[CONTRIBUTION FROM THE COATES CHEMICAL LABORATORY OF LOUISIANA STATE UNIVERSITY]

The Bromo-2-nitrobenzoic Acids

BY J. L. E. ERICKSON, J. M. DECHARY AND T. R. PULLIG

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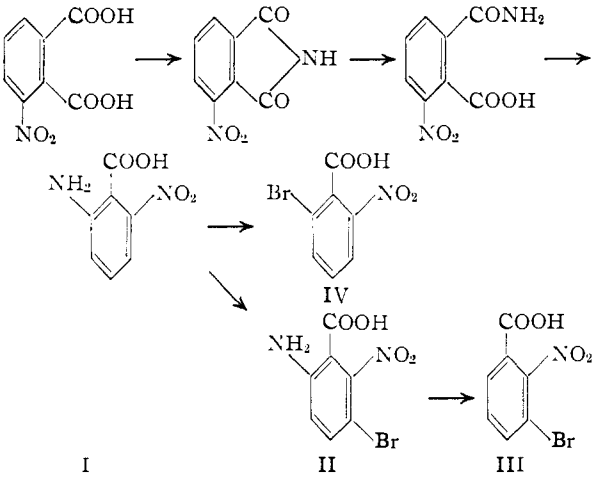
Synthetic methods of preparation for the four isomeric bromo-2-nitrobenzoic acids are described. 3-Bromo-2-nitrobenzoic acid was prepared by the deamination of a new compound, 5-bromo-6-nitroanthranilic acid. The synthesis of 4-bromo-2-nitrobenzoic acid was accomplished by the hydrolysis of 4-bromo-2-nitrobenzonitrile and also by the oxidation of 4-bromo-2-nitrotoluene. 5-Bromo-2-nitrobenzoic acid was prepared by the nitration of *m*-bromobenzoic acid, an old method. 6-Bromo-2-nitrobenzoic acid, a new compound, was obtained in excellent yield from 6-nitroanthranilic acid.

During the course of an investigation not reported here it became necessary to obtain considerable quantities of the four isomeric bromo-2-nitrobenzoic acids. A review of the literature revealed that only one of these acids, 5-bromo-2-nitrobenzoic acid, has been obtained in satisfactory yield. Insignificant quantities of two of them, 3-bromo- and 4-bromo-2-nitrobenzoic acid, have been prepared in very low or unspecified yield, and the remaining one, 6-bromo-2-nitrobenzoic acid, has not been reported at all.

3-Bromo-2-nitrobenzoic acid (III) has been obtained in small quantities by the neutral permanganate oxidation of a mixture of 3-bromo- and 4-bromo-2-nitrotoluene,[1] and an unspecified amount was prepared by the oxidation of pure 3-bromo-2-nitrotoluene.[2] From the nitration of *m*-bromobenzoic acid only 2.7% of III has been isolated,[3] although it has been shown by phase equilibrium studies[4] that 11.4% is present in the crude nitration product. Friedlander, *et al.*,[5] reported no yields, but described a more convenient method for the isolation of III. Using this procedure, we obtained III in a yield of only 3.7%, since the product of the reaction consisted mainly of 5-bromo-2-nitrobenzoic acid.

In the present work III and also 6-bromo-2-nitrobenzoic acid (IV) were prepared, however, in good yields and from the same readily available starting material. An attractive route to both III and IV was provided by 6-nitroanthranilic acid which was obtained by the following reaction sequence: The diammonium salt of 3-nitrophthalic acid was fused to eliminate water and ammonia, thus giving 3-nitrophthalimide. Upon treatment with aqueous potassium hydroxide, the imide was cleaved and 6-nitrophthalamic acid was obtained. The Hofmann rearrangement of 6-nitrophthalamic acid yielded 6-nitroanthranilic acid (I).[6] The over-all yield of I prepared from 3-nitrophthalic acid was about 40%, which seemed very satisfactory considering the number of reaction steps involved and the availability of the starting material.

Since no profitable direct method for the preparation of III has been reported, advantage was taken



of the *para*-orienting influence of the amino group in I on the position assumed by the incoming bromine substituent for the production of the intermediate (II). Thus, the conversion of II into III by the deamination reaction represents another application of this useful artifice to the synthesis of compounds difficult to obtain by straightforward methods.

