197. *The Synthesis of Some 5-Alkyl-2-methylbenzoic Acids.*

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5-Ethyl-2-methyl-, 2-methyl-5-*n*-propyl-, and 5-*tert.*-butyl-2-methylbenzoic acids have been synthesised and their constitutions established. The bromination and Friedel–Crafts acetylation of *p*-ethyl-, *p*-*n*-propyl-, and *p*-*tert.*-butyl-toluene, and the Friedel–Crafts acetylation of *p*-*iso*propyltoluene, have been investigated. Unless conditions are carefully controlled, the acetylations result in the replacement of the higher alkyl group by the acetyl group. A novel method of carboxylation of Grignard reagents is described.

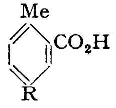
OF the alkyl-*o*-toluic acids (I—IV) required for the determination of their physical constants, only 2-methyl-5-*iso*propylbenzoic acid (III) had been prepared (Le Fèvre, *J.*, 1933, 983). However, certain of the intermediates necessary for the synthesis of the other three acids were known.

2-Amino-4-*tert.*-butyltoluene (Brady and Lahiri, *J.*, 1934, 1956) gave the 2-iodo-compound, which was converted into the carboxylic acid (IV) *via* its Grignard reagent. The synthesis was subsequently shortened, since bromination of *p*-*tert.*-butyltoluene gave 2-bromo-4-*tert.*-butyltoluene in good yield. The identity of the acid derived from this through its Grignard reagent with that obtained from the known 2-amino-derivative established the orientation of the bromination product. Thus, bromination of 4-*tert.*-butyltoluene, as might be expected, follows the same course as nitration.

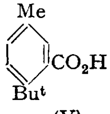
5-Ethyl-2-methylbenzoic acid (I) was obtained from 2-amino-4-ethyltoluene (Brady and Day, *J.*, 1934, 114) *via* the iodo-derivative. Bromination of *p*-ethyltoluene was first described by Remson and Morse (*Ber.*, 1878, **11**, 225) who claimed to have identified the product as the 2-bromo-derivative by its oxidation to 3-bromo-4-methylbenzoic acid. Defren (*Ber.*, 1895, **28**, 2651) also brominated *p*-ethyltoluene, without, however, establishing the constitution of the product. In the present work, bromination yielded a substance which, although boiling within a range of 1—2°, was apparently a mixture, since, on carboxylation of the Grignard reagent, an impure carboxylic acid resulted, which, even after several recrystallisations, still had an indefinite melting point, 20—30° lower than that of pure 5-ethyl-2-methylbenzoic acid. This is in agreement with the work of Brady and Day (*loc. cit.*), who showed that nitration of *p*-ethyltoluene yielded a mixture of 2- and 3-nitro-derivatives.

2-Methyl-5-*n*-propylbenzoic acid (II) was obtained from 4-methyl-3-nitropropiophenone (Errera, *Gazzetta*, 1891, **21**, I, 97), reduction of which, by the Clemmensen method, yielded 2-amino-4-*n*-propyltoluene in poor yield (cf. Brady and Day, *loc. cit.*, for the reduction of 4-methyl-3-nitroacetophenone); this readily gave the required acid by way of the iodo-compound and the Grignard reagent. Bromination of *p*-*n*-propyltoluene yielded a monobromo-derivative, shown to be the 2-bromo-compound by conversion through its Grignard reagent into 2-methyl-5-*n*-propylbenzoic acid identical with that previously prepared.

In all cases described above, a novel method of treatment with carbon dioxide under pressure was used, depending on preparation of the Grignard reagent in a strengthened glass vessel designed for making soda-water.



