

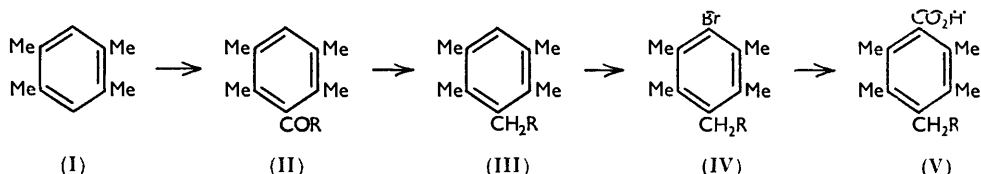
## 640. The Preparation of Some Alkyl-substituted Benzoic Acids. Part II.<sup>1</sup>

By MALCOLM CRAWFORD and J. H. MAGILL.

The preparation of 2-*tert.*-butyl-4 : 6-dimethylbenzoic acid, 2-*tert.*-butyl-4 : 5 : 6-trimethylbenzoic acid, various 3-alkyl-2 : 4 : 6-trimethylbenzoic acids, and 4-alkyl-2 : 3 : 5 : 6-tetramethylbenzoic acids is described.

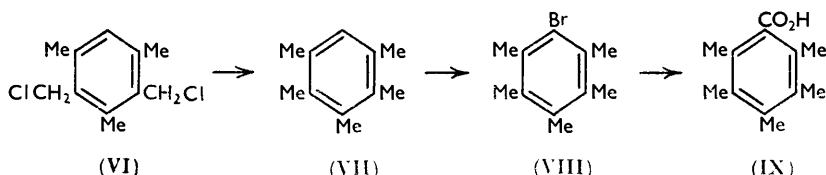
In a study of steric hindrance, benzoic acids heavily substituted by alkyl groups were required in addition to those described in Part I.<sup>1</sup> It was found that methyl groups could be conveniently introduced into the benzene ring by chloromethylation of a hydrocarbon and subsequent reduction. For other primary alkyl groups the Friedel-Crafts reaction followed by reduction of the resulting ketones by hydrogen under pressure proved useful. For subsequent introduction of the carboxyl group between alkyl groups the method used exclusively, because it is little affected sterically, was bromination followed by carbonation of the Grignard derivative. To ensure bromination in the correct position other vacant positions, if not equivalent, were blocked.

Route A (R = Me or Et)



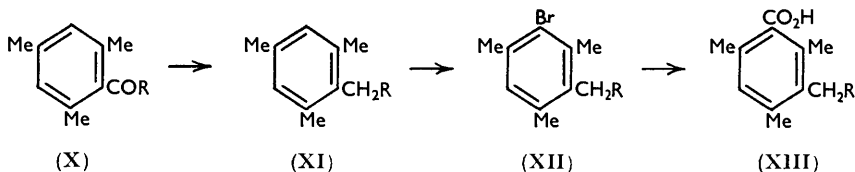
Alkyl-durene carboxylic acids (V) were obtained in good yield from durene (I) by route A. With (II; R = Et) partial hydrogenation of the ring to a *cyclohexene* took place to a slight extent. Pentamethylbenzoic acid (V; R = H) cannot be so prepared but a very convenient method is route B from the bischloromethylmesitylene (VI). This represents an improved synthesis of pentamethylbenzene (VII) over the usual method from xylenes<sup>2</sup> as there can be no contamination with hexamethylbenzene common in commercial samples since mesitylene cannot readily be trichloromethylated.

Route B



Alkylmesitoic acids (XIII) were prepared from acylmesitylenes (X) by route C, which is better than the Grignard method described in Part I.

