[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Chloro- and Bromoisobutyronitriles

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As early as 1898, Henry[2] reported the isolation of a mixture of α-chloroisobutyronitrile (V) and methacrylonitrile from the reaction of acetone cyanohydrin with phosphorus pentachloride. Later the preparation of α-chloroisobutyronitrile[3,4] and α-bromoisobutyronitrile[5] from the reaction of acetone cyanohydrin with phosphorus pentachloride and phosphorus tribromide, respectively, was described.

Since sizeable amounts of α-chloroisobutyronitrile was needed in this Laboratory, the development of a method that would give this compound in good yields was undertaken. During this investigation, the halonitriles obtained by the procedures of the earlier workers from acetone cyanohydrin were found to have the halogen in the β- rather than in the α-position. The purpose of this paper is to describe the preparation of the α- and β-chloro- and bromoisobutyronitriles by reactions that produce known structures, and to report a new method for the preparation of α-chloro and α-bromoisobutyronitrile in high yields.

Authentic samples of α-chloro and α-bromoisobutyronitriles were prepared by dehydration of the corresponding α-haloisobutyramides. α-Chloroisobutyramide was prepared from isobutyric acid (I) by the sequence of reactions I to IV.

The chlorination of I by the method of Kharasch and Brown,[6] followed by the fractionation of the mixture of the chloroacid chlorides II and III, gave a 16% yield of α-chloroisobutyryl chloride (II) and a 36% yield of β-chloroisobutyryl chloride (III). Kharasch and Brown[6] showed the lower boiling chloroacid chloride to be α-chloroisobutyryl chloride by hydrolysis to the known α-chloroisobutyric acid[7]; the higher boiling, isomeric chloroacid chloride is, therefore, β-chloroisobutyryl chloride (III). The α-chloroisobutyryl chloride (II) was converted to α-chloroisobutyronitrile (V) in 59% yield. The dehydration of α-bromoisobutyramide[8] gave α-bromoisobutyronitrile in 86% yield. These α-halonitriles are different from the halonitriles prepared from acetone cyanohydrin.[3,4,5]

$$\underset{\text{I}}{(CH_3)_2CHCOOH} \xrightarrow{SO_2Cl_2}$$

$$(CH_3)_2CClCOOH + ClCH_2CH(CH_3)COOH \xrightarrow{SOCl_2}$$

$$\underset{\text{II}}{(CH_3)_2CClCOCl} + \underset{\text{III}}{ClCH_2CH(CH_3)COCl}$$

$$\downarrow$$

$$\underset{\text{IV}}{(CH_3)_2CClCONH_2} \xrightarrow{P_2O_5} \underset{\text{V}}{(CH_3)_2CClCN}$$

β-Chloro and β-bromoisobutyronitrile may be prepared by the addition of the appropriate hydrogen halide to methacrylonitrile. In this manner, β-chloroisobutyronitrile[9] was prepared in 79% yield and β-bromoisobutyronitrile in 72% yield. These β-haloisobutyronitriles correspond in physical properties to the halonitriles obtained from the reaction of acetone cyanohydrin with phosphorus pentachloride and phosphorus tribromide, to which the α-halo structures had been assigned.[3,4,5] Further evidence that the halogen is in the β-position is the fact that methyl β-chloroisobutyrate (VIII) prepared from III is identical with the ester obtained from VI by the following sequence of reactions

$$CH_2{=}C(CH_3)CN \xrightarrow{HCl} \underset{\text{VI}}{ClCH_2CH(CH_3)CN} \xrightarrow[HOCH_3]{HCl}$$

$$\underset{\text{VII}}{ClCH_2CH(CH_3)C(OCH_3){=}NH{\cdot}HCl} \left[\begin{array}{l} \xrightarrow{H_2O} \underset{\text{VIII}}{ClCH_2CH(CH_3)COOCH_3} \\ \xrightarrow{\Delta} \underset{\text{IX}}{ClCH_2CH(CH_3)CONH_2} \end{array} \right.$$

β-Chloroisobutyramide (IX) could not be prepared in the pure state by the action of ammonia on the acid chloride (III). However, methyl β-chloroiminoisobutyrate hydrochloride (VII), derived from the nitrile (VI), was quantitatively pyrolyzed to β-chloroisobutyramide. A sample of β-bromoisobutyramide was prepared by hydration of the β-bromonitrile with sulfuric acid.[10]

The formation of the β-chloronitrile (VI) from the reaction of acetone cyanohydrin with phosphorus pentachloride undoubtedly results from the initial formation of methacrylonitrile and the subsequent addition of hydrogen chloride, which is present in the reaction mixture, to this nitrile.

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[2] Henry, *Chem. Zentr.*, **69**, II, 661 (1898).

[3] Sobieranski and Chrzaszczewski, *Roczniki Chem.*, **7**, 470 (1927); *C. A.*, **22**, 2146 (1928).

