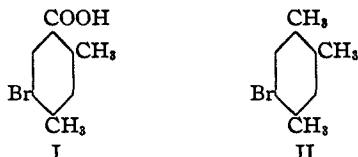


[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

5-Bromo-2,4-xylic Acid. Nuclear Halogenation with Alkaline Hypohalite Solutions

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Perkin and Stone¹ observed that bromination as well as cleavage occurs when 2,4-dimethylacetophenone reacts with alkaline hypobromite under conditions that usually lead to the corresponding benzoic acid. It was believed that the product was 6-bromo-2,4-xylic acid, because its melting point (180°) compared favorably with the value (183–184°) given before for this acid,² but was higher than those previously reported (172–173°³ and 174°⁴) for the 5-bromo isomer (I). Because of the combined orientating influence of the carbonyl and methyl groups it seemed likely to us that bromination had taken place in the 5-position, and that conclusions to the contrary were founded upon misleading data. Indeed this was found to be the case, for the brominated product of Perkin and Stone is identical with 5-bromo-2,4-xylic acid (I), which was prepared through the nitrile from 5-bromo-2,4-dimethylaniline.⁵



The statement⁴ that the action of bromine on 2,4-xylic acid gives the 5-bromo compound (I) has been verified, but the melting point given for the product was found to be too low. On the other hand, the claim³ that the same bromoxylic acid results from the oxidation of 5-bromopseudocumene (II) is erroneous; the product (m. p. 172–173°) is probably an isomer of I.

The ease with which bromination occurs in the case described above suggests that the nucleus of some aromatic compounds may be more susceptible⁶ to the action of hypohalite solutions than is generally realized. Experiment has demonstrated that this is the case. The same bromoxylic acid (I) was obtained by treatment of 2,4-dimethyl-

phenacyl chloride, 2,4-xylic acid and 2,4-dimethylmandelic acid with hypobromite. Under similar conditions β -isodurylic acid was transformed readily into 3-bromo-2,4,6-trimethylbenzoic acid, and alkaline hypochlorite converted 2,4-dimethylacetophenone into an acid melting at 164–165.5°, which is probably 5-chloro-2,4-xylic acid (reported⁷ to melt at 165°).

It appears that two methyl groups are necessary for this type of halogenation since, in the preparation^{8,9} of *p*-toluic acid from *p*-methylacetophenone, no nuclear halogenation was observed. *o*-Toluic acid also has been found to be unreactive toward hypobromite.

That the benzene ring in simple derivatives is not sufficiently reactive to impair the usefulness of hypobromite in effecting side chain transformations is indicated⁹ by the several cases in which oxidation to the corresponding benzoic acid was observed. Thus good yields of the appropriate benzoic acid were obtained by hypobromite treatment of the following compounds: phenylacetic acid, benzoin, desoxybenzoin, benzyl chloride, benzyl bromide, *o*-chlorobenzyl chloride, *o*-chlorobenzyl bromide, *o*-xylyl chloride, *o*-xylyl bromide and *m*-nitroacetophenone.⁹ Two moles of benzoic acid were obtained from benzoin and desoxybenzoin, and only the halomethyl group of the xylyl halides was oxidized. Because the speed of conversion of the benzyl halides into benzoic acids corresponds roughly to the hydrolysis rates¹⁰ of substituted benzyl halides, it is believed that oxidation of the halomethyl group is preceded by hydrolysis.

Experimental

5-Bromo-2,4-dimethylbenzonitrile.—In the usual manner 5-bromo-2,4-dimethylaniline⁶ (from the bromination of 2,4-dimethylacetanilide) was diazotized and converted into the nitrile. After crystallization from aqueous methanol the melting point was 88–89°.

Anal. Calcd. for C₉H₉NBr: C, 51.4; H, 3.9. Found: C, 51.3; H, 4.1.

5-Bromo-2,4-xylic Acid (I).—A mixture of 4 g. of the nitrile, 15 cc. of concd. sulfuric acid and 10 cc. of water was boiled for one-half hour. The product was a mixture

(1) W. H. Perkin, Jr., and Stone, *J. Chem. Soc.*, **127**, 2275 (1925).
 (2) W. A. Noyes, *Am. Chem. J.*, **20**, 802 (1898). This acid, prepared since from the nitrile, melted at 186° (Bures and Mandel-Borgmannová, *Chem. Abst.*, **22**, 4503 (1928)).
 (3) Süsseguth, *Ann.*, **215**, 244 (1882).
 (4) Gunter, *Ber.*, **17**, 1608 (1884).
 (5) Noelting, Braun and Thesmar, *ibid.*, **34**, 2256 (1901).
 (6) The nucleus of a naphthalene derivative has been halogenated with alkaline hypohalite solutions (Bull and Fuson, *THIS JOURNAL*, **56**, 737 (1934)).

