A STUDY OF THE ALKYLATION OF HYDRATROPONITRILE WITH AMYL HALIDES

Thesis for the Degree of M. S.
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Richard Lee Jacobs
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This is to certify that the

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has been accepted towards fulfillment
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Gordon L Goerner
Major professor

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By

Richard Lee Jacobs

A THESIS

Submitted to the School of Graduate Studies of Michigan
State College of Agriculture and Applied Science
in partial fulfillment of the requirements
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VITA

Name: Richard Lee Jacobs

Born: August 4, 1931 in Perrysburg, Ohio

Academic Career: Perrysburg High School, 1945-1949

Bowling Green State University,
Bowling Green, Ohio, 1949-1953

Michigan State College,
East Lansing, Michigan, 1953-1955

Degrees Held: B. A. -- Bowling Green State University, 1953

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AN ABSTRACT

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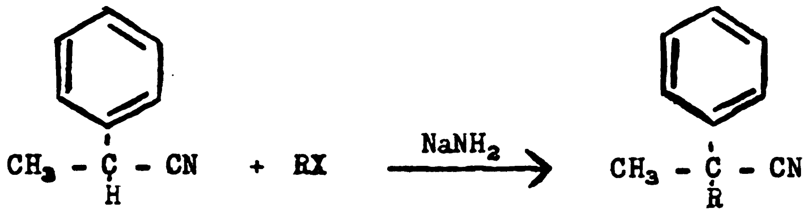
Approved Gordon L. Goerner

ABSTRACT

This study was undertaken to extend prior work concerning the alkylation of hydratroponitrile with alkyl halides. This alkylation reaction proceeds according to the following equation.



Further information has been obtained showing (1) that the halogen of the alkyl halide has little effect upon the yield of alkylated product and (2) that the structure of the alkyl group is the major factor in determining the yield.

Branched chain amyl halides were found to be somewhat more satisfactory alkylating agents than normal amyl halides. Tertiary amyl chloride reacted little or not at all. These conclusions support those obtained earlier by Workman (1).

Unsaturated hydrocarbons were isolated from the reaction mixture of tert.- amyl chloride and hydratroponitrile showing very definitely that one reason for the low yields of alkylated products obtained when tertiary alkyl halides are used as the alkylating agents, is the dehydrohalogenation of the tertiary alkyl group in the presence of an alkaline condensing agent.

Since the nitriles prepared (see Table I) have not previously been reported, their physical properties were determined and each characterized by an appropriate derivative. This latter involved a study of the reaction of hindered nitriles.

Four of these nitriles, namely, I, II, III and VI, were hydrolyzed to the acid and converted to the corresponding anilide. Two others, V and IV could not be hydrolyzed, but could be reduced to the corresponding amines and then characterized as their picrates.

This increasing difficulty in hydrolysis of a nitrile in proceeding from less highly branched to more highly hindered, was found to be in agreement with the <u>six-number</u> concept of Newman (2).

TABLE I

PHYSICAL PROPERTIES OF NITRILES

No.	Compound	B. p., °C.	mm.	N_D^{25}	d_4^{25}
I	2-Phenyl-2-methylheptanenitrile	108	1	1.4941	0.9281
II	2-Phenyl-2,5-dimethylhexanenitrile	104	1	1.4939	0.9264
III	2-Phenyl-2,4-dimethylhexanenitrile	99	ca.1	1.4969	0.9341
IV	2-Phenyl-2,3-dimethylhexanenitrile	115	2	1.5015	0.9421
V	2-Phenyl-2-methyl-3-ethylpentanenitrile	103	1	1.5042	0.9489
VI	2-Phenyl-2-cyclopentylpropanenitrile	112	1	1.5232	1.0010
VII	2-Phenyl-2,3,3-trimethylpentanenitrile				

REFERENCES

(1) W. R. Workman, M. S. Thesis, Michigan State College (1950).

(2) M. S. Newman, J. Am. Chem. Soc., 72, 4783 (1950).

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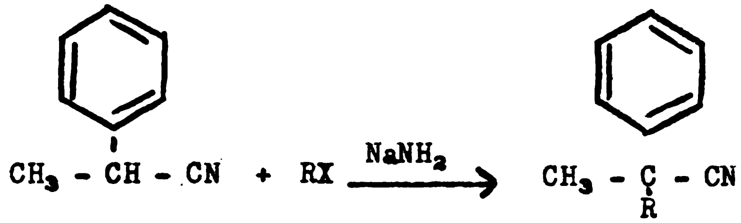
INTRODUCTION

INTRODUCTION

This problem is a continuation of a recent study (1) of the alkylation of hydratroponitrile with butyl halides, in which the effect of different halogens and the effect of the structure of the alkyl group upon the yield was investigated. This alkylation reaction proceeds according to equation I.

I



Workman (1) found that the halogen had little effect on the yield of alkylated product, but that the structure of the alkyl group did effect the yields, and that the yields decreased in the order

iso $\geq$ secondary $>$ normal $\gg$ tertiary

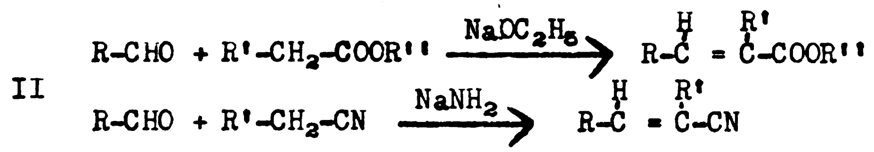
Since the previous study was limited in scope and since the results were not completely in agreement with the results of Tilford et al. (2,3) it appeared desirable to extend the study to the alkylation of hydratroponitrile with the amyl halides, and in particular certain amyl chlorides. The influence of the halogen upon the yield was studied using normal amyl bromide, chloride, and iodide. By employing normal, iso, and tertiary amyl chlorides, cyclopentyl chloride, 2- and 3-chloropentane and 2-methyl-1-chlorobutane, the effect of the structure of the alkyl group was determined. Attempts were made to isolate unsaturated hydrocarbons from certain of the reaction mixtures.

Since the nitriles prepared have not previously been reported, their physical properties were determined and each characterized by an appropriate derivative. The latter involved a study of the reactions of hindered nitriles.

HISTORICAL

HISTORICAL

Nitriles of the type RCH_2CN, which contain a reactive methylene group can be easily alkylated, to give mono or dialkylated products. The activating influence of the cyano group on an adjacent methylene group is analogous to that shown by carbalkoxy and carbonyl groups. Just as esters condense with carbonyl compounds, nitriles react with carbonyl compounds in the presence of a basic condensing agent to yield Claisen type condensation products, as shown by equation II.



II

$$\mathrm{R{-}CHO + R'{-}CH_2{-}COOR''} \xrightarrow{\mathrm{NaOC_2H_5}} \mathrm{R{-}\overset{H}{C} = \overset{R'}{C}{-}COOR''}$$

$$\mathrm{R{-}CHO + R'{-}CH_2{-}CN} \xrightarrow{\mathrm{NaNH_2}} \mathrm{R{-}\overset{H}{C} = \overset{R'}{C}{-}CN}$$

This reaction has been run using ketones as the carbonyl component (4).

Esters have been condensed with nitriles in the presence of a basic condensing agent, the resulting products being β-keto-nitriles as shown in equation III.

III

$$\mathrm{RCOOC_2H_5 + R'CH_2CN} \xrightarrow{\mathrm{NaNH_2}} \mathrm{R{-}\overset{O}{C}{-}\overset{R'}{C}H{-}CN}$$

This reaction is similar in many respects to the well known acetoacetic ester condensation.

The Dieckmann cyclization which occurs with esters of dibasic acids containing five or six carbon atoms, is an acetoacetic ester type condensation. Dinitriles undergo a similar cyclization in the presence of sodamide.

The one outstanding difference between esters of the type RCH_2COOEt and the corresponding nitriles, RCH_2CN, is the fact that these esters cannot be alkylated directly whereas a nitrile can be alkylated easily. The reactive methylene group of the nitrile thus resembles that in malonic or acetoacetic ester. The sodium salt of the nitrile is formed first and this is then alkylated by alkyl halides or by simple alkyl sulfates (equation IV).

$$\text{IV}\quad \begin{aligned} &RCH_2CN + NaNH_2 \longrightarrow [RCHCN]^- \, Na^+ \\ &[RCHCN]^- \, Na^+ + R'X \longrightarrow RCHR'CN + NaX \end{aligned}$$

The condensing agents which have been employed include sodamide, metallic sodium (5,6,), sodium **alkoxides** (ethoxide and isopropoxide) (6,7,8), potassium amide (9), potassium hydroxide (10,11), sodium hydride (12), and lithium diethylamide (13). Sodamide is the most commonly used of the condensing agents and was first employed by Bodroux and Taboury in 1910 (14).

