

Condensation of Isobutyrophenones with Dimethyl Homophthalate

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Summary: The polar and steric factors affecting the isomers ratio in the Stobbe condensation of dimethyl homophthalate with unsymmetrical ketones were investigated. The configurations of the *E*- and *Z*-half esters obtained were based on chemical and spectroscopic studies.

Many examples of aryl alkyl ketones and diaryl ketones have been previously studied [1-3]. In this work, isobutyrophenone, *p*-methyl-, *p*-chloroisobutyrophenone were studied as examples of ketones containing a bulky alkyl group: the isopropyl group. In all cases a mixture of the *E*- and *Z*-half esters was obtained. The *E*-isomer predominates in isobutyrophenone and *p*-methyl isobutyrophenone, in the case of *p*-chloroisobutyrophenone, the *E*-isomer constitutes 35 % of the isolated product.

Isobutyrophenone, *p*-methyl- and *p*-chloroisobutyrophenone were condensed with dimethyl homophthalate in the presence of sodium hydride to give the expected half ester mixture in 87, 71, 70 %, yield respectively, from which the *E*-isomer (1a-c) were isolated in pure crystalline state, together with an oily fraction whose constitution was revealed by saponification.

Structure and configuration of the half esters

The structure of the *E*-half esters (1a-c) was based on their analytical data, their i.r. spectra which exhibited strong bands for aryl acid and α,β -unsaturated ester groups. The position of the double bond in (1a-c) was supported by their oxidation in good yield to the original ketones by cold alkaline potassium permanganate.

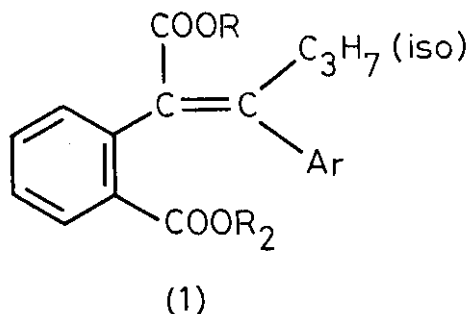
The $^1\text{H-nmr}$ spectra of the *E*-half esters (1a-c) was consistent with their proposed structure, the failure of separation of the *Z*-half esters renders the assignment of configuration based on their n.m.r. impossible.

Compound (1a) shows the following signals: δ 1.07 (d, 6H, CH_3CHCH_3), δ 3.69 (s, 3H, COOCH_3), δ 4.18 (m, 1H, CH_3CHCH_3), δ 6.61 -

7.3 (m, 9H, aromatic protons) δ 11.5 (s, 1H, -COOH).

Compound (1b) shows the following signals: δ 1.06 (d, 6H, CH_3CHCH_3), δ 2.16 (s, 3H, $\text{C}_6\text{H}_4\text{-CH}_3$); δ 3.68 (s, 3H, COOCH_3), δ 4.12 (m, 1H, CH_3CHCH_3), δ 6.7 - 7.9 (m, 8H, aromatic protons) and δ 11.5 (s, 1H, COOH).

Compound (1c) shows the following signals: δ 1.1 (d, 6H, CH_3CHCH_3), δ 3.7 (s, 3H, COOCH_3), δ 4.1 (m, 1H, CH_3CHCH_3), δ 6.6 - 7.4 (m, 8H, aromatic protons).

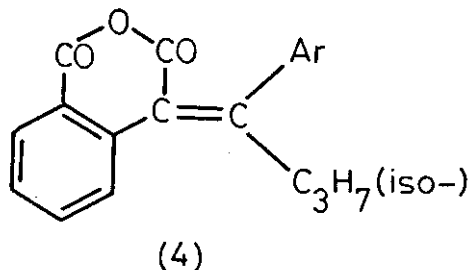
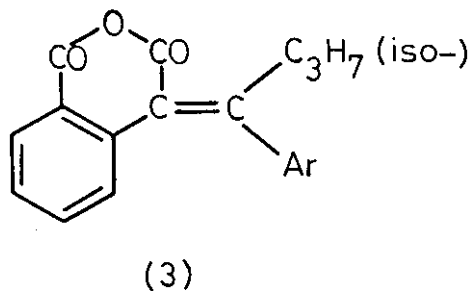


