BROMINATION OF P-XYLENOL SULFONIC ACID IN NITRO BENZENE

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INTRODUCTION

This problem was undertaken with the view of preparing halogenated xylenols in which the halogen occurs adjacent to the hydroxyl group. The method used was first introduced by Huston and Neeley in 1935.

HISTORICAL

A review of the literature concerning the bromination of 1.4-dimethyl-2-hydroxy benzene (P-Xylenol) reveals the following compounds together with their mode or modes of preparation:

5-brom-1.4-dimethyl-2-hydroxy-benzene.

1. Direct bromination of P-Xylenol in acetic acid using an equivalent mole quantity of each. Recrystalize from dilute acetic acid. Needles, M.P. 87°.

   Jacobsen, Ber., 11, 27 (1878).

   Auwers, Ericklentz, Ann. 302, 113 (1898).

3.5-dibrom-1.4-dimethyl-2-hydroxy-benzene.

1. Direct bromination of P-Xylenol in acetic acid using two moles bromine and one mole P-Xylenol or their equivalents. Recrystalize from dilute acetic acid. Needles, M. P. 79° .

   Auwers, Ericklentz, Ann., 301, 220;302, 114 (1898).

2. Treatment of 4.4'-dioxy-2.5.2!5'-tetramethyl-diphenylmethane in boiling acetic acid with

bromine. Needles, M. P. 79-80°.

Auwers, Rietz, Ann., 356, 169 (1907).

3.6-dibrom-1.4-dimethyl-2-hydroxy-benzene.

1. Diazotising a solution of 3.6-dibrom-2-amino-1.4-dimethyl-benzene in absolute alcohol using amyl nitrate and decomposing the compound formed with hot dilute sulfuric acid. Recrystalize from ligroin. Needles, M. P. 90-91°.

Auwers, Baum, Ber. 29, 2344 (1896).

3.5.6-tribrom-1.4-dimethyl-benzene.

1. Action of bromine on pseundocumenol along with other products. Recrystalize from dilute acetic acid. Needles, M. P. 178-179°.

Auwers, Anselmino, Ber., 32, 3592 (1899).

Auwers, Ann., 356, 134 (1907).

2. Action of bromine on P-Xylenol in the presence of iron using carbon tetrachloride as the solvent. Yield 75-80%.

Zincke, Breitwieser, Ber., 44, 179 (1911).

3. Action of excess bromine on cooled P-Xylenol. Recrystalize from alcohol. Needles M.P. 175°.

Jacobsen, Ber., 11, 27 (1878).

4. Action of bromine on 3.6-dibrom-5-oxy-1.2.4-trimethyl-benzol.

Auwers, Ber., 32, 3592 (1899).

5. Action of bromine on 3.6.3'.6'-tetrabrom-4.4'-dioxy-2.5.2'.5'-tetramethyl-dipheylmethane.

Auwers, Ann.,356,134 (1907).

Auers, Hof,Ber.,29, 1117 (1896).

Auers, Ercklentz, Ann., 302, 114 (1898).

5. Action of excess bromine on dry P-Xylenol.

Auwers, Ercklentz, Ann., 302, 114 (1898).

It is noted that in brominating P-Xylenol directly the entering bromine first takes the position para to the hydroxyl group and then when this is complete the vacant ortho position to the hydroxyl is attacked. If the para position can be blocked by some method the entering bromine should then go to the next active position or adjacent to the hydroxyl. In considering a method for the efficient blocking of the active para position an element or group must be chosen so that when the bromination is complete the element or group may be readily removed without destroying the compound formed. In the past the sulfonic group has met with more or less success in this respect.

In aqueous acid solution the sulfonic group is generally replaced by halogen during halogemation.

1. Chlorination of an aqueous solution of cymene-sulfonic acid produced tetrachlor-cymene. Bromination of trichlor-cymene sulfonic acid produced trichlor-monobrom-cymene.

Kelbe, Ber.,16, 617 (1883).

2. Addition of bromine to O-xylene-sulfonic acid in aqueous solution using hydrochloric acid as a catalyst resulted in the formation of brom-O-xylene (1.2.4.), dibrom-O-xylene (1.2.4.) and brom-O-xylene-sulfonic acid. M-xylene-sulfonic acid (1.3.4) formed monobrom-xylene (1.3.4).