The first report of the use of an alkyl halide as the alkylating reagent for nitriles was that by Meyer in 1889 (6). Since that time alkyl halides have been widely used. A summary of many of the simple alkyl halides, and halides containing other functional groups, which have been used as alkylating agents is to be found in the Masters thesis of W. R. Workman (1). This summary includes material through 1949. A tabulation of nitriles, alkyl halides, and alkyl halides containing other functional groups which have been reported since the study by Workman (1) is presented in Tables I and II.

TABLE I

ALKYLATION OF NITRILES BY ALKYL HALIDES

Halide	Nitrile	Product	Yield	Reference
Methyl iodide	2-Phenylbutanoic nitrile	2-Methyl-2-phenylbutanoic nitrile	70	13
Methyl iodide	2,3-Dimethoxyphenylacetonitrile	α-(2,3-dimethoxyphenyl)-propionitrile	75	18
Methyl iodide	Diphenylacetonitrile	2,2-Diphenylpropionitrile[a]	80-90	12
Methyl iodide	p-Methoxyphenylacetonitrile	p-Anisyldimethylacetonitrile		19
Ethyl bromide	2,3-Dimethoxyphenylacetonitrile	α-(2,3-dimethoxyphenyl)-butyronitrile	71	18
Ethyl bromide	2-Phenylpropionitrile	2-Methyl-2-phenylbutanoic nitrile[b]		13
n-Propyl bromide	Cyclohexyl cyanide	1-(n-Propyl)-cyclohexyl cyanide	76	3
n-Butyl bromide	Hydratroponitrile	2-Methyl-2-phenylhexanenitrile	71	20
n-Butyl bromide	Cyclohexyl cyanide	1-(n-Butyl)-cyclohexyl cyanide	95	3
iso-Butyl bromide	Cyclohexyl cyanide	1-(iso-Butyl)-cyclohexyl cyanide	75	3
n-Amyl bromide	Cyclohexyl cyanide	1-(n-Amyl)-cyclohexyl cyanide	86	3
iso-Amyl bromide	Cyclohexyl cyanide	1-(iso-Amyl)-cyclohexyl cyanide	62	3
2-Bromo pentane	Cyclohexyl cyanide	1-(1-Methylbutyl)-cyclohexyl cyanide	57	3
1-Bromo-2-methylbutane	Cyclohexyl cyanide	1-(2-Methylbutyl)-cyclohexyl cyanide	78	3
3-Bromopentane	Cyclohexyl cyanide	1-(1-Ethylpropyl)-cyclohexyl cyanide	55	3
n-Hexyl bromide	Cyclohexyl cyanide	1-(n-Hexyl)-cyclohexyl cyanide	80	3
1-Bromo-2-ethylbutane	Cyclohexyl cyanide	1-(2-Ethylbutyl)-cyclohexyl cyanide	62	3
1-Bromo-2-methylpentane	Cyclohexyl cyanide	1-(2-Methylpentyl)-cyclohexyl cyanide	60	3
Cyclohexyl bromide	Δ^3-Cyclohexenyl cyanide	1-(Cyclohexyl)- Δ^3-cyclohexyl cyanide	70	3
n-Heptyl bromide	Cyclohexyl cyanide	1-(n-Heptyl)-cyclohexyl cyanide	83	3
n-Octyl bromide	Cyclohexyl cyanide	1-(n-Octyl)-cyclohexyl cyanide	94	3
β-Cyclohexylethyl bromide	Cyclohexyl cyanide	1-(β-Cyclohexylethyl)-cyclohexyl cyanide	75	3
Dibromomethane	Phenylacetonitrile	1-Phenylcyclopropyl cyanide		2
1,3-Dibromopropane	Phenylacetonitrile	1-Phenylcyclobutyl cyanide		2
1,3-Dibromopropane	Cyclohexanenitrile	1-Cyclohexylcyclobutyl cyanide		2
1,4-Dibromobutane	Cyclohexanenitrile	1-Cyclohexylcyclopentyl cyanide		2
1,4-Dibromobutane	Phenylacetonitrile	1-Phenylcyclopentyl cyanide	85	2
1,4-Dibromobutane	α-Naphthylacetonitrile	1-α-Naphthylcyclopentyl cyanide		2
1,4-Dibromobutane	β-Phenylpropionitrile	1-Benzylcyclopentyl cyanide		2
1,4-Dibromobutane	Thenyl cyanide	1-(2-Thienyl)-cyclopentyl cyanide	33	3
1,5-Dibromopentane	β-Phenylpropionitrile	1-Benzylcyclohexyl cyanide		2
1,5-Dibromopentane	α-Naphthylacetonitrile	1-α-Naphthylcyclohexyl cyanide		2
1,5-Dibromopentane	Cyclohexanenitrile	1-Cyclohexylcyclohexyl cyanide		2
1,5-Dibromopentane	Phenylacetonitrile	1-Phenylcyclohexyl cyanide		2
1,5-Dibromopentane	Thenyl cyanide	1-(-Thienyl)-cyclohexyl cyanide	29	3
Cyclohexyl bromide	Δ^3-Cyclohexenyl cyanide	1-(Cyclohexyl)- Δ^3-Cyclohexyl cyanide	70	3

[a] Used sodium hydride in place of sodamide.
[b] Used lithium diethyl amide in place of sodamide.

TABLE II

ALKYLATION OF NITRILES BY ORGANIC HALIDES CONTAINING OTHER FUNCTIONAL GROUPS

Halide	Nitrile	Product	Yield	Reference
2-Dimethylaminoethyl chloride	α-Methylphenylacetonitrile	α-Methyl-α-(2-dimethylaminoethyl)-phenylacetonitrile	50	18
2-Diethylaminoethyl bromide	α-Methylphenylacetonitrile	α-Methyl-α-(2-diethylaminoethyl)-phenylacetonitrile	63	18
2-Dimethylaminopropyl chloride	α-Methylphenylacetonitrile	α-Methyl-α-(2-dimethylaminopropyl)-phenylacetonitrile	48	18
2-Dimethylaminoethyl chloride	α-Methyl-2,3-dimethoxyphenylacetonitrile	α-Methyl-α-(2-dimethylaminoethyl)-2,3-dimethoxyphenylacetonitrile	55	18
2-Diethylaminoethyl bromide	α-Methyl-2,3-dimethoxyphenylacetonitrile	α-Methyl-α-(2-diethylaminoethyl)-2,3-dimethoxyphenylacetonitrile	88	18
2-Dimethylaminopropyl chloride	α-Methyl-2,3-dimethoxyphenylacetonitrile	α-Methyl-α-(2-dimethylaminopropyl)-2,3-dimethoxyphenylacetonitrile	25	18
2-Dimethylaminoethyl chloride	α-Ethyl-2,3-dimethoxyphenylacetonitrile	α-Ethyl-α-(2-dimethylaminoethyl)-2,3-dimethoxyphenylacetonitrile	59	18
β-Diethylaminoethyl bromide	Δ^3-Cyclohexenyl cyanide	1-(β-Diethylaminoethyl)-Δ^3-cyclohexenyl cyanide	51	3
2-Chloro-1-dimethylaminopropane	Diphenylacetonitrile	2,2-Diphenyl-3-methyl-4-dimethylaminobutanenitrile + 2,2-Diphenyl-4-dimethylaminopentenenitrile	[a]	21
2-Chloro-1-piperidinopropane	Diphenylacetonitrile	2,2-diphenyl-3-methyl-1-piperidinobutanenitrile + 2,2-Diphenyl-4-piperidinopentanenitrile	[a]	21

[a] Never isolated either isomeric nitrile in pure form.

