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STOBBE CONDENSATION INVOLVING DIETHYL-β,β-DIMETHYL-GLUTARATE II

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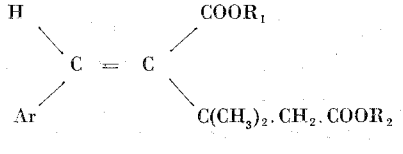
Diethyl-β,β-dimethylglutarate condenses with furan–2–aldehyde and thiophene–2–aldehyde in presence of sodium hydride to give predominantly the (Z)-half ester (1a,b) together with small amounts of the (E)-half eseter (2a,b). The structure of the (E)-half esters was based on thier cyclization to cyclopenteno-furan and cyclopenteno-thiophene derivatives (5a,b) respectively, as well as, spectroscopic evidence.

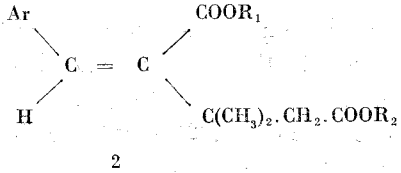
INTRODUCTION

Recently, we reported that Stobbe condensation succeeded with diglycolic esters, {1–3}, which are oxa analogues of the glutarates. A possible factor for this different behaviour might be that the crucial lactonisation step is influenced by the differences in the COC bond angle of the diglycollates and the corresponding CCC angle of the glutarates. It appeared reasonable to us that a gem-dimethyl effect at the β-carbon might modify the central bond angle in favour of lactonisation; and in fact the present work proves the validity of this structural variation. Also, recently its reported that diethyl-β,β-dimethylglutarate condenses with some aromatic aldehydes {4}. Furan–2–aldehyde and thiopene–2–aldehyde were condensed with diethyl-β,β- dimethylglutarate in the presence of sodium hydride to give predominantly oily (Z)-half esters (1a,b) which by saponification were converted to their corresponding dibasic acids (1c,d) in pure crystalline form. Smaller amounts of the crystalline (E)-half esters (2a,b) were also isolated.



1

	Ar	R_1	R_2
a	2–furyl	C_2H_5	H
b	2–thienyl	C_2H_5	H
c	2–furyl	H	H



2

	Ar	R_1	R_2
d	2–thienyl	H	H
e	2–bfuryl	H	C_2H_5
f	2–thienyl	H	C_2H_5

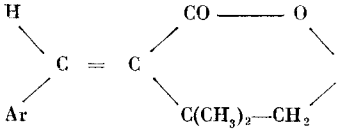
DISCUSSION

In the reported condensations involving heterocyclic aldehydes or ketones with succinic esters {5}, only one isomeric half-ester could be isolated.

The structure of the solid half-esters (za,b) is supported by their infrared absorption spectra which exhibit absorption at 1690 and 1718 cm^{-1} for α,β-unsaturated ester and nonconjugated carboxyl group {6} respectively.

Saponification of the solid half-esters (2a,b) gave the corresponding dibasic acids, (2c,d) in pure crystalline state. The oily (Z)-half ester after saponification gave high yields of their corresponding dibasic acids in pure crystalline form. All crystalline dibasic acids show νCO at 1695, 1720 cm^{-1} which corresponds to α,β-unsaturated and non-conjugated carboxyl group {6} respectively.

When the pure (Z) and (E) acids were treated with acetylchloride, they were converted to their corresponding (Z) and (E) cyclic anhydrides (3a,b) and (4a,b) which were obtained in a pure crystalline form. The infrared spectra of these compounds are in agreement with the proposed structure, since they show two absorption bands at 1800, 1745 cm^{-1} characteristic of six-membered ring anhydrides {6}.



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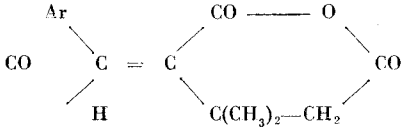


4

Atr

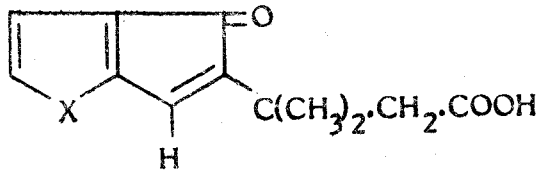
a 2-furyl

b 2-thienyl

Refluxing the anhydrides (3a,b) and (4a,b) with ethanol cleaves the ring at the non-conjugated carbonyl to give the corresponding 4-carboxyl half-ester (1e,f) and (2e,f) in Ca 80–85 %. The appearance of νCO at 1760, 1720 cm^{-1} agrees with non-conjugated ester and α,β-unsaturated acids, and is considered as a further proof for the structure of the anhydrides.

