[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Hydrogen Bromide–Acetic Acid Demethylation of 2,3-Dimethoxy-6-bromobenzoic Acid. An Example of Concomitant Bromine Migration[1,2]

GEORGE R. PETTIT AND DAVID M. PIATAK

Received November 12, 1959

Demethylation of 2,3-dimethoxy-6-bromobenzoic acid in hydrogen bromide–acetic acid solution was shown to yield 2,3-dihydroxy-5-bromobenzoic acid. Under similar conditions, 3,4-dimethoxy-6-bromonitrobenzene was found to yield substantial amounts of the unrearranged product of demethylation, 3,4-dihydroxy-6-bromonitrobenzene, accompanied by 3,4-dihydroxynitrobenzene. The structural and environmental features which appear to influence halogen migration in the bromohydroxybenzoic series are summarized.

Although rearrangement reactions involving migration of a bromine atom are encountered infrequently, a number of well documented examples are now known.[3] An early instance of this type of reaction involved rearrangement of 2,6-dibromo-*N*-nitroaniline to 2-nitro-4,6-dibromoaniline in hydrochloric acid solution.[3a] Several years later, Sen[3b] described the conversion of 2-bromo-5-hydroxytoluene to 2,4-dinitro-5-hydroxy-6-bromotoluene with nitric acid, while treatment of *p*-bromoaniline with 48% hydrobromic acid at 150° was found to afford aniline and 2,4-dibromoaniline.[3c] Both hydrochloric and hydrobromic acids were found capable of transforming 5-bromo-6-methoxy-8-aminoquinoline to 6-methoxy-7-bromo-8-aminoquinoline.[3d] Recently, Tomita and Kugo[3h] reported the results of demethylation studies with 3,4-dimethoxy-6-bromobenzoic acid, (Ia) and its diethoxy (Ib) derivative. When the reaction was carried out with hydrogen bromide in glacial acetic acid at 120–125°, the product in each case was shown to be 3,4-dihydroxy-5-bromobenzoic acid (II). In a subsequent series of experiments, Tomita and collaborators[3i-k] obtained the same product (II) employing 2-bromo-3,4-dimethoxybenzoic acid (III). Further, 3-methoxy-6-bromobenzoic acid was found to yield 3-hydroxy-4-bromobenzoic acid. Analogous results were realized employing 48% hydrobromic acid as solvent. However, the use of hydriodic acid, hydrochloric acid, hydrogen chloride in glacial acetic acid, or anhydrous aluminum chloride led to either partial or complete demethylation without effecting a rearrangement. Substitution of chlorine for the bromine substituent, or an aldehyde, acetyl, or methyl group for the carboxylic acid moiety of Ia also prevented halogen migration. Rearrangement of the bromine substituent was again not observed when either 2-bromo-4-methoxy- or 3-bromo-4-methoxybenzoic acid was subjected to demethylation in hydrogen bromide–acetic acid solution.

The interesting work of Tomita and coworkers[3h-k] suggested that the following minimum requirements must be met before halogen migration can be expected to occur in the bromohydroxybenzoic acid series: (1) a bromine atom must be suitably situated *ortho* to a carboxylic acid group and either *ortho* or *para* to a potential hydroxy substituent, (2) the bromine atom must occupy a position in the original molecule that would not be favored by simple bromination of the corresponding phenol derivative, and (3) a source of bromide ion must be available.

As part of a study concerned with the synthesis of certain catechol derivatives, it was of interest to test the reliability of these criteria as a basis for predicting related bromine rearrangements. Hydrogen bromide–acetic acid demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV) was first selected as a model experiment, since all requirements for concurrent bromine migration seemed to be satisfied.

A synthesis of the required bromobenzoic acid (IV) from 2,3-dimethoxybenzaldehyde *via* the 6-nitrobenzoic acid derivative (V) was reported by

(1) Abstracted in part from the Master of Science thesis submitted by D. M. Piatak to the Graduate School, University of Maine, August 1959.

(2) This study was supported in part by the Upjohn Company, Kalamazoo, Mich., and aided by a grant from the American Cancer Society.