(I; R = Et)
(II; R = Prⁿ)
(III; R = Prⁱ)
(IV; R = Buᵗ)



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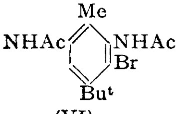
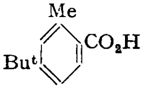
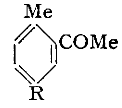


(VI)



(VII)



(VIII; R = Et)
(IX; R = Prⁿ)
(X; R = Prⁱ)

Once the acids had been prepared and their orientation established, an alternative method of preparation appeared possible. This was to acetylate the *p*-alkyltoluenes by the Friedel–Crafts method, and to oxidise the resulting alkylmethylacetophenones by hypobromite. Comparatively little work appears to have been done on these acetylations.

Meissel (*Ber.*, 1899, **32**, 2422) reported that *p-tert.*-butyltoluene with acetyl chloride in the presence of anhydrous ferric chloride gave an acetyl-4-*tert.*-butyltoluene of undetermined orientation. Lacourt (*Bull. Soc. chim. Belg.*, 1929, **38**, 16), using aluminium chloride, reported an 80% yield of an unoriented acetyl-4-*tert.*-butyltoluene, with small quantities of *p*-methylacetophenone as a by-product. Claus (*J. pr. Chem.*, 1890, **42**, 508) and others (see Allen, *Org. Synth.*, Coll. Vol. II, John Wiley & Sons, 1943, p. 3) stated that Friedel–Crafts acetylation of *p*-cymene with acetyl chloride gave mainly 2-methyl-5-*iso*propylacetophenone, which has now been confirmed. No references were found to the acetylation of *p*-ethyl- or *p-n*-propyl-toluene.

In the present work acetic anhydride (1 mol.) was added to a mixture of *p-tert.*-butyltoluene (1 mol.) and anhydrous aluminium chloride (3—4 mols.) in carbon disulphide, with subsequent heating. *p*-Methylacetophenone, formed by the elimination of the *tert.*-butyl group, and a *tert.*-butylmethylacetophenone were obtained. Hypobromite oxidation of the latter yielded a *tert.*-butylmethylbenzoic acid melting at 144°, *i.e.*, considerably higher than 5-*tert.*-butyl-2-methylbenzoic acid (101°) and the mixed melting point was *ca.* 70—72°. Our acid was therefore at first assumed to be 2-*tert.*-butyl-5-methylbenzoic acid (V). In an attempt to confirm this, 4-*tert.*-butyl-2 : 6-dinitrotoluene (Brady and Lahiri, *J.*, 1934, 1955) was converted into 2 : 6-diacetamido-4-*tert.*-butyltoluene, which yielded a monobromo-derivative, necessarily 2 : 6-diacetamido-3-bromo-4-*tert.*-butyltoluene (VI). Numerous attempts at simultaneous elimination of the two amino-groups from this compound (after hydrolysis), to yield 3-bromo-4-*tert.*-butyltoluene were unsuccessful, and the attempted synthesis of (V) was therefore abandoned. From certain physical constants, determined later, it appears unlikely that the acid of m. p. 144° is 2-*tert.*-butyl-5-methylbenzoic acid, but probable that migration of the butyl group has occurred during acetylation. Baur-Thurgau (*Ber.*, 1900, **33**, 2569) describes 4-*tert.*-butyl-2-methylbenzoic acid (VII) of m. p. 140°, obtained by oxidation of 4-*tert.*-butyl-2-methylacetophenone.

Friedel–Crafts acetylation of *p*-ethyl- and *p-n*-propyl-toluene, under the experimental conditions described above, gave pairs of ketones, but only the lower-boiling ketone (*p*-methylacetophenone) could be isolated in the pure state. Aluminium chloride being a dealkylating agent, the experiments were repeated with acetyl chloride in place of acetic anhydride, since only one molecular proportion of aluminium chloride was then necessary. Under the same experimental conditions as before, *p*-methylacetophenone was again formed in considerable quantity. Finally, a mixture of the hydrocarbon (1 mol.) and acetyl chloride (1 mol.) was dropped into a stirred suspension of aluminium chloride (1 mol.) in carbon disulphide at room temperature. This was successful, in the cases of *p*-ethyl-, *p-n*-propyl-, *p-iso*propyl-, and *p-tert.*-butyl-toluene, in avoiding the formation of 4-methylacetophenone, whilst giving the acetyl derivatives of the hydrocarbons in good yield.

