Solvent and Ion-pair Effects on the Self-condensation of Linear Aliphatic Aldehydes: Selective Synthesis of Substituted Acrylaldehydes and Glycol Monoesters[1]

By **Giuseppe Casnati, Andrea Pochini,*** **Giuseppe Salerno,** and **Rocco Ungaro,** Istituto di Chimica Organica dell'Università, Via M. D'Azeglio 85, 43100 Parma, Italy

Self-condensation of linear aliphatic aldehydes (1) in the presence of magnesium phenolates as catalysts has been studied. These reactions are shown to be strongly dependent on the solvent, the reagent: catalyst ratio, and the cation and anion constituting the ion-pair. Conditions for selective synthesis of 1,3-diol monoesters (2) and (3) and 2,3-dialkylacrylaldehydes (4) are given. The reaction mechanism is discussed.

ALKALI metal, magnesium, and aluminum alkoxides have been extensively used as catalysts for self-condensation reactions of aldehydes and ketones;[2] alkali metal phenolates have seldom been used.[2,3] The magnesium halide derivatives of alcohols and primary and secondary amines show good condensing properties with carboxy-compounds,[4,5] whereas phenoxymagnesium halides have been reported to show poor reactivity towards linear aliphatic aldehydes in diethyl ether.[4]

Recently, we have shown[6] that several electrophilic systems react with the aromatic nucleus of aryloxymagnesium bromides in benzene, affording selective *ortho*-alkylation products in high yields.

In order to obtain selective reactions with enolizable systems also, by employing highly co-ordinating cations, we have investigated the self-condensation of linear aliphatic aldehydes[1] with magnesium phenolates as metallating agents. In particular, by using two markedly different solvents [benzene and hexamethylphosphoric triamide (HMPT)] we have obtained evidence of the important role played by the cation and the anion of the ion-pair in directing the course of the reaction.

RESULTS

In order to avoid electrophilic attack by the carbonyl group on the aromatic nucleus of phenol itself, which occurs in benzene,[7] and in order to compare results in the two solvents, 2,4,6-trimethylphenoxymagnesium bromide was used as catalyst in most of the reactions.

Reactions in HMPT.—In HMPT, characterized by highly specific cationic co-ordinating power, a mixture of 1,3-diol monoesters (2) and (3) was obtained in high yield. The presence of two isomers was established on the basis of

---

[1] Preliminary communication, G. Casnati, A. Pochini, G. Salerno, and R. Ungaro, *Tetrahedron Letters*, 1974, 959.

[2] A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, 1968, **16**, 72.

[3] Z. Arnold and K. Hejno, Czech. P. 85–207 (*Chem. Abs.*, 1956, **50**, 10,781a).

[4] V. Grignard and M. Fluchaire, *Ann. Chim. (France)*, 1928, **9**, 1.

[5] V. Grignard and J. Colonge, *Compt. rend.*, 1932, **194**, 929; J. Colonge, *ibid.*, 1933, **196**, 1414; A. T. Nielsen, C. Gibbons, and C. Zimmermann, *J. Amer. Chem. Soc.*, 1951, **73**, 4696.

[6] G. Casiraghi, G. Casnati, M. Cornia, G. Sartori, and R. Ungaro, *J.C.S. Perkin I*, 1974, 2077; G. Casiraghi, G. Casnati, and G. Salerno, *J. Chem. Soc. (C)*, 1971, 2546; G. Casiraghi, G. Casnati, and M. Cornia, *Tetrahedron Letters*, 1973, 679.

[7] G. Casiraghi, G. Casnati, and R. Ungaro, unpublished data.

