A New Approach to Aromatic Substitution—*para*-Specific Alkylation of Acetophenone by Alkyl Radicals in Strongly Acidic Media

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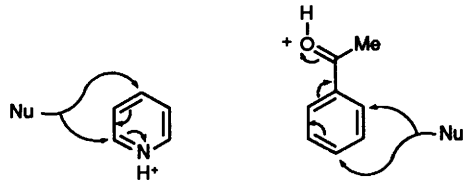
Acetophenone in 25% oleum is substituted by various alkyl radicals specifically in the *para*-position. The radicals used include cyclohexyl, 3-chloro-1-methylpropyl, 3-bromo-1-methylpropyl, 4-chloro-1-methylbutyl, 4-bromo-1-methylbutyl, 5-bromo-1-methylpentyl, 5-acetoxy-1-methylpentyl, 3-carboxy-1-methylpropyl, 4-carboxy-1-methylbutyl and 5-carboxy-1-methylpentyl. They were all generated by hydrogen atom abstraction at the radical position by dimethylaminium radicals, generated in turn from protonated dimethylchloramine and ferrous sulphate. Yields were generally poor to moderate but utilised simple conditions and cheap reagents.

Homolytic aromatic substitution is characterised by its lack of specificity.[1] However, the work of Minisci[2] has demonstrated that protonated π-deficient heteroaromatics such as pyridine undergo regiospecific α- and γ-substitution by nucleophilic alkyl and acyl radicals. If this mode of substitution were adaptable to the homoaromatic series it would considerably enhance synthetic approaches to specifically substituted compounds. In this paper we wish to establish this important principle by demonstrating that acetophenone in concentrated sulphuric acid undergoes unique *para*-substitution by alkyl radicals.[3]

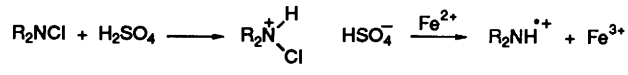
The analogy between protonated pyridine and protonated acetophenone is shown in Scheme 1. It underlines the important



Scheme 1

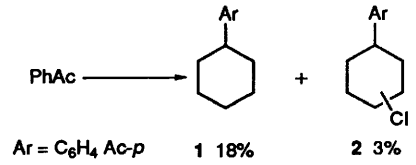
principle that a heteroatom within a ring or outside the ring (but conjugated to the ring) both have the same directing effect towards nucleophiles. This effect is dramatically enhanced by protonation at the heteroatom, and allows for the ready alkylation and acylation of protonated pyridines by alkyl and acyl radicals which are known to be nucleophilic in character.[2] Using acetophenone as a test case two key requirements need to be met: (i) Efficient protonation of the heteroatom is necessary, (ii) A means of generating free radicals in a strongly acidic medium needs identifying.

The first problem was readily overcome by use of 25% oleum in which acetophenone is soluble and efficiently protonated but otherwise unchanged. 65% Oleum proved ineffective. Also any water introduced by radical generation is chemically absorbed by generation of sulphuric acid. The second problem is less trivial. However one well established free radical process that proceeds well under such strongly acidic conditions is involved in the Hofmann–Loeffler–Freytag reaction, a key step of which is the generation of aminium radicals by protonation of weakly basic chloroamines and their one-electron reduction with



Scheme 2

ferrous ions[4] (Scheme 2). Using these strongly electrophilic radicals in the presence of suitable substrates from which hydrogen atom abstraction would yield nucleophilic radicals, we have made a preliminary study of the radical substitution of protonated acetophenone. We found that dimethylchloroamine was the best chloroamine to use, having better shelf-life and giving better yields than, for example, its diisopropyl analogue or *N*-chloromorpholine.



Scheme 3 *Reagents:* oleum, Me_2NCl, $FeSO_4$, C-C_6H_{12}, AcOH

Cyclohexylation of Acetophenone.—A mixture of oleum, acetic acid, acetophenone, cyclohexane and finely powdered ferrous sulphate maintained in the range 0–15 °C was treated dropwise with dimethylchloramine in oleum followed by a further 2 h of stirring in an ice-bath. Work-up gave unchanged acetophenone (58%), and *p*-cyclohexylacetophenone **1**, (8% based on acetophenone utilised and 18% on consumed acetophenone) as well as a small amount of a 4-(chlorocyclohexyl)-acetophenone **2** (3%) (Scheme 3). No other products were found and in particular no *ortho*- or *meta*-isomers could be detected. The chlorocyclohexyl derivative **2** is obviously formed either by further radical substitution of the initially formed product **1** or by formation of chlorocyclohexane which reacts competitively.‡ This reaction, using equimolar amounts of all the reagents except for the acids, is clearly unoptimised but demonstrates the highly specific potential of radical substitution of homoaromatic systems. The lack of any *ortho*-substitution is probably due to the very bulky solvation sphere around the protonated centre. Surprisingly, use of 2 or 4 mol equiv. of dimethylchloramine per mol equiv. of acetophenone did not improve the product yields.

In our endeavour to examine the stability of acetophenone to the reaction conditions, we noted the formation of phenacyl chloride in the absence of the cyclohexane, no doubt by an ionic pathway (Scheme 4).

