[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

α-BROMINATION OF PRIMARY NITRILES

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Received February 25, 1953

Recent work in this laboratory has shown that secondary nitriles could be halogenated in the α-position by the phosphorus pentahalides to give good yields of pure α-halo nitriles (1). This paper represents a continuation of that work and an investigation of the halogenation of primary nitriles (primary alkyl cyanides) to determine whether or not the α-halo nitriles or a derivative could be isolated in good yield. The results indicate that the α-bromo primary nitriles are not stable but that the corresponding α-halo amide could be prepared in reasonable yield.

In the bromination of secondary nitriles, equal yields of pure α-bromo nitriles could be isolated by either procedure 1, using phosphorus pentabromide, or procedure 2, using a catalytic amount of phosphorus tribomide and bromine. The latter procedure is especially convenient for the bromination of large quantities of nitrile. Recently a paper by Bruylants and Couvreur (2) reported the preparation of α-bromo nitriles, both primary and secondary, using N-bromosuccinimide as the brominating agent. Previously, Merckx and Bruylants (3) had studied bromine in the presence of sulfur as an agent for the bromination of aliphatic nitriles.

$$1.\ R_2CHCN(I) + PX_5 \rightarrow R_2CXCN(II) + HX + PX_3$$

$$2.\ I + X_2 \xrightarrow{PX_3} II + HX$$

$$3.\ RCH_2CN(III) + Br_2 \xrightarrow{PBr_3} RCHBrCN(IV) \mathrel{\substack{\xleftarrow{P_2O_5} \\ \xrightarrow[H_2SO_4]{}}} RCHBrCONH_2(V)$$

In this investigation the bromination of the following four primary nitriles was studied: butyronitrile, valeronitrile, capronitrile, and γ-phenylbutyronitrile. In contrast to the α-bromo derivatives of secondary nitriles, which were stable at room temperature and maintained a constant boiling point, refractive index, and density during fractionation, the α-bromo primary nitriles became colored on standing at room temperature and could not be fractionally distilled without change in refractive index and density. Bruylants (2) also pointed out the difficulty encountered in the attempted purification of α-bromo nitriles by fractional distillation and recorded experimentally a wide range of values for the density and refractive index of fractions with almost identical boiling points. To show that the method of preparation was not responsible for the instability of the α-bromo primary nitriles, the α-bromobutyronitrile and α-bromovaleronitrile were prepared from the pure crystalline amides by dehydration using phosphorus pentoxide. α-Bromocapronitrile was prepared from the pure amide

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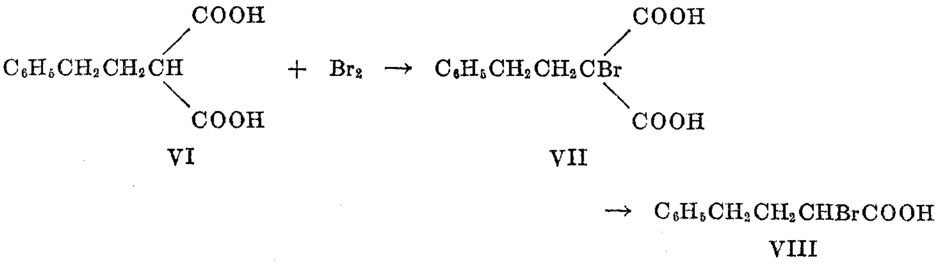
[1] Abstracted from a thesis submitted by Mr. William Holland to the Graduate School of Wayne University in partial fulfillment of the requirements for the degree of Master of Science.

using thionyl chloride as a dehydrating agent. The bromo nitriles from each of these preparations exhibited the same instability as material from the bromination reaction, even when fractionated at 30° under reduced pressure.

The crude α-bromo nitriles could be used immediately in the preparation of pure α-halo amides. *n*-Capronitrile gave a 62% yield of the crude α-bromo nitrile which could be converted to the pure crystalline α-bromo amide in 64% yield. These yields are only slightly lower than with diethylacetonitrile, a comparable six carbon secondary nitrile, which was converted to the α-bromo nitrile in 78% yield and then from the α-bromo nitrile to the amide in 70% yield (1).

γ-Phenylbutyronitrile was brominated and the bromo nitrile was hydrolyzed in acid solution without isolation to give the crude α-bromo acid in 57% yield. The α-bromo acid was converted to the pure crystalline α-halo amide in 60% yield.