a; $\text{R}_1 = \text{CH}_3$	$\text{R}_2 = \text{H}$	$\text{Ar} = \text{C}_6\text{H}_5$
b; $\text{R}_1 = \text{CH}_3$ -	$\text{R}_2 = \text{H}$	$\text{Ar} = \text{p-CH}_3\text{-C}_6\text{H}_4$
c; $\text{R}_1 = \text{CH}_3$ -	$\text{R}_2 = \text{H}$	$\text{Ar} = \text{p-Cl-C}_6\text{H}_4$
d $\text{R}_1 = \text{H}$	$\text{R}_2 = \text{H}$	$\text{Ar} = \text{C}_6\text{H}_5$
e; $\text{R}_1 = \text{H}$	$\text{R}_2 = \text{H}$	$\text{Ar} = \text{p-CH}_3\text{-C}_6\text{H}_4$
f; $\text{R}_1 = \text{H}$	$\text{R}_2 = \text{H}$	$\text{Ar} = \text{p-Cl-C}_6\text{H}_4$
g; $\text{R}_1 = \text{H}$	$\text{R}_2 = \text{CH}_3$	$\text{Ar} = \text{C}_6\text{H}_5$
h; $\text{R}_1 = \text{H}$	$\text{R}_2 = \text{CH}_3$	$\text{Ar} = \text{p-CH}_3\text{-C}_6\text{H}_4$
i; $\text{R}_1 = \text{H}$	$\text{R}_2 = \text{CH}_3$	$\text{Ar} = \text{p-Cl-C}_6\text{H}_4$

Saponification of the solid *E*-half esters (1a-c) gave the corresponding *E*-diacids (1d-f) in pure crystalline form. The structure of (1d-f) was based on their analytical data, their infrared spectra which showed single band at $\text{ca } 1680 \text{ cm}^{-1}$ for both aryl conjugated and α,β -unsaturated acids. The position of the double bond was determined by the oxidation of (1d-f) by cold alkaline potassium permanganate to their original ketones.

Saponification of the oily half ester fraction gave a further amount of the *E*-diacids (1d-f) together with an oily product. These *E*-diacids were added to the yield of the separated *E*-half esters to evaluate the isomer ratio.

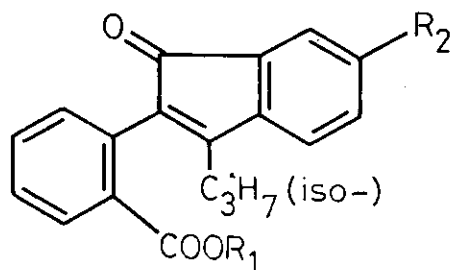
When the crystalline *E*-diacids were stirred with $\text{N,N}'$ -dicyclohexylcarbodiimide in dry benzene, they were converted to the corresponding cyclic anhydrides (3a-c) which exhibited the expected coupling bands at $1725 - 1790 \text{ cm}^{-1}$ for six-membered ring anhydrides in which both carbonyls are conjugated.



a, $\text{Ar} = \text{C}_6\text{H}_5$
b, $\text{Ar} = \text{p-CH}_3\text{-C}_6\text{H}_4$
c, $\text{Ar} = \text{p-Cl-C}_6\text{H}_4$

When the oily diacids were subjected to the same reagent, a neutral oily product was obtained in each case to which the *Z*-configuration was attributed according to their cyclisation reactions.

The (*E*)-configuration assigned to the half-esters (1a-c) was based on the failure of their anhydrides (3a-c) to cyclise under the effect of anhydrous aluminium chloride in acetylene tetrachloride. When the isomeric oily anhydrides were subjected to the action of aluminium chloride in acetylene tetrachloride, they were converted to the corresponding oxo-indenyl acids (5a-c) in 65, 59 and 55 % yields indicating that these anhydrides and the esters from which they are derived have the *Z*-configuration.



