

Structural Elucidation of *Z*- and *E*- Isomers of 5-Alkyl-4-ethoxycarbonyl-5-(4'-chlorophenyl)-3-oxa-4-pentenoic Acids

H. M. F. Madkour

Synthetic Organic Chemistry Laboratory, Department of Chemistry, Faculty of Science, Ain Shams University, Abbasiya, Cairo, Egypt

Fax: 00 2024831836, E-mail: hmfmadkour@hotmail.com

Received: 6 September 1999; revised form: 7 November 1999/Accepted: 7 February 2000/Published: 20 May 2000

Abstract: *Z*- and *E*-isomers of 5-alkyl-4-ethoxycarbonyl-5-(4'-chlorophenyl)-3-oxa-4-pentenoic acids were prepared via the condensation of *p*-chloroacetophenone and/or *p*-chloropropiophenone with diethyl-2,2'-oxydiacetate in the presence of sodium hydride as a basic catalyst. The *Z*-isomers of **2a** and **2b** were found to be predominant. The behaviour of the corresponding anhydrides towards the action of hydrazine, phenylhydrazine, primary aromatic amines, hydrocarbons and ethanolysis has also been investigated. The structures and configurations of the products have been elucidated by chemical and spectroscopic means.

Keywords: Aromatic ketones, 2,2'-oxydiacetate, stereoisomeric alkenes.

Introduction

The present study deals with the condensation of aromatic ketones with diethyl-2,2'-oxydiacetate and structural elucidation of the resulting *Z*- and *E*-isomers of 5-alkyl-4-carbethoxy-5-(4'-chlorophenyl)-3-oxa-4-pentenoic acids.[1] The investigation is also extended to cover the behaviour of the corresponding anhydrides towards hydrazines, aromatic amines and hydrocarbons under Friedel-Crafts acylation conditions [2-5].

Results and Discussion

The condensation of p-chloroacetophenone and p-chloropropiophenone with diethyl-2,2'-oxydiacetate in the presence of sodium hydride [5] afforded in each case a mixture of the expected stereoisomeric *E*- and *Z*-alkenes. The *E*-isomers **1a** and **1b** could be isolated in pure crystalline form, the remainder being an oily fraction whose composition was revealed by saponification.

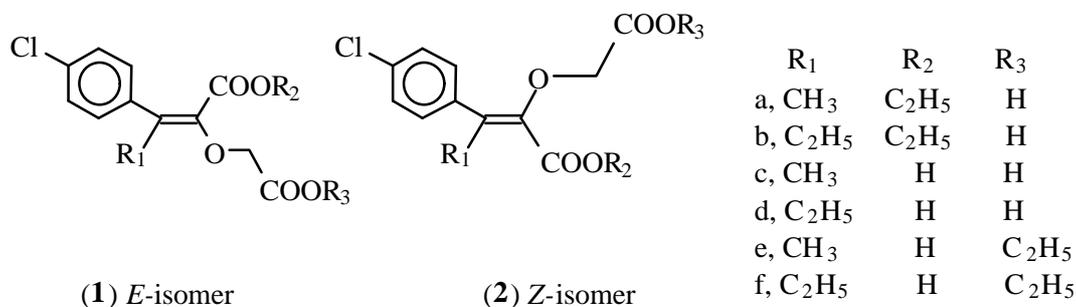


Figure 1.

The *Z*-hemiesters **2a** and **2b** were obtained in 40% and 42% yields, respectively (vide infra). The predominance of this configuration can be interpreted in terms of the mechanism involving the formation of the diastereoisomeric δ -lactonic intermediates I and II. The steric course of the condensation will be controlled by the initial attack by the ester carbanion on the ketone. Out of the possible diastereomeric condensate anions III and IV, III is expected to be more easily formed owing to the *transoid* orientation of the p-chlorophenyl group and ester groups (larger effective bulk than OCH₂COOC₂H₅). Cyclisation of III to I was also expected to be enhanced by the diequatorial accommodation of the bulky aryl and ester groups when I approaches a chair-like conformation during cyclization. The easier formation of I reasonably explains the higher yields of the *Z*-hemiesters. Furthermore, the predominance of this configuration in the two investigated ketones, indicates that the ratio of isomers is almost solely controlled by the conformational factor, and is almost independent of the polar effect of substituents.