Route C (R = Me or Et)



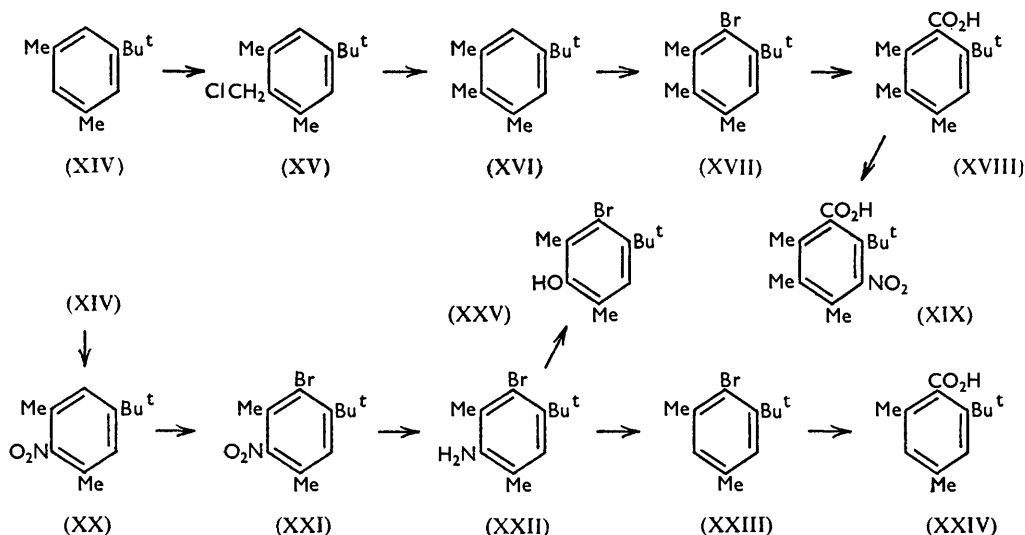
In acids (V), (IX), and (XIII) the carboxyl group is flanked by methyl groups. To obtain still more hindered acids with a carboxyl group between a methyl and a *tert.*-butyl

<sup>1</sup> Crawford and Stewart, *J.*, 1952, 4443, to be considered as Part I.

<sup>2</sup> Von Braun and Nelles, *Ber.*, 1934, 67, 1096.

group 1-*tert.*-butyl-3:5-dimethylbenzene (XIV) was used as starting material. A blocking group at C<sub>(4)</sub> is essential. In the very satisfactory route D1, already explored as far as (XVI),<sup>3</sup> methyl was used as a blocking group but it cannot be removed subsequently. It was introduced by chloromethylation and reduction.

#### Route D1



#### Route D2

Nitration of acid (XVIII) gave a nitro-acid (XIX) which is particularly crowded and contains a *tert.*-butyl group flanked by a nitro- and a carboxyl group. In the few such compounds known containing a doubly flanked *tert.*-butyl group the flanking groups are both usually nitro, which is sterically very small when at right angles to the ring.<sup>4-6</sup>

The attempt (route D2), already known as far as (XXI), to use a removable blocking group in the form of nitro- (XX) was not very successful. The difficulty lay in the reduction of the diazotised amine (XXII). A phenolic by-product (XXV) was obtained but the desired bromo-compound (XXIII) was difficult to purify. Hence the final acid (XXIV) was obtained only in small yield.

### EXPERIMENTAL

**Ethylidurene.**—Acetyldurene (25 g.), copper chromite (7 g.), and methanol (100 ml.) were treated with hydrogen at an initial pressure of 150 atm. and the temperature raised to 250°. The pressure was then 240 atm. where it was maintained with agitation for 16 hr. The cooled mixture was poured into water, giving *ethylidurene* as plates (22.2 g., 96%), m. p. 54° (from ethanol) (Found : C, 88.6; H, 11.1. C<sub>12</sub>H<sub>18</sub> requires C, 88.8; H, 11.2%).

**Bromoethylidurene.**—Ethylidurene (25 g.) in ice-cooled acetic acid (200 ml.) was treated gradually with bromine (26 g.) and a trace of iodine in acetic acid (50 ml.). The product was poured into dilute sodium hydrogen sulphite solution to precipitate *bromoethylidurene* (33 g., 87%), plates (from ethanol), m. p. 80° (Found : C, 59.6; H, 7.2; Br, 33.2. C<sub>12</sub>H<sub>17</sub>Br requires C, 59.8; H, 7.1; Br, 33.1%).

**Ethylidurene-carboxylic Acid.**—The foregoing bromo-compound (33 g.) dissolved in ether-benzene was converted into the Grignard compound which was poured on solid carbon dioxide. The acid (15 g., 57%) was crystallised from light petroleum (b. p. 100–120°), giving needles, m. p. 202–203° (Found : C, 75.7; H, 8.8. C<sub>13</sub>H<sub>18</sub>O<sub>2</sub> requires C, 75.7; H, 8.8%). The sodium salt is only very slightly soluble in water but the potassium salt readily soluble.

