Tetrahedron Vol. 40, No. 4, pp 749 to 755, 1984
Printed in Great Britain.

0040-4020/84 $3.00 + .00

δ-LACTONES FROM δ-KETOESTERS—II

MECHANISM CHANGES IN ALKYLATION REACTIONS AND SUBSTITUENT EFFECTS ON STEREOSELECTION

G. DI MAIO,* E. VECCHI and E. ZEULI
Istituto di Chimica Organica dell'Università "La Sapienza", Rome, Italy

and

M. DELFINI
Istituto di Chimica e Tecnologia dei Radioelementi, C.N.R. Padua, Italy

(*Received in the UK 25 March* 1983)

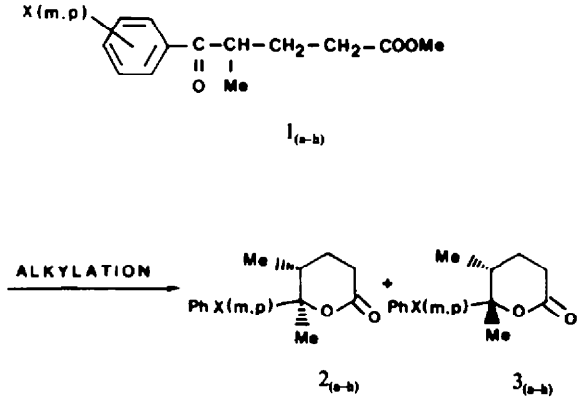
Abstract—Alkylation of methyl 4-methyl 5-oxo 5-phenyl (m and p-X substituted) pentanoates $\mathbf{1}_{a-h}$ give cis and trans tetrahydro 5,6-dimethyl 6-phenyl 2H pyran-2-ones. LFER of isomer ratios as function of the X substituent on the phenyl ring is seen in MeLi–Et_2O. The lactone ratios of reactions in THF with MeMgCl are not affected by the X phenyl substituent, while a more complex situation is showed by reactions of MeMgI in Et_2O and benzene. Changes in the cis: trans-ratios with variations in reactant and solvent are discussed in terms of equilibrium between folded and unfolded conformations in transition states.

In a previous study[1] we discussed the stereochemical outcome of Grignard alkylation reactions (conducted in THF with MeMgCl) of δ ketoesters of general formula **1** {X = p-Me(a), H(b), p-F(d), p-Cl (e), p-Br (f)}.

Diastereomeric δ-lactones **2(a, b, d, e, f)** and **3(a, b, d, e, f)** are the products of such reactions, and methods for their stereoselective synthesis[2] are desirable, since interesting biological activity has been shown for some members of the family.[3]

Recently an extensive study on the conformations of lactones has been published.[4]

The aim of the present work was to synthesize the δ-ketoesters **1**, with X = m-OMe (c), m-Br (g), m-CN (h), having the meta substituted phenyl group and isolate and characterize δ-lactones cis **2(c, g, h)** and trans **3(c, g, h)** produced by alkylation reactions, and to ascertain the stereochemical outcome of alkylation reactions on compounds **1(a–h)** in different reaction conditions in analogy to previous studies.[5,6]



RESULTS AND DISCUSSION

Methyl 4-methyl 5-oxo 5-phenyl pentanoates **1(a, b, d, e, f)** and lactones **2** and **3(a, b, d, e, f)** have been synthesized, isolated and characterized as already described.[1] Likewise, methyl 4-methyl 5-oxo 5-phenyl pentanoates **1(c, g, h)** have been synthesized by a Michael reaction with methyl acrylate on the suitable propiophenones (Experimental).

Structure characterization of δ-lactones

In close analogy with a preceding paper[1] compounds **2(c, g, h)** and **3(c, g, h)** were examined by ^{13}C and ^1H NMR spectroscopy in comparison with **2(b)** and **3(b)**.

Proton noise-decoupled ^{13}C NMR spectra of samples **2(c)** and **3(c)** are shown in Fig. 1(a) and (b) respectively.

^{13}C carbon atoms chemical shifts and corresponding assignments are reported in Table 1. The assignments were performed on the basis of off resonance experiments, undecoupled spectra, proton selective decoupling experiments, empirical rules,[7] comparison with model compounds.[8]

The compounds **2(c, g, h)** and **3(c, g, h)** exhibit two spectral regions: at upfield shift (0–90 ppm) due to the aliphatic carbon atoms of the δ-lactonic ring and at downfield shift (110–170 ppm) due to the aromatic ring carbon atoms and to the carbonylic carbon atoms of the δ-lactonic ring.

