

Organometallic Compounds of the Alkali Metals. Part III. Metallation of Alkylbenzenes by Alkyl-sodium and -potassium Compounds. The Character of Aromatic Metallation Reactions.*

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The metallation of toluene, ethylbenzene, *isopropylbenzene*, and *tert.*-butylbenzene has been investigated by an extension of the procedure described in Part II.* The tendency for reaction at the α -position of the side chain decreases in the order, toluene > ethylbenzene > *isopropylbenzene*. Isomer ratios have been determined for the metallation of *isopropylbenzene* by ethylpotassium, *n*-amylpotassium, and *n*-amylsodium: the *meta*-isomer has always predominated. Competition experiments have shown that the *isopropyl* and the *tert.*-butyl group act as deactivating substituents towards nuclear metallation. Partial rate factors have been determined for the metallation of *isopropylbenzene*. The results are considered to show that the rate-determining step in this type of reaction is a nucleophilic attack on hydrogen by the anion of the reagent: the substitution is termed "protophilic." The partial rate factors are regarded as a measure of the relative acidities of the corresponding hydrogen atoms.

SCHORIGIN (*Ber.*, 1910, **43**, 1938) described the metallation of toluene, ethylbenzene, xylenes, and mesitylene by ethylsodium, and observed that the α -position in the side chain was a favoured point of attack. Gilman and his co-workers (*J. Amer. Chem. Soc.*, 1940, **62**, 1514; 1946, **68**, 522), using a method similar to Schorigin's, found that ethyl-sodium and -potassium attack at the α -position in *isopropylbenzene*, although the possibility of nuclear substitution was not excluded in the latter case. Morton, Massengale, and Brown (*ibid.*, 1945, **67**, 1620) reported that *n*-amylsodium attacks *isopropylbenzene* "largely *para* and some *ortho* to the *isopropyl* group." Morton and Little subsequently (*ibid.*, 1949, **71**, 487) described further metallation experiments, using a mixture of *n*-amylsodium and sodium *isopropoxide*, said to be more reactive than *n*-amylsodium alone. The mixed reagent was reported to attack principally the *para*-positions of *isopropyl*- and *tert.*-butylbenzene.

The present paper deals with an extension to alkylbenzenes of the metallation procedure described in Part II (*loc. cit.*), whereby alkylpotassium compounds are produced *in situ* by the action of potassium upon the corresponding alkyl-lithium compounds. Information upon three main points has been sought: (a) the connection between the nature of the alkyl group in an alkylbenzene and the degree of metallation at the α -position by a particular reagent; (b) the effects of variations in reagent and temperature on the metallation of a particular alkylbenzene; (c) the effect of alkyl substituents on nuclear metallation. For investigation of (a), ethylpotassium has been used since it leads to negligible dimetallation (cf. Part II, *loc. cit.*). For (b), the metallation of *isopropylbenzene* has proved most convenient since, with this hydrocarbon, substitution occurs largely in the nucleus, and the isomer ratios may be easily determined by a chemical method. In this method, one portion of the mixture of isomeric monocarboxylic acids which results from carboxylation of the arylpotassium compounds is oxidised by chromium trioxide in acetic acid. This converts $\alpha\alpha$ -dimethylphenylacetic acid into benzoic acid, and *m*- and *p*-*isopropylbenzoic* acids into a mixture of *isophthalic* and *terephthalic* acids. The phthalic acids are separated *via* the dithallosalts (Bryce-Smith, *Chem. and Ind.*, 1953, 244). Oxidation of another portion of the acids by alkaline permanganate converts the *isopropylbenzoic* acids into the water-soluble 2-(carboxyphenyl)propan-2-ols but leaves unchanged any $\alpha\alpha$ -dimethylphenylacetic acid. The proportion of *o*-*isopropylbenzoic* acid is obtained by difference, for no method of direct estimation has been found. All attempts to detect the presence of β -phenylbutyric acid by oxidation experiments have failed, and in view of the relatively aliphatic character of β -positions in alkylbenzenes the possibility of β -metallation has been neglected.

* Part II, *J.*, 1953, 861.

The accuracy of this method of analysis has been judged by experiments with synthetic mixtures, and small corrections have been applied where necessary.

EXPERIMENTAL

Purification of Materials.—Benzene and *n*-pentane were purified as in Part II (*loc. cit.*). Toluene was sulphur-free material which was further purified by fractional distillation over sodium through a column of approx. 10 theoretical plates. Ethylbenzene was shaken repeatedly with portions of concentrated sulphuric acid until the acid layer was only slightly coloured, then washed, dried, and fractionated over sodium. *iso*Propylbenzene was a gift from the Anglo-Iranian Oil Co. Ltd., which is gratefully acknowledged: it was of 99.86 mole % purity and had f. p. -96.036° . *tert.*-Butylbenzene was prepared by Kharasch and Brown's method (*J. Amer. Chem. Soc.*, 1939, **61**, 2142) and purified as for ethylbenzene. All materials were thoroughly dried.

The general procedure for metallation by alkylpotassium compounds described in Part II (*loc. cit.*) has been used without modification in the present work.

(a) *Metallation of Toluene by Ethylpotassium.*—A solution of ethyl-lithium (0.138 mole) in toluene (120 ml.) was stirred with an alloy of potassium (6.6 g., 0.17 g.-atom) and sodium (1.5 g.). Evolution of ethane commenced within a few minutes at 20° , and after 84 hr. the reaction was 90% complete (titration of aliquot portions of the clear supernatant liquid obtained by sedimentation). After treatment with solid carbon dioxide in ether, phenylacetic acid (4.3 g.) was obtained, having m. p. and mixed m. p. 76.5° without recrystallisation. Evaporation of an ethereal extract of the mother-liquors gave a further 0.35 g. of almost pure acid, m. p. $74-75^\circ$. No other aromatic acids could have been present in significant amounts.