<sup>3</sup> Carpenter, Easter, and Wood, *J. Org. Chem.*, 1951, **16**, 603.

<sup>4</sup> Crawford and Stewart, *Nature*, 1952, **170**, 322.

<sup>5</sup> Bell and Buck, *J.*, 1956, 1890; Bell, *J.*, 1956, 3243.

<sup>6</sup> Carpenter and Easter, *J. Org. Chem.*, 1954, **19**, 77.

*Propyldurene*.—Propionyldurene (15 g.) was hydrogenated at 220 atm., and the product poured into water. The mixture was extracted with benzene and the extract dried and fractionated. *Propyldurene*, b. p. 120—125°/30 mm., solidified and was crystallised from light petroleum (b. p. 80—100°) or aqueous methanol. It formed plates, m. p. 49—50° (9.2 g., 49%) (Found: C, 88.5; H, 11.4.  $C_{13}H_{20}$  requires C, 88.5; H, 11.4%). A second fraction, b. p. 135—140°/30 mm., b. p. 230°/760 mm. (5.5 g.), was a 1 : 2 : 4 : 5-tetramethyl-3-propylcyclohexene (Found: C, 86.6; H, 13.2.  $C_{13}H_{24}$  requires C, 86.6; H, 13.4%). With bromine water it gave a white solid.

*Bromopropyldurene*.—Bromination of propyldurene (10 g.) gave the *bromo-compound* (12 g., 84%), flat crystals (from acetic acid), m. p. 52—53° (Found: C, 60.6; H, 7.5; Br, 31.8.  $C_{13}H_{19}Br$  requires C, 61.2; H, 7.5; Br, 31.3%).

*Propyldurene-carboxylic Acid*.—Carbonation of the Grignard reagent from the bromo-compound (5.5 g.) gave the *acid* (2.6 g., 54%), prisms (from aqueous methanol), m. p. 188—189° (Found: C, 76.3; H, 9.3.  $C_{14}H_{20}O_2$  requires C, 76.3; H, 9.2%). The sodium salt is very sparingly soluble in water.

*Pentamethylbenzene*.—Mesitylene (30 g.) was chloromethylated for 7 hr. at 70° with para-formaldehyde (15 g.) and concentrated hydrochloric acid (50 ml.), thus giving 2 : 4 : 6-trimethyl-*m*-xylylene dichloride (39 g., 70%), m. p. 106°, of which 35 g. in benzene (100 ml.) were stirred with zinc dust (35 g.) and 2*N*-sodium hydroxide (250 ml.) for 8½ hr. The benzene layer combined with benzene extracts of the aqueous layer was washed, dried, and distilled. The fraction of b. p. 210—230° solidified giving pentamethylbenzene (20 g., 85%), m. p. 52—53°.

*Ethylmesitylene*.—Acetylmesitylene (60 g.) in methanol (100 ml.) was hydrogenated at 240 atm. and 240° for 15 hr. in presence of copper chromite (6 g.). Ethylmesitylene (51 g., 92%), b. p. 90—93°/17 mm., was obtained. Clemmensen reduction took 165 hr. and gave a 70% yield.

*Nitropropylmesitylene*.—Nitration of propylmesitylene, m. p. 35—36°, prepared similarly to ethylmesitylene in 85% yield gave the *nitro-compound* (59% yield) as pale yellow needles (from methanol), m. p. 31° (Found: C, 69.6; H, 8.3; N, 6.7.  $C_{13}H_{17}O_2N$  requires C, 69.5; H, 8.3; N, 6.8%).

*Bromopropylmesitylene*.—Bromination of propylmesitylene (26 g.) gave two products which were separated by distillation at ca. 15 mm.: (a) *bromopropylmesitylene* (25 g.), b. p. 140°/14 mm. (Found: C, 59.8; H, 7.3; Br, 33.4.  $C_{12}H_{17}Br$  requires C, 59.8; H, 7.1; Br, 33.1%); and (b) *dibromopropylmesitylene* (3 g.), m. p. 57°, needles (from ethanol) (Found: C, 45.2; H, 5.1; Br, 49.6.  $C_{12}H_{16}Br_2$  requires C, 45.0; H, 5.0; Br, 49.9%).