We have noticed that phenacyl chloride was only formed in the presence of a potential nucleophilic radical source, when no

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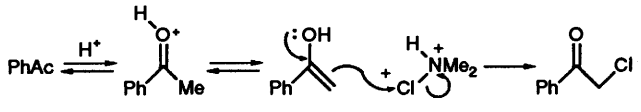
‡ Alkanes are known to be chlorinated with chloroamines and ferrous ions.[4,5]

Table 1 Alkylation of acetophenone in 25% oleum using dimethylchloramine, ferrous sulphate and an aliphatic substrate

Reagents (mol ratio)				PhAc Conversion	Product(s)			
PhAc	Me_2NCl	Substrate	T/°C	(%)		X	n	Yield (%)[a]
1	1	c-C_6H_{12}	0–15	42	**1**	—	—	18(8)
					2	—	—	3(1)
1	2	c-C_6H_{12}	0–15	75	**1**	—	—	19(14)
					2	—	—	1(0.75)
1	4	c-C_6H_{12}	0–15	82	**1**	—	—	20(16)
					2	—	—	6(5)
1	4	BuCl	0–15	42	**2**	Cl	2	12(5)
1	1	BuBr	0–15	8	**3**	Br	2	23(2)
1	4	BuBr	0–15	17	**3**	Br	2	17(3)
1	1	$C_5H_{11}Cl$	0–15	31	**3**	Cl	3	11(3)
1	1	$C_5H_{11}Br$	0–15	15	**3**	Br	3	44(7)
1	1	$C_6H_{13}Br$	0–15	17	**3**	Br	4	53(9)
1	1	$C_5H_{11}OAc$	0–15	37	**3**	OAc	3	16(6)
1	1	$C_4H_9CO_2H$	35–40	30	**3**	CO_2H	2	17(5)
1	1	$C_5H_{11}CO_2H$	0–15	38	**3**	CO_2H	3	43(16)
1	1	$C_5H_{11}CO_2H$	35–40	35	**3**	CO_2H	3	52(18)
1	1	$C_5H_{11}CO_2H$	45–50	23	**3**	CO_2H	3	58(13)

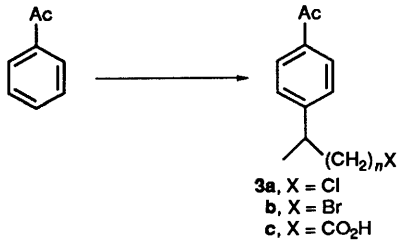
[a] Yields refer to isolated material; the first figure is based on consumed acetophenone, the second, in brackets, to utilised acetophenone.



Scheme 4

para-substitution of acetophenone was observed. Furthermore the aminium radical cation is very selective in its choice of hydrogen abstraction, always preferring to abstract remotely (at least δ) from a heteroatom and at a non-terminal position. The preference for abstraction at the penultimate carbon of straight-chain hydrocarbons by radicals is well known and especially the high regiospecificity of aminium radicals for $\omega - 1$ abstraction in radical halogenation of linear aliphatic compounds.[4,5] Thus chloroform, tetrahydrofuran and 1-halogenopropanes, acetic, propionic and butyric acids proved ineffective sources of nucleophilic free radicals, each resulting in phenacyl chloride formation. We thus next studied a series of linear functionalised alkanes.

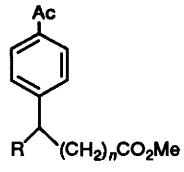
Halogenoalkylation of Acetophenone.—While 1-chloro and 1-bromo-propane were not effective as radical precursors, increasing yields of products were obtained with 1-halogenobutane, -pentane and -hexane. The products were always derived from abstraction at the penultimate methylene remote from the function and by attack at the *para*-position of acetophenone as indicated in Scheme 5. Thus from the bromoalkanes with n = 2–4, conversions of acetophenone were 8, 15 and 17% respectively using equimolar proportions of all the reagents and the yield based on converted acetophenone of alkylated product were 23, 44 and 53% respectively. Increase of the alkyl bromide to a 4 molar excess doubled the conversion but did not improve the yield. 1-Chlorobutane gave a 42% conversion of acetophenone but only 12% yield of product **3a** (n = 2) based on converted acetophenone. 1-Bromooctane gave a mixture of products, some bearing chlorine in the side-chain. 1,7-Dibromoheptane gave no substitution product.



Scheme 5 *Reagents:* oleum, AcOH, Me_2NCl, $FeSO_4$, $MeCH_2(CH_2)_nX$

Carboxyalkylation of Acetophenone.—Alkylation of acetophenone using an alkanoic acid was somewhat more efficient and initial studies indicated that higher temperatures gave better yields of products. Thus hexanoic acid gave 42% of product at 0–15 °C and 58% at 45–50 °C. Conversions of acetophenone again increased with chain length, pentanoic and hexanoic acid resulting in 30 and 38% conversion and 17 and 52% yield of product **3** (n = 2 and 3) respectively. The alkylation results are summarised in Table 1.