The structure of the α-bromo-γ-phenylbutyramide was proven by the following independent synthesis. Malonic ester was alkylated with β-phenylethyl bromide (3) to give 65% of diethyl-(β-phenylethyl)malonate. Saponification gave the malonic acid (VI) which was brominated to give bromo-(β-phenylethyl)malonic acid (VII) and then decarboxylated to give α-bromo-γ-phenylbutyric acid (VIII). Since Bergs (4) converted this bromo acid to a bromotetralone which, from the reactions of Strauss (5), must be 2-bromo-1-tetralone, the bromine atom in VIII must be located *alpha* to the carboxyl group. Treatment of VIII with thionyl chloride followed by ammonia gave an amide identical with the one from the bromination of the nitrile.



$$\underset{\text{VI}}{C_6H_5CH_2CH_2CH\begin{matrix}COOH\\COOH\end{matrix}} + Br_2 \rightarrow \underset{\text{VII}}{C_6H_5CH_2CH_2CBr\begin{matrix}COOH\\COOH\end{matrix}} \rightarrow \underset{\text{VIII}}{C_6H_5CH_2CH_2CHBrCOOH}$$

EXPERIMENTAL

Bromination of α-ethylbutyronitrile. A mixture of 15 g. (0.12 mole) of nitrile, 21 g. (0.13 mole) of bromine, and 1 g. of phosphorus trichloride was heated at 80° for five hours and then poured onto cracked ice. The organic layer was extracted with ether, washed with sodium carbonate, dried, and distilled to give 21.5 g. (87%) of pure α-bromo-α-ethylbutyronitrile, b.p. 103–105° (10 mm.) n_D^{25} 1.4599 (1).

Bromination of n-butyronitrile. Into a three-necked flask equipped with a mercury-sealed stirrer, condenser, and dropping-funnel was placed 100 g. (1.45 moles) of *n*-butyronitrile and one gram of phosphorus tribromide. After 10 g. of bromine had been added, the flask was heated to 70°. At this temperature hydrogen bromide was evolved and a total of 256 g. (1.60 moles) of bromine slowly added over a period of five hours.

After the hydrogen bromide had ceased to be evolved, the reaction was poured onto a mixture of cracked ice and sodium bicarbonate. The organic layer was extracted with ether and the ether was evaporated under reduced pressure. The residue was subjected to steam-distillation, after which the water-white organic layer of the distillate was distilled to give 135 g. (62%) of crude α-bromobutyronitrile, b.p. 75–82° (40 mm.). After fractionation of this material through a 30 × 2 cm. Vigreux column, a center fraction of 63 g. had b.p. 79–82° (40 mm.), n_D^{25} 1.4678, d_4^{20} 1.4852. Refraction gave the following results: first 5 g., b.p. 70° (16 mm.), n_D^{20} 1.4590, d_4^{20} 1.4087; middle 10 g., b.p. 71° (16 mm.), n_D^{20} 1.4660, d_4^{20} 1.4766; last 5 g., b.p. 71° (16 mm.), n_D^{20} 1.4685, d_4^{20} 1.5013.

Direct distillation of the bromo nitrile from the reaction mixture gave similar results. The reaction from 31.7 g. (0.46 mole) of *n*-butyronitrile, 80 g. (0.50 mole) of bromine, and 0.2 ml. of phosphorus tribromide was subjected to distillation at 9 mm. pressure. From the reaction 34 g. (50%) of crude bromo nitrile could be isolated, b.p. 42–43° (9 mm.). Refractionation through a 30-cm. Vigreux-type column gave 30 g. of nitrile, b.p. 39–40° (8 mm.), fractions of which exhibited the same change of refractive index and density as above.

The analytical results varied according to the fraction. The combined fractions with a one-degree boiling range contained 54.3% bromine and 7.9% nitrogen (Calc'd for C_4H_6BrN: Br, 54.0; N, 9.5).

The crude α-bromobutyronitrile (1 g.) was added to 2 g. of concentrated sulfuric acid and the mixture was warmed to 50° for three minutes and then poured onto cracked ice. Recrystallization of the resulting white solid from petroleum ether gave 0.5 g. of α-bromo-*n*-butyramide, m.p. 112–113° (6). A mixture melting point with the authentic amide prepared below was not depressed.

α-Bromo-n-butyramide. α-Bromo-*n*-butyric acid was prepared by the bromination of *n*-butyric acid in the presence of red phosphorus. From 35.2 g. (0.4 mole) of *n*-butyric acid, 58 g. (87%) of α-bromo-*n*-butyric acid was obtained, b.p. 128–130° (35 mm.).

