Summary

1. Hydrazodithiodicarbonamide has been found to tautomerize into the thiol-imino form under experimental conditions which have been determined, and the interconvertibility of the two forms established.

2. Imino-thiol-thiobiazole has been isolated as an intermediate compound during the formation of Freund's "Dithio-urazole"—now shown to be endo-imino-thiol-thiobiazole; the latter has been found to be formed either by the prolonged action of hydrochloric acid on the hydrazide or the imino-thiol-thiobiazole, or by acetic anhydride treatment on the thiobiazole with subsequent deacetylation.

3. Similar cases of isomerism have been observed with the alkyl and aryl substituted mono- and dithio-hydrazides.

BANGALORE, INDIA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE COLLEGE OF WASHINGTON]

SOME HALOGEN DERIVATIVES OF ACYL AND ALKYL RESORCINOLS

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Since the acyl and alkyl resorcinols have been given much attention by investigators recently, due to their germicidal and other interesting properties, we have undertaken to prepare and study certain halogen derivatives of these compounds, and also to improve the methods of preparation of the intermediate compounds already reported by others.

The acyl groups were introduced into the resorcinol nucleus by condensing the latter with the desired fatty acid in the presence of fused zinc chloride, a method proved to be very satisfactory for this purpose by Nencki[2] and others. The ketones were prepared without difficulty, and increased yields obtained by varying the conditions of temperature, concentration and time, as shown in the tables in the dissertation.[3] These acyl compounds were then reduced according to Clemmensen's method,[4] which employs amalgamated zinc with hydrochloric acid as reducing agent. The alkyl compounds obtained by reduction were halogenated in various solvents and in the presence of carriers.

The same halogenated alkyl resorcinol was obtained whether the halogenated ketone was reduced or the ketone reduced before halogenation. For example, dibromo-ethylresorcinol was prepared as follows.

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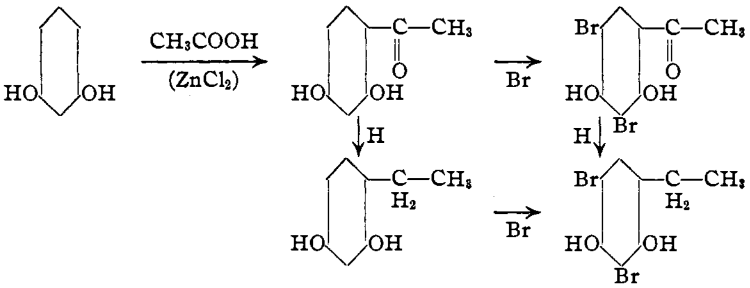
[1] This paper is an abstract of part of a thesis presented by J. C. Harris in partial fulfilment of the requirements for the degree of Master of Science.

[2] Nencki and Schmid, *J. prakt. Chem.*, **23**, 546 (1881).

[3] Dissertation, by J. C. Harris, 1930.

[4] Clemmensen, *Ber.*, **46**, 1837 (1913).



Von Pechmann and Duisberg[5] established the position of the acetyl group when they fused β-methylembelliferone with potassium hydroxide and obtained resacetophenone. Dahse[6] determined the position of the bromine atoms in the ketone by oxidation with chromic acid and obtained a dibromodihydroxybenzoic acid which was identical with that formed by bromination of β-resorcylic acid. The reduction of the dibromo ketone would definitely place this compound as 2,4-dihydroxy-3,5-dibromo-ethylresorcinol.

The corresponding dichloro-ethylresorcinol was prepared by reduction of the chlorinated ketone, but we were unable to isolate the same compound when ethylresorcinol was chlorinated, although it was evident that a similar reaction had taken place. The solubility of dichloro-ethylresorcinol in water is appreciably greater than that of the dibromo-ethylresorcinol, and we could not find an extraction agent which would bring about a clear separation and yet remain immiscible with the original solvent.

On bromination of resacetophenone in acetic acid with iodine as carrier, a tetrabromo derivative was obtained. On reduction by Clemmensen's reagent, the tetrabromo derivative gave 2,4-dihydroxy-3,5-dibromo-ethylresorcinol, indicating that two of the bromine atoms are in the nucleus and two in the methyl group of the side chain.