(3) For example, consult (a) K. J. P. Orton and C. Pearson, *J. Chem. Soc.*, 725 (1908); (b) A. B. Sen, *Proc. Natl. Acad. Sci. India*, **9**, 89 (1939) (*Chem. Abstr.*, **35**, 1038 (1941)); (c) R. Baltzly and J. S. Buck, *J. Am. Chem. Soc.*, **63**, 1757 (1941); (d) W. M. Lauer, C. T. Claus, R. W. von Korff, and S. A. Sundet, *J. Am. Chem. Soc.*, **74**, 2080 (1952); (e) M. Kohn, *J. Org. Chem.*, **18**, 530 (1953); (f) B. G. Gavrilov and N. A. Mal'tseva, *Uchenye Zapiski Leningrad Gosudarst Univ. im. A. A. Zhdanova No. 169, Ser. Khim. Nauk*, No. **13**, 203 (1953) (*Chem. Abstr.*, **49**, 14658 (1955)); (g) E. Fujita, T. Kitamura, and R. Hirano, *Yahugaku Zasshi*, **77**, 747 (1957) (*Chem. Abstr.*, **51**, 17916 (1957)); (h) M. Tomita and T. Kugo, *Yahugaku Zasshi*, **75**, 1354 (1955) (*Chem. Abstr.*, **50**, 10052 (1956)); (i) M. Tomita, Y. Kondo, and S. Tanaka, *Yahugaku Zasshi*, **76**, 1119 (1956) (*Chem. Abstr.*, **51**, 3505 (1957)); (j) M. Tomita, Kura, and S. Tanaka, *Yahugaku Zasshi*, **76**, 1122 (1956) (*Chem. Abstr.*, **51**, 3505 (1957)); (k) M. Tomita and K. Fujitani, *Yahugaku Zasshi*, **76**, 1126 (1956) (*Chem. Abstr.*, **51**, 3506 (1957)); (l) M. Martin-Smith and M. Gates, *J. Am. Chem. Soc.*, **78**, 5351 (1956); and (m) H. L. Goering and L. L. Sims, *J. Am. Chem. Soc.*, **79**, 6270 (1957).

Sugasawa[4] in 1933 although the acid (IV) was found to be an oil and only its crystalline anilide derivative was characterized. In our hands, this reaction sequence again gave an oily product which resisted crystallization. However, saponification followed by methylation of the product (VI) derived from the bromination of methyl-2-acetoxy-3-methoxybenzoate (VII)[5] led to a crystalline acid melting at 87–89°. The anilide derivative (m.p. 140.5–141.5°) was found to be identical with the specimen prepared by way of intermediate V, thus establishing the fact that bromination of the ester (VII) affords a 6-bromo derivative.[6] The latter route was most convenient for preparative purposes and subsequent experimental work was carried out with crystalline 2,3-dimethoxy-6-bromobenzoic acid (IV) prepared by this procedure.

The reaction between hydrogen bromide and the acid (IV) in glacial acetic acid at *ca.* 140° was found to yield a bromophenol melting at 222–223°. However, the expected product of demethylation and bromine migration, 2,3-dihydroxy-5-bromobenzoic acid, was reported to melt at 215°.[7] The product (m.p. 222–223°) was easily distinguishable from an authentic sample of the 6-bromo (IX, m.p. 182–185°) isomer prepared by aluminum chloride demethylation of 2-hydroxy-3-methoxy-6-bromobenzoic acid (VI). Since rigorous structural evidence had never been provided to support the 5-bromo (VIIIa)[7] formulation, it could not be temporarily excluded in favor of the unknown 4-bromo isomer. For this reason, a sample assumed to be the 5-bromophenol (VIIIa) was prepared as described by von Hemmelmayr.[7] The product (VIIIa), m.p. 222–224° was identical with the bromophenol (m.p. 222–223°) isolated from the demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV). In order either to eliminate or establish the 5-bromo (VIIIa) representation for the demethylation product, von Hemmelmayr's isomer[7] (VIIIa) was remethylated with dimethyl sulfate and the product was compared with an authentic specimen of 2,3-dimethoxy-5-bromobenzoic acid (VIIIb) obtained by silver oxide oxidation of the corresponding aldehyde X.[8] The two substances were found to be identical. Consequently, hydrogen bromide–acetic acid demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV) yields 2,3-dihydroxy-5-bromobenzoic acid (VIIIa), the predicted product of concomitant bromine migration.

The apparent dependence of bromine migration upon the presence of an *ortho* carboxylic acid group prompted an experiment directed at further defining the role of the acid substituent. Treatment of 3,4-dimethoxy-6-bromonitrobenzene (XI) with hot hydrogen bromide–acetic acid was chosen for this purpose. Nitration[9] of 4-bromoveratrole[10] (XII) provided a practical route to the nitro compound XI.