Owing to the small differences of resonances' chemical shift, unambigous assignements of resonances of aromatic moiety was not possible only on the ground of empirical rules for disubstituted benzenes: proton selective decoupling experiments and the study of spectral multiplicity were therefore necessary. The assignements of resonances of δ-lactonic

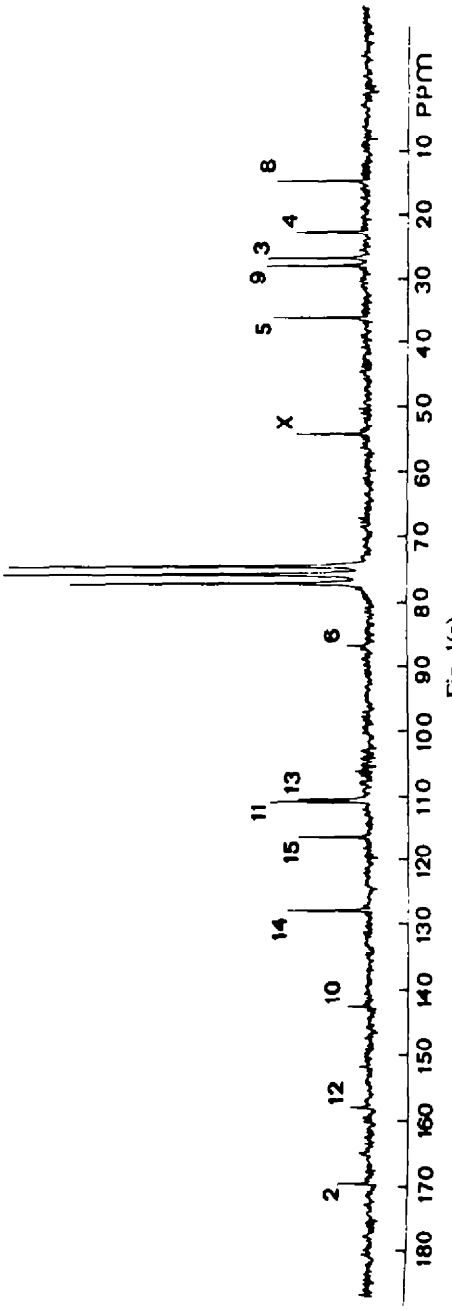


Fig. 1(a). Proton decoupled ^{13}C NMR spectrum at 22.63 MHz of sample 2(c). The × symbol indicates OMe group on C13 carbon atom.

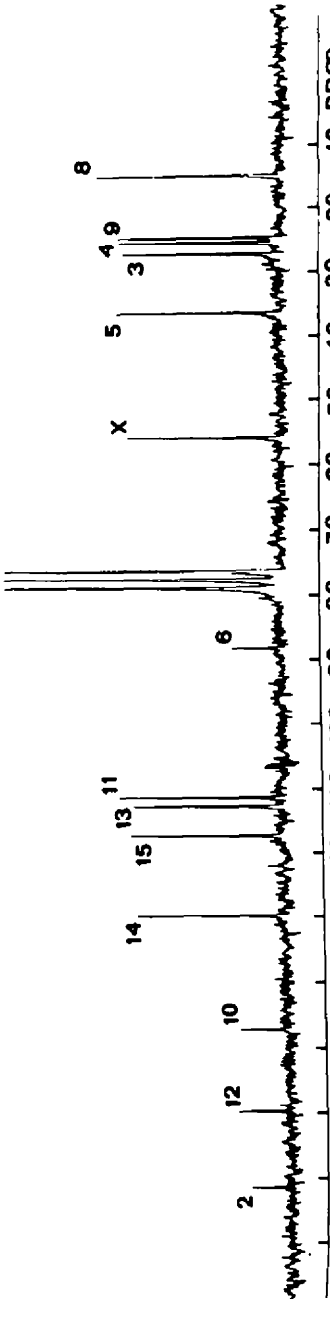


Fig. 1(b). Proton decoupled ^{13}C NMR spectrum at 22.63 MHz of sample 3(c). The × symbol indicates OMe group on C13 carbon atom.

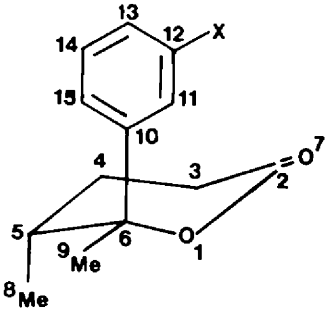
ring carbon atoms were performed as described in a previous paper.[1]

In analogy to the p-substituted[1] compounds the resonance of C9 and C10 carbon atoms are the most sensitive to stereochemical changes and are diagnostic, as well, in assigning the right structures. In fact C10 carbon showed a large up-field shift 2.5–3.5 ppm) due to the axial conformation of phenyl group in **2(c, g, h)** compounds with respect to the corresponding **3(c, g, h)** compounds; C9 methyl group on the contrary exhibits a downfield shift ($\simeq 4$ ppm) in the compounds **2(c, g, h)** with respect to the **3(c, g, h)** compounds. It is well known that such behaviour is due to the equatorial methyl group in the compounds 2.

