

## Friedel–Crafts Reactions. Part XXV.<sup>1</sup> Acetylation and Benzoylation of Iodobenzene and of *o*-, *m*-, and *p*-Iodotoluenes

By Peter H. Gore,\* Stewart Thorburn, and David J. Weyell, School of Chemistry, Brunel University, Kingston Lane, Uxbridge, Middlesex

The Friedel–Crafts acetylation and benzoylation of iodobenzene and the isomeric iodotoluenes have been investigated in a range of solvents and at a range of temperatures. Under specific conditions good yields of *p*-iodoacetophenone or *p*-iodobenzophenone may be obtained. The reactivities of the iodotoluenes follow the sequence *p*- < *o*- < *m*-. The main products formed in the acylation of *o*-iodotoluene are 3-iodo-4-methyl- and 4-iodo-3-methyl-acetophenones (or -benzophenones). *m*-Iodotoluene generally affords acetophenones or benzophenones in the order 4-iodo-2-methyl- > 2-iodo-4-methyl- > 2-iodo-6-methyl. In acylations *p*-iodotoluene gives very-low yields of 3-iodo-6-methylacetophenone only, or a mixture of 3-iodo-6-methyl- and 2-iodo-5-methyl-benzophenones; rearranged ketones, those formally derived from *o*-iodotoluene, are also formed. In addition all the iodo-substrates give by-products in major amounts: di-iodobenzenes, or di- and tri-iodotoluenes; aceto- or benzophenone, or the isomeric methylaceto- or methylbenzo-phenones. Acylations of *o*- and *p*-iodotoluenes also give isomeric chloromethylaceto-(or chloromethylbenzo-)phenones. Benzoylations carried out in ethylene chloride solution give low yields of 2-chloroethyl benzoate.

THERE have been many reports of Friedel–Crafts acylations of iodobenzene.<sup>2a,3</sup> Most of the early experiments are unsatisfactory because of the use as diluent of carbon disulphide, which only partially dissolves aluminium chloride or its acyl complex, and thereby causes extensive decomposition of the iodobenzene substrate with formation of free iodine;<sup>4-6</sup> and yet high yields (up to 80%) of *p*-isomers have been claimed.<sup>6,7</sup> In the presence of strong acids (including Lewis acids) di- and tri-iodo-compounds are formed from aromatic iodo-compounds.<sup>6,8-10</sup> In Friedel–Crafts acylations deiodinated ketonic products have been obtained.<sup>5,8</sup> The Friedel–Crafts acetylation and benzoylation of iodobenzene have therefore been reinvestigated.

Whereas other halogenotoluenes have been investigated many times,<sup>2b</sup> there exist only two reports describing Friedel–Crafts acylations of iodotoluenes. Buu-Hoï and Jacquignon<sup>11</sup> effected the acetylation of both *m*- and *p*-iodotoluene; mixtures of isomers appeared to have been formed. Quayle and Reid<sup>12</sup> examined the action of phthalic anhydride and aluminium chloride on *p*-iodotoluene, and found that the keto-acid formed did not contain iodine. No other acylations, nor indeed any other aromatic substitutions, of the isomeric iodotoluenes appear to have been investigated. The Friedel–Crafts acetylation and benzoylation of these substrates have therefore been undertaken, and the results are reported here. It was hoped to discover acylations involving the migration of halogen atoms, such as had been found

with certain derivatives of chlorobenzene<sup>13</sup> and bromobenzene.<sup>14,15</sup>

*Acylations of Iodobenzene.*—In all our acylations the Perrier addition procedure<sup>2c</sup> has been employed, since it avoids the use of free aluminium chloride, which is known<sup>6</sup> to cause extensive decomposition of the iodo-substrate. The products obtained were analysed by g.l.c.; the results obtained for acetylation in several solvents are collected in Table 1, and those for benzoylation in Table 2. The best overall yields of products were obtained at lower temperatures in acylations, but at higher temperatures in benzoylations. In every case both normal and abnormal acylation products are obtained, as well as substantial quantities (2–30% in acylations, 4–59% in benzoylations) of isomeric di-iodobenzenes. These last result from the disproportionation of iodobenzene,<sup>10</sup> even though free aluminium chloride could be present only in the case of reactions in carbon disulphide. In nitrobenzene solution, in which the catalyst is present as the complex  $\text{AlCl}_3 \cdot \text{O}_2\text{NPh}$ , the proportions of the di-iodo-compounds are relatively low, especially at the lower temperatures. Disproportionation of iodobenzene should lead to equimolar amounts of benzene and di-iodobenzenes. Benzene, being reactive, is rapidly acylated: the formation of acetophenone (3–11%) or benzophenone (2–36%) proceeds essentially by this path. However, the molar ratios of di-iodobenzene to aceto-(or benzo-)phenone are near unity, as

<sup>2</sup> J. Böeseken, *Rec. Trav. chim.*, 1901, **20**, 106; A. Klages, *Ber.*, 1902, **35**, 2642; P. J. Montagne, *Ber.*, 1918, **51**, 1486.

<sup>3</sup> W. E. Strain, J. T. Plati, and S. L. Warren, *J. Amer. Chem. Soc.*, 1942, **64**, 1436.

<sup>4</sup> H. Suzuki and R. Goto, *Bull. Chem. Soc. Japan*, 1963, **36**, 389; H. Suzuki, K. Maruyama, and R. Goto, *ibid.*, 1965, **38**, 1590.

<sup>5</sup> P. H. Gore, S. Thorburn, and D. J. Weyell, *J. Chem. Soc. (C)*, 1971, 2362.

<sup>6</sup> N. P. Buu-Hoï and P. Jacquignon, *Compt. rend.*, 1957, **244**, 786.

<sup>7</sup> O. R. Quayle and E. E. Reid, *J. Amer. Chem. Soc.*, 1925, **47**, 2357.

<sup>8</sup> P. A. Goodman and P. H. Gore, *J. Chem. Soc. (C)*, 1968, 2452.

<sup>9</sup> F. Mayer and W. Freund, *Ber.*, 1922, **55**, 2049; W. Borsche and A. Herbert, *Annalen*, 1941, **546**, 277.

<sup>10</sup> I. A. Troyanov and A. A. Dydyanskaya, *Ukrain. khim. Zhur.*, 1963, **29**, 88.

<sup>1</sup> Part XXIV, P. H. Gore, A. Y. Miri, and A. S. Siddiquei, preceding paper.

<sup>2</sup> P. H. Gore, in 'Friedel–Crafts and Related Reactions,' ed. G. A. Olah, Wiley, New York, 1964, vol. 2, (a) p. 163; (b) pp. 46, 164; (c) p. 3.

<sup>3</sup> A. G. Peto, in 'Friedel–Crafts and Related Reactions,' ed. G. A. Olah, Wiley, New York, 1964, vol. 2, pp. 653, 700, 726.

<sup>4</sup> F. C. Hahn and E. E. Reid, *J. Amer. Chem. Soc.*, 1924, **46**, 1645; W. Kimura, *Ber.*, 1934, **67**, 394; R. E. Lutz, P. K. Allison, G. Ashburn, P. S. Bailey, M. T. Clark, J. F. Codington, A. J. Deinet, J. A. Freck, R. H. Jordan, N. H. Leake, T. A. Martin, K. C. Nicodemus, F. J. Rowlett, jun., N. H. Shearer, jun., J. D. Smith, and J. W. Wilson, III, *J. Org. Chem.*, 1947, **12**, 617; H. K. Muller, *Annalen*, 1956, **599**, 61.

<sup>5</sup> E. Hoffmann, *Annalen*, 1891, **264**, 160.