As stated above, the orientation of the ketone obtained from 4-*tert.*-butyltoluene was not satisfactorily determined. In the other three cases, the products were proved to be the 5-alkyl-2-methylacetophenones (VIII, IX, and X), by hypobromite oxidation to the 5-alkyl-2-methylbenzoic acids previously synthesised from intermediates of known orientation.

EXPERIMENTAL

(Microanalyses are by Dr.Ing. A. Schoeller, Berlin. M. p.s and b. p.s are uncorrected.)

5-tert.-*Butyl-2-methylbenzoic acid* (IV).—2-Amino-4-*tert.*-butyltoluene (12 g.) in sulphuric acid (10 ml. in 150 ml. of water) was diazotised in the normal manner, then treated with potassium iodide (25 g. in 50 ml. of water), and left at room temperature for 1 hour. The mixture was then warmed cautiously on the steam-bath until the evolution of nitrogen ceased, a little sodium hydrogen sulphite added, and the mixture steam-distilled. The distillate was extracted with ether, the extract washed (2N-sulphuric acid, water, 2N-sodium hydroxide, and water) and dried ($CaCl_2$), and the solvent removed. The residue on distlllation *in vacuo* gave 4-tert.-*butyl*-2-*iodotoluene* (7 g.), b. p. 148°/28 mm. (Found : I, 46·1. $C_{11}H_{15}I$ requires I, 46·35%).

2-*Bromo*-4-tert.-*butyltoluene*.—Bromine (24 g.) was cautiously added to a mixture of *p-tert.*-butyltoluene (21 g.) (Verley, *Bull. Soc. chim.*, 1898, **19**, 68) and iodine (0·25 g.) with occasional cooling. After the initial reaction had subsided, the mixture was heated on the steam-bath to expel as much hydrogen bromide as possible, and then steam-distilled. The distillate was extracted with ether, the extract washed (water, 2N-sodium carbonate, 2N-sodium thiosulphate, and water) and dried ($CaCl_2$), the solvent removed, and the residue distilled *in vacuo.* The fraction of b. p. 115—120°/17 mm. was redistilled, giving 2-*bromo*-4-tert.-*butyltoluene* (19 g.), b. p. 117°/13 mm. (Found : Br, 35·0. $C_{11}H_{15}Br$ requires Br, 35·2%).

5-tert.-*Butyl-2-methylbenzoic Acid.*—Into a thoroughly dried " Sparklet " soda syphon was placed 2-bromo-4-*tert.*-butyltoluene (18 g.), magnesium ribbon (2 g.; dried at 110°), absolute ether (60 ml.), and dry ethyl bromide (two drops). A reflux condenser fitted with a calcium chloride tube was inserted into the neck of the syphon, which was then heated very cautiously (to avoid cracking) in a water-bath and kept at about 60° until the formation of the Grignard reagent was complete (about 12 hours). The syphon was then cooled in water, and next immersed in ice-water. The condenser was removed, the ordinary syphon-head (with the syphon-tube cut off) replaced, and the syphon cautiously charged with one " Sparklet " bulb of carbon dioxide. The gas was then immediately released, to remove as much air as possible, and the syphon again charged with carbon dioxide. The syphon was then left in ice-water for 2 days. The reaction mixture separated into an upper ethereal and a lower resinous layer. The pressure was then released, the syphon-head was removed, and the contents of the syphon were well shaken and poured on to a mixture of sulphuric acid (5N; 40 ml.) and ice (60 g.). After 10 minutes the ethereal layer was separated and extracted with 2N-sodium carbonate. The aqueous extract was acidified with dilute sulphuric acid. An oil separated, which rapidly solidified. This was filtered off, washed with water, and distilled in steam. The distillate was then cooled, and the acid filtered off and recrystallised from aqueous alcohol, giving 5-tert.-*butyl-2-methylbenzoic acid* as long white needles, m. p. 101° (6 g.) (Found : C, 75·0; H, 8·3. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). An identical product was obtained when 4-*tert.*-butyl-2-iodotoluene was employed.

