acidification. The lower melting form appears to be an unstable hydrate.

The 134° m. p. product had no free sulfhydryl or basic amino group, the neutralization equivalent was 237 (calcd. 229) and $[\alpha]^{25}_{D}$ in water (10 mg. per cc.) was −217°. The iodine number was erratic and very high (of the hydrate as well). This may have resulted from oxidation of the sulfur atom which may be less firmly bound in this compound than in the angelicalactone reaction product.

Anal. Calcd. for $C_{10}H_{15}O_3NS$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.79; H, 6.79; N, 6.00.

Discussion

In a number of the reactions described, the yields were quite low. This may be partly accounted for by the solubility of the reaction products and by efforts to obtain the compounds in a pure state at the expense of yield. The compounds isolated may not represent the sole reaction product in each instance, as the water solubility and amphoteric nature of some of the possible reaction products would make isolation of small quantities extremely difficult. The compounds isolated, however, do give evidence as to how some of the unsaturated lactone antibiotics might react with the sulfur amino acids present in enzyme proteins. The experimental conditions used for the reactions were within the *p*H and temperature ranges which might exist in bacterial environments.

If the antibiotic acitivity of certain unsaturated lactones is dependent upon the ability of these compounds to add, across the double bond, RSH groups essential for bacterial metabolism, the reaction may in some instances be modified by the lactone group. The α,β-unsaturated lactones may not require the lactone structure for activity; however, with some antibiotics, a double bond may exist only as long as the lactone group stabilizes an enol-aldehyde or enol-ketone structure. These lactones might react with the protein moiety of an enzyme by addition of free enzyme —SH groups to the double bond, followed by reaction of the lactone with free amino groups present in the vicinity.

Acknowledgment.—We wish to thank the Misses Alice Rainey and Patricia Curran for the microanalyses.

Summary

The reaction of cysteine and related aminothiol derivatives with several types of unsaturated lactones has been investigated. Reaction appears to proceed through addition of the thiol group to the double bond, followed in the case of $\Delta^{\beta,\gamma}$-butenolides by reaction of the lactone with the amino group and loss of water. A β-substitution in both the $\Delta^{\alpha,\beta}$- and $\Delta^{\beta,\gamma}$-butenolide series prevents reaction with cysteine.

The reactions may be of significance as indicating a possible mode of action of unsaturated lactone antibiotics with sulfhydryl and possibly amino groups of enzyme proteins.

Rensselaer, N. Y. Received September 6, 1945

[Contribution from the Stamford Research Laboratories of the American Cyanamid Company]

Some Amine Derivatives of Acrylonitrile

By O. F. Wiedeman and W. H. Montgomery

The reaction of acrylonitrile with ammonia to yield a mixture of β-cyanoethylamines has been reported by several investigators.[1,2,3] The β-cyanoethylamines have been prepared in these Laboratories with similar results, and in addition the as yet undescribed tertiary amine has been isolated.

$CH_2{=}CHCN + NH_3 \longrightarrow$

$H_2NCH_2CH_2CN$, β-Cyanoethylamine (or β-aminopropionitrile)

$HN(CH_2CH_2CN)_2$, Di-(β-cyanoethyl)-amine

$N(CH_2CH_2CN)_3$, Tri-(β-cyanoethyl)-amine

Tri-(β-cyanoethyl)-amine is a crystalline solid melting at 59°. It is interesting that it is only sparingly soluble in water while the primary and secondary amines are completely miscible with water. On cooling a hot aqueous or alcoholic solution of the impure tri-(β-cyanoethyl)-amine, it frequently separates as an oil instead of as crystals. However, with care and slow cooling it may be recrystallized from either solvent.

The instability of the primary amine has been previously discussed.[2,3] Buc, *et al.*, reported that vacuum-distilled samples were still stable after several months at room temperature or two years at 5°. Similar observations have been made here. However, many samples remained unchanged in tightly stoppered bottles at room temperature for several months and then decomposed within twenty-four hours for no apparent reason, yielding an orange mass (presumably acrylonitrile polymer) and developing a considerable ammonia pressure. Several additives were tested as a stabilizing influence. No effective stabilizer was found but carbon dioxide apparently accelerated decomposition.

The secondary amine is quite stable, although some decomposition occurs during distillation at 140–160° at 2–5 mm.

Whitmore, *et al.*, also reported the hydrogenation of β-aminopropionitrile to yield trimethylenediamine. The corresponding secondary and

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(1) Hoffmann and Jacobi, U. S. Patent 1,992,615.

