A STUDY OF THE ALKYLATION OF HYDRATROPONITRILF WITH BUTYL HALIDES

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Wesley Ray Workman

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This is to certify that the

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Gordon L Goerner
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A STUDY OF THE ALKYLATION OF HYDRATROPONITRILE WITH BUTYL HALIDES

By

Wesley Ray Workman

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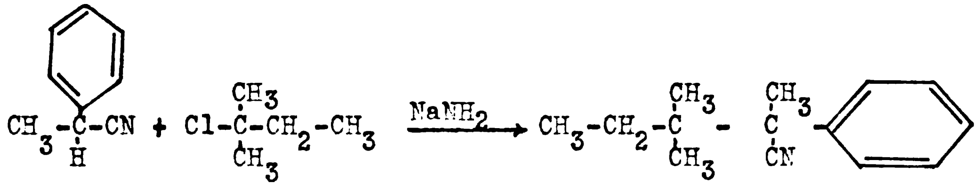
INTRODUCTION

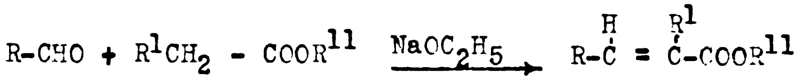
This problem is an outgrowth of several attempts to prepare α-phenyl-α,β,β-trimethylvaleronitrile from hydratroponitrile and tert.-amyl chloride, according to equation I. Because of the very low yields of this product, it appeared desireable to study the alkylation of hydratroponitrile in greater detail. The condensing agent used throughout this investigation was sodamide. By using normal butyl chloride, bromide and iodide, the effect of the halogen upon the yield was determined. The influence of the structure of the alkyl group was investigated by using normal, iso, secondary and tertiary butyl chlorides.

I



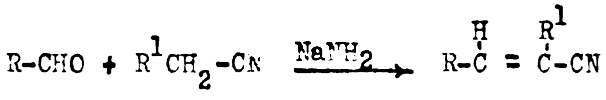
HISTORICAL

The activating influence of the cyano group on an adjacent methylene group is similar in many respects to that shown by carbalkoxy and carbonyl groups. A Claisen type condensation occurs between carbonyl compounds and esters (equation II). Nitriles react with carbonyl compounds

II 

$$R\text{-}CHO + R^1CH_2 - COOR^{11} \xrightarrow{NaOC_2H_5} R\text{-}\overset{H}{\overset{|}{C}} = \overset{R^1}{\overset{|}{C}}\text{-}COOR^{11}$$

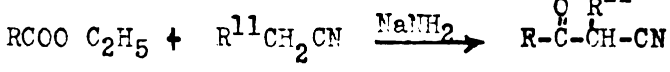
in an analogous fashion (equation III). In 1889 Meyer (39) reported

III 

$$R\text{-}CHO + R^1CH_2\text{-}CN \xrightarrow{NaNH_2} R\text{-}\overset{H}{\overset{|}{C}} = \overset{R^1}{\overset{|}{C}}\text{-}CN$$

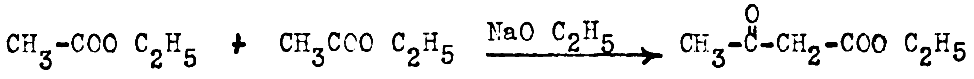
effecting the condensation of phenylacetonitrile and benzaldehyde in the presence of sodium ethoxide to produce α-phenyl-cinnamonitrile. Bodroux and Taboury used sodamide to condense phenylacetonitrile with benzaldehyde (8) and with p-methoxy-benzaldehyde (7). The use of ketones was also reported by Bodroux (6). He succeeded in condensing α-naphthyl-phenylketone, p-methylbenzophenone, and benzophenone with phenylacetonitrile.

Nitriles undergo a reaction with esters to give β-keto-nitriles (41) as shown in equation IV. This reaction is similar to the well-

IV 

$$RCOO\ C_2H_5 + R^{11}CH_2CN \xrightarrow{NaNH_2} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{R^{11}}{\overset{|}{C}}H\text{-}CN$$

known acetoacetic ester condensation (equation V). Levine and Hauser (37)

V 

$$CH_3-COO\ C_2H_5 + CH_3COO\ C_2H_5 \xrightarrow{NaO\ C_2H_5} CH_3-\overset{O}{\overset{\|}{C}}-CH_2-COO\ C_2H_5$$

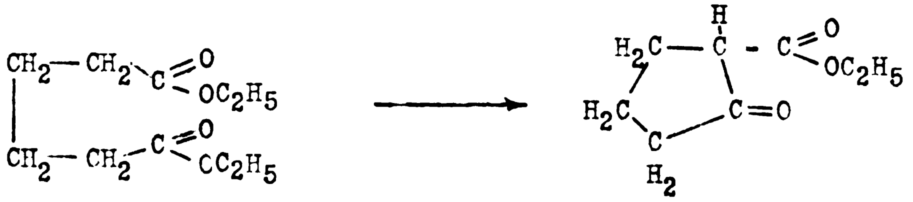
have studied the condensation of esters with nitriles, using sodamide as the condensing agent. Their results are summarized in Table I.