The reaction between 3,4-dimethoxy-6-bromonitrobenzene (XI) and hydrogen bromide–acetic acid at approximately 140° afforded 3,4-dihydroxy-6-bromonitrobenzene (XIIIa) in 30–35% yields accompanied by a small quantity of 3,4-dihydroxynitrobenzene (XIVa). The bromophenol XIIIa could be isolated from the initial reaction products; however, the dehalogenated phenol XIVa was only detected after partial chromatographic separation of the acetylated (acetic anhydride–pyridine) reaction mixture. A cursory examination of the remaining complex mixture of acetates did not reveal the presence of the predictable product of bromine migration, 3-bromo-4,5-dihydroxynitrobenzene,[11] prepared by bromination of 4-nitrocatechol (XIVa).[12]

Bromination of catechol acetonide (XV) with *N*-bromosuccinimide followed by nitration of the resulting 4-bromo derivative XVI gave 3,4-(dimethylmethylenedioxy) - 6 - bromonitrobenzene (XVII). Acid hydrolysis of the acetonide (XVII) provided an authentic specimen of the bromophenol XIIIa[13] arising from simple demethylation of 3,4-dimethoxy-6-bromonitrobenzene (XI). In both cases the bromophenol XIIIa was characterized as the diacetate XIIIb.

The present study augments the possibility of employing the guides suggested above as a basis for determining the predisposition of certain bromohydroxybenzoic acids toward halogen migration. Additional work will be necessary before a reasonable delineation of the mechanism can be presented.

---

(4) S. Sugasawa, *J. Chem. Soc.*, 1621 (1933).

(5) C. Weizmann and L. Haskelberg, *J. Org. Chem.*, **9**, 121 (1944).

(6) The structure of 2,3-dimethoxy-6-nitrobenzoic acid (V) rests with the ready conversion of 2,3-dimethoxy-6-nitrobenzaldehyde to an indigotin: W. H. Perkins, Jr., R. Robinson, and F. W. Stoyle, *J. Chem. Soc.*, 2355 (1924).

(7) F. von Hemmelmayr, *Montash.*, **33**, 971 (1913), prepared the 5-bromo (VIIIa) isomer by bromination of 2,3-dihydroxybenzoic acid.

(8) The bromodimethoxy acid VIIIb has been related to 2,3-dimethoxy-5-nitrobenzoic acid by L. Rubenstein, *J. Chem. Soc.*, 648 (1926), and structural evidence for the latter substance has been provided beyond doubt since decarboxylation yields 3,4-dimethoxynitrobenzene: J. C. Cain and J. L. Simonsen, *J. Chem. Soc.*, 156 (1914).

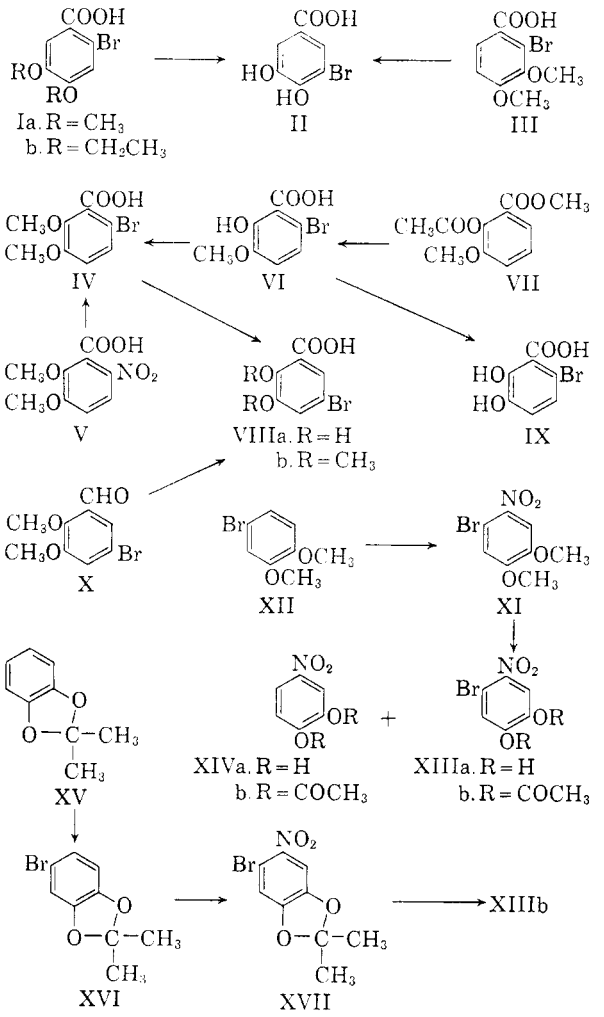
(9) A. Gaspari, *Accad. die Lincei Rend.*, **5**, I, 396 (1896) (*Chem. Zentr.*, **67**, (2) 154 (1896)).