Reference to the tables presented in both this study and the previous study by Workman (1), shows that a great variety of branched and straight chained alkyl halides have been used as alkylating agents. By far the greater amount of work has been with the bromides, due to the fact that the bromides are more readily available and are presumably more reactive. The alkyl groups vary in size from methyl to octyl, and compounds of the normal, iso, secondary, cycloalkyl, and benzyl type have been used. It is noteworthy that no report of the introduction of a tertiary alkyl group has been found except that of Workman (1), who was able to isolate a small amount of 2-phenyl-2,3,3-trimethylbutanenitrile from the alkylation of hydratroponitrile with tert.-butyl chloride. Tilford _et al_. (2,3) specifically stated that they were unable to isolate an alkylation product using tert.-butyl bromide in a similar reaction. Chlorobenzene and other halides containing an aromatic ring, which have been used as alkylating agents, are listed in the thesis by Workman. This is interesting inasmuch as malonic ester and acetoacetic ester are not "arylated" by aromatic halides.

The use of dibromomethane and other dihalides such as 1,5 dibromopentane is shown in Table I and results in the formation of cyclic compounds (2). This is similar to the "dialkylation" which has been obtained along with "monoalkylation" by several investigators. For reactions of this type it is necessary that the nitrile be of the general formula $R-CH_2-CN$ and that two moles of the condensing agent be used for each mole of the nitrile.

The reported yields vary widely, perhaps due to different investigators and different conditions of temperature, solvent, and time of reaction. The tables constructed by Workman show that the iodides give better yields than the corresponding bromides, although the evidence for this statement is meager. The chlorides have been little used, except for benzyl chloride, perhaps because as Sperber, *et al.* (15) stated, the chlorides react sluggishly at first and then with uncontrollable vigor.

A comparison of yields as affected by the structure of the alkyl halide is difficult. Comparisons of various work by Workman (1) showed only that the yields were dependent upon the nitrile as well as the alkyl group. Comparison of data from Tables I and II of the present study also support this view.

The data of Tilford *et al.* (2,3) shows that normal alkyl halides give better yields than iso or secondary halides. In contrast to this Workman showed that the order of increasing yield of alkylated product is normal secondary iso. These two studies along with the present study are the only examples in which constant or quite similar conditions were used throughout the investigation.

It should be mentioned, however, that the Tilford group employed the low temperature method of alkylation whereas the present study and the study by Workman employed the high temperature method of alkylation. Tilford condensed various nitriles with alkylene dibromides using two equivalents of sodamide, in a liquid ammonia and ether mixture at about -50°C. Workman employed temperatures of 90-95°C.

Condensations in which other functional groups are present in the alkyl halide are summarized in Table II. This table shows that a variety of halo-substituted amines have been used. The use of halo-substituted amines was introduced in 1939 by Eisleb (16,17), and has been frequently used since then. Further examples of the use of alkyl halides containing other functional groups may be found in Table IV of Workman's thesis.

EXPERIMENTAL

EXPERIMENTAL[a]

I. REAGENTS

Hydratropic aldehyde -- van Ameringen-Haebler Inc. Used as received.

n-Amyl chloride -- Columbia Organic Chemical Co. Used fraction distilled at 104° at 733 mm.

n-Amyl bromide -- Columbia Organic Chemical Co. Used fraction distilled at 125.5-126.5° at 733 mm.

n-Amyl iodide -- Columbia Organic Chemical Co. Used fraction distilled at 152° at 737 mm. The redistilled material was slightly red due to free iodine.

Isoamyl chloride -- Eastman Kodak Co.. White label. Used fraction distilled at 96-97° at 740 mm.

tert.-Amyl chloride -- Eastman Kodak Co. White label. Used fraction distilled at 82-83° at 742 mm.

2-Bromopentane -- Eastman Kodak Co. White label. Used as received.

n-Propyl chloride -- Eastman Kodak Co. White label. Used as received.

sec.-Butyl bromide -- Columbia Organic Chemical Co. Used as received.

3-Pentanone -- Eastman Kodak Co. White label. Used as received.

Hydroxylamine hydrochloride -- Eastman Kodak Co. White label. Used as received.

Acetic anhydride -- Eastman Kodak Co. White label. Used as received.

Phenyl Isothiocyanate -- Eastman Kodak Co. White label. Used as received.

Picric Acid -- Merck and Co., Inc. Used as received.

Lithium Aluminum Hydride -- Metal Hydrides, Inc. Repackaged in small bottles and stored in desiccator.

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[a] All analyses were by Mico-Tech Laboratories, Skokie, Ill.

Sodium Hydride -- Metal Hydrides, Inc. Repackaged in small bottles and stored in desiccator.

Pyridine -- Baker Analyzed Reagent -- The pyridine was dried before use by distilling from barium oxide.

Trioxymethylene -- Eastman Kodak Co. White label. Dried in a desiccator for a week over sulfuric acid.

Paraldehyde -- Eastman Kodak Co. Yellow label. Used as received.

Cyclopentanone -- Student preparation. Used fraction redistilled at 125° at 740 mm.

Thionyl chloride -- Matheson-Coleman-Bell. Used as received.

Thionyl chloride -- Eastman Kodak Co. Yellow label. Purified according to the directions of Fieser (22). Three-hundred milliliters of the practical grade thionyl chloride was placed in a 500 ml. one-necked flask equipped with a 14 in. Vigreux column, and 60 ml. of quinoline added. A condenser and adapter were attached to the side arm of the column and the mixture distilled. Small suction flasks equipped with calcium chloride drying tubes were used as receivers. Two-hundred and fifty milliliters of distillate were collected. This material was next placed in a clean 500 ml. one-necked flask and 120 ml. of linseed oil added. This mixture was distilled as before. The purified thionyl chloride distilled at 72° at 741 mm. The material was collected in glass stoppered bottles and the bottles sealed with paraffin.

Formaldehyde -- Prepared from trioxymethylene by depolymerizing with heat. Also used directly in the form of its trimer. In both cases the trioxymethylene was dried prior to use by keeping in a desiccator over concentrated sulfuric acid.

Acetaldehyde -- Prepared just prior to use by adding a few drops of concentrated sulfuric acid to paraldehyde and distilling through a 3 x 40 cm. column packed with 3/16 in. glass helices. The acetaldehyde distilled at 19° at 741 mm.

II. PREPARATION OF INTERMEDIATES

A. Preparation of 2-Chloropentane

The chloride was prepared from 2-pentanol and thionyl chloride following the procedure of Whitmore and Karnatz (23). The required 2-pentanol was prepared via the Grignard reagent from n-propyl chloride and acetaldehyde using a modification of the method developed by Wood and Scarf (24).

A typical run for the preparation of 2-pentanol follows. In a 3-l. three-necked flask equipped with a stirrer, an inlet tube for nitrogen, and a parallel side arm holding a reflux condenser and dropping funnel, were placed 48.6 g. (2 moles) of clean dry magnesium turnings and 100 ml. of anhydrous ether. The condenser and dropping funnel were protected with calcium chloride drying tubes, and the entire system swept out with dry nitrogen. Ten milliliters of n-propyl chloride was then added to the flask. After the reaction was initiated, the remainder of 158 g. (2 moles) of n-propyl chloride, which had previously been diluted with 700 ml. of anhydrous ether, was added slowly to the contents of the flask. The prepared Grignard reagent was allowed to stand overnight under a nitrogen atmosphere. Next 77 g. (1.75 moles) of freshly distilled acetaldehyde diluted with 300 ml. of anhydrous ether was added dropwise to the Grignard reagent. It was necessary to moderate the reaction by keeping the 3-l. flask in an ice bath. After all the acetaldehyde had been added, the mixture was stirred for three hours. The reaction mixture was hydrolyzed by pouring onto cracked ice, and the ether layer decanted. The remaining material was decomposed with 3-N. sulfuric acid and the resulting liquid filtered from unreacted magnesium. The liquid was then extracted with four 100 ml. portions of ether. The combined ether extracts were washed with water, dried over anhydrous sodium sulfate, and the ether distilled at atmospheric pressure. The concentrated mixture was then fractionated at atmospheric pressure through a 3 x 40 cm. column packed with 3/16 in. glass helices. The 2-pentanol used in the subsequent preparation of 2-chloropentane was collected at 114-116° at 741.5 mm, N_D^{20} 1.4062. Kharasch (25) reported a boiling point of 117-118.5° at 760 mm., N_D^{20} 1.4063-1.4067. Three runs gave yields of 57%, 75% and 82% of 2-pentanol.

Several attempts to prepare 2-chloropentane using Eastman "Practical Grade" thionyl chloride, which had been purified as described above, met with little success. When Matheson-Coleman-Bell brand thionyl chloride was used, the reaction proceeded as expected. These facts are shown very clearly in Table III.

