

# Condensation of Aryl Benzyl Ketones with Dimethyl- $\beta,\beta$ -Dimethyl-Glutarate. Synthesis of (Z)- and (E)-5-aryl-4-Carbomethoxy-3,3-Dimethyl-6-Phenyl-hex-4-Enoic Acids

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Phenyl-, *p*-tolyl and *p*-chlorophenyl benzyl ketone condense with dimethyl- $\beta,\beta$ -dimethylglutarate in the presence of sodium hydride to give the corresponding half-esters, the (Z)-isomers 2a-e being predominant. The structure and configuration of the half-esters were characterized by chemical and spectroscopic evidence.

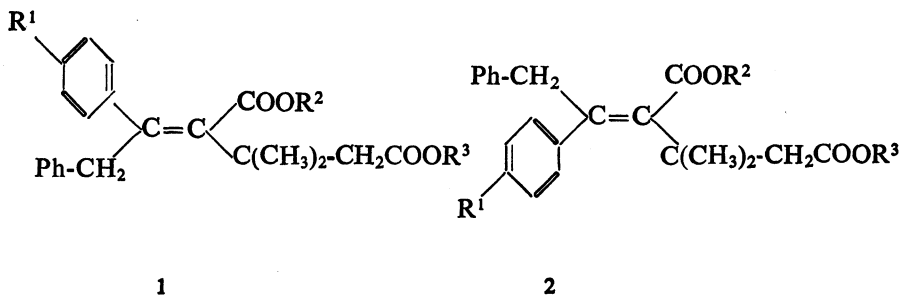
## INTRODUCTION

The present work was carried out to extend the scope of the recently investigated involving  $\beta,\beta$ -dimethylglutarate esters<sup>1</sup> and to investigate the factors governing isomer ratios in this reaction.

## RESULTS AND DISCUSSION

The condensation of phenyl-, *p*-tolyl and *p*-chlorophenyl benzyl ketones, only the (E)-isomer 1a and b could be isolated in pure crystalline form; the remainder being an oily fraction whose composition was revealed by saponification. In the case of *p*-chlorophenyl benzyl ketone, both isomers were obtained in pure crystalline state.

The position of unsaturation in the half-esters was shown by oxidation of the crystalline and oily condensation products in fairly good yield to the original ketones. Furthermore, the crystalline (E)-half esters 1a-c and the (Z)-half-ester 2c exhibited strong bands at *ca.* 1695, 1715  $\text{cm}^{-1}$  for non-conjugated carboxyl and  $\alpha,\beta$ -unsaturated ester groups<sup>2</sup>, respectively.

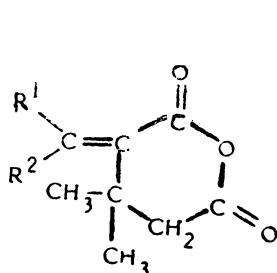


1			2				
	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>		R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
a	H	CH <sub>3</sub>	H	f	Cl	H	H
b	CH <sub>3</sub>	CH <sub>3</sub>	H	g	H	H	CH <sub>3</sub>
c	Cl	CH <sub>3</sub>	H	h	CH <sub>3</sub>	H	CH <sub>3</sub>
d	H	H	H	i	Cl	H	CH <sub>3</sub>
e	CH <sub>3</sub>	H	H				

Saponification of the four half-ester 1a-e and 2e gave the corresponding dibasic acids 1d-f and 2f in pure crystalline state. Saponification of the oily half-esters obtained from phenyl and *p*-tolyl benzyl ketones served to reveal their composition. The product was in each case, a mixture of stereoisomeric (E)- and (Z)-diacids 1d and 2d; 1e and 2e, respectively, which could be separated by fractional crystallisation. Their yields together with the isolated amount of pure (E)-half-esters 1a and b made possible the evaluation of the ratio of stereoisomeric (E)- and (Z)-half-esters 1a and 2a; 1b and 2b. The dibasic acid exhibited  $\nu_{\text{C}=\text{O}}$  1710 and 1695  $\text{cm}^{-1}$  for non-conjugated and  $\alpha,\beta$ -unsaturated carboxyl groups<sup>2</sup>. The later supports the position of unsaturation, which was also proved by oxidation.

The six dibasic acids 1d-f and 2d-f were converted by refluxing with acetic anhydride into the corresponding cyclic anhydrides 3a-f with exhibited the expected carbonyl coupling bands at 1745 and 1780  $\text{cm}^{-1}$ . The back saponification of the anhydrides to the original diacids proved the retention of configuration during anhydride formation.