TABLE I

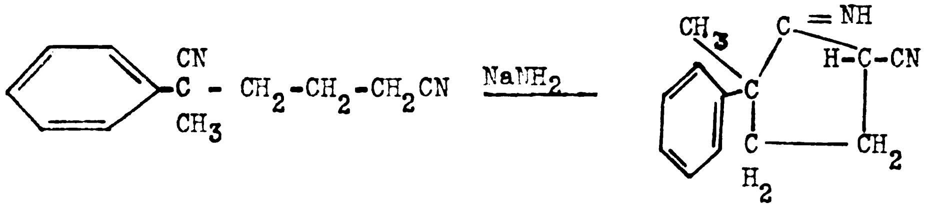
ACYLATION OF NITRILES BY ESTERS

Product	Yield, %
α-Acetylphenylacetonitrile	68
Propionylacetonitrile	40
α-Propionylphenylacetonitrile	60
n-Butyrylacetonitrile	33
α-Benzoylphenylacetonitrile	61
Ethyl cyanoacetate	40
Ethyl α-cyanophenylacetate	69

The Dieckmann cyclization is an acetoacetic ester type condensation which occurs with esters of dibasic acids containing five or six carbon

VI 

atoms (equation VI). Dinitriles undergo a similar cyclization (41) in the presence of sodamide. Newman and Closson (46) obtained an 85% yield of 3-methyl-3-phenyl-2-iminocyclopentylcyanide from α-phenyl,-α-methyladiponitrile as shown in equation VII.

VII 

There is, however, one outstanding difference between esters of the type $RCH_2COO\ Et$ and the corresponding nitriles, RCH_2CN. This is the fact that these esters cannot be alkylated directly whereas a nitrile can be easily alkylated. In this respect the reactive methylene group of the nitriles 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 VIII).

$$\text{VIII}\quad \begin{array}{l} RCH_2CN + NaNH_2 \longrightarrow [RCHCN]^- Na^+ \\ [RCHCN]^- Na^+ + R^1X \longrightarrow RCHR^1CN + NaX \end{array}$$

The condensing agents which have been used include sodamide, metallic sodium, (37,39) sodium alkoxides (sodium ethoxide and isopropoxide) (20, 39,40), potassium amide (4), and potassium hydroxide (26,47). The most commonly used condensing agent is sodamide, which was introduced by Bodroux and Taboury in 1910 (9). Among the commonly employed basic condensing agents, no references were found for the use of sodium tert.-butoxide or sodium triphenylmethyl.

The sodium salts formed by the action of sodamide on a nitrile were investigated by Rising and Zee, (51,52). They came to the conclusion that the salts existed in two forms: the "nitride" ion $R_2=C=N^-Na^+$ and a tautomeric "carbide" ion $R_2=C^- - CN\ Na^+$. The existence of the nitride ion was shown by the reaction of the sodium salt with acid. For example sodium phenylacetonitrile reacted with sulfuric acid to give hydrogen cyanide and benzyl alcohol. Under the same conditions sodium α-phenylbutyronitrile yielded 3,4-diphenyl-3-hexene. These reactions were assumed to proceed in the following steps.

$$C_6H_5HC = C = N^-Na^+ + H_2SO_4 \longrightarrow C_6H_5HC = C = NH + NaHSO_4$$

$$\text{IX} \qquad C_6H_5HC = C = NH \longrightarrow HN = C = \uparrow + C_6H_5HC =$$

$$C_6H_5HC = + HOH \longrightarrow C_6H_5H_2COH$$

The existence of the carbide ion was demonstrated by the reaction with alkyl halides. In this reaction the α-carbon atom was alkylated rather than the nitrogen.

$$\text{X} \qquad R_2C^- - CNNa^+ + R'X \longrightarrow R_2R'C - CN + NaX$$

It has been stated above that alkyl sulfates may be used as alkylating agents. In Table II are listed some alkylations using alkyl sulfates. It should be noted that only methyl and ethyl sulfates have been so employed. The yields are comparable to those obtained by the use of the corresponding halide (Table III). Cope and Hancock (20) report that the former are more conveniently used in the laboratory than are the alkyl halides.

The use of an alkyl halide as the alkylating agent was reported in 1889 by Meyer (39) and has been widely used since then. In Table III are summarized many of the simple alkyl halides used as alkylating agents in this type of reaction.

It is noticeable from this table that a great variety of branched and unbranched alkyl halides has been used. These groups vary in size

TABLE II

ALKYLATION OF NITRILES BY ALKYL SULFATES

Sulfate	Nitrile	Product	Yield %	Ref.
Methyl sulfate	Phenylacetonitrile	Hydratroponitrile	55	57
" "	α-Cyanoacetomesitylene	β-Methoxy-β-mesitylacrylonitrile	[a]	26
Ethyl sulfate	Valeronitrile	Ethylpropylacetonitrile		13
" "	Phenylacetonitrile	α-Phenylbutyronitrile	89	13
" "	Ethyl(1-methylbutylidene)-cyanoacetate	Ethyl ethyl-(1-methyl-1-butenyl)-cyanoacetate	80[b]	20
" "	Methyl(1-methylhexylidene)-cyanoacetate	Methyl ethyl-(1-methyl-1-hexenyl)-cyanoacetate	13	20

[a] Condensing agent was potassium hydroxide.
[b] Condensing agent was sodium isopropoxide.

