The Synthesis of Four Isomeric Diiodo-*m*-xylenes. Their Isomerization in Sulfuric and Polyphosphoric Acids[1]

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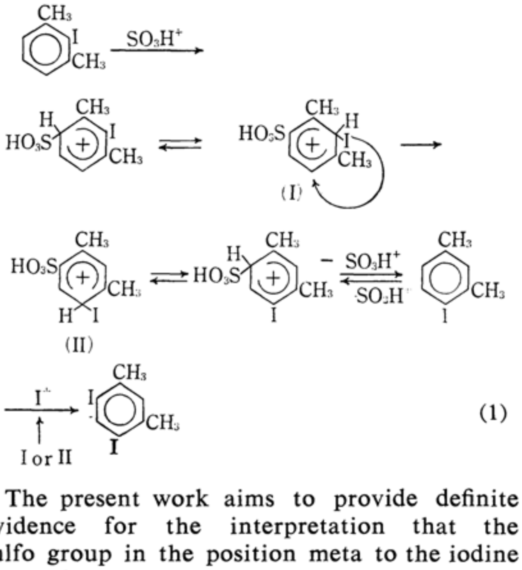
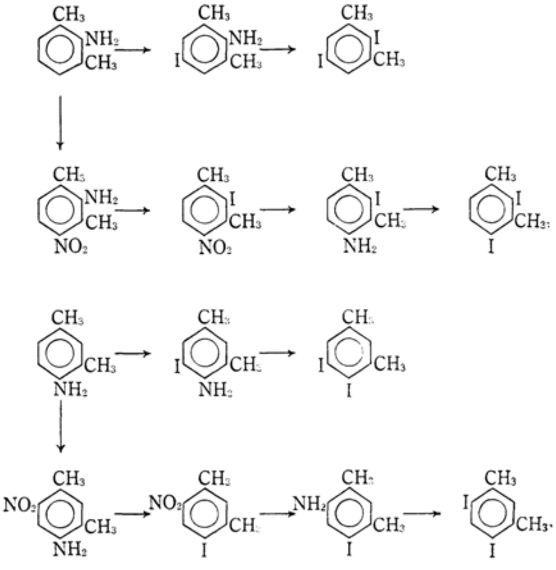
Since the general pattern of the Jacobsen reaction of aromatic iodo compounds is the progressive iodination of the starting materials, vicinally-substituted 2,4-diiodo-*m*-xylene may be expected to be a main product in the reaction of 2-iodo-*m*-xylene. As has been shown in a previous paper,[1] however, the latter compound readily undergoes disproportionation to give 4,6-diiodo-*m*-xylene and *m*-xylene-4-sulfonic acid. The mechanism proposed for this unexpected result involves the migration of the iodine atom of 2-iodo-*m*-xylene from the hindered position (=2) to a less hindered one (=4), facilitated by the increased steric stress caused by the entry of a bulky sulfo group in the position meta to the iodine atom. The 4-iodo-*m*-xylene thus formed, undergoing the normal Jacobsen reaction, affords 4,6-diiodo-*m*-xylene as a final product. This is shown by the following scheme:



(1)

The present work aims to provide definite evidence for the interpretation that the sulfo group in the position meta to the iodine atom plays an important role in such an easy intramolecular migration of an iodine atom. In the pursuit of this problem, it was necessary to ascertain whether any other isomers might be formed during the reaction, and if so, how they would behave under those conditions. Because of the difficulties encountered in the separation of each isomer, we inspected the product spectroscopically and gas chromatographically. Therefore, four isomeric diiodo-*m*-xylenes were prepared as authentic specimens. As little was known about diiodo-*m*-xylenes, we synthesized them from *m*-xylidines by the procedure shown below:



The direct iodination of 2-*m*-xylidine in a weakly alkaline medium proceeded smoothly and afforded a fairly high yield of the product, whereas that of 4-*m*-xylidine afforded a poorer yield under the same conditions, with much tarry matter formed. The diazotizations of the iodo-xylidines were carried out in concentrated sulfuric acid, while in an aqueous acid solution the diazotization was incomplete and the yields were often very poor. The replacement of the diazo group by an iodine atom was always accompanied by a remarkable formation of black resinous substances, which lowered the yields of the products considerably. The infrared spectra of four isomers are shown in Fig. 1. Absorption bands due to the aromatic C–I bond (990–1050 cm^{-1}) show remarkable changes according to the differences in relative positions of the iodine atoms in

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[1] The Reaction of Polysubstituted Aromatics, Part VII. Part VI: This Bulletin, 38, 1474 (1965).

