BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 2871—2873 (1971)

Direct Iodination of Trimethylbenzoic Acids and Tetramethylbenzoic Acids with Iodine-Periodic Acid[1)]

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No report seems to be found in literature on the preparation and properties of iodotrimethyl- and iodotetramethylbenzoic acids. In view of the high propensity for iodine atom to undergo displacement, an attempt to introduce carboxylic group into the nucleus of reactive iodopolymethylbenzenes seems to be practically meaningless. The commonly used indirect method wihch involves the replacement of amino group by iodine atom is unsuitable in the present case, since most of the required polymethylaminobenzoic acids are unknown and not readily available. In previous papers,[2,3)] *iodine used with periodic acid* has been proposed as a convenient iodinating agent for polyalkylbenzenes because of the simple procedure, excellent yield, and high purity of products. Although the reagent has not been used extensively for the iodination of polyalkyl compounds other than hydrocarbons, satisfactory results recently obtained with less activated compounds, such as halopolyalkylbenzenes and halobiphenyls,[4)] seem to promise a successful use of this reagent for one-step synthesis of iodopolymethylbenzoic acids from the corresponding polymethylbenzoic acids. Thus, some trimethylbenzoic acids and tetramethylbenzoic acids were treated with the above reagent in aqueous acetic acid containing a small amount of sulfuric acid as catalyst.

Trimethylbenzoic acids were readily iodinated with iodine-periodic acid to give the monoiodo derivatives in a high yield of 85% or higher. General character of the reaction suggests an ionic scheme, with the ease of iodination in the decreasing order 2,4,6>2,4,5> 2,3,4~2,3,6> 3,4,5-trimethylbenzoic acid. 2,4,5-Trimethylbenzoic acid gave almost exclusively 3-iodo-2,4,5-trimethylbenzoic acid. 5-Iodo-2,3,4-trimethylbenzoic acid was obtained from 2,3,4-trimethylbenzoic acid. The meta position to the carboxylic group was in every case preferred to ortho position. The position occupied by iodine atom in these systems was established by spectral comparison with the chloro or bromo analogs. Replacement of chlorine or bromine atom by iodine atom led to only a slight change in the general patterns of infrared and PMR spectra of these compounds.

With the use of excess reagent, 2,4,6-trimethylbenzoic acid (mesitoic acid) was readily converted into 3,5-diiodo-2,4,6-trimethylbenzoic acid, but diiodination of other isomeric acids was quite slow and usually accompanied by an appreciable extent of iododecarboxylation, giving diiodotrimethylbenzenes as an alkaline-insoluble part. 2,4,5-Trimethylbenzoic acid was especially hard to be diiodinated.

Iodination of tetramethylbenzoic acids proceeded with much ease. Of three isomeric acids, 2,3,4,6-tetramethylbenzoic acid was the most reactive, followed by 2,3,5,6-tetramethylbenzoic acid and 2,3,4,5-tetramethylbenzoic acid. The reaction was also subjected to iododecarboxylation to some extent, although iodotetramethylbenzoic acid was stable towards further action of the reagent (Fig. 1).

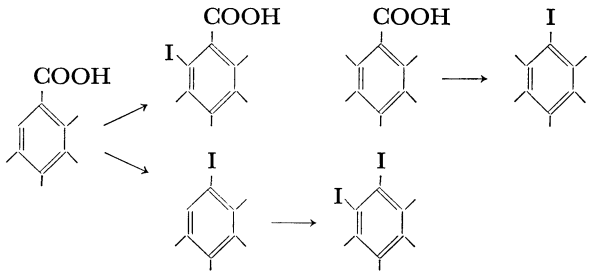

Fig. 1

In order to find a substitutional process on the alkyl side-chain, pentamethylbenzoic acid was treated with the above iodinating agent. The fully methylated benzoic acid readily underwent iodination to give a white crystalline solid, which, however, contained no acidic function and proved to be identical with iodopentamethylbenzene by direct comparison with the authentic specimen (Fig. 1). Spectral inspection of

1) The Reaction of Polysubstituted Aromatics. XXIII. Part XXII: This Bulletin, **44**, 2248 (1971).