TABLE III

ALKYLATION OF NITRILES BY ALKYL HALIDES

Halide	Nitrile	Product	Yield %	Ref.
Methyl iodide	Phenylacetonitrile	Hydratroponitrile	a	39
" "	"	"	66	21
" "	Diphenylacetonitrile	Diphenylmethylacetonitrile	95	36
Ethyl bromide	Acetonitrile	Diethylacetonitrile	75	58
" "	Butyronitrile	"	76.5	58
Ethyl iodide	Phenylacetonitrile	α-Phenylbutyronitrile	85	51
" "	"	"		9
" "	Diphenylactonitrile	Diphenylethylacetonitrile	88	36
" "	Cyclohexylphenylacetonitrile	Cyclohexylphenylethylacetonitrile	94	36
n-Propyl bromide	Acetonitrile	Tripropylacetonitrile	76	53
" "	Propionitrile	n-Propylmethylacetonitrile	65	58
" "	Phenylacetonitrile	Phenylpropylacetonitrile		28
" "	"	"		9
n-Propyliodide	Diphenylacetonitrile	Propyldiphenylacetonitrile	81	36
Isopropyl bromide	Ethylacetonitrile	α-Isopropylbutyronitrile	70.5	58
" "	Diethylacetonitrile	Diethylisopropylacetonitrile	56	58
" "	α-Isopropylbutyronitrile	α,α-Diisopropylbutyronitrile	45.5	58
" "	Phenylacetonitrile	Phenylisopropylacetonitrile		9
" "	"	"		33
Isopropyl iodide	Phenylacetonitrile	Isopropylphenylacetonitrile	90	29
" "	p-Tolylacetonitrile	Isopropyl-p-tolylacetonitrile		29
n-Butyl bromide	Acetonitrile	n-Butylacetonitrile	di=27 mono=56	4
" "	"	"	60	58
" "	Diethylacetonitrile	Diethylbutylacetonitrile	78	58
" "	"	n-Butyldiethylacetonitrile	65	44
" "	Phenylacetonitrile	n-Butylphenylacetonitrile		28
" "	"	Dibutylphenylacetonitrile	26	33
" "	"	"	66	53
" "	Diethyl,ethylcyono amine	$(C_2H_5)_2N-CH_2-CH(Bu)-CN$	16	53
" "	"	$(C_2H_5)_2N-CH_2-C(Bu)_2-CN$	71.5	53

(Continued next page)

TABLE III- CONTINUED

Halide	Nitrile	Product	Yield %	Ref.
n-Butyl bromide	Ethylcyanopyridine	$C_5H_{10}N-CH_2-C(Bu)_2-CN$	93	53
Isobutyl bromide	Phenylacetonitrile	Phenylisobutylacetonitrile		9
n-Amyl bromide	Butylacetonitrile	Diamylbutylacetonitrile	40	53
" "	Amylacetonitrile	Triamylacetonitrile	57	53
n-Hexyl bromide	Acetonitrile	Hexylacetonitrile	59	44
" "	Ethylisopropylacetonitrile	Ethylisopropylhexylacetonitrile	54	44
" "	Ethylbutylacetonitrile	Ethylbutylhexylacetonitrile	70	44
n-Heptyl bromide	Propionitrile	Diheptylmethylacetonitrile	43	53
" "	n-Butylacetonitrile	n-butyldiheptylacetonitrile	62	53
n-Octyl bromide	Acetonitrile	Octylacetonitrile	52	44
" "	Butylacetonitrile	Di-n-octylbutylacetonitrile	70.5	58
" "	Ethylbutylacetonitrile	Ethylbutyloctylacetonitrile	80	44
sec.-Octyl bromide	"	sec.-Octylethylbutylacetonitrile	33	44
Cyclohexyl bromide	Phenylacetonitrile	Phenylcyclohexylacetonitrile	65-77[b]	27
Benzyl chloride	Acetonitrile	Benzylacetonitrile	di 40 mono 48.5	 58
" "	"	"	di 49 mono 15	 4
" "	Propionitrile	Dibenzylmethylacetonitrile	quant.	58
" "	Butylacetonitrile	Butylbenzylacetonitrile		50
" "	Hexylacetonitrile	Hexylbenzylacetonitrile		50
" "	Diethylacetonitrile	Diethylbenzylacetonitrile		50
" "	Phenylacetonitrile	Benzylphenylacetonitrile	c	32
" "	"	"	c	39
" "	"	Dibenzylphenylacetonitrile		33
1-Phenyl-2-bromoethene	β-Naphthylacetonitrile	α-(β-Naphthyl)-γ-phenylbutyronitrile	67	45
β-(1-Naphthyl)-ethyl bromide	Phenylacetonitrile	β-(1-Naphthyl)ethylphenylacetonitrile	73	45
*Ethylene chloride	α-Naphthylacetonitrile	1-(-1-Naphthyl)-1-cyanocyclopropane	52[b]	19
Ethylene bromide	Phenylacetonitrile	1-Phenyl-1-carboxycyclopropane	37.8	16
1,3-Dibromopropane	"	1-Phenyl-1-carboxycyclobutane	14.5	16
1,2-Dichlorobutane	"	1-Phenyl-2-ethylcyclopropanecarbonitrile	40[b]	42
1,4-Dibromobutane	"	1-Phenyl-1-carboxycyclopentane	45.8	16
1,2-Dichloroisobutane	"	α-Phenyl-β-isopropylacrylonitrile	38[b]	42
1,5-Dibromopentane	Phenylacetonitrile	1-Phenyl-1-cyanocyclohexane	58	56

(Continued next page)

TABLE III- CONCLUDED

Halide	Nitrile	Product	Yield %	Ref.
1,5-Dibromopentane	Phenylacetonitrile	1-Phenyl-1-carboxylcyclohexane	22.2	16
1,6-Dibromohexane	"	1-Phenyl-1-carboxylcycloheptane	0	16
o-Dibromomethylbenzene	"	O, $\overbrace{CH_2-C_6H_4-CH_2-C}(C_6H_5)-COOH$	8.3	16
Self condensation	γ-Chlorobutyronitrile	Cyclopropylcyanide	40-55^d	47
" "	"	"	90^b	18
Chlorobenzene^f	Acetonitrile	Phenylacetonitrile	di 28 mono 31^e	4
" ^{f}	Propionitrile	Hydratroponitrile	43^e	4

[a] Condensing agent was sodium ethoxide.
[b] Prepared the sodium salt of the nitrile in liquid ammonia.
[c] Condensing agent was sodium metal.
[d] Condensing agent was potassium hydroxide.
[e] Condensing agent was potassium amide.
[f] An aryl halide.
[*] See Table IV for further examples.