The halogenated acyl resorcinols gave a wine-red color to an aqueous solution of ferric chloride, while the corresponding alkyl compounds gave merely a slight yellowish-green coloration. The melting points for the halogen derivatives are considerably higher than for the non-halogenated ketones, but show the usual decrease with lengthening of the side chain. Since there are two bromine atoms in the side chain of the tetrabromoresacetophenone, their introduction reduces the melting point. Inasmuch as the melting point of tribromopropionylresorcinol is higher than that of the dibromo compound it is possible that the third bromine atom of the former may be in the benzene nucleus.

We were unable to prepare tribromoresacetophenone, reported by Segalle[7] as produced by passing an excess of bromine into an acetic acid

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[5] Von Pechmann and Duisberg, *Ber.*, **16**, 2121 (1883).

[6] Dahse, *ibid.*, **41**, 1621 (1908).

[7] Segalle, *Monatsh.*, **17**, 315 (1896).

solution of the ketone. Numerous trials with different proportions and in different solvents, varying also the temperature and time, resulted in forming the dibromo compound, or in the presence of iodine as carrier, the tetrabromo derivative. However, when propionylresorcinol was brominated in glacial acetic acid, tribromopropionylresorcinol was obtained, also when iodine was used as carrier.

Halogenation products of propylresorcinol and butylresorcinol were prepared by the reduction method of Clemmensen, and the color change when tested with ferric chloride indicated complete reduction, but samples were oils of which we did not have a sufficient quantity for purification.

In the preparation of butyrylresorcinol, when the condensation was permitted to continue at boiling temperature for several minutes, the final purification gave two products: one the normal product melting at 69–70°, and the second a compound melting sharply at 111–112°, composed of clear colorless prism-shaped crystals. Several analyses were made of different trial samples but no conclusions can be reached as to its constitution until more work is done on the compound.

We are investigating further the halogen derivatives of other members of the resorcinol series, with acyl, alkyl and aryl side chains. We have also made a number of similar derivatives of hydroquinone and of the naphthols, and are continuing their study in this Laboratory.

Experimental Part

ω-Dibromo-3,5-dibromo-2,4-dihydroxyacetophenone.—Bromination took place in a hot glacial acetic acid solution of resacetophenone, using several crystals of iodine as carrier. On dilution with water, yellow crystals separated and were purified by crystallization from acetic acid and from alcohol. The characteristic sheaves of yellow platelets melt sharply at 110–110.5°.

Anal. Calcd. for $C_8H_4O_3Br_4$: Br, 68.35. Found: Br, 68.08, 68.42.

The compound is readily soluble in alcohol, benzene, ether, chloroform and acetic acid, difficultly soluble in petroleum ether and in boiling water. With ferric chloride a wine-red color is produced, as with other brominated ketones. On reduction tetrabromoresacetophenone gave 3,5-dibromo-2,4-dihydroxy-1-ethylbenzene, indicating that two of the bromine atoms of the tetrabromo derivative were in the methyl group of the side chain.

Dichloro-2,4-dihydroxyacetophenone was prepared by direct chlorination of resacetophenone in a variety of solvents and at different temperatures; the best yield (78%) was obtained when using 80% acetic acid as solvent, and the solution was heated to 80° at the beginning of the chlorine addition. Segalle[7] also used acetic acid in preparing the compound. The glistening white needles melt at 195–196°. They are insoluble in water, slightly soluble in chloroform, carbon disulfide, and petroleum ether, readily soluble in alcohol, benzene and acetic acid.

2,4-Dihydroxypropiophenone.—Propionic acid distilling between 135–145° was used in numerous trials, and most satisfactory results were obtained by dissolving 80 g. of fused zinc chloride in 80 g. of propionic acid, and adding 50 g. of resorcinol to the hot solution. The mixture was heated under reflux to an intense bubbling of the solution, which occurred between 160–165°. The solution was then allowed to cool slowly, and on the following day was warmed sufficiently to permit it to be poured into a water and ice mixture acidified with hydrochloric acid. The dark brown oil solidified on standing, and the product was purified by dissolving in alcohol and refluxing the solution with animal charcoal. Bright yellow needles separated, m. p. 96°, which were readily soluble in alcohol, benzene, ether and acetic acid, but difficultly soluble in carbon tetrachloride, chloroform, petroleum ether and water. A yield of 73% was obtained, which is lower than that reported by others[8] who used a larger proportion of acid, but the above method is more economical as technical propionic acid can be used. The oxime was prepared as bright yellow needles, m. p. 186–187°.