2) H. Suzuki, K. Nakamura, and R. Goto, This Bulletin, **39**, 128 (1966).

3) H. Suzuki, "Organic Syntheses," Vol. 51, in press (1971).

4) H. Suzuki and N. Yamamoto, This Bulletin, in press (1971).

Table 1. Physical properties of some monoiodo and diiodopolymethylbenzoic acids

Compound	Mp (°C)	PMR spectra ArH	PMR spectra CH_3 (τ)	IR spectra[a] (cm^{-1})	Elementary analysis, % Found	Elementary analysis, % Calcd
5-Iodo-2,3,4-trimethylbenzoic acid	252—253	1.82	7.68 (1)[b] 7.56 (1) 7.51 (1)	769 860 893 910 1031 1073 1246 1281 1704	C: 41.40 H: 3.89	41.41 3.82
3-Iodo-2,4,5-trimethylbenzoic acid	182—183	2.39	7.64 (1) 7.50 (1) 7.30 (1)	732 775 821 895 910 989 1252 1286 1696	C: 41.75 H: 4.02	41.41 3.82
3-Iodo-2,4,6-trimethylbenzoic acid	196—197	3.00	7.75 (1) 7.55 (1) 7.52 (1)	725 790 862 922 966 1026 1099 1211 1287 1690	C: 41.31 H: 4.11	41.41 3.82
2-Iodo-3,4,5-trimethylbenzoic acid	186—189	2.72	7.75 (1) 7.70 (1) 7.47 (1)	701 766 890 941 1198 1248 1292 1694	C: 42.25 H: 3.99	41.41 3.82
4,5-Diiodo-2,3,6-trimethylbenzoic acid	266—268		7.72 (1) 7.41 (1) 7.33 (1)	889 937 1034 1062 1164 1270 1284 1691 1712	C: 29.01 H: 2.66	28.87 2.42
3,5-Diiodo-2,4,6-trimethylbenzoic acid	242—243		7.56 (3)	784 869 954 1102 1248 1695	C: 28.78 H: 2.61	28.87 2.42
2,6-Diiodo-3,4,5-trimethylbenzoic acid	266—268		7.62 (1) 7.52 (2)	695 737 773 931 942 1003 1226 1316 1697	C: 28.95 H: 2.53	28.87 2.42
6-Iodo-2,3,4,5-tetramethylbenzoic acid	232—233		7.83 (1) 7.76 (1) 7.71 (1) 7.53 (1)	677 717 769 833 913 970 1197 1233 1300 1667	C: 43.26 H: 4.38	43.45 4.31
5-Iodo-2,3,4,6-tetramethylbenzoic acid	232—235		7.81 (1) 7.73 (1) 7.57 (1) 7.47 (1)	729 779 827 933 1043 1176 1269 1693 1712	C: 43.37 H: 4.39	43.45 4.31
4-Iodo-2,3,5,6-tetramethylbenzoic acid	274—276		7.70 (2) 7.50 (2)	682 742 899 937 994 1038 1084 1247 1298 1692 1712	C: 43.73 H: 4.18	43.45 4.31

a) Principal peaks in the regions, 650—1350 and 1500—2000 cm^{-1}.
b) Numerals in parentheses refer to the number of methyl groups. PMR spectra were determined in dioxane solutions.

the crude reaction product had no indication of the side-chain substitution.

All the iodotrimethylbenzoic acids, diiodotrimethylbenzoic acids and iodotetramethylbenzoic acids are well crystallized solids with high melting points. They dissolve very slightly in light petroleum, benzene, carbon tetrachloride, and cold aqueous ethanol, and are moderately or readily soluble in hot ethanol, dioxane and tetrahydrofuran. Some physical properties of these iodopolymethylbenzoic acids are summarized in Table 1.

