[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

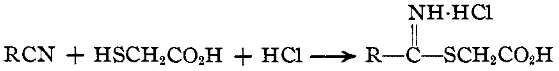
Identification of Nitriles. II. Addition Compounds of Nitriles with Mercaptoacetic Acid

BY F. E. CONDO, E. T. HINKEL, A. FASSERO AND R. L. SHRINER

Nitriles are usually characterized by (a) hydrolysis to the acid, (b) conversion to phenyl alkyl ketones by the action of the Grignard reagent,[1] and (c) formation of the 2,4,6-trihydroxyphenyl alkyl ketone by means of the Hoesch reaction.[2] Each of these methods has some disadvantages, and hence a further search has been made for easily prepared crystalline derivatives.

Nitriles react with alcohols in the presence of hydrogen chloride to form imido ester hydrochlorides. These are good crystalline compounds, but are rather sensitive to moisture, and many of them decompose at or near the same temperature. The analogous thiol compounds obtained by using mercaptans[3] appeared to be more stable. The lower mercaptans are rather disagreeable to use; hence a study was made of other thiol compounds. Thiophenol was found to add to acetonitrile, but the higher nitriles did not readily yield crystalline products.

The best reagent found was mercaptoacetic acid (thioglycolic acid) which readily added to nitriles in the presence of hydrogen chloride, forming α-iminoalkylmercaptoacetic acid hydrochlorides (I),[4] according to the equation



$$\mathrm{RCN + HSCH_2CO_2H + HCl \longrightarrow R{-}\overset{\overset{\displaystyle NH\cdot HCl}{\|}}{C}{-}SCH_2CO_2H}$$

I

By means of this reaction, stable crystalline derivatives could be prepared from both aliphatic and aromatic nitriles in good yields.

The reaction fails in the case of aromatic nitriles containing a group in a position ortho to the cyano group. This result parallels the observations of Pinner,[5] who noted that ortho substituted nitriles failed to form imino ester hydrochlorides when treated with an alcohol and hydrogen chloride.

Since these thioimino ester hydrochlorides are salts, they decompose upon attempting to determine their melting points. It was found, however, that the decomposition temperatures were sharp and reproducible, provided the determinations were made under the same conditions. Table I lists the derivatives of common nitriles, and shows the decomposition points of the compounds when determined by (a) placing the melting point sample in the bath at 20°, and (b) placing the sample in the bath 5° below the decomposition temperature observed by the first procedure.

These thioimino ester hydrochlorides also may be characterized by means of neutral equivalents. Electrometric titrations were carried out, using the glass electrode in order to determine the proper indicator to show the end-point. The curves obtained did not show very sharp breaks corresponding to one or two equivalents of alkali. This appeared to be due to the fact that an appreciable amount of time was necessary to obtain the readings, and so partial hydrolysis or reversal of the addition reaction took place. Hence, titrations were carried out as rapidly as possible, using phenolphthalein, thymol blue and thymolphthalein as indicators. In general, it was found that thymol blue gave the sharpest end-point, and neutral equivalents closely approximating the calculated values for reaction with two equivalents of alkali could be obtained. The data are shown in Table I.

Since many of these ester hydrochlorides decompose at nearly the same temperatures, it is necessary to consider also the boiling point of the nitrile and the neutral equivalent of the derivative in order to have sufficient data definitely to characterize a nitrile.

Previous investigators have shown that thioamides[3b,6] may be alkylated to produce thioimino ester hydrochlorides. In order to establish the

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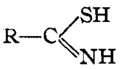
[1] Shriner and Turner, THIS JOURNAL, **52**, 1267 (1930).

[2] Howells and Little, *ibid.*, **54**, 2451 (1932).

[3] (a) Pinner and Klein, *Ber.*, **11**, 1825 (1878); (b) Bernthsen, *Ann.*, **197**, 341 (1879); (c) Autenrieth and Brüning, *Ber.*, **36**, 3464 (1903).

