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Alkyl Substituted Benzoic Acids. Part III.[1] Isopropylbenzoic Acids

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Isopropylation of bromo- or iodo-benzene gives a mixture of mono-, di-, and tri-isopropyl halogenobenzenes. When these are separated by fractionation and carbonated to give the corresponding benzoic acids, the large differences in acid strengths between the individual acids facilitate their separation from solutions of their salts by fractional precipitation with mineral acid. Benzoic acids with the following substituents were thus obtained pure 2-isopropyl, 4-isopropyl, 2,4-di-isopropyl, 2,6-di-isopropyl, 2,4,5-tri-isopropyl, and 2,4,6-tri-isopropyl, all, except possibly 4-isopropylbenzoic acid, more readily than by methods previously described.

THE isopropylation of bromo- or iodo-benzene with isopropyl alcohol and sulphuric acid under suitable conditions gives a mixture of mono-, di-, and tri-isopropylated products. The Grignard reagent from the monoisopropyl fraction obtained by fractional distillation gives on carbonation a mixture of isopropylbenzoic acids. These acids are readily separated by stepwise acidification of a solution of their sodium salts, to give 2- and 4-isopropylbenzoic acids in about equal amounts.

The di-isopropylbromobenzene fraction when similarly treated gives a weaker and a stronger acid in the ratio 3 : 1. The weaker one (the first to be precipitated) is 2,4-di-isopropylbenzoic acid, but the second does not correspond to a known di-isopropylbenzoic acid. It was shown to be 2,6-di-isopropylbenzoic acid by analysis, equivalent weight, i.r. absorption spectrum, and decarboxylation to *m*-di-isopropylbenzene. Its three distinct absorption peaks in the i.r. at 1799, 1871, and 1940 cm.$^{-1}$ are characteristic of 1,2,3-substitution as are also the bands at 707, 767, and 807 cm.$^{-1}$. Samples of

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[1] Part II. M. Crawford and J. H. Magill, *J. Chem. Soc.*, 1957, 3275.

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m-di-isopropylbenzene obtained by decarboxylation of the 2,4- and 2,6-acids had identical i.r. spectra and g.l.c. retention times. 3,5-Di-isopropylbenzoic acid, the only other similar acid likely to give *m*-di-isopropylbenzene on decarboxylation, is known [2] and has a much lower m.p. The new acid must therefore be 2,6-di-isopropylbenzoic acid, described [3] as having m.p. 110·5—112°; our sample melts at 119·5°. Its dissociation constant in aqueous solution was found [4] to be *ca.* 65×10^{-5}.

The tri-isopropylbromobenzene fraction, when similarly carbonated, gave two acids in the ratio *ca.* 1 : 2; the former (the weaker) was found to be 2,4,5-tri-isopropylbenzoic acid and the latter 2,4,6-tri-isopropylbenzoic acid. The order of precipitation agrees with their expected relative strengths.

The degree of isopropylation of bromobenzene can be raised, if more highly substituted acids are mainly required, by increasing the reaction time from 24 hr., which gives mainly monoisopropylation, to 72 hr., which leads to greater amounts of the di- and tri-isopropyl fractions.

Beckwith and Goodrich [5] mention 'the conflicting physical properties reported for *o*-isopropylbenzoic acid' and attribute these to the circumstance that most of the previous methods employ as the initial step the nitration or halogenation of isopropylbenzene, with the result that the m.p.s of the final products are affected by the presence of unwanted isomers. Similar remarks about the di- and tri-substituted compounds would be appropriate. The isomeric acids have distinctly different strengths because of the steric effect of the isopropyl groups in one or both of the *ortho*-positions. Thus the method of fractional precipitation can separate the acids particularly sharply and can completely remove the unwanted isomers. It is for this reason that the method gives very pure products.

The method starts with available compounds and requires no more elaborate apparatus than a fractionating column. Thus it is superior in its directness to the methods used previously for 2-isopropyl-,[6,7] 2,4-di-isopropyl-,[8] 2,4,5-tri-isopropyl-,[8] and 2,4,6-tri-isopropylbenzoic acids,[9] which are multi-stage or start from compounds such as 1,3,5-tri-isopropylbenzene which require preparation and careful purification.

EXPERIMENTAL

Isopropylation of Bromobenzene.—A mixture of bromobenzene (100 ml.), isopropyl alcohol (375 ml.), and concentrated sulphuric acid (425 ml.) was stirred slowly for 24 hr. Fast stirring resulted in considerable sulphonation. The product was poured into a large amount of ice–water and extracted with ether. The ether extract was dried, the solvent was removed, and the residue was fractionally distilled with a heated column (60 cm.). The following fractions were obtained: unchanged bromobenzene, b.p. 60°/30 mm.; monoisopropyl derivatives, b.p. 110°/30 mm. (main fraction); di-isopropyl derivatives, b.p. 140°/30 mm.; tri-isopropyl derivatives, b.p. 162°/30 mm.; and a small residue. Longer times increased the proportion of higher fractions, *e.g.* after 72 hr. the di- and tri-isopropyl fractions were the main ones.