[4] McElvain and Fajardo-Pinzon, THIS JOURNAL, **67**, 690 (1945).

[5] Chrzaszczewski and Popiel, *Roczniki Chem.*, **7**, 74 (1927); *C. A.*, **22**, 1343 (1928).

[6] Kharasch and Brown, THIS JOURNAL, **62**, 925 (1940).

[7] Balbiano (*Ber.*, **11**, 1693 (1878)) and Ostropjatow (*J. Russ. Phys.-Chem. Soc.*, **28**, 50 (1896)) established the structure of α-chloroisobutyric acid by its conversion to α-hydroxyisobutyric acid.

[8] The structure of the amide was established by Bischoff (*Ber.*, **24**, 1044 (1891)), who prepared it from both the ester and the acid bromide of α-bromoisobutyric acid. This acid has been converted into α-hydroxyisobutyric acid by Fittig and Thomson (*Ann.*, **200**, 86 (1880)) and by Hell and Waldbauer (*Ber.*, **10**, 449 (1877)).

[9] Berthet, *Bull. classe sci. Acad. roy. Belg.*, **27**, 212 (1941); *C. A.*, **37**, 3400 (1943).

[10] McElvain, "The Characterization of Organic Compounds," Macmillan Co., New York, N. Y., 1946, p. 146.

The validity of this conclusion is shown by the fact that with milder conditions than those previously employed,[3,4] methacrylonitrile was isolated in 35% yield from the reaction of phosphorus pentachloride on acetone cyanohydrin.

During this investigation a new method of preparation of α-chloro- and α-bromoisobutyronitriles was developed. When equimolar amounts of isobutyronitrile and phosphorus pentachloride were heated under reflux, hydrogen chloride was evolved smoothly; distillation of the reaction mixture yielded α-chloroisobutyronitrile (78%) and phosphorus trichloride (80%). This reaction is represented as

$$(CH_3)_2CHCN + PCl_5 \longrightarrow (CH_3)_2CClCN + PCl_3 + HCl$$

The chloronitrile obtained from this reaction is identical with the one (V) prepared by the dehydration of α-chloroisobutyramide (IV). Also, the chloroamide corresponding to the chloronitrile prepared from isobutyronitrile is identical with IV.

α-Bromoisobutyronitrile was prepared in a similar manner from an equimolar mixture of bromine, isobutyronitrile and phosphorus tribromide. The α-bromoisobutyronitrile was isolated in 76% yield and is identical with the bromonitrile obtained by the dehydration of α-bromoisobutyramide.[8]

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Experimental

α-Chloroisobutyramide.—To a solution of 150 ml. of concentrated ammonium hydroxide, which was cooled in an ice-bath and stirred vigorously, 17 g. of α-chloroisobutyryl chloride[6] was added at such a rate that the temperature did not rise above 10°. After the addition was finished, the reaction mixture was stirred for fifteen minutes and then the precipitated amide was filtered from the cold solution and dried. An additional 1 g. of amide was obtained when the filtrate was concentrated to 25 ml. and cooled. The dried solid was recrystallized from ethyl acetate; 10.1 g. (70%) of α-chloroisobutyramide, m. p. 115–118°, was obtained from the ethyl acetate solution and by concentration of the mother liquors. A sample, recrystallized from water, melted at 117–119°.

Anal. Calcd. for C_4H_8ClNO: Cl, 29.2; N, 11.5. Found: Cl, 29.2; N, 11.6.

α-Chloroisobutyronitrile. (a) From α-Chloroisobutyramide.—α-Chloroisobutyramide (21 g., 0.17 mole) and phosphorus pentoxide (30 g., 0.21 mole) were thoroughly mixed and placed in a flask equipped with a short still-head, which was attached to a Dry Ice trap. The mixture was heated to 150°; after about ten minutes at this temperature, α-chloroisobutyronitrile began to distil from the reaction flask. After 12.5 g. of nitrile had been collected and the rate of distillation began to diminish, the pressure within the system was reduced to 100 mm. In this way an additional 2.6 g. of nitrile was collected in the cold trap. The total yield of α-chloroisobutyronitrile was 15.1 g. (84%); b. p. 114–116°, $n^{25}D$ 1.4045; d^{25}_4 0.9808.

(b) From Isobutyronitrile.—A mixture of 25 g. (0.36 mole) of isobutyronitrile and 75 g. (0.36 mole) of phosphorus pentachloride was heated to the refluxing temperature. Hydrogen chloride was evolved smoothly and within an hour the solid phosphorus pentachloride had disappeared. After refluxing the clear solution until the hydrogen chloride ceased to be evolved (three hours), the reaction mixture was fractionated through a column of 8 theoretical plates. The first fraction consisted of 39.4 g. (80%) of phosphorus trichloride, b. p. 74–76°. After an intermediate fraction of 2.5 g., b. p. 76–114°, the α-chloroisobutyronitrile (29 g., 78%) was collected at 114–116°; $n^{25}D$ 1.4049.