(5)

- a; $R_1 = R_2 = H$
 a; $R_1 = H, R_2 = CH_3$
 c; $R_1 = H, R_2 = Cl$
 d; $R_1 = CH_3, R_2 = H$
 e; $R_1 = R_2 = CH_3$
 f; $R_1 = CH_3, R_2 = Cl$

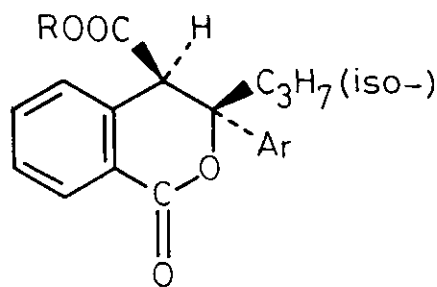
The indenyl acid (5a) was isolated in the form of its 2,4-dinitrophenylhydrazone. The structure of these oxo-indenyl acids (5a-c) was based on their elemental analysis, their yellow colour, their solubility in sodium carbonate, their conversion to 2,4-dinitrophenylhydrazone derivatives, their i.r. spectra which showed $\nu C=O$ for ring ketonic and carboxyl groups; their electronic absorption which exhibit absorption bands at λ_{max} 226 and 265, 415 nm ϵ_{max} 17136; 34 680; 1632 for (5b) and λ_{max} 202, 242, 402 nm with ϵ_{max} 19976, 36234 and 1074 for compound (5c) these values are in accord with those observed in compounds having the same chromophoric system [1,2].

When the *E*-half esters and their oily isomers were refluxed with acetic acid, acetic anhydride mixture in the presence of a catalytic amount of fused zinc chloride, an ester exchange reaction followed by cyclisation [4] took place giving the same cyclisation product, the oxo-indenyl ester (5d-f), in almost equal yields, indicating that isomerisation occurs under the acidic reaction conditions, this renders configuration assignment by this reaction impossible.

The indenyl esters (5d, 5e) were isolated as 2,4-dinitrophenylhydrazones; while (5f) was isolated in a pure crystalline state. Structural assignment was based on their conversion to 2,4-dinitrophenylhydrazone, the i.r. spectrum (5f) shows $\nu C=O$ at 1710, 1720 cm^{-1} for ring ketonic and aryl ester groups.

Methanolysis of the *E*-anhydrides (3a-c), by refluxing in methanol converted them to the isomeric half esters (1g-i) which are aryl esters rather than α,β -unsaturated esters. Their structures were based on both elemental analysis and i.r. spectra which shows $\nu C=O$ at 1680 and 1720 cm^{-1} .

Lactonisation of the half esters (1a-c) by refluxing with acetic acid, acetic anhydride mixture in the presence of sodium acetate converted them to 3-aryl-3-isopropyl-4-methoxycarbonyl-3,4-dihydroisocoumarin (6a-c). The structures of (6a-c) were based on their elemental analysis, their i.r. spectra which show absorption at 1700 and 1740 cm^{-1} for $\gamma C=O$ ester and δ -lactones.



(6)

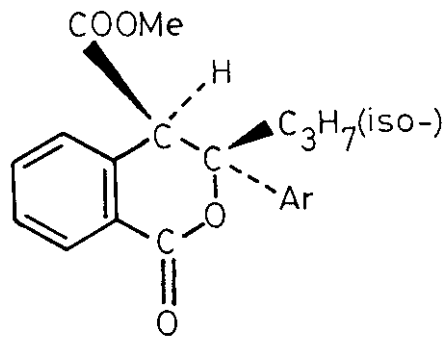
- a) $R = CH_3, Ar = C_6H_5$;
 b) $R = CH_3, Ar = p-CH_3-C_6H_4$
 c) $R = CH_3, Ar = p-Cl-C_6H_4$

These lactones (6a-c) were cleaved by the action of alcoholic potash to their corresponding half esters (1a-c), supporting the mechanism of the Stobbe condensation.

