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The Direct Iodination of Polyalkylbenzenes Bearing Bulky Groups[1)]

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The following polyalkylbenzenes bearing bulky groups have been subjected to direct iodination using iodine and periodic acid, and the corresponding mono-iodinated products have been obtained in fairly high yields: 4-*t*-butyl-1, 2-dimethylbenzene, 5-*t*-butyl-1, 3-dimethylbenzene, 5-*t*-butyl-1, 2, 3-trimethylbenzene, 1, 2, 4, 5-tetraisopropylbenzene and *p*-di-*t*-butylbenzene. The polyiodination of polymethylbenzenes has also proceeded smoothly, giving polyiodo compounds in high yields. A comparison of various direct methods has proved the above reagent to be the best iodinating agent for a variety of polyalkylbenzenes.

Because of our interest in the disproportionation of aromatic iodo compounds in sulfuric acid, some attempts to prepare the iodo derivatives of some polyalkylbenzenes bearing bulky groups by ordinary direct methods have been made. Up to the present, however, little attempt has been made to introduce an iodine atom into the rings of such polyalkylbenzenes. As the polyalkylbenzenes are unreactive towards molecular iodine, it is necessary to use some oxidizing agents for a successful direct iodination. In order to determine the best oxidizing agent for the reaction, we carried out a series of preliminary tests, using 5-*t*-butyl-1, 3-dimethylbenzene as a common substrate. Seven reagents have been tested as oxidizing agents or iodinium cation sources: silver sulfate,2) silver perchlorate,3) mercuric oxide,4) potassium persulfate,5) iodic acid,6) periodic acid, and *o*-iodoanisole.7) The experimental procedures employed for the tests were nearly the same as those described in the original papers. The results are shown in Table I. As is apparent from the table, *iodine used with periodic acid* was found to be the best iodinating agent for polyalkylbenzenes possessing bulky groups.

The following five polyalkylbenzenes have been subjected to the direct iodination: 4-*t*-butyl-1, 2-dimethylbenzene, 5-*t*-butyl-1, 3-dimethylbenzene, 5-*t*-butyl-1, 2, 3-trimethylbenzene, 1, 2, 4, 5-tetraisopropylbenzene and *p*-di-*t*-butylbenzene. All five polyalkylbenzenes underwent the iodination and afforded new iodo derivatives. Even 1, 2, 4, 5-tetraisopropylbenzene, which was almost completely inert towards the other iodinating agents, gave the iodo product in an acceptable yield. It is interesting that 5-*t*-butyl-1, 2, 3-trimethylbenzene was, in spite of its apparently highly-crowded structure, readily iodinated to give 5-*t*-butyl-4-iodo-1, 2, 3-trimethylbenzene. This is probably because the steric aversion towards the entry of the bulky iodine atom is in part surmounted by the combined inductive effects of the four alkyl groups. In sharp contrast to the iodo derivatives of lightly-alkylated benzenes,8) these iodinated products were relatively stable towards sulfuric acid and did not liberate iodine until they were heated with sulfuric acid at a moderately high temperature. Nor did they undergo disproportionation under ordinary conditions of the Jacobsen reaction.

As an extension of this work, the polyiodination of some polymethylbenzenes was also carried out. Subjected to the reaction were *o*-xylene, *p*-xylene, durene and prehnitene. The reaction occurred fairly smoothly and afforded polyiodo products in high yields. The increased introduction of the iodine atoms into the ring usually diminishes the reactivity of the compound, so the tri- or tetra-iodination of xylenes was difficult to effect. For the purpose of synthesizing highly-iodinated compounds, therefore, the disproportionation of diiodo compounds by the action of sulfuric acid (Jacobsen reaction) is preferable.9)

Although no exhaustive investigation to find the optimum conditions was carried out, the excellent results in the present experiments showed the superiority of this reagent. The ready availability and convenience of the agent, the simple reaction conditions, the complete absence of

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1) Part VIII. On the Reaction of Polysubstituted Aromatics. Part VII: This Bulletin, **38**, 1590 (1965).

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2) I. R. L. Barker and W. A. Waters, *J. Chem. Soc.*, **1952**, 150.

3) L. Birckenbach and J. Goubeau, *Ber.*, **65**, 395 (1932).

4) A. Töhl, ibid., **25**, 1521 (1892).

