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Tricyanomethane (Cyanoform), Carbamyldicyanomethane, and Their Derivatives

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Salts of tricyanomethane[1] (cyanoform) and carbamyldicyanomethane[1] have been prepared conveniently from malononitrile by new synthetic approaches. Reactions of the anions and of the free acids have been studied.

The weak cyanocarbon acid, malononitrile, has its strength considerably augmented by the introduction of substituents capable of delocalizing a negative charge at the central carbon atom. The strongly acid nature of malononitrile with alkoxycarbonyl (alkyl dicyanoacetate), cyano (cyanoform), arylsulfonyl, and acyl substituents has long been recognized.[2] In most of these compounds there is a pronounced tendency for the equilibrium between various tautomeric possibilities to be shifted toward the enol or enamine form; the free acids are, by and large, unstable, while the salts containing a well stabilized negative charge have a much higher degree of stability.

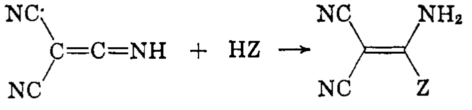
This paper describes new syntheses of tricyanomethane and carbamyldicyanomethane salts that make them easily accessible for the first time. Methods of preparing these compounds and their derivatives are shown in Chart I.

DISCUSSION

Salts of tricyanomethane have been prepared by various methods in the past; from sodiomalononitrile and cyanogen halides,[3,4,5a] from monobromomalononitrile and potassium cyanide[6] and from 1,1-dicyano-2-amino-2-alkoxyethylene and sodium hydroxide.[8,7]

As the anion of a strong acid,[8] the tricyanomethanide ion is a poor nucleophile, although alkyl tricyanomethanes have been prepared in low yield by treating silver tricyanomethanide with alkyl halides,[4] and bromotricyanomethane has been prepared by treatment with bromine.[5b] Bromotricyanomethane contains positive bromine as is evident from the fact that it reacts with water to give hypobromous acid, and with cyanide ion to yield cyanogen bromide and tricyanomethanide ion[5a]; a study of decomposition potentials of tricyanomethanide and halide ions indicates that in halotricyanomethanes the tricyanomethyl residue should be much more electronegative than bromine and somewhat more so than chlorine.[5a,5c]

Another reaction that has been reported is the addition of an active hydrogen compound to free tricyanomethane in solution[9] to yield 1,1-dicyanoethylene derivatives. Both alcohols[4] and hydrogen halides[8] have undergone this reaction, which can be regarded formally as the addition of an HZ fragment to the C=N bond of dicyanoketeneimine, a tautomeric form of tricyanomethane. Ammonia is reported to form the salt.[3]



$$(NC)_2C{=}C{=}NH + HZ \rightarrow (NC)_2C{=}C(NH_2)Z$$

Z = OR, Cl, Br

To study the reactions of tricyanomethane, a convenient preparation of its salt was desirable.

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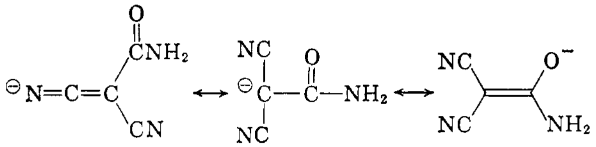
(1) The trivial name "cyanoform" lends itself poorly for systematic naming of derivatives. The names tricyanomethane and carbamyldicyanomethane are better in this respect but should not be construed as implying a covalent bonding of the active hydrogen. Both of these compounds are strong acids completely ionized in solution; their anions have a delocalized negative charge, *viz.*



and no one of the contributing forms may be picked as representing the structure of the anion. The chloro and bromo derivatives, however, are definitely covalent compounds. The infrared spectrum of crystalline carbamyldicyanomethane indicates that the compound exists largely, if not entirely, as the enol, 1,1-dicyano-2-hydroxy-2-aminoethylene.

(2) F. Arndt, H. Scholz, and E. Frobel, *Ann.*, **521**, 95 (1935).

(3) H. Schmidtmann, *Ber.*, **29**, 1172 (1896).

(4) A. Hantzsch and G. Oswald, *Ber.*, **32**, 641 (1899).

(5) (a) L. Birckenbach and K. Huttner, *Ber.*, **62B**, 153 (1929). (b) L. Birckenbach and K. Huttner, *Ber.*, **62B**, 2065 (1929). (c) L. Birckenbach and K. Kellermann, *Ber.*, **58**, 786 (1925).