TABLE IV

ALKYLATION OF NITRILES BY HALIDES CONTAINING OTHER FUNCTIONAL GROUPS

Halide	Nitrile	Product	Yield %	Ref.
Allyl chloride	Acetonitrile	Triallylacetonitrile	80-90	58
" "	Butyronitrile	Diallylethylacetonitrile	82.5	58
" "	Diethylacetonitrile	Diethylallylacetonitrile	90	58
1-Bromo-2-cyclohexene	Phenylacetonitrile	Δ^2-Cyclohexenylphenylacetonitrile	53	31
Ethylene dichloride	α-Phenylpropionitrile	α-Methyl-α-phenyl-γ-chlorobutyronitrile	20.1	28
" "	n-Propylphenylacetonitrile	α-n-Propyl-α-phenyl-γ-chlorobutyronitrile	23.6	28
" "	n-Butylphenylacetonitrile	α-n-Butyl-α-phenyl-γ-chlorobutyronitrile		28
Ethylene chlorobromide	Phenylacetonitrile	α-Phenyl-γ-chlorobutyronitrile	44	34
Ethylene chlorohydrin	"	α-Phenyl-γ-hydroxybutyronitrile	40	34
" "	"	" "		15
p-Chlorophenylmethylchloride	p-Chlorophenylacetonitrile	2,3-Bis-(p-Chlorophenyl)-propionitrile	36	55
2,3-Dichloro-α-naphthoquinone	Phenylacetonitrile	Chloro-α-naphthoquinonebenzyl cyanide	a	40
β-Bromoethylmethylether	Isobutyronitrile	γ-Cyano-γ,γ-dimethylpropylmethyl ether	53.5	58
β-Chloroethylvinylether	Phenylacetonitrile	γ-Phenyl-γ-cyanopropylvinyl ether	50	43
"	"	"		3
"	o-Tolylacetonitrile	γ-Cyano-γ-(o-tolyl)-propylvinyl ether		3
Ethyl α-bromopropionate	Hydratroponitrile	Ethyl 2-(1'-phenyl, 1'-cyano) ethylpropanoate	15	21
Ethyl α-bromoisovalerate	Phenylacetonitrile	Ethyl 2-(phenyl-cyano)-methyl, 3-methylbutanoate	Low	54
β-Chloroethylmethylformal	Phenylacetonitrile	γ-Cyano-γ-phenylpropylmethylformal		3
β-Chloroethyl ethylformal	"	γ-Cyano-γ-phenylpropylethylformal		3
Bromacetal	"	β-Cyano-β-phenylpropaldehydediethylacetal		2
γ-Iodobutyronitrile	Hydratroponitrile	α-Phenyl-α-methyladiponitrile	87.5	46
β-Piperidyl ethylchloride	Cyclohexylidenephenylacetonitrile	α-Δ'-Cyclohexenyl-α-phenyl-γ-piperidylbutyronitrile		31
"	Benzylphenylacetonitrile	γ-Phenyl- -benzyl-γ-piperidylbutyronitrile		24
Diethyl-β-chloroethylamine	Phenylacetonitrile	γ-Diethylamino-α-phenylbutyronitrile		24

(Continued next page)

TABLE IV - CONCLUDED

Halide	Nitrile	Product	Yield %	Ref.
Diethyl-β-Chloroethylamine	n-Hexylphenylacetonitrile	Diethylamino-α-hexyl-α-phenylbutyronitrile	75	24
Methylbenzyl-β-chloroethylamine	Phenylacetonitrile	γ-Benzylmethylamino-α-phenylbutyronitrile		2
4-Chloroquinoline	Phenylacetonitrile	α-(4-quinolyl)-phenylacetonitrile	76	22
4-Chloroquinoline	γ-Dimethylamino-α-phenylbutyronitrile	γ-Dimethylamino-α-(4-quinolyl)-α-phenylbutyronitrile	88	22
"	γ-Diethylamino-α-phenylbutyronitrile	γ-Diethylamino-α-(4-quinolyl)-α-phenylbutyronitrile	97	22
4,5-Dichloroquinoline	Phenylacetonitrile	α-(5-Chloro-4-quinolyl)phenylacetonitrile	100	22
"	γ-Dimethylamino-α-phenylbutyronitrile	γ-Dimethylamino-α-(5-chloro-4-quinolyl)-α-phenylbutyronitrile	86	22
"	γ-Diethylamino-α-phenylbutyronitrile	γ-Diethylamino-α-(5-chloro-4-quinolyl)-α-phenylbutyronitrile	98	22
4,7-Dichloroquinoline	Phenylacetonitrile	α-(7-Chloro-4-quinolyl)phenylacetonitrile	90	22
"	γ-Diemthylamino-α-phenylbutyronitrile	γ-Dimethylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile	95	22
"	γ-Diethylamino-α-phenylbutyronitrile	γ-Diethylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile	91	22

a Condensing agent was sodium ethoxide.
b Carried out at -78° in liquid ammonia.

from methyl to octyl and normal, secondary, iso and cycloalkyl groups have been employed. It is noteworthy that no report has been found regarding the introduction of a tertiary alkyl group. Benzyl chloride and other halides containing an aromatic ring are listed and chlorobenzene was used to "arylate" acetonitrile and propionitrile. This is interesting inasmuch as malonic ester and acetoacetic ester are not "arylated" by aromatic halides.