The bromination of I in glacial acetic acid gave 72% of the new 5-bromo-6-nitroanthranilic acid (II), and when this was diazotized in hydrochloric acid and the diazonium salt treated with hypophosphorous acid, III was obtained in a yield of 54%.

6-Bromo-2-nitrobenzoic acid (IV) has not been described in the literature, although the corresponding chlorine compound is known.[7] Diazotization of I in hydrobromic acid followed by treatment of the diazonium salt with cuprous bromide gave a yield of 86% of IV.

4-Bromo-2-nitrobenzoic acid[8] has been obtained from 4-amino-2-nitrobenzoic acid by means of the Sandmeyer reaction, but the necessary amino acid is available with certainty only through a rather involved method of preparation.[9] The hydrolysis of 4-bromo-2-nitrobenzonitrile[10] has been reported to give satisfactory results, but the nitrile has been obtained only in very low yield (15%).

We have been able to simplify the synthesis of the nitrile by the direct bromination of *o*-nitroani-

(1) H. Burton, F. Hammond and J. Kenner, *J. Chem. Soc.*, 1804 (1926).

(2) L. A. Elson, C. S. Gibson and J. D. A. Johnson, *ibid.*, 2741 (1929).

(3) H. Hubner, J. Ohly and O. Philipp, *Ann.*, **143**, 239 (1867); H. Hubner and A. Petermann, *ibid.*, **149**, 132 (1869).

(4) A. F. Holleman, *Rec. trav. chim.*, **20**, 225 (1901).

(5) P. Friedlander, S. Bruckner and G. Deutsch, *Ann.*, **388**, 33 (1912).

(6) (a) R. Kahn, *Ber.*, **35**, 471, 3857 (1902); (b) M. T. Bogert and V. J. Chambers, THIS JOURNAL, **27**, 652 (1905).

(7) J. B. Cohen and D. McCandlish, *J. Chem. Soc.*, **87**, 1271 (1905); V. Meyer, *Ber.*, **28**, 182 (1895).

(8) L. Ettinger and P. Friedlander, *ibid.*, **45**, 2079 (1912).

(9) J. J. Blanksma and D. Hoegen, *Rec. trav. chim.*, **65**, 333 (1946).

(10) J. Frejka and F. Vymetal, *Collection Czechoslov. Chem. Communs.*, **7**, 440 (1935); A. Claus and W. Scheulen, *J. prakt. Chem.*, **43**, 203 (1891).

line in glacial acetic acid to yield 4-bromo-2-nitroaniline. The latter was diazotized in sulfuric acid and converted in good yield (66%) into 4-bromo-2-nitrobenzonitrile which readily gave, upon hydrolysis, 4-bromo-2-nitrobenzoic acid.

An alternate method of preparation of 4-bromo-2-nitrobenzoic acid, the permanganate oxidation of 4-bromo-2-nitrotoluene, gave good results.

Experimental[11]

5-Bromo-6-nitroanthranilic Acid (II).—The bromination of 6-nitroanthranilic acid (I),[6] prepared from 6-nitrophthalamic acid,[6a,12] was accomplished by adding dropwise, and with vigorous stirring, 38.4 g. (0.24 mole) of bromine in 100 ml. of glacial acetic acid to 43.7 g. (0.24 mole) of finely powdered amino acid (I) in 600 ml. of glacial acetic acid at 15–20°. The addition of 34 g. (0.25 mole) of sodium acetate trihydrate in 50 ml. of water resulted in the formation of a clear solution which was added with constant stirring to 2,000 ml. of water and 500 g. of ice and gave 36.0 g. of a yellow precipitate, m.p. 198–201°. The mother liquor yielded 9.2 g. of product, m.p. 195–197°, thus making a total of 45.2 g. (72%) of crude product. Crystallization from alcohol and then from 50% aqueous acetic acid gave 41.8 g. (67%) of bright yellow needles, m.p. 201.5–202.5°.

Anal. Calcd. for $C_7H_5BrN_2O_4$: C, 32.21; H, 1.93; Br, 30.61; N, 10.73. Found: C, 32.21; H, 2.48; Br, 30.75; N, 10.68.