Carbonation.—Each fraction was converted into its Grignard reagent by the entrainment method by use of a large excess of magnesium to limit biaryl formation. To magnesium turnings (30 g.) under ether (60 ml.) methyl iodide (0·5 ml.) was added to start the reaction, after which a solution of the appropriate fraction (5 g.) and methyl iodide (5 g.) in ether (150 ml.) was added dropwise during 30 min. The mixture was heated under reflux for another 90 min., after which the product was poured through glass wool on crushed solid carbon dioxide. Ice-cold dilute hydrochloric acid was added and the aqueous layer was separated and extracted twice with ether. The extracts were added to the ether layer, which was washed with water and extracted with 5% sodium hydroxide solution; this in turn was extracted with chloroform to remove neutral products. Acidification of the alkaline solution gave an oil which solidified at low temperature to a low-melting solid mixture (*ca.* 3 g.) of acids.

Fractional Precipitation.—The mixed monoisopropylbenzoic acids (3 g.) were dissolved in a slight excess of 10% sodium carbonate solution and dilute hydrochloric acid was added from a burette to neutralise the solution. Successive small portions were then run in to precipitate batches of acid, eight in all. After each precipitation the solution was extracted with ether and the extract evaporated to dryness. The acid from the first three fractions (1·5 g.) melted at about 100°. The fourth fraction (0·65 g.) remained liquid. The acid from the last four fractions (0·85 g.) melted from 50 to 60°. More low-melting acid (0·4 g.) was obtained by fractional precipitation of fraction 4. The first three fractions were mixed and gave 4-isopropylbenzoic acid, m.p. 119° (from aqueous acetic acid) (lit.,[10] 120°). The remaining fractions on similar treatment gave 2-isopropylbenzoic acid, m.p. 63° (lit.,[6,7] 63—64°).

The mixed di-isopropylbenzoic acids (8 g.) were similarly treated to give first the weaker (4·7 g.), 2,4-di-isopropylbenzoic acid, m.p. 108° (lit.,[8] 107·8—108·2°). The stronger acid (1·7 g.) melted at 119·5° and depressed the m.p. of 4-isopropylbenzoic acid considerably. It was not 3,5-di-isopropylbenzoic acid (lit.,[2] m.p. 100°).

The mixed tri-isopropylbenzoic acids similarly gave, first, the weaker, 2,4,5-tri-isopropylbenzoic acid, m.p. 163° (lit.,[8] 162·0—163·2°), and then rather more than twice as much of the stronger 2,4,6-tri-isopropylbenzoic acid, m.p. 185° (lit.,[9,11] 186—187° and 178—180°).

2,6-*Di-isopropylbenzoic Acid.*—The stronger di-isopropylbenzoic acid (100 mg.) was decarboxylated by heating under reflux with quinoline (10 ml.) and copper chromite

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[2] C. E. Claff, *J. Amer. Chem. Soc.*, 1955, **77**, 3774.

[3] K. H. Fleurke, C. van der Stelt, and W. Th. Nauta, *Rec. Trav. chim.*, 1962, **81**, 93.

[4] M. Crawford and M. Woodhead, *Tetrahedron Letters*, 1962, 1189.

[5] A. L. J. Beckwith and J. E. Goodrich, *Austral. J. Chem.*, 1965, **18**, 1023.

[6] H. C. Brown, J. D. Brady, M. Crayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, 1957, **79**, 1897.

[7] J. L. Cotter, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, 1963, **28**, 1917.

[8] A. Newton, *J. Amer. Chem. Soc.*, 1943, **65**, 2441.

[9] R. C. Fuson and E. C. Horning, *J. Amer. Chem. Soc.*, 1940, **62**, 2962.

[10] J. W. Baker, J. F. J. Dippy, and J. E. Page, *J. Chem. Soc.*, 1937, 1774.

[11] J. Thiec, *Ann. Chim.* (*France*), 1954, **9**, 51.

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(50 mg.) for 2 hr. The cooled mixture was acidified with hydrochloric acid and extracted twice with ether (2 × 25 ml.). The extract was washed and dried and the solvent was removed. The remaining oil (68 mg.) was chromatographed on alumina; its uniformity was confirmed by g.l.c. Its i.r. spectrum (carbon disulphide) was identical with that of *m*-di-isopropylbenzene similarly prepared from 2,4-di-isopropylbenzoic acid. The acid is therefore 2,6-di-isopropylbenzoic acid, i.r. spectrum (CS_2) as expected for 1,2,3-substitution, whereas the 2,4-acid showed 1,2,4-substitution (Found: C, 75·7; H, 8·6%; Equiv., 204. Calc. for $C_{13}H_{18}O_2$: C, 75·7; H, 8·8%; Equiv., 206).

[7/1243 *Received, September 25th*, 1967]

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