(10) R. A. B. Bannard and G. Latremouille, *Can. J. Chem.*, **31**, 469 (1953).

(11) H. Cousin, *Ann. Chim. Phys.*, (7) **13**, 480 (1898).

(12) D. H. Rosenblatt, J. Epstein, and M. Levitch, *J. Am. Chem. Soc.*, **75**, 3277 (1953). After the present investigation was concluded K. Quelet and A. A. Ezz, *Bull. soc. chim. France*, 349 (1959), reported the hydrobromic acid demethylation of 3,4-dimethoxy-6-chloronitrobenzene. Only the product of demethylation, 3,4-dihydroxy-6-chloronitrobenzene, was isolated.

(13) R. G. Slooff, *Rec. trav. Chim.*, **54**, 995 (1935).



EXPERIMENTAL[14]

2,3-Dimethoxy-6-bromobenzoic acid (IV). *Procedure A.* Hydrogenation (3 atm.) of 2,3-dimethoxy-6-nitrobenzoic acid[6] (V, 1.5 g.) was carried out in ethanol (20 ml.) solution containing 3 drops of 48% hydrobromic acid with 75 mg. of 10% palladium-charcoal catalyst over a 1.75-hr. period. The mixture was filtered through Celite and treated with ethereal hydrogen bromide before removing the solvent *in vacuo*. A solution of the residue in 30 ml. of water was cooled to 5° and then allowed to react with sodium nitrite (0.55 g.) in 2 ml. of water. After allowing the diazotization mixture to remain at 5° an additional 45 min., a mixture containing copper (I) bromide, prepared from copper (II) sulfate (1.0 g.), 0.65 g. of copper powder, sodium bromide (2.6 g.), and 1 g. of sulfuric acid, was added. The resulting reaction mixture was stored at room temperature overnight before extraction with ether. The residue obtained by removing the solvent *in vacuo* was dissolved in chloroform and chromatographed on silica gel.[15] Seven fractions were eluted with the same solvent (160 ml. total). In each case, evaporation of solvent gave a dark colored oil which resisted crystallization; total yield 0.766 g. (44.7%). The chromatographic procedure was repeated and eight fractions were eluted with chloroform (85 ml. total). Evaporation of solvent from each fraction again gave oily residues; total weight 0.669 (38.8%). The latter three fractions (6–8, 0.204 g.) were combined and converted to the corresponding anilide derivative (thionyl chloride followed by aniline) which melted at 139–141°[16] (lit.,[4] m.p. 135–137°) after recrystallization from ethyl acetate–petroleum ether (b.p. 60–90°).

Procedure B. To 0.5 g. (0.002 mole) of 2-hydroxy-3-methoxy-6-bromobenzoic acid[5] and sodium hydroxide (0.2 g., 0.005 mole) dissolved in 50 ml. of water was added 0.5 ml. (0.0054 mole) of dimethyl sulfate. At the conclusion of a 2-hr. period at reflux, the *p*H was adjusted to 11 with sodium hydroxide. Heating at reflux was continued an additional 2 hr. After cooling, the solution was acidified with hydrochloric acid and extracted with ether. Removal of solvent from the dry (magnesium sulfate) ethereal extract gave 0.5 g. (97.6%) of oily product which was partially purified by chromatography on silica gel.[16] Elution with chloroform (80 ml.) yielded 0.45 g. (85.1%) of colorless oil which crystallized after drying (*in vacuo*). Repeated recrystallization from benzene–petroleum ether (b.p. 30–60°) gave pure material melting at 87–89°,[16] ν_{max}^{KBr} 1708 cm.$^{-1}$

Anal. Calcd. for $C_9H_9BrO_4$: C, 41.40; H, 3.47; Br, 30.61. Found: C, 41.11; H, 3.42; Br, 31.12.