In view of the fact that some tolyl metallic compounds can rearrange to the corresponding benzyl isomers (Bachmann and Clarke, *J. Amer. Chem. Soc.*, 1927, **49**, 2089; Gilman *et al.*, *ibid.*, 1940, **62**, 673, 1514), it was clearly desirable to demonstrate the absence of such rearrangement under the conditions of experiment (a). This was done as follows.

(b) *Preparation and Attempted Rearrangement of p-Tolylpotassium.*—A solution of *p*-tolyl-lithium was prepared by the reaction of *p*-bromotoluene (17.1 g., 0.1 mole) with lithium (1.5 g., 0.215 g.-atom) in ether (75 ml.); the yield was 95%. Ether was removed under reduced pressure with stirring, and the residue was heated at 60° for 30 min. under reduced pressure. Benzene (45 ml.) was added, and then an alloy of potassium (7.8 g., 0.2 g.-atom) and sodium (2 g.). The mixture was stirred at 20° for 10 hr. and then kept overnight. By filtration of a portion of the dark brown product and titration of the filtrate, the reaction was found to be essentially complete. A further amount of benzene (150 ml.) was added and the suspension of *p*-tolylpotassium was kept at 20° for 40 days with occasional shaking (nitrogen atmosphere). Reaction with solid carbon dioxide then afforded 8.4 g. of impure *p*-toluic acid, m. p. $155-158^\circ$. Recrystallisation from water gave the pure acid, m. p. 179° , together with a little impure benzoic acid, m. p. $112-114^\circ$ and mixed m. p. $115-116^\circ$, of which further recrystallisation did not raise the m. p. Phenylacetic acid was not obtained, and its characteristic odour was not in evidence.

In another experiment, a suspension of *p*-tolylpotassium in benzene was heated at 78° for 45 min. before carboxylation. *p*-Toluic acid was obtained, but no trace of benzoic or phenylacetic acid.

Since benzylpotassium is stable under the conditions of the above experiments, no rearrangement of the *p*-tolylpotassium could have occurred.

(c) *Metallation of Ethylbenzene by Ethylpotassium.*—To ethyl-lithium (0.117 mole) and ethylbenzene (65 ml.) was added an alloy of potassium (7.5 g., 0.19 g.-atom) and sodium (1.7 g.). After the mixture had been stirred for 66 hr. at an average temperature of 20° , the reaction was 89% complete. After carboxylation of the bright red product there were obtained 4.7 g. (27%) of a mixture of isomeric monocarboxylic acids, b. p. $264-270^\circ$: no dicarboxylic acids were found, but propionic acid (0.5 g.) was isolated. No 2:3-dimethylbutane or other neutral reaction products were detected. 1.0 g. of the mixture of acids was converted into the mixed amides in the usual manner. Repeated recrystallisation, first from water and then from light petroleum, gave hydratropamide (0.15 g.), m. p. $90-91^\circ$. Janssen (*Annalen*, 1889, **250**, 136) reported m. p. $91-92^\circ$.

Oxidation experiments. (i) A solution of 0.98 g. of the mixture of acids in water (60 ml.) and sodium hydroxide (3 ml. of 10% solution) was oxidised at 100° by potassium permanganate (3.5 g.), added during 20 min.; excess of permanganate remained after a further 40 min. at 100° . The solution was decolorised by sulphur dioxide and, while warm, was filtered from insoluble

acids (0.13 g.). The filtrate was saturated with salt and extracted with chloroform to give benzoic acid (0.35 g.), m. p. and mixed m. p. 121°. From the combined mother-liquors there was obtained a trace of material, m. p. 60—100° (very indefinite) : the presence in this of phthalic acid was shown by a strongly positive "phenolphthalein test." The insoluble *iso*- and terephthalic acids were converted into the dimethyl esters, and these were separated from each other by the method described in Part II (*loc. cit.*). The proportion was approx. 60% of *iso*- and 40% of terephthalic acid. Identities of the esters were confirmed by mixed m. p. determinations.

(ii) 1.08 g. of the original mixture of acids in glacial acetic acid (14 ml.) were oxidised at 100° by the gradual addition of chromium trioxide (5.5 g. of dry "AnalaR"). After 3 hr., water (40 ml.) and concentrated sulphuric acid (10 ml.) were added and the mixture was heated under reflux for 9 hr. more. A slight excess of oxidising agent remained. By this means there were obtained benzoic acid (0.45 g., 51%), m. p. and mixed m. p. 120—121°, and a mixture of *iso*- and terephthalic acids (0.27 g., 23%) in the proportion of approx. 60 : 40 respectively, *i.e.*, the same as in (i).

(iii) 1.06 g. of the original mixture of acids in glacial acetic acid (7 ml.) were oxidised at 80° by chromium trioxide (0.6 g.); and the mixture was heated at 100° for 4 hr. and then kept at room temperature for 14 days. The acetic acid was neutralised by addition of sodium hydroxide solution at 0—10° and there was added a solution of sodium hypobromite prepared from bromine (2 ml.) and sodium hydroxide (4.0 g.) in water (30 ml.). The mixture was kept at 0° for 30 hr. and then warmed at 70° for a further 2 hr. A mixture of *iso*- and terephthalic acids (0.12 g., 10%) was obtained; estimation *via* the thallos salts (Bryce-Smith, *loc. cit.*) showed that the respective proportions were 64 and 36%.

The fact that the ratio of *iso*- to terephthalic acid was largely independent of the method of oxidation suggests that this ratio is an approximate measure of the relative amounts of *m*- and *p*-ethylbenzoic acids present in the original mixture.