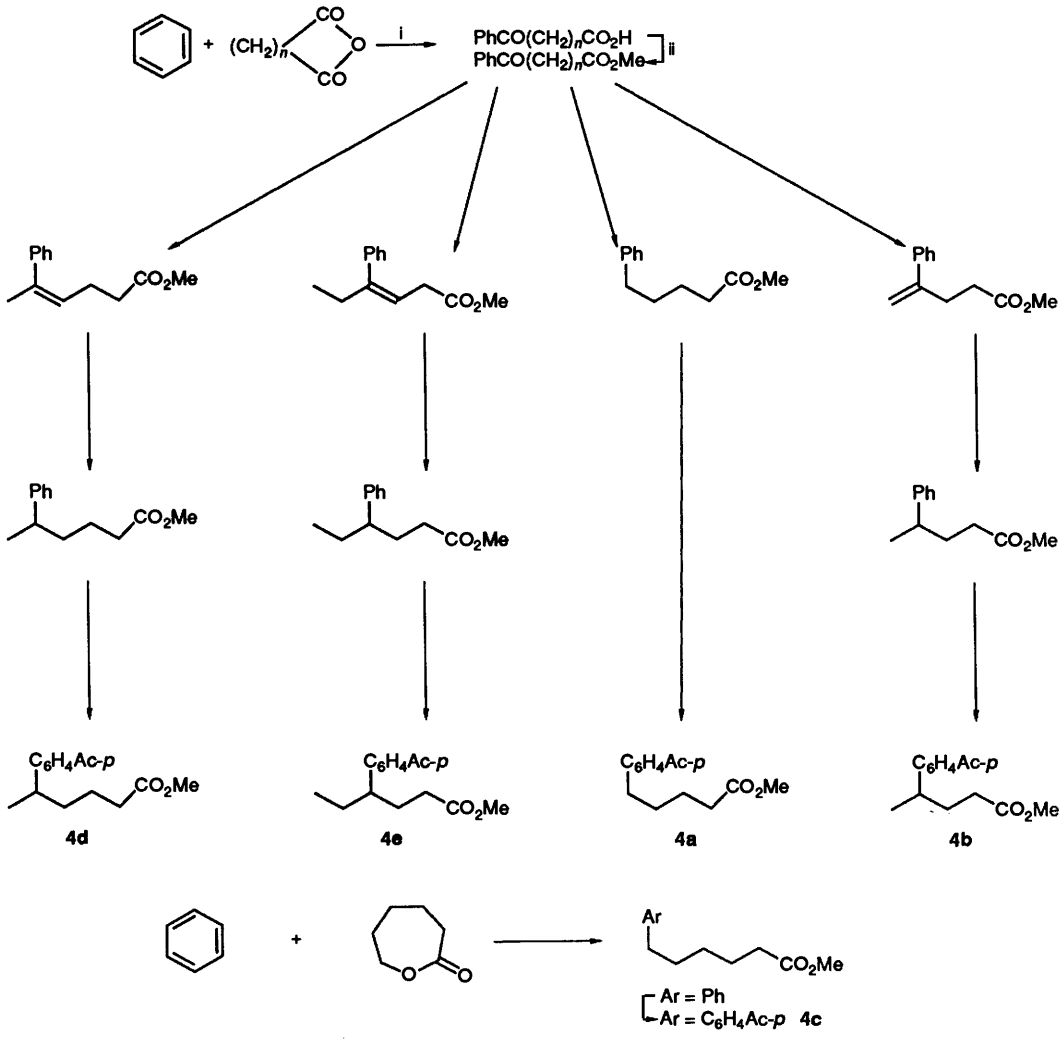
In order to put the structure of these acids beyond doubt, we have unambiguously synthesised various isomers of the products **4**. Thus 3–5 stage syntheses based on benzene typically involved acylation with succinic or glutaric anhydride



	R	n
4a	H	3
b	Me	2
c	H	4
d	Me	3
e	Et	2

followed by esterification and attack of the ketone group by reduction to a methylene, or by Wittig or Grignard reagents to attach methyl or ethyl groups. Final *para*-acetylation gave the products **4**. The syntheses are summarised in Scheme 6. The literature method for making 6-phenylhexanoic acid, as shown in Scheme 5, in fact yields a mixture of phenylhexanoic acid isomers including the 4-, 5- and 6-phenylhexanoic acids as the primary components and is totally unsuited for synthesis.

A careful comparison was made of the ^{13}C NMR spectra of these synthetic isomers with the products obtained by alkylation of acetophenone with the appropriate radical. No peaks characteristic of the products **4a**, **4c** and **4e** were evident in the methyl esters derived from **3c**. The synthetic products **4b** and **4d**



Scheme 6 *Reagents*: i, $AlCl_3$; ii, MeOH, H^+

were identical with the esters derived from the acids **3c**. It is worth noting that the two products **3c** (n = 2 and 3) require a 5-step synthesis giving overall yields of 7 and 12% respectively.

In conclusion, while we have demonstrated that specific *para*-alkylation of protonated acetophenone by free radicals is indeed a feasible process, a viable, high-yielding method is necessary before this interesting approach can be considered to be an alternative synthetic pathway. This challenge is now being addressed.

Experimental

M.p.s were determined in capillaries and are uncorrected. IR spectra were obtained on a Perkin-Elmer 257 and 297 instrument, ^1H NMR spectra on a Varian EM 360 instrument, and a ^{13}C NMR on a Varian CFT 20 in deuteriochloroform solution. Mass spectra were recorded on an AEI MS 12 or MS 902 instrument. Oleum refers to 25% w/w and *N*-chloro-dimethylamine, -diisopropylamine and -morpholine were made by literature methods.[6] Light petroleum was the fraction boiling at 60–80 °C.

Cyclohexylation of Acetophenone.—Dimethylchloramine (3.18 g, 0.04 mol) was added dropwise at 0 °C to oleum (30 cm^3) over 5 min with stirring. A separate solution was also made by addition with stirring in an ice-bath of the following compounds to oleum (30 cm^3): acetic acid (20 cm^3) acetophenone (4.80 g, 0.04 mol), cyclohexane (5.0 cm^3, 0.04 mol) and finely powdered hydrated ferrous sulphate (11.12 g, 0.04 mol). The former solution was then added dropwise to the latter. The addition took 1.5 h and the temperature was not allowed to rise above 15 °C. After a further 2 h stirring during which the temperature was allowed to rise to ambient, the mixture was poured into ice–water and extracted with diethyl ether (5 × 50 cm^3). The extract was washed with water, aqeuous sodium hydroxide and water, dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina with light petroleum and diethyl ether (9:1 giving firstly acetophenone (2.7 g, 58%) followed by *p*-cyclohexylacetophenone (0.60 g, 7.4%, 18% based on converted acetophenone) as a white crystalline solid, m.p. 68 °C (lit.,[7] m.p. 68–69 °C) ν_{max}/cm^{-1} 1680 (COs); δ_H 1.0–2.2 (11 H, m, C_6H_{11}), 2.53 (3 H, s, Me), 7.26 (2 H, d) and 7.88 (2 H, d) (aromatic Hs); δ_C 25.8 (t, 4′-C), 26.1 (q, Me), 26.5 (t, C-3′ and 5′), 33.9 (t, C-2′ and 6′), 44.4 (d, C-1′), 126.7 (d, C-2,6), 128.3 (d, C-3,5), 134.9 (s, C-4), 153.4 (s, C-1) and 197.35 (s, CO). This was followed by 4-(chlorocyclohexyl)acetophenone as a yellow oil (0.10 g, 1%, 3% based on converted acetophenone); ν_{max}/cm^{-1} 1680 (CO) and 820 (*p*-disubstituted benzene); δ_H 0.7–2.5 (10 H, m, C_6H_{10}), 2.52 (3 H, m, Me), 7.27 and 7.90 (4 H, two doublets, aromatic Hs); m/z 236/238 (M^+).

