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Stobbe-type Condensation Involving Dimethyl Diglycollate

by

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SUMMARY

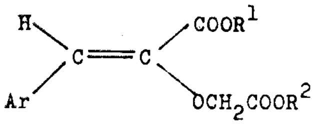
Condensation of 3,4-dimethyl-, 3,4-dimethoxy- and 3,4-dichlorobenzaldehyde with dimethyl diglycollate in the presence of sodium hydride gives predominantly the (Z)-half-esters (la-c) together with small amounts of the (E)-isomers (2a-c). The structure and configuration of the half-esters have been established on the basis of chemical and spectroscopic evidence. The ratio of isomers has been interpreted in terms of the relative ease of formation of the δ-lactone intermediates (6 and 7).

EXPERIMENTAL

In previous investigations[1,2], the ratio of stereoisomeric half esters obtained from the condensation of benzaldehyde and some p-substituted derivatives with diethyl diglycollate was interpreted in terms of steric factors governing the relative ease of formation of the diastereomeric δ-lactone intermediates.

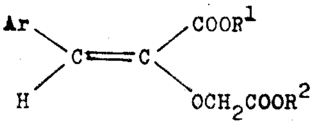
In the present work the condensation of 3,4-dimethyl-,3,4-dimethoxy-, and 3,4-dichlorobenzaldehyde with dimethyl diglycollate in the presence of sodium hydride gave predominantly the (Z)-half-esters la-c of which only the 3,4-dichlorophenyl half-ester 1c was obtained crystalline state; whereas the 3,4-dimethyl phenyl- and 3,4-dimethoxyphenyl half-esters 1*a*, *b* were obtained in the from of the corresponding (Z)-dibasic acids 1*d*, *e*. In all cases, smaller amounts of the crystalline (E)-half-esters 2a-c were isolated.

Chemical and spectroscopic evidence can be cited as strong support for the structure and configuration of the above half-esters. Thus the solid half-esters 2a-c and 1c exhibited IR bands at ca 1710 and 1695



(1)

	Ar	R^1	R^2
a,	$3,4\text{-}(CH_3)_2C_6H_3$	CH_3	H
b,	$3,4\text{-}(CH_3O)_2C_6H_3$	CH_3	H
c,	$3,4\text{-}Cl_2C_6H_3$	CH_3	H
d,	$3,4\text{-}(CH_3)_2C_6H_3$	H	H
e,	$3,4\text{-}(CH_3O)_2C_6H_3$	H	H

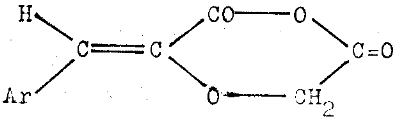


(2)

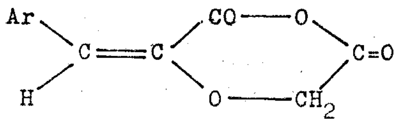
	Ar	R^1	R^2
f,	$3,4\text{-}Cl_2C_6H_3$	H	H
g,	$3,4\text{-}(CH_3)_2C_6H_3$	H	CH_3
h,	$3,4\text{-}(CH_3O)_2C_6H_3$	H	CH_3
i,	$3,4\text{-}Cl_2C_6H_3$	H	CH_3

cm^{-1} for α,β-unsaturated ester and non-conjugated carboxyl groups[3], respectively.

Saponification of the crystalline half-esters 2a-c and 1c gave the correspoding dibasic acids 2d-f and 1f in pure crystalline state. The oily (Z)-half esters 1a, b gave fairly high yields of the (Z)-diacids 1d, e in pure crystalline state. The dibasic acids exhibited ${}^{\nu}C{=}O$ for non-conjugated and α, β-unsaturated carboxyl groups[3] at ca 1715 and 1695 cm^{-1}, respectively. Chemical evidence for the structure of the above acids was obtained from their conversion to the corresponding cyclic anhydrides. Thus refluxing the (Z) and (E)-diacids with acetyl chloride gave the corresponding (Z)-and (E)-anhydrides 3a-c and 4a-c, respectively, in pure crystalline state. Supporting evidence for their structure is forthcoming from their IR spectra, which show two absorption bands at ca 1800 and 1745 cm^{-1} characteristic of six-membered ring anhydrides[3].