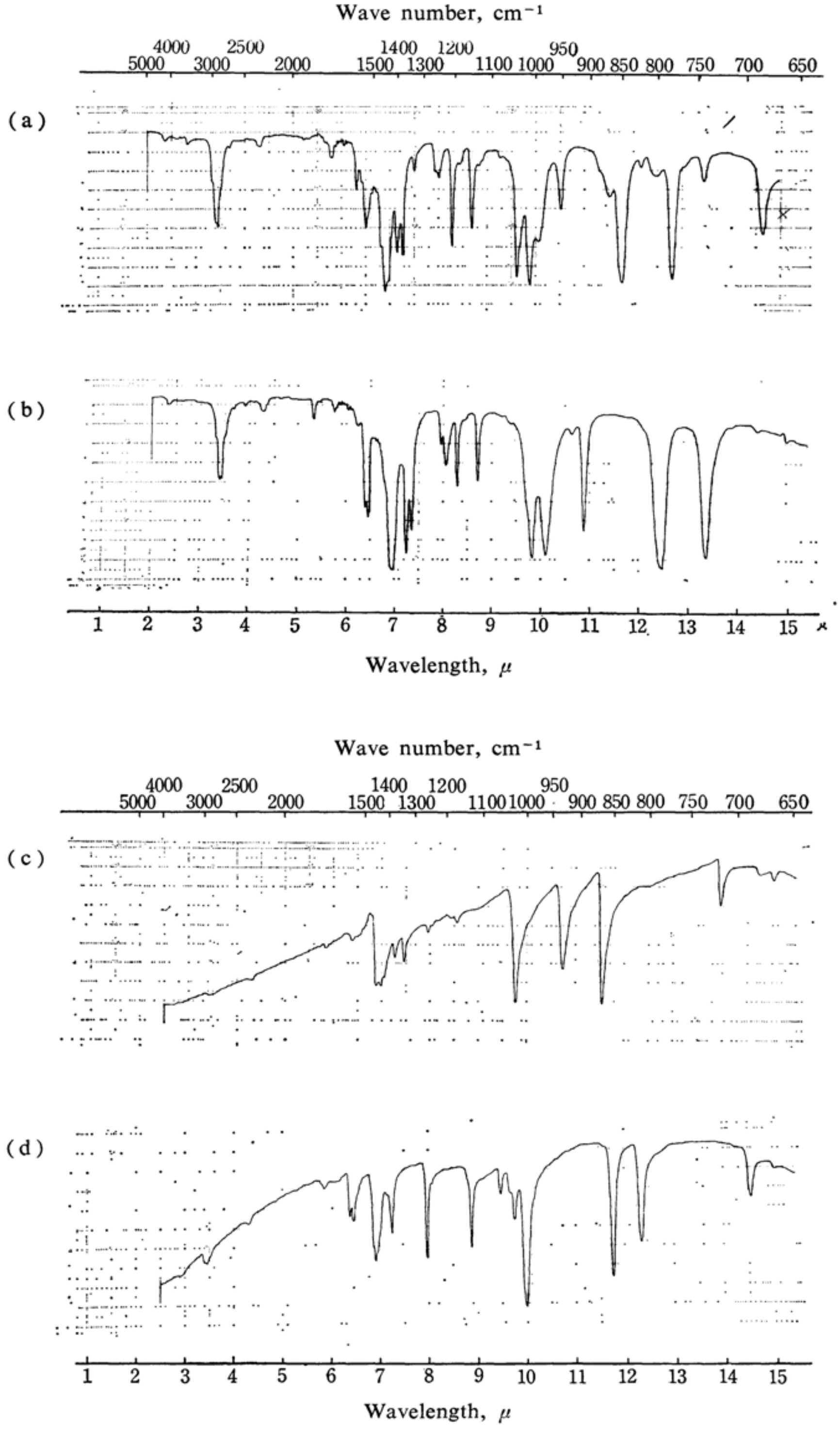


Fig. 1. Infrared spectra of diiodo-*m*-xylenes.