(7) Morgan and Hickinbottom, *J. Chem. Soc.*, **119**, 1879 (1921).
 (8) Coulson, *ibid.*, 1408 (1934).
 (9) VanArendonk and Cupery, *THIS JOURNAL*, **53**, 3184 (1931).
 (10) Olivier, *Rec. trav. chim.*, **49**, 697, 996 (1930).

of the acid (m. p. 180–181°, identical with Perkin and Stone's bromoxylic acid¹) and the amide, which melted at 197.5–198.5° after several crystallizations from aqueous methanol.

5-Bromo-2,4-dimethylbenzamide.—The bromoxylic acid prepared by the action of hypobromite on 2,4-dimethylphenacyl chloride was converted into the acid chloride by treatment with thionyl chloride. From the acid chloride and ammonia was obtained a good yield of the amide (m. p. 197–198°), which was found to be identical with the amide prepared from 5-bromo-2,4-dimethylbenzotrile.

Anal. Calcd. for C₉H₁₀ONBr: C, 47.3; H, 4.4. Found: C, 47.0; H, 4.3.

Oxidation of 5-Bromopseudocumene.—A mixture of 7 g. of 5-bromopseudocumene,¹¹ 15 cc. of concd. nitric acid and 30 cc. of water was heated on a steam cone for forty hours. An alkaline solution of the product was washed with ether, and then the free acid was crystallized from aqueous alcohol, and from ligroin. Colorless crystals resulted which melted at 172–173°; when mixed with 5-bromo-2,4-xylic acid the m. p. was 168–170°.

Action of Bromine on 2,4-Xylic Acid.—Xylic acid resisted the action of bromine in acetic acid to an astonishing degree when the ease of its reaction with hypobromite at room temperature is considered. Bromination was finally effected by allowing a mixture of 1.5 g. of xylic acid, 2 g. of bromine, 20 cc. of acetic acid, iron powder and a crystal of iodine to stand for nineteen days, and then heating the mixture on a steam cone for twenty-four hours. The product was crystallized from aqueous methanol and from ligroin. The m. p., 179–180°, was not depressed when mixed with 5-bromo-2,4-xylic acid (I).

Reactions with Hypobromite.—Since most of these experiments were performed in a similar manner only a few representative cases are described. An excess of hypobromite was always used except in one case (conversion of 2,4-dimethylphenacyl chloride into 2,4-xylic acid) which is described below. The reactions were carried out at room temperature, and with agitation when the reactants were insoluble.

(a) **2,4-Dimethylphenacyl Chloride.**—Hypobromite (10 cc. of bromine, 25 g. of sodium hydroxide and 250 cc. of water) and 25 g. of dimethylphenacyl chloride were agitated for three hours, and then washed with ether. Acidi-

fication caused 2,4-xylic acid to precipitate, which melted at 123.5–125° after crystallization from water-methanol.

When 2,4-dimethylphenacyl chloride (5 g.) was agitated for twenty hours with hypobromite (10 cc. of bromine, 17 g. of sodium hydroxide and 300 cc. of water) the product isolated after acidifying with sulfur dioxide, and purified by crystallization from aqueous methanol and then ligroin, melted at 180–181°. The same acid was obtained from 2,4-dimethylacetophenone by similar treatment.

(b) **2,4-Xylic Acid.**—Treatment of 1 g. of xylic acid for three hours with hypobromite prepared from 3 cc. of bromine, 5 g. of sodium hydroxide and 96 cc. of water yielded the same bromoxylic acid (I) obtained previously from 2,4-dimethylphenacyl chloride. The conversion of β -isodurylic acid into 3-bromo-2,4,6-trimethylbenzoic acid¹² was carried out in a similar manner during three hours.

(c) ***o*-Xylyl Bromide.**—A mixture of 10.4 g. of *o*-xylyl bromide and hypobromite (10 cc. of bromine, 30 g. of sodium hydroxide and 300 cc. of water) was agitated for one day (the xylyl bromide dissolved in seventeen hours), acidified and filtered. The product melted at 100–101.5° and amounted to 7 g. (91%). After crystallization from aqueous alcohol the m. p. was 102–103.5°.

Some of the other benzyl halides required several days for complete conversion.

Summary

By a synthesis from the corresponding nitrile it has been shown that the compound previously prepared¹ by the action of hypobromite on 2,4-dimethylacetophenone is 5-bromo-2,4-xylic acid. The same acid was obtained by the action of bromine on 2,4-xylic acid, but another acid was produced by the oxidation of 5-bromopseudocumene. Several cases of nuclear halogenation of polymethylbenzoic acids with alkaline hypohalite are described. Similar treatment of simpler benzene derivatives caused transformations in the side chain but not nuclear halogenation.

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(11) Huender, *Rec. trav. chim.*, **34**, 8 (1915).

(12) Schildneck and Adams, *THIS JOURNAL*, **53**, 349 (1931).