The anilide derivative, prepared as described in procedure A, was found to melt at 140.5–141.5°[16] after recrystallization from ethyl acetate–petroleum ether (b.p. 60–90°). Mixture melting point and infrared comparison (chloroform solution) of the anilide derivative with an authentic sample of 2,3-dimethoxy-6-bromobenzanilide (Procedure A) substantiated the assignment of structure IV to the crystalline acid (m.p. 87–89°).

Hydrogen-bromide–acetic acid demethylation of 2,3-dimethoxy-6-bromobenzoic acid (IV). A Pyrex glass tube containing 2,3-dimethoxy-6-bromobenzoic acid (0.93 g.) and 5 ml. of 41% hydrogen bromide–glacial acetic acid (sealed after adding the reactants at ice-salt temperature), was heated to 130° during 1.6 hr. and at 130–142° an additional 65 min. The tube was then cooled (45 min.), opened and the red-colored solution concentrated to dryness (*in vacuo*). The residue, m.p. 180–222° dec., recrystallized from methanol-chloroform as tan colored crystals; weight, 0.08 g. (9.6%), m.p. 190–210° (fraction A). Removal of solvent from the mother liquors and extraction of the residue with warm chloroform left a second fraction (B), 0.15 g. (18.1%), m.p. 219–222°. Evaporation of the chloroform extracts gave a third fraction (C); yield, 0.57 g. (68.7%), m.p. 194–203°. Recrystallization of fraction B from methanol-water afforded colorless crystals melting at 222–223° dec.,[16] ν_{max}^{KBr} 1665 cm.$^{-1}$

Anal. Calcd. for $C_7H_5BrO_4$: C, 36.07; H, 2.16; Br, 34.30. Found: C, 36.46; H, 2.23; Br, 33.86.

An infrared spectral study of the three crude fractions (A–C) indicated that only a small quantity of impurity existed. This observation was strengthened by further purification of fraction C, since recrystallization from water (Norit A) gave additional pure quantities of the product isolated from fraction B.

The product melting at 222–223° dec. was found to be identical with an authentic sample of *2,3-dihydroxy-5-bromobenzoic acid* (VIIIa)[7] by infrared comparison (tetrahydrofuran solution) and mixture melting-point determination.

Aluminum chloride demethylation of 2-hydroxy-3-methoxy-6-bromobenzoic acid (VI). A mixture of 2-hydroxy-3-methoxy-6-bromobenzoic acid (1.0 g.), anhydrous aluminum chloride (12.3 g.) and 80 ml. of dry benzene was heated at reflux during a 6-hr. period. An additional 7.5 g. of anhydrous aluminum chloride was added after 4 hr. at reflux and the reaction mixture cooled (ice bath) and cautiously treated with hydrochloric acid (50 ml.) and water (35 ml.). Extrac-

(14) Melting points are uncorrected and were observed employing a Fisher-Johns apparatus unless otherwise noted. The elemental analyses were provided by Dr. A. Bernhardt, Max-Planck-Institut, Mulheim, Germany. Infrared spectra were recorded by Messrs. E. Thomas and R. Young, Department of Chemistry, University of Maine.

(15) *Cf.* C. S. Marvel and R. D. Rands, Jr., *J. Am. Chem. Soc.*, **72**, 2642 (1950).

(16) Capillary tube melting point.

tion of the aqueous mixture with ether was preceded by separating and discarding the benzene solution. Removal of solvent from the dry ether extract afforded 0.85 g. (90.4%) of colorless crystals melting at 179–183° dec.[16] Repeated recrystallization from water gave an analytical sample,[17] m.p. 182–185° dec.,[16] ν_{max}^{KBr} 1642 cm.$^{-1}$

Anal. Calcd. for $C_7H_5BrO_4$: C, 36.08; H, 2.16; Br, 34.30. Found: C, 36.44; H, 2.27; Br, 34.19.

