[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Behavior of Piperonal Derivatives toward Bromination and Nitration[1]

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This work was done in an effort to obtain polybromo and polynitro compounds from piperonal for use in testing the effect of negative substituents in the formation of stereoisomeric benzaldoxime derivatives.[2]

Previously Orr, Robinson and Williams,[3] and later Parijs,[4] found that treatment of an acetic acid solution of piperonal with bromine gave a mixture of 6-bromopiperonal and 4,5-dibromocatechol methylene ether, which involved the replacement of the aldehyde group by halogen. When a sodium carbonate solution of piperonylic acid was treated with bromine water, only the dibromo ether was obtained.[5]

In the present work 6-bromopiperonal was treated with excess of bromine in the presence of aluminum bromide[6] at about 100°. When sodium acetate was present tetrabromocatechol methylene ether was isolated; in the absence of the acetate nearly all the ether was split to give tetrabromocatechol.[7] In both cases the aldehyde group was replaced by bromine.

Attempts were next made to protect the aldehyde group. The sodium bisulfite addition product[8] of piperonal and the corresponding 6-bromo compound gave, when brominated as indicated above, tetrabromocatechol methylene ether. When the diacetate was used[9] similar results were obtained.

Since 6-bromopiperonal could not be further brominated without loss of the aldehyde group, it was of interest to try to nitrate it. The product obtained by Fittig and Mielch[10] by the action of fuming nitric acid on 6-bromopiperonal, and recorded by Oelker[11] as a bromodinitropiperonal, was studied by Jones and Robinson,[12] who regarded it as a bromodinitrocatechol methylene ether, formed by the loss of the aldehyde group during nitration. Reduction of this product by stannous chloride and hydrochloric acid[13] caused the loss of bromine and gave a diamino

(1) From a portion of the thesis submitted by F. W. Oberst in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Iowa, 1930.

(2) Brady and Dunn, *J. Chem. Soc.*, **107**, 1858 (1915).

(3) Orr, Robinson and Williams, *ibid.*, **111**, 947 (1917).

(4) Parijs, *Rec. trav. chim.*, **49**, 28 (1930).

(5) Jones and Robinson, *J. Chem. Soc.*, **111**, 913 (1917).

(6) Prepared as directed by Bodroux [*Compt. rend.*, **126**, 1282 (1898)].

(7) Raiford and Howland, THIS JOURNAL, **53**, 1051 (1931).

(8) Raiford and Stoesser [*ibid.*, **50**, 2560 (1928)] used bisulfite to protect the aldehyde group in 2,5-dibromovanillin.

(9) Raiford and Lichty, *ibid.*, **52**, 4577 (1930).

(10) Fittig and Mielch, *Ann.*, **152**, 50 (1869).

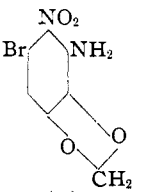
(11) Oelker, *Ber.*, **24**, 2594 (1891).

(12) Jones and Robinson, *J. Chem. Soc.*, **111**, 908, 919 (1917).

(13) Ref. 12, p. 927.

compound that the authors did not isolate but which was condensed immediately with phenanthrenequinone, thus indicating the ortho relations of the nitro groups[14] in the parent substance.

In the present work treatment of this bromodinitromethylene ether with ferrous hydroxide[15] gave the corresponding diamino compound without loss of bromine, and the product was isolated and characterized. When reduction was carried out with ammonium sulfide only one nitro radical was reduced to give an aminonitrobromo derivative which probably has the structure given (A). Support for this view was obtained by the behavior of the product when subjected to the indophenol test described by Autenrieth.[16]



(A)

A second point of interest was the study of other methods which it was hoped might give a bromonitropiperonal. Protection of the aldehyde radical, as indicated above for bromination, was unsuccessful. Treatment of the diacetate, and of the oxime of 6-bromopiperonal, respectively, with fuming nitric acid at 0° gave the bromodinitrocatechol methylene ether previously indicated, and when more dilute acid was used no reaction occurred. Parijs[17] found that treatment of an acetic anhydride solution of 6-bromopiperonal diacetate with "absolute nitric acid" split the methylene oxide ring and gave 6-bromoprotocatechuic aldehyde. Repetition of this experiment with fuming nitric acid, in the present work, caused loss of the aldehyde group, the opening of the methylene oxide ring and the formation of 3,4-dihydroxy-6-bromonitrobenzene. When nitric acid of lower concentration was used no reaction occurred.