(d) *Metallation of isoPropylbenzene by Ethylpotassium at 20°*.—To ethyl-lithium (0.115 mole) and *isopropylbenzene* (65 ml.) was added an alloy of potassium (9 g., 0.23 g.-atom) and sodium (1.8 g.). The mixture was stirred for 8 days, by which time the evolution of ethane had almost ceased, and was then poured on solid carbon dioxide and ether. Free alkali metals were destroyed, as always, by addition of aqueous *tert*-butyl alcohol. The acidified product was extracted with light petroleum (b. p. 40—60°; 2 × 50 ml.), a trace of insoluble material being removed by filtration. Distillation of the dried (Na₂SO₄) extract gave a forerun of propionic acid (0.4 g.); the bulk (5.85 g.) distilled at 145—152°/5 mm., and partly crystallised on long storage; *ca.* 0.1 g. of colourless crystalline dicarboxylic acids remained in the distillation flask. The main fraction was a mixture of α -dimethylphenylacetic acid and *isopropylbenzoic* acids; the isomeric composition was determined by the following two experiments, the conditions of which will be subsequently referred to as the "standard conditions."

(i) *Oxidation by chromium trioxide*. To 1.5282 g. of the homogeneous mixture of acids in boiling glacial acetic acid (21 ml.) was added dry "AnalaR" chromium trioxide (8.2 g.) in very small portions during 30 min. The mixture was kept at 130° (bath-temp.) for 24 hr. with occasional shaking and was then boiled under reflux for 30 min. with water (80 ml.) and concentrated sulphuric acid (27 ml.). The insoluble phthalic acids were filtered off at 20°, and washed with a little water and then with 2 ml. each of cold glacial acetic acid and chloroform; the yield was 1.1054 g. (71.3%). 0.2827 g. of these acids gave 0.3961 g. (40.6%) of thallos terephthalate and 0.1675 g. (59.2%) of *isophthalic* acid; a duplicate estimation gave 40.1 and 59.5%, respectively.

The efficiency of the above process was tested by performing the oxidation under similar conditions of a synthetic mixture (60 : 40) of *m*-* and *p*-*isopropylbenzoic* acids, whereby 87.5% of the *meta*-isomer appeared as *isophthalic* acid and 98.6% of the *para*-isomer as thallos terephthalate; a duplicate estimation gave 87.0 and 97.6% respectively. Corrections have been applied on the basis of these results.

(ii) *Oxidation by permanganate*. 1.6972 g. of the mixture of acids were dissolved in a solution of sodium hydroxide (1.2 g.) in water (75 ml.), and the solution was heated with potassium permanganate (5.1 g.) for 4 hr. at 100°. The solution was decolorised by passage of sulphur dioxide and then further acidified by hydrochloric acid. The crystals were filtered off. The filtrate was extracted twice with light petroleum (b. p. 40—60°), and the extract was itself extracted with 10 ml. of 10% sodium hydroxide solution. Acidification gave a further small quantity of solid acid, which was combined with the first crop. The acid obtained at this stage was almost pure α -dimethylphenylacetic acid, but contained a little *iso*- and terephthalic acids. The crystals were washed with chloroform-light petroleum until there was no further loss in weight. The total loss was 0.2016 g. (11.9%) and represented the weight of α -dimethyl-

* The writer is indebted to Dr. F. H. C. Stewart for supplying a specimen of this acid.

phenylacetic acid which had been present. Evaporation of the washings gave this acid, which was pure without recrystallisation (m. p. and mixed m. p. 79°). Ziegler and Schnell (*Annalen*, 1924, 437, 255) recorded m. p. 77—78°. A checking experiment showed that the acid is slightly attacked by alkaline permanganate under the above conditions. Account being taken of this, the corrected proportion of α -dimethylphenylacetic acid in the original mixture was 13%.

The aqueous liquors from the permanganate oxidation contained 2(carboxyphenyl)propan-2-ols and furnished a mixture of *iso*- and *tere*-phthalic acids when further oxidised by potassium dichromate and sulphuric acid. The yield was slightly lower than in the direct oxidation by chromium trioxide.

(e) *Metallation of isoPropylbenzene by Ethylpotassium at 85°*.—An experiment similar to (d) was performed with similar quantities, except that sodium was omitted. The mixture was stirred at 90° for 30 min. to initiate a reaction with the potassium and was then kept at 85° for a further 30 min. Separation of a brown putty-like solid prevented stirring beyond this period. A gas, presumably ethane, was evolved during the reaction, but no gas was evolved at 90° before the addition of potassium: this showed that ethyl-lithium does not metallate isopropylbenzene under these conditions. Carboxylation and the subsequent operations were carried out as described in (d). 3.5 g. of a liquid mixture of monocarboxylic acids were obtained. Dimetallation was negligible. Oxidation of 1.0300 g. of the acids with chromium trioxide under the standard conditions gave 0.6611 g. (63.5%) of a mixture of *iso*- and *tere*-phthalic acids. Estimation *via* the thallous salts gave 60.6, 61.0% of *isophthalic* acid and 39.1, 38.6% of *terephthalic* acid. Oxidation of 1.2260 g. of the original mixture of acids with alkaline permanganate under the standard conditions gave 0.2090 g. (17.0%) of α -dimethylphenylacetic acid, m. p. 78.5°. This acid did not form a *p*-bromophenacyl ester under the usual conditions. Neutral products from the metallation reaction were examined. 2 g. of a liquid (which contained much isopropylbenzene), b. p. 154—210°, were oxidised by chromium trioxide in glacial acetic acid. Benzoic acid was obtained, but no more than a trace of *iso*- and *tere*-phthalic acids. Had ethylisopropylbenzenes been present (cf. Part II, *loc. cit.*), only the *ortho*-isomer would have escaped detection by this method. No 2 : 3-dimethyl-2 : 3-diphenylbutane was found.