## 3



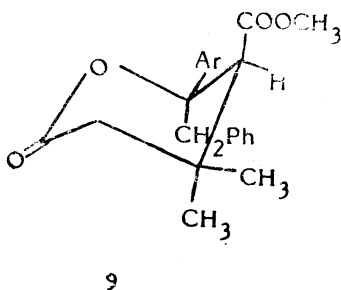
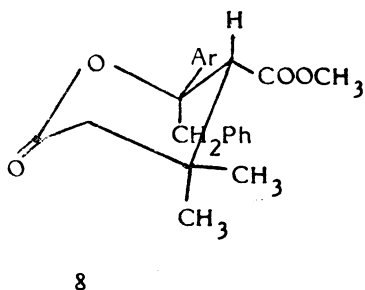
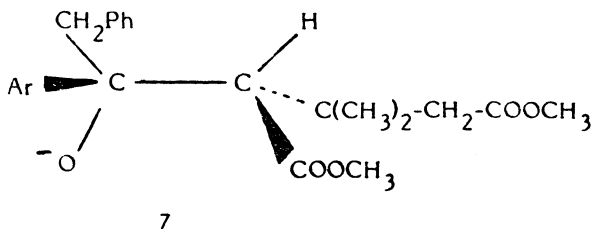
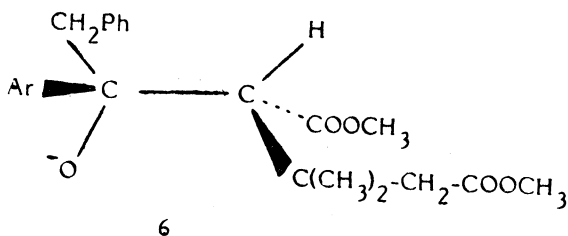
	R <sup>1</sup>	R <sup>2</sup>
a	Ph	Ph-CH <sub>2</sub>
b	Ph-CH <sub>2</sub>	Ph
c	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	Ph-CH <sub>2</sub>
d	PhCH <sub>2</sub>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>
e	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>
f	PhCH <sub>2</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>

## 3

The (E)-configuration assigned to the crystalline half-esters 1a-e was established by cyclisation of the derived anhydrides 3a, c and e with aluminium chloride to the corresponding indenyl acids 4a-c in high yield.

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case would involve formation of the diastereomeric  $\delta$ -lactonic intermediate 8 and 9. The steric course of condensation will be controlled by the initial attack of the ester carbanion on the ketone. Two possible diastereomeric condensate anions (as well as enantiomers) are expected. The condensate anions will assume the eclipsed conformation 6 and 7 prior to  $\delta$ -lactone formation. Conformation 6 can be more easily attained because of favourable trans-relationship of the bulky Ar and COOR groups. Furthermore, the diequatorial orientation of these groups in the  $\delta$ -lactonic intermediate 9 will facilitate ring closure. Both factors are expected to favour the predominance of the (E)-half esters (2).



### EXPERIMENTAL

All melting points are uncorrected. IR (KBr) and UV spectra were recorded on Unicam SP 1200 infracord and Unicam Sp 1800 spectrophotometers, respectively.

**(a) Stobbe condensation**

The ketone, dimethyl- $\beta,\beta$ -dimethylglutarate, and sodium hydride (1 : 1.5 : 1.5 mol) in excess dry benzene were stirred on water-bath for 15–20 hrs, and the reaction mixture was worked out as usual<sup>5</sup>.

Benzyl phenyl ketone (19.6 g) gave an acidic product (15.8 g, 44% yield) which was separated by dissolution in benzene followed by the addition of light petroleum into: (i) the less soluble (E)-5-aryl-4-methoxy-carbonyl-3, 3-dimethyl-6-phenyl-hex-4-enoic acid (1a) in colourless crystals (6.1 g) (cf. Table 1) and (ii) the soluble oily half-ester fraction (9.7 g) whose composition was revealed by saponification.

Benzyl *p*-tolyl ketone (21 g) gave an acidic product (15.2 g; 42% yield) which was separated by dissolved in benzene light petroleum (b.pt. 80–100°C) whereby it could be separated into two fractions: (i) the less soluble (E)-half-ester (1b), colourless crystals (5.1 g) (cf. Table 1), (ii) the soluble oily half-ester fraction (10.1 g) whose composition was revealed by saponification.

Benzyl *p*-chlorophenyl ketone (23 g) gave an acidic product (18.2 g; 47% yield) which was separated by dissolution in benzene-light petroleum (b.pt. 80–100°C) into two fraction: (i) the less soluble (E)-half-ester (1c), colourless crystals (5.1 g), (ii) the more soluble (Z)-half-ester 2c, colourless crystals (13.1 g) (cf. Table 1).

Oxidation of the crystalline and oily half-esters with cold alkaline permanganate gave the original ketones.