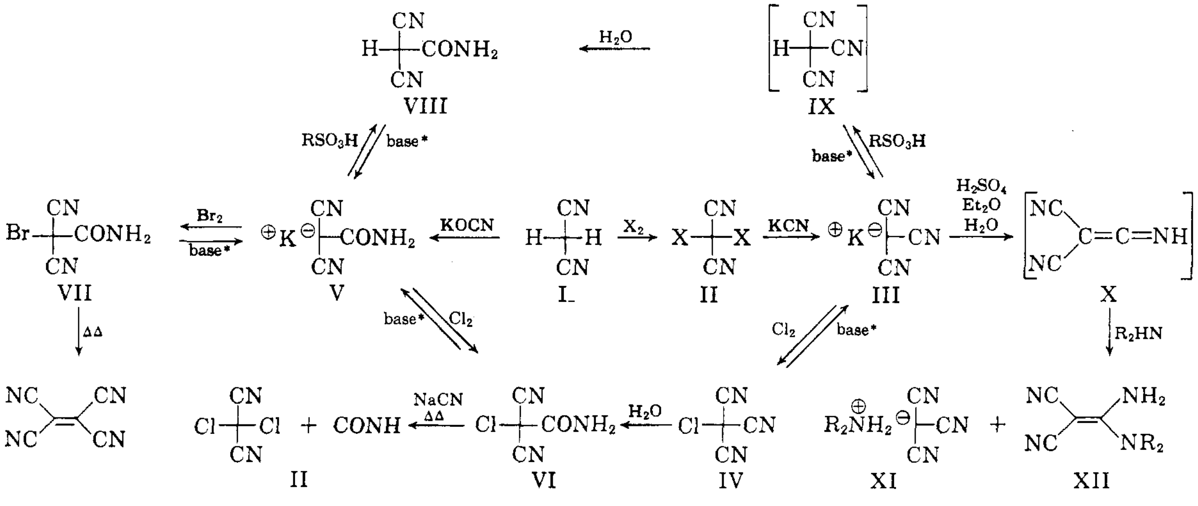
(6) E. Cox and A. Fontaine, *Bull soc. chim. France*, 948 (1954).

(7) W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2788 (1958).

(8) W. J. Middleton, E. L. Little, D. D. Coffman, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2795 (1958).

(9) Although anhydrous crystalline tricyanomethane has been reported,[6] we have been able to isolate it only as an unstable dihydrate. (This experiment will be reported in a paper by Dr. R. H. Boyd.) For practical purposes it is not necessary to isolate it, for aquoethereal tricyanomethane is a convenient reagent. The water in the aquoethereal solution seems to stabilize tricyanomethane, for our attempts to dry the solution with various agents have always resulted in the formation of an intractable orange polymer.

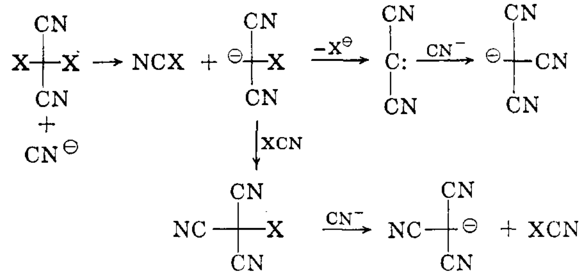
CHART I



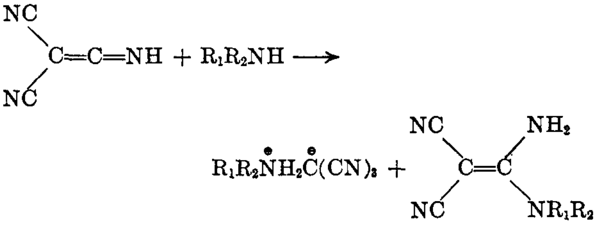
* The cation will depend on the base used.

