[Contribution from the Department of Organic Chemistry of Louvain University[1] (Belgium)]

REACTION OF N-BROMOSUCCINIMIDE WITH NITRILES. II.[2, 3] ALIPHATIC NITRILES

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The direct bromination of normal saturated nitriles, in the presence of halogen carriers, has been systematically studied by R. Merckx and P. Bruylants (1). In the homologous series from C_2 to C_{13}, the first two members do not react, while the nitriles C_4 to C_{13} give the α-brominated substitution products with yields increasing according to the chain length.

More recently, C. L. Stevens, *et al.* (2, 3) discovered a general method for the preparation of α-halogenated secondary nitriles (chlorinated and brominated) by the treatment of secondary nitriles of the general type R_2CHCN with phosphorus pentahalides.

From these investigations, methods are now available to obtain α-brominated nitriles, starting with nitriles excluding aceto- and propio-nitrile.

An easy way to obtain β, γ . . . ω-brominated derivatives is still to be found. The ω-derivatives may be prepared by the method of L. Henry (4a) (incomplete reaction of an α,ω-alkyldihalide with sodium cyanide), which has been applied by Cloke and Ayers (4b) in the preparation of δ-bromovaleronitrile from 1,4-dibromobutane. For β-derivatives [because of the analogy with the preferential substitution in the β-position which was observed in the photochlorination (5) of nitriles], it was considered that these β-substituted derivatives could be prepared by direct substitution, if suitable conditions could be found.

It was thus of interest to investigate the reaction of nitriles with N-bromosuccinimide, activated in various ways.

The reaction of five nitriles, aceto- (I), propio- (II), isobutyro- (III), butyro- (IV), and valero- (V) nitriles, was studied with N-bromosuccinimide. The results indicate that the reaction with N-bromosuccinimide does not systematically lead to β-bromoderivatives. An interesting contribution is the direct formation of α-bromoaceto- (Ib) and α-bromopropio-nitrile (IIb), which have thus far not been obtained by direct substitutuon. Also, α-bromoisobutyronitrile can be prepared easily and in good yield by bromination with N-bromosuccinimide.

Brominated nitriles were identified and, if not well known, purified; their refractive indices were measured at 15 and 30° and Raman spectra were also taken.

The reader should keep in mind that it is very difficult, even with the greatest care, to prepare very pure primary bromonitriles.

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[3] Bruylants, *Bull. soc. chim. Belges*, **59**, 107 (1950).

EXPERIMENTAL

Directions for bromination with N-bromosuccinimide, in the presence of benzoyl peroxide, have been described in a previous paper (6).

Acetonitrile (I). Bromination was first attempted in the presence of carbon tetrachloride and 10% of benzoyl peroxide. The reaction mixture, after 51 hours of refluxing, remained unchanged and the starting materials could be recovered.

Bromination in the presence of sulfur was complete in 14 hours. Distillation gave 12% of bromoacetonitrile, b.p. 60–62° (24 mm.). The reported (7) boiling point is 46° (13 mm.).

Propionitrile (II). This nitrile, b.p. 98°, was allowed to react with N-bromosuccinimide in the presence of carbon tetrachloride and with excess nitrile. In both reactions, benzoyl peroxide was used.

Bromination in carbon tetrachloride was completed by refluxing 0.5 mole of the reagents in 50 ml. of solvent for 24 hours. Fractionation gave a 52% yield of bromonitrile, 10% of which had b.p. 66–70° (10 mm.) and 90% of which had b.p. 85–88° (10 mm.).

Using the same quantitiy of N-bromosuccinimide, a 50% excess of nitrile and no solvent, the reaction was done after 11 hours at the reflux temperature. Distillation gave 45% of bromonitrile, b.p. 66–70° (50 mm.).

The last fraction was redistilled and the fraction with b.p. 68–69° (50 mm.) was further fractionated at 50 mm. into three fractions (A, B, and C) the density (standard Sprengel-Ostwald pycnometer) and refractive index (Pulfrich refractometer) of which were measured at 15 and 30° (± 0.1°). Values at 20° can be obtained by interpolation.