Anal. Calcd. for C_4H_6ClN: Cl, 34.3; N, 13.5. Found: Cl, 33.8; N, 13.3.

One gram of this nitrile was heated with 2 g. of sulfuric acid and poured onto cracked ice. The precipitated amide, 0.9 g., was filtered, dried, and recrystallized from petroleum ether; m. p. 118–120°. The mixed melting point of this amide with the α-chloroisobutyramide made from the known α-chloroisobutyryl chloride showed no depression, m. p. 118–120°.

β-Chloroisobutyronitrile.—Dry hydrogen chloride was passed into 10 ml. of ether until 4.6 g. (0.12 mole) was absorbed, and then 8.4 g. (0.12 mole) of methacrylonitrile was added. After the ether solution had stood for twelve hours at room temperature, it was distilled; 10.2 g. (79%) of β-chloroisobutyronitrile,[9] b. p. 50–52° (6 mm.); $n^{25}D$ 1.4323; d^{25}_4 1.061, was obtained. This nitrile contained 13.2% nitrogen (calcd. 13.5%).

The chloronitrile obtained from the reaction of phosphorus pentachloride with acetone cyanohydrin by the procedure of Sobieranski and Chrzaszczewski[3] had the same physical properties as that prepared above from methacrylonitrile.

Methyl β-Chloroiminoisobutyrate Hydrochloride.—A solution of 15.8 g. (0.15 mole) of β-chloroisobutyronitrile in 5.1 g. (0.16 mole) of absolute methyl alcohol was cooled in an ice-bath and treated with hydrogen chloride until 5.9 g. (0.16 mole) was absorbed. The resulting homogeneous liquid was placed in a refrigerator for twenty-four hours, during which time it solidified. An equal volume of ether was added and the salt filtered off, dried in a desiccator, and triturated with ether. After drying again, the methyl β-chloroiminoisobutyrate hydrochloride weighed 25.7 g. (99%).

Anal. Calcd. for $C_5H_{11}Cl_2NO$: ionic Cl, 20.6. Found: ionic Cl, 20.6.

β-Chloroisobutyramide.—Five grams of the methyl β-chloroiminoisobutyrate hydrochloride was heated to 115° until methyl chloride ceased to be evolved. The resulting amide, which crystallized on cooling, melted at 100–103°; the yield was quantitative. One recrystallization from a mixture of petroleum ether and ethyl acetate gave 3.2 g. (92%) of β-chloroisobutyramide, m. p. 104–105°.

Anal. Calcd. for C_4H_8ClNO: N, 11.5. Found: N, 11.4.

One gram of the β-chloroisobutyronitrile, prepared from methacrylonitrile, was heated with 1.5 g. of sulfuric acid and then poured onto 5 g. of cracked ice. The precipitate was filtered off and recrystallized from a mixture of benzene and petroleum ether. The yield of β-chloroisobutyramide, m. p. 102–104°, was 0.25 g. This amide is identical with the one prepared from the β-chloronitrile obtained from acetone cyanohydrin.

Attempts to recover the remainder of the amide from the water solution by evaporation led only to an impure product, m. p. 70–85°. All attempts to prepare β-chloroisobutyramide from β-chloroisobutyryl chloride gave a product that melted over a wide range (m. p. 60–80°) even after numerous recrystallizations. This material undoubtedly contained a considerable amount of the dehydrochlorination product from the β-chloroisobutyric acid derivative.

Methyl β-Chloroisobutyrate.—Eight grams of methyl β-chloroiminoisobutyrate hydrochloride was shaken with 15 ml. of water until the salt completely dissolved. Within twenty minutes at room temperature the solution became turbid and the methyl β-chloroisobutyrate began to form a separate layer. After three hours the ester was separated and the aqueous layer extracted with ether. The ether extracts and product were combined, dried, and concentrated. Distillation under reduced pressure gave

5.4 g. (85%) of methyl β-chloroisobutyrate,[11] b. p. 93–95° (106 mm.); n^{25}_D 1.4242; d^{25}_4 1.1031. This ester contained 25.6% chlorine (calcd. 26.0%).

Methyl β-chloroisobutyrate also was prepared from the β-chloroisobutyryl chloride obtained from the chlorination of isobutyric acid with sulfuryl chloride.[6] The ester so obtained had physical properties identical with those of the methyl β-chloroisobutyrate prepared from β-chloroisobutyronitrile.

