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Synthesis of Some New Saturated Butyrolactones

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γ-Oxoacids, β-(4-methylbenzoyl) propionic acid and β-(2,5-dimethylbenzoyl)propionic acid undergo condensation with various phenolic compounds in presence of concentrated sulphuric acid to give some new γ-butyrolactones in which γ-carbon atom is attached to two different phenyl rings. Structures of these compounds have been established on the basis of elemental analysis, chemical reactions and IR spectral data.

INTRODUCTION

Five-membered γ-lactones constitute an important group of organic compounds. Their occurrence in nature[1–3] and significant antibacterial, antifungal and antitumour activities[1,4,5] associated with these compounds brought them to limelight. A five-membered lactonic ring is present in many steroidal lactones which exist in plants as glucosides, and exert a specific and powerful action on the cardiac muscles of humans and animals[1]. In recent years, there has been a marked interest in the synthesis of free and fused, saturated and unsaturated butyrolactones[6–10]. These recent reports and the significant chemotherapeutic activity of some saturated butyrolactones on pathogenic viruses[11], generated an interest to synthesize some new saturated butyrolactones by a simple and convenient method. In the present work, we have condensed two γ-oxoacids, β-(4-methylbenzoyl)propionic acid (**1a**) and β-(2,5-dimethylbenzoyl)propionic acid (**1b**) with phenolic compounds (**3**) to obtain γ-butyrolactones (**4–9**) in which γ-carbon is attached to two different phenyl rings.

EXPERIMENTAL APPROACH

β-(4-Methylbenzoyl)propionic acid (**1a**) and β-(2,5-dimethylbenzoyl) propionic acid (**1b**) were prepared by the Friedel-Crafts reaction of succinic anhydride with toluene and *p*-xylene respectively[12].

Preparation of γ-butyrolactones: Each of the γ-oxoacids **1a** and **1b** were condensed with phenol, resorcinol, catechol, quinol, phloroglucinol and pyrogallol in presence of concentrated sulphuric acid to get the γ-butyrolactones (**4–9**). The phenols were taken in slight excess over the oxoacids.

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Typical procedure: γ-(2,4-dihydroxyphenyl)-γ-(4-methyl-phenyl)-γ-butyrolactones (**5a**): An intimate mixture of **1a** (3.84 g) and resorcinol (2.4 g) was heated at 150°C to get a homogenous solution. To this, concentrated sulphuric acid (5 drops) was added and the heating was continued between 150 and 160°C for *ca.* 0.5 h to give a hard and brittle mass on cooling. The condensed mass was crushed, washed well with water to remove excess of resorcinol, extracted with 2% aq. sodium hydroxide and filtered. The butyrolactone was precipitated from the filtrate by gradual addition of dil. hydrochloric acid. It was purified by repeated crystallisation from aq. ethanol as yellowish-brown micro-crystalline solid (5.5 g, 96.8%), m.p. 106–108°C [found (%): C, 71.25; H, 5.45; $C_{17}H_{16}O_4$ requires (%): C, 71.83; H, 5.63%; ν_{max}(KBr) (cm^{-1}) 3600–2500 (broad), 1765, 1730, 1680, 1585, 1490].

Rest of the butyrolactones given in the table were prepared in an identical manner as described above.

Acetylation of butyrolactone (**5a, b**): The butyrolactone **5a** or **5b** (1.0 g) was refluxed with acetic anhydride (20 mL) and fused sodium acetate (3.0 g) at 130–140°C for 3 h to give a light brown diacetyl derivative **10a** (0.95 g, m.p. 146–148°C) or pale yellow derivative **10b** (0.88 g, m.p. 120–121°C). The diacetyl derivatives (**10a, 10b**) were crystallised from aq. ethanol. Their analytical data are as follows: **10a** [found (%): C, 68.19; H, 5.36; $C_{21}H_{20}O_6$ requires (%): C, 68.47; H, 5.43%; ν_{max}(KBr) (cm^{-1}) 1765, 1745, 1600, 1550, 1500]; **10b** [found (%): C, 69.64; H, 5.98; $C_{22}H_{22}O_6$ requires (%): C, 69.10, H, 5.75%; ν_{max}(KBr) (cm^{-1}): 1765, 1755, 1600, 1575, 1485].