(2) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel, and Yanko, This Journal, **66**, 725 (1944).

(3) Buc, Ford and Wise, *ibid.*, **67**, 92 (1945).

TABLE I

SOME PHYSICAL PROPERTIES OF AMINE DERIVATIVES OF ACRYLONITRILE

	Name	Formula	Mol. wt.	B. p., °C.	mm.	Est. purity, %	Density, g./cc. 20°C.	Density, g./cc. 25°C.	Refractive index $n^{25}D$
1	Tri-(β-cyanoethyl)-amine	$N(CH_2CH_2CN)_3$	176.2	(M. p. 59°)		99			
2	Di-(γ-aminopropyl)-amine	$NH(CH_2CH_2CH_2NH_2)_2$	131.2	100	2–3	98	0.9307	0.9268	1.4802
3	Tri-(γ-aminopropyl)-amine	$N(CH_2CH_2CH_2NH_2)_3$	188.3	140–150	2–3	98	0.9591	0.9552	1.4910
4	Di-(β-cyanoethyl) ether	$O(CH_2CH_2CN)_2$	124.1	140	2–3	98	1.0497	1.0457	1.4404
5	γ-Aminopropanol	$NH_2CH_2CH_2CH_2OH$	75.1	60	2–3	98	0.9832	0.9794	1.4597
6	Di-(γ-aminopropyl) ether	$O(CH_2CH_2CH_2NH_2)_2$	132.2	130–140	3	97	0.9723	0.9685	1.4780

	pH in 1% aq. soln.	Solubilities[c]							Nitrogen,[b] % by wt.					
		H_2O	C_2H_5OH	$(C_2H_5)_2O$	Benzene	Acetone	$CHCl_3$	CCl_4	Total Calcd.	Total Found	Saponifiable Calcd.	Saponifiable Found	Amine Calcd.	Amine Found
1		sl	sl	sl	sl	s	s	sl	31.8	31.5	23.8	23.7		
2	12.0	s	s	s[d]	s	s	s	s	32.0	31.3			32.0	31.1
3	12.0	s	s	s[d]	s	s	s	s	29.8	29.3			29.8	28.0
4		sl	s	sl	s	s	s	i	22.6	22.3	22.6			
5	11.9	s	s	i	sl	s	s	sl	18.7[a]	18.7[a]	..	0.4	18.7	18.9
6	11.9	s	s	s[d]	s	s	s	s	21.2[a]	21.3[a]	0	0.5	21.2	20.3

[a] γ-Aminopropanol, calcd.: C, 47.9; H, 12.1. Found: C, 47.7; H, 11.8. Di-(γ-aminopropyl) ether, calcd.: C, 54.5; H, 12.2. Found: C, 56.6; H, 11.6. [b] Total nitrogen by Kjeldahl method. Saponifiable nitrogen by boiling with aqueous sodium hydroxide. Any free ammonia present would appear here. Amine nitrogen is a calculated value based on a titration. Potentiometric titrations show that methyl red was a suitable indicator for titrations of the amino propylamines, γ-aminopropanol and di-(γ-aminopropyl) ether. [c] s = soluble; sl = slightly soluble; i = practically insoluble. [d] In the samples marked "s" under "ether" above, a slight cloud formed in the presence of a large excess of ether. Probably this was due to a trace of dissolved water. The samples are hygroscopic, fume in air, and also absorb CO_2.

tertiary amines were also prepared in these Laboratories by hydrogenation of both pure primary and secondary β-cyanoethylamine and of a crude mixture of the three β-cyanoethylamines.

$$\begin{array}{lcl} H_2NCH_2CH_2CN & & H_2NCH_2CH_2CH_2NH_2 \\ HN(CH_2CH_2CN)_2 & \xrightarrow{[H]} & HN(CH_2CH_2CH_2NH_2)_2 \\ N(CH_2CH_2CN)_3 & & N(CH_2CH_2CH_2NH_2)_3 \end{array}$$

Physical properties are given in Table I.