A typical run for the preparation of 2-chloropentane follows. In a 1-l. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel was placed a mixture of 64 g. (0.73 mole) of 2-pentanol and 61 g. (0.77 mole) of dry pyridine. The flask was cooled in an ice bath and 108 g. (0.91 mole) of thionyl chloride was added dropwise to the contents of the flask. After all the thionyl chloride had been added, the ice bath was removed and the flask allowed to stand at room temperature for one hour. The flask was then placed in a water bath and heated during the course of two hours up to a temperature of 53°. The contents of the flask were then poured onto 200 g. of cracked ice, the resulting two layers separated, and the halide layer washed first with several portions of 10% sodium carbonate solution and then with water. The material was dried over anhydrous magnesium sulfate and a preliminary distillation carried out using an ordinary Wurtz flask. The distillate was then redistilled at atmospheric pressure through a 2 x 20 cm. column packed with 3/16 in. glass helices. The 2-chloropentane distilled at 94-95° at 747.4 mm., N_D^{20} 1.4062. The reported values are 95.5-96° at 755 mm., N_D^{20} = 1.4068 (25). The yields for the various runs are recorded in Table III.

B. Preparation of 3-Chloropentane

Pure 3-chloropentane was prepared from 3-pentanol and thionyl chloride using the procedure of Whitmore and Karnatz (23). The required 3-pentanol was prepared by catalytically reducing 3-pentanone according to the following directions.

In the glass liner of a 1-l. steel bomb was placed a mixture of 172 g. (2 moles) of 3-pentanone and 6 g. of copper chromium oxide catalyst (37), and this in turn incorporated into a high pressure hydrogenation apparatus. The hydrogenation was carried out at 150° under an initial hydrogen pressure of 1550 p.s.i. and was complete in 4 hours. The bomb was allowed to cool overnight and then the contents were filtered through a fritted glass funnel. The filtrate was distilled at atmospheric pressure through a 3 x 40 cm. column packed with 3/16 in.

glass helices. The 3-pentanol distilled at 111-112° at 747 mm., N_D^{25} 1.4077 (25). A 95% yield was obtained in each of two runs.

The 3-chloropentane was prepared from 3-pentanol in the same manner as already described for 2-chloropentane. In preparing the 3-chloropentane it was observed that, as in the case of 2-chloropentane, when Eastman brand thionyl chloride was used very little product was obtained. However, when Matheson-Coleman-Bell brand thionyl chloride was employed good yields of 3-chloropentane were obtained. Table III summarizes the yields obtained for the various runs of both 2-chloropentane and 3-chloropentane.

TABLE III

YIELDS OF 2- AND 3- CHLOROPENTANE

Run	% 2-Chloropentane[a]	Thionyl Chloride Used
I	trace	Eastman (purified)
II	trace	Eastman (purified)
III	trace	Eastman (purified)
IV	38.5	Matheson-Coleman-Bell
V	trace	Eastman (practical)
VI	42.2	Matheson-Coleman-Bell
	% 3-Chloropentane[b]	
I	trace	Eastman (purified)
II	36.1	Matheson-Coleman-Bell
III	39.3	Matheson-Coleman-Bell
IV	40.0	Matheson-Coleman-Bell
V	45.0	Matheson-Coleman-Bell

[a] Based on 2-pentanol
[b] Based on 3-pentanol

C. Preparation of 1-Chloro-2-Methylbutane

The chloride was prepared from 2-methyl-1-butanol and thionyl chloride following the procedure of Brown and Groot (26). The required 2-methyl-1-butanol was prepared via the Grignard reagent using sec.-butyl bromide and formaldehyde. The procedure used was as follows.

In a 2-l. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel was placed a mixture of 48.6 g. (2 moles) of clean dry magnesium turnings and 100 ml. of anhydrous ether. Five milliliters of sec.-butyl bromide was then added. After the reaction was underway the remainder of 274 g. (2 moles) of sec.-butyl bromide, which had been mixed with 800 ml. of anhydrous ether, was slowly added to the reaction mixture. The usual precautions regarding the exclusion of moisture were observed. The prepared Grignard reagent was allowed to stand overnight. Ninety grams (3 moles) of dried paraformaldehyde were placed in a 500 ml. one-necked flask. A delivery tube was constructed of 10 mm. glass tubing which led from the 500 ml. flask into the 2-l. flask holding the previously prepared Grignard reagent. The tube was not allowed to go below the surface of the liquid in the 2-l. flask. The 500 ml. flask was heated in order to depolymerize the paraformaldehyde and thereby create anhydrous gaseous formaldehyde. It was necessary to apply heat to the delivery tube to prevent plugging. Subsequent hydrolysis of the reaction mixture and distillation gave very little of the desired alcohol. When five moles of paraformaldehyde were used, even less alcohol than before was formed. In both of these runs, most of the material distilled at rather high temperatures and was believed to be the diamyl ether of formaldehyde.

The 2-methyl-1-butanol was finally obtained according to the method of Hickinbottom (33). Instead of producing gaseous formaldehyde, 70 g. (2.33 moles) of paraformaldehyde was added directly to the Grignard reagent prepared from 325 g. (2.37 moles) of sec.-butyl bromide and 57 g. (2.37 moles) of magnesium. The mixture was allowed to stand overnight and finally heated under reflux for ten hours. The reaction mixture was hydrolyzed by pouring onto chipped ice, the ether layer was decanted, and the remaining material decomposed with dilute sulfuric acid. The resulting solution was extracted several times with ether and the combined ether extracts dried over anhydrous potassium carbonate. The ether was distilled at atmospheric pressure. The concentrated mixture was then distilled at atmospheric pressure through a 3 x 40 cm. column packed with 3/16 in. glass helices. The 2-methyl-1-butanol distilled at 124-125° at 745.5 mm., N_D^{20} 1.4101. This alcohol is reported to distill at 128-129° at 760 mm., N_D^{20} 1.4111 (38).

2-Methyl-1-butanol was converted to the corresponding chloride as follows. In a 500 ml. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel was placed a mixture of 52.8 g. (0.6 mole) of 2-methyl-1-butanol and 47.4 g. (0.6 mole) of dry pyridine. The flask was placed in an ice bath and 119 g. (0.9 mole) of thionyl chloride added dropwise over the course of 45 minutes. The ice bath was removed and the reaction mixture allowed to stand overnight. The mixture was then refluxed for ten hours, cooled, and poured into a

500 ml. separatory funnel. The bottom layer was drawn off and the remaining material treated with ice. The material was washed with small portions of water, with small portions of a saturated sodium carbonate solution, and finally again with water. The crude product was dried over anhydrous calcium chloride. A preliminary distillation of the material using an ordinary Wurtz flask was followed by a careful distillation of the material at atmospheric pressure through a 3 x 40 cm. column packed with 3/16 in. glass helices. Two runs were made in which yields of 56% and 66% were obtained. The 1-chloro-2-methylbutane distilled at 97.5° at 735.5 mm., N_D^{20} 1.4125. These constants as reported by Brown and Groot are b.p. 99.5° at 750 mm., N_D^{20} 1.4126.

D. Preparation of Chlorocyclopentane

The chloride was prepared from cyclopentanol, concentrated hydrochloric acid, and calcium chloride according to the procedure of Yarnell and Wallis (27). The required cyclopentanol was prepared by catalytically reducing cyclopentanone using the following procedure.

In the glass liner of a 1-l. steel bomb was placed a mixture of 168 g. (2 moles) of redistilled cyclopentanone and 6 g. of copper chromium oxide catalyst (37), and the bomb incorporated into a high pressure hydrogenation apparatus. The hydrogenation was carried out at 150° and an initial hydrogen pressure of 1450 p.s.i. After seven hours, the uptake of hydrogen had ceased and the bomb was allowed to cool. The contents of the bomb were filtered through a fritted glass funnel and the filtrate distilled at atmospheric pressure through a

3 x 40 cm. column packed with 3/16 in. glass helices. The cyclopentanol distilled at 135.5° at 738.4 mm., N_D^{20} 1.4524. The recorded values are 139-141°, N_D^{20} 1.4530 (39). A 91% yield was obtained.