3,5-Dibromo-2,4-dihydroxypropiophenone.—Gnagy[9] prepared this compound by slow addition of an acetic acid solution of bromine to the ketone dissolved in acetic acid. We tried carbon disulfide as well as acetic acid as solvent, but obtained the best yield (51%) by use of 80% acetic acid, adding bromine slowly through a dropping funnel. The mixture was allowed to stand for a day, filtered, the filtrate diluted with water and allowed to stand two to four hours for crystal formation. The crystals were dissolved in alcohol, refluxed with animal charcoal and recrystallized by addition of water; m. p. 151–152°; white needles, difficultly soluble in petroleum ether, insoluble in water, but readily soluble in other solvents.

Tribromo-2,4-dihydroxypropiophenone.—The ketone, dissolved in glacial acetic acid, was treated with two and one-half times the amount of bromine theoretically required for the dibromo compound. The solution was heated to 80° before adding the bromine. On cooling, an equal volume of water was added and the crystals were filtered, washed and dried. Repeated crystallization from alcohol gave yellow flaky crystals, m. p. 157–158°, which may be dissolved with difficultly in hot water or petroleum ether, but are readily soluble in other solvents.

Anal. Calcd. for $C_9H_7O_3Br_3$: Br, 59.37. Found: Br, 59.15, 59.49.

Dichloro-2,4-dihydroxypropiophenone.—The ketone was dissolved in 80% acetic acid and chlorine was passed through until no further change was observed. A mass of white needle-like crystals separated, and dilution with water gave more of the same compound, which was recrystallized from acetic acid and water. The product was washed, dried and finally crystallized repeatedly from benzene giving white needles, m. p. 146–147°, very slightly soluble in petroleum ether, insoluble in water, but readily soluble in alcohol, benzene and other solvents.

Anal. Calcd. for $C_9H_8O_3Cl_2$: Cl, 30.18. Found: Cl, 29.97, 29.96.

2,4-Dihydroxybutyrophenone.—Sixty grams of technical butyric acid (b. p. 153–163°) and 50 g. of fused zinc chloride were refluxed and when dissolved 30 g. of resorcinol was added. The mixture was heated to an intense bubbling, which occurred at about 165°. The dark brown viscous product was allowed to cool slowly until the next day, then warmed and poured into an acidified mixture of ice and water. The ketone was washed free of zinc chloride, dried and distilled repeatedly under diminished pressure, giving a light yellow oil. The product was crystallized from a mixture of equal parts of chloroform and benzene, m. p. 68–70°. Johnson and Lane[8] purified the ketone by distillation under diminished pressure and crystallization from a mixture of three parts of carbon tetrachloride and one part of benzene.

Gnagy[9] dissolved the oil in aqueous sodium hydroxide, refluxed repeatedly with animal charcoal and precipitated with hydrochloric acid.

Second Product.—In repeating the above process, but maintaining the mixture at the boiling temperature of 165° for two to five minutes before cooling, a different

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[8] Johnson and Lane, THIS JOURNAL, **43**, 357 (1921).

[9] Gnagy, *ibid.*, **45**, 807 (1923).

substance was obtained. The condensation product was purified as above, but the crystallization from chloroform and benzene gave about 20% of clear colorless crystals, m. p. 111–112°, the rest being the normal compound with melting point of 68–70°. The new compound crystallized in large clear prisms and appeared to be pure, but analyses showed less carbon and hydrogen than found in the normal compound. Unfortunately not enough of the compound was available to make derivatives for further study. We prepared the oxime of the normal compound (m. p. 68–70°), obtaining pale yellow needles, m. p. 188–189°.

3,5-Dibromo-2,4-dihydroxybutyrophenone.—Direct bromination of the ketone in 80% acetic acid solution, as employed by Gnagy, gave satisfactory results, though the yield was low. A yield of 10% was obtained when 15 g. of the ketone was brominated with 30 g. of bromine, 100 g. of 80% acetic acid being used as solvent. The compound was much more difficult to purify than the halogenated propionyl or acetyl resorcinol. It was necessary to reflux the solution repeatedly with animal charcoal, and finally to crystallize by fractional crystallization from alcohol and water. The crystals melt at 108–109°. The compound can be reduced to the alkyl form.