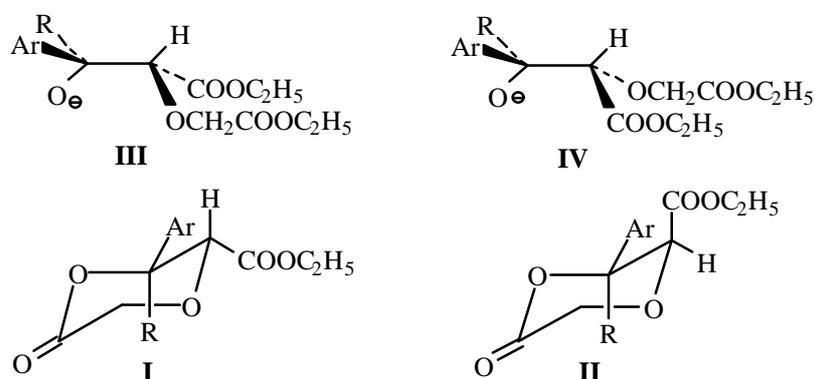


Figure 2.

Structure and Configuration of the Hemiesters

The crystalline *E*-hemiesters **1a** and **1b** exhibited strong bands at 1712 and 1686 cm^{-1} for α,β -unsaturated ester and non-conjugated carboxyl groups, respectively [6]. Saponification of the crystalline *E*-hemiester of **1a** and **1b** gave the corresponding *E*-diacids **1c** and **1d**. The oily *Z*-hemiester **2a** and **2b** gave fairly high yields of the *Z*-diacids **2c** and **2d** in pure crystalline state. The dibasic acids **1c**, **1d**, **2c** and **2d** were converted to the corresponding cyclic anhydrides **3a-d** by the use of *N,N*-dicyclohexylcarbodiimide (DCC) as dehydrating agent. The anhydrides **3a-d** exhibited the expected carbonyl coupling bands [6].

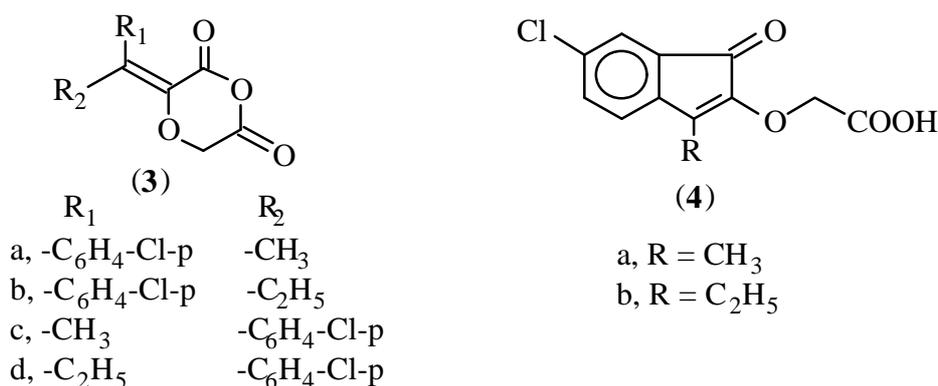


Figure 3.

The configuration of the *E*-hemiesters **1a** and **1b** was confirmed from cyclization of the derived anhydrides **3a** and **3b** with anhydrous aluminium chloride to the corresponding oxoindenyl acids **4a** and **4b** in good yields. Similar treatment of the *Z*-anhydrides **3c** and **3d** gave the corresponding dibasic acids **2c** and **2d** as the sole acidic products.

Beside elementary analyses, solubility in sodium carbonate solution, yellow colour, and formation of 2,4-dinitrophenylhydrazones, each of the indenyl acids **4a** and **4b** showed two bands for $\nu_{\text{C=O}}$. The position of the maxima in the electronic spectra (λ_{max} 253 and 296; ϵ_{max} 18500 and 16500), closely resemble those of 2-carboxymethyl analogues [7].

Treatment of the anhydrides **3a** and **3b** with hydrazine hydrate and phenylhydrazine in refluxing ethanol [2,3] led to cleavage at the non-conjugated carbonyl and gave the hydrazide derivatives **5a-d**.