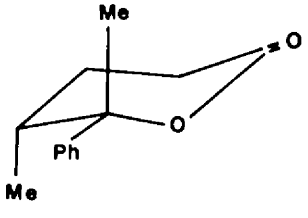
By considering samples **2(b)** and **3(b)** as model compounds for the aromatic system, the chemical shift of the carbon atoms showed a strong dependence on the substituent in 12 position.

The ^{1}H NMR spectra are straightforward: they (Table 2) exhibit singlets at δ: 1.75–1.55 attributed to C 9 Me group. The chemical shift difference between **2** and **3** series compounds were assigned respectively to an equatorial and an axial Me position. The C 8 Me group shows a doublet at δ: 0.82–1.08. The deshielding effect of the phenyl group is responsible for the higher field signals of the **2** series compounds with respect to the **3** series.

The above NMR data indicate once again that the conformational equilibrium relative to the isomer **2** (or **3**) is highly shifted towards conformers having the greatest number of axial substituents, as depicted below.



$2_{c,g,h}$



$3_{c,g,h}$

This conclusion was previously arrived at on the grounds of semiempirical potential energy calculations.[6]

Stereochemistry of alkylation reactions

Alkylation reactions on δ-ketoesters **1(a–h)** were performed with MeLi in Et_2O at 0° and 20°, with MeMgCl in THF at 60° and 0°[1] and with MeMgI in Et_2O and C_6H_6 at 20°. Stereochemical product ratios and yields (in parenthesis) are reported in Table 3.

From the data it can be observed that alkylation reactions with MeLi (columns 1 and 2) and with MeMgCl in THF (columns 3 and 4) have opposite stereochemistry for all substrates **1(a–h)**. Only reactions with MeLi obey to the Cram's rule.

Furthermore, with MeLi in Et_2O a free energy relationship exists between log cis/trans and the Hammett σ's of the X substituents ($\rho = 0.24$, correlation coefficient = 0.97 at 0°, and $\rho = 0.26$, correlation coefficient = 0.98 at 20° respectively. This behaviour clearly indicates that under these reaction conditions a folded/unfolded transition state equilibrium[9] exists and that its position is affected by the electronegativity of the X phenyl substituent thus causing the observed stereoselectivity shifts (1.70–2.57, column 1; 1.60–2.38, column 2). As expected, stereoselectivity decreases as reaction temperature increases from 0° to 20° (see columns 1 and 2).

When alkylation reactions are performed in THF with MeMgCl changes in the electronegativity of the X ring substituent do not produce variations in the stereochemical product ratios. This is in accordance with these reaction conditions not being suitable for the ester and the ketonic group to coordinate together a molecule of the alkylating agent.[9,10]

The stereochemical ratios of the alkylation reactions with MeMgI in Et_2O and in C_6H_6 (columns 5 and 6) are not readily explained. We also report, but cannot attempt to rationalize, these results as a function of the X phenyl substituent Hammett σ's. The two plots thus obtained (Fig. 2) have very similar shapes and suggest, in these cases, a more complex situation with regard to the interactions among solvent, Grignard reagent and **1(a–h)** substrates. Two different chelation mechanisms could operate both in Et_2O and in C_6H_6, one mechanism possessing a positive ρ for small σ values and the other with a negative ρ for larger values of σ.

EXPERIMENTAL

IR spectra were recorded using a Perkin–Elmer 457 spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol–C–60 HL and on a Bruker WH-90 spectrometer. ^{13}C NMR spectra were obtained at room temperature (28° ± 1°) in a 10 mm sample tube on a Bruker WH-90 instrument operating at 22.63 MHz in the Fourier transform mode. The sample concentration was 50 mg ml^{-1} in $CDCl_3$ used as ^{2}D internal lock. The same samples were used for both ^{1}H and ^{13}C NMR experiments. Measurements conditions were as follows: pulse width 4.5 sec (30° pulse), acquisition time 0.682 sec, spectral width 6000 Hz, number of data points 8 K, number of scans 3000. ^{13}C chemical shifts were measured taking the chemical shift of $CDCl_3$ as 77.02 ppm relative to TMS and are considered to be accurate to 0.05 ppm. The undecoupled spectra were obtained using the gated decoupling technique. Selective proton decoupling were also performed in order to univocally assign the resonances.