Kelbe, Stein, Ber., 19, 2137 (1886).

3. Sulfonation, followed by bromination of P-toluidine in aqueous acid solution gave rise to M-brom-P-toluidine as well as O-brom-P-toluidine.

Hafner, Ber., 22, 2902 (1889).

4. Sudborough and Lakumalani stated that a sulfonic group para to the amino group easily is displaced by halogen. They used P-sulfanilic acid to form symmetrical tribrom-aniline and symmetrical trichlor-aniline employing bromine and chlorine as agents respectfully. Chlorination of 2.6-dibrom-P-sulfanilic acid produced 2.6-dibrom-4-chlor-aniline.

Sudboroughm Lakumalani, J.Chem.Soc.,111,41(1913).

5. 2.6-Mcresol-disulfonic acid was converted to 2.6-dichlor-M-cresol by means of chlorine in aqueous acid solution.

Datta, Mitter, J.Am.Chem.Soc.,41, 2033 (1919).

6. Datta stated that in removing the sulfonic group by an entering halogen the reaction can not be easily controlled. Not only the mono substitution takes place but substitution continues to the di and tri substituted compound. One or more hydroxyl groups attached to the nucleus accelerates the replacement of the sulfonic acid group by bromine. Upon brominating the sulfonic acids of the following compounds the tribrom substituted compound was formed:

Phenol ---- 2.4.6-tribrom-phenol
M-cresol ---- 2.4.6-tribrom-M-cresol
P-cresol ---- 2.4.6-P-cresol
1.2.4-xylenol ---- 3.6-dibrom-1.2.4-xylenol

Datta, Bhoumik, J.Am.Chem. Soc., 43, 303 (1921).

7. Sodium chlorate was used to remove the sulfonic group in nitro-sulfonic-napthalenes. Chlorine was substituted in its place.

Friedlander, Schenk, Ber., 55, 45 (1922).

In some cases the sodium salt of the sulfonic acid group has served as an efficient blocking agent for the preparation of halogenated compounds.

1. The sodium salt of P-phenol-sulfonic acid was chlorinated in alkali solution giving rise to 2-chlor-phenol and it was also brominated in alkali solution forming 2-brom-phenol.

Takagi, Kutani, J.Pharm.Soc. Japan, 517,260 (1925).
(C. A.,20, 2669)

2. From the sodium salt of P-phenol-sulfonic acid 2.6-dichlor-phenol was formed by employing chlorine in alkali solution.

Tanaki, Kutani, J.Pharm.Soc. Japan, 541, 196 (1927).
(C.A. 21, 225)

3. Bromination of the sodium salt of P-phenol-disulfonic acid (1.2.4) gives rise to 2-brom-phenol.

Ballard, Huston, Organic Synthesis,Vol.14,p.14 (1934).

The sulfonic group has also been used in acid solution to an extent in blocking positions.

1. Blocking of the 4 and 6 positions during nitration of resorcinol.

Kauffmann, dePay, Ber.,37, 725 (1904).

2. The 4 and 6 positions of M-cresol was blocked using fuming sulfronic acid during nitration.

Gibson, J.Chem. Soc.,123, 1269 (1923).
Hodgson, Beard, J.Chem.Soc., 127, 498 (1925).

3. M-cresol formed 2-chlor-m-cresol and 2-brom-M-cresol when it was chlorinated or brominated in fuming sulfuric acid.

Huston, Peterson, J.Am.Chem.Soc., 55, 3880 (1933).

When the sulfonic acid group has served its purpose in relation to blocking it is readily removed by hydrolysis using superheated steam. In the case of the alkali solution it is made acid before hydrolysis.