Density and Refractive Index of Fractions

	FRACTION A, b.p. 68.0–68.3°/50 mm.	FRACTION B, b.p. 68.3–68.6°/50 mm.	FRACTION C, b.p. 68.6–69°/50 mm.
d_4^{15}	1.5453	1.5572	1.5673
d_4^{30}	1.5226	1.5340	1.5433
at 15° n_α	1.4707	1.4688	1.4647
n_D	1.4727	1.4707	1.4673
n_β	1.4810	1.4790	1.4753
at 30° n_α	1.4619	1.4605	1.4578
n_D	1.4648	1.4631	1.4604
n_β	1.4731	1.4713	1.4683

Fraction C is considered to be the purest α-bromopropionitrile.

Anal. Calc'd for C_3H_4BrN: Br, 59.63; $M_{R\alpha}$, 23.46;[4] M_{RD}, 23.60.

Found: Br, 58.52; $M_{R\alpha}$, 23.64; M_{RD}, 23.75.

If the values for the density and refractive indices of α-bromopropionitrile are introduced in the diagram proposed by Merckx and Bruylants (1) for α-brominated saturated nitriles, it will be seen that these values correspond to the values that can be extrapolated.

The α-bromopropionitrile, b.p. 68–69° (50 mm.) was transformed into an amide with concentrated sulfuric acid. Sublimation, followed by 2 recrystallizations in benzene, gave α-bromopropionic amide, m.p. 123° (8).

Anal. Calc'd for C_3H_6BrNO: N, 9.22. Found: N, 9.22.

A Raman spectrum of α-bromopropionitrile shows the following frequencies (in cm.$^{-1}$): 154.1; 269.1; 407.8; 472.6; 612.6; 656.1; 968.4; 988.5; 1170.5; 1432.7; 2240.1. Among them are the characteristic frequencies of bromine (472.7) and the $C\equiv N$ group (2240.1).

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[4] Increments for the L-L Refractions of atoms and groups at 20° according to Wibant and Langdyck, *Rec. trav. chim.*, **59**, 1227 (1940) and Bruylants and Merckx, *Bull. soc. chim. Belges*, **43**, 260 (1934).

A small quantity of material, b.p. 87–88° (12 mm.) was also isolated from the original bromination. This material had the following physical constants at 15° and 30°.

at 15° d^{15}_{4} 2.2836; n_α 1.5636; n_D 1.5670; n_β 1.5774
at 30° d^{30}_{4} 2.2563; n_α 1.5534; n_D 1.5570; n_β 1.5672

The substance became yellow after exposure to light for ¼ hour. The physical constants do not correspond to α,β-dibromopropionitrile. Since the molar refraction (Calc'd $M_{R\alpha}$ 31.22; M_{RD} 31.42. Found: $M_{R\alpha}$ 30.27; M_{RD} 30.43) corresponds to a dibromonitrile, the material is probably the α,α-dibromopropionitrile, which is thus far unknown.

Isobutyronitrile (III). This nitrile, b.p. 103–104°, was first brominated with N-bromosuccinimide without a solvent. When 50% excess of nitrile was used along with 10% of benzoyl peroxide, the reaction took place violently and after 1½ hours an 80% yield of bromonitrile could be isolated as a single fraction, b.p. 60–63° (50 mm.).

In a second experiment in which the benzoyl peroxide was omitted, the reaction was less violent. After 6½ hours an 80% yield of bromonitrile was isolated which was identical with the product from the first experiment.

Fractionation of the product gave a substance with b.p. 61.8–62.2° which was further divided into two parts by distillation. The purest fraction had the following physical constants: d^{15}_{4} 1.3636; d^{30}_{4} 1.3721; at 15°, n_α 1.4485; n_D 1.4505; n_β 1.4584; at 30, n_α 1.4418; n_D 1.4441; n_β 1.4515; $M_{R\alpha}$ 28.48 (calc'd. 28.08); M_{RD} 28.60 (calc'd 28.24).

Hydrolysis of the nitrile with sulfuric acid gave α-bromoisobutyramide, which was recrystallized from benzene, m.p. 144–145°.

Anal. Calc'd for C_4H_8BrNO: N, 8.44. Found: N, 8.24.

The product which was isolated from the bromination of isobutyronitrile is α-bromoisobutyronitrile (3).

n-Butyronitrile (IV). Without solvent the reaction of 0.5 mole of reagent, 50% excess of butyronitrile, b.p. 117.4°, and 10% of benzoyl peroxide was violent and complete in three hours. A 62% yield of bromonitrile was isolated. The product was separated into two fractions by fractionation.