Alkylation of acetophenone by 1-bromobutane. The above method was used but cyclohexane was replaced by 1-bromobutane (5.48 g, 0.04 mol). The crude product thus obtained was distilled in a Kugelrohr giving firstly acetophenone (4.52 g, 94%

at 50 °C/0.1 mmHg) followed by 3-(4-*acetylphenyl*)-1-*bromobutane* (0.18 g, 2%, 23% based on converted acetophenone at 70 °C (0.1 mmHg) as white crystals from light petroleum (b.p. 40–60 °C) m.p. 46.5–47.5 °C (Found: 56.8; H, 6.0, $C_{12}H_{15}BrO$ requires C, 56.5; H, 5.9%). ν_{max}/cm^{-1} 1670 (CO); δ_H 1.28 (3 H, d, *Me*CH), 2.13 (2 H, q, CH_2), 3.70 (3 H, s, Me), 2.7–3.7 (3 H, m, CH_2 and CH), 7.30 and 7.92 (4 H, two doublets, aromatic Hs); *m/z* 254/256 (M^+); δ_C 21.2 (q, *Me*CH), 26.3 (q, *Me*CO), 31.2 (t, CH_2CH), 38.1 (t, CH_2Br), 40.5 (d, CH), 127.2 (d, C-2 and C-6), 128.7 (d, C-3 and C-5), 135.6 (s, C-4), 151.1 (s, C-1) and 197.4 (s, CO).

Alkylation of acetophenone with 1-*chlorobutane.* Using the above method but employing 1-chlorobutane (3.70 g, 0.04 mol) in place of 1-bromobutane gave 1-(4-*acetylphenyl*)-1-*chlorobutane* as a pale yellow oil. ν_{max}/cm^{-1} 1680 (CO), 830 (*p*-disubst. benzene); δ_H 1.30 (3 H, d, Me), 2.06 (2 H, q, CH_2), 2.56 (3 H, s, Me), 3.07 (2 H, t, CH_2), 3.38 (1 H, sext, CH), 7.30 and 7.92 (two pairs CHs, d, aromatic Hs); *m/z* 210/212 (M^+) (Found: *m/z* 210.0810. $C_{12}H_{15}ClO$ requires *M*, 210.0810).

Alkylation for acetophenone with 1-*chloropentane.* Using the above procedure but replacing the 1-chlorobutane with 1-chloropentane (4.26 g, 0.04 mol) the crude product was distilled in a Kugelrohr to give 4-(4-*acetylphenyl*-1-*chloropentane* as an oil, b.p. 126–128 °C at 0.05 mmHg; ν_{max}/cm^{-1} 1675 (CO) and 820 (*p*-disubst. benzene); δ_H 1.27 (3 H, d, Me), 1.45–2.25 [4 H, m, $(CH_2)_2$], 2.56 (3 H, s, Me), 2.5–3.15 (1 H, m, CH), 3.45 (2 H, t, CH_2), 7.22 and 7.86 (two pairs CHs, d, aromatic Hs); *m/z* 224–226 (M^+) (Found: *m/z* 224.0965. $C_{13}H_{17}ClO$ requires *M*, 224.0967); δ_C 21.8 (q, *Me*CH), 26.2 (q *Me*CO), 30.4 (t, CH_2CH_2CH), 34.9 (t, CH_2CH), 39.3 (d, CH), 44.7 (t, CH_2CH), 126.9 (d, C-2 and C-6), 128.4 (d, C-3 and C-5), 135.25 (s, C-4), 152.3 (s, C-1) and 197.4 (s, CO).

Alkylation of acetophenone with 1-*bromopentane.* Using the above procedure but with 1-bromopentane (6.04 g, 0.04 mol) in place of 1-bromobutane, the crude material was distilled in a Kugelrohr to give 4-(4-*acetylphenyl*)-1-*bromopentane*, b.p. 100–105 °C at 0.03 mmHg (Found: C, 57.8; H, 6.35. $C_{13}H_{17}BrO$ requires C, 58.0; H, 6.4%); ν_{max}/cm^{-1} 1680 (CO), 825 (*p*-disubst. benzene); δ_H 1.26 (3 H, d, Me), 1.6–1.9 (4 H, m, CH_2CH_2), 2.55 (3 H, s, Me), 2.55–3.0 (1 H, m, CH), 7.25 and 7.90 (two pairs CHs, d, aromatic Hs); *m/z* 268/270 (M^+); δ_C 21.9 (q, *Me*CH), 26.3 (q, MeCO), 30.7 (t, CH_2CH_2CH), 33.4 (t, CH_2CH), 36.25 (t, CH_2Br), 39.3 (d, CH), 127.0 (d, C-2 and C-6) 128.5 (d, C-3 and C-5), 135.35 (s, C-4), 152.4 (s, C-1) and 197.4 (s, CO).