The synthesis from bromomalonitrile,[6] while the best of those reported, gives only moderate yields and considerable purification is necessary to remove dark-colored impurities. We have found that when dibromomalonitrile or its potassium bromide complex[10] is treated with two moles of potassium cyanide, potassium tricyanomethanide of high purity is obtained in excellent yields. If dichloromalononitrile is used, the reaction still proceeds satisfactorily—albeit the yields are appreciably lower with concomitant formation of colored impurities. For effective separation of potassium tricyanomethanide from potassium bromide, use is made of the former's solubility in 1,2-dimethoxyethane, from which it crystallizes as the solvate. Drying removes the solvent leaving pure potassium tricyanomethanide, which was used to prepare a number of new metal salts.

Of interest is the possible mechanism of tricyanomethanide ion formation from dihalomalononitrile. The central carbon atom in dihalomalononitriles is quite hindered sterically so that an S_N2 substitution mechanism is rather unlikely. The first step may involve cyanide ion attack on the halogen, giving rise to dicyanohalomethanide ion. This species may eliminate halide ion, and the resulting dicyanocarbene would be expected to react readily with the cyanide ion present to form tricyanomethanide ion. An alternative would be the reaction of dicyanohalomethanide ion with cyanogen halide to yield tricyanohalomethane, which does possess a positive halogen and would react immediately with cyanide ion forming tricyanomethanide ion and cyanogen halide.



We have also studied the reactions of aquoethereal tricyanomethane with amines and found that salt formation takes place with ease. Several stable substituted ammonium salts have been prepared. In certain instances, however, a secondary reaction was observed that proceeded via addition of the amine to the $C{\equiv}N$ bond to give 1,1-diamino-2,2-dicyanoethylenes, a known class of compounds.[6]



While only salts were isolated when primary amines, such as *t*-butylamine and isopropylamine, and tertiary amines, such as triethylamine and pyridine, were used, the secondary amines piperidine, pyrrolidine, and diethylamine not only formed salts but also gave isolable $C{=}NH$ bond addition products. Only benzamidinium tricyanomethanide was isolated when benzamidine was the base.[11]

All the salts are water-soluble, giving an imme-

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(10) R. A. Carboni, *Org. Syntheses*, **39**, 64 (1959).

(11) This salt is identical with a product from the reaction of 1-amino-1-chloro-2,2-dicyanoethylene to which we erroneously ascribed the structure 5-cyano-4,6-diamino-2-phenylpyrimidine in an earlier cyanocarbon paper from this laboratory.[15] An authentic sample of the pyrimidine has now been made by condensation of benzonitrile with 1,1-diamino-2,2-dicyanoethylene and by heating benzamidinium tricyanomethanide at 155°.

diate precipitate of silver tricyanomethanide upon treatment with silver ion; the ethylenes are, as a rule, water insoluble. Of great diagnostic value in determining the structure of the product is infrared spectroscopy. The salts exhibit the characteristic cyanoform anion bands; a strong nitrile at 4.60 and a sharp doublet at 8.02, 8.08 μ (sometimes a weaker band at 7.9 μ is observed). The ethylenes contain NH_2 absorption in the 3-μ region, a less intense nitrile band, and other typical bands. This allows one to make an estimate of the reaction course from a crude mixture of products.

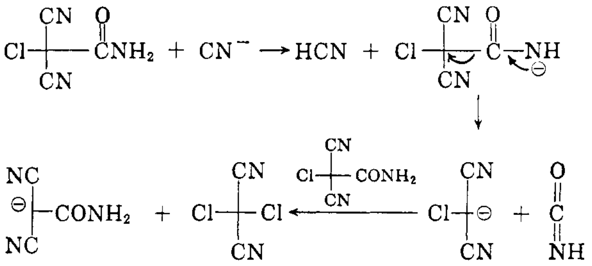
Although the addition of alcohols to the C=NH bond takes place with great ease,[3] we have found that water adds only very slowly. The product is the expected carbamyldicyanomethane.

We have obtained the same compound much more conveniently by condensing malononitrile with potassium cyanate to give potassium carbamyldicyanomethanide. By treatment with an ion-exchange resin, an aqueous solution of the compound is obtained, from which free carbamyldicyanomethane may be isolated. This compound, like tricyanomethane, is a strong acid but, unlike it, may be stored safely without any special precautions.

Treatment of potassium carbamyldicyanomethanide with chlorine or bromine gives rise to the corresponding carbamyldicyanohalomethanes in excellent yields. These compounds are quite soluble in solvents such as ether and chloroform. One interesting feature is the absence of nitrile absorption in the infrared, the amide bands being quite normal; actually, the crude materials show weak unconjugated nitrile band at 4.40 μ, which disappears on purification.