The changes indicated above are shown in the accompanying diagram.

Experimental Part

Tetrabromocatechol Methylene Ether.—To 5 g. of 6-bromopiperonal in a 1-liter flask attached by a ground glass joint to a return condenser there was added an excess of bromine containing about 1% of aluminum bromide, and the mixture heated in an oil-bath at about 100° for three hours.[18] From the cold mixture free bromine was extracted by a concentrated solution of sodium bromide. Crystallization of the residue from alcohol, using norite, gave long colorless needles of m. p. 208–209°.

Anal. Calcd. for $C_7H_2O_2Br_4$: Br, 73.06. Found: Br, 73.00.

To the mother liquor from the above crystallization water was added, the resulting colorless precipitate extracted with caustic alkali solution, and the extract acidified. Repeated crystallization of the product first from acetic acid and then from a mixture

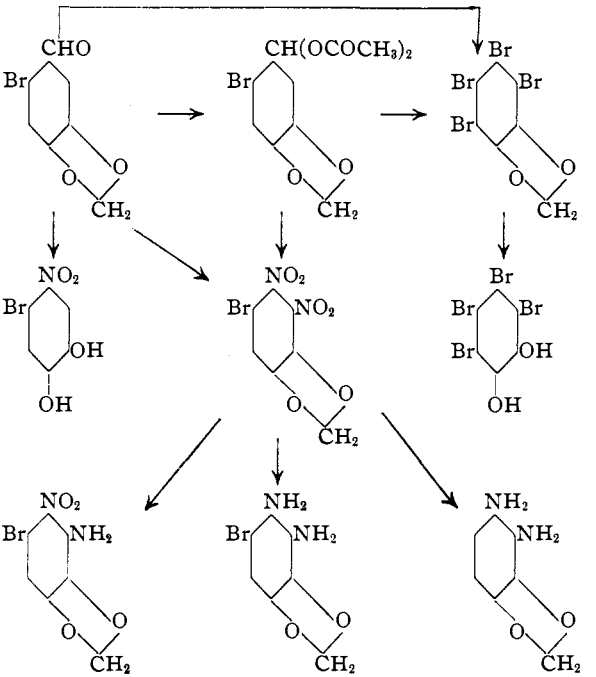
(14) This product is probably identical with that obtained by Herz [*Ber.*, **38**, 2859 (1905)] from methylenedioxynitroanthranilic acid. Here, also, the diamine was not isolated, but its solution was treated with phenanthrenequinone and the condensation product obtained.

(15) Pschorr and Sumuleanu, *ibid.*, **32**, 3410 (1899).

(16) Autenrieth, "Laboratory Manual for the Detection of Poisons and Powerful Drugs" (Warren, tr.), sixth ed., P. Blakiston's Son and Co., Philadelphia, 1928, p. 123.

(17) Parijs, Thesis, Leiden, 1928, p. 150; *Rec. trav. chim.*, **49**, 38 (1930).

(18) When a second portion was heated six hours the ether was split and only the catechol (see below) was isolated. With sodium acetate in the reaction mixture very little splitting occurred.



of benzene and ligroin gave colorless leaflets of tetrabromopyrocatechol; m. p. 190–191°;[19] yield, 37% of purified material.

Anal. Calcd. for $C_6H_2O_2Br_4$: Br, 75.12. Found: Br, 74.90.