The Isolation of Methacrylonitrile from the Reaction of Acetone Cyanohydrin with Phosphorus Pentachloride.—This reaction was carried out in ether solution instead of benzene[3] to facilitate the isolation of methacrylonitrile. To a solution of 25 g. (0.3 mole) of acetone cyanohydrin in 25 ml. of absolute ether, 31 g. (0.15 mole) of phosphorus pentachloride was added slowly with cooling and stirring. As the ether was heated to the refluxing temperature, the phosphorus pentachloride dissolved and hydrogen chloride was evolved. After two hours of refluxing, 50 ml. of ether was added and the reaction mixture poured onto cracked ice. The layers were separated, the aqueous layer was extracted with ether, and then the combined ether solutions were dried and the ether evaporated. The only products that could be isolated from the residue were 3.5 g. (35% based on the phosphorus pentachloride) of methacrylonitrile, b. p. 86–90°, and 7 g. of unchanged acetone cyanohydrin; 5 g. of undistillable material remained in the flask. Hydrogen chloride was passed into the methacrylonitrile fraction at 50° until 1.5 g. was absorbed. Distillation of this reaction product gave 3 g. (57%) of β-chloroisobutyronitrile, b. p. 52–56° (9 mm.); n^{25}_D 1.4330.

α-Bromoisobutyronitrile. (a) **From α-Bromoisobutyramide.**—The α-bromoisobutyramide[8] used in this preparation was made by allowing α-bromoisobutyryl bromide, b. p. 162–163°, to react with concentrated ammonium hydroxide in the cold; after recrystallization from petroleum ether, it melted at 147–148°. The amide (18.6 g., 0.11 mole) and phosphorus pentoxide (21.3 g., 0.15 mole) were intimately mixed and heated under reflux at 140° for four hours. The α-bromonitrile was distilled from the reaction mixture at atmospheric pressure until the rate of distillation diminished, then the last of the nitrile was collected by evacuation of the system to 100 mm. and condensation of the volatile material in a cold trap. Redistillation gave 14 g. (86%) of α-bromoisobutyronitrile, b. p. 137–139°; n^{25}_D 1.4460; d^{25}_4 1.376.

(b) **From Isobutyronitrile.**—A mixture of 25 g. (0.36 mole) of isobutyronitrile and 98 g. (0.36 mole) of phosphorus tribromide was cooled in an ice-bath and 58 g. (0.36 mole) of bromine added with shaking. The reaction mixture was heated gently until hydrogen bromide ceased to be evolved (three hours), after which time the mixture was fractionated. The first fraction, after a small forerun, was α-bromoisobutyronitrile, b. p. 137–140°. The product was slightly colored due to an excess of bromine; however, the color was removed by washing an ether solution of the nitrile with a sodium bisulfite solution. Redistillation gave 40.4 g. (76%) of the water-white α-bromoisobutyronitrile, b. p. 138–140°; n^{25}_D 1.4447.

Anal. Calcd. for C_4H_6BrN: Br, 54.0; N, 9.45. Found: Br, 53.7; N, 9.2.

β-Bromoisobutyronitrile.—This nitrile was prepared in the same manner as the β-chloronitrile. From 9.5 g. (0.12 mole) of hydrogen bromide and 7.9 g. (0.12 mole) of methacrylonitrile, 12.6 g. (72%) of β-bromoisobutyronitrile, b. p. 60–62° (5 mm.), n^{25}_D 1.4680, d^{25}_4 1.465, was isolated.

Anal. Calcd. for C_4H_6BrN: Br, 54.0; N, 9.45. Found: Br, 53.7; N, 9.1.

β-Bromoisobutyramide was prepared by gently heating 0.5 g. of the β-bromonitrile and 0.75 g. of sulfuric acid on a hot plate until a reaction occurred and then pouring the mixture onto a small amount of cracked ice. The precipitated amide, 0.2 g., was filtered and recrystallized from petroleum ether, m. p. 103–105°.

Anal. Calcd. for C_4H_8BrNO: N, 8.4. Found: N, 8.1.

Summary

α-Chloroisobutyronitrile and α-bromoisobutyronitrile have been prepared by the dehydration of the corresponding amides; α-chloroisobutyramide is described for the first time.

β-Bromoisobutyronitrile was prepared by the addition of hydrogen bromide to methacrylonitrile. This nitrile has the same properties as the compound isolated from the reaction of phosphorus tribromide with acetone cyanohydrin, to which the α-bromoisobutyronitrile structure had been assigned by earlier workers. Similarly, the β-chloroisobutyronitrile corresponds to the nitrile isolated from the reaction of phosphorus pentachloride on acetone cyanohydrin.

A new and simpler method is described for the preparation of α-chloro and α-bromoisobutyronitriles in high yields by the halogenation of isobutyronitrile with the appropriate phosphorus pentahalide.

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[11] Zalkind and Markov, *J. Applied Chem.* (*U. S. S. R.*), **10**, 1042 (1937); *C. A.*, **32**, 1652 (1938).