[4] The authors wish to thank Dr. Austin M. Patterson for his help in naming these compounds. They may be named (1) as derivatives of



the enolic form of the thioamide, or (2) as derivatives of mercaptoacetic acid. According to (1) the addition compound from acetonitrile would be "carboxymethyl acetothiimidate hydrochloride," and according to (2) "α-iminoethylmercaptoacetic acid hydrochloride." The latter name seems to be clearer, and is preferable to the former.

[5] Pinner, *Ber.*, **23**, 2917 (1890).

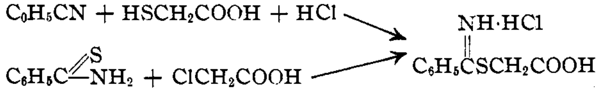
[6] Wallach, *Ber.*, **11**, 1590 (1878).

TABLE I

ADDITION COMPOUNDS OF NITRILES WITH MERCAPTOACETIC ACID

		α-Iminoalkylmercaptoacetic acid hydrochlorides						
Nitrile		Dec. points (corr.)			Neut. equivs.		Chlorine anal., %	
Formula	B. p., °C.	Cold bath	Hot bath	Molecular formula	Calcd.	Found (thymol blue)	Calcd.	Found
CH_3CN	82	114°	115°	$C_4H_8O_2NSCl$	84.7	87.5	20.92	20.93
C_2H_5CN	97	124	128	$C_5H_{10}O_2NSCl$	91.7	93.0	19.32	19.45
n-C_3H_7CN	118	135	137	$C_6H_{12}O_2NSCl$	98.7	99.6	17.95	17.85
i-C_4H_9CN	129	133	137	$C_7H_{14}O_2NSCl$	105.7	106.0	16.76	16.62
n-C_4H_9CN	141	137	138	$C_7H_{14}O_2NSCl$	105.7	105.8	16.76	16.68
i-$C_5H_{11}CN$	155	128	128	$C_8H_{16}O_2NSCl$	112.7	113.0	15.72	15.62
n-$C_5H_{11}CN$	163	136	136	$C_8H_{16}O_2NSCl$	112.7	112.9	15.72	15.69
n-$C_6H_{13}CN$	183	133	133	$C_9H_{18}O_2NSCl$	119.7	119.1	14.81	14.83
n-$C_7H_{15}CN$	200	134	135	$C_{10}H_{20}O_2NSCl$	126.7	126.6	13.99	14.01
C_6H_5CN	191	124	125	$C_9H_{10}O_2NSCl$	115.7	115.5	15.32	15.21
m-$CH_3C_6H_4CN$	214	168	169	$C_{10}H_{12}O_2NSCl$	122.7	122.3	14.44	15.07
p-$CH_3C_6H_4CN$	217	181	182	$C_{10}H_{12}O_2NSCl$	122.7	121.9	14.44	15.16
$C_6H_5CH_2CN$	234	144	146	$C_{10}H_{12}O_2NSCl$	122.7	122.3	14.44	14.34

structure of the compounds prepared in the present work, α-iminobenzylmercaptoacetic acid hydrochloride (II), obtained by the addition of mercaptoacetic acid and hydrogen chloride to benzonitrile, was shown to be identical with that obtained from thiobenzamide and chloroacetic acid.



$$C_6H_5CN + HSCH_2COOH + HCl \longrightarrow C_6H_5\overset{\overset{\displaystyle NH\cdot HCl}{\|}}{C}SCH_2COOH \longleftarrow C_6H_5C\overset{S}{\underset{}{\mathrel{/\!\!/}}}\!\!-NH_2 + ClCH_2COOH$$

II

Experimental Part

Nitriles.—The aliphatic nitriles were prepared by the action of sodium cyanide on the alkyl halides.[7] The aryl nitriles were made by the Sandmeyer reaction.[8]

α-Iminoalkylmercaptoacetic Acid Hydrochlorides.—Three methods were used in the preparation of the addition compounds. (A) The nitrile and a slight excess of mercaptoacetic acid were mixed together, cooled in an ice-bath and saturated with hydrogen chloride. The tube was stoppered and kept in the ice-bath until crystallization was complete. (B) The nitrile and mercaptoacetic acid were dissolved in an equal volume of absolute ether, the solution cooled in an ice-bath and saturated with dry hydrogen chloride. The tube was stoppered and kept cold until crystallization was complete. (C) The mixture of nitrile (2 g.) and mercaptoacetic acid (4 g.) was treated with 50 cc. of absolute ether, which had been previously saturated with dry hydrogen chloride at 5–10°. The flask was stoppered and placed in a refrigerator until crystallization was complete.