Fraction 1 amounted to 76% of the material and had b.p. 63–65° (20 mm.); n^{20}_{D} 1.4652. This material corresponds to α-bromobutyronitrile (2) and was converted by concentrated sulfuric acid to α-bromobutyric acid, which was recrystallized twice from benzene, m.p. 110–111°.

Anal. Calc'd for C_4H_8BrNO: N, 8.44. Found: N, 8.22.

Fraction 2 amounted to 24%, b.p. 69–73° (10 mm.); n^{20}_{D} 1.4754. This material appears to be β-bromobutyronitrile and is converted into β-bromobutyramide, m.p. 95–96° [reported (9), m.p. 92–93°], after recrystallization from a mixture of benzene and petroleum ether.

Anal. Calc'd for C_4H_8BrNO: N, 8.44. Found: N, 7.70.

The amide readily loses hydrogen bromide.

Valeronitrile (V). In the first experiment, the bromination was carried out with 50% excess nitrile, b.p. 141.2°, and in the presence of 10% of benzoyl peroxide. The reaction was violent and completed in 30 minutes. Distillation gave a 38% yield of bromonitrile which was separated into two fractions: Fraction 1 amounted to 30%, b.p. 65–70° (10 mm.). Fraction 2 amounted to 70%, b.p. 87–92° (10 mm.).

Bromination without peroxide also was a violent reaction but was not complete until 1½ hours. Distillation gave 28% of bromontrile which was separated into two fractions, 63%, b.p. 65–70° (10 mm.) and 37%, b.p. 87–92° (10 mm.). The ratio of the fractions varied according to the conditions. In each experiment, nearly all the unchanged valeronitrile could be recovered.

The fraction with b.p. 65–70° (10 mm.) consisted of α-bromovaleronitrile since it was hydrolyzed by concentrated sulfuric acid into α-bromovaleramide (10), m.p. 78–79°, after recrystallization from a mixture of benzene and petroleum ether.

The fraction with b.p. 87–92° (10 mm.) was refractionated and the fraction with b.p. 91–92.5° (10 mm.) was collected. This bromonitrile had d^{15}_{4} 1.4142, d^{30}_{4} 1.3965; at 15°, n_α

1.4759, n_D 1.4777, n_β 1.4851; at 30°, n_α 1.4693, n_D 1.4718, n_β 1.4791; $M_{R\alpha}$ 32.08 (calc'd. 32.71); M_{RD} 32.15 (calc'd 32.87).

The physical constants indicate that this bromonitrile is neither the α-bromo- nor the δ-bromo-isomer. Moreover, by acid hydrolysis a substance was obtained which did not correspond to β-bromovaleric acid (11). The compound can only be the unknown γ-bromovaleronitrile.

DISCUSSION OF RESULTS

The results of bromination of saturated nitriles under varying conditions are listed in Table I. Subheadings (a) and (b) concern the reaction with N-bromosuccinimide, while (c) is related to the direct bromination in the presence of sulfur, as in ref. 2.

The observed partition of monobrominated isomers is listed with the theoretical partition calculated from the number of hydrogen atoms which can be substituted. From this table the effects of orientation become evident.

Before commenting on these results, it would be useful to recall a few points about the mechanism of reactions with N-bromosuccinimide.

First, directed bromination can be carried out under varying conditions with toluene (12a) and methyl- and dimethyl-naphthalene (12 b, c). The authors conclude that reaction takes place by two mechanisms; an ionic mechanism, leading to attack of the nucleus, and a radical mechanism, leading to side chain substitution.

The analogy between direct bromination in the presence of a halogen carrier (Br_2/S, for instance) and the reaction with N-bromosuccinimide alone or activated in the same manner (NBS/S, for instance) should be noted. Both processes lead to the same products by the same type of ionic mechanism.

A further analogy exists between substitution reactions by chlorine and bromine. Catalytic chlorination (13) and bromination (2) of nitriles leads to the corresponding α-halogenated derivatives exclusively. Further, N-chloro and N-bromosuccinimide give the same halogenated derivatives when allowed to react with toluene or dimethyl naphthalene under the same conditions (12c).

From these facts, one would predict that with N-bromosuccinimide in the presence of benzoyl peroxide, a preferential β-substitution of the homologous series of nitriles would occur as in the photochemical chlorination in the gaseous phase.