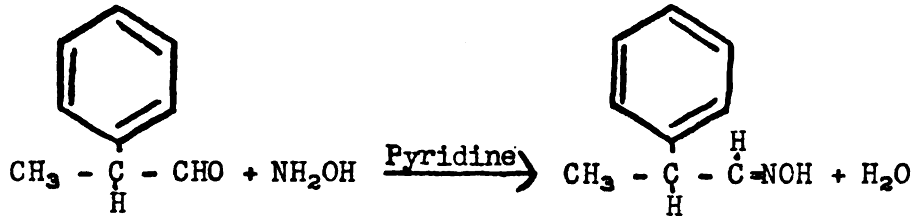
Cyclopentanol was converted to the corresponding chloride as follows. In a 2-l. two-necked flask equipped with a stirrer and reflux condenser was placed a mixture of 150 g. (1.74 moles) of cyclopentanol, 1020 ml. of concentrated hydrochloric acid, and 120 g. of anhydrous calcium chloride. The mixture was refluxed with stirring for a period of 4 hours. The flask was then cooled and the contents poured into a 2-l. separatory funnel. The bottom layer was drawn off and the remaining material washed first with several portions of 10% sodium carbonate solution and then with water. The crude product was dried over anhydrous magnesium sulfate. Distillation at atmospheric pressure through a 3 x 40 cm. column packed with 3/16 in. glass helices gave a 60% yield of chlorocyclopentane having a boiling point range of 112-120° at 739 mm., N_D^{20} 1.4510. Yarnell and Wallis (27) report values of 113.5-114.5° and N_D^{20} 1.4510.

E. Preparation of Sodamide

A modification of the method described by Hancock and Cope (28) was used. A typical run is as follows. A 1-l. three-necked flask was equipped with a stirrer, inlet tube, and a soda lime tube. The flask was cooled in a dry ice-acetone bath and 600 ml. of liquid ammonia was introduced through the inlet tube from an inverted ammonia cylinder. The cooling bath was removed, the inlet tube was replaced by a rubber stopper, and a few crystals of hydrated ferric nitrate were added. A small piece of sodium was cut, blotted with filter paper, and added to the liquid ammonia. The solution was stirred until the blue color dissappeared, after which 46 g. (2 moles) of sodium was added in small pieces as rapidly as it could be cut, while the solution was stirred vigorously. After the solution had turned from blue to gray, the flask was swirled by hand until the sodium which had been splattered onto the upper part of the flask was washed into the solution. The excess ammonia was then permitted to evaporate through the soda lime tube. After all of the ammonia had evaporated, the flask was evacuated to 12-13 mm. by a water pump for a period of approximately an hour. The vacuum was broken by nitrogen and after pulverizing the sodamide under a nitrogen atmosphere, the sodamide was transferred to nitrogen-filled clear glass bottles. About 30 g. of sodamide was placed in each bottle and the bottle corked and sealed with paraffin. The yield amounted to 95% based on the sodium used.

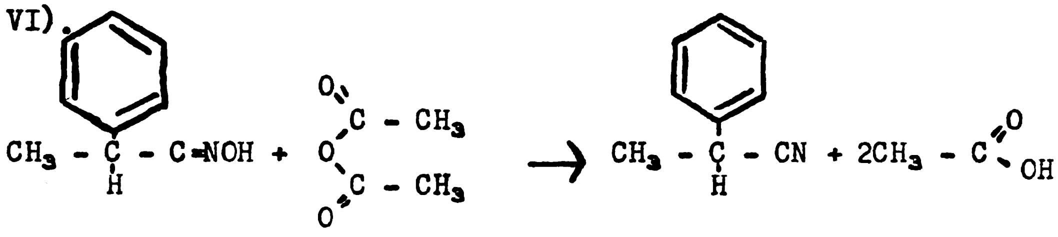
III. PREPARATION OF HYDRATROPONITRILE

Various methods are available for the preparation of hydratroponitrile. The most direct method is the monoalkylation of phenylacetonitrile by means of either methyl iodide (6,29) or methyl sulfate (30). However, the product is contaminated with the disubstituted nitrile. Another direct method is the condensation of propionitrile and chlorobenzene with potassium amide (9). Another method which leaves no doubt as to the composition of the nitrile was used by Newman and Closson (31) and also by Workman (1). Hydratropaldehyde was converted to hydratropaldoxime by means of hydroxylamine and pyridine (Equation V).

V 

$$CH_3-\underset{H}{C}(C_6H_5)-CHO + NH_2OH \xrightarrow{\text{Pyridine}} CH_3-\underset{H}{C}(C_6H_5)-\overset{H}{C}{=}NOH + H_2O$$

The oxime was then dehydrated to the nitrile by acetic anhydride (Equation VI).

VI 

$$CH_3-\underset{H}{C}(C_6H_5)-C{=}NOH + (CH_3CO)_2O \longrightarrow CH_3-\underset{H}{C}(C_6H_5)-CN + 2CH_3-C\overset{O}{\leqslant}_{OH}$$

This procedure was followed in preparing hydratroponitrile throughout the present work, A typical preparation is as follows.

In a 3-l. one-necked flask equipped with an efficient reflux condenser was placed a mixture of 300 g. (2.23 moles) of hydratropaldehyde, 600 ml. of water, 375 g. of hydroxylamine hydrochloride, and

1200 ml. of pyridine. This was refluxed 5 hours and then poured into three liters of 6 N. acetic acid. The organic layer was separated and the aqueous layer extracted with benzene. The organic layers were combined and distilled without drying. The fraction distilling between 115-145° (mostly at 142°) at 20 mm. was assumed to be the crude hydratropaldoxime. This amounted to 216 g. or a yield of 65% based on the original aldehyde.

The hydratropaldoxime was converted to the nitrile by refluxing for 5 hours with 720 ml. of acetic anhydride in a 2-l. one-necked flask equipped with a 3 x 40 cm. column packed with 3/16 in glass helices. The acetic acid was removed as it formed. The resulting mixture was then fractionated under diminished pressure. One-hundred and fifty-four grams of nitrile boiling at 114-116° at 19 mm., N_D^{20} 1.5120, N_D^{25} 1.5090 was collected. The reported constants are 107-110° at 11 mm. (31) and N_D^{20} 1.5120 (1). This corresponded to an 81% yield based on the aldoxime.

The yields on all runs are shown in Table IV.

TABLE IV

YIELDS OF HYDRATROPONITRILE

Run	Wt. of Aldehyde	Oxime, %	Nitrile[a], %	Nitrile[b], %
I	100 g.	54.1	75.8	40.9
II	100	61.3	80.8	50.1
III	300	65.0	81.1	53.1
IV	300	58.3	70.6	41.1
V	300	69.8	80.9	56.5
VI	225	73.5	83.1	60.7

[a] Based on oxime
[b] Based on aldehyde

IV. ALKYLATION OF HYDRATROPONITRILE

The procedure used for the alkylation of the hydratroponitrile was the high temperature method developed by Ziegler and Ohlinger (32). A typical run is as follows. In a 1-l. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel was placed a mixture of 33 g. (0.25 mole) of hydratroponitrile, 32 g. (0.30 mole) of 1-chloro-2-methylbutane, and an equal volume of dry tolune. This was warmed to 85°. A suspension of powered sodamide (12-13 g.) in toluene was added in small portions from the dropping funnel. Little reaction was observed until the temperature rose to 95°. At this temperature the reaction became vigorous, and each addition of sodamide was followed by rapid refluxing and foaming. After all the sodamide had been added, the mixture was refluxed for an hour, cooled, and treated with water. The organic layer was washed with several portions of water, and the combined aqueous layers were then extracted with toluene. The combined toluene layers were dried over anhydrous sodium sulfate and the toluene distilled at atmospheric pressure through a 3 x 40 cm. column packed with 3/16 in. glass helices.

The concentrated mixture was then distilled at about 1 mm. pressure through a 2 x 20 cm. column packed with 3/16 in. glass helices. The following is a sample run.

Fraction	Wt. in g.	B.p., °C.	N_D^{25}
1	1.5	59-91	1.4910
2	2.3	91-98	1.4966
3	2.0	98-99	1.4969
4	7.4	98-100	1.4969
5	6.3	98.5-99	1.4969
6	5.9	98-99	1.4969
7	1.6	98-99	1.4969
8	6.8	97-99	1.4969
9	6.5	98.5-100	1.4969
10	6.8	97-98	1.4969
11	2.0	98-99	1.4969
12	1.2	99-83	1.4970

One gram of tar remained. A total of 45.3 g. of material with a boiling point range of 97-100°, N_D^{25} 1.4969 was collected. This amounts to a 90.2% yield based on starting nitrile. Table V summarizes the yields obtained from the various halides.