Bromination of butyrolactones (**5a, b**): The butyrolactone **5a** or **5b** (1.0 g) was dissolved in minimum quantity of ethanol and excess bromine (2.0 mL) was added to it dropwise. The contents were left overnight and addition of sufficient quantity of water gave brick red dibromo compound **11a** [0.98 g, m.p. 168–169°C (from aq. ethanol) (found %: Br, 36.58; $C_{17}H_{14}O_4Br_2$ requires (%): Br, 36.19); ν_{max}(KBr) (cm^{-1}): 3600–2800 (broad), 1780, 1720, 1600, 1555, 1510]; or **11b** [1.0 g, m.p. 180°C (decomp) (from aq. ethanol) (found (%): Br, 35.47, $C_{18}H_{16}O_4Br_2$ requires (%): Br, 35.08%; ν_{max}(KBr) (cm^{-1}) 3600–2500 (broad), 1780, 1725, 1600, 1575, 1480].

Caustic potash fusion of (**5a, b**): The butyrolactone **5a** or **5b** (1.0 g) was mixed with a paste of KOH pellets (10 g) at 250°C for about 4 h. The contents were cooled, dissolved in water and filtered. The excess of alkali was just neutralised with dil. HCl when a residue (A) settled down which was filtered and washed with water. The filtrate was further acidified by adding an excess of dil. HCl, giving a white residue (B); it was also filtered and washed with water. The filtrate so obtained was shaken with ether. Evaporation of ether afforded a residue (C). Residues A, B and C were identified as unreacted butyrolactone **5a** or **5b** the γ-oxoacid **1a** or **1b**, and resorcinol respectively by direct comparison (m.m.p., CO—TLC and CO—IR) with their authentic samples.

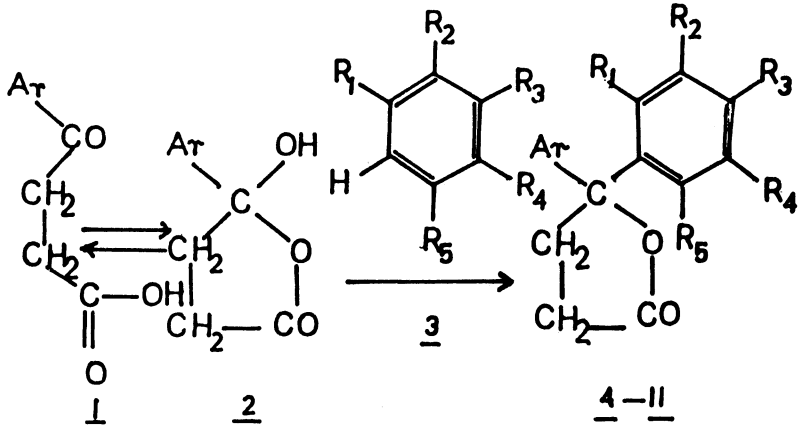
RESULTS AND DISCUSSION

It has been observed that γ-oxoacids generally exist as lactol or as an

equilibrium mixture of ring and chain tautomers[13–15]. In many reactions, these acids undergo cyclisation to their lactol tautomeric form[16, 17]. The two γ-oxoacids, β-(4-methylbenzoyl) propionic acid (**1a**) and β-(2,5-dimethylbenzoyl) propionic acid (**1b**) have been examined by IR spectroscopy and are found to exist as a mixture of ring (**2**) and chain (**1**) tautomeric forms. IR spectra (ν_{max}) (cm^{-1}) of **1** showed absorption bands at 1700–1695, 1670–1668 and 1772–1755 (very feeble) characteristic of carboxyl C=O, ketonic C=O and lactonic C=O groups respectively. Broad bands around 2740–2640 and 3335–3320 cm^{-1} were assigned to carboxylic and lactol OH groups respectively.