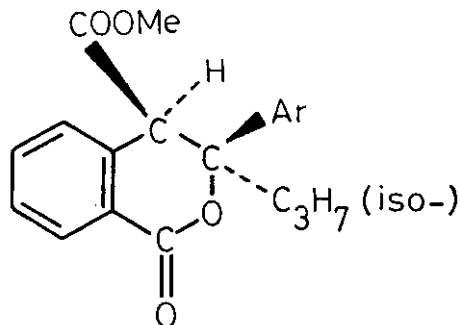
Interpretation of isomers ratio

It was found in the case of isobutyrophenone and *p*-methylisobutyrophenone that the *E*-isomer is predominating, while in the case of *p*-chloroisobutyrophenone, it constitutes only 35 % of the total acidic product. This may be interpreted in terms of the polar non-bonding interaction in the intermediate paraconic esters (A) and (B).

In the case of isobutyrophenone and *p*-methylisobutyrophenone intermediate (A) is favoured to minimise the repulsive forces between the negative



(A)



(B)

Characterisation data of the compounds (1-3)

Compd.	M.p. °C (solvent of crystn)	Formula (Mol.wt)	Analysis		
			C	H	Cl
1a	172-4	C ₂₀ H ₂₀ O ₄	74.10	6.48	
	(A)	(324)	74.14	6.17	
1b	146-8	C ₂₁ H ₂₂ O ₄	74.60	6.5	
	(B)	(338)	75.02	6.4	
1c	171-2	C ₂₀ H ₁₉ O ₄ Cl	66.9	5.3	9.9
	(A)	(358.5)	66.8	5.7	9.5
1d	208-10	C ₁₉ H ₁₈ O ₄	73.5	5.8	
	(A/C)	(310)	73.5	5.7	
1e	200-1	C ₂₀ H ₂₀ O ₄	74.1	6.2	
	(C)	(324)	74.1	6.0	
1f	223-5	C ₁₉ H ₁₇ O ₄ Cl	66.12	4.9	10.30
	(A/C)	(344.5)	66.00	5.0	10.03
1g	113-5	C ₂₀ H ₂₀ O ₄	74.1	6.4	
	(A/d)	(324)	74.1	6.0	
1h	130-2	C ₂₁ H ₂₂ O ₄	74.6	6.5	
	(A)	(338)	74.8	6.3	
1i	156-7	C ₂₀ H ₁₉ O ₄ Cl	66.9	5.3	9.90
	(d)	(358.5)	66.6	5.0	9.45
3a	128-30	C ₁₉ H ₁₆ O ₃	78.1	5.5	
	(B)	(292)	78.1	5.4	
3b	144-6	C ₂₀ H ₁₈ O ₃	78.4	5.9	
	(d)	(306)	78.5	5.5	
3c	166-8	C ₁₉ H ₁₅ O ₃ Cl	69.8	4.6	10.9
	(d)	(326.5)	69.3	4.2	10.9

field of the ester group and that of the aryl group. Intermediate (A) then is cleaved to the *E*-isomers (1a-c). In the case of *p*-chlorophenyl, however, due to the -I effect of Cl, there is a negative field on the aryl group, and structure (B) is favoured by the attractive force between the field of the ester group and that of the aryl group and thus the *E*-isomer appears as a minor product.

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, and ¹H-NMR spectra on Bruker Spectrospin.

a) *Stobbe condensation*: A mixture of dimethyl homophthalate, the ketone, and sodium hydride (1.5 : 1 : 1.5 mol.) in excess dry benzene was stirred for 12 hrs, at 60-70°C. At the end of the reaction, the mixture was acidified with acetic acid, water added and the organic fraction taken up in ether. The ethereal layer was then washed with 10 % sodium carbonate solution, and the half esters were separated as follows:

1) An insoluble sodium salt precipitated in the alkaline extract, which was filtered off, and acidified with dilute hydrochloric acid to give the crystalline *E*-half esters (1a-c) (specifications on Table 1).