Experimental

2,4,6-Trimethylbenzoic acid (mesitoic acid), 2,4,5-trimethylbenzoic acid, and three isomeric tetramethylbenzoic acids were prepared by the Friedel-Crafts carboxylation of the corresponding hydrocarbons with oxalyl chloride.[5,6] A similar treatment of 1,2,3-trimethylbenzene gave a mixture of 2,3,4-trimethylbenzoic acid and 3,4,5-trimethylbenzoic acid. Fractional crystallization of the product mixture from aqueous ethanol gave the former acid as a more soluble and the latter acid as a less soluble part. 3,4,5-Trimethylbenzoic acid was also prepared by the oxidation of 3,4,5-trimethylacetophenone with sodium hypochlorite.[7] 2,3,6-Trimethylbenzoic acid was obtained by carbonation of the Grignard reagent from 3-bromo-1,2,4-trimethylbenzene.[8] Pentamethylbenzoic acid was prepared from hexamethylbenzene through side-chain nitrooxylation followed by potassium permanganate-pyridine oxidation.[9]

Infrared spectra were measured on Nujol mulls with a Jasco 402G spectrophotometer and only prominent peaks are recorded. PMR spectra were determined in dioxane solutions with a JEOLCO 3H-60 spectrometer against internal TMS.

Procedure for the Iodination of Polymethylbenzoic Acids. The general procedure is illustrated below by the reaction of mesitoic acid.

3-Iodo-2,4,6-trimethylbenzoic Acid (Iodomesitoic Acid). A mixture of mesitoic acid (4.1 g), iodine (2.55 g), periodic acid dihydrate (1.14 g), and 80% acetic acid (40 ml) containing catalytic amounts of sulfuric acid was heated with stirring at 70—75°C for about 15—20 min until the color of iodine disappeared. After cooling, water was added and the crystalline deposit was collected. The crude product was dissolved into aqueous sodium hydroxide and any trace of

5) G. A. Varvoglis and N. E. Alexandrou, *Chimika Chronika*, **26A**, 137 (1961).
6) H. Suzuki, *Nippon Kagaku Zasshi*, **91**, 484 (1970).
7) H. Suzuki, This Bulletin, **42**, 2618 (1969).
8) H. A. Smith and J. A. Starfield, *J. Amer. Chem. Soc.*, **71**, 81 (1949).
9) H. Suzuki, *Nippon Kagaku Zasshi*, **91**, 179 (1970).

insoluble by-product was removed over decolorizing charcoal. The clear filtrate was made acidic with concentrated hydrochloric acid and the precipitate was collected, thoroughly washed with water, and crystallized from aqueous ethanol to give *iodomesitoic acid* as colorless fine needles, mp 196—197°C. Yield, 6.2 g (86%).

When mesitoic acid was treated with twice the amount of the reagent under the same conditions, white crystals soon deposited from the mixture. They were collected and crystallized from aqueous ethanol to yield *diiodomesitoic acid* in 78% yield. Colorless large leaflets, mp 242—243°C.

Iododecarboxylation of Pentamethylbenzoic Acid. Pentamethylbenzoic acid (3.2 g) was suspended in 80% aqueous acetic acid (40 m*l*) containing a small amount of sulfuric acid as catalyst, and treated with iodine (1.7 g) and periodic acid dihydrate (0.75 g) in a similar manner as above. After several hours, iodine was mostly consumed and white crystalline powder deposited from the solution. It was filtered and crystallized from dilute ethanol to give colorless prisms (3.8 g), mp 139—141°C. It was identified as iodopentamethylbenzene (mp 141—142°C)[10] by direct comparison with the authentic specimen. IR: 901, 996, 1010, 1060, and 1197 cm^{-1}. PMR (CCl_4): 7.95 (Me), 7.86 (2 Me), and 7.63τ (2 Me).

10) H. Suzuki, T. Sugiyama, and R. Goto, This Bulletin, **37**, 1858 (1964).