Whitmore, *et al.*, also hydrogenated di-(β-cyanoethyl) ether and obtained a product described as bis-(γ-aminopropyl) ether. The results of similar preparations in these Laboratories suggested that the product described above was probably γ-aminopropanol resulting from hydrogenolysis of the ether.[4] In the present investigation hydrogenation of pure di-(β-cyanoethyl) ether yielded a mixture of products including propylamine, γ-aminopropanol and a product believed to be mainly di-(γ-aminopropyl) ether.

$$\begin{array}{l} O(CH_2CH_2CN)_2 \xrightarrow{[H]} O(CH_2CH_2CH_2NH_2)_2 \text{ and} \\ \qquad HOCH_2CH_2CH_2NH_2 + CH_3CH_2CH_2NH_2 \end{array}$$

The boiling point and refractive index of γ-aminopropanol are in good agreement with values reported by Whitmore, *et al.*, for "bis-(γ-aminopropyl) ether," namely, b. p. 110° at 30 mm. *vs.* 113° at 32 mm. and $n^{20}D$ 1.4617 *vs.* 1.4618. Our di-(γ-aminopropyl) ether has the much higher boiling point of 135° at 3 mm. Other physical properties are given in Table I

The authors are indebted to members of the Analytical Department of these Laboratories for carbon, hydrogen and nitrogen determinations.

Experimental

Reaction of Acrylonitrile with Ammonia.—Acrylonitrile was added dropwise with stirring to concentrated aqua ammonia (28% NH_3) maintained at 30° with cooling water. The rate of addition was adjusted so that little or no upper layer was present at any time. On completion of the run, water and ammonia were removed by distillation at 50–100 mm. Three runs were made, see Table II, using different ratios of acrylonitrile to ammonia. Excess ammonia increased the relative amount of primary amine formed. The actual recovery of acrylonitrile as β-cyanoethylamines decreased as more ammonium hydroxide was used.[5]

TABLE II

PREPARATION OF β-CYANOETHYLAMINES FROM ACRYLONITRILE + AMMONIUM HYDROXIDE

	Run no. 1	2	3
Total volume of ammonium hydroxide, cc.	6500	500	36000
Total volume of acrylonitrile, cc.	12000	880	6000
Total weight of acrylonitrile, g.	9600	704	4800
Moles NH_3/moles acrylonitrile	0.53	0.56	5.9
% of acrylonitrile recovered as its equivalent of:			
Mono-(β-cyanoethyl)-amine	1.7	5.8	23.9
Di-(β-cyanoethyl)-amine	88.5	83.5	58.9
Tri-(β-cyanoethyl)-amine	6.0	1.0	3.3
Total β-cyanoethylamines	96.2	90.3	86.1

A sample of primary β-cyanoethylamine was freshly redistilled at 60° at 2 mm. Portions of it were treated empirically with various additives to determine their effects on stability. All samples were stored in tightly stoppered bottles at room temperature. Materials added were,

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(4) For a discussion of reactions of this type, see Homer Adkins. "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937.

(5) We are indebted to Dr. Jared H. Ford of the Upjohn Co. for information concerning losses of β-aminopropionitrile during evaporation of the water.

respectively, 0.1% of hydroquinone, 0.1% catechol, 0.1% ammonium carbonate, 1% water, 0.05% sulfuric acid (gave a precipitate of amine sulfate), a strip of mild steel, 1 and 10% of concentrated aqua ammonia (28% NH_3) and carbon dioxide added as a gas (amine carbonate precipitated). No additive was beneficial and only carbonates were detrimental. The samples containing carbon dioxide and ammonium carbonate decomposed after one month while all others lasted two to two and one-half months.

Tri-(β-cyanoethyl)-amine was recovered by hot water extraction of the residues from the vacuum distillation of the primary and secondary amines. On cooling the hot water extract, the amine frequently separated as an oil. The recovery of crystalline material was facilitated by stirring the hot extract with Darco, filtering, and cooling slowly, and also by adding seed crystals of the triamine just as the aqueous solution became turbid on cooling. Recrystallization from alcohol gave similar results.

Preparation of γ-Aminopropylamines.—A portion of the mixture of β-cyanoethylamines produced in run 3, after removal of water, was hydrogenated without further treatment. In addition, portions of the purified primary and secondary β-cyanoethylamines were hydrogenated individually. The reductions were carried out at pressures of 50–250 atmospheres for five to ten hours at 90–125°. The apparatus used was the Adkins[4] type of rocking autoclave built by the American Instrument Company. Batches of 5–10 moles were reduced in the presence of 1.1 moles of anhydrous ammonia per mole of amine and 2–3 g. of Raney nickel catalyst per mole.