In a similar fashion chlorotricyanomethane was prepared from potassium tricyanomethanide. This material resembles the carbamyldicyanohalomethanes in its solubility, but is much more volatile and unstable. It contains a strong nitrile band at 4.40 μ. While it is stable at room temperature, it tends to pick up moisture and is transformed into carbamyldicyanochloromethane.

The halogen in both carbamyldicyanohalomethanes is positive, as is that of halotricyanomethane, and is readily removed by bases. Thus, reaction of carbamyldicyanochloromethane with one equivalent of sodium cyanide under mild conditions leads quantitatively to cyanogen chloride and sodium carbamyldicyanomethanide. Even such a weak base as pyridine gives rise to pyridinium carbamyldicyanomethanide. When an equimolar mixture of sodium cyanide and carbamyldicyanochloromethane is pyrolyzed, however, different results are obtained; dichloromalononitrile and isocyanic acid are formed as distillable liquids in fair yield. These findings are explained in terms of a nonselective, multicentered attack by the base as follows:



Attempted sublimation of carbamyldicyanobromomethane led to extensive decomposition; the sublimate was found to contain some tetracyanoethylene.

EXPERIMENTAL

Potassium tricyanomethanide (III).[12] Potassium cyanide (104 g., 1.6 moles) was stirred at room temperature in 850 ml. of 1,2-dimethoxyethane. Dibromomalononitrile–potassium bromide complex[7] (203 g., 0.8 mole) was added to the stirred and externally cooled (10–20°) solution in small portions. The yellowish slurry was stirred at room temperature for 2 hours and then brought briefly to reflux. The hot solution was filtered through a preheated sintered-glass funnel (crystals of potassium tricyanomethanide glymate start separating at this point) and left standing overnight. About 1 l. of ether was added and the product was filtered. Washing with more ether removed reddish impurities.

The material was air dried until all the glyme had evaporated to yield 109 g. (85%) of white solid with an infrared spectrum identical with that of authentic potassium tricyanomethanide. The contamination by potassium bromide was slight, as analysis showed less than 0.3% of bromine to be present in the sample.

Potassium tricanomethanide from dibromomalononitrile. The above reaction was scaled up to a 2-mole scale using dibromomalononitrile instead of the KBr complex. Analogous processing yielded potassium tricyanomethanide in 82–95% yield.

Substitution of dibromomalonitrile by dichloromalonitrile gave a somewhat less pure product in yields around 60%.[12]

Salts of tricyanomethane. Addition of an aqueous solution (20%) of potassium tricyanomethanide to aqueous solutions (10%) of various metal salts yielded solid precipitates with silver nitrate, cupric sulfate, cobaltous acetate, cadmium bromide, nickelous sulfate, lead acetate, ferrous sulfate, and manganous chloride, but not with magnesium acetate, barium chloride, cerium nitrate, zinc acetate, ferric chloride, strontium chloride, mercuric chloride, chromium acetate, tetramethylammonium chloride, tetraethylammonium bromide, and *N*-methylquinolinium iodide.

Ferrous tricyanomethanide. A hot aqueous solution (20 ml.) of potassium tricyanomethanide (6.4 g., 0.05 mole) was mixed with a hot aqueous solution (50 ml.) of ferrous sulfate (7 g., 0.025 mole). On cooling yellow crystals (5 g., 41% yield) of the ferrous salt slowly formed.

Anal. Calcd. for $FeC_8H_6 \cdot {}^1/_2\ H_2O$: Fe, 22.8. Found: Fe, 22.7, 22.4.

Cupric tricyanomethanide. A hot aqueous solution (20 ml.) of potassium tricyanomethanide (6.4 g., 0.05 mole) was mixed with a hot aqueous solution (25 ml.) of cupric sulfate (66 g., 0.025 mole). On cooling, brown crystals (5 g., 40% yield) of the cupric salt slowly formed.

Anal. Calcd. for CuC_8N_6: Cu, 26.1. Found: Cu, 25.89, 25.90.

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(12) The preparation of tricyanomethanide salts by the action of alkali cyanides on dihalomalononitriles was discovered by Dr. W. J. Chambers in an experiment with dichloromalononitrile.