The use of ethylene dichloride and other dihalides such as 1,6-dibromohexane is also shown in Table III and may result in the formation of cyclic compounds. This is similar to "dialkylation" which has been obtained along with "monoalkylation" by several investigators (4, 33,53,58). 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.

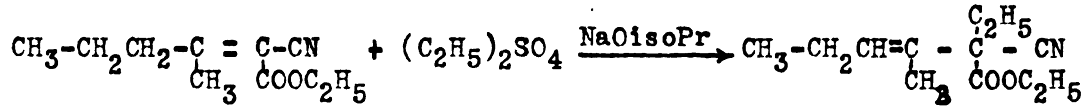
The reported yields vary widely, perhaps due to different investigators and conditions of temperature, solvent, and time of reaction. The iodides appear to give better yields than the corresponding bromides, although the evidence for this statement is meager. The chlorides have been little used, except for benzyl chloride, perhaps because as Sperber, et al. (53) stated, the chlorides react sluggishly at first and then with uncontrollable vigor.

A comparison of yields as effected by the structure of the alkyl halide is difficult. The work of Newbery and Webster (44) and of Ziegler and Ohlinger (58) shows only that the yields are dependent upon the nitrile as well as the alkyl group. For example, when acetonitrile is used, normal hexyl bromide gives greater yields than normal octyl bromide, but the reverse is true when ethylbutylacetonitrile is used.

Condensations in which other functional groups are present in the alkyl halide are summarized in Table IV. This table shows that a dihalide may be condensed with a nitrile, only one halogen reacting, to give a cyanohalide as the product. Haloesters react to give low yields of cyanoesters (21,54). The use of halo-substituted amines was introduced in 1939 by Eisleb (23,24) and has been frequently used since then. The yields appear to be very good, especially with the quinoline derivatives (22). Cutler, et al. (22) "arylated" phenylacetonitrile and α-substituted phenylacetonitriles with 4-chloro, 4,5-dichloro, and 4,7-dichloroquinolines in yields of 76 to 100 percent.

The alkylation of nitriles having no hydrogen on the α-carbon atom was reported in 1938 by Cope and Hancock (20). The α-carbon atoms of such nitriles are connected by a double bond to other carbon atoms. An example of the reaction reported by Cope and Hancock is shown in equation XI.

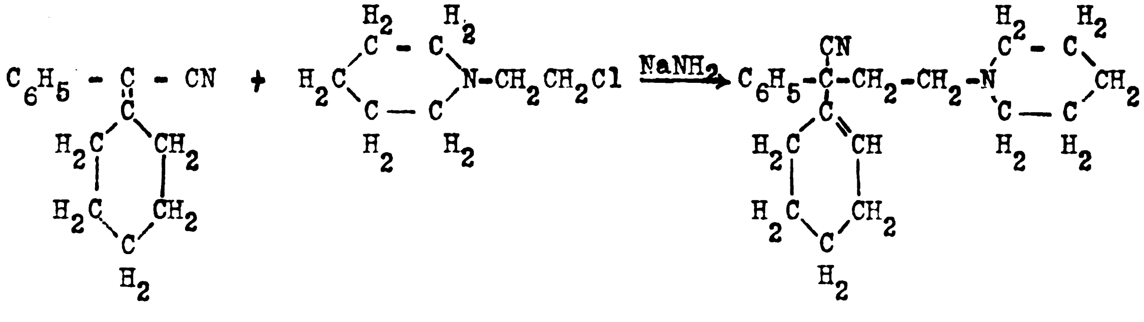
XI



$$CH_3-CH_2CH_2-\underset{CH_3}{C}=\underset{COOC_2H_5}{C}-CN + (C_2H_5)_2SO_4 \xrightarrow{NaOisoPr} CH_3-CH_2CH=\underset{CH_3}{C}-\overset{C_2H_5}{\underset{COOC_2H_5}{C}}-CN$$

Recently Jackman and coworkers (31) reported a similar reaction.

XII



EXPERIMENTAL

Reagents

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

n-Butyl chloride - Columbia Organic Chemical Co. Used fraction distilled at 76.8° - 77.0° C. at 734 mm.

n-Butyl bromide - Columbia Organic Chemical Co. Used fraction distilled at 98° - 99.2° C. at 750 mm.

n-Butyl iodide - Columbia Organic Chemical Co. Used fraction distilled at 127° - 128.5° C. at 735 mm.

Isobutyl chloride - Eastman Kodak Co., white label. Used as received.

sec.-Butyl chloride - Columbia Organic Chemical Co. Used fraction distilled at 67.5° - 68° C. at 748 mm.

