Reactions of 3-Chloropropionitrile and Alkyl 3-Chloropropionates with Amines

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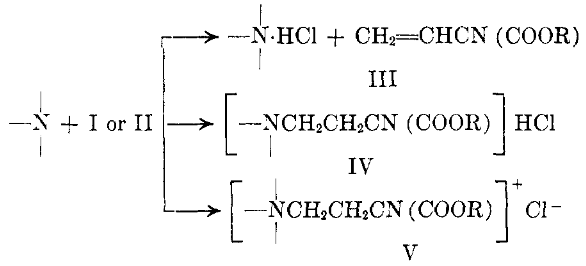
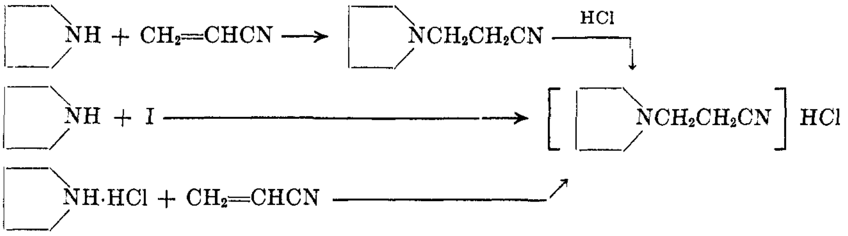
Numerous reports exist in the literature concerning the reaction of 3-chloropropionitrile (I) and alkyl 3-chloropropionates (II) with basic materials. With triethylamine,[1] quinoline,[2] diethylaniline,[3] or alcoholic sodium hydroxide,[4] I and II undergo dehydrochlorination leading to amine hydrochlorides and the corresponding acrylic compound. It has now been shown that reaction of I or II with amino compounds can give amine hydrochlorides (III), 3-aminopropionitrile hydrochlorides (IV), or quaternary salts (V), depending upon the nature of the amine.



Primary or secondary aliphatic amines, upon reaction with I in refluxing ethanol, gave high yields of the corresponding 3-aminopropionitrile hydrochlorides (IV) as shown in Table I. With tertiary aliphatic amines, dehydrochlorination of I and production of the tertiary amine hydrochloride (III) results.[5] The formation of IV from primary and secondary amines may occur by either of two routes: dehydrochlorination and subsequent cyanoethylation of the amine hydrochloride, or a one-step concerted displacement-rearrangement reaction. While the actual mechanism by which IV is formed has not been established, the feasibility of the former route was demonstrated by cyanoethylating pyrrolidine hydrochloride in refluxing ethanol to give good yields of 3-(1-pyrrolidinyl)-propionitrile hydrochloride. This product was identical with the hydrochloride prepared from 3-(1-pyrrolidinyl)propionitrile and with the product obtained by the reaction of I with pyrrolidine. Cyanoethylation of amine hydrochlorides has not previously been reported.



With aromatic amines the behavior of I and II is again dependent upon the nature of the amine. With aniline, I gave only III upon refluxing in ethanol. While cyanoethylation of aromatic amines is known to be acid-catalyzed[6] (and aniline hydrochloride has been reported to catalyze cyanoethylation of aniline[7]), cyanoethylation of aniline hydrochloride apparently did not occur under the reaction conditions employed.

Heterocyclic aromatic amines react with I or II to give III or V by dehydrochlorination or quaternization reactions, respectively, as shown in Table I. Pyridine, with either I or II, readily gave quaternary salts ranging from crystalline to gelatinous solids. With II, yields decreased with increasing size of the alkyl group. With methyl or benzo-substituted pyridines, the location of the substituent group dictates whether quaternization or dehydrochlorination predominates. In the picoline series, reaction of α-picoline and I gave only α-picoline hydrochloride, while both β- and γ-picoline quaternized with I in high yields. Reaction of I with the isomeric quinolines showed a similar difference; whereas quinoline caused only dehydrochlorination of I, isoquinoline gave an 86% yield of 1-(2-cyanoethyl)isoquinolinium chloride. Thus, α-substituted or α,β-benzo-substituted pyridines are sufficiently hindered sterically that dehydrochlorination of I is the predominant reaction, while under the same conditions the β- or γ-substituted or β,γ-benzo-substituted pyridines quaternize readily with I, as does pyridine itself.