(3)



(4)

a, Ar = $3,4\text{-}(CH_3)_2C_6H_3$; b, Ar = $3,4\text{-}(CH_3O)_2C_6H_3$;
c, Ar = $3,4\text{-}Cl_2C_6H_3$

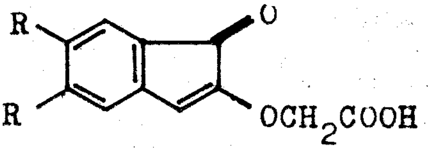
Methanolysis of the anhydrides 3a-c and 4a-c by refluxing methanol led to the expected ring cleavage at the nonconjugated carbonyl to give the corresponding 4-carboxy half esters 1g-i and 2g-i in ca 75 % yield. The presence of non-conjugated ester and α,β - unsaturated carboxyl groups[3] was shown by $^{\nu}C{=}O$ at ca 1760 and 1720 cm^{-1}, thus providing additional proof for the structure of the anhydrides.

The (E)-configuration assigned to the crystalline half-esters 2a-c was established by cyclisation of the derived anhydrides 4a-c with aluminium chloride to the corresponding oxoindenyl acids 5a-c in high yield.

Beside elemental analysis, solubility in sodium carbonate, yellow colour, and formation of 2,4-dinitrophenylhydrazones, each of the oxoindenyl acids 5a-c showed $^{\nu}C{=}O$ at ca 1718 and 1700 cm^{-1} for ring ketonic and carboxyl groups[3]. Medium IR bands at 850 cm^{-1} due to γ C–H of the isolated para hydrogens of the fused aromatic ring rejected the alternative 6,7-disubstituted formula. The positions of maxima in their electronic spectra (λ_{max} 246–250, 292–294, ε 38,000 – 42,000, 32,000 – 38,000) resemble those for analogous compounds[1].

The longer wavelength bands extends well into the violet region thus reflecting the yellow colour of these compounds.

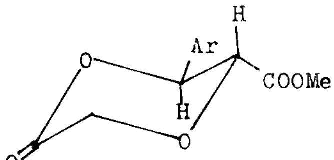
The configuration of the (Z)-anhydrides 3a-c was deduced from the fact that upon treatment with aluminium chloride, the corresponding diacids 1d-f were the sole isolable acidic products.



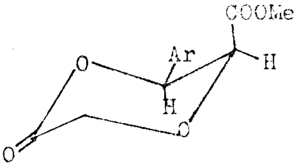
(5)

a, R = CH_3 , b, R = OCH_3 ; c, R = Cl

Predominance of the (Z)-configuration 1*a-c* among the half-esters irrespective of the polar effects of substituents is in agreement with the recently reported observation[1,2], and can be similarly interpreted in term of steric factors governing the relative ease of formation of the diastereomeric δ-lactone intermediates 6 and 7. The route leading to 6 is facilitated by accomodation of both bulky groups in equatorial position.



(6)



(7)

EXPERIMENTAL

Melting points are not corrected, Infrared (KBr) spectra were measured on a Unicam SP 1200 Infracord; electronic spectra on a Unicam SP 1800 spectrophotometer.

(E) and (Z)-5-Aryl-4-methoxycarbonyl-3-oxa-pent-4-enoic acids (1a-c) and (2c) by Stobbe Condensation.

Dimethyl diglycollate, the aldehyde and sodium hydride (1.5:1:1.5 mol) in excess dry benzene were stirred on a water-bath for 10–15 hrs, and the reaction mixture was worked up as usual[4].

3,4– *Dimethylbenzaldehyde* (13.4 g): (stirring for 12 hrs) gave a half-ester mixture (16.2 g, 58 % yield), which was dissolved in benzene-light petroleum (b.p. 80–100 °C) where by it could be separated into two fractions: (i) the less soluble (E)-half-ester la (3.1 g) (cf. Table 1), (ii) the more soluble fraction (13.1 g). The latter was obtained as an oil and its composition revealed by saponification (see later).