In each case the crystals were removed by filtration and thoroughly washed with absolute ether. They were placed in a vacuum desiccator containing concentrated sulfuric acid, potassium hydroxide and paraffin wax in order to remove the last traces of hydrogen chloride and ether. Procedures (A) and (B) above gave the best yields, 80–90%. The yield depends on the length of time the mixture is allowed to stand. The aliphatic nitriles reacted more rapidly than those of the aromatic series. Crystallization of the addition compound derived from an aliphatic nitrile often started within fifteen minutes, and was usually complete in two to three hours, whereas with the aromatic nitriles the process sometimes required twelve to sixteen hours by procedure (A) or (B) and two to three days when procedure (C) was used. The yields by procedure (C) were lower than by (A) or (B), but the product was of higher purity, and was not sticky and hygroscopic as was sometimes the case when procedure (A) was used. For identification work, procedures (B) and (C) are preferred, and may be used with 0.2 to 0.5 g. of nitrile and proportional amounts of the other reagents, provided care is taken to exclude moisture.

Neutral Equivalents.—An accurately weighed sample was dissolved in 100 cc. of carbon dioxide-free distilled water and *rapidly* titrated with standard, carbonate-free, sodium hydroxide solution, using thymol blue (*p*H change, 8.0–9.6) as the indicator. In the case of derivatives of nitriles containing more than five carbon atoms, it was necessary to dissolve them in 50% alcohol. The end-point was the olive-green color intermediate between yellow and blue. The data are given in Table I.

Analyses.—Although the chlorine in these hydrochlorides is ionic, it was necessary to decompose the compound with sodium peroxide in a Parr bomb, and then determine the chlorine. Direct precipitation of silver chloride by addition of silver nitrate to the thioimido ester hydrochlorides gave erroneous results. In two cases as shown in Table I, namely, the compounds derived from *m*- and *p*-tolunitrile, the chlorine analyses are high. The preparation of these compounds has been repeated many times and various purification processes have been tried. Apparently a small amount of the chlorimide, formed by addition of hydrogen chloride to the nitrile, is occluded by the product, and this results in the high values for chlorine.

α-Iminobenzylmercaptoacetic Acid Hydrochloride.—Equivalent amounts of chloroacetic acid and thiobenzamide were dissolved in absolute ether and the solution allowed to stand for two weeks at room temperature. The crystals which had separated were removed by filtration and triturated with dry acetone. After thorough washing with dry acetone and absolute ether, the crystals decomposed at 124–125°.

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[7] "Organic Syntheses," John Wiley & Sons, New York, 1932, Coll. Vol I, p. 101.

[8] *Ibid.*, p. 500.

Anal. Calcd. for $C_9H_{10}O_2NSCl$: Cl, 15.32; neut. equiv., 115.7. Found: Cl, 15.39; neut. equiv., 115.9.

No depression in the decomposition point occurred when this product was mixed with the compound obtained by the addition of mercaptoacetic acid to benzonitrile in the presence of hydrogen chloride.

Summary

A series of α-iminoalkylmercaptoacetic acid hydrochlorides have been prepared by the addition of mercaptoacetic acid (thioglycolic acid) to nitriles in the presence of hydrogen chloride. These addition products are stable, possess characteristic decomposition points, and may be titrated as dibasic acids by the use of thymol blue as the indicator.