Amidation of the *E*-anhydrides **3a** and **3b** with aromatic amines, namely, aniline, *p*-toluidine, α -naphthylamine and benzylamine at 170°C afforded the 5-alkyl-*N*-aryl-4-carboxy-5-(*p*-chlorophenyl)-3-oxapent-4-enoic imides **6a-h**.

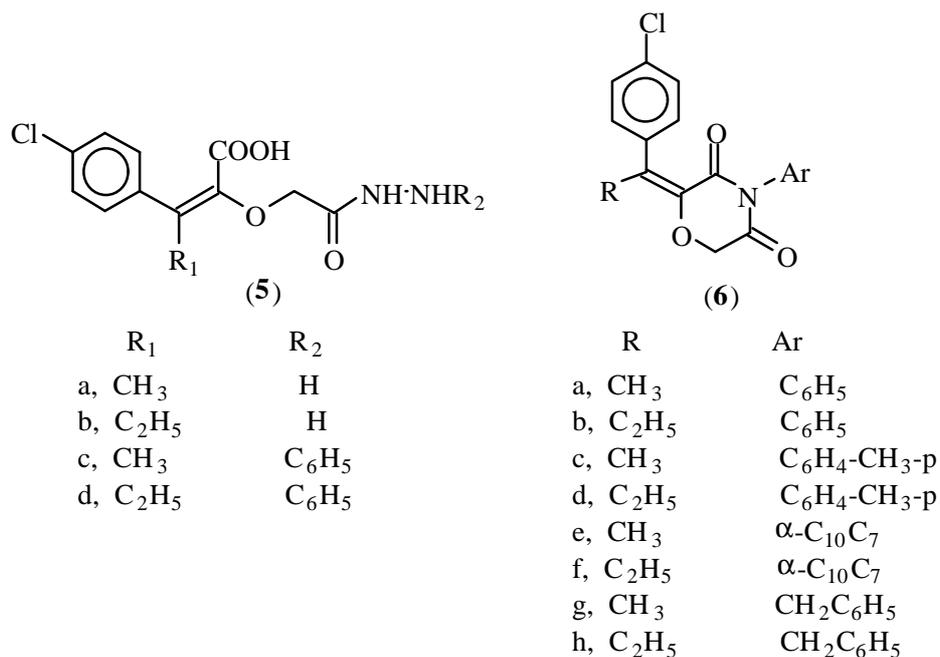
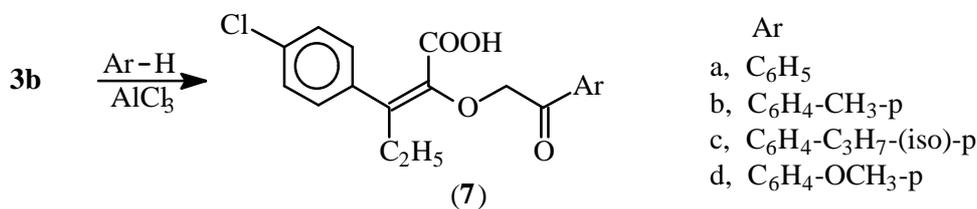


Figure 4.

On the other hand, the anhydride **3b** was subjected to reactions with aromatic hydrocarbons such as benzene, toluene, cumene and anisole in the presence of anhydrous aluminium chloride under Friedel-Crafts' reaction conditions and gave the 2-aryl-methoxy-3-(p-chlorophenyl)-pent-2-enoic acids **7a-d**.



Scheme 1.

The carboxy hemiesters **1e**, **1f**, **2e** and **2f** were obtained through ethanolysis of the anhydrides **3a-d** in ca 80% yield. The presence of non-conjugated ester and α,β-unsaturated carbonyl groups was shown by the ν_{C=O} at 1745 and 1700 cm⁻¹, thus providing additional proof for the position of unsaturation in the original hemiesters.

Experimental

General

All elemental analyses gave satisfactory results : C ± 0.36, H ± 0.16, N ± 0.31, Cl ± 0.42. IR (KBr disks) and U.V. spectra were measured with Unicam SP 1400 and SP1800 spectrophotometers, re-

spectively. The $^1\text{H-NMR}$ spectra were measured on a Varian EM-390 at 90 MHz using TMS as the internal lock and reference compound.