Cobaltous tricyanomethanide. A hot aqueous solution (20 ml.) of potassium tricyanomethanide (6.4 g., 0.05 mole) was mixed with a hot aqueous solution (20 ml.) of cobaltous sulfate (4.4 g., 0.025 mole). On cooling, orange crystals (4 g., 32% yield) of the cobaltous salt slowly formed.

Anal. Calcd. for $CoC_8H_6\cdot{}^1/_2\,H_2O$: Co, 23.8. Found: Co, 23.9, 23.9.

Nickelous tricyanomethanide. A hot aqueous solution (20 ml.) of potassium tricyanomethanide (6.4 g., 0.05 mole) was mixed with a hot aqueous solution (25 ml.) of nickelous sulfate (7 g., 0.025 mole). On cooling, light blue crystals (5.1 g., 41% yield) of the nickelous salt slowly formed.

Anal. Calcd. for $NiC_8H_6\cdot{}^1/_2\,H_2O$: Ni, 23.7. Found: Ni, 23.5, 23.3.

Manganous tricyanomethanide. A hot aqueous solution (25 ml.) of potassium tricyanomethanide (6.4 g., 0.05 mole) was mixed with a hot aqueous solution (10 ml.) of manganous chloride (5 g., 0.025 mole). On cooling white crystals (3 g., 26% yield) of the manganous salt slowly formed.

Anal. Calcd. for MnC_8H_6: Mn, 23.3. Found: Mn, 23.0, 23.0.

Chlorotricyanomethane (IV). Potassium tricyanomethanide (20 g., 0.115 mole) was suspended in 500 ml. of ether, and 8 ml. of liquid chlorine (a small excess) was allowed to distill into the stirred suspension. The suspension was stirred one-half hour and filtered. The solid was shown by infrared analysis to contain some potassium tricyanomethanide. It was ground, stirred with excess chlorine in 300 ml. of ether, and filtered. Both ether filtrates were combined and concentrated to yield an oily solid.

Products from two runs of the above size were combined and sublimed at 40° and 100 mm. The sublimate was somewhat oily; yield 16 g. (41%). Several resublimations yielded colorless long needles, m.p. 46–47°. The yields were sometimes lower and not always reproducible.

Anal. Calcd. for C_4N_3Cl: C, 38.3; H, 0.0; N, 33.5; Cl, 28.3; mol. wt., 125.5. Found: C 39.2; H,0 .4; N, 33.9; Cl, 27.3, 29.2; mol. wt., 123, 127 (ebullioscopic in methylene chloride).

The mass spectrum was in good agreement with the chlorotricyanomethane structure. A small parent peak at 125 was observed along with some smaller fragments such as 99 [$CCl(CN)_2$], 90 [$C(CN)_2$], 73 (CClCN), and 64 [$C(CN)_2$].

After sublimation of chlorotricyanomethane there remained an oil which consisted of carbamyldicyanochloromethane and a liquid, the infrared spectrum of which was characterized by the following bands: 4.40 (unconjugated nitrile), 6.29, 8.80, 9.12, 9.22, 9.80, 11.04, 11.90 (broad), 12.3, and 14 μ (broad). The amount of carbamyldicyanochloromethane, m.p. 85–87°, (identical in all respects with authentic material prepared from potassium carbamyldicyanomethanide) varied from run to run and was inversely proportional to the yield of chlorotricyanomethane.

Chlorotricyanomethane is extremely volatile and has a pungent choking odor. It sublimes readily at atmospheric pressure, and samples left exposed disappear rapidly.

Reaction of chlorotricyanomethane with sodium cyanide. Chlorotricyanomethane (0.3 g.) was dissolved in 10 ml. of acetonitrile and 120 mg. of sodium cyanide was added to the stirred solution. The mixture was stirred overnight at room temperature in a stoppered flask. Decolorizing charcoal was added and the mixture was filtered. Evaporation of the solvent gave 0.25 g. of a white solid. The infrared spectrum of this material was identical with that of authentic sodium tricyanomethanide.