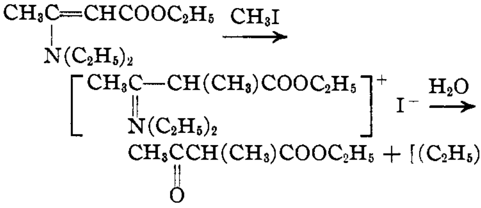
URBANA, ILL. RECEIVED NOVEMBER 16, 1936

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Alkylation of Beta-Aminocrotonic Esters

BY WALTER M. LAUER AND GEORGE W. LONES

An important study of the alkylation of ethyl β-diethylaminocrotonate with methyl iodide has led Robinson[1] to formulate the reaction as follows

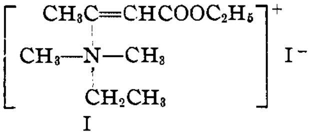


$$\underset{\textstyle N(C_2H_5)_2}{\underset{|}{CH_3C}}{=}CHCOOC_2H_5 \xrightarrow{CH_3I} \left[\underset{\textstyle N(C_2H_5)_2}{\underset{\|}{CH_3C}}-CH(CH_3)COOC_2H_5\right]^+ I^- \xrightarrow{H_2O} \underset{\textstyle O}{\underset{\|}{CH_3C}}CH(CH_3)COOC_2H_5 + [(C_2H_5)_2NH_2]^+I^-$$

since diethylammonium iodide and ethyl α-methylacetoacetate were obtained after the reaction mixture was treated with water. An alternative view that the methyl group first attached itself to the nitrogen and subsequently rearranged from the nitrogen to carbon atom is still possible provided the methyl group is assigned a greater migratory aptitude than the ethyl group.

The present work was carried out in order to distinguish between these two mechanisms. The results definitely eliminate the second view and bring additional support to the formulation of Robinson.

Alkylation of ethyl β-dimethylaminocrotonate with ethyl iodide formed a product which on hydrolysis yielded ethyl α-*ethyl*acetoacetate. Now, if the initial step in the process involves the formation of a compound of structure (I)



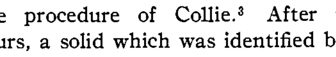
$$\left[\begin{array}{c} CH_3C{=}CHCOOC_2H_5 \\ | \\ CH_3-N-CH_3 \\ | \\ CH_2CH_3 \end{array}\right]^+ I^-$$

I

and we assign a greater migratory aptitude to the methyl group than to the ethyl group in order to account for the fact that alkylation of ethyl β-diethylaminocrotonate with methyl iodide yields ethyl α-methylacetoacetate, then the expected rearrangement product of I upon hydrolysis would give ethyl α-*methyl*acetoacetate. Instead ethyl α-*ethyl*acetoacetate was obtained.

Likewise, ethyl β-methylaminocrotonate and ethyl β-di-*n*-propylaminocrotonate upon treatment with ethyl iodide followed by hydrolysis yielded ethyl α-ethylacetoacetate. Thus, the substituent which is introduced in the α-position is determined by the alkyl halide used and is independent of the alkyl group or groups already joined to the nitrogen atom.

In the case of ethyl β-di-*n*-propylaminocrotonate it was possible to isolate the ethyl iodide addition product (II)



$$\left[\underset{\textstyle N(n\text{-}C_3H_7)_2}{\underset{\|}{CH_3C}}-CH(C_2H_5)COOC_2H_5\right]^+ I^-$$

II

which upon hydrolysis gave ethyl α-ethylacetoacetate and di-*n*-propylammonium iodide.

Experimental

Ethyl β-aminocrotonate was prepared according to the method of Michaelis,[2] and alkylated with ethyl iodide following the procedure of Collie.[3] After refluxing for twenty hours, a solid which was identified by means of a Volhard titration as ammonium iodide had separated out even though attempts were made to exclude moisture. The reaction mixture, after filtration, was then allowed to stand overnight with 5% sodium hydroxide. After acidification with dilute sulfuric acid, hydrolysis was completed by refluxing. Methyl propyl ketone (identified as the 2,4-dinitrophenylhydrazone, m. p. 141–142°) was obtained upon distillation.

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[1] Robinson, *J. Chem. Soc.*, **109**, 1083 (1916).

[2] Michaelis, *Ann.*, **366**, 337 (1909).

[3] Collie, *ibid.*, **226**, 316 (1884).