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The Jacobsen Reaction of Iodopseudocumenes and Related Compounds. Orientation in the Iodination of Halopseudocumenes[1]

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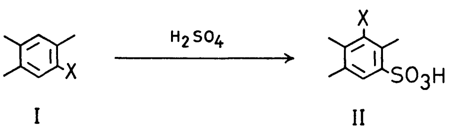
The Jacobsen reaction of iodopseudocumenes and related compounds was investigated. Both 3- and 5-iodopseudocumenes gave essentially the same product which consisted of 3,5-diiodopseudocumene (VI, 53%), 3,6-diiodopseudocumene (VII, 44%) and 5,6-diiodopseudocumene (VIII, 3%). The unexpected result was interpreted in terms of a mechanism involving a prior interconversion of the 3- and 5-iodo isomers followed by the ordinary process of aromatic disproportionation. 6-Iodopseudocumene gave VII as the major product. By prolonged contact with concentrated sulfuric acid, VI and VIII were found to undergo partial isomerization to give VII. Early structural assignment by Smith and Moyle for two diiodopseudocumenes was revised. Reactions of 4- and 5-iodohemimellitenes with sulfuric acid gave 4,6-diiodohemimellitene (XII) as the major product. A diiodohemimellitene melting at 114°C was found to be a mixture of XII and 4,5-diiodohemimellitene (XI), the former being predominant. Isomeric chloro-, bromo-, and iodopseudocumenes were iodinated with iodine-periodic acid dihydrate and the orientation in the products was determined.

5-Chloropseudocumene (I, X=Cl) reacts with concentrated sulfuric acid to give 3-chloropseudocumene-5-sulfonic acid (II, X=Cl).[4] 5-Bromopseudocumene (I, X=Br) behaves similarly, giving 3-bromopseudocumene-5-sulfonic acid (II, X=Br) along with small amounts of 3,5,6-tribromopseudocumene.[5] The reaction is known as the Jacobsen reaction.



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5-Iodopseudocumene (III) was reported to afford two diiodopseudocumenes and two sulfonic acids derived from an iodopseudocumene and pseudocumene, respectively.[6] Although Kürzel did not designate specific structures for these products, Smith and Moyle formulated them as 3,6-diiodopseudocumene (VII), 5,6-diiodopseudocumene (VIII), 3-iodopseudocumene-5-sulfonic acid (II, X=I), and pseudocumene-5-sulfonic

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1) The Reaction of Polysubstituted Aromatics. XXX. Part XXIX: H. Suzuki and K. Nakamura, *Synthesis*, **1972**, 606.

2) C. L. Moyle and L. I. Smith, *J. Org. Chem.*, **2**, 112 (1937).

3) H. Suzuki and R. Goto, This Bulletin, **36**, 389 (1963).

4) O. Jacobson, *Ber.*, **22**, 1580 (1889).

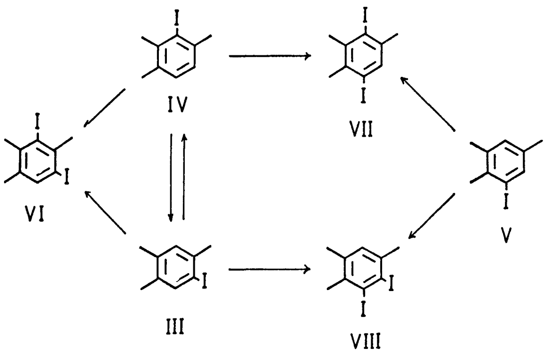
3) L. I. Smith and C. L. Moyle, *J. Amer. Chem. Soc.*, **58**, 1 (1936).

6) C. Kürzel, *Ber.*, **22**, 1586 (1889).

acid (II, X=H), respectively.[2] The assignment has since been cited.[7] However, the 3,6-orientation of iodine atoms in the disproportionation product of III is rather unexpected because the Jacobsen reaction of aromatic iodo compounds is usually known to proceed like a progressive iodination of the starting compound.[8] Thus the reaction of III and related compounds with sulfuric acid was re-examined in some detail.