<sup>6</sup> S. A. Koopal, *Rec. Trav. chim.*, 1915, **34**, 154; cf. O. von Dumreicher, *Ber.*, 1882, **15**, 1866.

predicted, in only a few cases. Loss of benzene from the reaction mixture prior to acylation, especially in reactions carried out at higher temperatures, could account for ratios which are too high. The abnormal trends observed for reactions in ethylene chloride can not be explained in this way.

In acylations the yield of normal ketonic products is mostly superior to that in the corresponding benzoylations. The highest overall yields of the iodoacetophenones are obtainable in ethylene chloride or nitrobenzene solution, especially for reactions carried out at

ation of *o*-chlorobenzophenone, in Friedel-Crafts benzoylations of chlorobenzene carried out in nitrobenzene solution, had been found to increase progressively from 3% at 0° to 12% at 175°.<sup>17</sup>

In most of the benzoylations carried out in ethylene chloride a volatile product, 2-chloroethyl benzoate, was formed. It was the sole product (yield 9%) in an attempted benzoylation of iodobenzene with tin(IV) chloride as catalyst. Direct formation of this ester from benzoyl chloride (*i.e.* by an electrophilic mechanism) appears improbable. Partial hydrolysis, due to moisture,

TABLE 1  
Friedel-Crafts acylation of iodobenzene by the Perrier procedure

Solvent	Temp. (°C)	Yield of crude product (g) <sup>a</sup>	Products						
			Iodoacetophenones			Di-iodobenzenes (%)	Acetophenone (%)	Ratio of di-iodobenzenes to acetophenone	
			Yield (%)	Proportions					
				<i>o</i> -	<i>m</i> -	<i>p</i> -			
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	11.2	85.4	0.9 <sup>b</sup>	1.5 <sup>b</sup>	97.6	11.2	3.4	3.3 : 1
	40	7.1	81.7	0.9	1.9	97.2	9.8	8.5	1.2 : 1
	50	3.2 <sup>c</sup>	80.6	0.6	1.7	97.7	10.4	9.0	1.2 : 1
	25 <sup>d</sup>	0.3							
CS <sub>2</sub>	25	9.0	59.3	2.0	2.0	96.0	29.6	11.1	2.7 : 1
MeNO <sub>2</sub>	25	<sup>e</sup>							
PhNO <sub>2</sub>	25	3.0	87.9			100	2.0	10.1	0.2 : 1
	65	1.9	72.7	1.1	2.2	96.7	19.0	8.3	2.3 : 1

Theoretical yield of iodoacetophenone (scale 0.05 mol) is 12.3 g. <sup>b</sup> *o*- and *m*-Isomers were reported to be formed, if at all, in less than 0.5% yield each (ref. 16). <sup>c</sup> Polymer (2.1 g.) was also formed. <sup>d</sup> Catalyst here was not AlCl<sub>3</sub> but SnCl<sub>4</sub>. Only polymeric materials were isolated; a similar result was recorded at 50°.

TABLE 2  
Friedel-Crafts benzoylation of iodobenzene by the Perrier procedure

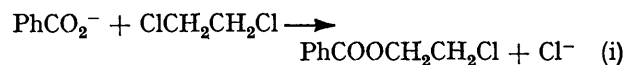
Solvent	Temp. (°C)	Yield of crude product (g) <sup>a</sup>	Products						
			Iodobenzophenones			Di-iodobenzenes (%)	Benzophenone (%)	Ratio of di-iodobenzenes to benzophenone	
			Yield (%)	Proportions					
				<i>o</i> -	<i>m</i> -	<i>p</i> -			
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	0.9	19.1			100	23	2.1	11 : 1
	50	7.3	25.5	5.1	3.5	91.4	44	26	1.7 : 1
	70	10.3	20.8	7.2	2.6	90.2	38	36	1.1 : 1
	87 <sup>b</sup>	0.8 <sup>c</sup>							
CS <sub>2</sub>	25	0.3	13.3			100	59	23	2.5 : 1
MeNO <sub>2</sub>	25	2.6	49.7	8.9	1.2	89.5	45	4.1	11 : 1
PhNO <sub>2</sub>	50	4.3	88.4	7.6	1.6	90.8	4.4	6.4	0.7 : 1
	70	10.1	67.1	13.7	2.2	84.1	19	14	1.4 : 1
	100	12.1	63.2	13.4	4.6	82.0	23	13	1.7 : 1

<sup>a</sup> Theoretical yield of iodobenzophenone (scale 0.05 mol) is 15.4 g. <sup>b</sup> Catalyst was SnCl<sub>4</sub>; duration 46 days. <sup>c</sup> Sole product was 2-chloroethyl benzoate. This ester was also present in the product from the AlCl<sub>3</sub>-catalysed reactions carried out in ethylene chloride.

25°. Nitrobenzene, again especially at lower temperatures, is to be recommended for the iodobenzophenones. Under other experimental conditions the yields of normal acylation products can be low. Almost exclusive formation of the *p*-isomers was observed. In the acylations the proportions of both *o*- and *m*-isomers are invariably low (<ca. 2%) (in fact they were not detected in earlier work<sup>16</sup>), but some benzoylations result in significant amounts of these, especially the *o*-isomer. The proportion of *o*-iodobenzophenone formed tends to increase with an increase in reaction temperature, especially in nitrobenzene solution. Similarly, the extent of form-

<sup>16</sup> G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Amer. Chem. Soc.*, 1964, **86**, 2198.

could afford a benzoate species (*e.g.* PhCO<sub>2</sub><sup>-</sup>), which could give the ester by a nucleophilic substitution (i); displacement of the chloride ion could be catalyst-promoted. A fast displacement of bromine by a benzoate ion in dipolar aprotic solvents, by a process claimed to

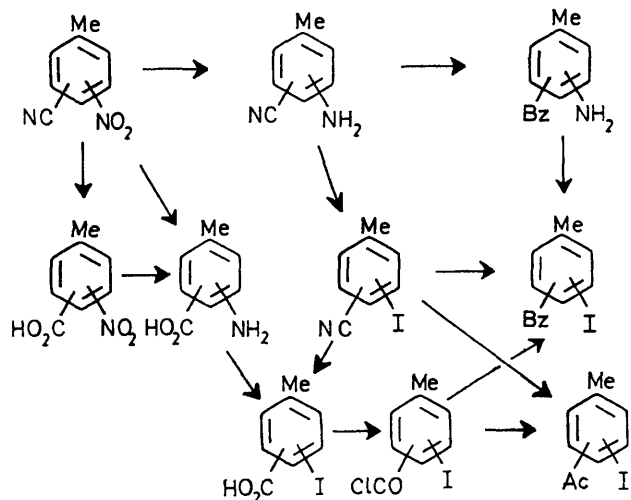


be S<sub>N</sub>2, has been reported for the analogous reaction with ethylene bromide.<sup>18</sup>

<sup>17</sup> P. A. Goodman and P. H. Gore, *J. Chem. Soc. (C)*, 1968, 966.

<sup>18</sup> S. E. Drewes and P. C. Coleman *J.C.S. Perkin I*, 1972, 2148.

*Acylation of Iodotoluenes.*—(a) *Synthesis of the isomeric ketones.* The synthesis of the acetyl and benzoyl derivatives of the iodotoluenes (ten isomers of each necessary for the complete product analyses) was carried out by the reactions outlined in the Scheme. The reactions were fairly standard; unaccountably some of them failed, and alternative procedures were required.