In contrast, 2-ethylhexyl 3-chloropropionate reacted with quinoline to give the carbalkoxyethyl quinolinium chloride in 5% yield with no dehydro-

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[1] Ciba, Ltd., Swiss Patent 280,474 (1952).

[2] C. S. Marvel, *J. Am. Chem. Soc.*, **62**, 3495 (1940).

[3] C. Moureu, M. Murat, and L. Tampier, *Ann. chim.* (*Paris*) [9] **15**, 21 (1921).

[4] W. Bauer, to Rohm and Haas, U. S. Patent **1,864,884** (1932).

[5] Both trimethyl and triethylamine caused dehydrochlorination with I, although M. S. Newman and R. W Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955), report quaternary salt formation with trimethylamine and chloroethylene carbonate while triethylamine gave the expected dehydrochlorination.

[6] H. A. Bruson, *Org. Reactions*, **V**, 85–86 (1949).

[7] A. F. Bekhli and A. G. Serebrennikov, *J. Gen. Chem. U.S.S.R.*, **19**, 1553 (1949); *Chem. Abstr.*, **44**, 3448 (1950).

[8] H. Wagner, *Z. Kryst. Mineral.*, **43**, 167, 176 (1907).

[9] F. Ullmann, *Ber.*, **31**, 1699 (1898).

TABLE I

REACTION OF $ClCH_2CH_2Q$ WITH AMINES

Amine	Q	Time hr.	% Product			m.p.[a] °C.	Formula	Calcd.				Found			
			III	IV	V			C	H	Cl	N	C	H	Cl	N
Ammonia[b]	CN	0.5	97	8.4	—	126–128	$C_3H_7ClN_2$	—	—	—	26.3	—	—	—	26.4
n-Butylamine	CN	72	—	82	—	176–177	$C_7H_{15}ClN_2$	51.6	9.3	21.8	17.2	51.2	9.1	21.5	17.1
Pyrrolidine	CN	72	—	89	—	171–173	$C_7H_{13}ClN_2$	52.4	8.2	—	17.4	52.8	7.4	—	17.0
Morpholine	CN	24	—	84	—	212.5–213	$C_7H_{13}ClN_2O$	47.9	6.9	20.1	15.9	46.9	7.6	19.2	15.2
Trimethylamine	CN	1.0	95	—	—	>255[c]	—	—	—	—	—	—	—	—	—
Triethylamine	CN	1.0	96	—	—	255–256[d]	—	—	—	—	—	—	—	—	—
Aniline	CN	24	55	—	—	193–194[e]	—	—	—	—	—	—	—	—	—
Pyridine	CN	92	—	—	91	145–148	$C_8H_9ClN_2$	—	—	21.0	16.6	—	—	20.9	17.4
"	$COOC_2H_5$	90	—	—	87	waxy	$C_{10}H_{14}ClNO_2$	—	—	16.5	6.5	—	—	17.7	7.3
"	$COOC_4H_9$	72	—	—	83	waxy	$C_{11}H_{18}ClNO_2$	—	—	14.6	5.8	—	—	14.9	6.4
"	$COOC_8H_{17}$	72	—	—	88	jelly	$C_{16}H_{26}ClNO_2$	—	—	11.8	4.7	—	—	12.6	4.7
"	$COOC_9H_{19}$	72	—	—	70	jelly	$C_{17}H_{28}ClNO_2$	—	—	11.7	4.6	—	—	12.4	4.5
"	$COOC_{13}H_{27}$	90	—	—	42	jelly	$C_{21}H_{36}ClNO_2$	—	—	9.6	3.8	—	—	10.9	3.8
Quinoline[f]	CN	87	85	—	—	114–117	—	—	—	—	—	—	—	—	—
"	$COOC_8H_{17}$	69	—	—	5.7[g]	waxy	—	—	—	—	—	—	—	—	—
Isoquinoline	CN	87	—	—	86	220–222	$C_{12}H_{11}ClN_2$	65.9	5.1	16.2	12.8	65.3	5.3	16.1	11.7
Quinaldine	CN	48	79	—	—	220–221	$C_{10}H_{10}ClN$	67.5	5.6	19.8	7.8	67.1	5.8	19.4	7.5
8-Quinolinol	CN	69	77	—	—	228–229	C_9H_8ClNO	59.6	4.5	19.6	7.7	59.9	4.5	19.6	7.7
α-Picoline	CN	48	98	—	—	75–77	C_6H_8ClN	55.6	6.2	27.4	10.8	54.5	6.5	25.5	10.7
β-Picoline	CN	72	—	—	88	65–75[h]	$C_9H_{11}ClN_2$	—	—	19.4	15.4	—	—	20.5	13.6
γ-Picoline	CN	72	—	—	90	161–163	$C_9H_{11}ClN_2$	59.3	6.1	19.4	15.4	58.6	6.3	19.2	15.0
Acridine	CN	72	85	—	—	233–235	$C_{13}H_{10}ClN$	72.5	4.7	16.5	6.5	72.5	5.1	16.1	6.7