(a) 4,5-Diiodo-*m*-xylene (liquid film)
(b) 2,4-Diiodo-*m*-xylene (liquid film)
(c) 4,6-Diiodo-*m*-xylene (KBr disk)
(d) 2,5-Diiodo-*m*-xylene (KBr disk)

the nucleus. The appearance of the doubling of the band in the 990—1040 cm^{-1} region may be correlated with the presence of the iodine atoms at hindered positions. Both 4, 5- and 2, 4-diiodo-*m*-xylenes show a strong doubling in this region, whereas the 2, 5-diiodo isomer shows an incomplete doubling and the 4, 6-diiodo isomer no doubling. Similar doublings are also observed in the infrared spectrogram of some other aromatic polyiodo compounds carrying hindered iodine atoms. However, these findings are not conclusive.

The Isomerization of Diiodo-*m*-xylenes in Concentrated Acids.—Two of the four diiodo-*m*-xylenes, 2, 4- and 4, 5-diiodo-*m*-xylenes underwent the isomerization easily in concentrated sulfuric acid and fairly readily in polyphosphoric acid (PPA) at a high temperature, but not at all in concentrated hydrochloric acid or perchloric acid. All four isomers underwent disproportionation with hot sulfuric acid to give mixtures of tri- and tetraiodo-*m*-xylenes.

In Sulfuric Acid.—The instability of diiodo-*m*-xylenes in sulfuric acid was found to be in the increasing order of 4, 5->2, 4->2, 5->4, 6-. The iodine atom located in the position of highest crowding migrated to the position which was less hindered and of the next highest electron density. Figure 2a shows the isomerization of 2, 4-diiodo-*m*-xylene to 4, 6-diiodo-*m*-xylene; after 5 hr. there still remained strong absorption bands due to the vicinal compound (803 cm^{-1}), while those due to the symmetrical compound (865 cm^{-1}) were comparatively weak. This indicates that 2, 4-diiodo-*m*-xylene cannot be a possible major intermediate of reaction 1, because 2-iodo-*m*-xylene is rapidly converted to 4, 6-diiodo-*m*-xylene under the same conditions. The increase in temperature (up to 50—60°C), however, brought about an immediate disproportionation to give mixtures of tri- and tetraiodo-*m*-xylenes, with little liberation of elementary iodine. 2, 5-Diiodo-*m*-xylene was more stable towards sulfuric acid than was 2-iodo-*m*-xylene and underwent disproportionation only at an elevated temperature. 1, 3-Dimethyl-5-*t*-butyl-2-iodobenzene was also comparatively stable in reaction to cold sulfuric acid, whereas iodomesitylene readily underwent disproportionation. These facts clearly indicate the importance of the buttressing effect of the sulfo groups taking the meta position to the iodine atom; that, is, the bulky substituent group (the iodine atom or the *t*-butyl group) at position 5 inhibits the entry of a sulfo group

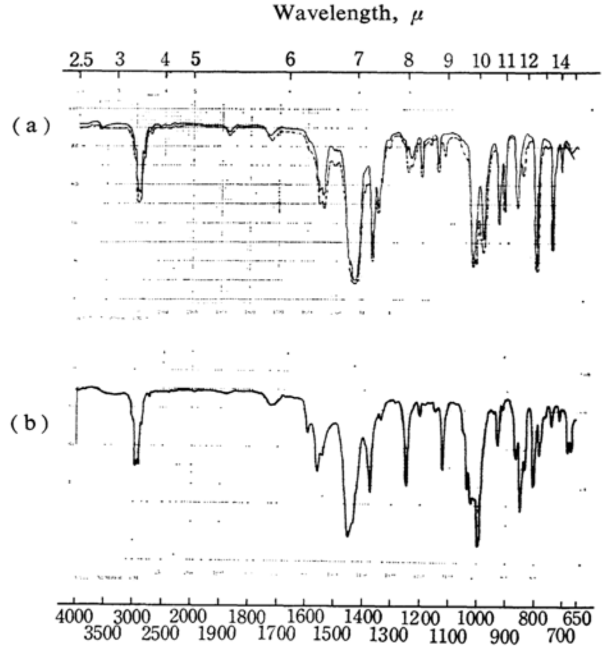


Fig. 2. Infrared spectra of reaction products (liquid film).
(a) Full line Exp. No. 1
Dotted line Exp. No. 2
(b) Exp. No. 4*
* This spectrum was taken with the uncrystallized oily part of the product.