MS were recorded on a AEI MS 12 spectrometer: the relative intensities of the peaks (in parenthesis) are referred

Table 1. ^{13}C NMR chemical shifts of compounds **2(b, c, g, h)** and **3(b, c, g, h)** in $CDCl_3$, at 25° (data in ppm from TMS)

Compound X =	2_b* -H	2_c m-OMe	2_g m-Br	2_h m-CN	3_b* -H	3_c m-OMe	3_g m-Br	3_h m-CN
C 2	170.96	170.64	171.45	170.23	170.96	171.46	170.12	170.55
C 3	28.07	27.63	27.39	27.05	26.74	26.72	26.95	27.37
C 4	23.88	23.44	23.86	23.55	24.41	24.98	24.74	23.62
C 5	36.89	36.67	36.23	36.18	36.00	35.79	36.01	36.50
C 6	88.27	87.60	87.40	86.92	88.05	87.83	87.09	87.18
C 8	15.94	15.63	15.10	15.46	14.53	14.56	14.58	14.81
C 9	28.95	28.64	28.95	29.05	24.23	24.20	24.74	24.46
C 10	141.85	143.60	144.49	144.40	145.29	147.19	147.14	146.73
C 11	125.31	111.95	128.14	128.80	124.65	111.07	127.70	128.80
C 12	128.05	159.05	122.50	112.74	128.40	159.81	122.40	112.88
C 13	127.30	111.55	130.36	131.00	127.30	112.36	130.36	131.26
C 14	128.05	130.38	129.47	129.19	128.40	129.58	129.47	129.52
C 15	125.31	117.59	123.75	129.52	124.65	117.02	123.31	129.52
X		118.47		54.97		118.51		55.27

* See ref. 1.

Table 2. ^1H NMR chemical shifts of compounds **3(b, c, g, h)** and **3(b, c, g, h)** in CCl_4 at 25° (data in ppm from TMS)

Compounde	C9: δ Me(s,3H)	C8: δ Me (d,3H) J=6.7 Hz	δ Ph	δ X
2_b*	1.73	0.85	7.27 (5H)	
2_c	1.69	0.85	6.5-7.3 (4H)	3.74 (s,3H)
2_g	1.71	0.84	7.0-7.5 (4H)	
2_h	1.75	0.82	7.2-7.8 (4H)	
3_b*	1.58	1.01	7.24 (5H)	
3_c	1.55	1.08	6.5-7.3 (4H)	3.74 (s,3H)
3_g	1.57	1.06	7.0-7.5 (4H)	
3_h	1.61	1.05	7.2-7.8 (4H)	

* See Ref 1.

Table 3. Stereochemical product ratios and reaction yields (parenthesis) for alkylation reactions with MeLi at 0° and 20°, MeMgCl in THF at 60° and 0° and MeMgI in Et_2O and C_6H_6 at 20° on compounds **1(a–h)**

Starting compound X =	Hammett σ	Reaction conditions: MeLi / Et_2O 0°C (1)	MeLi / Et_2O 20°C (2)	MeMgCl / THF 60°C (3)	MeMgCl / THF 0°C (4)	MeMgI/Et_2O 20°C (5)	MeMgI/C_6H_6 20°C (6
1_a p-Me	-0.14	1.70 (45)	1.60 (58)	0.69 (65)*	—— **	0.81 (66)	1.08 (40)
1_b H	0	1.78 (60)	1.67 (68)	0.70 (75)*	—— **	0.82 (89)	1.08 (39)
1_c m-OMe	0.1	1.77 (50)	1.70 (55)	0.75 (68)	0.56 (45)	0.92 (60)	1.13 (35)
1_d p-F	0.15	1.85 (70)	1.80 (72)	0.64 (81)*	0.45 (48)*	0.96 (90)	1.24 (38)
1_e p-Cl	0.24	2.10 (60)	2.02 (70)	0.68 (73)*	0.51 (40)*	1.38 (86)	1.34 (46)
1_f p-Br	0.26	2.02 (45)	1.97 (50)	0.66 (65)*	0.49 (38)*	1.44 (89)	1.39 (56)
1_g m-Br	0.37	2.12 (40)	2.14 (44)	0.75 (60)	0.49 (35)	1.13 (82)	1.01 (58)
1_h m-CN	0.62	2.57 (60)	2.38 (69)	0.64 (55)	0.54 (42)	0.98 (55)	0.79 (39)

* See ref. 1.
** Compounds 1_a and 1_b are unreactive in this reaction condition.[1]