The dibenzoyl derivative was obtained in colorless flakes from dilute alcohol; m. p. 197–198°.

Anal. Calcd. for $C_{20}H_{10}O_4Br_4$: Br, 50.47. Found: Br, 50.26.

3-Amino-4-nitro-5-bromocatechol Methylene Ether.—Hydrogen sulfide was bubbled slowly through a mixture of 10 g. of the required dinitro compound,[20] 25 cc. of water and 4 cc. of concentrated ammonia solution at about 60° for several hours while the mixture was shaken[21] continually. The yellow color of the starting material changed to deep reddish-orange. The product was purified repeatedly as follows. To its solution in hot alcohol, a little water was added, the mixture allowed to cool, the gummy deposit removed by filtration and rejected. Further dilution of the filtrate and long standing gave orange crystals. The yield of purified material was about 10%; m. p. 109–110°. When heated above this point the product exploded.

Anal. Calcd. for $C_7H_5O_4N_2Br$: Br, 30.65. Found: Br, 30.81.

A mixture of equal weights of the above-described amine and anhydrous sodium acetate was boiled for thirty minutes with excess of acetic anhydride, and the diacetyl derivative precipitated by adding water to the cold mixture; yield, 60%. Recrystallization from alcohol gave dull yellow plates; m. p. 146–147°. Strong light caused the product to become green and decompose.

(19) Stenhouse [*Ann.*, **177**, 187 (1875)] recorded 187° for this product prepared by action of bromine on protocatechuic acid.

(20) Obtained by the method used by Oelker [*Ber.*, **24**, 625 and 2593 (1891)] in preparing his supposed bromodinitropiperonal.

(21) Voorhees with Adams, THIS JOURNAL, **44**, 1403 (1922).

Anal. Calcd. for $C_{11}H_9O_6N_2Br$: Br, 23.18. Found: Br, 22.56.

Boiling the diacetyl derivative with a mixture of sodium carbonate and alcohol for an hour converted it into the monoacetyl compound, which separated on addition of water. Crystallization from alcohol gave nearly colorless flakes; m. p. 192–193°.

Anal. Calcd. for $C_9H_7O_5N_2Br$: Br, 26.40. Found: Br, 26.75.

When this product was boiled with acetic anhydride in the presence of sodium acetate it was converted back to the diacetate described above.

3,4-Diamino-5-bromocatechol Methylene Ether.—To a solution of 105 g. of ferrous sulfate in 400 cc. of hot water in a one-liter flask there was added 15 g. of the required dinitro compound, and then 100 cc. of concentrated ammonia water. The mixture was boiled for half an hour, filtered hot, and the filtrate allowed to stand. The crystals that separated were dissolved in hot benzene, boiled with norite, the mixture filtered and three volumes of low boiling ligroin added to the filtrate. A 25% yield of steel-gray plates was obtained; m. p. 89–90° with decomposition.

Anal. Calcd. $C_7H_7O_2N_2Br$: N, 12.12; Br, 34.63. Found: N, 11.96; Br, 34.60.

The dibenzoyldiamino derivative was obtained as colorless needles from alcohol; m. p. 255–256°.

Anal. Calcd. for $C_{21}H_{15}O_4N_2Br$: Br, 18.22. Found: Br, 17.70.

The tetraacetyldiamino derivative was prepared by boiling for fifteen minutes a mixture of equal weights of the amine and anhydrous sodium acetate with excess of acetic anhydride. Water was added to the cold mixture, the resulting liquid concentrated and allowed to crystallize. Recrystallization from dilute acetic acid, after decolorizing with norite, gave colorless flakes; m. p. 133–134°.

Anal. Calcd. for $C_{15}H_{15}O_6N_2Br$: Br, 20.05. Found: Br, 20.43.