SCHEME Synthetic procedures used in the preparation of the isomeric iodomethylacetophenones and iodomethylbenzophenones

Thus, phenyl Grignard reagent could not be made to react with 2-iodo-4-, 2-iodo-6-, or 3-iodo-5-methylbenzonitrile; nor methyl Grignard reagent to react with 2-iodo-3-, 2-iodo-5-, 3-iodo-2-, 3-iodo-4-, or 4-iodo-3-methylbenzonitrile. Steric hindrance can explain only a few of these failures. However steric hindrance was presumably the reason that hydrolysis with alkali of 2-iodo-6-methylbenzonitrile proceeded only as far as the amide stage.

(b) *General results.* For the acylations of the iodotoluenes we did not use carbon disulphide, because of its unsatisfactory solvent characteristics; instead the two mildly solvating solvents chloroform and ethylene chloride, and two strongly solvating solvents nitromethane and nitrobenzene, were employed. Although the Perrier addition sequence was used throughout, the iodotoluenes underwent disproportionation to an appreciable extent.<sup>10</sup> From the non-ketonic fractions of most of the benzylation reactions, for instance, 2,4,5-triodotoluene could be isolated. Several isomers of diiodotoluene are also formed.<sup>10</sup> Toluene, generated through these side reactions, is quickly acylated. The relative proportions of the methylacetophenones were not determined, but the proportions of *o*-, *m*-, and *p*-methylbenzophenones (Tables 4, 6, and 8) were (within experimental error) those obtained with toluene directly under the appropriate experimental conditions. It seems,

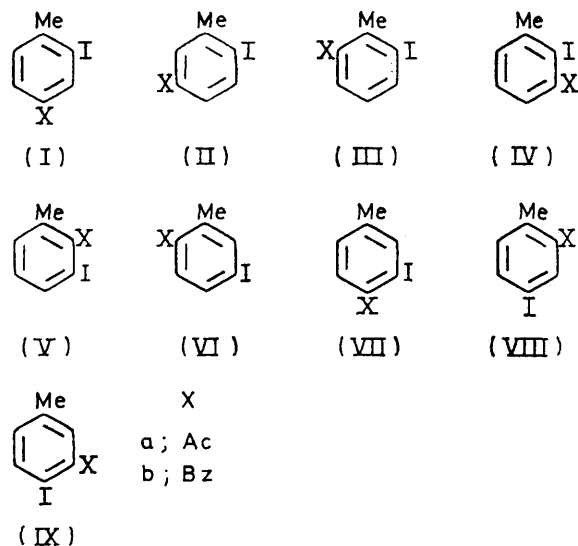
<sup>19</sup> P. H. Gore and P. A. Goodman, *Zhur. org. Khim.*, 1967, **3**, 1145.

<sup>20</sup> H. C. Brown, G. Marino, and L. M. Stock, *J. Amer. Chem. Soc.* 1959 **81**, 3310.

therefore, that deiodinated ketones are formed from the iodotoluenes mainly *via* free toluene, and other mechanisms, *e.g.* synchronous dehaloacylation,<sup>19</sup> can only be of minor importance.

The yields of deiodinated ketones mostly exceeded those of the normal ketones, especially with *p*-iodotoluene. The proportion of side reactions for each set of experimental conditions decreased in the sequence of isomers *p*- > *o*- > *m*- (> iodobenzene); and was greater for benzoylations than for acylations. The most successful 'normal' acylations were achieved in the nitro-solvents, in particular in nitrobenzene solution at 25°. These findings confirm that (1) the disproportionation is essentially a side reaction, (2) acetylation proceeds more rapidly than benzylation,<sup>20,21</sup> (3) as with related disubstituted benzene derivatives (*e.g.* dichlorobenzenes,<sup>13</sup> or the xylenes<sup>22,23</sup>), the reactivity of the iodotoluene substrate decreases in the sequence *m*- > *o*- > *p*-, and (4) the harmful side-effects of the catalyst are minimised by the use of nitro-solvents.

The ketonic fractions of the reactions carried out with *o*- and especially with *p*-iodotoluenes (but not with *m*-) contained substantial amounts of several unknown compounds. Their relative retention volumes on g.l.c. suggested that they were isomers of chloromethylacetophenones or -benzophenones. The formation of chloro-substituted ketones is explicable by analogy with the known formation of chloriodobenzenes under mild conditions from iodobenzene and solvated aluminium chloride,<sup>10</sup> and deiodoacylations analogous to those already discussed.



(c) *o*-Iodotoluene. All the acylation reactions of *o*-iodotoluene afford three of the four possible isomers (Tables 3 and 4). Normal acylation proceeds essentially

<sup>21</sup> P. H. Gore, C. K. Thadani, and S. Thorburn, *J. Chem. Soc. (C)*, 1968, 2502; P. H. Gore, J. A. Hoskins, and S. Thorburn, *J. Chem. Soc. (B)*, 1970, 1343.

<sup>22</sup> H. C. Brown, B. A. Bolto, and F. R. Jensen, *J. Org. Chem.*, 1958, **23**, 417.

<sup>23</sup> H. C. Brown and F. R. Jensen, *J. Amer. Chem. Soc.*, 1958, **80**, 2296.

at the two positions *para* to the substituents. Thus, in acetylations 3-iodo-4-methylacetophenone (Ia) and 4-iodo-3-methylacetophenone (IIa) account for >99% of the product. Small traces of a third isomer, 3-iodo-2-methylacetophenone (IIIa) are also formed. The fourth isomer, (IVa) is not formed. Friedel-Crafts benzoylations likewise give mainly the *para*-isomers (Ib) and (IIb). A third isomer (IVb) is formed in traces,

acetyl isomer (IXa) was not formed in any of our reactions (Table 7).

Benzoylations of *p*-iodotoluene in contrast gave both the normal acylation products (VIIIb) and (IXb), the former always predominating. The total yields of ketones, however, were invariably small (Table 8).

In both acylation modes the main iodo-ketones (except in nitromethane solution) were iodoaceto-(or iodobenzo-)

TABLE 3  
Friedel-Crafts acetylation of *o*-iodotoluene by the Perrier procedure

Solvent	Temp. (°C)	Methyl- acetophenones (total yield)	Products (%)				
			Iodomethylacetophenones			Unknowns *	
			Total yield	Proportions of isomers			
(IIIa)	(Ia)	(IIa)					
CHCl <sub>3</sub>	25	42	18	0.4	49	51	8.2 (6)
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	44	20	0.5	56	44	12 (6)
	50	58	19	0.7	56	44	15 (6)
MeNO <sub>2</sub>	25	12	16		63	37	3.0 (3)
PhNO <sub>2</sub>	25	8.2	27	0.3	57	43	0.8 (2)
	50	11	26	0.4	57	43	2.3 (4)

\* Percentage yield (w/w); the number of peaks on g.l.c. is given in parentheses. Retention volumes were intermediate between those for the methylacetophenone and the iodomethylacetophenones.

TABLE 4  
Friedel-Crafts benzoylation of *o*-iodotoluene by the Perrier procedure

Solvent	Temp. (°C)	Products (%)								
		Methylbenzophenones			Iodomethylbenzophenones			Unknowns *		
		Total yield	Proportions of isomers		Total yield	Proportions of isomers				
<i>o</i> -	<i>m</i> -	<i>p</i> -	(Ib)	(IIb)	(IVb)					
CHCl <sub>3</sub>	25	34	5.5	2.0	93	5.1	56	42	1.6	0.9 (2)
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	43	9.3	3.4	87	5.1	52	48		5.1 (3)
	50	52	8.5	2.1	89	3.1	51	49		8.7 (3)
MeNO <sub>2</sub>	25	22	7.0	1.0	92	11	47	53		2.1 (3)
PhNO <sub>2</sub>	25	18	6.1	1.4	93	10	53	45	1.9	1.2 (2)
	50	42	9.5	1.9	89	13	52	46	1.6	4.9 (3)

\* Percentage yield (w/w); the number of peaks on g.l.c. is given in parentheses. Retention volumes were intermediate between those for the methylbenzophenones and the iodomethylbenzophenones.

its orientation being different from that formed in the acetylations. In all the acylations the two main isomers are formed approximately in equal amounts.