[a] Uncorrected. [b] Excess aqueous NH_3 used; isolated also 80% $NH(CH_2CH_2CN)_2$ from liberated acrylonitrile. [c] Reported m.p. 277–278°.[8] [d] Reported m.p. 253–254°.[8] [e] Reported m.p. 198°.[9] [f] With benzene as solvent, 51 hr. gave 72% III. [g] Infrared examination showed COOR and aliphatic CH absorption. [h] Crude product could not be recrystallized from ethanol-ether.

chlorination observed. That the quaternary salt from II could be isolated while that from I was not, is possibly attributable to the relative electronegativities of the cyano and ester groups in I and II; β-elimination occurring more readily with the group possessing the greater electron-withdrawing effect.

EXPERIMENTAL

The following general procedure was used in the reaction of 3-chloropropionitrile and alkyl 3-chloropropionates with amines. To a solution of the amine in absolute ethanol (200–300 ml. per mole) was added an equimolar quantity of the 3-chloropropionic acid derivative. With aliphatic amines the reaction was usually exothermic, while no temperature rise was noted with most aromatic amines. The resulting solution was refluxed from 0.5 to 90 hr., and the ethanol was distilled off under reduced pressure until solidification occurred. The residue was washed with anhydrous ether to remove unreacted starting materials and ethanol, and dried in a vacuum oven at 40–50°. The products obtained with a variety of amines are reported in Table I. Those from I were generally crystalline solids (either IV or V), while those from II ranged from waxy solids to gels. Recrystallization, where possible, was from ethanol-ether mixtures. All products (III, IV and V) were hygroscopic.

1-(2-Cyanoethyl)pyrrolidinium chloride. This material was prepared by reaction of pyrrolidine and I, from hydrogen chloride and 3-(1-pyrrolidinyl)propionitrile, and by cyanoethylation of pyrrolidine hydrochloride. A solution of 43 g. (0.4 mole) of pyrrolidine hydrochloride, 21 g. (0.4 mole) of acrylonitrile, and 80 ml. of absolute ethanol was refluxed for 72 hr., and worked up as above to give 55 g. (90%) of a slightly yellowish solid. One recrystallization from ethanol-ether gave white plates, m.p. 168–170°, of 3-(1-pyrrolidinyl)-propionitrile hydrochloride. A mixed melting point of this material and that prepared by reaction of I and pyrrolidine (Table I) was not depressed.