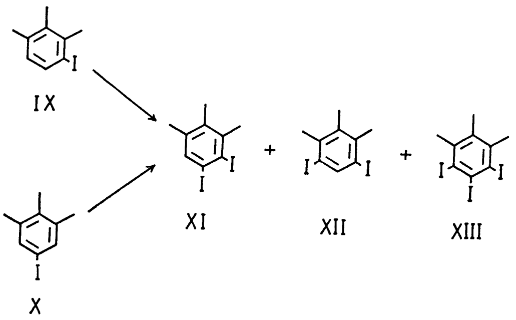
Kürzel reported that III dissolved in sulfuric acid and left to stand at room temperature gave an oily mass which, by vacuum distillation and subsequent cooling, could be separated into colorless plates melting at 73°C and an oily substance freezing below 0°C.[6] We repeated the experiment and examined the oily product by gas chromatography as well as by direct comparison with the infrared and ^{1}H-NMR spectra of authentic specimens. The product was found to be a mixture of all three isomeric diiodopseudocumenes consisting of 3,5-diiodopseudocumene (VI; mp 8—9°C; bp 202—204°C/21 mmHg; 53%), VII (mp 75—76°C; 44%), and VIII (mp 51—52°C; bp 197—199°C/18 mmHg; 3%).[9] Some 3,5,6-triiodopseudocumene (mp 193—195°C) was also formed, whose amount steadily increased on prolonged treatment with sulfuric acid. It was therefore concluded that the Kürzel diiodopseudocumenes were most likely to be VI and VII, the former being possibly accompanied by some other isomers.

The idea that the unusual 3,6-orientation of iodine atoms in the product might arise from a rearrangement of the initially formed VI and VIII does not seem likely, since diiodopseudocumenes were found to be quite slow to isomerize under the same conditions. Thus the only other possibility is that III in contact with sulfuric acid partly isomerized to 3-iodopseudocumene (IV), which was then iodinated to give VI and VII. In order to confirm this, IV and 6-iodopseudocumene (V) were prepared and treated in a similar manner. The 3-iodo isomer gave essentially the same product as that obtained from III, whereas the 6-iodo isomer gave VII along with a very small amount of VIII. When a dilute solution of III or IV in dichloromethane was stirred with a small amount of sulfuric acid at room temperature, both isomers were found to undergo mutual interconversion, giving a mixture of III (87—92%) and IV (8—13%). In contrast, V showed little tendency to isomerize but underwent slow disproportionation.



The composition and constitution of sulfonated products were not further investigated, but the only major sulfonic acid obtained from either one of the reaction mixtures was identified as pseudocumene-5-sulfonic acid (II, X=H). An iodopseudocumenesulfonic acid (amide; mp 193—194°C) isolated in small amounts from the reaction mixture of V was probably 6-iodopseudocumene-3-sulfonic acid.

The other isomeric iodotrimethylbenzenes similarly underwent facile disproportionation. Both 4- and 5-iodohemimellitene (IX and X) reacted with sulfuric acid to give 4,6-diiodohemimellitene (XII) as the major product which was usually accompanied by an appreciable amount of 4,5-diiodohemimellitene (XI) and some 4,5,6-triiodohemimellitene (XIII). A diiodohemimellitene melting at 114°C, obtained from the Jacobsen reaction of 5-iodohemimellitene,[3] was found to be an intimate mixture of XI and XII, the latter being predominant. Iodomesitylene gave either diiodomesitylene or triiodomesitylene depending on the conditions employed.[10]



So far no quantitative data have been found in literature on the electrophilic reaction of halopseudocumenes. Accordingly, it seemed of interest to extend our work to the ordinary iodination of various isomeric halopseudocumenes, in order to see how they behave towards electrophilic iodine under the condition in which no migration of substituent groups was allowed. The iodination with iodine-periodic acid dihydrate was clean and smooth, and the products were determined by means of gas chromatography and ^{1}H-NMR spectroscopy. The results are summarized in Table 1. Combined directing effects of substituent groups agreed fairly well with the ones predicted from the additivity principle. For 3-chloropseudocumene some discrepancy was observed, which probably arose from the underestimation by the additivity principle of the rate of substitution at the position *para* to chlorine atom.