The results in Table I show that preferential β-substitution is not the case. Propio- (IIa, b) and isobutyro-nitriles (IIIa, b) especially give only the α-brominated derivatives and no β-isomers, in the presence (IIa; IIIa) or absence (IIb; IIIb) of benzoyl peroxide.

In the reactions with butyronitrile, if one compares reactions IVa with IVb the influence of the peroxide clearly appears. The influence becomes stronger in the case of valeronitrile (Va, b, c), where the presence of peroxide (Va) modifies even (Vb) the ratio of α- and β-isomers.

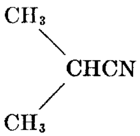
The results may be explained in the following way. In the case of propio- and of isobutyro-nitrile, and even more in the case of acetonitrile, the polar character

TABLE I

MONOBROMINATION OF SATURATED NITRILES

(a) (b) $C_nH_{2n+1}\text{—}CN + SNBr \rightarrow C_nH_{2n+1}Br\text{—}CN + SNH$

(c) $C_nH_{2n+1}\text{—}CN + Br_2 \rightarrow C_nH_{2n+1}Br\text{—}CN + HBr \nearrow$

NITRILES		SOLVENT	REAGENT	MONOBROMINATED ISOMERS, %								TOTAL YIELD, %
				α		β		γ		δ		
				Calc'd	Obs.	Calc'd	Obs.	Calc'd	Obs.	Calc'd	Obs.	
I. CH_3CN	a.	CCl_4	$NSBr/Bz_2O_2$ 10%	100	0	—	—	—	—	—	—	0
	b.	Nitrile	NSBr/S	100	*100*							12
	c.	Nitrile	Br_2/S	100	*0*	—	—	—	—	—	—	0
II. CH_3CH_2CN	a.	CCl_4	$NSBr/Bz_2O_2$ 10%	30	*10/90*[1]	70	0	—	—	—	—	50
	b.	Nitrile	$NSBr/Bz_2O_2$ 10%	30	*100*	70	0	—	—	—	—	45
	c.	Nitrile	Br_2/S	30	0	70	0	—	—	—	—	0
III. 	a.	Nitrile	$NSBr/Bz_2O_2$ 10%	15	*100*	85	0					80
	b.	Nitrile	NSBr/—	15	*100*	85	0					80
IV. $CH_3(CH_2)_2CN$	a.	Nitrile	$NSBr/Bz_2O_2$ 10%	28.5	*76*	28.5	*24*	43	0	—	—	62
	b.	Nitrile	Br_2/S	28.5	*100*	28.5	0	43	0	—	—	>85
V. $CH_3(CH_2)_2CN$	a.	Nitrile	$NSBr/Bz_2O_2$ 10%	22.2	*30*	22.2	*0*	22.2	*70*	33.4	*0*	38
	b.	Nitrile	NSBr/—	22.2	*63*	22.2	*0*	22.2	*37*	33.4	*0*	28
	c.	Nitrile	Br_2/S	22.2	*100*	22.2	*0*	22.2	*0*	33.4	*0*	>85

[1] α,α′-Dibromoderivative is formed simultaneously.

of the reagent has a prevailing influence and this tends to enhance the ionic reaction; peroxide is ineffective (Ia; IIa, b; IIIa, b).

As the polar character of the nitrile decreases with chain length, there is a competition between the radical reaction and the ionic reaction (IVa; Va, b).

If the reaction would take place according to a "pure" ionic mechanism, the α-brominated isomer only should be isolated, as in the experiments IVb and Vc, carried out with free bromine in the presence of sulfur. If radical substitution were to take place only, then large quantities of the β-isomer should be present.

The present results indicate a competition between the ionic and free radical mechanism, in the same manner as Ditmer, *et al.* (14) observed in the reaction of N-bromosuccinimide with the two methylthiophenes.

SUMMARY

A study of the reaction of N-bromosuccinimide with normal saturated nitriles, carried out on a series of five homologous members, showed that the α-brominated substitution derivatives predominated; their β-isomers were found only in small quantities or not at all among the reaction products, even when the reaction was activated with benzoyl peroxide.

The reaction can be carried out in the presence of halogen carriers and thus used to prepare α-brominated derivatives, especially of the first two members of the series which cannot be prepared by direct bromination.

Physical constants, density and refractive indices have been measured at 15 and 30° for α-bromopropionitrile and α-bromoisobutyronitrile.

α,α-Dibromopropionitrile and γ-bromovaleronitrile were isolated and characterized.

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