The (E)-configuration assigned to compounds (2a,b) is supported by the ring closure of their corresponding anhydrides (4a,b) under the

influence of anhydrous aluminium chloride in nitrobenzene to cyclopenteno-furan and cyclopenteno-thiophene derivatives (5a,b) respectively.



5

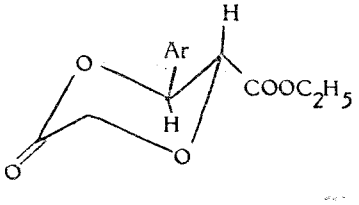
a, X = O

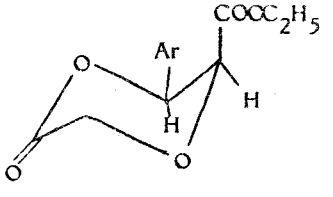
b, X = S

The structure of these cyclization products is based on: i) their elemental analysis, ii) their solubility in Na_2CO_3, iii) their yellov colour, iv) the formation of 2,4–dinitrophenylhydrazone derivative, v) the appearance of an absorption at 1713, 1698 cm^{-1} in their i.r. spectra which may be attributed to νCO for ring ketonic and carboxyl groups {6}, and vi) the positions of maxima in their electronic spectra (λ_{max} at 248–250, 294–296; ε_{max} Ca 31,000–39,000, 33,000 – 40,000) cîosely resemble those of analonous compounds {1}.

When the (Z)-anhydrides (3a,b) were subjected to the same cyclization reaction, they failed to cyclise, and the sole isolable products were their corresponding dibasic acids (1c,d).

The predominance of the(Z)-half esters in the condensation of heterocyclic aldehydes is in agreement with the reported observation, {1–3}, and can be interpreted in terms of the steric factors governing the relative ease of formations of the diastereomeric λ-lactone intermediates (6 and 7), the formation of (6) is favoured by the presence of the two bulky groups (Ar and $COOC_2H_2$) in equatorial positions.





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.

(Z) and (E)-5(2-furyl or 2-thienyl-3,3-dimethyl-4-ethoxycarbonyl-pent-4-enoic acids (2a,b) by Stobbe condensation.

Diethyl-β,β-dimethylglutarate, the aldehyde and sodium hydride (1.5:1:1.5 mol) in excess dry benzene were stirred on a water-bath for 5–10 hrs, and the reaction mixture was worked up as used {1}.

Furan-2-aldehyde: (9.6 g): (stirring for 10 hrs) gave half-ester mixture (13.3 g; 50% yield) which was dissolved in benzene light petroleum (b.p. 60–80°) whereby it could be separated into two fractions: (i) The less soluble (E)-half ester 2a (5.2 g) (cf. Table 1), (ii) The more soluble fraction (8.1 g). The latter was obtained as an oil and its composition was revealed by saponification (see later).

Thiophene-2-aldehyde: (10.8 g): (stirring for 5 hrs) gave a half-ester mixture (12.0 g; 42 % yield) which was disolved in benzene-light petroleum (b.p. 60–80°) whereby it could be separated into two fractions: i) the less soluble (E)-half ester 2b (4.0 g) (cf. Table 1), ii) The more soluble fraction (8.0 g). The latter was obtained as an oil and its composition was proved by saponification.

Saponification of the half-ecters

The half-ester was refluxed with 10% qaueous sodium hydroxide (10 ml/gm ester) for 3 hrs., (cf. Table 1).

The crystalline (E) half-ester 2a (2g) gave the (E)-dibasic acid 2C (1.5 g; 83 % yield). The oily half-ester mixture (8 g) gave upon saponification (6.5 g; 71 % yield) of an acidic product which was separated by fractional crystallisation from benzene-light petroleum (b.p. 100–120°) into the less soluble (E)-dibasic acid 2C (1.2 g; 18 %) and the more soluble (Z)-dibasic acid 1C (5.3 g; 82 %).

The crystalline (E)-half ester 2b (2 g) gave the (E)-dibasic acid (1.4 g; 77 % yield). The oily half-ester fraction (8.0 g) gave (6.2 g 86 % yield) of an acidic product which was separated as in 2a to the (E)-dibasic acid 2d (2.1 g; 33 % yield) and the (Z)-dibasic acid 1d (4.1 g; 67 % yield).

Conversion of the dibasic acids (1c,d and 2c,d) to the cyclic anhydrides (3a,b and 4a,b).