Dichloro-2,4-dihydroxybutyrophenone.—Twenty grams of butyrylresorcinol was dissolved in 100 g. of 80% acetic acid and chlorine passed through in excess. On dilution white crystals separated, which were refluxed in alcoholic solution with animal charcoal, and finally crystallized from benzene. The white needles (yield, 21%) were very slightly soluble in petroleum ether and in water, but readily soluble in alcohol, benzene or carbon tetrachloride. The melting point was 110.5–111°.

Anal. Calcd. for $C_{10}H_{10}O_3Cl_2$: Cl, 28.48. Found: Cl, 28.80, 28.76, 28.96.

2,4-Dihydroxy-1-ethylbenzene.—Resacetophenone was reduced by the Clemmensen method.[10] A yield of 82% was obtained as follows. Mossy zinc was amalgamated by covering with a 5% solution of mercuric chloride for one hour, then the liquid was drained off and the zinc used immediately without washing. Two hundred grams of the amalgamated zinc was placed in a flask, 50 g. of the ketone added, and 300 cc. of 20% hydrochloric acid gradually poured in to maintain steady evolution of hydrogen while the mixture was gently boiled. When a drop of the liquid gave no red color test with aqueous ferric chloride, which in this trial required about three hours, the solution was decanted, saturated with sodium chloride, cooled and extracted with ether. This general procedure was followed in all reductions and gave much better yields than the use of sodium amalgam or other reducing agents tried. When crystallized from benzene, the pale yellow crystals melt sharply at 97–98°, as reported by Clemmensen, and also by Johnson and Hodge.[11]

3,5-Dibromo-2,4-dihydroxy-1-ethylbenzene. Reduction Method.—Dibromoresacetophenone was reduced by Clemmensen's method until the ferric chloride test showed complete reduction. The warm suspension was saturated with salt, cooled and extracted with ether. On evaporation of the ether the oily residue was dissolved in alcohol and refluxed repeatedly with animal charcoal. On cooling the diluted alcoholic solution silky crystals slowly separated. The long silky needles when first filtered were transparent, but became opaque when dried. They melted sharply at 74°.

Anal. Calcd. for $C_8H_8O_2Br_2$: Br, 54.01. Found: Br, 53.93, 54.21.

Bromination Method.—Ethylresorcinol was dissolved in a variety of solvents and the calculated amount of bromine for the dibromo product was added. The solvents tried were glacial acetic acid, 80% acetic acid, ether, carbon disulfide, chloroform and carbon tetrachloride; ether gave the best results with a 60% yield in several trials.

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[10] Clemmensen, *Ber.*, 47, 51 (1914).

[11] Johnson and Hodge, THIS JOURNAL, 35, 1020 (1913).

The bromine was added slowly through a dropping funnel, and the mixture allowed to stand for several hours. The ether was then permitted to evaporate slowly, leaving clumps of characteristic waxy buttons. These were dissolved in alcohol, and crystallized by the procedure outlined above, giving crystals melting at 73.5–74.5°. A mixed melting point, taken using equal parts of the compound prepared by the two methods, did not vary by more than a half degree from the melting points of the two separate samples.

Anal. Calcd. for $C_8H_8O_2Br_2$: Br, 54.01. Found: Br, 54.25, 53.88.

The compound is very slightly soluble in water, but readily soluble in most other solvents.

Dichloro-2,4-dihydroxyethylbenzene.—Dichlororesacetophenone (m. p. 190–193°) was reduced and purified by the same method used with the dibromo derivative. The crystals are small snow-white prisms, which become opaque on standing. Crystallized from alcohol, the crystals melt at 78–79°.

Anal. Calcd. for $C_8H_8O_2Cl_2$: Cl, 34.26. Found: Cl, 33.98, 34.04.

The compound is soluble in the same solvents as the dibromo derivative, but it is somewhat more readily soluble in water than any of the other compounds prepared in this study.

Attempts were made to prepare the compound by chlorination of ethylresorcinol in acetic acid and other solvents. The same compound apparently was formed, but owing to its solubility in water and other solvents, it proved more difficult to purify than when prepared by the reduction method.