3-Bromo-2-nitrobenzoic Acid (III).—The nitration of *m*-bromobenzoic acid was carried out essentially by the method of Friedlander, *et al.*[5] From 100 g. of *m*-bromobenzoic acid there were obtained 4.5 g. of III, m.p. 247.5–249.5°, and 93.5 g. of 5-bromo-2-nitrobenzoic acid, m.p. 138–140°. For larger quantities of III, **the deamination of II** is recommended as a superior method of preparation. A mixture of 41.8 g. (0.16 mole) of finely powdered II, 130 ml. of hydrochloric acid (sp. gr. 1.18) and 85 ml. of water was stirred for 4 hours. The resulting yellow precipitate of amine hydrochloride was cooled to 0°, and 11.0 g. (0.16 mole) of sodium nitrite in 85 ml. of cold water was added with stirring over a period of 40 minutes. The light yellow precipitate of the diazonium salt gave a brisk evolution of nitrogen when treated with 420 ml. of 30% hypophosphorous acid (precooled to 0°). After stirring for 24 hours the precipitate was separated by filtration, washed with cold water, and recrystallized from dilute methyl alcohol (decolorizing charcoal), giving 21.5 g. (54%) of fine, white needles, m.p. 247.5–249.5°. When III was mixed with a sample obtained by the nitration of *m*-bromobenzoic acid, the m.p. was unchanged.

6-Bromo-2-nitrobenzoic Acid (IV).—In a 500-ml. three-necked flask equipped with stirrer, dropping funnel and thermometer were placed 18.2 g. (0.10 mole) of 6-nitroanthranilic acid (I), 58 ml. (0.50 mole) of 48% hydrobromic acid and 150 ml. of water. The mixture was stirred at 65–70° for a few minutes to dissolve all of the solid material. The deep orange solution was chilled to −5° and stirred rapidly to obtain the hydrobromide as a fine, yellow precipitate. A cold solution of 6.9 g. (0.10 mole) of sodium nitrite in 40 ml. of water was added to the hydrobromide over a period of 30 minutes, and the thin, yellow suspension of the diazonium salt was stirred at −5° for 40 minutes longer. The suspension was then added over a period of 15 minutes to 45 ml. of a stirred, 48% hydrobromic acid solution of cuprous bromide, prepared by treatment of a solution of 31.4 g. of cupric sulfate pentahydrate in 110 ml. of hot water with 15.4 g. of sodium bromide and subsequent reduction of the cupric bromide formed with 6.8 g. of sodium bisulfite dissolved in 45 ml. of hot, 10% sodium hydroxide solution. Stirring was continued at 50–60° for 2 hours, and the light tan precipitate of the crude acid was collected, washed with 50 ml. of cold 10% hydrobromic acid followed by 50 ml. of water, and dissolved in 100 ml. of 7% potassium hydroxide. Concentrated hydrochloric acid was added dropwise until a small quantity (1.8 g.) of a reddish precipitate formed, which was filtered off and not further examined. The addition of an excess of hydrochloric acid to the filtrate gave 21.2 g. (86%) of pale yellow needles, m.p. 177–177.5°. Recrystallization from very dilute methyl alcohol (charcoal) gave large, white needles, m.p. 177.3–177.5°.

Anal. Calcd. for $C_7H_4BrNO_4$: C, 34.17; H, 1.64; Br, 32.48; N, 5.59. Found: C, 34.44; H, 1.82; Br, 32.27; N, 5.55.

4-Bromo-2-nitroaniline[13] is usually prepared by the hydrolysis of 4-bromo-2-nitroacetanilide which is obtained from *p*-bromoacetanilide. The direct bromination of *o*-nitroaniline, however, affords a more convenient method of preparation of this compound. A solution of 80 g. (0.50 mole) of bromine in 75 ml. of glacial acetic acid was added dropwise over a period of 2 hours to a chilled (10°), vigorously stirred solution of 69 g. (0.50 mole) of *o*-nitroaniline in 600 ml. of glacial acetic acid. The ammonium salt was collected by filtration, washed with 200 ml. of glacial acetic acid, and hydrolyzed by stirring with 1000 ml. of cold water. The free amine was collected and, when crystallized from methyl alcohol, gave 84 g. (77%) of deep orange needles, m.p. 111–112°. The addition of the combined acetic acid filtrate and washings to 3.5 l. of cold water gave a precipitate of 9.0 g. of 4,6-dibromo-2-nitroaniline. Upon recrystallization from methyl alcohol, bright yellow needles, m.p. 127–128°, were obtained.