(d) *m*-Iodotoluene. With *m*-iodotoluene three of the possible four isomers are again formed in the acylation reactions (Tables 5 and 6). The preferred position of attack is *para* to the iodo-group [to give (VI)], though appreciable amounts of the other *p*-isomer (VII) are also formed. The 2-position of *m*-iodotoluene, flanked by two substituents, does not appear to be significantly hindered sterically, since up to 5% of isomer (Va) (in acetylations), or up to 21% of isomer (Vb) (in benzoylations, which are reactions of lower steric requirements than are acetylations<sup>20</sup>), were formed.

(e) *p*-Iodotoluene. The acylations of *p*-iodotoluene exhibit several unusual features. Of the two normal acetylation products (VIIIa) and (IXa) only the former is obtained, and that in very low yield (both overall and as a proportion of the total isomers). The high value (66%) quoted for nitromethane solution is suspect owing to the small size of the g.l.c. peaks. The other normal

phenones derived not from the substrate used, *p*-iodotoluene, but from *o*-iodotoluene. Acetylations of *p*-iodotoluene, therefore, gave as main products the ketones

TABLE 5  
Friedel-Crafts acetylation of *m*-iodotoluene by the Perrier procedure

Solvent	Temp. (°C)	Methylaceto- phenones (total yield)	Products (%)			
			Iodomethylacetophenones			Unknowns *
			Total yield	Proportions of isomers		
(Va)	(VIa)	(VIIa)				
CHCl <sub>3</sub>	25	22	46	1.2	69	30
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	31	42	1.0	60	39
	50	28	47	1.3	60	38
MeNO <sub>2</sub>	25	2.8	18	5.3	85	10
PhNO <sub>2</sub>	25	0.7	37	0.8	70	29
	50	2.1	36	0.8	74	25

(Ia) and (IIa); and benzoylations the ketones (Ib) and (IIb). The formation of these rearranged ketones, though anomalous, is not entirely unexpected. It has

been shown that Friedel-Crafts benzylation of *p*-chlorobenzene affords 3,4-dichlorobenzophenone in 11% yield.<sup>13,19</sup> Acetylation of *p*-dibromobenzene is reported to give 2,4-dibromoacetophenone.<sup>15</sup> *p*-Bromotoluene, on acetylation, affords two anomalous ketones, 4-bromo-3-methylacetophenone (derived from *o*-bromotoluene)

mobile, but that rearrangements would be less likely to occur in the 'anhydrous' conditions obtaining. The formation of the ketones (I) and (II) from *p*-iodotoluene is explicable, therefore, in terms of a rapid conversion of *p*- into *o*-iodotoluene, which competes with the slower acylation of the *p*-isomer. Such a view would require

TABLE 6  
Friedel-Crafts benzylation of *m*-iodotoluene by the Perrier procedure

Solvent	Temp. (°C)	Products (%)							
		Methylbenzophenones			Iodomethylbenzophenones				
		Total yield	Isomers			Total yield	Proportions of isomers		
<i>o</i> -	<i>m</i> -		<i>p</i> -	(VIIb)	(Vb)		(VIb)		
CHCl <sub>3</sub>	25	8.5	5.6	1.2	93	18	31	8.6	60
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	23	10	7.3	83	29	37	11	52
	50	41	7.6	2.4	90	18	31	21	48
MeNO <sub>2</sub>	25	1.6	10	1.1	89	36	39	13	48
PhNO <sub>2</sub>	25	2.6	6.3	1.2	93	37	34	9.5	56
	50	6.3	10	1.9	88	68	40	11	49

TABLE 7  
Friedel-Crafts acetylation of *p*-iodotoluene by the Perrier procedure

Solvent	Temp. (°C)	Products (%)					Unknowns <sup>a</sup>
		Methylacetophenones (total yield)	Iodomethylacetophenones				
			Total yield	Isomers			
			(VIIIa)	(Ia)	(IIa)		
CHCl <sub>3</sub>	25	36	11	6.2	57	37	27 (4)
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	42	11.5	5.9	66	28	25 (5)
	50	51	10	5.9	73	21	22 (5)
MeNO <sub>2</sub>	25	22	0.6	66 <sup>b</sup>	21	13	2.9 (3)
PhNO <sub>2</sub>	25	8.7	4.8	23	45	32	13 (1)
	50	9.2	4.0	17	47	36	3.5 (4)

<sup>a</sup> Percentage yield (w/w) of unknown peaks on g.l.c.; the number of peaks is given in parentheses. Retention volumes were between those of the last methylacetophenone and the last iodomethylacetophenone. <sup>b</sup> See text.

TABLE 8  
Friedel-Crafts benzylation of *p*-iodotoluene by the Perrier procedure

Solvent	Temp. (°C)	Products (%)							Unknowns <sup>a</sup>		
		Methylbenzophenones			Iodomethylbenzophenones						
		Total yield	Isomers			Total yield	Proportions of isomers				
<i>o</i> -	<i>m</i> -		<i>p</i> -	(IXb)	(VIIIb)		(Ib)	(IIb)			
CHCl <sub>3</sub>	25	44	5.8	1.9	92	2.1	8.0	10	39	43	1.6 (2)
C <sub>2</sub> H <sub>4</sub> Cl <sub>2</sub>	25	52	11	3.6	86	1.2	8.7	16	39	36	5.6 (3)
	50	54	9.9	2.5	88	3.6	6.4	12	24	57	9.2 (3)
MeNO <sub>2</sub>	25	21	7.9	1.3	91	1.7	20	38	23	19	
PhNO <sub>2</sub>	25	31	6.9	1.4	92	5.2	14	15	39	32	0.8 (2)
	50	48	8.9	1.6	90	6.0	11	30	26	33	5.2 (2)

<sup>a</sup> Percentage yield (w/w) of unknown peaks on g.l.c.; the number of peaks is given in parentheses. Retention volumes were intermediate between those of 4-methylbenzophenone and 3-iodo-4-methylbenzophenone.

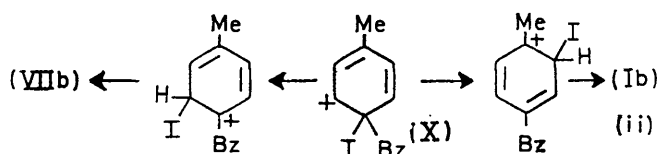
and 4-bromo-2-methylacetophenone (derived from *m*-bromotoluene).<sup>14</sup>

Isomerisations of fluoro-, chloro-, and bromo-toluenes, have been reported to take place through the agency of aluminium chloride promoted by water.<sup>24</sup> The mechanism was believed to involve a fast, proton-initiated, intermolecular halogen shift of *o*- or *p*-halogenotoluenes, and slower intramolecular 1,2-shifts. The migrational aptitudes followed the order Br > Cl > F. One may conclude that iodine atoms in our compounds would be very

that the formation of the isomers (I) and (II), in both acetylation and benzylation, occurs in the same proportions as they do if *o*-iodotoluene is the initial substrate. There is generally good agreement of these data [ratios (I) : (II)] in nitromethane and in nitrobenzene solutions. In the acetylations of *p*-iodotoluene conducted in chloroform or ethylene chloride, however, the ratios of isomers [(Ia) : (IIa)] formed are much higher than expected. In the latter solvent at 50°, for example, this ratio is 3.5 : 1

<sup>24</sup> G. A. Olah and M. W. Meyer, *J. Org. Chem.*, 1962, **27**, 3464.

whereas under the same conditions *o*-iodotoluene gives a ratio of these same isomers of 1:3. Therefore, in these cases there is evidence of a mode of formation of ketone (Ia) from *p*-iodotoluene additional to that *via* *o*-iodotoluene. Conversely, benzylation under identical experimental conditions gives a ratio [(Ib) : (IIb)] of 0.42 : 1, which is less than half of that expected (*ex o*-iodotoluene 0.96 : 1). This suggests an additional mode of formation here of the ketone (IIb) from *p*-iodotoluene. An *ipso*-complex of the type (X) could undergo a 1,5-halogen shift,<sup>25</sup> which would lead to the ketone (Ib) [see (ii)]. The ketone



(VIIb) would result from a 1,2-halogen shift, but such a rearrangement apparently does not occur here. We are unable to account for an anomalously low ratio of ketones [(Ib) : (IIb)].