The γ-oxoacids (**1**) reacted with phenols (**3**) through their lactol form **2** to form γ-butyrolactones (**4–9**) as shown in scheme. With excess of phenols, the entire

SCHEME



4,	$R_1 = R_2 = R_4 = R_5 = H$;	$R_3 = OH$
5,	$R_2 = R_4 = R_5 = H$;	$R_1 = R_3 = OH$
6,	$R_1 = R_4 = R_5 = H$;	$R_2 = R_3 = OH$
7,	$R_2 = R_3 = R_5 = H$;	$R_1 = R_4 = OH$
8,	$R_2 = R_4 = H$;	$R_1 = R_3 = R_5 = OH$
9,	$R_4 = R_5 = H$;	$R_1 = R_2 = R_3 = OH$
10,	$R_2 = R_4 = R_5 = H$;	$R_1 = R_3 = OCOCH_3$
11,	$R_5 = H$; $R_2 = R_4 = Br$;	$R_1 = R_3 = OH$
1–11,	**a,** Ar = 4-Methylphenyl	
	b, Ar = 2,5-Dimethylphenyl	

acid taken reacts as lactol. The structures of γ-butyrolactones have been derived on the basis of elemental analysis, bromination, acetylation, KOH degradation and in IR spectral studies. The typical γ-butyrolactone (**5**) on acetylation and bromination gave diacetyl derivative (**10**) and dibromderivative (**11**) respectively. On fusion with KOH, **5** gave the starting γ-oxoacid (**1**) and resorcinol.

IR spectra of the butyrolactones **4–9** and **11** showed a strong and broad band between 3600 and 2500 cm^{-1} due to stretching vibrations of bonded OH. The diacetyl derivative **10** displayed absorption band at 1755–1745 cm^{-1} which may be assigned C=O stretching of phenolic acetate. Presence of a sharp and strong band between 1780 and 1765 cm^{-1} in all the compounds is due to lactonic carbonyl stretching, and it supports the existence of five-membered γ-lactone ring in the proposed structures.

TABLE-1
PHYSICAL, ANALYTICAL AND SPECTRAL DATA OF γ-BUTYROLACTONES

Compound No.	Yield (%)	m.p. (°C)	Mol. formula	Analysis (%) Found (Calcd.)		ν_{max} (cm^{-1})
				C	H	
4a	71.6	120 (d)	$C_{17}H_{16}O_3$	76.40 (76.11)	5.81 (5.97)	1765
4b	88.6	120–122	$C_{17}H_{18}O_3$	76.38 (76.59)	6.19 (6.38)	1770
5b	73.8	150–151	$C_{18}H_{18}O_4$	72.50 (72.48)	5.75 (6.04)	1775
6a	97.1	185 (d)	$C_{17}H_{16}O_4$	71.62 (71.83)	5.50 (5.63)	1750
6b	68.2	155 (d)	$C_{18}H_{18}O_4$	72.68 (72.48)	6.15 (6.04)	1775
7a	91.1	200 (d)	$C_{17}H_{16}O_4$	71.53 (71.83)	5.40 (5.63)	1770
7b	67.1	160 (d)	$C_{18}H_{18}O_4$	72.58 (72.48)	6.10 (6.04)	1780
8a	74.2	115–117	$C_{17}H_{16}O_5$	68.36 (68.00)	5.54 (5.33)	1770
8b	70.0	240 (d)	$C_{18}H_{18}O_5$	68.84 (68.78)	5.89 (5.73)	1780
9a	90.4	>300	$C_{17}H_{16}O_5$	68.40 (68.00)	5.45 (5.33)	1765
9b	63.6	>300	$C_{18}H_{18}O_5$	69.64 (69.10)	5.98 (5.75)	1775

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