Alkylation of acetophenone with 1-*bromohexane.* When the above procedure was followed but employing 1-bromohexane (6.60 g, 0.04 mol) in place of 1-bromopentane, the crude product was distilled as above to give 5-(4-*acetylphenyl*)-1-*bromohexane*, b.p. 124.6 °C at 0.05 mmHg (Found: C, 59.4; H, 6.7, $C_{14}H_{19}BrO$ requires C, 59.4; H, 6.8%); δ_H 1.40 (3 H, d, MeCH), 1.3–2.1 [6 H, m, $(CH_2)_3$], 2.55 (3 H, s, Me), 2.5–3.0 (1 H, m, CH), 3.32 (2 H, t, CH_2), 7.26 and 7.90 (two pairs CHs, d, aromatic Hs); *m/z* 282/284 (M^+); δ_C 21.5 (q, Me), 25.7 (q, *Me*CO), 26.0 [t, $CH_2(CH_2)_2CH$], 32.3 (t, CH_2CH), 36.6 (t, CH_2Br), 39.4 (d, CH), 126.4 (d, C-2 and C-6), 128.1 (d, C-3 and C-5), 134.9 (s, C-4), 152.7 (d, C-1) and 197.1 (s, CO).

Alkylation of acetophenone with pentyl acetate. By the above method employing pentyl acetate (5.20 g, 0.04 mol) in place of 1-bromohexane, the crude material was distilled in a Kugelrohr to give 4-(4-*acetylphenyl*)*pentyl acetate* as a viscous pale green oil, b.p. 140–143 °C at 0.05 mmHg (Found: C, 72.55; H, 7.9, $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1%); ν_{max}/cm^{-1} 1735 (acetate CO), 1680 (CO) and 830 (*p*-disubstituted benzene); δ_H 1.27 (3 H, d, *Me*CH), 1.4–1.75 [4 H, m, $(CH_2)_2$], 2.00 (3 H, s, $MeCO_2$), 2.26 (3 H, s, Me), 4.01 (3 H, m, CH_2O and CH), 7.28 and 7.92 (two pairs CHs, d, aromatic Hs); *m/z* 248 (M^+); δ_C 20.15 (1, *Me*CO_2), (q, Me), 21.3 (q, MeCH), 25.7 (H, Me), 26.4 (t, CH_2CH_2CH), 33.7 (t, CH_2CH_2), 39.2 (d, CH), 63.7 (t, CH_2O), 126.7 (d, C-2 and C-6), 128.1 (d, C-3 and C-6), 135.2 (s, C-4), 152.2 (s, C-1), 170.05 (s, *CO*, O) and 196.7 (s, CO).

Alkylation of acetophenone with valeric acid. The procedure used for 1-bromobutane alkylation was employed with valeric acid (4.08 g, 0.04 mol) in place of the bromobutane and at 35–40 °C instead of at 0–15 °C. The crude material was chromatographed on silica gel when elution with light petroleum and ethyl acetate (9:1) gave firstly acetophenene, then valeric acid. Using light petroleum and ethyl acetate (4:1) gave 4-(4-*acetylphenyl*)*pentanoic acid*, m.p. 63–75 °C; ν_{max}/cm^{-1} 1710 (CO_2H), 1680 (CO) and 820 (*p*-disubst. benzene); δ_H 1.20 (3 H, d, Me), 1.8–2.55 [4 H, m, $(CH_2)_2$], 2.57 (3 H, s, Me), 2.6–3.05 (1 H, m, CH), 7.29 and 7.92 (two pairs CHs, d, aromatic Hs) and 9.45 (1 H, s, OH); *m/z* 220 (M^+) (Found: *m/z* 220.1087, $C_{13}H_{16}O_3$ requires *M*, 220.1098).

Alkylation of acetophenone with hexanoic acid. Using the method employed for valeric acid but with hexanoic acid (4.6 g, 0.04 mol) instead of valeric acid, the crude product was purified by Kugelrohr distillation to give 5-(4-*acetylphenyl*)*hexanoic acid* as a viscous pale yellow oil, b.p. 154–155 °C at 0.04 mmHg (Found: C, 71.4; H, 7.8, $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); ν_{max}/cm^{-1} 1770 (CO_2H), 1680 (CO) and 830 (*p*-disubst. benzene); δ_H 1.26 (3 H, d, Me), 1.60 [4 H, m, $(CH_2)_2$], 2.51 (2 H, t, CH_2), 2.57 (3 H, s, Me), 2.5–3.05 (1 H, m, CH), 7.26 and 7.92 (two pairs CHs, d, aromatic Hs) and 11.05 (1 H, s, OH); *m/z* 234 (M^+); δ_C 21.1 [t, $CH_2CH_2(CH)_2$], 22.1 (q, MeCH), 25.5 (1, Me), 33.2 (t, CH_2CH), 39.0 (d, CH), 126.45 (d, C-2 and C-6), 128.0 (d, C-3 and C-5), 138.5 (s, C-4), 152.3 (s, C-1), 177.6 (s, CO_2H) and 197.5 (s, CO).

Preparation of Methyl 5-(4-*Acetylphenyl*)*pentanoate* **4a**.—5-Phenylvaleric acid was prepared according to the literature in two steps by the aluminium chloride-catalysed acylation of benzene with glutaric anhydride[8] (43%) followed by Clemmensen reduction of the 4-benzoylbutyric acid so obtained[9] (91%). A mixture of 5-phenylvaleric acid (6.5 g, 0.036 mol) methanol (50 cm^3) and sulphuric acid (2 cm^3, 98%) was heated under reflux overnight, the solvent removed and the residue poured into ice–water (200 cm^3). Extraction with diethyl ether (3 × 50 cm^3) and washing of this extract successively with water, 10% aqueous sodium hydroxide and water gave, after drying ($MgSO_4$) and evaporation methyl 5-phenylvalerate (3.60 g, 51%) which distilled as a colourless oil b.p. 90–93 °C at 0.2 mmHg (lit.,[10] b.p. 173 °C at 35 mmHg).