This procedure was followed in every run. In all the alkylation reactions, heat was liberated. Except for the reactions involving n-amyl iodide, 2-chloropentane, and tert.-amyl chloride no unchanged hydratroponitrile was recovered. In the reactions using tert.-amyl chloride, 2-chloropentane, and 3-chloropentane, the reflux condenser was equipped with an outlet tube which led into a dry-ice-acetone trap so that any volatile materials given off by the reaction mixture would be caught. However, only in the case of tert.-amyl chloride did any material other than ammonia collect in the trap. This material, which amounted to several grams, was distilled. Fractions were collected which had boiling points and refractive indices corresponding to 2-methyl-1-butene and 2-methyl-2-butene. These fractions gave positive tests for unsaturates. In one run using tert.-amyl chloride, sodium

TABLE V

YIELDS OF ALKYLATED HYDRATROPONITRILES

Halide	Run	Yield[a]	B.p.	
		%	°C.	mm.
n-Amyl chloride	I	77.7	111-116	4-6
	II	77.1	122-142	4
n-Amyl bromide	I	75.7	128-132	6
n-Amyl iodide	I	60.0 (73)[b]	119-123	4
iso-Amyl chloride	I	84.7	107-110	2-3
	II	83.7	110-120	2-4
1-Chloro-2-Methyl-butane	I	89.8[c]	97-99	ca. 1
	II	90.2[c]	97-99	ca. 1
2-Chloropentane	I	69.3 (88)[b]	106-120	2
2-Bromopentane	I	83.7	98-101	1
3-Chloropentane	I	87.3	106-116	2-1
	II	84.3	103-108	ca. 1
Chlorocyclopentane	I	90.5	117-120	1-2
	II	86.0	115-120	1-2
tert.-Amyl chloride	I	trace	118-132[d]	2
	II	trace	113-148[d]	1
	III[e]	trace	119-124[d]	2

[a] Based on starting weight of hydratroponitrile.

[b] Based on hydratroponitrile consumed. Some unchanged nitrile was recovered.

[c] Commercial sodamide used (Farchan Research Laboratories)

[d] Necessary to heat distillation head with a flame, as material tended to solidify.

[e] Sodium hydride was used as the condensing agent instead of sodamide

hydride was used in place of sodamide, and a lower reaction temperature was used. Here also unsaturates were identified from the material caught in the trap.

V. PREPARATION OF DERIVATIVES

The usual derivatives prepared from nitriles are amides and acids. Workman (1) has briefly reviewed the preparation of these derivatives. He found that, whereas hydratroponitrile was readily converted to the amide by 85% sulfuric acid, the butyl-substituted hydratroponitriles were much more difficultly hydrolyzed. After numerous attempts under the most drastic conditions, he was able to convert 2-phenyl-2-methylhexanenitrile and 2-phenyl-2,4-dimethylpentanenitrile to the anilides of the corresponding acids. 2-Phenyl-2,3-dimethylpentanenitrile failed to hydrolyze.

In the present investigation, several attempts to convert the nitriles to amides by means of sulfuric acid were unsuccessful and this method of attack was abandoned. Nitriles I, II, III, and VI (see Table VI) were successfully converted to anilides by a modification of Workman's procedure as follows.

Solid potassium hydroxide (2 g.) was dissolved in 10 ml. of ethylene or butylene glycol in a 50 ml. Erlenmeyer flask. The nitrile (3 g.) was added, the flask equipped with a glass tube to serve as an air cooled condenser, and the whole heated in an oil bath at 200° until ammonia was no longer liberated. The contents of the flask were then poured into 75 ml. of water. The water solution was extracted with

TABLE VI

PHYSICAL PROPERTIES OF ALKYLATED HYDRATROPONITRILES

No.	Compound	B.p.,		N_D^{25}	D_4^{25}	N, %[a]
		°C.	mm.			
I	2-Phenyl-2-methylheptanenitrile[b]	108	1	1.4941	0.9281	7.22
II	2-Phenyl-2,5-dimethylhexanenitrile[b]	104	1	1.4939	0.9264	7.19
III	2-Phenyl-2,4-dimethylhexanenitrile	98.5	ca.1	1.4969	0.9341	6.99
IV	2-Phenyl-2,3-dimethylhexanenitrile	115	2	1.5015	0.9421	7.06
V	2-Phenyl-2-methyl-3-ethylpentanenitrile	103	1	1.5042	0.9489	7.17
VI	2-Phenyl-2-cyclopentylpropanenitrile[b]	112	1	1.5232	1.0010	7.31[c]

[a] Calculated for $C_{14}H_{19}N$: N, 6.96

[b] Physical properties were determined on redistilled samples

[c] Calculated for $C_{14}H_{17}N$: N, 7.03

ether to remove any unreacted nitrile, and then heated on a steam bath to remove the last traces of ether. Next the solution was made acid to congo-red paper with concentrated hydrochloric acid. All attempts to isolate a solid acid at this point were unsuccessful. The acid solution was extracted with benzene, the benzene evaporated and the resulting liquid refluxed briefly with 5 ml. of thionyl chloride. The excess thionyl chloride was distilled and the last traces purged with benzene. The resulting solution was cooled and poured into a cold mixture of 6 ml. of aniline and 25 ml. of benzene. The aniline solution was extracted with 10% hydrochloric acid, 10% sodium hydroxide and water. Evaporation of the benzene left a brown solid, which was recrystallized from aqueous ethyl alcohol (Norite). The resulting colorless solution deposited fine white needles upon cooling. More product was obtained by diluting the alcoholic solution with water and cooling. Table VII summarizes the anilides prepared.

Nitriles IV and V were not attacked under the conditions described above. Even when they were refluxed at 210° for 24 hours with butylene glycol and potassium hydroxide, only a slight trace of presumed anilide could be isolated although the flask was badly etched. These nitriles were smoothly reduced to the corresponding amines with lithium aluminum hydride according to the procedure of Amundsen and Nelson (34). Derivatives of these amines were then prepared. The procedure follows.

In a 500 ml. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel was placed a mixture of 4 g. (0.106 mole) of lithium aluminum hydride and 100 ml. of anhydrous ether. Ten grams of the nitrile was dissolved in 30 ml. of anhydrous ether and added dropwise to the slurry in the flask. The addition caused gentle refluxing to occur. The solution was refluxed for an additional hour. The excess hydride was decomposed by adding dropwise in order, 4 ml. of water, 3 ml. of 20% sodium hydroxide, and 14 ml. of water. The ether solution was decanted and the solid material in the flask rinsed with ether. The solid was discarded. After removal of the ether, the residual oil was distilled under reduced pressure. The following amines were obtained.

No.	Name	Grams	B.p.		N_D^{25}	N, %[a]
			°C.	mm.		
VIII	1-Amino-2-phenyl-2,3-dimethylhexane	9.4	136-139	7	1.5149	6.50
IX	1-Amino-2phenyl-2-methyl-3-ethyl pentane	8.9	169-171	36	1.5170	6.73

[a] Calculated for $C_{14}H_{21}N$: N, 6.82

Some difficulty was encountered in preparing derivatives of the two amines. Acetamides, benzamides, and benzenesulfonamides were derivatives which failed to form. The phenylthiourea (35) of amine IX was a satisfactory derivative. The phenylthiourea of VIII melted over a wide range and behaved as though it contained diphenylurea. Picrates (35) of both amines were obtained from an alcoholic solution of picric acid and were recrystallized from aqueous ethyl alcohol. These derivatives are shown in Table VII.

TABLE VII

DERIVATIVES PREPARED

Compound	Formula	M.p., °C.	Nitrogen, %	
			Calculated	Found
Anilide of 2-phenyl-2-methylheptanoic acid	$C_{20}H_{25}NO$	99.5-100.5	4.74	5.04
Anilide of 2-phenyl-2,5-dimethylhexanoic acid	$C_{20}H_{25}NO$	110-111[a]	4.74	4.88
Anilide of 2-phenyl-2,4-dimethylhexanoic acid	$C_{20}H_{25}NO$	110-111[a]	4.74	4.64
Picrate of 1-amino-2-phenyl-2,3-dimethylhexane	$C_{20}H_{26}N_4O_7$	196-197[b]	12.90	13.02
Picrate of 1-amino-2-phenyl-2-methyl-3-ethylpentane	$C_{20}H_{26}N_4O_7$	176-178[c]	12.90	12.87
Phenylthiourea of 1-amino-2-phenyl-2-methyl-3-ethylpentane	$C_{21}H_{28}N_2S$	149-150	8.23	8.34[d]
Anilide of 2-phenyl-2-cyclopentylpropanoic acid	$C_{20}H_{23}NO$	108.5-109.5	4.77	4.98

[a] A mixture of the 2,4- and 2,5-dimethyl isomers melted at 97-99°.