(f) *Metallation of isoPropylbenzene by n-Amylpotassium at 20°*.—A solution of *n*-amyl-lithium (0.142 mole) in isopropylbenzene (65 ml.) was stirred with an alloy of potassium (11 g., 0.28 g.-atom) and sodium (2.2 g.) for 7 days. No gas was evolved and the dark brown solid product did not settle, so the progress of the reaction could not be followed by the usual methods. Distillation of the mixture of acids which was obtained after carboxylation gave fractions with the following b. p.s at 8 mm.: (i) 120—140° (4.1 g.), (ii) 140—150° (0.3 g.), (iii) 150—165° (8.5 g.), (iv) residue > 165° (*ca.* 0.2 g.). Fraction (i) was hexanoic acid; (iii) was the required mixture of isomeric monocarboxylic acids; (iv) crystallised during the final stages of distillation and was almost certainly a mixture of isopropylphthalic acids. Oxidation of 1.6126 g. of the liquid fraction (iii) with chromium trioxide under the standard conditions gave 1.1586 g. (71.0%) of a mixture of *iso*- and *tere*-phthalic acids: a duplicate oxidation gave 70.6%. Estimation *via* the thallous salts gave 55.7, 56.0, 55.1% of *iso*- and 44.0, 43.7, 44.5% of *tere*-phthalic acid. Oxidation of 1.5034 g. of fraction (iii) with alkaline permanganate under the standard conditions gave 0.1776 g. (11.8%) of α -dimethylphenylacetic acid, m. p. 78.5°.

(g) *Metallation of isoPropylbenzene by n-Propylpotassium at 90°*.—A solution of *n*-propyl-lithium (0.107 mole) in isopropylbenzene (90 ml.) was stirred at 90° for 4 hr. with potassium (8.2 g., 0.21 g.-atom). A portion of the evolved gas was condensed in a trap cooled in liquid air, and found to be an approx. 4 : 1 mixture of propane and propene. Carboxylation of the organometallic product gave 4.5 g. of a mixture of monocarboxylic acids, b. p. 140—145°/4 mm., together with 0.5 g. of dicarboxylic acids. Oxidation of 1.547 g. of the monocarboxylic acids with alkaline permanganate under the standard conditions gave 0.270 g. (17.5%) of α -dimethylphenylacetic acid, m. p. 77—78°. This experiment was performed before a satisfactory means of estimating the nuclear isomers had been found, and reliable figures for these are therefore not available. Some rather crude initial experiments indicated that the proportions of nuclear isomers were of the same order as those subsequently found in experiment (e). No alkylation products or 2 : 3-dimethyl-2 : 3-diphenylbutane was detected.

(h) *Metallation of isoPropylbenzene by n-Amylsodium at 20°*.—A suspension of *n*-amylsodium was prepared by the addition (2½ hr.) of a solution of *n*-amyl chloride (16 g., 0.15 mole: Eastman-Kodak material shaken with concentrated sulphuric acid, washed, and refracted); b. p. 106—108° in *n*-pentane (50 ml.) to sodium (11.5 g., 0.5 g.-atom: wire of 0.5 mm. diam.) in *n*-pentane (100 ml.). The temperature was kept at -10° to -15° and the mixture was vigorously stirred. The usual conditions for the exclusion of air and moisture were observed.

After a further $\frac{1}{2}$ hour's stirring at 0°, the mixture was kept overnight at -50°. *n*-Pentane was removed by distillation at reduced pressure and *isopropylbenzene* (70 ml.) was then added. The mixture was stirred at an average temperature of 20° for 10 days, and was then poured on solid carbon dioxide and ether. Distillation of the resulting acids gave, after a small forerun of hexanoic acid (0.75 g.), the required mixture of aromatic monocarboxylic acids (8.45 g.), b. p. 160—170°/9 mm. A yellow-brown gum (0.5 g.) remained as distillation residue, but there was no apparent formation of dicarboxylic acids. The main fraction solidified on cooling and was homogenised by melting before samples were taken for analysis. Oxidation of 1.6341 g. of the acids with chromium trioxide under the standard conditions gave 1.4623 g. (88.5%) of a mixture of *iso*- and *tere*-phthalic acids. Estimation *via* the thalious salts gave 48.5% of *isophthalic* acid and 51.3, 51.5% of *terephthalic* acid. Dimethyl *isophthalate* had m. p. 63° and mixed m. p. 66° (pure 67°); dimethyl *terephthalate* had m. p. and mixed m. p. 141.5° The acids (2.1300 g.) were oxidised under the standard conditions by potassium permanganate except that a higher proportion (7 g.) was used. There was isolated α -dimethylphenylacetic acid (0.0136 g., 0.7%), m. p. and mixed m. p. 78° without recrystallisation. Practically no neutral reaction products were found. A neutral liquid (0.2 g.), b. p. *ca.* 270°, may have been impure *n*-amyl-*isopropylbenzene* (Found : C, 88.3; H, 10.25. Calc. for C₁₄H₂₂ : C, 88.4; H, 11.6%).

(i) *Metallation of tert.-Butylbenzene by Ethylpotassium at 85°*.—A solution of ethyl-lithium (0.114 mole) in *tert.*-butylbenzene (70 ml.) was stirred at 95° with potassium (8.5 g., 0.22 g.-atom) until reaction commenced (30 min.), and was then cooled to 85°. After 40 min., the solids agglutinated into a putty-like mass and stirring became impossible. Gas evolution continued for a further 2 hr. at 85°. Carboxylation was effected in the usual manner, the lumps of solid potassium compound being cautiously broken up by means of a spatula. Mono- and dicarboxylic acids were separated on the basis of the latter's virtual insolubility in light petroleum (b. p. 40—60°). The dicarboxylic acids (1.7 g.) had m. p. 315—325°. The *tert.*-butylbenzoic acids were freed from propionic acid and remaining traces of dicarboxylic acids through a silica gel column, methylene dichloride being the eluant (yield, 6.05 g.) (Found : C, 74.0; H, 7.85. Calc. for C₁₁H₁₄O₂ : C, 74.1; H, 7.9%).