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6) H. O. Wirth, O. Königstein and W. Kern, *Ann.*, **634**, 84 (1960).

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8) H. Suzuki and R. Goto, *J. Chem. Soc. Japan, Pure Chem. Sect.* (*Nippon Kagaku Zasshi*), **84**, 284 (1963).

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TABLE I. DIRECT IODINATION OF 5-*t*-BUTYL-1, 3-DIMETHYLBENZENE BY VARIOUS METHODS

Reagent, g.		Solvent, ml.		Hydrocarbon g.	Temp. °C	Time hr.	Yield %	Remark
Iodine Periodic acid dihydrate	3.39 1.54	Acetic acid Water Sulfuric acid	17 3 0.6	5.40	60—65	4	91	All iodine disappeared within 4 hr. On cooling, the product separated out as white crystals. No by-product. The use of iodic acid gave similar result (86%), except that the reaction needed much longer time for completion.
Iodine Silver sulfate	10.77 4.13	Cyclohexane Sulfuric acid Water	10 20 2	3.32	10—15	4	46	Removal of silver iodide from the product was troublesome. At elevated temperature (35—40°C), resinous materials and an oil with a camphor-like odor were formed.
Iodine Silver perchlorate	5.10 4.14	Chloroform	30	3.58	10—15	3	43	Resinous materials always accompanied the reaction. In one experiment, a violent explosion occurred.*
Iodine Silver perchlorate Magnesium oxide	8.50 6.91 1.30	Cyclohexane	30	5.40	40—43	3	26 50**	Resinous materials were always formed.
Iodine Mercuric oxide	10.86 4.38	Cyclohexane	20	3.25	45—50	35	55	Reactions were slow and incomplete. Mercuric oxide became pasty and greatly disturbed the smooth agitation.
Iodine Potassium persulfate	2.78 2.64	Acetic acid Water	20 5	3.62	60—65	6	62	Reactions proceeded slowly. Persulfate was in part consumed for the formation of iodic acid.
o-Iodoanisole	4.68	Cyclohexane Sulfuric acid	10 10	3.25	25—30	4	83**	Small amounts of 2, 4-diiodoanisole tenaciously clinged to the product were difficult to remove.

* The reaction had been being carried out at sunny window side, magnetically stirring with a plastic-covered stirrer, when the explosion suddenly occurred.

** Yields based on unrecovered hydrocarbon.

polymeric by-products in the final reaction mixtures, and the excellent yields of iodo derivatives recommend this method for a wide variety of polyalkylbenzenes.

Experimental

Materials.—Commercially-available *o*- and *p-xylene* were used. *Durene* and *prehnitene* were prepared according to the literature.[10,11] *4-t-Butyl-1, 2-dimethylbenzene* (I; b. p. 101—103°C/22—23 mmHg), *5-t-butyl-1, 3-dimethylbenzene* (II; b. p. 95—96°C/22—23 mmHg), and *p-di-t-butylbenzene* (III; m. p. 78—79°C) were prepared by the *t*-butylation of *o*-xylene, *m*-xylene and *t*-butylbenzene respectively.

1, 2, 4, 5-Tetraisopropylbenzene (VI) was prepared by the direct isopropylation of cumene using propylene and small amounts of 98% sulfuric acid as the catalyst. A white, oily, crystalline cake which formed in the flask was scraped out and filtered by suction until no more oil could be removed. Several recrystallizations from hot 2-propanol yielded large white needles; m. p. 118—119°C.[12]

5-t-Butyl-1, 2, 3-trimethylbenzene was prepared by the lithium hydride reduction[13] of 4-*t*-butyl-2, 6-dimethylbenzyl chloride, which had been prepared by the chloromethylation of 5-*t*-butyl-1, 3-dimethylbenzene.

4-t-Butyl-2, 6-dimethylbenzyl Chloride (V).—A mixture of II (160 g.), 37% formalin (180 g.) and concentrated hydrochloric acid (500 ml.) was stirred and heated to 65—70°C over a 7 hr. period, while a stream of hydrogen chloride was being bubbled through this mixture. After it had stood overnight, the upper organic phase was extracted with ether, washed with a saturated aqueous sodium bicarbonate solution, dried over calcium chloride, and fractionated. Colorless, rather thick oil distilled at 151—152°C/24 mmHg.[14,15] Yield, 171 g. (82%).