To a stirred mixture of aluminium chloride (9.0 g, 0.067 mol) and methyl 5-phenylvalerate (1.92 g, 0.01 mol) was added acetic anhydride (6 cm^3) and the mixture was heated under reflux for 30 min. To the cooled reaction mixture was added carefully with stirring a solution of concentrated hydrochloric acid (25 cm^3, 33%) and water (100 cm^3). The resulting solution was extracted with diethyl ether (4 × 30 cm^3) and the extract was washed successively with water, aqeuous sodium hydroxide (10%) and water, dried ($MgSO_4$) and evaporated to give a thick oil which was distilled at 130–134 °C at 0.1 mmHg to yield the *title compound* (0.71 g, 30%) as a pale green viscous oil (Found: C, 71.8; H, 7.9, $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); ν_{max}/cm^{-1} 1740 (CO_2Me), 1680 (CO) and 830 (*p*-disubst. benzene); δ_H 1.5–1.9 [4 H, m, $(CH_2)_2$], 2.55 (3 H, s, Me), 2.0–3.0 (4 H, m, CH_2Ar and CH_2CO), 3.65 (3 H, s, CO_2Me), 7.25 and 7.88 (two pairs CHs, d, aromatic Hs); *m/z* 234 (M^+); δ_C 24.2 (t, CH_2), 25.8 (q, Me), 29.9 (t, CH_2), 33.4 (t, CH_2), 35.1 (t, CH_2), 50.8 (q, CO_2Me), 128.15 (d, C-2, -3, -5 and -6), 135.1 (s, C-4), 147.45 (s, C-1), 173.2 (s, CO_2Me) and 196.9 (s, CO).

Preparation of methyl 4-(4-*acetylphenyl*)*pentanoate* **4b**. Methyl 3-benzoylpropionate was prepared by literature methods involving acylation of benzene with succinic anhydride and aluminium chloride to give 3-benzoylpropionic acid[8] (71%)

followed by esterification with methanol and concentrated sulphuric acid catalyst (76%). This ester was distilled b.p. 158 °C at 8 mmHg (lit.,[11] b.p. 187–187.5 °C at 30 mmHg).

A 3-necked 250 cm^3 flask was fitted with a rubber septum, a magnetic stirrer bar and a nitrogen inlet. To this flask was added sodium hydride (50% dispersion in oil; 0.84 g, 0.035 mol) which was washed with light petroleum (3 × 50 cm^3). Freshly distilled dimethyl sulphoxide (15 cm^3) was added by syringe and the mixture heated at 75–80 °C for 1 h. To the ice-cooled system was added methyltriphenylphosphonium bromide (12.5 g, 0.036 mol) in warm dimethyl sulphoxide (100 cm^3).

To the resulting solution was added methyl 3-benzoylpropionate (5.76 g, 0.03 mol) and the mixture stirrred for 48 h and then poured into water (300 cm^3) and extracted with light petroleum (4 × 100 cm^3). The extract was washed with 1:1 aqueous dimethyl sulphoxide (2 × 50 cm^3), then water (2 × 100 cm^3) and dried ($MgSO_4$) and the solution percolated through alumina (50 g) (to remove triphenylphosphine oxide). Evaporation of the solvent gave *methyl 4-phenylpent-5-enoate* as a yellow oil (2.00 g, 35%). ν_{max}/cm^{-1} 1735 (CO_2Me) and 1630 (C=C); δ_H 1.7–2.75 [4 H, m, (CH_2)], 3.2 (3 H, s, Me), 4.7 (1 H, m, olefinic H), 4.95 (1 H, m, olefinic H) and 6.6–7.4 (5 H, m, aromatics).

This ester was directly hydrogenated as follows. The ester (2.00 g, 0.011 mol) in methanol (50 cm^3) was treated with palladium on charcoal (0.2 g, 10%) and hydrogenated at atmospheric pressure during 30 min. The solution was filtered and the solvent evaporated from the filtrate to give an oil which was distilled to yield methyl 4-phenylvalerate (1.47 g, 73%) as a pale yellow oil, b.p. 102–104 °C at 1 mmHg (lit.,[12] b.p. 100–101 °C at 0.95 mmHg); ν_{max}/cm^{-1} 1730 (CO); δ_H 1.25 (3 H, d, Me), 1.5–2.35 [4 H, m, $(CH_2)_2$], 2.70 (1 H, sext, CH), 3.59 (3 H, s, Me) and 2.80 (5 H, b, aromatics).

To a stirred mixture of aluminium chloride (9.00 g, 0.067 mol) and methyl 4-phenylpentanoate (1.47 g, 0.008 mol) was added acetic anhydride (3 cm^3) and the mixture heated under reflux for 1 h. The resulting solution was poured into ice-water (200 cm^3) and then extracted with diethyl ether (4 × 25 cm^3). The extract was washed with diethyl ether (4 × 25 cm^3). The extract was washed with water, then aqueous sodium hydroxide (10%) and finally water and dried ($MgSO_4$). Evaporation of the solvent followed by distillation of the residue at 103–104 °C at 0.03 mmHg gave *methyl 4-(4-acetylphenyl)pentanoate* **4b** as a colourless oil (1.00 g, 56%) (Found: C, 71.6; H, 7.62. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%); ν/cm^{-1} 1740 (CO_2Me) and 1680 (CO) 830 (*p*-disubst. benzene); δ_H 1.28 (3 H, d, Me), 1.7–2.4 [4 H, m, $(CH_2)_2$], 2.58 (3 H, s, Me), 2.5–3.05 (1 H, m, CH), 3.61 (3 H, s, Me), 7.26 and 7.92 (two pairs CHs, d, aromatic Hs).

This material was identical (IR, ^1H NMR, ^{13}C NMR) with the product obtained from esterification of the product derived by alkylation of acetophenone with valeric acid prepared as follows. 4-(4-Acetylphenyl)pentanoic acid (2.00 g, 0.01 mol) in methanol (5 cm^3) was treated with concentrated sulphuric acid (3 drops) and heated under reflux for 4 h. The cooled solution was diluted with water and extracted with diethyl ether (4 × 25 cm^3) and the extract washed with water, then aqueous sodium hydrogen carbonate (10%) and water, dried ($MgSO_4$) and evaporated. The residue was distilled at 103–105 °C at 0.1 mmHg to give methyl 4-(4-acetylphenyl)pentanoate (1.50 g, 71%) as a pale yellow oil.