**(b) Saponification of the Half-Esters**

The product obtained from (a) were hydrolysed by refluxing with 10% aqueous sodium hydroxide (10 ml per g of half-ester) for 3 hrs (80–90% yield). All diacids melt with decomposition.

The oily half-ester (9.7 g) from phenyl benzyl ketone gave an acidic product (8.1 g) which was digested with benzene-light petroleum (b.pt. 60–80°C) to give (i) the above (E)-dibasic acid (1d) (2.2 g) as insoluble fraction and (ii) the (Z)-diacid 2d as soluble fraction (5.9 g).

The oily half-ester (10.1 g) from *p*-tolyl benzyl ketone gave an acidic product (8.9 g) which was treated with boiling light petroleum to give (i) the (E)-dibasic acid (1e) (2.3 g) as insoluble fraction and (ii) the (Z)-dibasic acid 2e as soluble fraction (6.6 g).

Oxidation of the dibasic acids with cold alkaline potassium permanganate gave the original ketones.

**(c) Conversion of the Dibasic Acids into the Corresponding Cyclic anhydride 3**

The diacids were refluxed with acetyl chloride (10 ml per g acid) for 3 hrs and the neutral products obtained in 80–90% yield (cf. Table 2).

TABLE 1  
(E)- and (Z)-5-ARYL-4-CARBOMETHOXY-3,3-DIMETHYL-6-PHENYL  
HEX-4-ENOIC ACID (1a-c) AND (2c)

No.	M.pt. °C solvent of cryst. <sup>a</sup>	Formula Mol. Wt.	Analysis % Calcd./ (Found)		
			C	H	Cl
1a.	126-28	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub>	75.00	6.81	
	L.p. 80°	(352)	(75.20)	(6.90)	
1b.	144-46	C <sub>23</sub> H <sub>26</sub> O <sub>4</sub>	75.41	7.10	
	L.p. 100°	(366)	(75.70)	(7.20)	
1c.	179-81	C <sub>22</sub> H <sub>23</sub> ClO <sub>4</sub>	68.31	5.95	9.18
	bz.	(386.5)	(68.40)	(6.10)	(9.20)
2c.	156-58	C <sub>22</sub> H <sub>23</sub> ClO <sub>4</sub>	68.31	5.95	9.18
	L.p. 80°	(386.5)	(68.50)	(5.80)	(9.40)

(a) bz = Benzene, L.p. 80° = Light petroleum (b.pt. 80-100°C), L.p. 100° = Light petroleum (b.pt. 100-120°C).

TABLE 2  
(E)- and (Z)-5-ARYL-4-CARBOXY-3,3-DIMETHYL-6-PHENYL-HEX-  
4-ENOIC ACID (1d-f) AND (2d-f) AND THEIR CORRESPONDING  
ANHYDRIDES (3a-f)

No.	M.pt. °C solvent of cryst. <sup>a</sup>	Formula Mol. Wt.	Analysis % Calcd./ (Found)		
			C	H	Cl
1d.	189-91	C <sub>21</sub> H <sub>22</sub> O <sub>4</sub>	74.56	6.51	
	bz	(338)	(74.80)	(6.70)	
2d.	137-39	C <sub>21</sub> H <sub>22</sub> O <sub>4</sub>	74.56	6.51	
	L.p. 80°	(338)	(74.70)	(6.60)	
1e.	156-58	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub>	75.00	6.82	
	L.p. 80°	(352)	(75.30)	(7.00)	
2e.	127-29	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub>	75.00	6.82	
	L.p. 80°	(352)	(75.10)	(6.90)	
1f.	202-4	C <sub>21</sub> H <sub>21</sub> ClO <sub>4</sub>	67.65	5.63	9.53
	bz	(372.5)	(67.80)	(5.70)	(9.60)
2f.	177-79	C <sub>21</sub> H <sub>21</sub> ClO <sub>4</sub>	67.65	5.63	9.53
	L.p. 100°	(372.5)	(67.90)	(5.70)	(9.70)
3a.	156-58	C <sub>21</sub> H <sub>20</sub> O <sub>3</sub>	78.75	6.25	
3b.	L.p. 80°	(320)	(79.00)	(6.40)	
	109-11	C <sub>21</sub> H <sub>20</sub> O <sub>3</sub>	78.75	6.25	
3c.	L.p. 80°	(320)	(78.80)	(6.30)	
	171-73	C <sub>22</sub> H <sub>22</sub> O <sub>3</sub>	79.04	6.59	
3d.	bz	(334)	(79.30)	(6.80)	
	89-91	C <sub>22</sub> H <sub>22</sub> O <sub>3</sub>	79.04	6.59	
3e.	L.p. 80°	(334)	(79.20)	(6.70)	
	110-12	C <sub>21</sub> H <sub>19</sub> ClO <sub>3</sub>	71.09	5.36	10.01
3f.	L.p. 80°	(354.5)	(71.10)	(5.50)	(10.10)
	148-50	C <sub>21</sub> H <sub>19</sub> ClO <sub>3</sub>	71.09	5.36	10.01
	bz	(354.5)	(71.20)	(5.60)	(10.20)

<sup>a</sup>bz = Benzene. L.p. 80° = Light petroleum (b.pt. 80-102°C).