5-*Ethyl-2-methylbenzoic acid* (I) was prepared from 2-amino-4-ethyltoluene through 4-*ethyl*-2-*iodotoluene*, b. p. 116—117°/10 mm. (Found : I, 51·4. $C_9H_{11}I$ requires I, 51·6%), and its Grignard reagent. It crystallised from aqueous alcohol in long needles, m. p. 73·5° (Found : C, 73·2; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·4%).

2-*Methyl*-5-n-*propylbenzoic acid* (II).—4-Methyl-3-nitropropiophenone (25 g.) was reduced with amalgamated zinc (200 g.; prepared as described by Brady and Day, *J.*, 1934, 117) and hydrochloric acid (200 ml. of concentrated acid in 200 ml. of water), a further 600 ml. of concentrated acid being added during 6 hours. After cooling, sodium hydroxide (400 g. in 600 ml. of water) was added, and the mixture distilled in steam. The distillate was extracted with ether, the extract dried (KOH), the solvent removed, and the residue distilled *in vacuo.* 2-Amino-4-*n*-propyltoluene (2 g.) was obtained as a colourless oil, b. p. 128—130°/13 mm., with an unpleasant odour. The *acetyl* derivative crystallised from aqueous alcohol as a felted mass, m. p. 127° (Found : C, 75·1; H, 9·0; N, 7·4. $C_{12}H_{17}ON$ requires C, 75·4; H, 9·0; N, 7·3%). The poor yield of the amine obtained in this preparation compares with that of 2-amino-4-ethyltoluene obtained by Brady and Day (*ibid.*, p. 120) in the reduction of 4-methyl-3-nitroacetophenone.

2-*Iodo*-4-n-*propyltoluene* was obtained from the amine in the normal manner as a colourless oil, b. p. 131—133°/14 mm. (Found : I, 48·6. $C_{10}H_{13}I$ requires I, 48·8%).

p-*n*-Propyltoluene (von Auwers, *Annalen*, 1919, **419**, 112) yielded 2-*bromo*-4-n-*propyltoluene* as a colourless oil, b. p. 105°/12 mm. (Found : Br, 37·4. $C_{10}H_{13}Br$ requires Br, 37·6%). Both 2-bromo- and 2-iodo-4-*n*-propyltoluene, on conversion into the Grignard reagent and treatment with carbon dioxide, yielded 2-*methyl*-5-n-*propylbenzoic* acid, long needles, m. p. 57° (from aqueous alcohol) (Found : C, 74·2; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%).

Friedel–Crafts Experiments.—*Method* I. Acetic anhydride (69 g., 1 mol.) was run into the mechanically stirred mixture of *p*-*tert.*-butyltoluene (100 g., 1 mol.), carbon disulphide (200 ml.), and freshly sublimed aluminium chloride (320 g., *ca.* 3·5 mols.) during 30 minutes. The warm mixture was refluxed with stirring for a further 2 hours, and then poured on ice. The carbon disulphide layer was separated, the aqueous layer was extracted with ether, the combined carbon disulphide and ethereal extracts were washed with water and dried ($CaCl_2$). The solvent was removed, and the residue fractionally distilled at 17 mm. The fraction boiling below 110° (8 g.) consisted mainly of unchanged hydrocarbon. That of b. p. 110—120° (21 g.) was purified through its semicarbazone and yielded pure *p*-methylacetophenone (10 g.), b. p. 113°/17 mm. The semicarbazone, a white microcrystalline solid from aqueous alcohol, had m. p. 207° (unchanged on admixture with an authentic specimen) (Found : C, 62·6; H, 7·0; N, 21·9. Cal. for $C_{10}H_{13}ON_3$: C, 62·8; H, 6·9; N, 22·0%). The fraction of b. p. 120—140° (7 g.) was discarded, and that distilling between 140 and 155° (43 g.) was converted into the semicarbazone which, recrystallised three times from aqueous alcohol and then hydrolysed, gave a pure tert.-