2) The alkaline filtrate gave upon acidification a semi solid, which upon trituration with light

Characterisation data of the compounds (5,6)

Compd No.	M.p. °C (solvent of crystn)	Formula (Mol.wt.)	Analysis			M.p. °C (solvent of crystn)	2:4-diniorophenylhydrazones				
			Calcd./Found				Formula (Mol.wt.)	Analysis			
			C	H	Cl			C	H	Cl	N
5a						200-2 (A/C)	C ₂₅ H ₂₀ N ₄ O ₆ (480)	63.5 64.0	4.2 4.6		11.9 11.8
5b	204-6 (A/C)	C ₂₀ H ₁₈ O ₃ (306)	78.4 78.5	5.9 5.7		230-2 (C)	C ₂₆ H ₂₂ N ₄ O ₆ (494)				11.5 11.3
5c	212-4 (A)	C ₁₉ H ₁₅ O ₃ Cl (326.5)	69.80 69.72	4.6 4.2	10.9 10.4	240-2 (C)	C ₂₅ H ₁₉ N ₄ O ₆ Cl (514.5)				11.06 10.80
5d						185-7 (A/d)	C ₂₆ H ₂₂ N ₄ O ₆ (494)	68.7 68.9	4.8 4.7		12.30 12.02
5e						214-6 (A)	C ₂₇ H ₂₄ N ₄ O ₆ (508)	64.8 64.3	4.8 4.6		11.2 11.1
5f	91-3 (e)	C ₂₀ H ₁₇ O ₃ Cl (340.5)	70.5 70.9	4.99 5.20	10.4 10.9	258-60 (f)	C ₂₆ H ₂₁ N ₄ O ₆ Cl (528.5)	59.9 59.7	4.03 4.00	6.8 6.5	10.7 10.4
6a	180-2 (f)	C ₂₀ H ₂₀ O ₄ (324)	74.1 74.3	6.5 6.2							
6c	168-70 (f)	C ₂₀ H ₁₉ O ₄ Cl (358.5)	66.9 66.7	5.3 4.9	9.9 10.3						

A = Benzene, B = Light petroleum (b.p. 100-120°), C = Methanol, d = Light petroleum (b.p. 60-80°) e = Light petroleum (b.p. 40-60°) and f = Toluene.

petroleum - benzene gave a further amount of the *E*-half ester, and an oily product.

Isobutyrophenone (14.8 g) : gave a total half ester mixture (28.2 g, 87% yield) separated into 13.2 g of the *E*-methyl-2-*O*-carboxyphenyl-4-methyl-3-phenyl-pent-2-enoate (1a) and 14.7 g of the oily isomer.

p-Methyl isobutyrophenone (16.2 g): gave 24.2 g, 71% yield of total half ester mixture separated into 9.5 g of *E*-methyl-2-*O*-carboxyphenyl-4-methyl-3-*p*-tolyl-pent-2-enoate (1b) and 15.1 g of the oily product.

p-Chloroisobutyrophenone (18.25 g): gave a total half ester mixture (26.1 g, 70% yield) containing 5.8 g of the *E*-methyl-2-*O*-carboxyphenyl-4-methyl-3-*p*-chlorophenyl-pent-2-enoate (1c) and 20.3 g of the oily product.

Oxidation of the half esters (1a-c) with cold alkaline potassium permanganate gave the original ketones.

b) Saponification the half esters: when the solid *E*-half esters (1a-c) were refluxed with 10 % aqueous sodium hydroxide (10 ml/1 g half ester) for

3 hrs, they were converted to their corresponding *E*-diacids (1d-f) (cf. Table) in 90% yield.

The oily half esters upon saponification, gave an additional amount of the *E* diacids and an oily acidic product: Isobutyrophenone 14.7 g oil yields on saponification 5.1 g *E*- diacid (1d) and 9.6 g oil.

p-Methylisobutyrophenone: 15.1 g oily half ester on saponification yields 4.5 g of the *E*-diacid (1e) and 10.1 g oil.

p-Chloroisobutyrophenone: 20.2 g oil upon saponification yields 3.1 g of the *E*-diacid (1f) and 17 g acidic oil.