Table 1. (Z) and (E)-5-(2-furyl or 2-thienyl)-3,3-dimethyl-4-ethoxy carbonylpent-4-enoic acids and their corresponding diacids (1 c,d) and anhydrides (3a,b and 4a,b).

No.	m.p. (°C) (solvent of cryst.)	Formula (Mol. wt.)	Analysis % Calcd./Found C	H	S
2a	156–158 (l.p. 100)	$C_{14}H_{18}O_5$ (266)	63.15 63.50	6.76 6.90	
2b	179–181 (bz)	$C_{14}H_{18}O_4S$ (282)	59.57 59.60	6.38 6.60	11.34 11.70
1c	199–201 (bz)	$C_{12}H_{14}O_5$ (238)	60.50 60.80	5.88 6.10	
1d	166–168 (l.p. 100)	$C_{12}H_{14}O_4S$ (254)	56.92 57.10	5.51 5.70	12.59 12.70
2c	212–214 (bz)	$C_{12}H_{14}O_5$ (238)	60.50 60.70	5.88 6.00	
2d	189–191 (l.p. 100)	$C_{12}H_{14}O_4S$ (254)	56.92 57.20	5.51 5.80	12.59 12.80
3a	110–112 (l.p. 80)	$C_{12}H_{12}O_4$ (220)	65.45 65.70	5.45 5.60	
3b	122–124 (l.p. 100)	$C_{12}H_{12}O_3S$ (236)	61.01 61.30	5.08 5.20	13.55 13.70
4a	98–100 (l.p. 80)	$C_{12}H_{12}O_4$ (220)	65.45 65.60	5.45 5.70	
4b	133–135 (l.p. 100)	$C_{12}H_{12}O_3S$ (236)	61.01 61.20	5.08 5.30	13.55 13.80

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

This was carried out by 3 hrs. refluxing of the dibasic acid with acetyl chloride (10 ml/1g acid), (75–83 % yield). For details see Table 1.

Action of aluminium upon the cyclic anhydrides (4a,b).

Aluminium chloride (1.2 mol) and solution of the (E)-anhydride (4a,b) (1 mol) in nibrobenzene (15 ml/1g anhydride) were stirred for 6 hrs and left overnight at room temperature.

The acidic reaction product (85–89 % yield) was obtained as yellow crystals and identified as (5 a,b). For details cf. Table 2. When the (Z)-anhydride (3 a,b) was subjected to the same reaction, the corresponding dibasic acids were recovered in considerably high yield.

Conversion of the anhydrides (3a,b and 4a,b) to the 4-carboxy half-ester (1e,f and 2e,f).

Table 2. Cyclopent-1-ene-3-oxo [4,5b] (furano or thiopheno) 2′2′-dimethyl propionic acid (5a,b) and their 2,4-dinitro-phenyl hydrazones.

No	m.p. (°C) (solvent of cryst.[a])	Formula (Mol. wt.)	Analysis % Calcd./Found C	H	S%	2,4-DNP derivatives m.p.(°C) (Cryst.[b])	Formula (Mol. wt.)	Analysis Calcd./Found N%
5a	146–148 (bz)	$C_{12}H_{12}O_4$ (220)	65.45 65.70	5.45 5.60		207–209 (400)	$C_{18}H_{16}O_7N_4$	14.00 14.20
5b	199–201 (bz)	$C_{12}H_{12}O_3S$ (236)	61.01 61.10	5.08 5.20	13.55 13.70	228–230 (416)	$C_{18}H_{16}O_6SN_4$	14.23 14.40

a) bz = benzene b = ethanol.

The anhydride was refluxed for 6 hrs with excess absolute ethanol (30 ml/1g anhydride) to yield (72–77 % yield) of their position isomers (1 e,f and 2 e,f). For details cf. Table 3.

Table 3. Ethyl-(Z)-and (E)-3-(2-furyl) (or 2-thienyl)-3,3-dimethyl--4-carboxy-pent-4-enoates (1 e,f 2 e,f).

No	m.p. (°C) (solvent of cryst.)	Formula (Mol. wt.)	Analysis % Calcd/Found		
			C	H	S
1e	121–123 (bz)	$C_{14}H_{18}O_5$ (266)	63.15 63.20	6.76 6.80	
1f	136–138 (bz)	$C_{14}H_{18}O_4S$ (2782)	59.57 59.80	6.38 6.50	11.34 11.50
2e	149–151 (l.p. 100)	$C_{14}H_{18}O_5$ (266)	63.15 63.40	6.76 6.90	
2f	102–104 (l.p. 80)	$C_{14}H_{18}O_4S$ (282)	59.57 59.70	6.38 6.40	11.34 11.60

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

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