butylmethylacetophenone (21 g.), b. p. 147°/17 mm. (Found : C, 81·8; H, 9·6. $C_{13}H_{18}O$ requires C, 82·1; H, 9·55%). The *semicarbazone*, white needles from aqueous alcohol, had m. p. 197° (Found : C, 68·0; H, 8·7; N, 16·7. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·6; N, 17·0%). The mixed m. p. with the semicarbazone of *p*-methylacetophenone was *ca.* 174°. Meissel (*Ber.*, 1899, **32**, 2422) records a b. p. of 240—245° for 2-(or 3-)acetyl-4-*tert.*-butyltoluene, whilst Lacourt (*Bull. Soc. chim. Belg.*, 1929, **38**, 16) gives b. p. 133—135°/12 mm., and the m. p. of the semicarbazone as 190°. Baur-Thurgau (*Ber.*, 1898, **31**, 1345) gives the b. p. of 4-*tert.*-butyl-2-methylacetophenone as 255—258°.

Method II. To freshly sublimed aluminium chloride (51 g., 1 mol.) and carbon disulphide (100 ml.), cooled with water, was added a mixture of *p*-ethyltoluene (46 g., 1 mol.) and acetyl chloride (30 g., 1 mol.) during *ca.* 90 minutes. Stirring was then continued at room temperature for a further 6 hours. The dark brown mixture was poured on crushed ice, and worked up as in Method I. The crude product was fractionally distilled *in vacuo* (15 mm.). The fraction boiling below 100° (4 g.) consisted of unchanged hydrocarbon. That of b. p 100—112° (1 g.) was proved to contain no *p*-methylacetophenone by means of the semicarbazone. The fraction distilling between 112 and 122° (45 g.) was crude *5-ethyl-2-methylacetophenone* (VIII). It was purified by conversion into the semicarbazone; recrystallisation three times from aqueous alcohol, hydrolysis, and redistillation gave the pure *ketone* (20 g.) as a colourless pleasant-smelling liquid, b. p. 112—113°/13 mm. (Found : C, 81·3; H, 8·6. $C_{11}H_{14}O$ requires C, 81·5; H, 8·7%). The *semicarbazone*, white needles, had m. p. 135° (Found : C, 65·9; H, 7·9; N, 19·0. $C_{12}H_{17}ON_3$ requires C, 65·8; H, 7·8; N, 19·2%).

The following ketones were prepared in a similar manner : *2-Methyl-*5-n-*propylacetophenone* (IX), b. p. 122°/11 mm. (Found : C, 81·9; H, 9·2. $C_{12}H_{16}O$ requires C, 81·8; H, 9·1%) [*semicarbazone*, white needles (from aqueous alcohol), m. p. 163° (Found : C, 66·8; H, 8·1; N, 18·2. $C_{13}H_{19}ON_3$ requires C, 66·95; H, 8·2; N, 18·0%)]. 2-Methyl-5-*iso*propylacetophenone (X), b. p. 125°/14 mm. (Klages and Lickroth, *Ber.*, 1899, **32**, 1563, give b. p. 142°/37 mm.; Lacourt, *Bull. Soc. chim. Belg.*, 1929, **38**, 17, gives 124—125°/12 mm.) [semicarbazone, white needles (from aqueous alcohol), m. p. 149° (Lacourt, *loc. cit.*, gives m. p. 147°) (Found : C, 66·8; H, 8·3; N, 18·0%)].

Oxidation of the Alkylmethylacetophenones.—Bromine (39·6 g., 3 mol.) was dissolved, with cooling, in cold aqueous sodium hydroxide (600 ml. of 4%) contained in a large bottle. 5-Ethyl-2-methylacetophenone (13·4 g., 1 mol.) was added, and the bottle mechanically shaken until the yellow colour of the solution had disappeared (*ca.* 30 hours). A heavy layer of bromoform separated. The liquors were washed twice with ether, the washings being discarded, the aqueous layer was acidified, and the precipitated acid extracted with ether. The ethereal solution was extracted with 2N-sodium carbonate, and the alkaline extract acidified. After filtration and washing with water, the acid was distilled in steam and finally recrystallised from aqueous alcohol, 5-ethyl-2-methylbenzoic acid (8·6 g.), m. p. 73·5°, being obtained.