TABLE III

PREPARATION OF γ-AMINOPROPYLAMINES FROM β-CYANOETHYLAMINES

Charge (β-cyanoethylamines)	1 Primary	2 Secondary	3 Mixture: 30% primary 65% secondary 4% tertiary
% by wt. of cyanoamine charge recovered as:			
Mono-(γ-aminopropyl)-amine	54	14	28
Di-(γ-aminopropyl)-amine	12	58	42
Tri-(γ-aminopropyl)-amine	3	13	13
	69	85	83

Hydrogenation of Di-(β-cyanoethyl) Ether.—A sample of di-(β-cyanoethyl) ether, prepared by reaction of ethylene cyanohydrin with acrylonitrile, was freshly redistilled at 140° at 2–3 mm. It was hydrogenated at pressures of 50–150 atm. and at temperatures between 80 and 125° for periods of two to ten hours. About 3–4 g. of Raney nickel catalyst was added per mole. The presence of 1.2 moles of anhydrous ammonia per mole of ether was found to reduce the percentage of low boiling products while increasing the amount of γ-aminopropanol formed and raising the yield of di-(γ-aminopropyl) ether. The best run was carried out in the presence of ammonia at 110–115° and 100 atm. for two hours, yielding 25–30% by weight of low boiling impurities (from which some propylamine was isolated), 35–40% of γ-aminopropanol, 20% of di-(γ-aminopropyl) ether and 15% residue.

We have recently obtained a copy of a French patent (879,788) which describes the preparation of di-(γ-aminopropyl) ether by a similar procedure. There is no mention of by-products and no yield is given, but the boiling point, 167° at 8 mm., is in fair agreement with our value of 135° at 3 mm.

Summary

Tri-(β-cyanoethyl)-amine (γ,γ′,γ″-nitrilotripropionitrile) has been prepared from acrylonitrile and ammonia as a crystalline solid melting at 59°.

Di-(γ-aminopropyl)-amine and tri-(γ-aminopropyl)-amine have been prepared by hydrogenation of β-cyanoethylamines. Physical properties are given.

Hydrogenation of di-(β-cyanoethyl) ether yields some di-(γ-aminopropyl) ether but also forms γ-aminopropanol and propylamine by hydrogenolysis.

STAMFORD, CONN. RECEIVED AUGUST 7, 1945

[CONTRIBUTION NO. 170 FROM THE CHEMICAL DEPARTMENT, E. I. DU PONT DE NEMOURS & COMPANY]

N-Substituted α-Aminoisobutyronitriles from Acetone Cyanohydrin

BY RALPH A. JACOBSON

α-Aminonitriles can be prepared by treating α-hydroxynitriles with ammonia,[1] or by one of the many modifications of the Strecker synthesis.[2] In connection with some work on another problem, a number of substituted α-aminoisobutyronitriles were required as intermediates. We found that they can be obtained conveniently under mild conditions by the reaction of acetone cyanohydrin and the proper amine, a procedure utilized by Bucherer and Grolee[3] for the preparation of α-phenylaminoisobutyronitrile. The results of our experience with this reaction are briefly discussed in the present paper.

One instance will illustrate the advantage of this procedure for the preparation of certain nitrogen-substituted α-aminoisobutyronitriles. Stewart and Cook,[4] for example, had much difficulty in preparing α-diethylaminoisobutyronitrile from acetone, sodium bisulfite, diethylamine and potassium cyanide by Knoevenagel's method.[5] The authors reported that the yield was very poor (not stated) and that the preparation could not be duplicated. More recent attempts to prepare this compound by the same method were also unsuccessful.[6] In contrast, we obtained α-diethylaminoisobutyronitrile in 58% yield merely by warming acetone cyanohydrin with diethylamine.[7] The preparation was one of a series, and no attempt was made to improve the yield. In some

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[1] (a) Dubsky and Wensink, *Ber.*, **49**, 1134 (1916); (b) Bucherer and Steiner, *J. prakt. Chem.*, **140**, 308 (1934).

[2] For instance, Zelinsky and Stadnikoff, *Ber.*, **39**, 1726 (1906).

[3] Bucherer and Grolee, *ibid.*, **39**, 986 (1906).

[4] Stewart and Cook, THIS JOURNAL, **50**, 1980 (1928).

[5] Knoevenagel and Mercklin, *Ber.*, **37**, 4087 (1904).

[6] Luten, *J. Org. Chem.*, **3**, 588 (1939).

[7] The specific reaction rates of this reaction have been measured in acetone and in alcohol by a titration procedure, and the corresponding rate laws and reaction mechanism discussed by Stewart and Li, THIS JOURNAL, **60**, 2782 (1938). However, the reaction was not employed as a preparative method.