In sharp contrast to the product from the Jacobsen reaction, the above iodination products from III and V contained a substantial amount of VIII. Although

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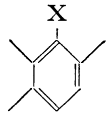
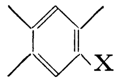
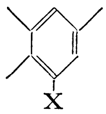
7) For example, L.I. Smith, "Organic Reactions," Vol. 1, John Wiley & Sons, Inc., New York (1944); H. J. Shine, "Aromatic Rearrangement," Elsevier, London (1967); H. Cerfountain, "Mechanistic Aspects in Aromatic Sulfonation and Desulfonation," Interscience, London (1968).

8) H. Suzuki, This Bulletin, **36**, 1643 (1963); H. Suzuki and R. Goto, *Nippon Kagaku Zasshi*, **84**, 167 (1963).

9) The structures of all these compounds were determined by independent synthesis.[16]

10) A. Tohl and R. Eckel, *Ber.*, **26**, 1099 (1893).

Table 1. Products from the iodination of halopseudocumenes with iodine-periodic acid dihydrate

Halopseudocumene		Product composition (%)[a]	
3-Halo series		5-Iodo	6-Iodo
	X=Cl	40.5	59.5
	=Br	57.8	42.2
	=I	69.3	30.7
5-Halo series		3-Iodo	6-Iodo
	X=Cl	61.8	38.2
	=Br	74.6	25.4
	=I	79.9	20.1
6-Halo series		3-Iodo	5-Iodo
	X=Br	62.8	37.2
	=I	63.3	36.7

a) Determined gas chromatographically. Dihalopseudocumenes appeared in the order; 3,6- >3,5- >5,6-.

VI and VIII could be partly converted into VII on prolonged contact with sulfuric acid, such isomerization was not so rapid and complete as to rationalize the marked difference in the composition. The result can be reasonably explained in terms of a mechanism involving partial isomerization of III to IV which, even in a small concentration, would undergo preferential iodination due to favorable electronic and steric reasons. The predominance of VII in the product mixture probably resulted from its greater stability towards the deiodination-reiodination process.

The present result represents the second clearly observed deviation from the established rule for the Jacobsen reaction of aromatic iodo compounds. The first example was observed in the reaction of 2-iodo-*m*-xylene, which underwent rapid isomerization into the 4-iodo isomer followed by disproportionation, giving 4,6-diiodo-*m*-xylene as the final product.[11]

Experimental

All melting and boiling points are uncorrected. Infrared spectra were measured on Nujol mulls with a Jasco DS-402 G spectrophotometer. ^{1}H-NMR spectra were obtained for carbon tetrachloride solutions on a JEOL PS-100 spectrometer using TMS as an internal reference. Gas chromatographic data were obtained on a Hitachi Model F6-D gas chromatograph using a capillary column (0.5 ϕ, 45 m) coated with Apiezon Grease L at column temperature of 165°C.

5-Iodopseudocumene (*III*; mp 36—37°C[6]; bp 135—136°C/21 mmHg) was prepared from a commercial pseudocumidine (2,4,5-trimethylaniline). IR: 868, 946, and 1145 cm^{-1}; NMR; 7.90 (2 Me), 7.72 (Me), 3.14 (aromatic H), and 2.55 τ (aromatic H).

3-Iodopseudocumene (IV). 2,3,6-Trimethylphenylmagnesium bromide was prepared in the usual manner from 3-bromopseudocumene (bp 112—114°C/18 mmHg; 15 g)[12], magnesium (1.9 g), and dried tetrahydrofuran (70 ml). Iodine (*ca.* 20 g) was slowly added to the Grignard solution. The mixture was heated under gentle reflux for 30 min and hydrolyzed with excess dilute hydrochloric acid. The organic layer was separated, dried and concentrated, and the residue was distilled to give product (16.2 g, 87%) boiling at 140—141°C/25 mmHg. IR: 778, 802, 984, 1131, and 1169 cm^{-1}; NMR: 7.75 (Me), 7.64 (2 Me), and 3.18 τ (2 aromatic H).