Crawford and Stewart (*J.*, 1953, 288) recorded the following solubilities (g./100 g.) for the copper salts of *tert.*-butylbenzoic acids in benzene-ethanol (9 : 1) at 25° : *para*-0, *meta* 4.8, *ortho* 35. This suggested a method for determining the proportion of the *para*-isomer in a mixture. Also, the copper salt of the *ortho*-acid appears to be much more soluble in ethanol than is the salt of the *meta*-acid. A separation was attempted on this basis. 0.9050 G. of the homogeneous mixture of acids gave 1.0810 g. of copper salts (102% as C₂₂H₂₆O₄Cu). The salts were heated under reflux with 26 ml. of benzene-ethanol (9 : 1), and the mixture cooled to 25° and filtered to give 0.3771 g. (35.5% as C₂₂H₂₆O₄Cu) of insoluble salt : this gave 0.2787 g. (30.9%) of *p*-*tert.*-butylbenzoic acid, m. p. 163°, which after recrystallisation from aqueous ethanol had m. p. 164.5°. Attempts to obtain the pure *meta*-acid (m. p. 127°) failed. All the crops of acids had m. p. >85°, which made improbable the presence of any considerable amounts of *o*-*tert.*-butylbenzoic acid, m. p. 68.5°, or β -methyl- β -phenylbutyric acid, m. p. 59° : the latter acid would result from β -metallation. The copper salts were all hygroscopic and appeared to be readily solvated. With allowance for probable losses, the proportion of the *para*-isomer is put at 35—40%. No satisfactory method for oxidising the *tert.*-butylbenzoic acids to phthalic acids has been found.

(j) *Competitive Metallation of Benzene and isoPropylbenzene by Ethylpotassium*.—A solution of ethyl-lithium (0.19 mole) in benzene (46.8 g., 0.6 mole) and *isopropylbenzene* (72.0 g., 0.6 mole) was stirred with potassium (14.8 g., 0.38 g.-atom) at 85° for $4\frac{1}{4}$ hr. Refluxing did not occur. It was found that 99% of the ethyl-lithium had been consumed. After carboxylation there were obtained 8.0 g. of a first crop of solid acids. The aqueous liquors were saturated with salt and extracted twice with light petroleum. The first crop of acids was heated with glacial acetic acid (35 ml.), cooled, and filtered. The insoluble residue was further treated with acetic acid (20 ml.) (yield, 1.55 g.). [This material was a mixture of *iso*- and *tere*-phthalic acids, the ratio of which has already been quoted in Part II (*loc. cit.*)] The combined acetic acid filtrates were diluted with water (100 ml.) and extracted four times with light petroleum (b. p. 40—60°) to obtain all the solid monocarboxylic acids. Finally, repeated ether-extraction gave 0.25 g. of a high-melting solid, assumed to be a mixture of *isopropylphthalic* acids. The combined light petroleum extracts were fractionated to remove solvent, and the colourless solid residue was kept under reduced pressure over potassium hydroxide and paraffin wax until there was no further loss in weight. The relative proportions of benzoic and cuminic acids in the mixture (6.2 g.) were determined as follows. 2.3748 g. of the acids in glacial acetic acid (15 ml.)

were oxidised at 130° by gradual addition of chromium trioxide (5.5 g.). The mixture was kept at 130° for 23 hr. and was worked up in the usual manner to furnish 0.4649 g. of a mixture of *iso*- and *tere*-phthalic acids, equivalent to 0.732 g. (31%) of total cuminic acids (cf. Expt. e) (Found, for the original mixture of acids: C, 69.9; H, 5.75. Calc. for a mixture containing 69% C₇H₆O₂ and 31% C₁₀H₁₂O₂: C, 70.2; H, 5.7%). The aqueous liquors from the oxidation experiment furnished benzoic acid (1.5 g.), m. p. 120° (an estimated 0.05 g. of this was derived from the oxidation of α -dimethylphenylacetic acid). The *iso*- and *tere*-phthalic acids were separated *via* the thallos salts: *iso*- 61.6, *tere*- 37.9, 37.7%. These percentages are within 1% of those found from the metallation of *isopropylbenzene* in the absence of benzene (Expt. e). The slight dimetallation which occurred was taken into account when the total rate factor was calculated, but no correction was applied for the slight change in the proportions of benzene and *isopropylbenzene* during the course of the metallation reaction. The corrected proportions by weight were: cuminic acids 27.5, benzoic acid 72.5%.

The total rate factor, $F_{C_6H_6}^{C_6H_5Pr^I} = 0.28(3)$.

The total rate factor for nuclear metallation = 0.23.