TABLE 3  
3-BENZYL- $\beta$ -METHYL- $\beta$ -(1-OXO)-2-INDENYL BUTYRIC ACIDS (4a-c) AND THEIR CORRESPONDING HYDRAZONES AND 1-NAPHTHOL DERIVATIVES (5a-c)

No.	M.pt. (°C) solvent of cryst <sup>a</sup>	Formula Mol. Wt.	Analysis% Calcd./ (Found)			2,4-Dinitrophenylhydrazones		Analysis % Calcd./ (Found) N	
			C	H	Cl	M.pt. (°C) solvent of cryst. <sup>a</sup>	Formula Mol. Wt.		
4a.	172-74 bz	C <sub>21</sub> H <sub>20</sub> O <sub>3</sub> (320)	78.75 (78.90)	6.25 (6.40)		226-28 E	C <sub>27</sub> H <sub>24</sub> O <sub>6</sub> N <sub>4</sub> (500)	11.20 (11.30)	
4b.	186-88 bz	C <sub>22</sub> H <sub>22</sub> O <sub>3</sub> (334)	79.04 (79.20)	6.59 (6.70)		208-10 bz	C <sub>28</sub> H <sub>26</sub> O <sub>6</sub> N <sub>4</sub> (514)	10.89 (11.00)	
4c.	133-35 L.p. 80°	C <sub>21</sub> H <sub>19</sub> ClO <sub>3</sub> (354.5)	71.09 (71.30)	5.36 (5.50)	10.01 (10.20)		235-37 E	C <sub>27</sub> H <sub>23</sub> ClO <sub>6</sub> N <sub>4</sub> (534.5)	10.48 (11.60)
5a.	128-30 L.p. 80°	C <sub>21</sub> H <sub>20</sub> O <sub>3</sub> (320)	78.75 (78.90)	6.25 (6.30)					
5b.	194-96 bz	C <sub>22</sub> H <sub>22</sub> O <sub>3</sub> (334)	79.04 (79.30)	6.59 (6.80)					
5c.	166-68 bz	C <sub>21</sub> H <sub>19</sub> ClO <sub>3</sub> (354.5)	71.09 (71.20)	5.36 (5.50)	10.01 (10.30)				

<sup>a</sup>bz = Benzene, L.p. 80° = Light petroleum (80-100°C, E = Ethyl alcohol).

**(d) Action of Aluminium Chloride Upon the Cyclic Anhydrides**

To a solution of the anhydride (1 mol) in nitrobenzene (10 ml per g anhydride), aluminium chloride (1.2 mol) was added and the mixture stirred for 6 hrs. at room temperature (30°C), left to stand overnight, then worked up as usual. The acidic product was crystallised from benzene as yellow crystals (yield *ca.* 45–60%) (for details, cf. Table 3).

**(e) Methanolysis of the Cyclic Anhydrides 3**

The anhydrides were refluxed with 6 hrs with absolute methanol (30 ml per g anhydride) and the resulting half-esters (60–70%) yield crystallised from light petroleum (b.pt. 80–100°C), (for details, cf. Table 4).

TABLE 4  
METHYL-(E)- AND (Z)-5-ARYL-4-CARBOXY-3,3-DIMETHYL-6-PHENYL-  
HEX-4-ENOIC ACID (1 g-i) AND (2g-i)

No.	M.pt.(°C)	Formula Mol. Wt.	Analysis % Calcd./ (Found)		
			C	H	Cl
1g.	156–58	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub> (352)	75.00 (75.20)	6.81 (6.90)	
2g.	173–75	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub> (352)	75.00 (75.30)	6.81 (7.00)	
1h.	139–41	C <sub>23</sub> H <sub>26</sub> O <sub>4</sub> (366)	75.41 (75.50)	7.10 (7.30)	
2h.	147–48	C <sub>23</sub> H <sub>26</sub> O <sub>4</sub> (366)	75.41 (75.60)	7.10 (7.20)	
1i.	119–21	C <sub>22</sub> H <sub>23</sub> ClO <sub>4</sub> (386.5)	68.31 (68.60)	5.95 (6.10)	9.18 (9.30)
2i.	151–53	C <sub>22</sub> H <sub>23</sub> ClO <sub>4</sub> (386.5)	68.31 (68.50)	5.95 (6.20)	9.18 (9.20)

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