3,4– *Dimethoxybenzaldehyde* (16.6 g): (striring for 15 hrs) gave a half-ester mixture (17.0 g, 51 % yield), which was dissolved in benzene-light petroleum (b.p. 80–100 °C) whereby it could be separated into two fractions: (i) the less soluble (E)-half-ester 1b (4.0 g) (cf. Table 1), (ii) the more soluble fraction (13.0 g). The latter was obtained as an oil and whose composition was revealed by saponification (see later).

Table 1 (Z) – and (E)-5-Aryl-4-methoxycarbonyl-3-oxapent-4-enoic acids 1c and 2a-c

Nr.	m.p. (°C) Solvent of cryst.a)	Formula (Mol. wt.)	Analysis Calcd. /Found %C	 %H	 %Cl
1c	97 – 99	$C_{13}H_{12}Cl_2O_5$	48.9	3.7	22.2
	bz	(319)	49.3	3.9	22.5
2a	111–113	$C_{15}H_{18}O_5$	64.7	6.4	
	l.p.80	(278)	65.0	6.8	
2b	129–131	$C_{15}H_{18}O_7$	58.0	5.8	
	l.p. 60	(310)	58.3	6.1	
2c	134–136	$C_{13}H_{12}Cl_2O_5$	48.9	3.7	22.2
	l.p. 80	(319)	49.3	3.9	22.4

a) bz = benzene l.p. 80 = light petroleum (b.p. 80–100 °C) l.p. 60 = light petroleum (b.p. 60–80 °C).

3,4– *Dichlorobenzaldehyde* (17.3 g): (stirring for 10 hrs) gave a half-ester mixture (20.1 g, 63 % yield) which was separated by fractional crystallisation from benzene-light petroleum (b.p. 80–100 °C) to give: (i) the less soluble (E)-half ester (1c) (4.8 g) and (ii) the more soluble (Z)-half-ester 2c (15.3 g) (cf. Tablel).

Saponification of the half-esters:

The half-ester was refluxed with 10 % aqueous sodium hydroxide (10 ml per gram ester) for 3 hrs (cf Table 2).

The crystalline (E)-dimethyl half-ester la (2 g) gave the (E)-dimethyl dibasic acid ld (1.6 g, 88 % yield). The oily dimethyl half-ester fraction (13 g) gave the (Z)-dibasic acid 2d (10.1 g).

The crystalline (E)-dimethoxy half-ester lb (3 g) gave the (E)-dimethoxy dibasic acid le (2.3 g, 81 % yield). The oily dimethoxy half-ester fraction (13 g) gave the (Z)-dibasic acid 2e (9.1 g).

The crystalline (E)-and (Z)-dichloro-half-esters 1c and 2c gave the corresponding (E)- and (Z)-dibasic acids lf and 2f in *ca* 85 % yield.

Conversion of the dibasic acids (ld-f) and (2d-f) to the cyclic anhydrides (3a-c) and (4a-c).

This was carried out by 3 hrs refluxing of the dibasic acid with acetyl chloride (10 ml per 1 g acid); (80–85 % yield). For details see Table 2.

Table 2 (Z) – and (E)-5-Aryl-4-carboxy-3-oxapent-4-enoic acids 1d-f and 2d-f and their corresponding anhydrides 3a-c and 4a-c.

Nr.	m.p. (°C) Solvent of cryst.a)	Formula (Mol. wt.)	Analysis Calcd. /Found %C	 %H	 %C1
1d	127–129	$C_{13}H_{14}0_5$	62.4	5.6	
	l.p. 60	(250)	62.7	5.9	
1e	143–145	$C_{13}H_{14}0_7$	55.3	4.9	
	l.p. 80	(282)	55.7	5.1	
1f	122–124	$C_{11}H_8C1_20_5$	45.3	2.7	24.4
	bz	(291)	45.7	3.0	24.8
2d	150–152	$C_{13}H_{14}0_5$	62.4	5.6	
	l.p. 100	(250)	62.6	5.9	
2e	199–201	$C_{13}H_{14}0_7$	55.3	4.9	
	l.p. 100	(282)	55.6	5.1	
2f	169–171	$C_{11}H_8C1_20_5$	45.3	2.7	24.4
	bz	(291)	45.6	3.0	24.8
3a	103–105	$C_{13}H_{12}0_4$	67.2	5.1	
	l.p. 100	(232)	67.3	5.4	
3b	119–121	$C_{13}H_{12}0_6$	59.1	4.5	
	l.p. 100	(264)	59.3	4.6	
3c	106–108	$C_{11}H_6C1_20_4$	48.3	2.2	26.0
	l.p. 100	(273)	48.6	2.5	26.3
4a	128–130	$C_{13}H_{12}0_4$	67.2	5.1	
	l.p. 80	(232)	67.5	5.3	
4b	153–155	$C_{13}H_{12}0_6$	59.1	4.5	
	bz	(264)	60.3	4.8	
4c	157–159	$C_{11}H_6C1_20_4$	48.3	2.2	26.0
	l.p. 100	(273)	48.5	2.5.	26.1