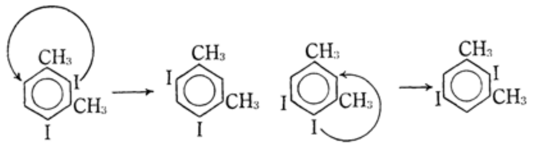
TABLE I. ACTION OF SULFURIC AND POLYPHOSPHORIC ACIDS UPON DIIODO-*m*-XYLENES

Expt. No.	Diiodo-*m*-xylene g.		Sulfuric acid g.	PPA* g.	Temp. °C	Time hr.	Product g.	Main component
1	2,4-	1.0	5.0		15—20	3	0.8	2,4- and 4,6-diiodo-*m*-xylene
2	2,4-	1.5		10.0	180—190	1	0.9	2,4- and 4,6-diiodo-*m*-xylene
3	4,5-	0.9	5.0		15—20	3	0.6	2,5- and 4,5-diiodo-*m*-xylene
4	4,5-	1.0		7.0	180—190	1	0.5	2,5- and 4,5-diiodo-*m*-xylene
5	2,5-	1.2		5.0	180—190	1	0.9	2,5-diiodo-*m*-xylene
6	2,5-	0.8	5.0		50—60	3	0.5	tri- and tetraiodo-*m*-xylene
7	4,6-	1.0	5.0		15—20	3	0.7	4,6-diiodo-*m*-xylene tri- and tetraiodo-*m*-xylene
8	4,6-	1.0		7.0	180—190	1	0.6	4,6-diiodo-*m*-xylene

* PPA = polyphosphoric acid

into the unoccupied position so greatly that the iodine atom at the 2-position, in spite of the similar structural conditions, resists both intra- and intermolecular migration. We could not detect any diiodo-*m*-xylenes other than 4,6-isomer in the final reaction products from 2- and 4-iodo-*m*-xylenes.

In Polyphosphoric Acid (PPA). — The isomerization of aromatic iodo compounds in PPA seems never to have been described. Diiodo-*m*-xylenes were stable in cold PPA, but they gradually decomposed in resinous substances and in elementary iodine in acid at high temperature; in PPA only 2,4- and 4,5-diiodo-*m*-xylenes, which have an iodine atom at the highly-hindered position, underwent a slow isomerization to 4,6- and 2,5-diiodo-*m*-xylenes respectively (Figs. 2a and 2b).



Under the same conditions, 4,5-diiodo-*m*-xylene isomerized much more readily than the 2,4-isomer. The migration caused by PPA differs from those caused by sulfuric acid in the following two points: first, the migration of the iodine atom needs much more severe conditions and a longer reaction time, and second, the reaction is limited to the isomerization — no disproportionation is observed. The possibility of a thermal isomerization was excluded, because no change was observed in the absence of the acid at those temperatures. These facts may be taken to indicate that the migration of an iodine atom proceeds through a benzenonium intermediate, as is shown in Eq. 1, where the iodine atom expelled by a proton migrates, seeking the position of the next highest electron density, intramolecularly (isomerization). The substantial steric stress developed in the benzenonium intermediate is relieved during the migration of the iodine atom from the 2- to the 4-position, thus contributing to the ease of migration.