Preparation of methyl 6-(4-acetylphenyl)hexanoate **4c**. 6-Phenylhexanoic acid was prepared according to the literature from benzene, ε-caprolactone and aluminium chloride.[13] (^{13}C NMR spectroscopy showed that this material after subsequent esterification and acetylation was a mixture of isomers). The crude acid was directly esterified according to the literature with methanol to give the methyl ester.[14] The yields were 89 and 91% respectively.

To a mixture of aluminium chloride (9.00 g, 0.0675 mol) and methyl 6-phenylhexanoate (6.18 g, 0.03 mol) was added acetic anhydride (9 cm^3) with stirring. After 45 min at reflux, the cooled solution was treated with 10% aqueous hydrochloric acid (30 cm^3) and extracted with diethyl ether (4 × 30 cm^3). The solution was washed with water, aqueous sodium hydroxide (10%) and then water, dried ($MgSO_4$) and evaporated. The residue was distilled at 140–142 °C at 0.05 mmHg to give a pale yellow oil, *methyl 6-(4-acetylphenyl)hexanoate* (4.00 g, 54%) (Found: C, 72.4; H, 8.2. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%); ν_{max}/cm^{-1} 1740 (CO_2Me), 1680 (CO) and 830 (*p*-disubst. benzene); δ_H 2.60 (3 H, s, Me), 0.5–3.0 [10 H, m, $(CH_2)_5$], 3.61 (3 H, s, Me), 7.25 and 7.92 (two pairs CHs, d, aromatic CHs); other peaks are also present; *m/z* 248 (M^+); δ_C 26.8 (t, CH_2), 28.0 (s, Me), 31.2 (t, CH_2), 33.3 (t, CH_2CO), 35.7 (t, $ArCH_2CH_2$), 37.7 (t, $ArCH_2$), 52.9 (q, OMe), 130.6 (s, C-2, -3, -5 and -6), 150.1 (s, C-1), 175.05 (s, CO_2) and 198.5 (s, CO). Other peaks are also present including those due to methyl 5-(4-acetylphenyl)hexanoate and methyl 4-(4-acetylphenyl)hexanoate.

Preparation of methyl 5-(4-acetylphenyl)hexanoate **4d**. Benzoylbutyric acid (see above) was esterified with methanol to give methyl 4-benzoylbutyrate b.p. 146–148 °C at 8 mmHg as a colourless oil (lit.,[15] b.p. 147–148 °C at 8 mmHg).

To an ice-cooled solution of methyl 4-benzoylbutyrate (15.40 g, 0.075 mol) in dry diethyl ether (100 cm^3) was added dropwise with stirring methylmagnesium iodide [prepared from methyl iodide (17.00 g, 0.12 mol) and magnesium (2.88 g, 0.12 g atom) in ether (15.0 cm^3)]. The vigorous reaction was maintained near 0 °C during the addition (3–4 h) during which a white precipitate developed. After addition the mixture was heated under reflux for 4 h and the cooled solution treated with aqueous hydrochloric acid (100 cm^3, 10%). The mixture was heated under reflux for a further 6 h with stirring, cooled, the layers separated and the aqueous layer discarded. The ethereal layer was washed with water and then combined alkaline extract was acidified with concentrated hydrochloric acid, and again extracted with diethyl ether (5 × 50 cm^3). The extract was washed with water and dried ($MgSO_4$) and the oil resulting from evaporation was distilled at 140–144 °C at 0.03 mmHg to give 5-phenylhex-4-enoic acid (3.91 g, 27%) as a pale green oil;[16] ν_{max}/cm^{-1} 1700 (CO); δ_H 2.05 (3 H, d, Me), 2.0–3.0 [4 H, m, $(CH_2)_2$], 5.0–6.0 (1 H, m, CH), 7.38 (5 H, b, aromatics) and 11.45 (1 H, s, OH).

A mixture of 5-phenylhex-4-enoic acid (3.90 g, 0.002 mol) methanol (50 cm^3) and sulphuric acid (1 cm^3, 98%) was boiled for 4 h, methanol removed and the residue poured into aqueous sodium carbonate (50 cm^3, 5%) and ice. The solution was extracted with diethyl ether (4 × 50 cm^3) washed with water and dried ($MgSO_4$). Evaporation of the solvent gave *methyl 5-phenylhex-4-enoate* (3.70 g, 88%); ν_{max}/cm^{-1} 1740 (CO); δ_H 2.05 (3 H, b, Me), 2.2–2.8 (4 H, m, CH_2CH_2), 3.65 (3 H, s, OMe), 5.0–6.0 (1 H, m, CH) and 7.4 (5 H, b, aromatics). To this ester (3.00 g, 0.015 mol) in methanol (70 cm^3) was added palladium on charcoal (0.2 g, 10%) and the solution hydrogenated at atmospheric pressure (2 h). The filtered solution was evaporated and the residue distilled to give methyl 5-phenylhexanoate (3.00 g, 99%) as a colourless oil b.p. 104 °C at 0.03 mmHg (lit.,[17] b.p. 142 °C at 1 mmHg); ν_{max}/cm^{-1} 1740 (CO); δ_H 1.29 (3 H, d, Me), 1.4–2.0 [4 H, m, $(CH_2)_2$], 2.0–3.1 (3 H, m, CH and CH_2), 3.65 (3 H, s, OMe) and 7.25 (5 H, b, aromatics).