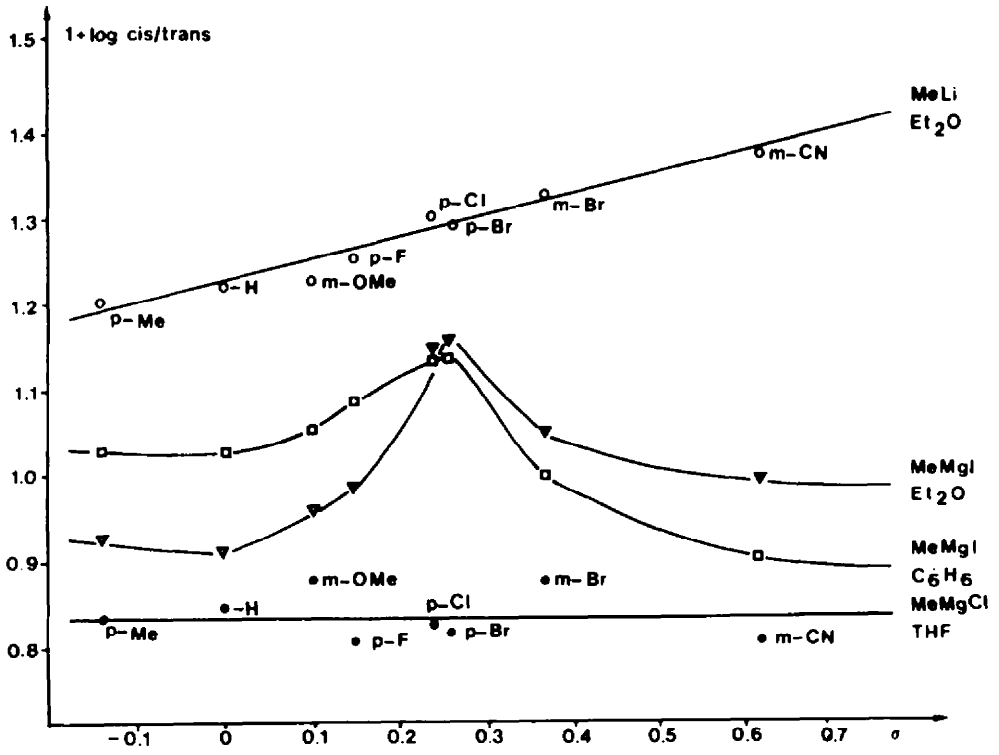


Fig. 2. Plot of 1 + log cis/trans vs Hammet σ's of × substituent for alkylation reactions of compounds $1_{(a-h)}$.

to the most intense one taken as 100%. The spectra were recorded at 70 eV.

GLC analyses were carried out on a Carlo Erba Fractovap G1 using a 2 mm i.d. column packed with 3% SP 2250 on Supelcoport 100/120 mesh. The GLC analysis conditions were $T_{oven} = 248°$, $T_{det} = T_{inj} = 260°$, N_2 flow = 30 ml/min, theoretical plates = 3000.

HPLC analyses and separations were carried out on a Waters apparatus equipped with a detector UV Perkin–Elmer LC 55 at $\lambda = 265$ nm, using respectively a 30 cm × 3.9 mm i.d. μ Porasil Waters and a 30 cm × 7.9 mm i.d. μ Porasil Waters columns.

Starting materials

Compounds: **1(c, g, h)** were synthesized using the method of Bertocchio and Dreux[10] from the suitable propiophenones (1 mole) and methyl acrylate (Fluka) (0.25 mole) as described.[1] The crude reaction product was purified as further described for each pentanoate **1(c, g, h)**.

3-Methoxypropiophenone was prepared from 3-hydroxy propiophenone and dimethyl sulfate according to Johnson.[12] The 3-hydroxy propiophenone was obtained starting from 3-amino propiophenone.[13,14] This last compound was prepared by $SnCl_2$ reduction[13] of 3-nitro propiophenone which was obtained by nitration of propiophenone.[15] 3-Bromopropiophenone was synthesized from propiophenone (Merck) according to Pearson.[16] 3-CN propiophenone as described by Pratesi.[13]

Methyl 4-methyl 5-oxo 5(3'methoxy)phenyl pentanoate **1c.** The crude product was distilled in order to remove the excess 3-methoxypropiophenone (b.p. 89–90°/0.3 mm Hg). The residue was chromatographed on silica gel (Merck) (R = 1:60) using benzene/EtOAc 9/1 as eluant. The fractions containing **1(c)** were collected as a colourless oil and distilled (b.p. 170–172°/0.3 mm Hg) to give 22 g of **1(c)** (yield 35%). **1(c)** was analyzed by GLC in the above specified conditions (ret. time: 2 min, 30 sec). NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ:1.16 (1.03) d, J = 6.7 Hz, 3H; 3.59 (3.32) s, 3H; 3.83 (3.32) s, 3H; 6.8–7.6 m, 4H. MS *m/e*: 77(15), 91(9), 107(18), 135(100), 136(9), 250(18), 251(2). IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3020w, 3000w, 2980sh, 2970m, 2950m, 2920sh, 2880w, 2840w, 1735s, 1685sh, 1680s, 1600s, 1580s, 1490m, 1460m, 1450m, 1435s, 1375m, 1360sh, 1320m, 1290w, 1265s, 1200m, 1170m, 1120w, 1040m, 1010w, 1000w, 900w, 880w, 830w, 800m, 750m. (Found: C, 67.30; H, 7.27. $C_{14}H_{18}O_4$ requires C, 67.20; H, 7.20%.)