2,3-Dihydroxybenzoic acid. Anhydrous aluminum chloride (80 g.) was added to a solution of 2,3-dimethoxybenzoic acid[18] (18.7 g.) in 900 ml. of chlorobenzene and the mixture was heated at reflux. After 1 hr. an additional 30 g. of aluminum chloride was added and heating was continued for 2 hr. The residue, obtained by removing the solvent *in vacuo*, was cooled and cautiously treated with 800 ml. of hydrochloric acid. The brown colored product (11.2 g., m.p. 204–210°) was collected and reprecipitated from dilute sodium bicarbonate solution (Norit A). Recrystallization from water gave 8.3 g. (52.5%) of colorless crystals melting at 207–208°.[19]

2,3-Dihydroxy-5-bromobenzoic acid (VIIIa). A solution of 2,3-dihydroxybenzoic acid (3.0 g., 0.019 mole) in 100 ml. of glacial acetic acid was treated with 3.1 g. (0.019 mole) of bromine. Before removing the solvent *in vacuo*, the mixture was allowed to remain at room temperature for 24 hr. The colorless crystalline residue weighed 4.6 g. and melted at 215–222° after recrystallization from methanol-water; yield 3.2 g. (70.4%). A second recrystallization from the same solvent gave 2.5 g. melting at 222–224°.[16] Von Hemmelmayr[7] reported a melting point of 215° for the anhydrous compound and 187° for the hydrate.

Methylation of 2,3-dihydroxy-5-bromobenzoic acid (VIIIa). To 1.4 g. (0.006 mole) of 2,3-dihydroxy-5-bromobenzoic acid, obtained by bromination of 2,3-dihydroxybenzoic acid, and sodium hydroxide (1.4 g., 0.035 mole) in 30 ml. of water was added 2.2 g. (0.017 mole) of dimethyl sulfate. After 2 hr. at reflux, the mixture was adjusted to *p*H 11 with sodium hydroxide. Two additional hours at reflux followed by cooling and acidification with hydrochloric acid led to 1.1 g. (70.1%) of solid melting at 105–125°. Successive recrystallizations from water (Norit A) and benzene–petroleum ether (b.p. 60–90°) yielded colorless crystals, m.p. 118.5–120°.[16] The product was found to be identical (mixture melting point and infrared comparison) with an authentic sample of 2,3-dimethoxy-5-bromobenzoic acid (VIIIb) prepared as described below.

2,3-Dimethoxy-5-bromobenzoic acid (VIIIb). Sodium hydroxide (2.3 g., 0.057 mole) in 25 ml. of water was slowly added to a suspension of 2,3-dimethoxy-5-bromobenzaldehyde[20] (2.9 g., 0.012 mole) in a solution of silver nitrate (4.8 g., 0.028 mole) and water (50 ml.) heated at reflux. The mixture was filtered after 1 hr. at reflux and the filtrate acidified with concentrated hydrochloric acid. The colorless needles, 2.7 g. (87.4%) melting at 121–123°, were collected and recrystallized from water; yield 2.6 g. (84.1%), m.p. 122–124° (lit.,[21] m.p. 120°).

3,4-Dimethoxy-6-bromonitrobenzene (XI). A 10-g. sample of 4-bromoveratrole (XII),[10] b.p. 71–74° (0.07–0.10 mm.), was slowly added to a stirred solution of conc. nitric acid (70 ml.) and acetic acid (210 ml.) maintained at *ca.* 10°. After remaining at 15° for 1 hr., the mixture was diluted with water and the oily yellow product isolated by extraction with ether. Crystallization of the ethereal residue (11.1 g., 92.1%) from ethanol gave 9.9 g. (82%), m.p. 122–124° (lit.,[9] m.p. 124.5–125°).

Hydrogen bromide–acetic demethylation of 3,4-dimethoxy-6-bromonitrobenzene (XI). In a typical experiment, 3,4-dimethoxy-6-bromonitrobenzene (1.8 g.) was added to 7 ml. of 35% hydrogen bromide–glacial acetic acid solution contained in a cooled (ice-salt) Pyrex glass tube. The tube was sealed and heated at 141° during 1 hr. and then maintained at 140–142° for 50 min. before allowing the solution to cool (66 min.). Acetic anhydride–pyridine was added to the residue obtained by removing the solvent *in vacuo*, and the resulting solution was stored at room temperature overnight. Concentration to dryness *in vacuo* gave a pale yellow solid which led to colorless crystals, m.p. 116–120°, after recrystallization from benzene–petroleum ether (b.p. 60–90°); yield, 1.0 g. (45.8%). One additional recrystallization from the same solvent afforded 0.8 g. (36.7%) melting at 119–121°. A mixture melting-point determination and infrared spectral comparison (chloroform solution) with an authentic specimen of 3,4-diacetoxy-6-bromonitrobenzene (XIIIb, prepared as described below) was in complete accord with the assignment of formulation XIIIb to the product melting at 119–121°.