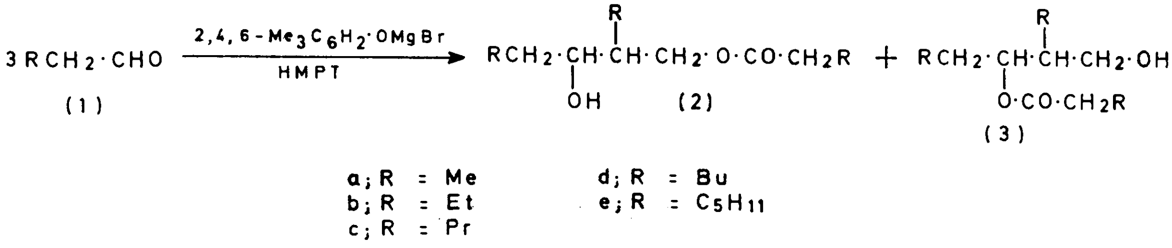
n.m.r. spectra and g.l.c. analysis on polar columns (neopentyl glycol succinate, dinonyl phthalate, diethylene glycol succinate). Nevertheless they could not be separated by distillation. In order to identify the products, a more complete analysis was performed on the reaction mixture derived from butanal [compounds (2b) and (3b)]. Basic hydrolysis was carried out, and by extraction of the alkaline solution with ether, 2-ethylhexane-1,3-diol was obtained and identified by n.m.r. and i.r. spectroscopy and comparison with an authentic sample obtained by reduction of 2-ethyl-3-hydroxyhexanal. By extraction of the acidified solution with ether, only butyric acid was obtained. 2-Ethyl-3-hydroxyhexyl butyrate (2b) and 2-hydroxymethyl-1-propylbutyl butyrate (3b) were synthesized independently and their i.r. and n.m.r. spectra compared. The i.r. spectra of compounds (2b) and (3b) were identical, except between 1 100 and 1 000 cm^{-1}; a band at 1 085 cm^{-1} (CH·OH) for (2b) and a band at 1 030 cm^{-1} (CH_2·OH) for (3b) could be distinguished. The n.m.r. spectra were identical from δ 0.8 to 3, whereas substantial differences were observed in the δ 3—5 region: (2b) showed a 1 H multiplet centred at δ 3.6 (RC*H*OH·CH_3) and a 2 H multiplet at δ 4.2 (CH·C*H*$_2$·O·CO); (3b) showed a 2 H multiplet at δ 3.6 (CH·C*H*$_2$·OH) and 1 H multiplet at δ 5.0 (CH_2·C*H*R·O·COR). All these signals were present in the spectrum of the product obtained from butanal. The relative amounts of (2b) and (3b) (2 : 1), determined from the ratio between the signals at δ 4.2 and 5.0,[8] were in good agreement with that calculated from g.l.c. results on polar columns.

TABLE 1

Reactions of linear aliphatic aldehydes in the presence of 2,4,6-$Me_3C_6H_2$·OMgBr in HMPT; [a] aldehyde : ion-pair ratio 1 : 1

Substrate	Conversion (%) [b]	Product yield (%) [b,c] [(2) + (3)]
(1a)	95	94
(1b)	90	95
(1c)	95	92
(1d)	95	90
(1e)	95	96

[a] At 0 °C for 24 h. [b] By g.l.c. [c] Difference from 100 is represented by unidentified by-products. In all cases condensation products (4) are absent.



SCHEME 1

In all cases, the 1,3-diol monoesters (2) and (3) were almost the sole products; simple esters and polycondensation products, usually present in products of reactions with other catalysts,[9] were absent.

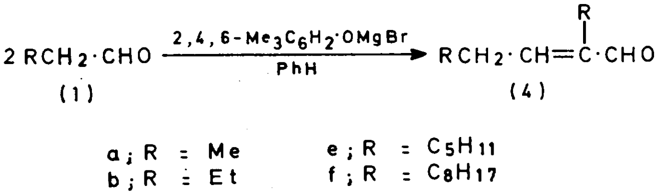
TABLE 2

Reaction of linear aliphatic aldehydes in the presence of 2,4,6-$Me_3C_6H_2$·OMgBr in benzene with aldehyde : ion-pair molar ratio 1 : 1

Substrate	Reaction conditions T/°C	Time (h)	Conversion (%) [a]	Product (4) yield (%) [a,b]
(1a)	0	24	80	95
(1a)	80	2	100	93
(1b)	0	24	70	94
(1b)	80	0.5	98	90
(1e)	0	24	80	96
(1e)	80	3	80	90
(1f)	80	2	100	95

[a] By g.l.c. [b] Difference from 100 is represented by unidentified by-products. In all cases trimerisation products [(2) and (3)] are absent.