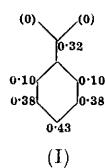
(k) *Competitive Metallation of Benzene and tert.-Butylbenzene by Ethylpotassium*.—A solution of ethyl-lithium (0.19 mole) in benzene (46.8 g., 0.6 mole) and *tert.*-butylbenzene (80.5 g., 0.6 mole) was stirred with potassium (14.8, 0.38 g.-atom) at 85° for 3 hr. Refluxing did not occur. Carboxylation gave 9.7 g. of a mixture of colourless solid acids. *iso*- and *Tere*-phthalic acids (1.98 g.) were removed as in the previous experiment. There was also obtained 0.30 g. of a solid, m. p. 285—295°, assumed to be a mixture of *tert.*-butylphthalic acids. The solid monocarboxylic acids were freed from propionic acid and traces of dicarboxylic acids by passage of a solution in light petroleum through a column of silica gel (yield, 6.8 g.) (Found: C, 69.65; H, 5.55%; equiv., 135.2, 135.5. Calc. for a mixture containing 76.5% C₇H₆O₂ and 23.5% C₁₁H₁₄O₂: C, 70.05; H, 5.65%; equiv., 135.2). In calculation of the total rate factor, the slight dimetallation was taken into account:

$$F_{C_6H_6}^{C_6H_4Bu^t} = 0.19.$$

The proportion of *para*-substitution in *tert.*-butylbenzene being taken as 35% (Expt. i), the corresponding partial rate factor is 0.4.

DISCUSSION

The principal results of this work may be summarised as follows. (a) The *isopropyl* and the *tert.*-butyl group deactivate all positions in the aromatic nucleus towards metallation by ethylpotassium: the total rate factors for nuclear substitution in *isopropylbenzene* and *tert.*-butylbenzene are 0.23 and 0.19, respectively. With the former group (and probably with the latter also), the order of increasing deactivation is *para* < *meta* < *ortho*, as is shown by the partial rate factors for *isopropylbenzene* (I).



(I)

(b) Orientation in the metallation of *isopropylbenzene* appears not to be influenced greatly by the size of the alkyl group in the reagent, but more by the nature of the metal: in comparison with potassium, sodium leads to somewhat increased *para*-substitution at the expense of *ortho*- and α -substitution.

(c) Metallation at the α -positions in toluene, ethylbenzene, and *isopropylbenzene* forms the following proportions of the total substitution in these compounds: toluene, 100%; ethylbenzene, 50%; *isopropylbenzene*, 13%.

(d) Ratios of isomers vary slightly with the reaction temperature, as shown below:

Ratios of isomers (%) in the metallation of *isopropylbenzene*.

Reagent	Temp.	α	<i>ortho</i>	<i>meta</i>	<i>para</i>	Reagent	Temp.	α	<i>ortho</i>	<i>meta</i>	<i>para</i>
C ₂ H ₅ K	20°	13.0	9.0	48.5	29.5	<i>n</i> -C ₅ H ₁₁ K	20°	13.0	9.5	45.5	32.0
C ₂ H ₅ K	85	19.0	11.5	44.5	25.0	<i>n</i> -C ₅ H ₁₁ Na	20	1.0	3.0	49.5	46.5
<i>n</i> -C ₃ H ₇ K	90	19.0	14 *	43 *	24 *						

* Approximate value.

The yields of acids from metallation experiments are generally not quantitative, but this fact does not complicate interpretation of the present data. Beyond the products indicated, no neutral or acid derivatives of the aromatic hydrocarbon have been detected.

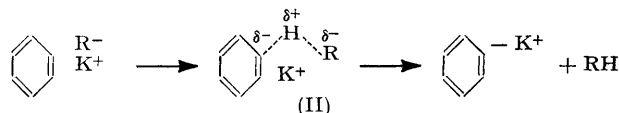
The side reaction seems to be an innocuous thermal decomposition of the alkylpotassium compound which, if analogous to the decomposition of alkyl-lithium compounds, will proceed mainly, *e.g.*, as follows: $C_2H_5K \longrightarrow C_2H_4 + KH$ (Ziegler and Gellert, *Annalen*, 1950, **567**, 179: cf. Carothers and Coffman, *J. Amer. Chem. Soc.*, 1930, **52**, 1254).

Several mechanisms for aromatic metallation reactions have been advanced, but none has yet been established beyond doubt. Thus, Morton and his co-workers (*Chem. Reviews*, 1944, **35**, 1; *J. Amer. Chem. Soc.*, 1945, **67**, 1620; 1949, **71**, 487) have regarded the reactions as electrophilic in nature. This view appeared to be supported by evidence that the *isopropyl* group is an *ortho-para*-directing substituent. Some 50% of *meta*-substitution has now been observed in the metallation of *isopropylbenzene* by *n*-amylsodium: it seems probable that the acid, m. p. 47–49°, isolated by Morton *et al.* (*loc. cit.*) from such an experiment was *m-isopropylbenzoic acid* (m. p. 50°), and not the *ortho*-isomer as claimed. In some of these workers' later experiments, sodium *isopropoxide* was present, and it seems possible, albeit unlikely, that this compound influences the orientation. Roberts and Curtin (*ibid.*, 1946, **68**, 1658), on the basis of experiments using alkyl-lithium compounds, suggested that metallation involves a nucleophilic attack on hydrogen by the anion of the reagent; but this view was not accepted by Morton (*ibid.*, 1947, **69**, 969). Klapproth and Westheimer (*ibid.*, 1950, **72**, 4461) demonstrated that aromatic mercuration can show either electrophilic or homolytic characteristics, depending upon the experimental conditions. There is some doubt whether much more than a formal analogy can be drawn between mercuration and the present metallation reactions; *e.g.*, the substitution patterns in toluene are totally different.