In several related experiments it was found that 3,4-dihydroxy-6-bromonitrobenzene (XIIIa) could be isolated directly in yields of 30–35% by crystallizing the crude reaction product from toluene (Norit A).

Evaporation of solvent from the mother liquors left an orange colored glass (1.2 g.) which resisted crystallization. Chromatography in 1:2 petroleum ether (b.p. 60–90°) benzene on 36 g. of Woelm neutral alumina, deactivated with 2.2 ml. of 10% acetic acid,[22] and elution with 75 ml. of the same solvent gave colorless crystals (0.21 g.) melting at 128–155°. Removal of solvent from a second fraction (50 ml.) yielded 0.56 g. of colorless crystals, m.p. 90–113°, while elution with two additional 50-ml. portions of the same solvent afforded 0.14 g., m.p. 68–75°, and 0.044 g. melting at 72–75°. Two recrystallizations of the latter residue from benzene–petroleum ether produced a pure sample of *3,4-diacetoxynitrobenzene* (XIVb), m.p. 80–81°. Identity was established by mixture melting-point determination and infrared comparison (chloroform solution) with an authentic sample (m.p. 80–81°, lit., [23,24] m.p. 78° and 84°). Initial attempts directed at further purification of the remaining mixture of acetates did not detect the presence of 3,4-diacetoxy-5-bromonitrobenzene, the predictable product of rearrangement, which had been prepared by acetylation (acetic anhydride–pyridine) of 3,4-dihydroxy-5-bromonitrobenzene.[11] After recrystallization from benzene–petroleum ether, an analytical sample of 3,4-diacetoxy-5-bromonitrobenzene melted at 110–111°, $\nu_{max}^{CHCl_3}$ 1786 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_8BrNO_6$: C, 37.76; H, 2.54; Br, 25.12. Found: C, 37.80; H, 2.55; Br, 25.44.

3,4-(Dimethylmethylenedioxy) bromobenzene (XVI). A mixture of dimethylmethylenedioxybenzene[13] (XV, 3.0 g., 0.02 mole), *N*-bromosuccinimide (3.6 g., 0.02 mole) and 6 ml. of chloroform was heated at reflux during 6 hr. The mixture was diluted with ether and washed successively wth 2*N* sodium hydroxide and water. Removal of dry (sodium sulfate) solvent left an oily residue (3.9 g.). Distillation gave 3.4 g. (74.4%) of colorless oil, b.p. 97–102° (8 mm.). The main fraction (1.7 g.) boiled at 101–102° (lit.,[13] b.p. 122° at 20 mm.).

(17) The microanalysis of this sample was performed by Mr. Joseph F. Alicino, Metuchen, N. J.

(18) G. A. Edwards, W. H. Perkins, Jr., and F. W. Stoyle, *J. Chem. Soc.*, 195 (1925).

(19) W. H. Perkins, Jr., and V. M. Trikojus, *J. Chem. Soc.*, 2925 (1926).

(20) G. Stock and H. Conroy, *J. Am. Chem. Soc.*, **73**, 4743 (1951).

(21) W. Davies, *J. Chem. Soc.*, 1575 (1923).

(22) A subsequent experiment utilizing Merck acid-washed alumina gave comparable results. In both experiments, rapid chromatographic separation was essential, since extensive cleavage of the adsorbed acetates was found to occur when contact time was extended over a 2-hr. period.

(23) H. van Erp, *Ber.*, **64B**, 2813 (1931).

(24) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 522 (1951).

3,4-Diacetoxy-6-bromonitrobenzene (XIIIb). A solution composed of 3,4-(dimethylmethylenedioxy)-6-bromonitrobenzene (XVII, 1.05 g.),[13] concd. hydrochloric acid (4 ml.) and dioxane was heated at steam bath temperature for 15 min. The solvent was removed (*in vacuo*) and replaced with acetic anhydride–pyridine. Heating (steam bath) was continued for 30 min. and the solid which separated upon cooling the acetylation mixture collected and discarded. Evaporation (*in vacuo*) of the filtrate to dryness and recrystallization of the residue, 0.91 g. (74.6%), from benzene (Norit A)–petroleum ether (b.p. 60–90°) gave a specimen of the acetate XIIIb, m.p. 120–122° (lit.,[13] m.p. 122°).