4-Bromo-2-nitrobenzonitrile.—A solution prepared by shaking 78 g. (0.36 mole) of 4-bromo-2-nitroaniline with 144 g. (1.44 moles) of 98% sulfuric acid was added very slowly to 800 ml. of water, which was very vigorously stirred and maintained at 2°. To the resulting finely divided, yellow precipitate was added over a period of one hour 25.5 g. (0.37 mole) of sodium nitrite dissolved in 200 ml. of cold water, and the mixture was stirred at 5° for one hour or until a clear, light yellow solution of the diazonium salt was obtained. The cold solution (5°) was added rapidly in 100-ml. portions to a hot, well-stirred solution (70°) of cuprous cyanide, freshly prepared in a 5-l. flask from 200 g. of cupric sulfate pentahydrate in 600 ml. of hot water and 225 g. of 95% potassium cyanide in 400 ml. of water. The addition of each portion resulted in a brisk evolution of nitrogen and the formation of a light brown solid, which was collected and extracted with methyl alcohol. The alcohol extract yielded 54.0 g. (66%) of nitrile, tan crystals, m.p. 91–93°. Recrystallization from dilute methyl alcohol (charcoal) gave colorless needles, m.p. 99°.

4-Bromo-2-nitrobenzoic Acid.—The hydrolysis of 4-bromo-2-nitrobenzonitrile was accomplished by heating a mixture of 30 g. (0.132 mole) of the nitrile, 108 g. of concentrated sulfuric acid and 48 g. of water at 180° for 1.5 hours. The resulting solution was poured into a mixture of ice and water and gave a precipitate, which was collected and added to a 10% solution of sodium hydroxide. The alkaline solution was filtered from unchanged nitrile and carefully brought to neutralization with concentrated hydrochloric acid. A small quantity (2.0 g.) of dark colored, solid impurities was removed from the solution by filtration, and the addition of an excess of hydrochloric acid to the clear filtrate gave 24.0 g. (74%) of 4-bromo-2-nitrobenzoic acid, m.p. 163–164°. The compound is extremely soluble in methyl alcohol, easily soluble in hot water, and is best crystallized from 10 parts of hot benzene, from which it separates as colorless, stout needles, m.p. 164–165°.

A second method of preparation of 4-bromo-2-nitrobenzoic acid, **the oxidation of 4-bromo-2-nitrotoluene**, gave satisfactory results. In a 500-ml. three-necked flask, fitted with a condenser and thermometer, were placed 21.6 g. (0.10 mole) of 4-bromo-2-nitrotoluene,[14] 180 ml. of pyridine and 140 ml. of water. The solution was heated on an oil-bath under slow reflux while 47.4 g. (0.30 mole) of potassium permanganate was added in small portions over a period of 8 hours. A sufficient quantity of alcohol was added to reduce excess permanganate. The hot mixture was filtered; the filtrate was evaporated to a small volume and treated with 50 ml. of 10% sodium hydroxide solution and then extracted with ether. The ethereal extract

(11) All melting points are uncorrected.

(12) C. M. Moser and T. Gompf, *J. Org. Chem.*, **15**, 583 (1950), described this compound as 3-nitrophthalamic acid. *Cf.* E. Chapman and H. Stephen, *J. Chem. Soc.*, **127**, 1792 (1925).

(13) We are indebted to Mr. M. J. Mitchell of this Laboratory for his assistance in the preparation of this compound.

(14) Prepared essentially by the method of W. Rottig, *J. prakt. Chem.*, **142**, 35 (1935).

yielded 10.2 g. of unchanged 4-bromo-2-nitrotoluene. Addition of an excess of hydrochloric acid to the aqueous alkaline solution gave 10.1 g. (41%) of a crystalline precipitate of 4-bromo-2-nitrobenzoic acid, which was recrystallized from benzene and melted at 163.5–165°.

BATON ROUGE 3, LOUISIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Reactions of Hindered α-Bromo- and Hydroxysuccinic Acids[1a,b]

BY WYMAN R. VAUGHAN AND KIRBY M. MILTON[1c]

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A number of dibenzo[2,2,2]bicycloöctadiene-2,3-dicarboxylic acids have been prepared and their reactions have been studied. The preparation of one such compound involves a well-defined *trans* addition of hydrogen bromide to the olefinic double bond of dibenzo[2,2,2]bicycloöctatriene-2,3-dicarboxylic acid. The resulting product in alkali undergoes, *inter alia*, *cis* elimination of bromide with the carboxyl beta to it thus suggesting that care must be used in invoking this reaction to establish structural geometry. The steric disposition of groups about the bromine and hydroxyl of the adducts is such as to inhibit completely intermolecular nucleophilic displacements, in place of which a number of anomalous reactions are observed. Infrared spectra for the adducts and their derivatives are given.