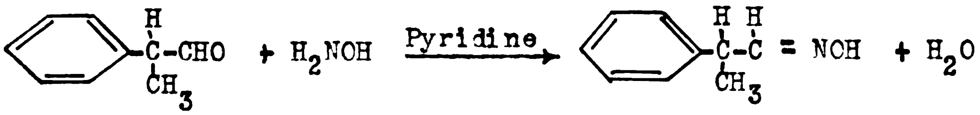
tert.-Butyl chloride - Columbia Organic Chemical Co. Used fraction distilled at 50° - 51° C. at 749 mm.

Sodamide - The sodamide used throughout this investigation was prepared by a modification of the method described by Hancock and Cope (27). 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 500 ml. of liquid ammonia was introduced through the inlet tube from an inverted ammonia cylinder. The Dry Ice 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 disappeared, after which 90 g. 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 grey, 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 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 36 g. of sodamide was placed in each bottle, the bottle corked, and sealed with paraffin. The yield amounted to 95% based on the sodium used.

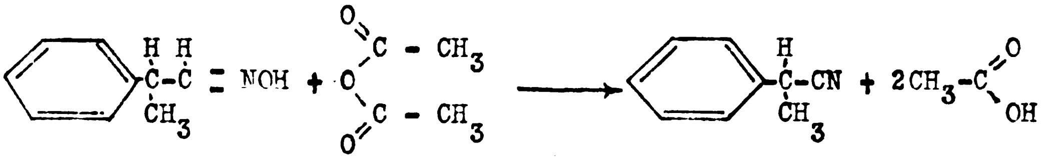
Preparation of Hydratroponitrile

Hydratroponitrile has been prepared by various means. The most direct method is the monoalkylation of phenylacetonitrile by means of either methyl iodide (21,39) or methyl sulfate (57). However, the product obtained is contaminated with the disubstituted nitrile. This was shown by Bruzau (14), who converted the product obtained from treatment of phenylacetonitrile with sodamide and methyl iodide into the amide. He separated the solid amides and showed them to be derived from the mono- and disubstituted acids. Another direct method is the condensation of propionitrile and chlorobenzene with potassium amide as reported by Bergstrom (4). The success of the latter method depends upon the wide difference between the boiling points of the mono- and disubstituted nitriles.

Another method which leaves no doubt as to the composition of the nitrile was used by Newman and Closson (46). They converted hydratropaldehyde to hydratropaldoxime by means of hydroxylamine and pyridine.

XIII 

The oxime was then dehydrated to the nitrile by acetic anhydride. This

XIV 

procedure was used in preparing hydratroponitrile throughout this work.

A typical preparation is as follows. To a mixture of 100 g. of hydratropaldehyde, 200 ml. of water, and 125 g. of hydroxylamine hydrochloride was added 400 ml. of pyridine. This was refluxed five hours and then poured into a liter of 6 N. acetic acid. The organic layer was separated and the aqueous layer extracted with benzene. The two organic layers were combined and distilled without drying. The fraction distilling between 90°-145° C. (mostly at 141°-142° C.) at 20 mm. was assumed to be the crude hydratropaldoxime. This amounted to 72.4 g. or a yield of 65% based on the original aldehyde.

This hydratropaldoxime was converted to the nitrile by refluxing with 240 ml. of acetic anhydride over a period of about five hours.

Acetic acid was removed as it was formed through a 3 x 40 cm. column packed with 3/16 in. glass helices. The resulting mixture was then fractionated under reduced pressure. Forty-five grams of nitrile boiling at 110°-114° C. at 21 mm. was collected. This corresponded to a yield of 71% based on the aldoxime. The yields on all runs are shown in Table V.

TABLE V

YIELDS OF HYDRATROPONITRILE

Run	Wt. of aldehyde	Oxime, %	Nitrile,[1] %	Nitrile,[2] %
I	100 g.	65	71	46
II	100	69.8	72	50
III	100	72	54	27
IV	500	37		
V	500	47	56.5	27
VI	500	62	77.4	48.5
VII	430	52	*30	15
VIII	430	74	73	54

[1] Based on oxime.

[2] Based on aldehyde.

* Lost about half of product because of an accident.

Alkylation of Hydratroponitrile

The procedure used for the alkylation of the hydratroponitrile was similar to that of Ziegler and Ohlinger (58). 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 34 g. (.26 moles) of hydratroponitrile, 28 g. (.3 moles) of n-butyl chloride, and an equal volumn of dry toluene. This was warmed to 80° C. 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°-95° C. 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 then extracted with toluene. The combined toluene layers were dried over anhydrous sodium sulfate and the toluene distilled at atmospheric pressure. The concentrated mixture was then vacuum distilled through a 2 x 20 cm. column packed with 3/16 in. glass helices. The fractions collected were:

I	B.P., 50°-97° at 2 mm.	Weight = 4.6 g.
II	B.P., 97°-107° at 2 mm.	Weight = 29.7 g.

The fraction which distilled between 97°-107° C. at 2 mm. was the monoalkylated hydratroponitrile and amounted to a theoretical yield of 61% based on the weight of starting nitrile.

This procedure was followed in every run. When n-butyl iodide was used the initiation temperature was about 97° C. and with tert.-butyl chloride it was impossible to obtain a temperature of 80° C. before the addition of sodamide. The following table summarizes the yields obtained from the various halides.