ORONO, ME.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID COMPANY]

Cyanoethylation. I. The Selective Cyanoethylation of 2-Aminoethanethiol Hydrochloride

RICHARD J. GAUL,[1] WINFRIED J. FREMUTH, AND MICHAEL N. O'CONNOR

Received November 19, 1959

Over the *p*H range of 3.2 to 6.9 aqueous solutions of 2-aminoethanethiol hydrochloride react with acrylonitrile exclusively on the sulfhydryl group to give good yields of 3-(2-aminoethylthio)propionitrile hydrochloride. The selective sulfhydryl cyanoethylation is most rapid in the *p*H range of 6 to 6.9. In basic solutions a rapid and nonselective reaction is observed.

An obscure literature observation interpreted the fact that 2-aminoethanethiol (m.p. 99°[2]) melted nearly 30° higher than its hydrochloride (m.p. 70°[3]) as indicating that the free base existed as the Zwitterion Ib. This statement prompted us to utilize the cyanoethylation of 2-aminoethanethiol as a means of investigating this problem.

If the above rationalization is correct, then aqueous solutions of 2-aminoethanethiol, and similarly constituted mercaptoamines, should behave as shown. As the *p*H of the solution is increased the predominant species should pass from the ammonium salt (Ia) through the Zwitterion (Ib) to the free amine (Ic).

$$\underset{\text{Ia}}{HSCH_2CH_2NH_3^+} \rightleftharpoons \underset{\text{Ib}}{{}^-SCH_2CH_2NH_3^+} \rightleftharpoons \underset{\text{Ic}}{{}^-SCH_2CH_2NH_2}$$

From the accumulated data on the behavior of mercaptans and amines toward acrylonitrile, we would predict the following:

1. In strongly acid solution Ia would predominate and cyanoethylation either would not occur or would take place slowly and exclusively on sulfur.
2. As the *p*H is increased progressively more of Ib would be formed. The rate of the reaction should increase and reach a maximum at the *p*H corresponding to the isoelectric point. Addition should occur exclusively to the mercaptide anion.
3. In basic solution, where Ic would predominate, the reaction would, likewise, be rapid but completely nonselective.

To test these predictions, aqueous solutions of 2-aminoethanethiol covering the *p*H range 1.5–8.8 were allowed to react with excess acrylonitrile for at least one hour. The results are summarized in Table I.

At *p*H 1.5 no reaction was observed. At *p*H 3.6 a moderate reaction produced exclusively 3-(2-aminoethylthio)propionitrile hydrochloride as inferred from analytical data and failure of the product to give a color reaction with sodium nitroprusside.[4] The rate of the reaction increased, with retention of selectivity, up to *p*H 6.8 and, from our qualitative data, reached a maximum in the *p*H region 6–6.8.

In alkaline solution a fast, nonselective reaction produced an uncrystallizable sirup. To eliminate disulfide formation *via* air oxidation of 2-aminoethanethiol in alkaline solution, another reaction was run first at *p*H 6.4 then at *p*H 8.8. The same sirupy product was obtained.

The above evidence supports the postulate that aminoethanethiol exists as the internal salt both in the solid state and in solution and suggests that the cyanoethylation of similarly constituted aliphatic mercaptoamines[5] in slightly acid solutions should give good yields of the *S*-monocyanoethylated products.

EXPERIMENTAL

3-(2-Aminoethylthio)propionitrile hydrochloride. Acrylonitrile (63.6 g., 1.2 moles) was added at once to a stirred solution of 34 g. (0.3 mole) of 2-aminoethanethiol hydrochlo-

(1) Address correspondence to Department of Chemistry, John Carroll University, Cleveland 18, Ohio.

(2) S. Gabriel and J. Coleman, *Ber.*, **45**, 1643 (1912).

(3) E. J. Mills, Jr., and M. T. Bogert, *J. Am. Chem. Soc.*, **62**, 1173 (1940).

(4) M. D. Cheronis and J. B. Entriken, *Semimicro Qualitative Organic Analysis*, T. Y. Crowell Co., N. Y., 1947, p. 141.

(5) Mercapto-*t*-carbinamines might possibly be an exception since the cyanoethylation of *t*-carbinamines is acid catalyzed, *cf.*, L. S. Luskin, M. J. Culver, G. E. Gantert, W. E. Craig, and R. S. Cook, *J. Am. Chem. Soc.* **78**, 4042 (1956); E. Profft, *Ber.*, **90**, 1734 (1957).