In attempting to interpret the present results, it is assumed that alkyl- and aryl-potassium compounds are polar, and function as undissociated ion-pairs: this seems to follow from their physical properties. (For discussions of the evidence relevant to structure, see Morton, *Chem. Reviews*, 1944, **35**, 1; Sidgwick, "The Chemical Elements and their Compounds," Oxford, pp. 81, 100; Coates, *Quart. Reviews*, 1950, **4**, 217.) Possible rate-determining steps for metallation by alkylpotassium compounds appear to be limited to the following: (a) an electrophilic attack on carbon by the cation of the reagent; (b) a nucleophilic attack on hydrogen by the anion of the reagent; (c) the formation of a tetrapolar transition state involving the simultaneous operation of (a) and (b) in various degrees of relative importance; (d) the addition of RK to the nucleus, followed by loss of RH: and there is the final possibility that the reaction is homolytic. Several of these mechanisms can be excluded. An electrophilic attack by the metal cation (Morton *et al.*, *loc. cit.*) can be reconciled neither with the extensive *meta*-substitution which occurs in *isopropylbenzene*, nor with the fact that alkyl groups—electron donors—behave as deactivating substituents. Furthermore, if both reagent, RK, and product, ArK, are regarded as ion-pairs, the dominant rôle in the reaction can scarcely be attributed to the metal cation, since this emerges with little or no change in its electronic configuration. These considerations likewise exclude any "push-pull" mechanism of type (c) where the electrophilic attack is energetically the more important. The main objection to an addition-elimination reaction of type (d), apart from the reluctance of benzene to undergo addition reactions, is that in cases where addition does occur (*e.g.*, the addition of alkyl-lithium compounds to pyridine), it is always followed by loss of the metal hydride. Alkylsodium compounds metallate olefins, R·CH:CH₂, mainly at the α -position (Morton and Holden, *J. Amer. Chem. Soc.*, 1947, **69**, 1675): this would not be expected if the first step were one of addition to the double bond. A homolytic mechanism (which need not involve attack by free radicals) can also be excluded with fair certainty, although the published data suitable for comparison are rather sparse. Dannley and Zaremsky (*Amer. Chem. Soc. Meeting*, Sept., 1953) have reported that the homolytic phenylation of *isopropylbenzene* (which probably does not involve the abstraction of a hydrogen atom in the rate-determining stage) leads to the following proportions of attack at the nuclear positions: *ortho*, 10; *meta*, 60; *para*, 30%. These are very similar to the present metallation ratios; but the similarity does not extend to total (and hence, partial) rate factors. The total rate factors for the phenylation of *isopropyl-* and *tert.-butyl-benzene* are 2.1 and 0.75 respectively (Cadogan, Hey, Pengilly, and Williams, personal communication), whereas the correspond-

ing figures for metallation are 0.28 and 0.19. Such differences in the relative reaction rates are considered to imply basically different mechanisms, and the similarity in isomer ratios is thought to be fortuitous. This belief is reinforced by Dannley and Zaremsky's observation (*loc. cit.*) that only slight α -phenylation of toluene occurs, substitution being mainly in the nucleus. Gregg and Mayo (*Discuss. Faraday Soc.*, 1947, 2, 328) have shown that the ease of abstraction of a hydrogen atom from the α -position in alkylbenzenes is much greater than from the nucleus in benzene and alkylbenzenes, and increases in the order toluene < ethylbenzene < isopropylbenzene. α -Metallation follows the reverse order, and the rate of metallation at a position in benzene is some three times as great as at the α -position in isopropylbenzene.* It follows that the rate-determining step in both side-chain and nuclear metallation is not the abstraction of a hydrogen atom. This receives negative support from the present failure to detect dimers of benzyl-type radicals among the reaction products. An electron-transfer mechanism, which would involve the formation of alkyl radicals and, in consequence, of benzyl-type radicals, is also clearly improbable.

The possibilities remaining are either a nucleophilic attack on hydrogen (Roberts and Curtin, *loc. cit.*; cf. Bradley and Jadhav, *J.*, 1948, 1622) or a "push-pull" mechanism in which such attack is energetically the more important. Both are consistent with the present results, but the conception of reagent and substitution product as ion-pairs suggests a tetrapolar transition state of the type pictured in (II). In this picture, the function of



the metal cation is purely electrostatic, the motive force for the reaction arising from the difference in energies between the alkyl and aryl carbanions. Doubtless, the field of the reagent will act to magnify the incipient polarisation of the C-H bond, the positive field of the cation facilitating withdrawal of the proton: to this extent, the cation may be said to participate. In order to describe substitution reactions which involve the abstraction of a proton in the rate-determining stage, it seems appropriate to revive the term "protophilic," at one time used synonymously with "nucleophilic." Such reactions are not "nucleophilic substitutions" in the usual sense, for the aromatic nucleus retains the electrons of the original C-H bond: a nucleophilic substitution involving RK would require attack on carbon by R⁻, with expulsion of a hydride ion and the formation of an alkylbenzene; indeed, this occasionally seems to happen (Part II, *loc. cit.*).

The protophilic viewpoint requires that reaction should be more hindered than helped by any effect which causes the accession of electrons to the site of substitution. This accords with the observed deactivating effect of alkyl substituents in metallation. Moreover, Shoppee (*J.*, 1930, 968; 1931, 1225; 1932, 696) has found that the introduction of alkyl substituents retards prototropic rearrangement reactions. It is a feature of the transition state (II) that feasible alternative pentadienate structures cannot be drawn: the nucleus loses no electrons, and its resonance should not be appreciably disturbed (in contrast with current views on the mechanism of electrophilic and nucleophilic aromatic substitution). Therefore, inductive effects should be of more importance than electromeric upon the transition state, as pointed out by Roberts and Curtin (*loc. cit.*). Suppose we express the perturbation transmitted to nuclear positions by an alkyl substituent as inversely proportional to the corresponding partial rate factors. The perturbation ratio *ortho* : *meta* : *para* in the metallation of isopropylbenzene by ethylpotassium is then 10 : 2.65 : 2.3. For saturated carbon chains, it has been assumed by several workers (*e.g.*, Dewar, *J.*, 1949, 463; Gold, *Trans. Faraday Soc.*, 1950, 46, 109; following Derick, *J. Amer. Chem. Soc.*, 1911, 33, 1181) that the transmitted inductive effects of substituents are proportional to $1/3^n$, where n is the number of carbon atoms traversed. Application of this to the case of

* In the absence of data from competition experiments, it might be argued that the decreasing tendency for α -metallation in this series could be due equally well to increasing nuclear activation as to decreasing activation of the α -positions. The α -position in toluene must be the most reactive, for it is attacked readily by phenylsodium, for example, under conditions where the other hydrocarbons are inert.