From these and related previous studies,[2] it may be concluded that this new type of rearrangement observed in the Jacobsen reaction of some 2,6-disubstituted iodobenzenes, especially 2-iodo-*m*-xylene, is essentially caused by the entry of a bulky and powerfully electron-attracting sulfo group in the position meta to the iodine atom blocked on both sides by substituent groups. This conclusion follows from these observations: (1) 2,4-diiodo-*m*-xylene did not isomerize so readily as 2-iodo-*m*-xylene under the same conditions; (2) 2,5-diiodo-*m*-xylene and 5-*t*-butyl-1,3-dimethyl-2-iodobenzene were rather more stable in relation to sulfuric acid than was 2-iodo-*m*-xylene; (3) isomerization occurred more readily in sulfuric acid than in PPA, and diluted sulfuric acid could not bring about any isomerization; (4) some color changes were observed during the reaction, and the color disappeared upon the addition of water; (5) the iodinium cation, when completely detached from the nucleus, could not attack *m*-xylene-4-sulfonic acid to any great extent, and (6) in the presence of an excess of mesitylene, the iodine atom of 2-iodo-*m*-xylene was readily transferred to the hydrocarbon, resulting in the formation of iodomesitylene and *m*-xylene-4-sulfonic acid. The reaction mechanism described at the beginning of this paper is consistent with these experimental observations.

Experimental

General Procedure for Isomerization.—The reactions were carried out with magnetic stirring in small stoppered vessels which were heated externally. The mixtures were diluted with water;

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[2] H. Suzuki and R. Goto, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 284 (1963); H. Suzuki, This Bulletin, **36**, 1642 (1963).

the precipitated substances were separated and then chromatographed on an alumina column to remove higher iodinated products. The solid or oily substances which remained after the evaporation of the solvent were inspected by means of infrared spectroscopy and gas chromatography as has been described in the preceding paper.[1]

Synthesis of Four Isomeric Diiodo-*m*-xylenes.—All the procedures employed in these preparations were well-known to exclude the possibility of the migration of the iodine atom under ordinary conditions, so the definite location of the substituent groups attached to the ring could readily be ascertained by the annexed scheme. The structure proof of each isomer was also achieved by means of infrared spectroscopy (Fig. 1).

2-Amino-4-nitro-*m*-xylene (I). — A solution of 22 g. of 2-*m*-xyledine in 220 g. of concentrated sulfuric acid was cooled to 5°C; then 18 g. of concentrated nitric acid (d=1.38) was slowly but vigorously stirred in. During this operation, the temperature of the reaction mixture was held below 15°C. After 30 minutes' agitation, the mixture was poured onto crushed ice; the resulting aqueous solution was neutralized with a sodium hydroxide solution with cooling. The precipitated amine was collected by filtration and recrystallized from a petroleum ether - tetrahydrofuran mixture. The yield was 26 g. (86%); the product, golden yellow needles, melted at 81—82°C (reported,[3] 81—82°C).

2-Iodo-4-nitro-*m*-xylene (II).—To a solution of 21 g. of I in 300 ml. of sulfuric acid was added, with stirring and cooling to hold the temperature below 5°C, 10 g. of finely powdered sodium nitrite. The mixture was stirred for an additional 30 min. and then poured onto crushed ice. The resulting solution of the diazonium salt was filtered, and the filtrate was added slowly to a solution of 33 g. of potassium iodide in a little water. After the mixture had stood overnight, the precipitated tan solid was collected by filtration and chromatographed through a short alumina column with benzene. The evaporation of the benzene afforded 28 g. of pale yellow crystals of a pure iodo compound; m. p. 51—52°C. Yield, 80%.

Found: C, 34.60; H, 2.66; N, 4.93. Calcd. for $C_8H_9INO_2$: C, 34.68; H, 2.90; N, 5.06%.

2-Iodo-4-amino-*m*-xylene (III). — One hundred grams of stannous chloride dihydrate was dissolved in 200 ml. of hydrochloric acid diluted with 200 ml. of ethanol. To this solution was slowly but vigorously stirred in 25 g. of finely powdered II. The reaction preceeded with a moderate evolution of heat, the white crystalline solid which was gradually precipitated was collected by filtration. This material was then suspended in water, and an excess of a sodium hydroxide solution was added until the precipitated stannic hydroxide redissolved. The resulting solution was steam-distilled until the distillate became clear. The product was then separated from the distillate by ether extraction. The evaporation of the ether gave 17.0 g. of a pale yellow oil, which solidified to white needles in an ice box and which melted at 17—18°C. Yield, 76%.

Acetanilide; white needles from aqueous ethanol, m. p. 171—172°C.

Found: C, 41.82; H, 4.38; N, 4.58. Calcd. for $C_{10}H_{12}NIO$: C, 41.55; H, 4.19; N, 4.84%.