a) bz = benzene, l.p. 100=light petroleium (b.p. 100–120 °), l.p. 80 = light petroleum (b.p. 80–100 °C), l.0p. 60 = light petroleum (b.p. 60–80 °C).

Action of Aluminium chloride upon the Cyclic Anhydrides

Aluminium chloride (1.2 mol) and a solution of the (E)-anhydride (1 mol) in nitrobenzene (15 ml per g anhydride) were stirred for 6 hrs and left overnight at room temperature. The acidic reaction product (75–80 % yield) was obtained as yellow crystals. For detalis cf. Table 3.

When the (Z)-anhydrides 4a-c were subjected to the same procedure, the corresponding dibasic acids were recovered in considerably high yield.

Conversion of the anhydride (3 and 4a-c) to the 4-carboxy half-esters (1 and 2g-i).

The anhydride was refluxed for 6 hrs with excess of absolute methanol (30 ml per 1g anhydride) (75–80 % yield). For details, see Table 4.

Table 3 5,6–Disubstituted 1–oxo–2–indenoxyacetic acids 5a–c and their 2–4–dintrophenylhydrazones

Nr.	M.p. (°C) a)	Formula (mol. wt.)	Analysis Calcd./Found %C	%H	%Cl	2,4– Dinitrophenylhydrazones M.p. (°C) b)	Formula (Mol.wt.)	Analysis: Calcd/Found %N	%Cl
5a	169–171	$C_{13}H_{12}O_4$	67.2	5.1		219–221	$C_{19}H_{17}N_4O_7$	15.2	
		(232)	67.6	5.3			(413)	15.3	
5b	166–168	$C_{13}H_{12}O_6$	59.1	4.5		207–209	$C_{19}H_{17}N_4O_9$	14.1	
		(264)	59.1	4.9			(445)	14.5	
5c	186–188	$C_{11}H_6Cl_2O_4$	48.3	2.2	26.0	233–235	$C_{17}H_{11}Cl_2N_4O_7$	13.9	15.5
		(273)	48.5	2.5	26.4		(454)	14.2	15.7

a) crystallised from benzene b) crystallised from ethyl alcohol

Table 4 Methyl (Z) – and (E)-5-Aryl-4-carboxy-3-oxapent-4-enoates 1g-i and 2g-i.

Nr.	m.p. (°C) Solvent of cryst.a)	Formula (Mol. Wt.)	Anaylsis Calcd./Found %C	%H	%Cl
1g	155–157	$C_{15}H_{18}O_5$	64.7	6.4	
	l.p. 100	(278)	64.7	6.6	
1h	89–91	$C_{15}H_{18}O_7$	58.0	5.8	
	bz	(310)	58.2	6.1	
1i	141–143	$C_{13}H_{12}Cl_2O_5$	48.9	3.7	22.2
	bz	(319)	49.2	3.9	22.5
2g	169–171	$C_{15}H_{18}O_5$	64.7	6.4	
	bz	(278)	64.9	6.7	
2h	111–113	$C_{15}H_8O_7$	58.0	5.8	
	l.p. 100	(310)	58.3	6.1	
2i	109–111	$C_{13}H_{12}Cl_2O_5$	48.9	3.7	22.2
	bz	(319)	49.1	3.9	22.6

a) bz = benzene, l.p. (100 = light petroleum (b.p. 100–120 °C)

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