Found: C, 44.21; H, 4.49%. Calcd for $C_9H_{11}I$: C, 43.92; H, 4.51%.

6-Iodopseudocumene (*V*; bp 138—139°C/24 mmHg) was prepared from 6-bromopseudocumene (bp 120—121°C/22 mmHg)[5] in a similar manner. IR: 785, 848, 1005, 1124, and 1256 cm^{-1}; NMR: 7.84 (Me), 7.77 (Me), 7.71 (Me), 3.22 and 2.60 τ (aromatic H).

Found: C, 44.19; H, 4.52%. Calcd for $C_9H_{11}I$: C, 43.92; H, 4.51%.

4-Iodohemimellitene (*IX*; bp 144—145°C/22 mmHg) and *5-iodohemimellitene* (*X*; mp 34—36°C)[13] were prepared from the corresponding trimethylanilines.[14,15] Synthesis of diiodo and triiodo derivatives of pseudocumene and hemimellitene used as authentic specimens will be described in the accompanying paper.[16]

General Procedure for the Jacobsen Reaction. i) A solution of iodotrimethylbenzene (4.9 g, 0.02 mol) in dichloromethane (20 ml) was stirred vigorously with concentrated sulfuric acid (4.9 g, 0.05 mol) at room temperature. After 15 hr the reaction was quenched by the addition of water, and the organic layer was separated, washed with dilute aqueous sodium sulfite and dried over anhydrous magnesium sulfate. The oily substance (3.3—3.8 g) obtained after removal of the solvent was directly examined by infrared and ^{1}H-NMR spectroscopy as well as by thin-layer and gas-chromatography.

ii) Iodotrimethylbenzene (4.9 g, 0.02 mol) was stirred with concentrated sulfuric acid (15 g, 0.15 mol) overnight at room temperature. The dark mixture was poured on crushed ice and a pasty solid was extracted with a mixture of dichloromethane and light petroluem. The extract was washed with dilute aqueous sodium sulfite and then passed over a short alumina column to remove some polymeric substance formed during the course of reaction. The eluate was evaporated and the residual oil or semi-solid (1.5—2.0 g) were directly subjected to gas chromatographic and spectral inspection.

Procedure for the Iodination of Halopseudocumenes.[17] A mixture of halopseudocumene (0.05 mol), iodine (5.1 g), periodic acid dihydrate (2.28 g), and 80% acetic acid (40 ml) containing catalytic amount of sulfuric acid was heated with stirring at 70—75°C for several hours until the color of iodine disappeared. After cooling, water was added and an oily precipitate or a semisolid mass was extracted with ether; the ethereal extract was dried over calcium chloride and distilled. A mixture of iodinated halopseudocumenes (90—97%) was obtained mostly distilling over in the range shown below;

Iodinated chloropseudocumenes, bp 167—170°C/16 mmHg
Iodinated bromopseudocumenes, bp 173—177°C/16 mmHg
Diiodopseudocumenes, bp 197—200°C/20 mmHg

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[11] H. Suzuki and R. Goto, *Nippon Kagaku Zasshi*, **84**, 284 (1963); H. Suzuki, K. Maruyama, and R. Goto, This Bulletin, **38**, 1474, 1590 (1965).

[12] L. I. Smith and M. A. Kiess, *J. Amer. Chem. Soc.*, **61**, 284 (1939).

[13] C. Liebermann and M. Kardos, *Ber.*, **46**, 198 (1913).

[14] M. G. Barclay, A. Burawoy, and G. H. Thomson, *J. Chem. Soc.*, **1944**, 109.

[15] F. M. Beringer and I. Ugelow, *J. Amer. Chem. Soc.*, **75**, 2635 (1953).

[16] H. Suzuki and Y. Haruta, This Bulletin, **46**, 589 (1973).

[17] H. Suzuki, K. Nakamura, and R. Goto, *ibid.*, **39**, 128 (1966); H. Suzuki, "Organic Syntheses," Vol. 51, p. 94 (1971).