Reactions in Benzene.—A different but equally selective reaction was observed when benzene was used as solvent. In this case, simple self-condensation products (4) were obtained in high yield. This process seems to be general for both low and high molecular weight aldehydes; for the latter, the difficulty of obtaining self-condensation products in high yield has recently been stressed.[10] Also significant is the absence of polycondensation [11] products and products of types (2) and (3).[10]



SCHEME 2

TABLE 3

Reactions of butanal in the presence of 2,4,6-$Me_3C_6H_2$·OMgBr in benzene with various ion-pair : aldehyde molar ratios at 40 °C

Ion-pair: aldehyde molar ratio	Reaction time (h)	Conversion (%) [a]	Product yield (%) [a,b] (4)	(2) + (3)
1 : 1	3	98	90	0
1 : 2	3	95	85	5
1 : 5	3	85	24	67
1 : 10	24	95	16	78
1 : 20	24	85	8	84

[a] Difference from 100 is represented by unidentified by-products. [b] By g.l.c.

---

[8] *Cf.* H. F. White, C. W. Davisson, and V. A. Yarborough, *Analyt. Chem.*, 1964, **36**, 1959.

[9] M. S. Kulpinsky and F. F. Nord, *J. Org. Chem.*, 1943, **8**, 256; M. Häusermann, *Helv. Chim. Acta*, 1951, **34**, 2172; G. Hesse and M. Maurer, *Annalen*, 1962, **658**, 21.

[10] M. Cossu-Jouve, M. C. Savon, and E. Ucciani, *Bull. Soc. chim. France*, 1973, 2429, and references therein.

[11] Ref. 2, p. 61.

TABLE 4

Reactions of butanal in the presence of 2,4,6-trimethylphenol salts in benzene at 40 °C [a]

Cation	Reaction time (h)	Conversion (%) [b]	Product yield (%) [b] (4)	(2) + (3)	Others
$MgBr^+$	3	98	90	0	10
Mg^{2+}	1	100	19	63	18
Li^+	2	92	11	45	44
Na^+	2	100	18	20	62 [c]

[a] Ion-pair : aldehyde molar ratio 1 : 1. [b] By g.l.c. [c] Butyric acid and butanol were qualitatively identified in the reaction mixture.

TABLE 5

Reaction of butanal in the presence of various magnesium phenolates in benzene at 40 °C

Catalyst	Ion-pair: aldehyde molar ratio	Re-action time (h)	Con-version (%) [a]	Product yield (%) [a,b] (4)	(2) + (3)
$(PhO)_2Mg$	1 : 1	4	80	85	6
$(PhO)_2Mg$	1 : 20	24	45	51	33
$(2,4,6\text{-}Me_3C_6H_2O)_2Mg$	1 : 1	1	100	19	63
$(2,4,6\text{-}Me_3C_6H_2O)_2Mg$	1 : 20	1	100	10	84
$(2,6\text{-}Bu^t{}_2C_6H_3O)_2Mg$	1 : 1	6	80	70	12
$(2,6\text{-}Bu^t{}_2C_6H_3O)_2Mg$	1 : 20	32	10	Trace	Trace

[a] By g.l.c. [b] Difference from 100 is represented by unidentified products.

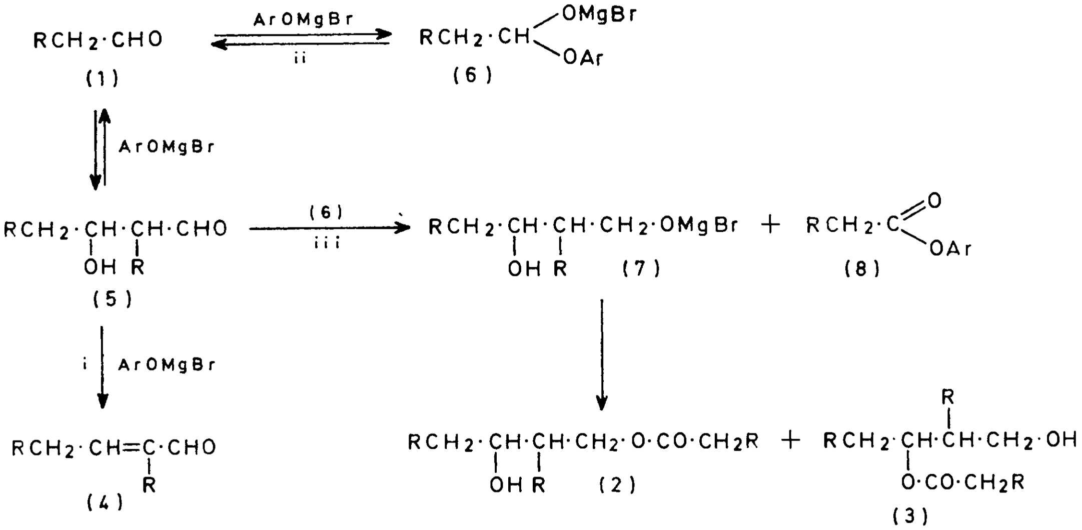
The reaction course in benzene is strongly influenced by the ion-pair : aldehyde ratio. The results for butanal are given in Table 3. An inverted product distribution is observed on going from an aldehyde : ion-pair ratio of 1 : 1 to a ratio of 20 : 1, although the selectivity of the reaction is maintained.