2,4-Diiodo-*m*-xylene (IV).—A solution of 17 g. of 2-iodo-4-amino-*m*-xylene in 150 ml. of concentrated sulfuric acid was cooled to 5°C and diazotized by the addition of 8.5 g. of sodium nitrite at 5—10°C. After 30 minutes' agitation, the mixture was poured onto crushed ice and the resulting solution was filtered. The filtrate was added slowly to a solution of potassium iodide dissolved in a small amount of water. The mixture was then allowed to stand overnight, and the black oil which precipitated was separated by decantation and chromatographed through an alumina column with petroleum ether. The evaporation of the solvent, followed by distillation, gave 11.5 g. of a colorless oil, boiling at 176—177°C/18 mmHg, which solidified in an ice box and which melted at 6—7°C. The yield was 47%.

Found: C, 26.93; H, 2.23. Calcd. for $C_8H_8I_2$: C, 26.84; H, 2.25%.

The infrared spectrum showed a band at 803 cm^{-1} for two adjacent hydrogen atoms. The pattern in the 1650—2000 cm^{-1} region also confirms the vicinal structure. Aromatic carbon-iodine bands were observed at 990 and 1017 cm^{-1}.

2-Amino-5-iodo-*m*-xylene (V).—To a suspension of 17 g. of sodium hydrogen carbonate in 150 ml. of water, 10 g. of 2-*m*-xylidine and 80 ml. of ether were added; the mixture was then stirred rapidly while 20 g. of iodine was added at such a rate that the color of the free iodine disappeared within a few minutes. Stirring was then continued for an additional hour, after which the reaction mixture was steam-distilled until 4 l. of the distillate had been collected. The amine separated as white needles in the distillate, which was filtered and recrystallized from boiling petroleum ether. The resulting large needles weighed 11.0 g. and melted at 52—53°C. Yield, 49%.

Found: C, 39.20; H, 4.14; N, 5.70. Calcd. for C_8H_9IN: C, 38.88; H, 4.08; N, 5.67%.

2, 5-Diiodo-*m*-xylene (VI).—Ten grams of V was diazotized in 80 ml. of sulfuric acid with 5.0 g. of sodium nitrite in the same manner as has been described above. The mixture was then poured onto crushed ice, and the resulting solution was, after filtration, added to a concentrated solution of 16.0 g. of potassium iodide in water. The mixture was allowed to stand overnight, and the brown solid which precipitated was removed by filtration and chromatographed through a short alumina column, using light-boiling ligroin as an eluant. The evaporation of the solvent gave 3.6 g. of the product, white needles with a m. p. of 64—65°C. The yield was low (25%) because of the formation of a large amount of resinous matter.

Found: C, 27.05; H, 2.30. Calcd. for $C_8H_8I_2$: C, 26.84; H, 2.25%.

The infrared spectrum showed a band at 850 cm^{-1} which may be attributed to one isolated ring-hydrogen. The absence of ring CH absorption in the

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[3] E. Noelting, A. Braun and G. Thesmar, *Ber.*, **34**, 2242 (1901).

910—950 cm^{-1} region was associated with the presence of a center of symmetry (A_2 vibration). The pattern in the 1650—2000 cm^{-1} region also supports the 1,2,3,5-tetra substitution. Aromatic carbon-iodine band was observed at 1000 and 1023 cm^{-1}.

4-Amino-5-iodo-*m*-xylene (VII). — 4-*m*-Xylidine was directly iodinated with free iodine by the same method as has been used above. In this case, however, the reaction proceeded with some difficulty and resinous matter was formed in an appreciable amount. The product separated out as white needles from the steam-distillate. Recrystallization from boiling petroleum ether gave white needles, m. p. 65°C. Reported,⁴⁾ 65°C. The yield was 16% on the basis of the *m*-xylidine used.

4, 5-Diiodo-*m*-xylene (VIII). — The diazonium salt solution prepared from VII was slowly added to a solution of potassium iodide in water. The mixture was then allowed to stand overnight, and the black oil which precipitated was chromatographed as usual. The evaporation of the solvent, followed by the distillation of the residual oil, afforded a pale pink-colored oil, boiling at 176—177°C/18 mmHg, which did not solidify upon standing in an ice box. The yield was very poor.