(f) *Quantitative predictions.* Competitive acylation in order to determine the relative reactivities of iodobenzene and its derivatives was not feasible, because of the complexity of the acylation reactions. However, an estimate was obtained of the isomer proportions for the Friedel-Crafts benzoylations of the iodotoluenes in nitrobenzene solution at 25°. We used known values for the corresponding benzylation of the related substrate

TABLE 3

Observed and calculated percentages of isomers formed in Friedel-Crafts benzoylations of iodotoluenes in nitrobenzene at 25°

Substrate	Isomer	Found (%)	Calc. (%)
<i>o</i> -Iodotoluene	(IVb)	1.9	0.8
	(Ib)	53	37
	(IIb)	45	61
<i>m</i> -Iodotoluene	(IIIb)		1.6
	(Vb)	9.5	0.9
	(VIIb)	34	24
3-Iodo-5-methylbenzophenone			0.04
	(VIb)	56	75
<i>p</i> -Iodotoluene	(VIIIb)	52	66
	(IXb)	48	34

chlorobenzene<sup>17</sup> ( $k_{\text{chlorobenzene}}/k_{\text{benzene}} = 0.0260$ ), an estimate of 1.15 for the reactivity ratio  $k_{\text{iodobenzene}}/k_{\text{chlorobenzene}}$  (from data<sup>26</sup> on the related but not closely similar system, Friedel-Crafts benzylations in nitromethane solution), and extrapolated isomer percentages (Table 2) for iodobenzene at 25° (2.3% *o*-, 0.7% *m*-, and 97% *p*-). This

\* For details of Supplementary Publications, see Notice to Authors No. 7 in *J. Chem. Soc. (A)*, 1970, Issue No. 20.

<sup>25</sup> P. Rys, P. Skrabal, and H. Zollinger, *Angew. Chem.*, 1972, **11**, 874.

<sup>26</sup> G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, 1962, **84**, 1695.

<sup>27</sup> H. C. Brown and H. L. Young, *J. Org. Chem.*, 1957, **22**, 719, 724.

<sup>28</sup> M. Godfrey, *J. Chem. Soc. (B)*, 1971, 1545.

led to the following estimates of the partial rate factors for the benzylation of iodobenzene in nitrobenzene at 25°:  $o_f = 2.1 \times 10^{-3}$ ,  $m_f = 6.3 \times 10^{-4}$ ,  $p_f = 1.7 \times 10^{-1}$ , which can be used together with reported data<sup>23,27</sup> on the benzylation of toluene under these experimental conditions ( $o_f = 32.6$ ,  $m_f = 5.0$ , and  $p_f = 831$ ). In this way qualitatively correct results are obtained on overall relative reactivities: *m*-iodotoluene 42, *o*-iodotoluene 8.0, iodobenzene 1.00, and *p*-iodotoluene 0.17. Table 9 shows calculated and experimental isomer percentages of normal benzylation products, and these show a good correspondence. This is remarkable in view of the several assumptions made for our predictions, and the fact that doubt remains<sup>28</sup> about the validity of achieving additivity of substituent effects for aromatic electrophilic substitutions.

## EXPERIMENTAL

I.r. spectra were recorded for liquid films. A dagger (†) is used to indicate that appropriate u.v., i.r., and n.m.r. data are available in Supplementary Publication No. SUP 20851 (11 pp., 1 microfiche).\*

*G.l.c.*—The products from the acylation experiments were analysed with the aid of two columns: (A) a stainless steel column (2 m  $\times$   $\frac{1}{4}$  in ext. diam.), packed with Bentone 34 (1.5%) and silicone fluid (3.5%) in HMDS Chromosorb W, and (B) a stainless-steel column (2 m  $\times$  2 mm ext. diam.), packed with SE 30 (10%) in Celite (100–120 mesh). The carrier gas was nitrogen, and the detectors were flame-ionisation type. Peak areas were evaluated by triangulation. Mass detector responses were determined, and applied when appropriate. For acylations of iodobenzene column (A) was used at 140°. For benzoylations of iodobenzene column (B) was used at 200°. For acetylations of the iodotoluenes column (A) at 160° or column (B) at 175° was used; for the benzoylations of these substrates column (A) at 210° or column (B) at 200° was used. Kováts<sup>29</sup> retention indices were determined on column (B) and are given the Supplementary Publication (see preamble).

*Materials.*—The isomeric iodotoluenes used were >99% pure (i.r.; g.l.c.).

*2-Iodoacetophenone.* This ketone was prepared by the magnesiumalonate method of Bowman,<sup>30</sup> as an oil, b.p. 90–92° at 0.3 mmHg,  $n_D^{26}$  1.6148 (lit.,<sup>31</sup> b.p. 86–88° at 0.5 mmHg,  $n_D^{26}$  1.6148); the semicarbazone had m.p. 179–180.5° (lit.,<sup>32</sup> 178.5–179.5°).

*3-Iodoacetophenone.* The ketone was obtained similarly from 3-iodobenzoyl chloride (b.p. 146–147° at 17 mmHg) as an oil (75%), b.p. 76–78° at 0.2 mmHg,  $n_D^{25}$  1.6172 (lit.,<sup>33</sup> b.p. 85–86° at 0.5 mmHg,  $n_D^{25}$  1.620); the semicarbazone had m.p. 219–220°.

*4-Iodoacetophenone.* The ketone is best prepared by a Friedel-Crafts acetylation of iodobenzene (Perrier method) in ethylene chloride solution at 25° for 1 week, as crystals (yield 80%), m.p. 85–86° (from light petroleum).

<sup>29</sup> E. Kováts, *Helv. Chim. Acta*, 1958, **41**, 1915; 1959, **42**, 2709; L. S. Ettre, *Analyt. Chem.*, 1964, **36**, 31A.

<sup>30</sup> R. E. Bowman, *J. Chem. Soc.*, 1950, 322.

<sup>31</sup> G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, 1966, **31**, 677.

<sup>32</sup> W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 1941, 487.

<sup>33</sup> D. E. Pearson, H. W. Pope, W. W. Hargrave, and W. E. Stamper, *J. Org. Chem.*, 1958, **23**, 1412.

**2-Iodobenzophenone.** Anhydrous aluminium chloride (3.3 g) was added in portions to a stirred solution of 2-iodobenzoyl chloride (6.7 g) in dry benzene (20 ml), and the solution was stirred at 50° for 24 h. The ketone was isolated in the usual way, as an oil (73%), b.p. 179° at 3 mmHg (lit.,<sup>34</sup> 210—211° at 13 mmHg).

**3-Iodobenzophenone.** This isomer was obtained like the previous ketone, as an oil (67%), b.p. 184—186° at 2 mmHg (lit.,<sup>34</sup> b.p. 226° at 18 mmHg; m.p. 42.5°).