In 1935 Huston and Neeley (J.Am. Chem. Soc., 57, 2176) tried to prepare 2-brom-phenol and 2.6-dibrom-phenol by brominating phenol using fuming sulfuric acid as a blocking agent. They found that if too much sulfuric acid was used, sulfonation would occur to a large extent and thus greatly diminish the yield of product. Enough sulfuric acid for sulfonation of the phenol produced a solid when a small quantity of bromine was added; Upon addition of more bromine symmetrical tribrom-phenol was produced. To overcome the obstacles of small yields and solidification an inert anhydrous solvent was employed. Freshly distilled nitrobenzene was found to be well adapted to the procedure. Fuming sulfuric acid was used as the dehydrating agent. Both phenol and cresol were subjected to sulfonation and then chlorinated or brominated in the inert anhydrous medium followed by hydrolysis using superheated steam. The resulting compounds and their yields were:

2-brom-phenol	-------10%
2.6-dibrom-phenol	-------72%
2-chlor-phenol	-------70%
2.6-dichlor-phenol	-------72%

6-brom-O-cresol --------60%

6-chlor-O-cresol --------30%

2-brom-M-cresol -------- 7%

4-brom-M-cresol -------- 8%

2.6-dibrom-M-cresol -------23%

2-chlor-M-cresol -------14%

4-chlor-M-cresol ------- 5%

2.4-dichlor-M-cresol-------25%

2.6-dichlor-M-cresol------- 6%

In connection with the bromination of phenols by this method it was believed that xylenols should also fall into the category.

EXPERIMENTAL

In studying the possible bromination compounds of 1.4-dibrom-2-hydroxy-benzene it is noted that the 3 and 6 monobrom and the 5.6-dibrom ring substituted compound are unaccounted for. The 3-brom-1.4-dimethyl-2-hydroxy-benzene should be formed by using Huston and Neeley's method and runs were made to prove this.

A mixture of 13.5 grams (1/9 mole) of 1.4-dimethyl-2-hydroxy-benzene and 33 grams (1/3 mole) of concentrated sulfuric acid (d.1.84) were heated with stirring at 100-110° for two hours and an oil bath. The mixture was allowed to cool and 66.6 grams (1/2 mole) of nitrobenzene was added. After the addition the mixture was cooled in ice and 5 grams of fuming sulfuric acid (60%) was added at such a rate that the temperature did not rise above 10°. Then 18 grams (1/9 mole) of bromine dissolved in 17 grams of nitrobenzene was added dropwise. Stirring and ice cooling were continued for an hour after the addition to complete bromination. The reaction was then allowed to come to room temperature and 300 cm. of water containing 3 grams of dissolved sodium bisulfite was added. The mixture was thoroughly stirred for fifteen minutes to complete extract the brominated phenol sulfonic acid. The water layer was separated from the nitrobenzene by means of a separatory funnel. The solution of the sulfonic acid was placed in a 500cm. flask suitable for steam distillation. The water and dissolved nitrobenzene was evaporated off using an oil bath at 200° . When the temperature of the sulfonic acid solution reached 115°, superheated steam, superheated by means of a copper coil, was passed through it. The oil bath was kept at 200° during the entire hydrolysis. The hydrolysis was complete when the flask was dry and only charred material remained. The brominated phenol was extracted from the distillate with ether. The ether was removed by evaporation using the steam bath. The remaining phenol was subjected to distillation under reducer pressure using a modified Claisen flask having a 20cm. column. The compound came over between 102-104°

(11mm.). Analysis and properties of this compound indentified it as 3-brom-1.4-dimethyl-2-hydroxy-benzene. Yield - 22% (5 grams).

After combination of two runs of the above procedure the compound was solidified and allowed to liquify slowly. When it became slushy it was filtered by suction until all was considered liquified (1 hour). A white solid remained on the filter paper. Its weight was .30 grams. It had a melting point of 55-58°. The substance was believed to be a mixture of P-xylenol and its mono and di-brom substitution products. Repeating this procedure failed to give any more of the substance.

Analysis. Br, 6.34

3-brom-1.4-dimethyl-2hydroxy-benzene.

Prepared by sulfonation and subsequent bromination of P-xylenol in anhydrous nitrobenzene. A yellow liquid.

Analysis. Calc. for $C_8H_9O\ Br$: Br,39.76. Found:Br,39.44

Melting point (capillary)---------16.5-17.5°.

Boiling point ---------77-81° --- 0.5 mm.

102-104°--- 11.0 mm.

225.5-226°-737.0 mm.

