[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

A STUDY OF THE ALKYLATION OF HYDRATROPONITRILE WITH BUTYL HALIDES[1]

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The alkylation of nitriles containing at least one hydrogen on the α-carbon atom in the presence of sodamide or sodium alkoxides is a relatively well-known reaction. Migrdichian (1) has reviewed much of the relevant literature. In general the alkylations have been accomplished by the use of alkyl bromides, although alkyl iodides have been used to some extent. The use of chloro compounds has apparently been limited almost entirely to benzyl chloride and certain other allyl-type chlorides. Butyl chloride has been reported (2) to react sluggishly at first and then with uncontrollable vigor in the alkylation of acetonitrile and capronitrile.

The yields of alkylated nitrile, in many cases in excess of 90%, appear in general to be dependent upon three factors: (a) the alkyl halide, (b) the nitrile (3, 4), and (c) the temperature and manner in which the alkylation is carried out. Both a low-temperature method (5) and a high-temperature method (80 to 100°) due to Ziegler and Ohlinger (4) have been reported. Tilford, *et al.* (6) have shown that cyclohexyl cyanide was alkylated in best yields by normal alkyl bromides and in poorer yields by secondary and branched chain bromides, whereas tertiary butyl bromide gave no product whatever.

The present investigation was carried out (a) to determine the effect of the halogen of the alkyl halide upon the yield of an alkylated nitrile, (b) to determine the effect of the structure of the alkyl group upon the yield of an alkylated nitrile, and (c) to attempt to prepare highly branched nitriles such as α-phenyl-α,β,β-trimethylbutyronitrile (V). Hydratroponitrile (α-phenylpropionitrile) was selected for alkylation in the hope of obtaining V and also because only monoalkylation could occur. After a number of preliminary experiments, the high-temperature alkylation procedure of Ziegler and Ohlinger was adopted and was used throughout the work. The results are shown in Table I. On the basis of the reaction of the normal butyl halides, it appears that chlorides, bromides, and iodides react about equally well as alkylating agents under the high-temperature conditions. After this was observed, hydratroponitrile was alkylated using isobutyl, *sec*-butyl, and *tert*-butyl chlorides. Surprisingly, the yields by the first two of these halides were approximately the same and appeared to be slightly better than than those obtained from *n*-butyl chloride. *tert*-Butyl chloride, as expected, gave either no product or a very small yield. This may be due to one or a combination of the following: (a) Alkaline condensing agents are known to cause dehydrohalogenation of *tert*-alkyl halides with the formation of alkenes. (b) Steric hindrance may prevent the bulky anion from approaching the *tert*-alkyl halide from the back and displacing the chloride ion. (c) When *tert*-butyl chloride was the

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TABLE I

YIELDS OF ALKYLATED HYDRATROPONITRILES

	CONVERSION, %[a]	YIELD, %[b]	B.P. range, °C.	MM.
HALIDE				
n-Butyl chloride	61	71	97–107	2
n-Butyl bromide	61[c]	74	92–113	3–4
n-Butyl iodide	62	77	90–107	2
Isobutyl chloride	69	79	95–112	4–5
	60[d]	76	93–106	3
sec-Butyl chloride	67	78	95–115	4
	68	76	91–114	4
tert-Butyl chloride	12	34	90–107	3
	Trace			
	Trace			
	4.3	14	107–112	4
	6.4	26	107–112	4
	6.0	20	107–113	3

[a] Based on starting weight of hydratroponitrile. [b] Based on recovery of unchanged hydratroponitrile. [c] Reported yield 71% (7). [d] Redistilled before calculation of yield.

alkylating agent, it was not possible to heat the reaction mixture to 80° before the addition of the sodamide, hence the reaction may not have been carried out under the optimum conditions.