**4-Iodobenzophenone.** This ketone was isolated from Friedel-Crafts benzoylation reactions (Table 2), as crystals, m.p. 101—102° (from light petroleum). A 75% yield should be obtainable from a Perrier reaction allowed to proceed in nitrobenzene solution at 50° for several weeks.

**Methylnitrobenzonitriles.** The isomeric methylnitrobenzonitriles, used as key intermediates (Scheme), were all known compounds.† Seven isomers were obtained by Sandmeyer reactions<sup>35</sup> on nitrotoluidines, which were commercially available. 2-Methyl-5-nitrobenzonitrile, m.p. 105—107°, was prepared from *o*-toluonitrile with fuming nitric acid at 45—50°. 3-Methyl-2-nitrobenzoic acid, m.p. 225—228° (lit.,<sup>37</sup> 213—220°) was converted (74%) into the amide, m.p. 191—193° (lit.,<sup>38</sup> 192°), dehydration of which (POCl<sub>3</sub>) gave 3-methyl-2-nitrobenzonitrile (84%), m.p. 84—85° (lit.,<sup>35</sup> 84°). 3-Methyl-4-nitrobenzonitrile, m.p. 81—82° (lit.,<sup>35</sup> 80°) was obtained similarly (73%).

**Aminomethylbenzonitriles.** Hydrogenation of the methylnitrobenzonitriles was effected in ethyl acetate over 5% palladium-charcoal or in absolute ethanol over 10% palladium-charcoal (for 2-amino-6-methylbenzonitrile and

**Iodomethylbenzophenones.** Three methods (A—C) were employed for the syntheses of the isomeric iodomethylbenzophenones; the best results obtained are collected in Table 11. Nine of the ten isomers were new compounds.†

TABLE 11

M.p.s or b.p.s and microanalytical data of the isomeric iodomethylbenzophenones

Substituted benzo-phenone		Method	Yield (%)	M.p. <sup>a</sup> (°C), or b.p. (°C) [mmHg]	Found (%) <sup>b</sup>	
Me	I				C	H
2	3	A	35	151—152 [0.7]	52.5	3.5
2	4	A	67	144—146 [0.2]	52.5	3.5
2	5	A	61	60—61	52.1	3.5
2	6	B	48	84—85	52.1	3.5
3	2	A	34	84—85	52.0	3.5
3	4	A	59	77—78 <sup>c</sup>	52.1	3.5
3	5	B	52	152—154 [0.35]	52.3	3.5
3	6	A	25	62—63	52.3	3.5
4	2	C	53	74—75 <sup>d</sup>	52.4	3.6
4	3	A	54	97—98	52.7	3.5

<sup>a</sup> From methanol. <sup>b</sup> C<sub>14</sub>H<sub>11</sub>IO requires C, 52.2; H, 3.4%. <sup>c</sup> Lit. m.p. 78° (E. Müller and E. Hertel, *Annalen*, 1944, 555, 183). <sup>d</sup> Semicarbazone had m.p. 217—219° (Found: C, 46.7; H, 3.7; N, 11.6. C<sub>15</sub>H<sub>14</sub>IN<sub>3</sub>O requires C, 47.5; H, 3.7; N, 11.1%).

**Method A. Grignard reaction with iodomethylbenzonitrile.** The iodomethylbenzonitrile (6.1 g) in anhydrous ether was added to a stirred, boiling solution prepared from iodobenzene (22.4 g) and magnesium turnings (2.4 g) in anhydrous ether (40 ml). Boiling and stirring was continued for 20 h, then the mixture was cooled and treated with a saturated solution of ammonium chloride. The combined ethereal extracts were extracted with 2N-sulphuric acid, and the acidic extracts were heated at 95° for 3 h. Isolation in the usual way gave in most cases a brown gum, extraction of which with light petroleum gave the crude ketone, which was purified by distillation or crystallisation. The method was successful with seven isomers (Table 11), but failed with 2-iodo-4-, 2-iodo-6-, and 3-iodo-5-methylbenzonitriles.

**Method B. Friedel-Crafts reaction of iodomethylbenzoyl chloride with benzene.** These reactions were carried out with an excess of benzene at 50° for 30 h; reasonable yields were obtained with 2-iodo-6- and 3-iodo-5-methylbenzoyl chlorides (see later), but the reaction failed with 2-iodo-4-methylbenzoyl chloride.

**Method C. (i) 2-Amino-4-methylbenzophenone.** This ketone was prepared by the action of phenylmagnesium bromide on 2-amino-4-methylbenzonitrile as yellow needles, m.p. 65.5—66° (lit.,<sup>39</sup> 66°). 2-Acetamido-4-methylbenzophenone had m.p. 87—88° (from aqueous ethanol) (Found: C, 75.9; H, 6.0; N, 5.4. C<sub>16</sub>H<sub>15</sub>NO<sub>2</sub> requires C, 75.9; H, 6.0; N, 5.5%).

(ii) 2-Iodo-4-methylbenzophenone. This was obtained in the usual way by the diazo-reaction. Purification of the ketone was achieved by chromatography over alumina, and crystallisation (see Table 11).

**Iodomethylacetophenones.** Two methods (D and E) were

TABLE 10

M.p.s and microanalytical data of the isomeric iodomethylbenzonitriles

Substituted 1-cyanobenzene		Yield (%)	M.p. (°C)	Found (%) <sup>a</sup>		
Me	I			C	H	N
2	3	67	52—53 *	39.9	2.7	5.8
2	4	49	70—71 *	39.8	2.6	5.6
2	5	69	72—74 * <sup>b</sup>	39.5	2.6	5.9
2	6	70	91—92 *	39.8	2.5	6.0
3	2	56	50—51 †	39.7	2.5	5.7
3	4	88	76—77 *	39.3	2.5	6.0
3	5	57	55—56 *	39.5	2.6	5.7
3	6	56	53—54 *	39.3	2.4	5.9
4	2	65	86—87 *	39.8	2.3	5.8
4	3	76	57—58 * <sup>c</sup>	39.2	2.6	5.5

\* From light petroleum. † From benzene-light petroleum.

<sup>a</sup> C<sub>8</sub>H<sub>6</sub>IN requires C, 39.5; H, 2.5; N, 5.8%. <sup>b</sup> Lit., m.p. 72—73° (V. Baliah and K. Apartajithan, *Tetrahedron*, 1963, 19, 2177). <sup>c</sup> Lit. m.p. 57.5° (J. Kenner and E. Witham, *J. Chem. Soc.*, 1912, 103, 232).

3-amino-4-methylbenzonitrile), at room temperature. The amines had correct microanalytical figures (C, H, and N), m.p.s very close to those reported, and the anticipated spectroscopic properties.†

**Iodomethylbenzonitriles.** Diazotisation of the aminoethylbenzonitriles in 20% (v/v) sulphuric acid, followed by reaction in the usual way with an excess of potassium iodide, afforded the corresponding iodomethylbenzonitriles in good yield. Eight isomers were new compounds; † details are given in Table 10.

<sup>34</sup> P. J. Montagne, *Rec. Trav. chim.*, 1915, 34, 156.

<sup>35</sup> S. Gabriel and A. Thieme, *Ber.*, 1919, 52, 1079.

<sup>36</sup> C. Candea and E. Mackovski, *Bull. Soc. chim. France*, 1938, 5, 1350.

<sup>37</sup> A. Tomisek, B. Graham, A. Griffith, C. S. Pease, and B. E. Christensen, *J. Amer. Chem. Soc.*, 1946, 68, 1587.

<sup>38</sup> M. C. Geerling and J. P. Wibaut, *Rec. Trav. chim.*, 1934, 53, 1015.