TABLE VI

YIELDS OF ALKYLATED HYDRATROPONITRILE

Halide	Run	Yield[a] %	Conversion[b] %	B.p., °C./P., mm.
n-Butyl chloride	I	61	71	97-107/2
n-Butyl bromide	I	61	74	92-113/3-4
n-Butyl iodide	I	62	77	90-107/2
Isobutyl chloride	I	69	79	95-112/4-5
	II	60[c]	76	93-106/3
sec.-Butyl chloride	I	67	78	95-115/4
	II	68	76	91-114/4
tert.-Butyl chloride	I	12	34	90-107/3
	II	trace		
	III	trace		
	IV	4.3	14	107-112/4
	V	6.4	26	107-112/4
	VI	6.0	20	107-113/3

[a] Based on weight of starting nitrile.
[b] Based on weight of starting nitrile converted.
[c] Redistilled before calculation of percent yield.

The physical constants of these nitriles were determined after combining the products of the individual runs and redistilling through a 3 x 40 cm. column packed with 3/16 in. glass helices.

TABLE VII

PHYSICAL PROPERTIES OF ALKYLATED HYDRATROPONITRILES

Compound	B.p.		n_D^{20}	D_4^{20}	[a] γ $\frac{\text{dynes}}{\text{cm.}}$	Nitrogen,[d] %	
	°C.	mm.					
Hydratroponitrile	82	3	1.5120	.9853	41.2	[b]10.76	10.89
α-Phenyl-α-methyl-Capronitrile	102	2	1.4997	.9405	36.7	[c] 7.58	7.58
α-Phenyl-α, γ-di-Methylvaleronitrile	102	2	1.4992	.9407	35.6	[c] 7.63	7.68
α-Phenyl-α, β-di-Methylvaleronitrile	105	2	1.5062	.9558	37.4	[c] 7.50	7.68
α-Phenyl-α, β, β-tri-Methylbutyronitrile	107	4	1.5156	.9724	38.6	[c] 7.67	7.68

[a] Surface tension measurements were made at 21° C. by the ring method.
[b] Calculated for C_9H_9N: 10.62%
[c] Calculated for $C_{13}H_{17}N$: 7.47%
[d] By method of Dumas.

Preparation of Derivatives

The derivatives commonly prepared from nitriles are amides and acids. Amides are generally prepared by treating the nitrile with sulfuric acid having a concentration of 20 to 100% and at various temperatures. Aqueous alkali or alkaline hydrogen peroxide may also be employed in the preparation of amides from nitriles. A nitrile may be converted to the corresponding acid by heating with sulfuric acid of various concentrations longer than is necessary for the conversion to the amide. Solutions of 20% hydrochloric acid or alcoholic alkali have also been used to prepare acids from nitriles. If the acid obtained is a liquid, the usual solid derivatives of it may be prepared (41).

Hydratroponitrile was easily converted to the amide by hydrolysis with sulfuric acid. One part of hydratroponitrile by weight was warmed on a steam bath with five parts concentrated sulfuric acid and one and one half parts water by volume for fifteen minutes. This mixture was poured into an ammonium hydroxide and ice mixture. The white crystals were filtered off and recrystallized from hot water. The hydratropamide melted at 93.5°-94° C. (reported by Bruzau as 94°-98° C. (14)), and it was obtained in 56% yield from the original nitrile.

Anal. Calc'd. for $C_9H_{11}N$: N, 9.38. Found: N, 9.24, 9.27.
(By Dumas' Method)

Attempts to prepare solid amides from the other nitriles were not successful. The same method that was used to prepare hydratropamide was tried as well as several modifications of it. Some of the modifications attempted (for the most part on α-phenyl-α-methylcapronitrile) are the following:

1. Four parts of concentrated sulfuric acid and one part of nitrile were allowed to stand at room temperature for four weeks.
2. Four parts of concentrated sulfuric acid and one part of nitrile were warmed on a steam bath for three hours.
3. Same as No. 2, but heated for ten hours.
4. Same as No. 2, but heated for thirteen hours.

5. A mixture of nine parts concentrated sulfuric acid, three parts water and two parts nitrile was stirred while heated at 70° C. for eight hours.
6. A mixture of eleven parts concentrated sulfuric acid, one part water, and two parts nitrile was heated for one half hour on a steam bath.
7. A mixture of eight parts sulfuric acid, three parts water and two parts nitrile was heated with frequent shaking on a steam bath for an hour.
8. A mixture of three parts concentrated sulfuric acid, two parts water and one part nitrile was heated over an open flame for ten minutes.

Other attempts at hydrolysis involved either phosphoric acid, alkaline hydrogen peroxide or alcoholic alkali and are as follows:

1. A mixture of eight grams of 100% phosphoric acid and two grams of nitrile was heated at 175°-180° C. for three hours.
2. A mixture of 27 g. of 100% phosphoric acid and five grams of nitrile was heated at 180° C. for five hours.
3. A mixture of 30 ml. of 3% hydrogen peroxide, three ml. of 25% sodium hydroxide and two grams of nitrile was heated at 60° C. with stirring for three hours.
4. Same as No. 3 except that 30% hydrogen peroxide was used.
5. A mixture of two grams of potassium hydroxide, 40 ml. of ethyl alcohol and two grams of nitrile was refluxed for 48 hours.

A method was devised whereby the nitrile was converted to the anilide of the corresponding acid. A mixture of 20 ml. of amyl alcohol, one gram of potassium hydroxide and five grams of nitrile (either α-phenyl-α-methylcapronitrile or α-phenyl-α,γ-dimethylvaleronitrile, but not α-phenyl-α,β,β-trimethylbutyronitrile or α-phenyl-α,β-dimethylvaleronitrile) was refluxed for ten hours. The amyl alcohol was distilled, the residue acidified with 10% hydrochloric acid, 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 residue cooled before pouring into a cold mixture of benzene and aniline. This mixture was extracted with 10% hydrochloric acid, 10% sodium hydroxide and water. Evaporation of the benzene left a brown solid. The solid was dissolved in aqueous ethyl alcohol, treated with Norite and the hot solution filtered. The resulting colorless solution deposited fine white needles upon cooling. More product was obtained by diluting the alcoholic solution with water and cooling.