To a mixture of aluminium chloride (4.00 g, 0.03 mol) and methyl 5-phenylhexanoate (2.06 g, 0.01 mol) was added acetic anhydride (6 cm^3) with stirring and then the solution was boiled for 30 min. The cooled solution was treated with hydrochloric acid (30 cm^3, 10%) and ice and extracted with diethyl ether. The extract was washed with water, aqueous sodium hydroxide (10%) and water and then dried. Evaporation of the ether

followed by distillation of the residue gave the *title compound* (2.01 g, 81%) as a pale green oil (Found: C, 72.5; H, 8.0. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.1%); ν_{max}/cm^{-1} 1740 (CO_2-Me), 1680 (CO) and 830 (*p*-disubst. benzene); δ_H 1.24 (3 H, d, Me), 1.58 (4 H, m, CH_2CH_2), 2.26 (2 H, t, CH_2CO), 2.56 (3 H, s, Me), 2.5–3.1 (1 H, m, CH), 3.63 (3 H, s, Me), 7.27 and 7.90 (4 H, two d, aromatic Hs); δ_C 21.6 (t, CH_2), 22.8 (q, Me), 36.0 (q, MeCO), 33.7 (t, CH_2CO), 39.2 (t, CH_2CH), 39.6 (d, CH), 50.9 (q, OMe), 126.9 (d, C-2 and -6), 128.5 (d, C-3 and 5), 135.4 (s, C-4), 152.6 (s, C-1), 173.3 (s, CO_2) and 197.0 (s, CO).

This material was identical (IR, ^1H NMR, ^{13}C NMR) to that made by esterification of the product of alkylation of acetophenone with hexanoic acid, using methanol and sulphuric acid in the above manner.

Preparation of methyl 4-(4-*acetylphenyl*)*hexanoate* **4e**. To an ice cooled solution of methyl 3-benzoylpropionate (9.60 g, 0.05 mol) in dry ether was added dropwise with stirring ethylmagnesium bromide [prepared from ethyl bromide (7.70 g, 0.07 mol), magnesium (1.68 g, 0.07 g atom) and dry ether (100 cm^3)] over 3–4 h, a temperature < 5 °C being maintained. The solution was allowed to warm to ambient temperature when dry toluene (150 cm^3) was added and the ether removed by distillation. The resulting mixture was heated under reflux for 4 h and then cooled and treated with aqueous hydrochloric acid (50 cm^3, 10%) and again refluxed for 2 h. The cooled layers were separated and the aqueous phase further extracted with ether. The combined organic phases were washed with water and then extracted with aqueous sodium carbonate (5 × 50 cm^3). The alkaline layer was acidified and extracted with diethyl ether and this extract was washed with water, dried ($MgSO_4$) and evaporated. The residual oil was distilled to give 4-phenylhex-3-enoic acid as a pale green oil, b.p. 164–166 °C at 5 mmHg (3.52 g, 39%) (lit.,[14] b.p. 163–167 °C at 5 mmHg) ν_{max}/cm^{-1} 1710 (CO) and 1600 (C=C); δ_H 1.15 (3 H, t, Me), 1.77 (2 H, q, CH_2), 5.45 (2 H, d, CH_2), 3.5–4.0 (1 H, m, CH), 7.14 (5 H, b, aromatics) and 9.63 (1 H, s, OH).

This acid (3.50 g, 0.018 mol) in methanol (50 cm^3) and sulphuric acid (10 drops, 9.8%) was boiled for 6 h, the excess of methanol evaporated and the residue poured in aqueous sodium carbonate (20 cm^3, 10%) and ice and extracted with diethyl ether (4 × 30 cm^3). The extract was washed with water, dried ($MgSO_4$) and evaporated and the residue distilled to give methyl 4-phenylhex-3-enoate as a pale green oil,[17] b.p. 107–108.5 °C at 0.05 mmHg (2.53 g, 66%).

This ester (2.50 g, 0.012 mol) was taken directly in methanol (75 cm^3) treated with palladium on charcoal (0.2 g, 10%) and hydrogenated at atmospheric pressure (30 min); the mixture was then filtered and evaporated. Distillation of the residue at 93–94 °C at 0.01 mmHg gave methyl 4-phenylhexanoate as a colourless oil (2.40 g, 96%) (lit.,[18] b.p. 95 °C at 0.01 mmHg); ν_{max}/cm^{-1} 1740 (CO); δ_H 0.80 (3 H, t, Me), 1.2–3.0 (7 H, m, CH and three CH_2s), 3.58 (3 H, s, OMe) and 7.21 (5 H, b, aromatics).

To a mixture of aluminium chloride (6.0 g, 0.045 mol) and methyl 4-phenylhexanoate (1.30 g, 0.0063 mol) was added acetic anhydride (6 cm^3) with stirring. The solution was boiled for 40 min, cooled and treated with hydrochloric acid solution (50 cm^3, 10%) and ice and then extracted with diethyl ether.

The extract was washed with water, aqueous sodium hydroxide (10%) and then water and dried ($MgSO_4$). Evaporation of the ether gave an oil which was distilled at 150–152 °C at 0.05 mmHg to give *methyl* 4-(4-*acetylphenyl*)*hexanoate* (1.05 g, 64%) as a pale yellow oil (Found: C, 72.4; H, 8.3, $C_{15}H_{20}O_3$ requires C, 72.53; H, 8.1%); ν_{max}/cm^{-1} 1740 (CO_2Me), 1680 (CO) and 830 (*p*-disubst. benzene); δ_H 0.81 (3 H, t, Me), 2.65 (3 H, s, Me), 1.2–3.0 [6 H, m, $(CH_2)_3$], 3.58 (3 H, s, OMe), 7.35 and 08.05 (4 H, d, aromatics); *m/z* 248 (M^+); δ_C 11.4 (q, Me), 25.7 (q, COMe), 28.8 (t, CH_2), 31.6 (t, CH_2), 46.9 (d, CH), 50.75 (q, OMe), 127.55 (d, C-2 and -6), 128.1 (d, C-3 and -5), 135.5 (s, C-4), 149.9 (s, C-1), 172.95 (s, CO_2) and 196.65 (s, CO).

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