2 : 4 : 6-*Trimethyl-3-propylbenzoic Acid*.—The Grignard reagent from the foregoing monobromo-compound (6 g.) was carbonated to give the *acid* (2.65 g., 52%), prisms from light petroleum (b. p. 80—100°), m. p. 115° (Found: C, 75.6; H, 8.9.  $C_{13}H_{18}O_2$  requires C, 75.7; H, 8.8%).

1-*Bromo-6-tert.-butyl-2 : 3 : 4-trimethylbenzene*.—1-*tert.-Butyl-3 : 4 : 5-trimethylbenzene* (50 g.) was brominated for 6 hr. at 50° in acetic acid. The *bromo-compound* separated on pouring of the mixture into water, forming flat needles (65 g., 90%) (from aqueous methanol), m. p. 51—52° (Found: C, 60.8; H, 7.4; Br, 31.5.  $C_{13}H_{19}Br$  requires C, 61.2; H, 7.5; Br, 31.3%).

6-*tert.-Butyl-2 : 3 : 4-trimethylbenzoic Acid*.—The Grignard reagent from the foregoing bromo-compound (25.5 g.), which needed much benzene to keep it in solution, was carbonated with carbon dioxide. The *acid* (7 g.) crystallised as flat needles, m. p. 139—140°, from light petroleum (b. p. 80—100°) (Found: C, 76.0; H, 9.1.  $C_{14}H_{20}O_2$  requires C, 76.3; H, 9.2%).

6-*tert.-Butyl-2 : 3 : 4-trimethyl-5-nitrobenzoic Acid*.—Nitration of the foregoing acid (3 g.) with fuming nitric acid in acetic anhydride below 20° gave the *nitro-acid* (1.5 g.), yellow needles, m. p. 201—203° [from light petroleum (b. p. 80—100°)] (Found: C, 63.5; H, 7.5; N, 5.4.  $C_{14}H_{19}O_4N$  requires C, 63.4; H, 7.2; N, 5.3%).

3-*Bromo-4-tert.-butyl-2 : 6-dimethylaniline*.—1-*Bromo-6-tert.-butyl-2 : 4-dimethyl-3-nitrobenzene* (100 g.), prepared according to Carpenter, Easter, and Wood<sup>3</sup> in 50% ethanol (100 ml.), was reduced with iron (60 g.) and aqueous ethanolic hydrochloric acid. The product had b. p. 110—112°/1 mm., and was converted into the *hydrochloride* (71 g.), m. p. 210° (Found: C, 49.6; H, 6.7.  $C_{12}H_{18}NBr.HCl$  requires C, 49.3; H, 6.5%).

2-*tert.-Butyl-4 : 6-dimethylbenzoic Acid*.—The foregoing amine (44 g.) in ethanol (170 ml.) and 40% sulphuric acid (76 g.) was heated under reflux with sodium nitrite (21 g.). After 1½ hr. the mixture was cooled and extracted with benzene, and this extract in turn washed with

sodium hydroxide solution, dried, and distilled. The dark red fraction (25 g.), b. p. 110—114°/0.8 mm., dissolved in light petroleum, was chromatographed on alumina. One fraction was redistilled, b. p. 149—152/13 mm., to a pale brown viscous oil of rather low bromine content. As a means of further purification could not be found, it (4 g.) was converted into the Grignard reagent and carbonated, giving the acid (1 g.), which formed a *hemihydrate* as needles, m. p. 153—154°, from aqueous acetic acid (Found: C, 72.6; H, 8.9.  $C_{13}H_{18}O_2, \frac{1}{2}H_2O$  requires C, 72.5; H, 8.9%).

*3-Bromo-4-tert.-butyl-2:6-dimethylphenol*.—From the sodium hydroxide extract and some of the chromatographic fractions in the foregoing preparation this *phenol* (5.5 g.) was obtained; it formed needles, m. p. 49—52° (Found: C, 56.7; H, 6.8.  $C_{12}H_{17}OBr$  requires C, 56.1; H, 6.7%).

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