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Arylthiomethyl Quaternary Ammonium Salts from the Alkylation of Some Dialkylaminomethyl Aryl Sulfides

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Grillot *et al.*[1] have prepared in this laboratory dialkylaminomethyl aryl sulfides by the condensation of secondary amines and formaldehyde with thiophenols. It was of interest to us to determine if alkylation of these aminomethyl sulfides with an equivalent of an alkyl halide would produce quaternary ammonium salts rather than sulfonium salts. This was to be expected on the basis of reports by Kirchner, Soria, and Cavallito[2] who prepared quaternary ammonium salts of dialkylaminopropyl alkyl sulfides by allowing the latter to react with methyl and ethyl iodide and of Renshaw and Searle[3] who earlier observed that ammonium salt formation took precedence over sulfonium salt formation when the nitrogen and sulfur in an aminoalkyl alkyl sulfide were separated by from one to three carbon atoms.

Since alkylation of dimethylaminomethyl phenyl sulfide by benzyl chloride produces a salt which is identical to the benzyl phenylthiomethyl dimethylammonium chloride prepared by Barber and Green[4] by the action of *N*,*N*-dimethylbenzylamine on phenyl chloromethyl sulfide,[5,6] then in these aminomethyl aryl sulfides alkylation must occur preferentially on the nitrogen atom. In this latter synthesis it was found to be more satisfactory to prepare phenyl chloromethyl sulfide by the method of Bordwell and Pitt[7] than by Barber's method.[5,6]

Data concerning a group of new phenylthiomethyl trialkylammonium iodides and picrates prepared by the action of an alkyl iodide on a dialkylaminomethyl phenyl or *p*-chlorophenyl sulfide are listed in Table I.

It was expected that the quaternary ammonium iodides formed would be crystalline since crystallinity is a general characteristic of this type of salt. However there are several instances in the literature where compounds of this nature are not crystalline. For instance, Barber and Green[4] found that some of the quaternary salts prepared from *N*,*N*-dimethylbenzylamine were oils. Renshaw and Searle[3] found that derivatives obtained from methyl iodides were highly crystalline, while those from ethyl iodide tended to form oils. A characteristic common to these oils is the bulkiness of at least one of the substituents attached to the nitrogen. It appears possible that these large groups prevent the molecules from orienting themselves into a crystal structure.

EXPERIMENTAL

Benzyl phenylthiomethyl dimethylammonium chloride. Method A. Thioanisole was prepared by the method of Gilman and Beaber.[8] The fraction distilling at 69–71°/11 mm., obtained in a yield of 91%, was collected. The boiling point reported in the literature[8] is 58–60°/6 mm.

The method of Bordwell and Pitt[7], in which thioanisole is treated with sulfuryl chloride, was employed in the preparation of phenyl chloromethyl sulfide. The latter compound was obtained as an oil boiling at 85–87°/3 mm. in a yield of

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[1] G. Grillot, H. Felton, B. Garrett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Am. Chem. Soc.*, **76**, 3969 (1954).

[2] F. K. Kirchner, A. E. Soria, and C. J. Cavallito, *J. Am. Chem. Soc.*, **77**, 4599 (1955).

[3] R. R. Renshaw and D. E. Searle, *J. Am. Chem. Soc.*, **59**, 2056 (1937).

[4] H. J. Barber and M. B. Green, *J. Appl. Chem.*, **4**, 115 (1954).

[5] H. J. Barber, H. J. Cottrell, R. F. Fuller, and M. B. Green, *J. Appl. Chem.*, **3**, 253 (1953).

[6] H. J. Barber, R. F. Fuller, M. B. Green, and H. J. Zwartouw, *J. Appl. Chem.*, **3**, 266 (1953).

[7] F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).

[8] H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, **47**, 1449 (1925).