of the dimedone.

When ethyl γ-bromoacetoacetate was reacted with ethyl sodio-oxaloacetate, the bromo ester condensed with itself, the product being ethyl succinylsuccinate. This compound has been prepared by the self-condensation of ethyl γ-haloacetoacetates in the presence of bases.[11] Ethyl sodio-oxaloacetate can obviously supply the base.

EXPERIMENTAL

Ethyl α-bromo-oxaloacetate was prepared by the method of Conover and Tarbell[12].

Reaction of ethyl α-bromo-oxaloacetate with ethyl oxaloacetate

(a) *With ethyl sodio-oxaloacetate.* Finely powdered ethyl sodio-oxaloacetate (6 g) was added to a solution of ethyl α-bromo-oxaloacetate (5 g) in ether (50 cc) and the mixture was shaken for several hours and then set aside overnight. The mixture was filtered and the ethereal filtrate evaporated to dryness. The residue was washed with ice-cold ether giving tetraethyl 2,3-dihydro-3-hydroxyfurantetracarboxylate (V, 2·1 g; 30%), m.p. 82–83° undepressed by an authentic specimen.

(b) *With pyridine as catalyst.* A mixture of ethyl α-bromo-oxaloacetate (5 g) and ethyl oxaloacetate (5 g) in ether (10 cc) was treated with freshly distilled and dried pyridine (2 cc), and set aside overnight. The mixture was filtered and the ethereal filtrate washed with dil H_2SO_4 and then with water. The residue on evaporation of the ether was a yellow oil which slowly crystallized giving V. On washing with ice-cold ether it was obtained as colourless needles (0·25 g), m.p. 80–83°, undepressed by an authentic specimen.

Tetraethyl furantetracarboxylate (I; R = Et)

A mixture of tetraethyl 2,3-dihydro-3-hydroxyfurantetracarboxylate (V) (2 g), acetic anhydride (5 cc) and pyridine (5 cc) was heated on a water bath for 2 hr. The mixture was poured into ice-water (30 cc) and neutralized with sodium carbonate. The solution was extracted with ether, and the ether layer washed with N H_2SO_4 and water and dried (Na_2SO_4). The product was chromatographed on neutral alumina (Woelm brand, 30 g). Elution with benzene–light petroleum (b.p. 40°–60°) gave tetraethyl furantetracarboxylate (I; R = Et; 0·4 g), m.p. and mixed m.p. 34°.

Reaction of bromodimedone with ethyl sodio-oxaloacetate

Bromodimedone was prepared as follows.[13] A stirred mixture of dimedone (10 g) sodium acetate (6·3 g) and glacial acetic acid (100 cc) was slowly treated with bromine (4 cc) in glacial acetic acid (70 cc). After stirring for a further 1 hr, water (600 cc) was added and the deposited solid collected and washed free from bromide. After drying in a desiccator it weighed 11·5 g, m.p. 173–174°.

Bromodimedone (2 g) was added to a suspension of ethyl sodio-oxaloacetate (3 g) in ether (50 cc) and the mixture was shaken for 20 hr. The mixture was filtered and the filtrate freed from ether giving a lachrymatory oil from which the tetra ester (V, 1·5 g), m.p. and mixed m.p. 82–83° was deposited. The lachrymatory oil smelled strongly of ethyl α-bromo-oxaloacetate.

Ozonolysis of the tetraester (V)

A solution of the tetraester (5 g) in ethyl acetate (100 cc) cooled in solid CO_2, was treated with ozonized oxygen for 8·5 hr, when it was no longer absorbed. The ozonide was then hydrogenated

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[11] W. Mewes, *Liebigs Ann.* **245**, 58 (1888); R. Schonbrodt, *Ibid.* **253**, 168 (1889).

[12] L. H. Conover and D. S. Tarbell, *J. Amer. Chem. Soc.* **72**, 5221 (1950).

[13] T. Voitila, *Chem. Abstr.* **33**, 7742 (1939).

over palladized charcoal giving a viscous liquid which was diluted to 15 cc with ethanol. (A). This solution (2 cc) was treated with an excess of ammonia (5 cc, *d*, 0·880). Considerable heat was evolved and a deep violet solution was obtained from which oxamide (0·2 g) was deposited. (B). Anhydrous hydrogen chloride was passed into the ethanolic solution (13 cc) for 2 min, the solution was then refluxed for 0·5 hr, and the ethanol was removed. The residue was dissolved in chloroform, washed several times with water, dried and distilled giving ethyl oxalate (0·75 g), b.p. 188°.

Action of diazomethane on the tetraester (V)

The tetraester (500 mg) was dissolved in ether (5 cc) and set aside with an excess of diazomethane in ether for 1 week. The product was an oil, which showed no maximum at 1650 cm^{-1} but a new maximum at 1540 cm^{-1}.

1,4-*Diethyl cyclohexan*-2,5-*dionedicarboxylate* (ethyl succinylsuccinate)

Ethyl γ-bromoacetoacetate[14] (from ethylacetoacetate, 50 g) was shaken for 20 hr with excess ethyl sodio-oxaloacetate in ether. The salts formed were collected at the pump, and the ether removed to afford ethyl succinylsuccinate (4·3 g), as pale yellow needles, m.p. 124 125°, undepressed on admixture with an authentic specimen.[15] (Found: C, 56·6; H, 6·0. Calc. for $C_{14}H_{18}O_7$: C, 56·4; 6·1%). It formed an acetate (acetic anhydride-pyridine), m.p. and m.p. 170°. (Found: C, 56·6; H, 6·0. Calc. for $C_{16}H_{20}O_8$: C, 56·5; H, 5·9%).

Acknowledgements—The authors are grateful to Messrs. A. Boake, Roberts & Co. Ltd., for gifts of ethyl sodio-oxaloacetate and to the Rohm and Haas Co. for samples of ethyl β-ethoxyacrylate and diethyl ethoxymaleate. One of us (I. J. C.) is indebted to the County of Armagh Education Committee and to the Ministry of Education for Northern Ireland for maintenance grants.

We are grateful to Dr. L. M. Jackman for the N.M.R. data.

[14] A. Burger and G. E. Ullyot, *J. Org. Chem.* **12**, 342 (1947.)

[15] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **48**, 772 (1915.)