Z- and E-isomers of 5-alkyl-4-ethoxycarbonyl-5-[4'-chlorophenyl]-3-oxa-4-pentenoic acids 1a,b and 2a,b

The ketone, diethyl-2,2'-oxydiacetate and sodium hydride (1:1.5:1.5 mol.) in excess dry benzene were stirred at 60-70° for 10 hrs and the reaction mixtures were worked up as usual. [8]

(a) p-Chloroacetophenone (0.01 mole; 15.5g) gave an acidic product (20.7g; 69.2%) which was separated by dissolution in benzene into: (i) the less soluble *E*-isomer **1a**, isolated as colourless crystals (7.1g). M.p. 155-7°. $^1\text{H-NMR}$ (DMSO- d_6): δ 1.3 (t, 3H, $J = 7.5$ Hz CH_2CH_3), 2.1 (s, 3H, $\text{CH}_3\text{C}=\text{C}$), 3.6 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 4.1 (s, 2H, OCH_2COO) and 7.1-7.3 (m, 4H, Ar-H). (ii) The soluble oily hemiester fraction (13.6g) whose composition was revealed by saponification (see below).

(b) p-Chloropropiophenone (0.01 mole; 16.8g) gave an acidic product (22.6g; 72.2%) which was separated by dissolution in benzene-light petroleum into two fractions: (i) the less soluble *E*-hemiester **1b**, colourless crystals (8.2g), m.p. 160-2°. (ii) The soluble oily hemiester fraction (14.4g) whose composition was revealed by saponification (see below).

Saponification of the hemiesters

The hemiesters were hydrolyzed by refluxing with 10% aqueous sodium hydroxide (10 ml of alkali solution/1g of the hemiester) for 3 hrs. The pure crystalline hemiesters **1a**, **1b** gave the corresponding diacids **1c** and **1d** in ca. 80% yield. The oily hemiester (13.6g) from p-chloroacetophenone gave an acidic product (12.1g) which was digested with ether to give (i) the above *E*-diacid **1c** (1.3g) as insoluble fraction and (ii) the *Z*-diacid **2c** as soluble fraction (10.7g).

The oily hemiester (14.4 g) from p-chloropropiophenone gave an acidic product (13.2g) which was treated with boiling benzene to give (i) the *E*-diacid **1d** (1.2g) as insoluble fraction and (ii) The *Z*-diacid **2d** as soluble fraction (12g). (cf. Table 1).

The $^1\text{H-NMR}$ spectra of compound **1d** shows the following peaks at δ 1.1 (t, 3H, $J = 7.5$ Hz, CH_2CH_3), 2.6 (q, 2H, $J = 7.5$ Hz, CH_2CH_3), 3.7 (s, 2H, OCH_2COO) and 7.4-7.6 (m, 4H, Ar-H).

The relative amounts of products given in (a) should thus now be modified as follows : Total hemiester mixture (20.7g), *E*-configuration hemiester (7.1g + 1.43g = 8.58g, 29% yield). *Z*-configuration hemiester (11.83g, 40% yield). For case (b), total hemiester mixture (22.6g), *E*-configuration hemiester (1.32g + 8.20g = 9.52g, 30% yield). The yield of *Z*-configuration hemiester is 13.29 g (42% yield).

Formation of cyclic anhydrides 3a-d

A mixture of the diacid and N,N' -dicyclohexylcarbodiimide (DCC) (1:1 molar ratio) in excess dry benzene was stirred at room temperature for 2 hrs, left to stand overnight, then worked up as usual [7-8]. The $^1\text{H-NMR}$ spectrum of compound **3a** displayed peaks at δ 1.8 (s, 3H, $\text{CH}_3\text{C}=\text{C}$), 4.2 (s, 2H,

OCH₂CO) and 7.3 (m, 4H, Ar-H). The ¹H-NMR spectrum of compound **3d** exhibited peaks at δ 1.6 (t, 3H, J = 6.5 Hz, CH₂CH₃), 3.6 (q, 2H, J = 6.5 Hz, CH₂CH₃), 4.0 (s, 2H, OCH₂CO) and 7.7-7.9 (m, 4H, Ar-H).