Methyl 4-methyl 5-oxo 5(3'bromo)phenyl pentanoate **1(g).** The crude product was distilled in order to remove the excess 3-bromo propiophenone (b.p. 102–104°/0.6 mm Hg). The residue was chromatographed on silica gel (Merck) (R = 1:70) using CCl_4/EtOAc 9/1 as eluant.The fractions containing **1(g)** were collected as a pale yellow viscous oil and distilled (b.p. 122–123°/0.4 mm Hg) to give 30 g of **1(g)** (yield 40%). **1(g)** was analyzed by GLC in the above specified conditions (ret. time: 3 min, 20 sec). NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.15 (0.90) d, J = 6.7 Hz, 3H; 3.55 (3.30) s, 3H; 7.0–8.1 m, 4H. MS *m/e*: 43(12), 50(16), 55(18), 75(21), 76(26), 77(10), 105(11), 155(28), 157(27), 184(100), 186(98), 298(7), 299(2), 300(7), 301(2). IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3035w, 2990m, 2980m, 2970sh, 2940w, 1735s, 1685s, 1585w, 1565s, 1460s, 1440s, 1420s, 1380m, 1330w, 1260sh, 1210s, 1180s, 1140w, 1120sh, 1080m, 1020w, 1000sh, 990m, 800m, 740s, 680sh, 675m. (Found: C, 52.05; H, 5.04.$C_{13}H_{15}O_3$ Br requires C, 52.17; H, 5.02%.)

Methyl 4-methyl 5-oxo 5(3' cyano)-phenyl pentanoate **1(h).** The crude product was submitted to a sublimation in order to remove the excess 3-cyano propiophenone (95–99°/0.4 mm Hg). The residue was chromatographed on silica gel (Merck) (R = 1:30) using petroleum ether 40–70°/diethyl ether 7/3 as eluant. The fractions containing **1(h)** were collected as a viscous oil and distilled (b.p. 150–152°/0.2 mm Hg) to give 27 g of **1(h)** (yield 44%). **1(h)** was analyzed by GLC in the above specified conditions (ret. time: 3 min, 41 sec.).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.20 (0.88) d, J = 6.7 Hz, 3H; 3.62 (3.36) s, 3H; 7.3–8.4 m 4H. MS *m/e*: 55(13), 73(19), 83(16), 102(26), 130(100), 159(15), 172(15), 186(18), 213(26), 214(12), 245(5), 246(1). IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3020w, 2980sh, 2950m, 2240m, 1735s, 1690s, 1600m, 1580w, 1480sh, 1465m, 1450m, 1440m, 1425sh, 1375m, 1365sh, 1315w, 1290w, 1260m, 1235sh, 1200w, 1175m, 1160sh, 1120w, 1090w, 1070w, 1015m, 1000sh, 995m, 915w, 900sh, 840w, 815m, 795w, 750m. (Found: C, 68.46; H, 6.19. $C_{14}H_{15}NO_3$ requires C, 68.57; H, 6.12%).

Purification of solvents. Performed as described.[6]

Grignard reagents preparation. Performed as described.[6] The obtained solutions were titrated[17] and diluted to 0.1 N just before reactions. MeLi in Et_2O (Merck) was employed as received, titrated[18] and diluted to 0.1 N just before reactions.

Alkylation reactions on **1(a)–1(h)**

A soln 0.1 N (2.5 mmol) of the alkylating reactant (in Et_2O, C_6H_6 or THF) was added to a rapidly stirred soln of 2.5 mmol of **1(a)–1(h)** dissolved in 25 ml of the selected solvent (anhydrous Et_2O, C_6H_6 or THF). The reaction was carried out in a dry and temperature controlled apparatus, under pure N_2. Reactions were interrupted after 40 min by adding a sat.ac. NH_4Cl and a weighed amount of GLC standard. The reaction mixtures were extracted with diethyl ether; the ethereal solns, washed with water, were combined, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was analyzed by GLC on SP 2250 to measure the total material balance, which was always in the range of 90–98%. Under our experimental conditions lactones **2(a)–2(h)** and **3(a)–3(h)** are the only products of the alkylation reactions on **1(a)–1(h)** respectively. Under all the GLC conditions employed on packed or capillary columns the lactonic fractions could not be resolved in two peaks. *Isolation of lactones* **2(c, g, h)** *and* **3(c, g, h)**. The crude reaction product on **1(c)** was chromatographed by HPLC on the described apparatus, using hexane/EtOAc 73/27 as eluant at φ = 5.0 ml/min. In order of elution we obtained as pure fractions: the residual portion of **1(c)**, 150 mg of *trans* **3(c)** and 160 mg of cis **2(c)**. The purity of **2(c)** and **3(c)** was tested by HPLC on analytical column. Ret. times at φ = 1.3 ml/min (hexane/EtOAc 73/27) 8 min, 9 sec for **3(c)** and 9 min, 21 sec for **2(c)**. For compound **2(c)**: b.p. 145°/3 mm Hg. MS *m/e*: 44(15), 55(51), 77(15), 107(12), 135(77), 150(100), 151(19), 234(22), 235(4). IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 3050w, 3020w, 2970m, 2940m, 2890sh, 2850w, 1730s, 1610sh, 1605m, 1585m, 1490m, 1465sh, 1455m, 1430m, 1380w, 1345w, 1325w, 1290sh, 1275sh, 1260s, 1245sh, 1220sh, 1180w, 1165m, 1125sh, 1105m, 1065sh, 1040s, 1010w, 975m, 870w, 785m, 760w, 705m. (Found: C, 71.65; H, 7.57. $C_{14}H_{18}O_3$ requires C, 71.79; H, 7.69%.)