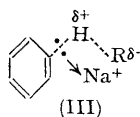
a substituent in benzene gives a ratio, 10 : 3.65 : 2.2, for the magnitudes of inductive influences transmitted to *ortho*-, *meta*-, and *para*-positions respectively: it is assumed that the effect reaches each position additively by two routes. If an inverse-square law were obeyed, the corresponding ratio would be 10 : 3.0 : 2.15. Whatever the precise distance relationship may be in aromatic compounds, it appears that the observed perturbation ratios are of the order expected from the prevailing operation of inductive effects. This, of course, neglects the influence of steric factors on the rate of substitution at *ortho*-positions: such factors may perhaps be of small account in the metallation of *isopropyl*-benzene, since the proportion of *ortho*-metallation is the same with ethylpotassium as with the rather more bulky *n*-amylpotassium. The close similarity of the isomer ratios in these two cases eliminates the possibility of any appreciably selective effect on collision frequencies arising from the non-coincidence of the centres of charge and mass in the reagents.

The ease of α -metallation, decreasing in the order toluene > ethylbenzene > *isopropyl*-benzene, follows the order of decreasing electron recession from the side chain to the nucleus by the hyperconjugation effect. This recession would favour a protophilic attack at the α -position. Admittedly, hyperconjugation is a mesomeric, rather than an inductive, effect; but α -metallation presents a special case, for the charge on the resulting benzyl anion (unlike that on a nuclear anion) may be de-localised by resonance. It is noteworthy that the release of a proton from a C-H bond appears to be aided by arylation at the carbon atom and hindered by alkylation, whereas the release of a hydrogen atom is aided by both (Gregg and Mayo, *loc. cit.*).

It is clear from the foregoing discussion that the rate of metallation at a given position must be related to the acidity of the hydrogen which is replaced (cf. the acidity series of Conant and Wheland, *ibid.*, 1932, 54, 1212, and McEwen, *ibid.*, 1936, 58, 1124). Application of the Brønsted relationship to transition states of the type $\left[\text{Et} \cdots \overset{\delta^-}{\text{H}} \cdots \overset{\delta^+}{\text{H}} \cdots \overset{\delta^-}{\text{Ar}} \right] \text{K}^+$ gives the equation $\log_{10}(k/k') = \alpha(\text{p}K' - \text{p}K)$ where k and k' are the rates of metallation at two similar positions. The factor α is less than unity, and is a measure of the degree of unit charge on hydrogen in the transition state. Since the value of this is unknown, the equation cannot be applied quantitatively at present. Qualitatively, the equation indicates that each hydrogen atom in *isopropyl*benzene is less acidic than a hydrogen atom in benzene, the order of decreasing acidity being *para* > *meta* > α > *ortho* (> β). The values of 10^5K at 25° for *p*- and *m*-*isopropyl*benzoic acid (personal communication from Mr. F. W. Laxton, Chelsea Polytechnic) are 4.43 and 5.4 respectively, compared with 6.3 for benzoic acid (*ortho*-alkylbenzoic acids are abnormally strong, owing to steric factors which seem unlikely to intervene significantly in *ortho*-metallation; cf Dippy, *Chem. Reviews*, 1939, 25, 151). Thus, in metallation, the deactivation of *meta*- and *para*-positions by the *isopropyl* group accords with the effect of this group on the strengths of the corresponding carboxylic acids, but the relative effects on *meta*- and *para*-positions are reversed. Closer similarity is perhaps not to be expected. It should be noted that the acidity relationship will not generally apply to metallation reactions of the type discussed by Roberts and Curtin (*loc. cit.*), where loose co-ordination occurs between the reagent and the attacked species. The predominance of *ortho*-substitution in such cases is probably more an expression of steric facilitation than of any inherent reactivity of the *ortho*-positions.

Some modification of the above conclusions appears to be necessary in the case of metallation by alkylsodium compounds. So far, experimental difficulties have militated against the use of *n*-amylsodium in competition experiments, but comparison of the isomer ratios for the metallation of *isopropyl*benzene by *n*-amylsodium and by *n*-amylpotassium shows the former reagent slightly to favour substitution at the negative end of the hydrocarbon molecule. This apparent trend towards electrophilic behaviour is not great, but is thought to be significant. It might be explained as follows. The efficiency of nuclear screening in alkali-metal cations decreases with decreasing atomic weight. To this cause may probably be traced the marked covalent character of organolithium compounds, and their evident ability loosely to co-ordinate with certain compounds containing unshared electrons, particularly ethers: the failure of benzylpotassium to metallate dibenzofuran under conditions where benzylsodium is effective (Gilman *et al.*, *J. Amer. Chem. Soc.*, 1941,

63, 2479) suggests, however, that organopotassium compounds have little tendency to co-ordinate. Thus, in passing from potassium to sodium, electron shifts illustrated in



(III) may begin to make a finite reduction in the overall energy of the transition state; *i.e.*, electrophilic attack by the metal cation may assume a greater relative importance. Alternatively, the effect may be one of loose co-ordination of the metal with the aromatic π -electrons (such as can occur in the case of certain silver salts), thus causing slight localisation of the reagent at the more negative regions of the hydrocarbon. If some such explanation is correct, we may expect the *trend* towards electrophilic behaviour to be more noticeable in organolithium compounds; and even electrophilic mercuration may yet take its place in a general pattern.

Investigation of the mechanism of aromatic metallation is being continued.

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