The reaction in benzene is greatly affected by the nature of the cation in the ion-pair. The results are summarized in Table 4.

Analogously, different reactivity and product distribution are also observed when the nature of the anion is varied (see Table 5). Data refer in this case to reactions with symmetric magnesium salts where the aromatic portion is almost inert towards the aldehyde.[7]

DISCUSSION

On the basis of the results obtained, some hypotheses may be advanced regarding the mechanism of these processes, which are still unclear especially as far as 1,3-diol monoester formation is concerned. A common initial pathway leading to the aldol (5) can be suggested for the reactions in both benzene and HMPT (see Scheme 3). The aldolisation reaction is favoured in both solvents, although the relative importance of the anion and the cation in producing the aldol (5) can be different.[12] Once formed, the intermediate (5) follows different pathways according to the reaction conditions. In benzene with an ion-pair–aldehyde molar ratio of 1 : 1, the dehydration process (path i) leading to the product (4) is favoured because of the highly acidic character of the cationic counterion ($MgBr^+$). In contrast, in HMPT the acidic character of the cation is strongly depressed by specific co-ordination of the solvent and a type (ii) equilibrium is brought about because of the enhanced nucleophilicity of the phenolate anion (see Scheme 3). At this point a Tischenko-type reaction occurs between the aldol (5), which acts as acceptor of hydride ion, and the aldehyde which, through its ' hemiacetal ' (6), behaves as a hydride donor (path iii).



SCHEME 3

Finally, the products (2) and (3) arise from a trans-esterification process between the glycol (7) and the ester (8). This last step has been verified by a simulation experiment.

The suggested mechanism may also explain the results obtained in benzene when a greater aldehyde : ion-pair ratio is used: in this case, favouring a greater co-ordination of the aldehyde to the cation, the yield of products (2) and (3) increases over (4).

In both solvents and in the presence of 2,4,6-trimethylphenoxymagnesium bromide, simple esters ($RCH_2{\cdot}O{\cdot}CO{\cdot}CH_2R$), which are frequently formed as by-products in similar processes,[2,9] according to a

[12] E. Dubois and M. Dubois, *Chem. Comm.*, 1968, 1567; J. E. Dubois and F. F. Fort, *Tetrahedron*, 1972, **28**, 1653.

Tischenko-type reaction (two moles of aldehyde), are not observed.

The high selectivity of the hydride shift reaction of the aldol (5) is still not understood. No data are available concerning the oxidation potential of carbonyl compounds in solvents of high donor capacity, which could support the greater tendency towards reduction exhibited by β-hydroxy-aldehydes (aldols) in comparison with linear aldehydes. The selectivity may be explained if we consider that the O–Mg bond in the 'hemiacetal' (6) is only weakly ionized and consequently the hydride donor power of the intermediate is reduced.

An important role is played by magnesium (both $MgBr^+$ and Mg^{2+}) in the reactions in benzene with an ion-pair : aldehyde molar ratio of 1 : 1. This highly co-ordinating cation may stabilize the aldol (5) by chelation, as has been recently reported.[13] In contrast, with less highly co-ordinating cations like lithium and sodium, stabilization of the intermediate cannot be achieved and the reaction course becomes uncontrolled.