For compound **3(c)**: b.p. 145°/3 mm Hg. MS *m/e*: 44(16), 55(50), 77(12), 107(23), 135(93), 150(100), 151(20), 234(21), 235(4). IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 3050w, 3020w, 2990sh, 2960sh, 2940m, 2890sh, 2850w, 1730s, 1610sh, 1605m, 1585m, 1490m, 1465sh, 1455m, 1430m, 1390w, 1380w, 1350w, 1330w, 1295sh, 1270sh, 1245sh, 1205w, 1175w, 1120sh, 1110w, 1080w, 1065w, 1045s, 1010w, 1000sh, 975w, 965sh, 880w, 790m, 765w, 705m. (Found: C, 71.72; H, 7.63. $C_{14}H_{18}O_3$ requires C, 71.79; H, 7.69%.)

The crude reaction product on **1(g)** was chromatographed by HPLC on the described apparatus using hexane/EtOAc 77/23 as eluant at φ = 7.0 ml/min. We obtained as pure fractions, in order of elution, the residual portion of **1(g)**, 130 mg of *trans* **3(g)** and 160 mg of cis **2(g)**. The purity of **2(g)** and **3(g)** was tested by HPLC on analytical column. Ret. times at φ = 2.3 ml/min (hexane/EtOAc 77/23) 4 min, 36 sec for **3(g)** and 5 min, 24 sec for **2(g)**. For compound **2(g)**: b.p. 170°/3 mm Hg. MS *m/e*: 43(30), 55(15), 56(91), 75(11), 76(12), 77(13), 84(100), 155(12), 157(12), 183(43), 185(42), 198(14), 199(12), 200(10), 201(10), 239(12), 241(12), 267(13), 269(13), 282(26), 283(4), 284(26), 285(4). IR spectra showed ν_{max}^{film} cm^{-1}: 3060w, 3020w, 2980s, 2940sh, 2920sh, 2890sh, 1735s, 1600m, 1575sh, 1570m, 1560sh, 1480m, 1465m, 1450sh, 1420m, 1385m, 1345m, 1330m, 1280sh, 1250s, 1230sh, 1210sh, 1160s, 1125w, 1115m, 1105w, 1095w, 1075s, 1065sh, 1040m, 1015w, 1000w, 980s, 890w, 880sh, 820sh, 790s, 760w, 720sh, 700s. (Found: C, 55.20; H, 5.34. $C_{13}H_{15}O_2Br$ requires C, 55.12; H, 5.30%.) For compound **3(g)**: b.p. 165°/3 mm Hg. MS *m/e*: 43(30), 55(14), 56(90), 75(11), 76(12), 77(13), 84(100), 155(18), 157(18), 183(58), 185(59), 198(14), 199(13), 200(11), 201(10), 239(14), 241(14), 267(14), 269(14), 282(22), 283(4), 284(23), 285(4). IR spectra showed ν_{max}^{film} cm^{-1}: 3060w, 3020w, 2980sh, 2970m, 2940m, 2880w, 1735s, 1595m, 1575sh, 1570m, 1565sh, 1480m, 1460m, 1420m, 1390w, 1380w, 1365w, 1350w, 1330m, 1305w, 1275sh, 1265s, 1235s, 1210w, 1175m, 1110s, 1095w, 1075s, 1065s, 1040m, 1010s, 1000sh, 975m, 970sh, 955sh, 910w, 885w, 815w, 790s, 750w, 720sh, 705s.

(Found: C, 55.08; H, 5.22. $C_{13}H_{15}O_2Br$ requires C, 55.12; H, 5.30%.)