Similar oxidation of 2-methyl-5-*n*-propylacetophenone yielded 2-methyl-5-*n*-propylbenzoic acid, m. p. 57°. In both cases, the carboxylic acids were identical with those prepared *via* the Grignard reagents. Hypobromite oxidation of 2-methyl-5-*iso*propylacetophenone yielded 2-methyl-5-*iso*propylbenzoic acid (III), which crystallised from aqueous alcohol in needles, m. p. 70·5° (Le Fèvre, *J.*, 1933, 983, gives m. p. 70°; Lester and Bailey, *J. Amer. Chem. Soc.*, 1946, **68**, 375, give 71°) (Found : C, 74·1; H, 8·1. Calc. for $C_{11}H_{14}O_2$: C, 74·2; H, 7·9%), identical with those obtained by carboxylation of the Grignard reagent from 2-bromo-4-*iso*propyltoluene (Le Fèvre, *loc. cit.*).

When the *tert.*-butylmethylacetophenone described above was oxidised in the same manner, a tert.-*butylmethylbenzoic acid* was obtained which crystallised from aqueous alcohol in glistening white plates, m. p. 144° (mixed m. p. with 5-*tert.*-butyl-2-methylbenzoic acid, *ca.* 70—72°) (Found : C, 74·5; H, 8·3%; equiv., 196. $C_{11}H_{15}{\cdot}CO_2H$ requires C, 75·0; H, 8·3%; equiv., 192).

Attempt to synthesise 2-tert.-*Butyl-5-methylbenzoic Acid* (V).—4-*tert.*-Butyl-2 : 6-dinitrotoluene (78 g.) was reduced with excess of granulated tin and hydrochloric acid in the normal manner. After about 20 hours' refluxing, the mixture was cooled and poured into sodium hydroxide (850 g. in 1700 ml. of water), and the whole thoroughly shaken. After cooling, the diamine was extracted with ether, the extract washed and dried (KOH), and the solvent removed, leaving crude 2 : 6-diamino-4-*tert.*-butyltoluene as an oil, which rapidly solidified to colourless crystals, darkening on storage. The crude diamine (45 g.) was boiled for 2—3 minutes with acetic anhydride (54 g., 5% excess); the product, after recrystallisation from alcohol, was 2 : 6-*diacetamido*-4-tert.-*butyltoluene*, a felted mass, m. p. 298° (61 g.) (Found : C, 68·5; H, 8·5; N, 10·8. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·5; N, 10·7%).

2 : 6-*Diacetamido*-3-*bromo*-4-tert.-*butyltoluene* (VI).—2 : 6-Diacetamido-4-*tert.*-butyltoluene (46 g., 1 mol.) and glacial acetic acid (150 ml.) were warmed on the water-bath to dissolve as much of the solid as possible, then cooled to room temperature, and a solution of bromine (28·1 g., 1 mol.) in acetic acid (20 ml.) added, with shaking. The mixture was heated under reflux on the steam-bath, dissolution being complete within 10 minutes. After 1 hour, white crystals began to separate. Heating was continued until all the bromine disappeared (*ca.* 8 hours). The cooled product was then poured into water (1200 ml.), filtered off, washed with water, and recrystallised twice from alcohol. 2 : 6-*Diacetamido*-3-*bromo*-4-tert.-*butyltoluene* (31 g.) was obtained as a white, granular solid, m. p. 252° (decomp.) (Found : C, 52·9; H, 6·3; N, 7·9; Br, 23·2. $C_{15}H_{21}O_2N_2Br$ requires C, 52·8; H, 6·2; N, 8·2; Br, 23·5%.

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