5-t-Butyl-1, 2, 3-trimethylbenzene (VI).—In a 500-ml. four-necked flask, fitted with a thermometer, a reflux

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10) "Organic Syntheses," Coll. Vol. 2, 248 (1948).

11) "Organic Reactions," Vol. 1, John Wiley and Sons, Inc., New York, N. Y. (1942), p. 382; S. F. Birch, R. A. Dean, F. A. Fidler and R. A. Lowry, *J. Am. Chem. Soc.*, **71**, 1362 (1949); L. Horner and W. Spietschka, *Ann.*, **579**, 159 (1953).

12) A. Newton, *J. Am. Chm. Soc.*, **65**, 320 (1943).

13) J. E. Johnson, R. H. Blizzard and H. W. Carhart, ibid., **70**, 3664 (1948).

14) R. C. Fuson, J. J. Denton and J. W. Kneisley, ibid., **63**, 2652 (1941).

15) M. J. Schlatter, ibid., **76**, 4952 (1954).

condenser and a dropping funnel containing 125 g. of V dissolved in a small amount of tetrahydrofuran, lithium hydride (10 g.), lithium aluminum hydride (4 g.) and tetrahydrofuran (300 ml.) were placed and rapidly stirred with a mechanical stirrer. Then a solution of V was added drop by drop at such a rate that a gentle refluxing was maintained in the system. After the completion of dropping, the flask was immersed in a water bath and warmed at 50—60°C for several hours in order to complete the reaction. The reaction mixture was then carefully poured into large amounts of water, and the crystalline solid which precipitated was extracted with ether. Drying over calcium chloride, followed by fractional distillation, gave 96 g. (92%) of colorless oil, b. p. 115—116°C/19 mmHg, which readily solidifieds to large plates and which melted at 30—31°C.[14,15]

The use of magnesium ribbon or zinc dust as reducing agents leads to a remarkable formation of the coupling product, 4, 4′-di-*t*-butyl-2, 2′, 6, 6′-tetramethyl-1, 2-diphenylethane, m. p. 215—217°C.[14]

Solvent.—The solvent used for the reaction was aqueous acetic acid, with small amounts of sulfuric acid added as a catalyst ($CH_3COOH : H_2O : H_2SO_4 = 100 : 20 : 3$).

Monoiodinated Products.—*4-t-Butyl-2, 6-dimethyliodobenzene.*—A mixture of II (5.40 g.), periodic acid dihydrate (1.54 g.), iodine (3.39 g.) and the solvent (20 ml.) was magnetically stirred and warmed at 60—65°C. After 4 hr., the elementary iodine had almost entirely disappeared and a heavy oil had precipitated. Upon cooling, the solidified product was collected by filtration and recrystallized from petroleum ether to give large plates, m. p. 59—60°C. The yield was 8.7 g. (90%). Because of its great tendency to avoid the hindered position, the iodine atom is supposed to be present at a position para to the *t*-butyl group.

Found: C, 49.73; H, 5.74. Calcd. for $C_{12}H_{17}I$: C, 50.00; H, 5.95%.

I was iodinated in a similar manner. This reaction, however, needed a little more time (6—7 hr.). The oil which precipitated was extracted with ether, and the ethereal solution was distilled after being washed with a dilute aqueous sodium bisulfite solution. There was obtained *5-t-butyl-2, 3-dimethyl-iodobenzene,* boiling at 146—147°C/14 mmHg, in a 81% yield. The unsymmetrical structure was confirmed by the aromatic substitution pattern of an infrared spectrum.

Found: C, 50.27; H, 6.07. Calcd. for $C_{12}H_{17}I$: C, 50.00; H, 5.95%.

6-t-Butyl-2, 3, 4-trimethyliodobenzene.—This was obtained, using a similar procedure, from VI (5.86 g.), periodic acid dihydrate (1.56 g.), iodine (3.39 g.) and the solvent (20 ml.). The crude product was chromatographed with an alumina column (1.7×35 cm.) using petroleum ether as an eluant; it was then recrystallized from hot ethanol to afford 8.9 g. of colorless plates melting at 74—75°C.

Found: C, 51.54; H, 6.41. Calcd. for $C_{13}H_{19}I$: C, 51.77, H, 6.35%.