The low reactivity of 2,6-di-t-butylphenoxymagnesium(2+) (Table 5) may be due to steric hindrance to the formation of the 'hemiacetal' (6), but this simple explanation cannot be used to justify the difference in product distribution observed between reactions of the same salt of the phenol and its 2,4,6-trimethyl derivative. These differences and those observed with symmetric (Mg^{2+}) and asymmetric ($MgBr^+$) magnesium salts of the same anion (Table 4) are evidence of the remarkable dependence of these reactions both on the acidic and on the basic character of the catalysts which, in turn, seem to be strongly dependent on the structure of the ion pair.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord 137 instrument for liquid films. N.m.r. spectra were recorded on a JEOL C-60-HL instrument for solutions in [^{2}H]chloroform with tetramethylsilane as internal standard. Mass spectra were obtained with a Hitachi–Perkin-Elmer RMW-6-D instrument at 70 eV. G.l.c. was performed on a Varian 2700 Aerograph with a flame ionization detector and 150 cm × 1/8 in stainless steel columns packed with various liquid phases on 60—80 silanized Chromosorb W. Quantitative determinations were made isothermally by the internal standard method, and peak areas were calculated by use of a digital Hewlett–Packard 3373 B integrator. Kieselgel 60 (70—230 mesh) (Merck) was used for column chromatography. T.l.c. was performed on Merck HF_{254} silica gel. All the reactions involving aldehydes were carried out under nitrogen. Commercial HMPT was distilled under reduced pressure in a nitrogen atmosphere over $LiAlH_4$ and stored under nitrogen.

Reactions in HMPT. General Procedure.—2,4,6-Trimethylphenoxymagnesium bromide (0.02 mol) was prepared in anhydrous diethyl ether from ethylmagnesium bromide and 2,4,6-trimethylphenol. The ether was distilled off gradually and replaced by HMPT (70 ml). The solution was heated at 90 °C for 30 min to remove the remaining ether, then cooled at 0—5 °C in an ice-bath. The aldehyde (0.02 mol) dissolved in HMPT (30 ml) was added dropwise and the mixture was stirred at this temperature for 24 h. It was then treated with saturated aqueous ammonium chloride and extracted with diethyl ether; the extracts were submitted to g.l.c. analysis. Quantitative analysis of the 1,3-diol monoester [(2) + (3)] mixture was performed on a 5% SE 30 column. The ethereal extracts were washed several times with 1N-potassium hydroxide to remove the phenol, then with water, and finally dried (Na_2SO_4). The mixture of 1,3-diol monoesters was isolated by vacuum distillation. Analytical and physical data are reported in Table 6. I.r. and n.m.r. spectra * of compounds (2) and (3) were essentially identical with those of the products derived from butanal, discussed earlier. In all cases the ratio of (2) to (3) was *ca.* 2 : 1 (from n.m.r. spectra). In the mass spectra the molecular ion was absent; the most intense peaks in all cases were $RCH_2{\cdot}CO^+$ (base peak) and $RCH_2{\cdot}C(OH)_2{}^+$.

TABLE 6

Physical and analytical data of 1,3-diol monoesters

Compounds (2) + (3)	B.p. (°C) (mmHg)	Found (%)		Formula	Required (%)	
		C	H		C	H
(2a) + (3a)	70—71 [1]	61.7	10.5	$C_9H_8O_3$	62.0	10.4
(2b) + (3b)	71—72 [0.03]	66.8	11.1	$C_{12}H_{24}O_3$	66.6	11.2
(2c) + (3c)	128—129 [1.2]	70.0	11.6	$C_{15}H_{30}O_3$	69.6	11.7
(2d) + (3d)	115—116 [0.15]	71.7	12.2	$C_{18}H_{36}O_3$	71.9	12.1
(2e) + (3e)	139—140 [0.01]	73.9	12.3	$C_{21}H_{42}O_3$	73.6	12.4

Reactions in Benzene. General Procedure.—2,4,6-Trimethylphenoxymagnesium bromide (0.02 mol) was prepared in anhydrous diethyl ether; the solvent was then distilled off and replaced by anhydrous benzene. After cooling, a solution of the aldehyde (0.02—0.4 mol) in benzene was added dropwise with stirring (total volume of solution 100 ml). At the end of the reaction (for the condition see Tables 2 and 3) the mixture was treated with saturated aqueous ammonium chloride and extracted with diethyl ether. The combined extracts were dried (Na_2SO_4) and analysed by g.l.c. The following columns were used for 2,3-disubstituted acrylaldehydes: Carbowax 20 M (10%) + Apiezon L (5%) [70 °C for (4a) and 130 °C for (4b)]; diethylene glycol succinate (10%) [150 °C for (4e)]; Carbowax 20 M (5%) [195 °C for (4f)]. All these products showed i.r., n.m.r., and mass spectra identical with those of authentic specimens otherwise synthesized [2] and consistent with data reported.[10]