Found: C, 27.00; H, 2.31. Calcd. for $C_8H_8I_2$: C, 26.84; H, 2.25%.

The infrared spectrum showed a peak at 849 cm^{-1} which may be attributed to one isolated ring-hydrogen. A band at 950 cm^{-1} was attributed to the B vibration of the ring CH bond which distinguished 4,5-diiodo-*m*-xylene from the 2,5-diiodo isomer. Aromatic carbon-iodine bands were observed at 1012 and 1040 cm^{-1}.

4-Amino-6-nitro-*m*-xylene (IX). — 4-*m*-Xylidine was dissolved in concentrated sulfuric acid and nitrated as in the preparation of I. The crude amine obtained was then triturated and extracted several times with small amounts of cold tetrahydrofuran in order to remove the accompanying isomer, 2-nitro-4-amino-*m*-xylene. Then the product was recrystallized from an aqueous ethanol solution. The yield was 50%, and the product, orange yellow needles, melted at 122—124°C. Reported,⁵⁾ 124°C.

4-Iodo-6-nitro-*m*-xylene (X).—The amine IX was converted into this compound by the same method as that used in the preparation of II. The product was purified through an alumina column using light-boiling ligroin as an eluant. Recrystallization from boiling petroleum ether afforded large pale yellow crystals which melted at 87—88°C. The yield was 60%.

Found: C, 34.96; H, 2.27; N, 4.87. Calcd. for $C_8H_9INO_2$: C, 34.68; H, 2.90; N, 5.05%.

4-Iodo-6-amino-*m*-xylene (XI).—Fifty grams of stannous chloride dihydrate was dissolved in a mixture of 200 ml. of concentrated hydrochloric acid and 200 ml. of ethanol; to the resultant solution 12.5 g. of X was added and it was gradually heated to a gentle refluxing. After the complete dissolution of the crystal, refluxing was continued for an additional 2 hr., and then the mixture was cooled. An excess of sodium hydroxide was added to redissolve the precipitated tin hydroxide, after which the mixture was steam-distilled. The amine was readily steam-distilled and solidified in a condenser as white crystals, which were collected and recrystallized from boiling petroleum ether. The product was obtained as a cluster of white leaflets which weighed 9.4 g. (84%); m. p. 68—69°C.

Found: C, 39.03; H, 4.27; N, 5.45. Calcd. for C_8H_9NI: C, 38.88; H, 4.08; N, 5.67%.

4, 6-Diiodo-*m*-xylene (XII).—The amine XI was diazotized and converted into this compound by the same procedure as that used in the preparation of IV. The crude product was purified through an alumina column using petroleum ether, from which 4,6-diiodo-*m*-xylene separated as large plates, m. p. 72—74°C. Reported,⁶⁾ 72°C. The yield was 72%.

Found: C, 27.17; H, 2.53. Calcd. for $C_8H_8I_2$: C, 26.84; H, 2.25%.

Peaks (865 and 931 cm^{-1}) and a pattern (1650—2000 cm^{-1}) indicating the appropriate aromatic substitution were present in the infrared spectrum. Aromatic carbon-iodine band was observed at 1023 cm^{-1}.

Summary

Four isomeric diiodo-*m*-xylenes have been synthesized and their isomerization in concentrated acids investigated in order to elucidate the mechanism of the new rearrangement observed in the Jacobsen reaction of 2-iodo-*m*-xylene. 2,4- and 4,5-Diiodo-*m*-xylene, in the presence of cold sulfuric or hot polyphosphoric acid, isomerize to 4,6- and 2,5-diiodo-*m*-xylene respectively. All four isomers readily undergo disproportionation with hot sulfuric acid to give mixures of tri- and tetraiodo-*m*-xylenes. No disproportionation has been observed in the reaction with polyphosphoric acid. The important role played by a sulfo group in this reaction has been discussed.

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4) M. Kerschbaum, ibid., **28**, 2798 (1895).

5) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **53**, 1576 (1931); E. Noelting and A. Collin, *Ber.*, **17**, 265 (1884).

6) A. Töhl and E. Bauch, ibid., **26**, 1105 (1893).