<sup>39</sup> E. Ritchie, *J. Proc. Roy. Soc. New South Wales*, 1946, 80, 33.

used to prepare the isomeric iodomethylacetophenones, only two of which were previously known (see Table 12).† For semicarbazones see Table 13.

TABLE 12

M.p.s or b.p.s and microanalytical data of the isomeric iodomethylacetophenones

Substituted acetophenone		Method	Yield (%)	M.p. <sup>a</sup> (°C), or b.p. (°C) [mmHg]	Found (%) <sup>b</sup>	
Me	I				C	H
2	3	E	75	93—94 [0.5]	41.9	3.5
2	4	D	31	94 [0.5] <sup>e</sup>	42.1	3.5
2	5	D	59	31—32 <sup>d</sup>	42.0	3.7
2	6	E	67	51—52	41.8	3.5
3	2	E <sup>e</sup>	25	90—91 [0.3]	41.6	3.7
3	4	E	32	40.5—41 <sup>f</sup>	41.3	3.5
3	5	E	52	102 [4.0]	41.5	3.5
3	6	E	46	85—86 [0.1]	41.9	3.5
4	2	E	82	92—93 [0.3]	41.2	3.4
4	3	E	45	43.5—44 <sup>f</sup>	41.5	3.5

<sup>a</sup> From propan-2-ol. <sup>b</sup> C<sub>8</sub>H<sub>7</sub>IO requires C, 41.6; H, 3.5%. <sup>c</sup> Lit. b.p. 134° at 8 mmHg (T. Sato and M. Oki, *Bull. Chem. Soc. Japan*, 1957, **30**, 958); lit.<sup>41</sup> b.p. 153—154° at 13 mmHg. <sup>d</sup> Lit. b.p. 134—135° at 5 mmHg (V. Baliah and K. Apartajithan, *Tetrahedron*, 1963, **19**, 2177). <sup>e</sup> Purified via the semicarbazone. <sup>f</sup> Ketone of uncertain structure had m.p. 42—43° (ref. 43) or 39° (ref. 40).

TABLE 13

Semicarbazones of iodomethylacetophenones

Substituted acetophenone semicarbazone		M.p. (°C)	Found (%) <sup>a</sup>		
Me	I		C	H	N
2	3	203—206	38.1	3.8	13.0
2	4	202—204	37.6	3.8	13.8
3	2	200—205	38.2	3.9	13.3
3	6	199—202	37.8	3.9	13.3

<sup>a</sup> C<sub>10</sub>H<sub>12</sub>IN<sub>3</sub>O requires C, 37.8; H, 3.8; N, 13.2%.

**Method D. Grignard reaction with iodomethylbenzotrile.** This was analogous to method A, but with methylmagnesium iodide as the Grignard reagent. The intermediate imines underwent hydrolysis rapidly, and therefore washing of the ethereal extracts with acid was omitted. The method failed with 2-iodo-3-, 2-iodo-5-, 3-iodo-2-, 3-iodo-4-, and 4-iodo-3-methylbenzotriles.

**Method E. Magnesiummalonate procedure.** Treatment of a solution of diethyl ethoxymagnesiummalonate with the appropriate benzoyl chloride was followed by hydrolysis and decarboxylation.<sup>30</sup>

**Preparation of substituted benzoyl chlorides needed for methods B and E.** (i) **Hydrolysis of iodomethylbenzotriles.** **General method.** Hydrolysis was achieved by boiling the nitrile (7 g) for 4—6 h with 5N-sodium hydroxide solution (20 ml) and diethylene glycol (20 ml). In this way were

obtained 2-iodo-4-methylbenzoic acid (80%), m.p. 133—134° (lit.<sup>40</sup> 127°); 3-iodo-4-methylbenzoic acid (95%), m.p. 208—209° (lit.<sup>41</sup> 205—206°); 3-iodo-2-methylbenzoic acid (75%), m.p. 123—124° (lit.<sup>42</sup> 124°); and 4-iodo-3-methylbenzoic acid (95%), m.p. 223—224° (ethanol) (Found: C, 36.8; H, 2.6. C<sub>8</sub>H<sub>7</sub>IO<sub>2</sub> requires C, 36.7; H, 2.7%) (lit.<sup>43</sup> m.p. 198—199°).

From the hydrolysis giving 3-iodo-2-methylbenzoic acid, a neutral component (15%), 3-iodo-2-methylbenzamide, m.p. 166° (from ethanol), was isolated (Found: C, 37.1; H, 3.1; N, 5.4. C<sub>8</sub>H<sub>8</sub>INO requires C, 36.8; H, 3.1; N, 5.4%);  $\nu_{\max}$  (mull) 3440, 3250 (NH), and 1658 cm<sup>-1</sup> (C=O).

(ii) **Hydrolysis of 2-iodo-6-methylbenzotrile.** 2-Iodo-6-methylbenzotrile (10 g) was boiled with 10N-sodium hydroxide solution (50 ml) and diethylene glycol (50 ml) for 1.5 h. Dilution with water gave a precipitate of 2-iodo-6-methylbenzamide (95%), m.p. 201—202° (from ethanol) (Found: C, 37.2; H, 3.1; N, 5.7%),  $\nu_{\max}$  (mull) 3470, 3250 (NH), and 1648 cm<sup>-1</sup> (C=O).

Treatment of the amide with nitrous acid<sup>44</sup> gave 2-iodo-6-methylbenzoic acid, m.p. 112—114° (lit.<sup>42</sup> 115°).

(iii) **Methylnitrobenzoic acids.** 5-Methyl-2-nitrobenzoic acid, m.p. 132—134° (lit.<sup>45</sup> 134°), was obtained together with 3-methyl-2-nitrobenzoic acid, m.p. 218—222°, by nitration of *m*-toluic acid.<sup>46</sup> 3-Methyl-5-nitrobenzoic acid, m.p. 176—177° (lit.<sup>35</sup> 174°), was obtained from the nitrile by hydrolysis with sulphuric acid (ca. 80%) at 125°.

(iv) **Aminomethylbenzoic acids.** 3-Methyl-2-nitrobenzotrile (12 g) in absolute ethanol (500 ml) was hydrogenated at 25° and normal pressure over 5% palladium-charcoal (1.2 g) until uptake of hydrogen had slowed considerably. The catalyst was filtered off, and the solvent removed to give an oily solid, probably a mixture of 2-amino-3-methylbenzotrile [ $\nu_{\max}$  2190 cm<sup>-1</sup> (C≡N)] and 2-amino-3-methylbenzamide [ $\nu_{\max}$  1630 cm<sup>-1</sup> (C=O)]. The mixture was then boiled with 4N-sodium hydroxide (100 ml) for 4 h, to give 2-amino-3-methylbenzoic acid (9.9 g, 89%), m.p. 174—175° (lit.<sup>35</sup> 172°).

From the corresponding nitro-acids, by hydrogenation at room temperature and pressure in absolute ethanol over 10% palladium-charcoal, were obtained 3-amino-5-methylbenzoic acid (95%), m.p. 180—182° (lit.<sup>35</sup> 183°), and 2-amino-5-methylbenzoic acid (64%), m.p. 174—176° (lit.<sup>45</sup> 179°); methyl ester, m.p. 62—63° (lit.<sup>47</sup> 58°).