The crude reaction product on **1(h)** was chromatographed by HPLC on the described apparatus, using hexane/EtOAc 63/37 as eluant at φ = 6.0 ml/min. We obtained as pure fractions, in order of elution, the residual portion of **1(h)**, 140 mg of *trans* **3(h)** and 170 mg of cis **2(h)**. The purity of **2(h)** and **3(h)** was tested by GLC on analytical column. Ret. times at φ = 1.7 ml/min (hexane/EtOAc 63/37) 6 min, 36 sec for **3(h)** and 7 min, 24 sec for **2(h)**. For compound **2(h)**: b.p. 155°/3 mm Hg. MS *m/e*: 43(20), 55(21), 56(100), 84(61), 102(15), 130(50), 146(16), 159(18), 186(15), 201(25), 214(5), 229(9), 230(2). IR spectra showed ν_{max}^{Nujol} cm^{-1}: 3060w, 2240s, 1715s, 1600w, 1580w, 1330m, 1315m, 1280s, 1265s, 1235s, 1205w, 1190s, 1150m, 1130m, 1115s, 1100s, 1060s, 1040s, 1020sh, 1000w, 980s, 970sh, 950w, 935w, 925w, 910w, 895s, 850m, 800s, 760m, 725w, 705sh, 695m. (Found: C, 73.42; C, 73.42; H, 6.62. $C_{14}H_{15}NO_2$ requires C, 73.36; H, 6.55%.) For compound **3(h)**: b.p. 165°/3 mm Hg. MS *m/e*: 43(21), 55(20), 56(100), 84(60), 102(25), 130(59), 146(15), 159(18), 186(15), 201(24), 214(4), 229(9), 230(2). IR spectra showed ν_{max}^{Nujol} cm^{-1}: 3060w, 2240s, 1720s, 1600w, 1580w, 1330m, 1310w, 1270s, 1240s, 1210w, 1190w, 1165m, 1125sh, 1110s, 1090w, 1065m, 1040s, 1020s, 970s, 910m, 830w, 800s, 760w, 715m, 695m. (Found: C, 73.31; H, 6.50. $C_{14}H_{15}NO_2$ requires C, 73.36; H, 6.55%.)

Acknowledgements—The authors are indebted to Messrs S. Lociuro, P. Tagliatesta and S. Valia for technical assistance and to the Consiglio Nazionale delle Ricerche (C.N.R.) for financial support.

REFERENCES

[1]S. Lociuro, E. Vecchi, E. Zeuli and M. Delfini, *Tetrahedron* **38**, 3339 (1982). Part I of this work.
[2]E. Cooke, T. C. Paradellis and J. T. Edward, *Can. J. Chem.* **60**, 29 (1982).
[3]S. Axiotis, J. Dreux, M. Perrin and J. Royer, *Tetrahedron* **38**, 499 (1982).
[4]N. L. Allinger, *Pure & Appl. Chem.* **54**, 2515 (1982).
[5]G. Di Maio, M. T. Pellegrini and P. A. Tardella, *Ric. Sci.* **38**, 234 (1968).
[6]A. Colantoni, G. Di Maio, E. Vecchi, E. Zeuli and C. Quagliata, *Tetrahedron* **34**, 357 (1978).
[7]F. W. Wherli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra*, Chap. 2, p. 47. Heyden, London (1976).
[8a]H. Pyysalo, J. Enquist, E. Honkanen and A. Pippuri, *Finn. Chem. Lett.* 129 (1975); [b]H. Pyysalo and J. Enquist, *Ibid.* 136 (1975).
[9]G. Di Maio, E. Vecchi and E. Zeuli, *Tetrahedron Letters* **23**, 5211 (1982).
[10]C. Cianetti, G. Di Maio, V. Pignatelli, P. Tagliatesta; E. Vecchi and E. Zeuli, *Tetrahedron* **39**, 657 (1983).

[11]R. Bertocchio and J. Dreux, *Bull. Soc. Chim. Fr.* **7**, 823 (1962).
[12]W. S. Johnson, C. A. Erickson and J. Ackerman, *J. Am. Chem. Soc.* **74**, 2251 (1952).
[13]P. Pratesi, E. Grana and L. Villa, *Il Farmaco Ed. Sci.* **28**, 753 (1973).
[14]W. H. Hartung, J. C. Munch, E. Miller and F. Crossley, *J. Am. Chem. Soc.* **53**, 4149 (1931).
[15]B. L. Zenits and W. H. Hartung, *J. Org. Chem.* **11**, 444 (1946).
[16]D. E. Pearson, H. W. Pope, W. W. Hagrove, *Organic Synthesis Collective*, Vol. V, p. 117. Wiley, New York (1973).
[17]T. Zerewitinoff, *Ber. Dtsch. Chem. Ges.* **40**, 2023 (1907). *Ibid.* **47**, 1959 (1914).
[18]H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.* **66**, 1515 (1944).