The observation that 2-bromodibenzo[2,2,2]-bicycloöctadiene - 2,3 - *cis* - dicarboxylic anhydride (*cis* - 9,10 - dihydroanthracene - 9,10 - *endo* - α-bromo - α,β-succinic anhydride) (IA) affords 2-hydroxydibenzo[2,2,2]bicycloöctadiene - *trans* 2,3 - dicarboxylic acid (*trans*-9,10-dihydroanthracene-9,10-*endo*-α-hydroxy-α,β-succinic acid) (IVB) led the investigators[2] to suggest that such substances might well prove excellent for study of the Walden inversion.

It seemed to the present authors, however, that such compounds would be still better suited for study of the reactions of hindered halides and alcohols since the substituents on C^{α} (C^2) are almost as inaccessible to external nucleophilic displacement as in apocamphyl chloride and apocamphanol.[3] Striking dissimilarities between the latter substances and those under investigation include the possibility of structural inversion owing to the absence of the complete "cage" and the presence of adjacent polar groups capable of participating in nucleophilic reactions. Hence the possibility of observing other than simple S_N2 reactions was anticipated.

Accordingly the preparation of a number of related substances was carried out, either by the addition of anthracene to the appropriate dienophile, or by subsequent reaction of the resulting adducts with the proper reagents. The *cis* and *trans* structures of the key compounds are illustrated by Figs. 1 and 2, respectively, and Table I lists the principal substances studied.

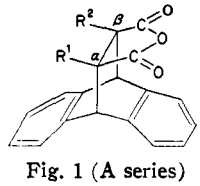

Fig. 1 (A series)

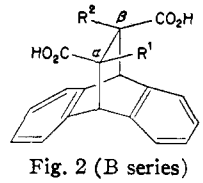

Fig. 2 (B series)

TABLE I

Compound	*cis*-Anhydride R¹	*cis*-Anhydride R²	Compound	*trans*-Acid R¹	*trans*-Acid R²
IA[2]	Br	H	IB	Br	H
IIA	Br	CH_3	IVB	OH[2]	H
IIIA	OH	CH_3	IIIB	OH	CH_3

In addition the anthracene adducts of propiolic, tetrolic and acetylenedicarboxylic acids were prepared and characterized (Fig. 3).

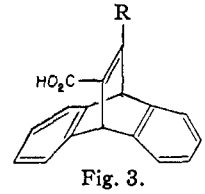

Fig. 3.

V, R = H VII, R = CO_2H
VI, R = CH_3

Normal Reactions: The Bromoanhydrides

Examination of Stuart models of compounds IA and IIA reveals that the β-carboxyl is favorably situated for nucleophilic displacement of the α-bromine. Thus the previously reported[2] reaction: IA → IVB, and the presently reported reaction: IIA → IIIB, follow the usual course of behavior for β-haloacids[4]: after opening of the anhydride the β-carboxylate ion attacks the rearside of C^{α} displacing bromide ion, and the β-lactone thus produced does not survive but is cleaved by hydroxide which attacks the β-carbonyl carbon.[5] The resulting indirect inversion on C^{α} is in accord with the observations of others,[6] and the resemblance to the normal behavior of β-haloacids is strengthened by the concurrent production[6] of the olefinic compounds V and VI (Fig. 3) from IA and IIA (Fig. 1), respectively, by the simultaneous *trans* elimination of bromide ion and carbon dioxide. The structures of the unsaturated acids were established by comparison with independently synthesized V and VI.

(1) (a) Abstracted from the Ph.D. dissertation of Kirby M. Milton, University of Michigan, 1951. (b) Presented before the Division of Organic Chemistry at the 119th Meeting of the American Chemical Society at Boston, Massachusetts, April 5, 1951. (c) Abbott Laboratories Fellow, 1949–1950.

(2) W. E. Bachmann and L. B. Scott, THIS JOURNAL, **70**, 1458 (1948).

(3) P. D. Bartlett and L. H. Knox, *ibid.*, **61**, 3184 (1939).

(4) H. Johansson and S. M. Hagman, *Ber.*, **55**, 647 (1922).

(5) T. L. Gresham, J. E. Jansen and F. W. Shaver, THIS JOURNAL, **70**, 998 (1948).

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