α-Bromo-*n*-butyryl chloride (7) was prepared in 85% yield from 58 g. (0.35 mole) of the acid using thionyl chloride. The 55 g. of acid chloride had b.p. 67–68° (40 mm.), d_4^{20} 1.5320.

The acid chloride was converted to the amide by slow addition to an excess of ammonium hydroxide at 0°. The resulting mixture was evaporated to dryness and the amide was extracted with boiling chloroform. The amide crystallized from the cold chloroform solution. From 50 g. of acid chloride 31.5 g. (71%) of α-bromo-*n*-butyramide, m.p. 112–113° was obtained.

α-Bromo-n-butyronitrile from α-bromo-n-butyramide. A mixture of 24 g. (0.17 mole) of the α-bromo amide and 30 g. (0.21 mole) of phosphorus pentoxide were thoroughly mixed and heated in a distillation flask under 8 mm. pressure. At 100° the α-bromo nitrile began to distil and after two hours, 19 g. (87%) of the nitrile had been collected in a trap cooled in a Dry Ice-acetone bath. Fractionation through a 30-cm. Vigreux column gave 17 g. of nitrile, b.p. 30–31° (4 mm.), n_D^{20} 1.4600, d_4^{20} 1.4132. This material contained 52.3% bromine and 9.4% nitrogen (Calc'd, 54.0% bromine and 9.5% nitrogen). Refractionation gave fractions that exhibited the same variation in refractive index and density as cited above.

Bromination of n-valeronitrile. This nitrile was brominated using the procedure that involved steam-distillation as given for *n*-butyronitrile. From 100 g. (1.2 moles) of *n*-valeronitrile, 200 g. (1.25 moles) of bromine, and 1 g. of phosphorus tribromide, there was obtained 88.0 g. (45%) of crude α-bromovaleronitrile. Fractionation gave 70 g., b.p. 92–95° (40 mm.), n_D^{20} 1.4598, d_4^{20} 1.3486. The material contained 50.0% bromine (Calc'd 49.3%) and further fractionation gave fractions which boiled at a constant temperature but the refractive index and density of which varied in the same manner as the α-bromo-*n*-butyronitrile.

Hydrolysis of 32 g. of the crude nitrile with 50 ml. of concentrated sulfuric acid gave 26 g. (73%) of α-bromo-*n*-valeramide, m.p. 83.5–84° (8).

α-Bromo-n-valeramide. This amide was prepared in a similar manner to the preparation of the α-bromo-*n*-butyramide from the α-bromo acid *via* the α-bromo acid chloride. From 70 g. (0.35 moles) of α-bromo-*n*-valeryl chloride, b.p. 85–90° (30 mm.), there was obtained 43 g. (70%) of α-bromo-*n*-valeramide, m.p. 83–84°. A mixture melting point with amide from the hydrolysis of the nitrile was not depressed.

α-Bromo-n-valeronitrile. The α-bromo amide (50 g.) was dehydrated using the phosphorus pentoxide procedure as given for the α-bromo-*n*-butyronitrile to give 39 g. (87%) of crude α-bromo-*n*-valeronitrile, b.p. 92–94° (40 mm.). Refractionation gave the following results: first 5 g., b.p. 92–93° (40 mm.), n_{D}^{20} 1.4610, d_4^{20} 1.3337; middle 5 g., b.p. 93–94° (40 mm.), n_{D}^{20} 1.4630, d_4^{20} 1.3363; last 5 g., b.p. 94° (40 mm.), n_{D}^{20} 1.4640, d_4^{20} 1.3373.

Bromination of n-capronitrile. The procedure used for *n*-valeronitrile was followed and from 97 g. (1 mole) of *n*-capronitrile, 160 g. (1 mole) of bromine, and 1 g. of phosphorus tribromide, 109 g. (62%) of crude α-bromo-*n*-capronitrile was obtained, b.p. 102–106° (34 mm.). Fractionation gave 90 g. of α-bromo nitrile: first 10 g., b.p. 102–104° (34 mm.), n_{D}^{20} 1.4532 d_4^{20} 1.2444; middle 10 g., b.p. 104° (34 mm.), n_{D}^{20} 1.4656, d_4^{20} 1.3171; last 10 g., b.p. 105–106° (34 mm.), n_{D}^{20} 1.4690, d_4^{20} 1.3387.

A portion (34 g.) of the combined distillate was hydrolyzed with sulfuric acid to give 24 g. (64%) of α-bromo-*n*-caproamide, m.p. 56–57° (8).