Reactions of Butanal with Aryloxy-sodium, -lithium, and -magnesium Salts.—Sodium and symmetric (Mg^{2+}) magnesium phenolates were prepared according to known methods.[14] The lithium salt was prepared by adding equimolecular amounts of butyl-lithium in hexane to an ethereal solution of the phenol; the solvent was evaporated off and the salt dried under vacuum. All operations involving the preparation and use of these salts were performed in an inert atmosphere.

---

* N.m.r. data for the mixtures are available as Supplementary Publication No. SUP 21395 (3 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[13] H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, 1973, **95**, 3310.

[14] M. F. Berny and R. Perrin, *Bull. Soc. chim. France*, 1967, 1013; M. F. Berny and M. O. Berrest, *ibid.*, 1968, 4709.

The salts (0.02 mol) were suspended in benzene and the aldehyde was added dropwise; the final volume was adjusted to 100 ml with benzene. The mixture was stirred at 40 °C (for reaction times see Table 4) then worked up as described in the general procedure for $MgBr^+$ salts.

2-*Ethyl*-3-*hydroxyhexyl Butyrate* (2b).—2-Ethylhexane-1,3-diol was prepared by reduction of 2-ethyl-3-hydroxyhexanal [15] with sodium borohydride in ethanol. Butyroyl chloride (0.05 mol) was added slowly to a solution of the diol (0.05 mol) and dry pyridine (0.05 mol) in anhydrous benzene (20 ml) at room temperature with stirring. After 10 min, pyridine hydrochloride was filtered off. The solution was washed with water and the solvent removed under vacuum to give a crude *product* (90%), which on g.l.c. [neopentyl glycol succinate (5%); 100 °C] showed a single peak. It was further purified by column chromatography (hexane–ethyl acetate, 8 : 2) (Found: C, 66.4; H, 11.1. $C_{12}H_{24}O_3$ requires C, 66.6; H, 11.2%); $\nu_{max.}$ 3 450, 1 735, 1 180, and 1 085 cm^{-1}.

2-*Hydroxymethyl*-1-*propylbutyl Butyrate* (3b).—2-Formyl-1-propylbutyl butyrate (b.p. 73—74° at 2 mmHg; $\nu_{max.}$ 1 720 and 1 180 cm^{-1}) was first prepared by esterification of 2-ethyl-3-hydroxyhexanal with butyroyl chloride and dry pyridine according to the procedure described above. This product (1.5 g) dissolved in ethanol (10 ml) was hydrogenated (5 atm) over platinum oxide for 24 h at room temperature. After filtration and evaporation, the crude *product* was purified by column chromatography (hexane–ethyl acetate, 7 : 3) (Found: C, 66.8; H, 11.2. $C_{12}H_{24}O_3$ requires C, 66.6; H, 11.2%); $\nu_{max.}$ 3 450, 1 735, 1 180, and 1 030 cm^{-1}. A good g.l.c. separation of compounds (2b) and (3b) was achieved by using dinonyl phthalate (5%) at 110 °C or neopentyl glycol succinate (5%) at 100 °C.

Transesterification Experiment.—2-Ethylhexane-1,3-diol (5 mmol) in anhydrous diethyl ether was added dropwise to a solution of ethylmagnesium bromide (5 mmol) in the same solvent. The ether was then removed and replaced by HMPT (50 ml) as described previously. 2,4,6-Trimethylphenyl butyrate (5 mmol) was then added and the mixture stirred at room temperature for 24 h, then treated with saturated aqueous ammonium chloride and extracted with diethyl ether. Qualitative g.l.c. analysis of the extracts showed that the main components of the product were 2,4,6-trimethylphenol and a mixture of monoesters (2b) and (3b), together with small amounts of starting materials.

This work was partially supported by a C.N.R. grant.

[4/2457 *Received*, *25th November*, *1974*]

---

[15] R. H. Saunders, M. J. Murray, F. F. Cleveland, and V. I. Komarewsky, *J. Amer. Chem. Soc.*, 1943, **65**, 1309.