3,5-Dibromo-2,4-dihydroxy-1-propylbenzene.—When propylresorcinol was brominated in acetic acid solution, on dilution an oil separated, which was washed and its alcoholic solution refluxed with animal charcoal, then filtered and the filtrate diluted. No crystals were formed, so the solution was evaporated to dryness on a steam-bath, and the residue cooled with ice. This gave buttons of waxy crystalline material similar to those of the dibromo-ethylresorcinol. Working at zero temperature, a few white crystals were obtained, but these soon melted to a pale brown oil. Attempts were made to obtain a crystallizable product by reduction of the dibromopropionylresorcinol, using the Clemmensen method. This also gave a pale brown oil, which was dissolved in alcohol and water, and cooled to 0° for several hours, when fine white needles formed. The needles melted at the same temperature as those obtained by the bromination method. Owing to the limited quantity and difficulty of separating from the solvent, the compound was not analyzed.

Tribromo-2,4-dihydroxy-1-propylbenzene.—Tribromopropionylresorcinol (m. p. 157°) was reduced by the Clemmensen method. The reduction was complete, as indicated by the ferric chloride test. On extraction with ether and distilling off the solvent the residue was dissolved in alcohol and refluxed with animal charcoal. On dilution a yellow oil was obtained which did not crystallize when kept at zero temperature for several days. The compound is being investigated further.

Reduction of Tetrabromoresacetophenone.—Ten grams of tetrabromoresacetophenone was refluxed in 300 cc. of hydrochloric acid (20%) with the Clemmensen reagent. At the end of thirty minutes the solution gave a yellowish-green color when tested with ferric chloride solution, indicating complete reduction of the carbonyl group. The solution was saturated with salt, cooled and extracted with ether. On evaporation of the ether an oil remained which was recrystallized from alcohol and water, giving long silky crystals melting at 74–75°. As the appearance and melting point corresponded closely to those of dibromo-ethylresorcinol, a mixed melting point was made and gave 74–75°, indicating that the two compounds were identical. Two of the bromine atoms of tetrabromoresacetophenone must therefore be in the methyl group of the side chain of the ketone, since the 3,5-dibromo-2,4-dihydroxy-1-ethylbenzene was prepared by reduction of 3,5-dibromo-2,4-dihydroxyacetophenone.

Summary

1. Improvements in methods of preparation and purification of acyl and alkyl resorcinols are reported.
2. Six new halogen derivatives of acyl and alkyl resorcinols were prepared and their properties described.
3. Evidence was presented to establish the position of the bromine atoms in dibromo-ethylresorcinol and tetrabromoresacetophenone.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

NAPHTHOL STUDIES. I. THE BROMINATION OF 1,5-DIHYDROXYNAPHTHALENE

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The halogenation of juglone was first investigated by Wheeler and Scott.[2] Two atoms of chlorine entered the quinone nucleus when chlorination took place in warm glacial acetic acid. However, under like conditions three atoms of bromine were substituted in the molecule. Only a dichloro and a tribromo derivative could be obtained by direct action of the halogens. Attention has now been turned to the halogenation of the dihydric naphthol, 1,5-dihydroxynaphthalene, from which by oxidation with chromic acid, juglone is obtained. By varying the conditions we have introduced into the nuclei two, three and four atoms of bromine, whereas in another study now in progress in this Laboratory only two and three atoms of chlorine have been introduced into the rings. These halogenated naphthols have been oxidized to halogenated naphthoquinones, but none of them corresponds to the halogenated juglones.

The commercial raw material, the dihydroxynaphthalene, was purified by recrystallization from hot water. For bromination glacial acetic acid solutions were used for preparing the dibromo and tribromo derivatives. Iodine was used as a catalyst and a temperature of 80° was necessary in order to obtain the best yields. In order to introduce four atoms of bromine, a chloroform solution of the diacetate was necessary, a catalyst such as iodine and six moles of bromine.

We believe that the structures indicated in the charts are the correct ones

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[1] This paper is a portion of a thesis presented by David R. Ergle to the Faculty of the University of North Carolina in partial fulfilment of the requirements for the degree of Doctor of Philosophy in 1930.

[2] Wheeler and Scott, THIS JOURNAL, 41, 833 (1919).