[b] Yellow platelets from aqueous alcohol.

[c] Yellow needles from aqueous alcohol.

[d] Anal. Calc'd: S, 9.42; Found, 9.31.

DISCUSSION OF RESULTS

DISCUSSION OF RESULTS

It was necessary to prepare 2-chloropentane and 3-chloropentane in the manner described for two reasons, (1) they are not readily available and (2) they tend to rearrange, the amount of rearrangement depending on the method used in their preparation. The unequivocal methods used to obtain the two alcohols and the use of thionyl chloride in the presence of pyridine to convert the alcohols to the corresponding chloride insures pure samples of 2- and 3-chloropentane since there is evidence that this reaction gives the least amount of rearrangement. That these two compounds were free of rearranged product is shown by the fact that the derivatives prepared from the amines obtained by reduction of the appropriate nitrile were quite different. The behavior of the two amines towards various reagents also indicated that they were different.

The chlorocyclopentane and 1-chloro-2-methyl-butane and the corresponding alcohols also had to be prepared as they are not readily available.

Further information has been gained concerning the relative reactivity of the halogen in the alkyl halide for the reaction under consideration, namely, the alkylation of nitriles. From Table V it can be observed that n-amyl bromide and n-amyl chloride are of about equal reactivity, with n-amyl chloride giving only 1% better yield than n-amyl bromide. n-Amyl iodide gives a somewhat lower yield. One possible reason for the lower yield is that the n-amyl iodide could not be obtained completely free of iodine, as shown by the red color in the iodide used. Also, several grams of hydratroponitrile were recovered. In the case of the n-amyl chloride and n-amyl bromide alkylations, no unchanged, hydratroponitrile was recovered. If one compares the percentages of conversion, it is seen that very little difference in yields of alkylated product exists. These results substantiate the statement by Workman that the yield of alkylated product is not greatly affected by the halogen in the alkyl halide.

From Table V it can be observed also that the structure of the alkyl group affects the yield of alkylated product considerably. The best yields were obtained when chlorocyclopentane and 1-chloro-2-methylbutane were the alkylating agents. The lowest yield, neglecting tert.-amyl chloride, was obtained when the n-amyl halides were used. The yields from iso-amyl chloride, 2- and 3-chloropentane, and 2-bromopentane were quite comparable and intermediate between the two extremes, mentioned above. These results agree with those obtained by Workman and show (1) that normal, secondary, and iso alkyl halides give generally good yields and (2) that alkyl halides of the secondary and iso type give better yields than the normal alkyl halides. It should be noted that these results are not in agreement with those obtained by Tilford and co-workers (2,3) who report that cyclohexyl cyanide was alkylated in best yields by normal alkyl bromides and in poorer yields by secondary and branched chain bromides. These authors also state that tert.-butyl bromide gave no yield whatever of alkylated product.

It should be mentioned that in this work, very little or no unchanged hydratroponitrile was recovered from the individual alkylation reactions, except for those runs involving n-amyl iodide and tert.-amyl chloride and one run involving 2-chloropentane. Only in the case of the tert.- amyl chloride condensations was there any indication of dehydrohalogenation with the formation of alkenes. No unsaturated hydrocarbons were obtained from the other reactions which were investigated, namely, those involving 2- and 3-chloropentane.

The failure to obtain more than a trace of 2-phenyl-2,3,3-trimethylpentanenitrile (VII) from the reaction of tert.-amyl chloride with hydratroponitrile was expected since Workman and others have reported little or no alkylation when employing tertiary alkyl halides. Workman suggested that his failure to obtain more than a trace of 2-phenyl-2,3,3-trimethylbutanenitrile from the reaction of tert.-butyl chloride with hydratroponitrile was due to one, or a combination of, the following factors:

(1) When tert-butyl chloride was the alkylating agent, a temperature of 80° was not reached before the addition of sodamide. The initiation temperature for the reaction, using the other alkyl halides, was above 90°. Hence the reaction may not have been carried under the optimum conditions.

(2) Steric hindrance may prevent the bulky anion from approaching the tertiary alkyl halide from the back and displacing the chloride ion.

(3) Alkaline condensing agents are known to cause dehydrohalogenation of tertiary alkyl groups with the formation of alkenes. Sodamide is, of course, an alkaline condensing agent and might be expected to give this elimination type of reaction rather than alkylation.

In the present study it appears that possibility (1) above, namely, the failure to have the optimum temperature for reaction, can not account for the low yields of alkylation product when tert.- amyl chloride was used. Despite the fact that higher reaction temperatures (95-105°) were employed throughout and that correspondingly higher yields of alkylated products were obtained in the other cases, the yields were again very low when tert.- amyl chloride was the alkylating agent. Since the same reaction temperature was used for the tert.- amyl chloride as for the other amyl chlorides, it appears that the temperature factor is of only minor importance or, perhaps, of no importance in accounting for the low yield of tertiary alkylated product.

Workman was unsuccessful in his attempts to isolate isobutylene from the alkylations of hydratroponitrile with tert.-butyl chloride. Hence he could not demonstrate whether or not dehydrohalogenation occurred (factor 3 above). In the present study, when tert.-amyl chloride was used as the alkylating reagent, precautions were taken to trap any volatile components given off during the alkylation reaction. Several grams of low boiling, volatile material were obtained which gave characteristic tests for unsaturation, namely decolorizing a 5%

solution of bromine in carbon tetrachloride without the evolution of hydrogen bromide, and decolorizing a 2% solution of potassium permanganate. Distillation of this material gave several fractions which had boiling points and refractive indices corresponding to both 2-methyl-1-butene and 2-methyl-2-butene.. The isolation of these alkenes demonstrates that dehydrohalogenation is a definite factor in the failure to obtain an alkylated product with tertiary alkyl halides.

In one effort to avoid the dehydrohalogenation effect of the amide ion on tert.-amyl chloride, sodium hydride was substituted for sodamide since sodium hydride does not react with alkyl halides (40). In place of 12 g. (0.33 mole) of sodamide, 7.2 g. (0.3 mole) of sodium hydride was used. A lower reaction temperature and longer reflux period were also employed. In this case more low boiling material was obtained than before. The tests for unsaturation were positive and the physical constants paralleled those of 2-methyl-1-butene and 2-methyl-2-butene.. Hence it was demonstrated that the anion from hydratroponitrile was effective in the dehydrohalogenation of tert.-amyl chloride. Further attempts to prepare 2-phenyl-2,3,3-trimethylpentanenitrile were abandoned.

It has been observed that an increase in the number of alkyl groups on the α-carbon of the nitrile increases the difficulty of hydration or hydrolysis of these compounds. For example hydratroponitrile with an α-hydrogen and an α-methyl group is easily hydrated to the amide. When the α-hydrogen is replaced by an alkyl group, the resulting nitrile can no longer be hydrated to the amide (1). Workman observed that the introduction of a methyl group on the β-carbon in addition to the methyl group on the α -carbon produced a compound, 2-phenyl-2,3-dimethylpentanenitrile XIII, (See Figure II), which could not be hydrolyzed.

In the present investigation it was found that none of the nitriles prepared (Table VI and Figure I) could be hydrolyzed to the amide. Four of them (I, II, III, and VI) were ultimately hydrolyzed to the acid and converted to anilides; two (IV and V) failed to hydrolyze. The massing of methyl or ethyl groups near the cyano group tends to lessen the ease of hydrolysis of the latter. For example, when a methyl group is in the δ -position (nitrile II), conversion was easily affected. When the methyl group was in the γ -position (nitrile III), the hydrolysis was more difficult to achieve. When the methyl or ethyl group occupied a β -position (nitriles IV and V), hydrolysis failed completely.

This increasing difficulty in hydrolysis of the nitrile in proceeding from hydratroponitrile to the more highly branched nitriles can be explained in a semi-quantitative manner by applying the *rule of six* or *six-number* concept advanced by Newman (36). In considering the nitriles prepared by Workman, (see Chart II) one finds that hydratroponitrile (X) with an *effective six-number* of 2 was easily hydrolyzed to the amide by 66% sulfuric acid in fifteen minutes. 2-Phenyl--2-methylhexanenitrile (XI) and 2-phenyl-2,4-dimethylpentanenitrile (XII), in which the *effective six-number* is 5 could be hydrolyzed and converted to the anilides but not to the amide. When the *effective six-number* rose to 8, as in 2-phenyl-2,3-dimethylpentanenitrile (XIII), Workman found it impossible to effect hydrolysis to the amide or acid.