Table 1. *Z*- and *E*-isomers of 5-alkyl-4-ethoxycarbonyl-5-(4-chlorophenyl)-3-oxa-4-pentenoic acids and their corresponding anhydrides **1-3**.

Compound	M.p (°C) & Solvent	IR (cm ⁻¹)	
		ν _{C=O}	ν _{OH}
1c	235 Benzene	1700-1698	br. 3100-3500
1d	230-2 Light petroleum ¹	1705-1688	br. 3110-3460
2c	218 Light petroleum ¹	1700-1690	br.3080-3500
2d	207-9 Light petroleum ¹	1710-1695	br.3180-3480
3a	173.5 Light petroleum ¹	1780-1742	
3b	176.8 Benzene	1772-1753	
3c	167-9 Light petroleum ¹	1780-1750	
3d	135-7 Light petroleum ¹	1775-1742	

¹b.p. 80-100°C.

Action of anhydrous aluminium chloride upon the cyclic anhydrides **3a,b**

To a solution of the anhydride (1 mole) in dry tetrachloroethylene (10 mL per g anhydride) anhydrous aluminium chloride (1.2 mole) was added and the mixture was stirred for 10 hrs at room temperature, left to stand overnight, then worked up as usual [7,8]. The anhydride **3a** gave the oxoindenyl acid **4a** as yellow needles from benzene, (44% yield), m.p. 205-7°. ¹H-NMR (DMSO-d₆): δ 2.1 (s, 3H, CH₃), 4.0 (s, 2H, OCH₂COOH) and 7.4-7.6 (m, 3H, Ar-H), 11.2 (s, 1H, COOH). The DNP (dinitrophenyl) hydrazone of **4a** was obtained as red crystals from light-petroleum (b.p. 90-110°), m.p. 267°. The anhydride **3b** gave the oxoindenyl acid **4b** as yellow crystals from a mixture of benzene-methanol, 54% yield, m.p. 240-2°. The DNP hydrazone of **4b** was obtained as orange crystals from methanol, m.p. > 300°. ¹H-NMR (DMSO-d₆) : δ 1.4 (t, 3H, J = 6.0 Hz, CH₂CH₃), 2.8 (q, 2H, J = 6.0 Hz, CH₂CH₃), 3.7 (s, 2H, OCH₂COOH), 7.3-7.5 (m, 3H, Ar-H) and 10.9 (s, 1H, COOH).

Formation of hydrazide derivatives **5a-d**

A solution of **3** (0.01 mol) and hydrazine hydrate and/or phenylhydrazine (0.05 mol) in 50 mL etha-

nol was refluxed for 2 hrs. Evaporation of alcohol left a solid product which crystallised from a suitable solvent to give **5** (cf. Table 2).

Formation of 4-aryl-2-(2'-alkyl-2'-(4-chlorophenyl)methylene-3,5-dioxo-2,3,5,6-tetrahydro-1,4-[4H]oxazine derivatives 6a-h

A mixture of **3** (0.01 mol) and the appropriate amines (0.01 mol) was fused at 170°C for 2 hrs. The solid formed after cooling and treatment with ice/HCl was crystallised from the appropriate solvent to give **6a-h** (cf. Table 2). The ¹H-NMR spectrum (DMSO-d₆) of compound **6d** displayed the following peaks at δ 1.2 (t, 3H, J = 6.5 Hz, CH₂CH₃), 2.1 (s, 3H, CH₃-Ar), 2.8 (q, 2H, J = 6.5 Hz, CH₂CH₃) 3.8 (s, 2H, OCH₂CO) and 6.9-7.4 (m, 8H, Ar-H). The ¹H-NMR spectrum (DMSO-d₆) of compound **6g** exhibited the following peaks at δ 1.9 (s, 3H, CH₃C=C), 3.6 (s, 2H, OCH₂CO), 5.1 (s, 2H, N-CH₂Ph) and 6.7-7.7 (m, 9H, Ar-H).

Table 2. Physical data of hydrazide derivatives **5a-d** and 1,4-oxazine derivatives **6a-h**.