Density --------1.4082 at 20°

Index of refraction (sunlight)--1.5630 at 20°

Moleculer refraction Calc. for $C_8H_9O\ Br$: 44.83.Found,44.76

Derivatives:

Aryloxy acetic acid according to the procedure of Koelsch, (J.Am.Chem.Soc., 53,304 (1931)).

White needles-------------------M.P. 139.5°

Analysis.Calc. for $C_{10}H_{11}O_3Br$: Br,30.86. Found: Br,30.80.

3.5-dinitro-benzoyl ester according to the procedure of Brown, (Kremers, J.Am.Phar.Assn.,11,607 (1922)).

Yellow solid ------------------M.P.169.5°

Analysis. Calc. for $C_{15}H_{11}O_6N_2Br$: Br,20.22.Found:Br,20.18

PROOF OF THE STRUCTURE OF 3-BROM-1.4-DIMETHYL-2-HYDROXY-BENZENE. 2.4 grams of the compound formed from the preceeding bromination was dissolved in 100 cm. of chloroform and cooled by means of an ice bath. While being stirred 3.2 grams of bromine dissolved in 2o cm of chloroform was added slowly. After addition of the bromine the solution was stirred four hours. The chloroform was evaporated off and the white solid remaining was recrystalized from alcohol. M.P. 78.5-79°.

Analysis. Calc. for $C_8H_8Br_2O$: Br, 57.10. Found, Br.56.99.

6.1 grams of 1.4-dimethyl 1-2 hydroxy-benzene was dissolved in 200 cm. chloroform. While stirring it was cooled in an ice salt mixture of 8 grams of bromine dissolved in 100 cm. of chloroform was added dropwise over a period of four hours. After the addition the mixture was stirred for ten hours. Upon evaporating off the chloroform a white solid remained which was recrystalized from alcohol. M.P. 84-85°.

Analysis. Calc for C_8H_9OBr: Br, 39.76. Found:Br,39.95.

This compound was a 5-brom-P-xylenol.

5 grams of 5-brom-P-xylenol was dissolved in 100 cm. of chloroform and cooled with ice. 4 grams of bromine dissolved in 50 cm. of chloroform were added dropwise while the solution was being stirred. Stirring was continued for two hours after the addition of the bromine. The chloroform was removed by evaporation and the compound recrystalized from alcohol. M.P. 78.5 - 79.5°.

Analysis.Calc. for $C_8H_8OBr_2$: Br,57.10.Found:Br,57.12.

The 3.5-dibrom-2-hydroxy-1.4-dimethyl-benzene thus formed is identical with the compound resulting from the bromination of the bromine compound formed in the procedure; therefore the former compound must be 3-brom-P-xylenol and upon bromination the active para position takes up the entering bromine forming the 3.5-dibrom compound.

SULFONATION OF 1.4-DIMETHYL-2-HYDROXY-BENZENE is not well described in the literature (Jacobsen,Ber, <u>11</u>, 27 (1878)). During the process of a run sulfonation is supposed to take place. A run was stopped just before the addition of nitrobenzene to see how far sulfonation took place. The process was a heating of a mixture of 13.5 grams of P-xylenol and 33 grams of concentrated sulfuric acid (d. 1.84) while stirring at 100-110° for 2 hours using an oil bath and then allowing the mixture to cool. 200 cm. of water was added and the mixture was stirred until all was in solution. Barium carbonate was added until no further precipitation took place. Carbon dioxide was then bubbled in until the solution was saturated. The solution was heated for ten minutes, cooled and filtered. The water was evaporated off and a white solid remained. The 1.4-dimethyl-2-hydroxy-4-sulfonic acid was recrystallized from water. Yield 80%. M.P. 156-161° (decomposes).

Analysis. Calc.for $C_8H_{10}O_4S$: S, 15.85; Found: S,15.84.

SUMMARY

1. 3-brom-1.4-dimethyl-2-hydroxy-benzene was made and its structure proven.
2. Bromination of 1.4-dimethyl-2-hydroxy-4-benzene sulfonic acid in anhydrous nitrobenzene gave rise to 3-brom-1.4-dimethyl-2-hydroxy-benzene.
3. 1.4-dimethyl-2-hydroxy-4-benzene sulfonic acid was prepared in a good yield.