2, 3, 5, 6-Tetraisopropyliodobenzene.—A mixture of IV (8.25 g.), periodic acid (1.54 g.), iodine (3.30 g.) and the solvent (35 ml.) was stirred and heated in such a manner that the temperature of the reaction mixture was held in the 75—80°C range. The iodine which sublimed on the upper part of the reaction vessel was scraped off by an occasional shaking. After 30 hr.'s heating, the hot mixture was poured into water, and the crystalline mass which precipitated was collected by filtration. Direct chromatography on an alumina column (1.7×65 cm.), using petroleum ether as an eluant, gave the unchanged hydrocarbon (7.0 g.), followed by the monoiodo product (1.9 g.). The latter compound was recrystallized several times from hot ethanol to obtain about 1.6 g. of white needles, m. p. 161—163°C.

Found: C, 58.35; H, 7.93. Calcd. for $C_{18}H_{29}I$: C, 58.07; H, 7.85%.

2, 5-Di-t-butyliodobenzene. — To a solution of III (6.38 g.) and iodine (3.38 g.) in the solvent (30 ml.), periodic acid dihydrate (1.60 g.) was added. The mixture was then agitated and heated at 75—80°C for about 30 hr. The reaction proceeded so slowly that the frequent shaking of the reaction vessel was necessary to scrape off the iodine which sublimed. After it had cooled, the solidified material was collected by filtration and washed with a dilute aqueous sodium bisulfite solution. As an attempted separation of the iodinated product from the unchanged hydrocarbon by alumina chromatography was found to be unsuccessful, the white crystalline cake was subjected to fractional distillation. There was obtained, after the removal of the low-boiling, unchanged hydrocarbon, 2.2 g. of a colorless oil boiling at 156—157°C/13—14 mmHg.

Found: C, 54.11; H, 6.96. Calcd. for $C_{14}H_{21}I$: C, 54.11, H, 6.70%.

Polyiodinated Products. — *4, 5 -Diiodo - 1, 2 - dimethylbenzene.*—A mixture of *o*-xylene (3.54 g.), periodic acid dihydrate (3.04 g.), iodine (6.8 g.) and the solvent (20 ml.) was heated to 70°C and stirred until the purple color of the elementary iodine had almost disappeared (3—4 hr.). Then the mixture was poured into a dilute sodium bisulfite solution in order to remove the unreacted iodine. The tan solid which precipitated was then collected and chromatographed over a short alumina column (1.7×20 cm.). Recrystallization from ethanol gave 10.2 g. (85%) of colorless plates, m. p. 93—94°C. Raman and Varma reported a m. p. of 74—76°C.[16] Since they used nitric acid as an oxidizing agent, their product was necessarily contaminated with a small amount of nitro compounds. The symmetrical structure of the product was confirmed by the substitution pattern of an infrared spectrum.

Found: C, 26.69; H, 2.03. Calcd. for $C_8H_8I_2$: C, 26.84; H, 2.26%.

By a similar procedure, *2, 5-diiodo-1, 4-dimethylbenzene* was obtained from *p*-xylene. The product, recrystallized from benzene-ethanol, melted at 104—105°C. (Reported, m. p. 104°C).[16]

Found: C, 26.90; H, 2.31. Calcd. for $C_8H_8I_2$: C, 26.85; H, 2.26%.

The use of double the amounts of iodine and periodic acid has proved to have no effect. The reaction stopped at the stage of diiodination, and no tri- or tetra-iodo compounds were formed.

Diiodoprehnitene.—Prehnitene (4.47 g.) dissolved in the solvent (20 ml.) was iodinated with iodine (6.8 g.) and periodic acid (3.04 g.) in the manner described above. The reaction was completed within 1.5 hr,

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[16] P. S. Varma and K. S. V. Raman, *J. Indian Chem. Soc.*, **12**, 343 (1935).

and a pink-colored solid was precipitated. The product was collected and recrystallized from hot benzene. White needles; m. p. 190—191°C. Sparingly soluble in ethanol and petroleum ether. The yield was 10.8 g. (84%).

Found: C, 30.99; H, 3.38. Calcd. for $C_{10}H_{12}I_2$: C, 31.11; H, 3.13%.

Durene was converted by the same procedure to diiododurene, m. p. 140—141°C. Slightly soluble in hot ethanol and readily soluble in hot benzene, but nearly insoluble in petroleum ether.

Found: C, 31.00; H, 3.26. Calcd. for $C_{10}H_{12}I_2$: C, 31.11; H, 3.13%.