Compound	M.p (°C) & Solvent	IR (cm ⁻¹)	
		ν _{C=O}	ν _{NH,OH}
5a	190-2 Benzene	1705-1660	3510-3210
5b	210-2 Methanol	1696-1656	3450-3205
5c	122-3 Light petroleum	1692-1678	3480-3250
5d	220-2 Benzene	1700-1662	3510-3200
6a	140-2 Light petroleum	1782-1705	
6b	165-7 Benzene	1776-1700	
6c	205-7 Methanol	1780-1705	
6d	200 Methanol	1772-1690	
6e	240-2 Benzene	1785-1710	
6f	205-7 Methanol	1760-1700	
6g	172-3 Benzene	1782-1710	
6h	196-7 Methanol	1777-1700	

Reaction of **3b** with aromatic hydrocarbons: formation of **7a-d**

A solution of **3b** (0.01 mol) in 100 mL of distilled aromatic hydrocarbon was added gradually to a cold suspension of anhydrous aluminium chloride (0.01 mol) in a large excess of aromatic hydrocarbon (100 mL). The whole mixture was then added to cold hydrochloric acid. The organic layer was separated and dried; the evaporation of solvent left a semisolid product which was crystallized from an appropriate solvent to give **7a-d** (cf. Table 3). The $^1\text{H-NMR}$ spectrum (DMSO- d_6) of compound **7c** displayed peaks at δ 1.1 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.4 (d, 6H, $\text{CH}(\text{CH}_3)_2$), 2.7 (q, 3H, $J = 7.0$ Hz, CH_2CH_3), 3.1-3.5 (m, 1H, $\text{CH}(\text{CH}_3)_2$) and 7.2-7.9 (m, 8H, Ar-H). The $^1\text{H-NMR}$ spectrum (DMSO- d_6) of compound **7d** exhibited peaks at δ 1.2 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 2.8 (q, 2H, $J = 7.0$ Hz, CH_2CH_3), 3.7 (s, 3H, OCH_3), 4.1 (s, 2H, OCH_2CO) and 7.0-7.8 (m, 8H, Ar-H).

Ethanolysis of anhydrides **3a** and **3b**

The anhydride was refluxed for 3 hrs with excess absolute ethanol (99.0%). Evaporation of alcohol left the isomeric hemiesters **1e** and **1f** (cf. Table 3).

Table 3. Physical data of products of the reaction of **3** with aromatic hydrocarbons and ethanol.

Compound	M.p ($^{\circ}\text{C}$) & Solvent	IR (cm^{-1})	
		$\nu_{\text{C=O}}$	$\nu_{\text{NH,OH}}$
7a	>280 Ethanol	1702-1696	br. 3400
7b	260-2 Benzene-methanol	1700-1686	br. 3210-3450
7c	>300 Benzene-methanol	1700-1698	br. 3430
7d	250-2 Benzene-methanol	17072-1688	br. 3510
1e	117-9 Light petroleum	1732-105	br. 3500-3180
1f	220-3 Benzene	1728-1700	br. 3480-3120

References and Notes

1. Madkour, H.M.F.; Salem, M.A.I.; Abdel-Rahman, T.M.; Azab, M.E. *Heterocycles* **1994**, *38*, 57.
2. El-Hashash, M.A.; Madkour, H.M.F.; Amine, M. S. *Pak. J. Sci. Ind. Res.* **1991**, *34*, 288.
3. Mahmoud, M.R. *Ind. J. Chem.* **1994**, *33B*, 1028-1032.
4. Mahmoud, M.R. *J. Chem. Soc. Pak.* **1989**, *11*, 144-150.
5. El-Newaihy, M.F.; Salem, M.R.; Enayat, E.I.; El-Bassiony, F.A. *Aust. J. Chem.* **1979**, *32*, 1159.

6. Bellamy, L.J. *The Infrared Spectra of Complex Molecules*, 3rd Edn.; Chapman & Hall: London, 1975; Vol. 1.
7. Abdel-Hamid, H. A.; Enayat, E. I.; Mahmoud, M. R. *J. Chem. Soc. Pak.* **1990**, *12*, 128-133.
8. Mahmoud, M.R.; El-Nagdy, S.; El-Bassiouny, F.A. *J. Chem. Soc. Pak.* **1988**, *10*, 261-267.

Samples Availability: Not available.

© 2000 by MDPI (<http://www.mdpi.org>). Reproduction is permitted for noncommercial purposes.