Oxidation of the solid diacids (1d-f) with cold alkaline potassium permanganate gave the original ketone, identified by its D.N.P.

c) Conversion of the dibasic acids to the cyclic anhydrides: A mixture of the acid and *N,N'*-dicyclohexylcarbodiimide (1 : 1 mol.) in dry benzene (15 ml/1 g acid) was stirred at room temperature for 2-3 hrs then left overnight. The precipitated dicyclohexyl urea was filtered off. Evaporation of the filtrate gave the corresponding anhydride.

The crystalline *E*-diacids (1d-f) gave their corresponding *E*-anhydrides (3a-c) in 75-84 % yield (cf. Table).

The isomeric oily diacids gave a neutral oil identified latter as the *Z*-anhydrides (4a-c).

d) Action of the aluminium chloride upon the cyclic anhydrides: A solution of the *Z*-oily anhydride (1 mol) in excess dry acetylenetetra chloride (15 ml/g anhydride), anhydrous aluminium chloride (1.2 mol) was added and the reaction mixture stirred for 12 - 15 hrs at room temperature, the mixture was left for 3 days with occasional stirring, then acidified with ice-cold dilute hydrochloric acid. The solvent removed by steam distillation and the product taken up in ether washed with sodium carbonate solution (10 %). The alkaline extract on acidification gave the following products.:

The oily *Z*-anhydride (4a) (2 g) gave 1.3 g of an oil which was separated as the 2,4-dinitrophenyl-hydrazone of 2-*O*-carboxyphenyl-3-isopropyl-ind-2-enone (5a).

The anhydride (4b) (1.7 g) gave 1 g of 2-*O*-carboxyphenyl-3-isopropyl-6-methyl-ind-2-enone (5b).

The anhydride (4c) (2.2 g) was converted into 2-*O*-carboxyphenyl-6-chloro-3-isopropyl-ind-2-enone(5c) (1.2 g) (cf. Table).

When the crystalline *E*-anhydride (3a-c) were subjected to the same reaction they were recovered as the diacids (1d-f).

e) Methanolysis of the crystalline *E*-anhydrides (3a-c): When refluxed for 6 hrs in dry methanol (30 ml per gr. anhydride) the isomeric half esters of (1a-c). 2-*O*-carbomethoxyphenyl-4-methyl-3-aryl-pent-2-enoic acid (1g-i) were isolated (cf. Table).

f) Cyclisation of the half-esters: A mixture of the half-ester, (1g) acetic acid (10 ml), acetic an-

hydride (10 ml) and freshly fused zinc chloride (0.1 g) was refluxed for 4 hrs, cooled and poured onto ice cold water, the organic material taken up in ether, washed successively with water, sodium carbonate (10 %) and water, and the ether then removed leaving a neutral product identified as 2-*O*-carbomethoxyphenyl-3-isopropyl-6-substituted-ind-2-enone (5d-f) (cf. Table). 5d and 5e were isolated as D.N.P.

Each pair of crystalline *E*-half ester and its isomeric oily *Z*-half ester gave the same indenyl ester (5d-f) with almost equal yields.

Lactonisation of the half esters: A mixture of the crystalline *E*-half ester (1 g), acetic acid (10 ml), acetic anhydride (10 ml), anhydrous sodium acetate (0.5 g) was refluxed for 6 hrs, poured onto ice cold water, taken up in ether and the ether washed successively with water, carbonate and water, then distilled off under reduced pressure leaving 3-aryl-3-isopropyl-4-methoxycarbonyl-3,4-dihydroisocoumarin (6a,c) in crystalline form, while 6b was isolated as an oil (cf. Table).

When the lactones (6a-c) were treated with cold ethanolic potash, for 3 hrs, followed by acidification, the *E*-half esters (1a-c) were precipitated in good yield.

References

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