FIGURE I

STRUCTURE OF NEW NITRILES[a]

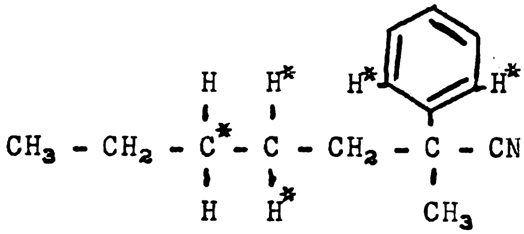
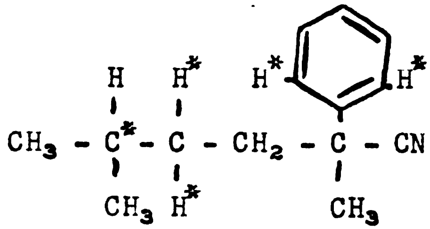
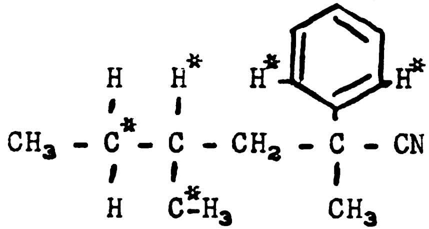
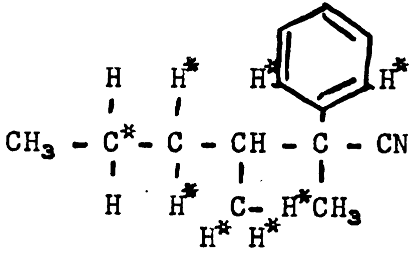
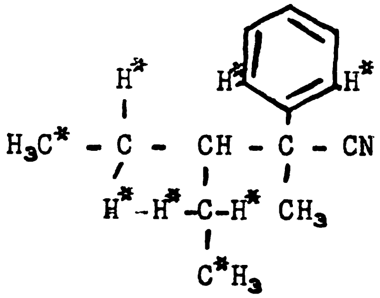
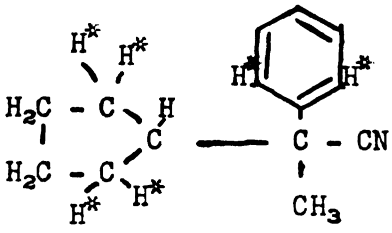
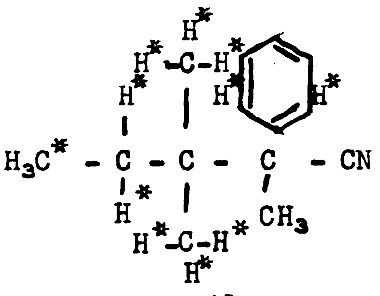
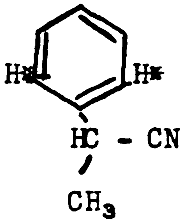
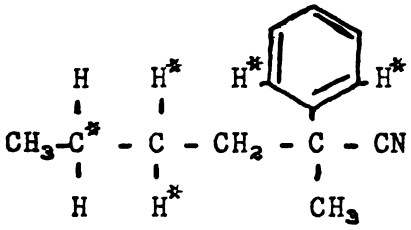
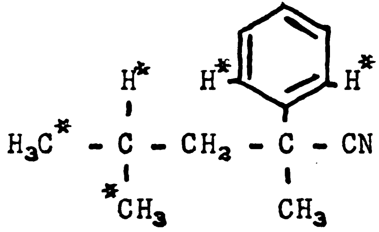
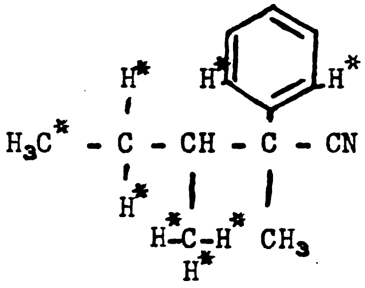
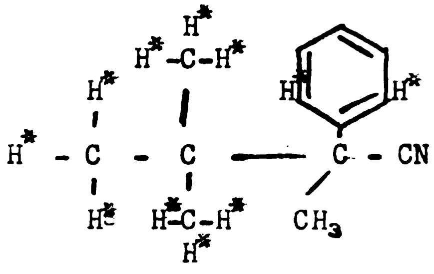
No.	Structure	Six-number
I		5
II		5
III		5
IV		8
V		8
VI		6
VII		11

FIGURE II

STRUCTURE OF NITRILES PREPARED BY WORKMAN

No.	Structure and Name	Six-number
X	 Hydratroponitrile	2
XI	 2-Phenyl-2 methylhexanenitrile	5
XII	 2-Phenyl-2,4-dimethylpentanenitrile	5
XIII	 2-Phenyl-2,3-dimethylpentanenitrile	8
XIV	 2-Phenyl-2,3,3-trimethylbutanenitrile	11

Although no attempt was made to hydrolyze 2-phenyl-2,3,3-trimethylbutanenitrile (XIV), one would predict that this nitrile would be even more difficult to hydrolyze, since the effective six-number is 11.

When this concept is applied to the nitriles prepared in the present study, it is possible to predict those nitriles which should be hydrolyzed. When the effective six-number is 5 or 6 (note that only a limited number of hydrogen atoms in the six position can be effective at one time in nitrile VI because of the ring structure), it should be possible to effect hydrolysis. Experimentally it was found that nitriles I, II, III and VI with effective six-numbers of 5, 5, 5 and 6 respectively could be hydrolyzed and converted to the anilide. It would be predicted that nitriles with an effective six-number of 8 would not undergo hydrolysis. Such was found to be the case for nitriles IV and V. It should be impossible to hydrolyze nitrile VII which has an effective six-number of 11. From this it is apparent that the critical value for the six-number in the case of these hindered nitriles lies between six and eight.

SUMMARY

SUMMARY

1. The alkylation of hydratroponitrile with normal amyl chloride, bromide, and iodide in the presence of sodamide using the high temperature procedure of Ziegler and Ohlinger shows that the halogen of the alkyl halide has little effect on the yield of 2-phenyl-2-methylheptanenitrile. The alkylations using 2-bromopentane and 2-chloropentane also support the above contention.

2. In the alkylation of hydratroponitrile with normal, iso, and tertiary amyl chloride, cyclopentyl chloride, 2- and 3-chloropentane, and 2-methyl-1-chlorobutane the structure of the alkyl group definitely effects the yield, the yields being in the order iso secondary normal tertiary. The results support those of Workman.

3. Unsaturated hydrocarbons were isolated from the reaction mixture of tert.-amyl chloride and hydratroponitrile showing that one reason for the low yields of alkylated product obtained when tertiary alkyl halides are used as alkylation agents is due to dehydrohalogenation of the tertiary alkyl group in the presence of an alkaline condensing agent.

4. Seven nitriles not previously reported in the literature have been prepared, and their physical properties determined. Four of these, 2-phenyl-2-methylheptanenitrile, 2-phenyl-2,5-dimethylhexanenitrile, 2-phenyl-2-cyclopentylpropanenitrile, and 2-phenyl-2,4-dimethyl-

hexanenitrile, have been hydrolyzed to the acids and converted to the anilides. Two of the nitriles, 2-phenyl-2,3-dimethylhexanenitrile, and 2-phenyl-2-methyl-3-ethylpentanenitrile have been reduced to the corresponding amines with lithium aluminum hydride, and their picrates prepared. The phenylisothiocyanate derivative of 1-amino-2-phenyl-2-methyl-3-ethyl pentane was also prepared.

5. The difficulty of hydrolysis of these nitriles has been discussed and rationalization in terms of the <u>six-number</u> concept of Newman applied.

SUGGESTIONS FOR FURTHER RESEARCH

1. Investigate in more detail the effect of the position of alkyl groups on ease of hydrolysis of nitriles. Apply the six-number concept to the rate of hydrolysis of these hindered nitriles.

2. Reinvestigate the present work using the low temperature method employed by Tilford and co-workers.

3. Study the same series of amyl halides using a different nitrile, to shed further light on the role of the structure of the nitrile as it affects the yield of alkylated product.

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