The above results differ somewhat from those of Tilford and co-workers. They obtained better yields with normal alkyl bromides than was obtained with the normal butyl halides in the present work. The yields which they obtained from branched alkyl bromides were approximately the same as those obtained with isobutyl chloride, whereas the 2- and 3-bromopentanes gave somewhat lower yields than *sec*-butyl chloride. However, they failed to isolate an alkylation product using *tert*-butyl bromide. This latter result is in agreement with previous failures in this laboratory in attempts to alkylate hydratroponitrile with *tert*-amyl chloride under low-temperature conditions.

In Table II are listed the physical properties of the nitriles prepared in this

TABLE II

PHYSICAL PROPERTIES OF NITRILES

No.	COMPOUND	B.P.		n_D^{20}	d_4^{20}	$\gamma \frac{\text{dynes}}{\text{cm.}}$[a]	N,[b] %
		°C.	MM.				
I	Hydratroponitrile	82	3	1.5120	0.9853	41.2	10.82[c]
II	α-Phenyl-α-methylcapronitrile	102	2[d]	1.4997	.9405	36.7	7.58
III	α-Phenyl-α,γ-dimethylvaleronitrile	102	2	1.4992	.9407	35.6	7.65
IV	α-Phenyl-α,β-dimethylvaleronitrile	105	2	1.5062	.9558	37.4	7.59
V	α-Phenyl-α,β,β-trimethylbutyronitrile	107	4	1.5156	.9724	38.6	7.67

[a] Surface tension measurements were made at 21° by the ring method. [b] Calc'd for $C_{13}H_{17}N$: N, 7.47. [c] Calc'd for C_9H_9N: N, 10.62. [d] Reported b.p. 147° (16 mm.) (7).

work. The products of the appropriate individual alkylations were combined and redistilled, and the physical constants were determined on the redistilled nitriles.

Attempts to prepare derivatives of the nitriles were only partially successful. Hydratroponitrile was easily hydrated to the amide by 66% sulfuric acid in 15 minutes. A series of attempts to hydrate α-phenyl-α-methylcapronitrile to the amide by heating with sulfuric acid of varying strengths for as long as 13 hours failed. Other unsuccessful attempts involved heating the nitrile with (a) 100% phosphoric acid at 180° for five hours, (b) a mixture of 25% sodium hydroxide and 30% hydrogen peroxide at 60° for three hours, and (c) alcoholic potassium hydroxide solution for 48 hours. This difficulty of hydration has been confirmed recently by Arcus, *et al.* (7) who succeeded in partially converting this nitrile (II) into a mixture of amide and acid by refluxing it with alcoholic potassium hydroxide for a period of ten days. α-Phenyl-α-methylcapronitrile and α-phenyl-α,γ-dimethylvaleronitrile were hydrolyzed partially after refluxing for ten hours with potassium hydroxide in amyl alcohol and were converted to the corresponding anilides without isolating the intermediate acid or acid chloride. Both α-phenyl-α,β-dimethylvaleronitrile and α-phenyl-α,β,β-trimethylbutyronitrile failed to hydrolyze under these conditions or when heated with benzyl alcohol or diethylene glycol in place of amyl alcohol. It is thus seen that branching on the α-carbon atom and the massing of methyl groups near the cyano group increases the difficulty of hydrolysis of the nitrile.

This increasing difficulty in hydrolysis or hydration of the nitrile in proceeding from hydratroponitrile to the highly branched compound V is in agreement with the *rule of six* or *six-number* concept advanced by Newman (8). The *effective six-number* of these compounds increases from 2 for hydratroponitrile to 5, 5, 8, and 11 for nitriles II, III, IV, and V respectively. Nitriles II and III with the same *effective six-number* could be hydrolyzed, but the hydrolysis of IV and V failed under the conditions used. In the latter two compounds the cyano group is more effectively shielded by the methyl groups in the β-position than by those further removed as in compounds II and III.

EXPERIMENTAL

The melting points given below are uncorrected.

Hydratroponitrile. The preparation of hydratroponitrile was carried out by the procedure of Newman and Closson (9). It was collected at 110–114° at 21 mm. The hydratropic aldehyde was purchased from Van Amerigen-Haebler, Inc.