3,4-Diaminocatechol Methylene Ether.—A mixture of 10 g. of the dinitrobromo compound, 30 g. of tin and 60 cc. of a 30% solution of concentrated hydrochloric acid in alcohol was heated for an hour under a reflux condenser, cooled, made alkaline with sodium hydroxide, and extracted with ether. Distillation of the ether left a residue that was dissolved in benzene, the solution boiled with norite, filtered, treated with two volumes of low boiling ligroin and allowed to cool. Repetition of this treatment gave 38% of brown solid; m. p. 100–101°.

Anal. Calcd. for $C_7H_8O_2N_2$: N, 18.42. Found: N, 18.43.

3,4-Dihydroxy-6-bromonitrobenzene.—A 50% yield of this product was obtained by treatment of an acetic anhydride solution of 6-bromopiperonal with red fuming nitric acid, sp. gr. 1.6, at 0°. Crystallization from toluene gave yellow needles; m. p. 162–163°.

Anal. Calcd. for $C_6H_4O_4NBr$: Br, 34.18. Found: Br, 34.28.

The diacetyl derivative, obtained in 89% yield, was crystallized in colorless flakes from dilute alcohol; m. p. 117–118°.

Anal. Calcd. for $C_{10}H_8O_6NBr$: Br, 25.15. Found: Br, 25.29.

Summary

Attempts to introduce a second bromine atom into 6-bromopiperonal causes replacement of the aldehyde group by halogen, and the hydrogen bromide formed may open the methylene oxide ring unless sodium acetate is present. Loss of the aldehyde radical could not be prevented by use of the diacetate or the bisulfite addition compound of the starting material. The products isolated were tetrabromocatechol methylene ether and tetrabromocatechol.

It has been shown that reduction of 3,4-dinitro-5-bromocatechol methylene ether may give an aminonitrobromo, a diaminobromo or a diamino compound containing no bromine, depending on conditions of reduction.

Nitration of an acetic anhydride solution of 6-bromopiperonal, as described, replaced the aldehyde radical by the nitro group, split the methylene oxide ring, and gave 3,4-dihydroxy-6-bromonitrobenzene.

Further work is in progress.

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The Influence of the Migrating Group in the Fries Isomerization

BY R. BALTZLY AND A. BASS

It has hitherto been supposed that the position taken up by the migrating group in the Fries isomerization was determined chiefly, if not entirely, by the structure of the phenol whose ester was used and by the temperature of the reaction mixture. Differences in the metallic halide used as catalyst, and in the solvent, have been considered to affect the speed and completeness of the reaction, but not its direction. That among the esters of normal, fatty acids the nature of the acyl group might be significant has, in fact, been denied by Rosenmund and Schnurr[1] in their work on the course and mechanism of this reaction. In his criticism of Rosenmund's conclusions, v. Auwers[2] did not attack this point. At the same time, Coulthard, Marshall and Pyman[3] have reported formation of *o*-hydroxy ketones of the *m*-cresol series under those conditions in which Rosenmund and Schnurr predicted and *reported formation* of the *para* compounds.

It was of some importance to us to be sure of the nature of the products, so we have carried out isomerizations in this series both at low temperature in nitrobenzene and at high temperature without solvent, and have found that with the esters of the higher fatty acids the same ketone was obtained under both sets of conditions. The products had the properties of *o*-hydroxy ketones and could be methylated and then oxidized to methoxyterephthalic acid.

The *m*-cresyl esters of the lower acids gave varying amounts of *p*-hydroxy ketone. Only in the case of the acetate could Rosenmund's results

(1) Rosenmund and Schnurr, *Ann.*, **460**, 56 (1926).

(2) v. Auwers and co-workers, *Ber.*, **61**, 416, 1495 (1928); **64**, 2216 (1931); *Ann.*, **460**, 240 (1928); **464**, 293 (1928); **483**, 44 (1930).

(3) Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930). It is to be noted here that these authors employ a system of numbering beginning at the methyl group in the cresol series, whereas we prefer to start with the hydroxyl. Consequently, our 6-butyryl-*m*-cresol is their 4-butyryl compound, and *vice versa*.