(v) **Iodomethylbenzoic acids.** These acids were obtained in the usual way from the amino-acids by the diazo-reaction. 2-Iodo-3-methylbenzoic acid (41%) had m.p. 149—150° (lit.<sup>45</sup> 150°). 3-Iodo-5-methylbenzoic acid (41%) had m.p. 185—186° (from benzene-light petroleum) (Found: C, 36.9; H, 2.8. C<sub>8</sub>H<sub>7</sub>IO<sub>2</sub> requires C, 36.7; H, 2.7%). 2-Iodo-5-methylbenzoic acid was purified via its methyl ester, b.p. 104—105° at 0.6 mmHg, or its ethyl ester, b.p. 118—122° at 0.5 mmHg; it had m.p. 123—124° (from water) (lit.<sup>48</sup> 126.5—129°) (Found: C, 36.7; H, 2.7%).

(vi) **Iodomethylbenzoyl chlorides.** The appropriate acid was boiled under reflux with thionyl chloride (5 ml per g of acid); the excess of reagent was distilled off and the residue was distilled under reduced pressure (Table 14).

**Attempted reduction of 4-iodo-3-nitrotoluene.** Attempts to

<sup>40</sup> E. Kloeppel, *Ber.*, 1893, **26**, 1733.

<sup>41</sup> A. M. Fleifel, *J. Org. Chem.*, 1960, **25**, 1024.

<sup>42</sup> D. Peltier, *Compt. rend.*, 1954, **237**, 357.

<sup>43</sup> T. Sato, *Bull. Chem. Soc. Japan*, 1959, **32**, 1130.

<sup>44</sup> M. V. Bouveault, *Bull. Soc. chim. France*, 1893, **9**, 368; J. J. Sudborough, *J. Chem. Soc.*, 1895, **67**, 601.

<sup>45</sup> D. Peltier and A. Pichevin, *Compt. rend.*, 1957, **245**, 436.

<sup>46</sup> G. E. Dunn and R. Prysiazniuk, *Canad. J. Chem.*, 1961, **39**, 285.

<sup>47</sup> I. Niculescu-Duvaz, M. Ionescu, A. Cambanis, M. Vitan, and V. Feyns, *J. Medicin. Chem.*, 1968, **11**, 500.

<sup>48</sup> R. C. Hinton, F. G. Mann, and I. T. Millar, *J. Chem. Soc.*, 1958, 4704.



reduce 4-iodo-3-nitrotoluene with iron-acetic acid,<sup>49</sup> iron(II) sulphate-ammonia,<sup>50</sup> or hydrazine-Raney nickel W-7<sup>51</sup> all proved unsatisfactory. The product from the first procedure was converted into 3-acetamido-4-iodotoluene, m.p. 152—153° (lit.,<sup>50</sup> 151°) (Found: C, 39.4; H, 3.6; N, 5.2. Calc. for C<sub>9</sub>H<sub>10</sub>IO: C, 39.3; H, 3.7; N, 5.1%).

TABLE 14  
Iodomethylbenzoyl chlorides<sup>a</sup>

Substituted benzoyl chloride		B.p. (°C) [mmHg]	Yield (%)	$\nu_{\max.}/$ cm <sup>-1</sup> (C=O)
Me	I			
2	3	92—94 [0.8]	87	1768
2	6	70 [0.2]	84	1780
3	2	102—104 [1.0]	84	1762
3	4	96—98 [0.3]	79	1752
3	5	80—82 [0.25]	96	1748
3	6	95—96 [0.3]	87	1756
4	2	99—100 [0.5]	71	1752
4	3	110 [1.3]	82	1739

<sup>a</sup> Elemental microanalysis were not carried out.

*Friedel-Crafts Acylations.*—(a) *General method (Perrier procedure).* The acyl chloride (0.05 mol) was added with stirring to aluminium chloride (6.7 g, 0.05 mol) in the solvent (75 ml). To the resultant solution the iodo-compound (0.05 mol) in the solvent (25 ml) was added at the appropriate temperature in one portion. The reaction was allowed to proceed for 120 h, ice (50 g) and 10N-hydrochloric acid (25 ml) were then added, and the mixture was stirred for 1—2 h. After filtration, if necessary, the organic phase was washed with 2N-hydrochloric acid, water, sodium hydrogen sulphite solution, water, sodium hydrogen carbonate solution, and water, dried (MgSO<sub>4</sub>), filtered, and evaporated. When nitrobenzene was the solvent it was removed by distillation *in vacuo* through a 10 cm fractionating column packed with glass helices.

For reactions of iodobenzene a sample of the product (1 g) dissolved in benzene was chromatographed on a column of alumina (Spence type H), with benzene as eluant, until only pure solvent was being eluted. The solvent was then removed and the residue analysed by g.l.c.

For reactions with the iodotoluenes the crude product was separated into non-ketonic and ketonic fractions as follows. A sample (2.0 g) of the product, say from a benzoylation in ethylene chloride solution, was dissolved in light petroleum

(b.p. 40—60°; 100 ml) and passed onto a column of alumina (75 g). Elution with successive portions (100 ml) of light petroleum gave non-ketonic fractions (0.502 g, 0.504 g, 0.008 g, nil); further elution with portions (100 ml) of benzene gave ketonic fractions (0.872 g, 0.129 g, nil). The non-ketonic fractions contained unchanged iodotoluene and rearrangement products. The ketonic fractions were combined and analysed by g.l.c.

(b) *Isolation of products.* A benzoylation reaction carried out on iodobenzene (0.1 mol scale) in ethylene chloride was worked up in the usual way. The crude product was steam-distilled until the distillate was clear. The residue was extracted with ether, and the extract was washed with sodium hydroxide solution and water. Evaporation to dryness and crystallisation (methanol) then gave *p*-iodobenzophenone. The steam-distillate was extracted with ether; the extract was washed with sodium hydroxide solution and water, dried, and evaporated, to give an oil which was fractionally distilled. The first fraction, b.p. 60—70° at 12—13 mmHg, was iodobenzene. The second fraction (4.5 g), b.p. 108—126° at 2.5 mmHg, showed i.r. spectral evidence for a ketone and an aromatic ester. Refractionation gave three fractions; the first (2.1 g), b.p. 103—113° at 2.5 mmHg, was dissolved in hot methanol (5 ml) and allowed to crystallise, giving *p*-di-iodobenzene (0.5 g; m.p. 130—131°). The third fraction (1.2 g), b.p. 140—150° at 2.5 mmHg, on treatment with Brady's reagent afforded benzophenone 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 239—240.5°.

The ester component was obtained from an attempted benzoylation of iodobenzene in ethylene chloride, catalysed by tin(IV) chloride. The high-boiling fraction from this reaction was an oil, b.p. 96—98° at 0.9 mmHg,  $n_D^{22}$  1.5290, identical (i.r.) with 2-chloroethyl benzoate, prepared<sup>52</sup> from benzoyl chloride and ethylene chlorohydrin, as an oil (b.p. 108—110° at 2 mmHg;  $n_D^{22}$  1.5292), which also gave identical retention data in g.l.c. experiments.

From most of the benzoylations, but few of the acetylations, of the iodotoluenes it was possible to isolate 2,4,5-tri-iodotoluene, m.p. and mixed m.p. 121—122°,<sup>10</sup> by crystallisation.

We thank Dr. R. E. Bowman for the provision of facilities at Parke-Davis Co. (to D. J. W.).

[3/1374 Received, 29th June, 1973]

<sup>49</sup> H. L. Wheeler, *Amer. Chem. J.*, 1910, **44**, 139.

<sup>49</sup> H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 1926, 2038; A. B. Galun, A. Kaluszyner, and E. D. Bergmann, *J. Org. Chem.*, 1962, **27**, 1426.

<sup>51</sup> D. Balcon and A. Frost, *J. Amer. Chem. Soc.*, 1953, **75**, 4334.

<sup>52</sup> C. H. Bamford and E. F. T. White, *J. Chem. Soc.*, 1960, 4490.