Sodamide. A modification of the procedure of Hancock and Cope (10) was used. The sodamide was prepared in liquid ammonia as described. The excess ammonia was then permitted to evaporate through the drying tube. The flask was evacuated for about an hour by a water-pump at a pressure of 12 to 13 mm. The vacuum was broken by nitrogen, and after pulverizing the sodamide under a nitrogen atmosphere, it was transferred to nitrogen-filled bottles. The bottles were corked and sealed with paraffin until needed.

Alkylation of hydratroponitrile. Preparation of α-phenyl-α-methylcapronitrile. The procedure used was similar to that of Ziegler and Ohlinger (4). In a 1-l. three-necked flask equipped with a stirrer, reflux condenser, and dropping-funnel was placed a mixture of 34 g. (0.26 mole) of hydratroponitrile, 28 g. (0.3 mole) of *n*-butyl chloride and an equal volume of dry toluene. The mixture was warmed to 80°. A suspension of powdered sodamide (12–13 g.) in toluene was added in small portions from the dropping-funnel. Little reaction was observed until the temperature rose to 90 to 95°. At this temperature the reaction became vigorous and each addition of sodamide was followed by rapid refluxing and foaming. After all of the sodamide had been added, the mixture was refluxed for an hour, cooled, and treated with water. The organic layer was washed twice with water, and the combined aqueous layers were extracted with toluene. The combined toluene extracts were dried and the toluene was distilled. The residual mixture was fractionated under reduced pressure through a 2 × 20 cm. column packed with $\frac{3}{16}$ in. glass helices. There was obtained a forerun of 4.6 g., b.p. 50 to 97° (2 mm.) which was largely unchanged hydratroponitrile. α-Phenyl-α-methylcapronitrile was collected at 97–107° (2 mm.) and it amounted to a 61% conversion of the starting nitrile.

The above procedure and equipment was used throughout the investigation. The same weight of reactants was used in each reaction and the isolation procedures were identical.

Derivatives. Hydratropamide was obtained by warming the nitrile with five parts of concentrated sulfuric acid and $1\frac{1}{2}$ parts of water by volume for 15 minutes. After recrystallization from hot water it melted at 93.5–94° [reported 94–98° (11)].

α-Phenyl-α-methylcaproanilide. A mixture of 20 ml. of amyl alcohol, 1 g. of potassium hydroxide, and 5 g. of II was refluxed for ten hours. The amyl alcohol was distilled, and the residue was acidified and extracted with benzene. After evaporation of the benzene, the resulting liquid was refluxed with thionyl chloride for one-half hour. The excess thionyl chloride was distilled and the cold residue was poured into a mixture of benzene and aniline. The benzene solution was extracted with 10% hydrochloric acid, then with 10% sodium hydroxide solution, and washed with water. After evaporation of the benzene, the brown solid was recrystallized from hot aqueous alcohol (Norit), giving fine white needles, m.p. 111.5°.

Anal. Calc'd for $C_{19}H_{23}NO$: N, 4.98. Found: N, 5.12.

α-Phenyl-α,γ-dimethylvaleroanilide, obtained from III as described above, melted at 120°.

Anal. Calc'd for $C_{19}H_{23}NO$: N, 4.98. Found: N, 5.08.

A mixture of the above anilides melted at 105–107°.

SUMMARY

1. The alkylation of hydratroponitrile with *n*-butyl chloride, bromide, and iodide in the presence of sodamide using the procedure of Ziegler and Ohlinger shows that the halogen of the alkyl halide has little effect on the yield of α-phenyl-α-methylcapronitrile.

2. In the alkylation of hydratroponitrile with *n*-butyl, isobutyl, *sec*-butyl, and *tert*-butyl chlorides, the structure of the alkyl group effects the yield, the yields being in the order iso > secondary > normal ≫ tertiary.

3. Four nitriles, three of them new, have been prepared and their physical properties have been determined. The difficulty of hydrolysis of these nitriles has been discussed.

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