α-Bromo-n-caproamide. From 117 g. (0.548 mole) of α-bromo-*n*-caproyl chloride, b.p. 94–98° (30 mm.), and 300 ml. of concentrated ammonium hydroxide there was obtained 67 g. (63%) of α-bromo-*n*-caproamide, m.p. 54.5–55°. A mixture melting point with the amide prepared by hydrolysis of the nitrile was not depressed.

α-Bromo-n-capronitrile. A mixture of 94 g. (0.48 mole) of α-bromo-*n*-caproamide and 80 g. (0.67 mole) of thionyl chloride was heated to the reflux temperature until gas ceased to be evolved. The reaction was then poured onto cracked ice and the organic layer was extracted with ether. The ether solution was washed with sodium bicarbonate solution, dried, and the ether distilled at reduced pressure. Distillation of the remaining material gave 57 g. (67%) of crude α-bromo-*n*-capronitrile, b.p. 105–110° (34 mm.). Refractionation gave the following results: first 5 g., b.p. 104–105° (34 mm.), n_{D}^{20} 1.4521, d_4^{20} 1.2146; middle 5 g., b.p. 105–106° (34 mm.), n_{D}^{20} 1.4565, d_4^{20} 1.2456; last 5 g., b.p. 107° (34 mm.), n_{D}^{20} 1.4600, d_4^{20} 1.2638.

Bromination of γ-phenyl-n-butyronitrile. Phosphorus pentabromide was prepared from 187 g. (0.69 mole) of phosphorus tribromide and 110 g. (0.69 mole) of bromine, to which 100 g. (0.69 mole) of γ-phenylbutyronitrile and 200 ml. of carbon disulfide was added. The mixture was allowed to stand at room temperature for five days and then poured onto cracked ice. The mixture was heated until the carbon disulfide had evaporated and then kept at 60° with intermittent shaking for 48 hours to hydrolyze the nitrile to the acid. After this time the mixture was extracted with ether and the ether layer, when extracted with sodium bicarbonate solution, gave 109 g. of oil which was distilled under reduced pressure to give 88 g. (57%) of crude α-bromo-γ-phenylbutryic acid, b.p. 165–170° (6 mm.), n_{D}^{20} 1.5477. An aliquot was converted in 60% yield to α-bromo-γ-phenylbutyramide, m.p. 130–131°.

Anal. Calc'd. for $C_{10}H_{12}BrNO$: C, 49.60; H, 4.99.

Found: C, 50.25; H, 4.96.

Bromo-(β-phenylethyl)malonic acid (VII). Diethyl (β-phenylethyl)malonate, b.p. 158–161° (8 mm.) was prepared in 65% yield from 30 g. of β-phenylethyl bromide and 45 g. of malonic ester (9). The malonic ester was saponified in 55% yield according to the directions of Fischer (9) to give (β-phenylethyl)malonic acid, m.p. 130–131°. This preparation had a neutral equivalent of 105 (Calc'd 104). The malonic acid was brominated in ether solution according to Fischer (9) to give a 44% yield of bromo-(β-phenylethyl)malonic acid (VII), m.p. 155–157° (dec.), N.E. 144 (Calc'd 144).

α-Bromo-γ-phenylbutyric acid (VIII). The bromomalonic acid (VII, 4.6 g.) was decarboxylated at 170°. After the carbon dioxide ceased to be evolved the acid was distilled, b.p. 147–150° (1 mm.). Fractionation through a 350 × 7 mm. column gave 3.0 g. (78%) of pure α-bromo-γ-phenylbutyric acid, b.p. 145–147° (1 mm.); n_{D}^{25} 1.5514; d_4^{25} 1.444.

Anal. Calc'd for $C_{10}H_{11}BrO_2$: C, 49.40; H, 4.56.

Found: C, 49.50; H, 4.43.

α-Bromo-γ-phenylbutyramide. The α-bromo acid from the decarboxylation was treated with thionyl chloride and then added slowly to cold ammonium hydroxide. The solid was filtered and after recrystallization from ethyl acetate had m.p. 130–131°. A mixture melting point with the amide from the bromination of the nitrile was not depressed. The yield was 60%.

SUMMARY

The bromination of four primary nitriles (primary alkyl cyanides) was studied. The α-bromo nitriles from the bromination reaction as well as from an independent synthesis were not stable during distillation procedures or on standing at room temperature. However, the crude nitriles could be converted to stable pure α-bromo amides in satisfactory yield.

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