	M.p.	%N[a]	
α-Phenyl-α-methylcaproanilide	111.5°C.	5.14	5.10
α-Phenyl-α,γ-dimethylvaleroanilide	120° C.	5.17	4.99

[a] Calc'd. for $C_{19}H_{23}NO$: N, 4.98 (By Dumas' Method).

A mixture of these anilides melted at 105°-107° C.

This procedure did not yield a derivative for either of the other two nitriles. Further attempts using benzyl alcohol and diethylene glycol as the solvents did not result in hydrolysis of the nitrile. Thus no solid derivatives were obtained for either α-phenyl-α,β-dimethylvaleronitrile or α-phenyl-α,β,β-trimethylbutyronitrile.

DISCUSSION OF RESULTS

The preparation of pure hydratroponitrile from hydratropaldehyde is a satisfactory method of preparation. However, as is shown in Table V, the yield of nitrile varies. One possible reason for this is the fact that hydratropaldehyde is easily oxidized in the air. In runs I through V, the aldehyde was obtained from the same bottle and runs IV and V were made from aldehyde which probably contained more acid than was present for earlier preparations. Runs VI, VII and VIII were made simultaneously from a second bottle of hydratropaldehyde.

Some information has been obtained concerning the relative reactivity of the halogen in the alkyl halide for the reaction under consideration. Table VI shows that n-butyl iodide gives only a one percent better yield than n-butyl chloride and n-butyl bromide, namely 62% against 61% for each of the latter halides. It appears that the yield of alkylated product is not affected by the halogen in the alkyl halide.

The structure of the alkyl group does affect the yield considerably. Table VI shows that secondary and isobutyl chlorides give a better yield than n-butyl chloride, and the latter a much better yield than tert.-butyl chloride. These results seem to be in agreement with those shown in Table III, where it may be observed that normal, secondary and isoalkyl halides give generally good yields. This work shows, however, alkyl halides of the secondary and iso type give better yields than the normal alkyl halides.

The very small yield of α-phenyl-α, [illegible], β-trimethylbutyronitrile may be due to one of, or a combination of, the following three factors:

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

(2) Steric hindrance may prevent the tert.-butyl group from becoming attached to the α-carbon atom. When molecules of the nitriles were constructed from Hirschfelder models, free rotation between the tert.-butyl group and the rest of the molecule was found to be impossible.

(3) Alkaline condensing agents such as sodium ethoxide are known to cause dehydrohalogenation of tert.-alkyl groups with the formation of an unsaturated hydrocarbon. Sodamide is, of course, an alkaline condensing agent and might be expected to give this type of reaction. Attempts were made to isolate some isobutylene from the ammonia given off during the reaction, but the results were inconclusive.

An increase in the number of alkyl groups on the α-carbon of the nitrile increases the difficulty of hydration or hydrolysis. For example, hydratroponitrile, with an α-hydrogen and an α-methyl group, was easily hydrated to the amide. When the α-hydrogen was replaced by one of the butyl groups, the new nitrile could no longer be hydrated to the amide by the methods tried.

The massing of methyl groups near the cyano group tends to lessen the ease of hydrolysis of the cyano group. For example, α-phenyl-[illegible]-methylcapronitrile and α-phenyl-α, γ-dimethylvaleronitrile were both hydrolyzed with about the same difficulty. Hence a methyl group in the

γ position has little effect on the cyano group. However, when the methyl group was in the β instead of the γ position, as in α-phenyl-α, β-dimethylvaleronitrile, it was impossible to affect hydrolysis by any of the drastic conditions used. α-Phenyl-α, β, β-trimethylbutyronitrile should be still more difficult to hydrolyze.

Table VII shows the similarity in the physical properties of α-phenyl-α-methylcapronitrile and α-phenyl-α, γ-dimethylvaleronitrile. Since these properties are so similar, there was the possibility that they were identical compounds. However, the mixed melting point of the two anilides was 105°-107° C. as compared to 111.5° and 120° for the pure anilides.

SUMMARY

1. The reaction between hydratroponitrile and n-butyl chloride, bromide, and iodide in the presence of sodamide indicates that the halogen has little effect on the yield of α-phenyl-α-methylcapronitrile.

2. The reaction between hydratroponitrile and n-butyl, isobutyl, sec.-butyl and tert.-butyl chlorides indicates that the structure of the butyl group does effect the yield. Yields decrease in the order iso $\geq$ secondary $>$ normal $\gg$ tertiary.

3. Four nitriles not previously reported in the literature have been prepared and their physical properties determined. Two of these, α-phenyl-α-methylcapronitrile and α-phenyl-α,γ-dimethylvaleronitrile, have been hydrolyzed to the acids and converted to the anilides.

SUGGESTIONS FOR FURTHER RESEARCH

1. Determine the effect of the structure of the nitrile on the yield of alkylated nitrile under the same conditions used in this investigation.

2. Investigate the arylation of nitriles with phenyl halides, substituted phenyl halides and naphthyl halides.

3. Determine the effect of the positions of methyl groups on the rate of hydration of nitriles to amides.

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