Potassium carbamyldicyanomethanide (V).[13] Malononitrile (66 g., 1 mole) was dissolved in 400 ml. of dimethylformamide. Finely ground potassium cyanate (81 g., 1 mole) was added slowly with vigorous stirring. The reaction mixture was heated with continued stirring under reflux conditions for 0.75 hour and then, while still hot, filtered. The filtrate was cooled to 0°, which caused 106 g. (71% yield) of the potassium salt of 1-amino-1-hydroxy-2,2-dicyanoethylene to separate as white crystals. This salt melts at 277° with decomposition.

Anal. Calcd. for $C_4H_2N_3OK$: C, 32.7; H, 1.5; N, 28.6. Found: C, 33.0; H,1.7; N, 28.7.

The infrared spectrum of this substance contains bands at 2.82, 3.00, 3.12, 4.54, 4.61, 6.10, 6.17, 6.35, 7.1, 8.68 (w), 9.35 (w), 13.24 and 13.55 μ (broad).

Carbamyldicyanomethane (VIII). A solution of 15 g. of potassium carbamyldicyanomethanide in 100 ml. of water was passed slowly through a sulfonated ion exchange (Amberlite IR120 (H)) column ($8^1/_2$ in. long). The column was washed with about 700 ml. of water until the eluate was no longer acidic to litmus. The solution was then evaporated to dryness under reduced pressure. The solid residue was recrystallized from acetonitrile to give white crystals of carbamyldicyanomethane in 85% yield. This acid decomposes above 300°.

Anal. Calcd. for $C_4H_3N_3O$: C, 44.0; H, 2.8; N, 38.5; mol. wt., 100. Found: C, 44.2; H, 2.9; N, 38.7; mol. wt., 98, 88.

The infrared spectrum contained characteristic bands at 2.93, 3.02, 3.12, 4.50, 4.55, 6.07, 6.24, 6.70, 7.90, 8.57 (w), 9.47, 12.15 (broad), and 13.92 μ.

Carbamyldicyanohalomethanes. Carbamyldicyanochloromethane. (VI). Powdered potassium carbamyldicyanomethanide (147 g., 1 mole) was stirred at room temperature in 1100 ml. of ether. Chlorine was bubbled in at a rate such that the ether refluxed gently. When the chlorine color persisted the addition was stopped. The suspension was filtered and the cake washed with ether; the combined ethereal solutions were evaporated *in vacuo* yielding 143 g. (99%) of carbamyldicyanochloromethane. After several recrystallizations from chloroform, colorless needles were obtained, m.p. 85–86°.

Anal. Calcd. for $C_4H_2ClON_3$: C, 33.5; H, 1.4; Cl, 24.7. Found: C, 34.2; H, 1.7; Cl, 25.0.

Carbamyldicyanobromomethane (VII). Substitution of 160 g. (1 mole) of bromine for chlorine in the above reaction, and identical processing yielded 173 g. (92%) of crude carbamyldicyanobromomethane, m.p. 100–106°. Recrystallization from chloroform gave needles, m.p. 110–111°.

Anal. Calcd. for $C_4H_2BrON_3$: C, 25.6; H, 1.1; Br, 42.5. Found: C, 26.3; H, 1.3; Br, 42.2.

Both carbamyldicyanohalomethanes are quite soluble in ether, ethyl acetate, and tetrahydrofuran, and moderately soluble in chloroform. They turn dark on storage but can be easily repurified by ether extraction, as the dark impurities are insoluble. The infrared spectra of both carbamyldicyanohalomethanes are quite similar. The common bands are 2.92, 3.09, 5.72 (shoulder 5.80), 6.14, 7.37, and 8.74 μ. The only significant difference occurs in the 11 μ range; here carbamyldicyanochloromethane has a band at 11.50 μ, whereas the bromo compound has a band at 11.85 μ.

Reaction of carbamyldicyanohalomethanes with bases. A. Carbamyldicyanochloromethane with potassium cyanide. Five grams of carbamyldicyanochloromethane was stirred in 100 ml. of tetrahydrofuran with 2.3 g. of potassium cyanide at room temperature for 10 minutes and then refluxed for 1 hour. After stirring overnight, the solid was filtered and shown by infrared analysis to be potassium carbamyldicyanomethanide; yield 4.8 g. (94%).

B. Reaction of carbamyldicyanohalomethanes with pyridine. Ten grams of carbamyldicyanochloromethane was dissolved in 250 ml. of ether. There was added to the stirred solution at 0° 11 g. of pyridine (in the absence of cooling, exothermic reaction led to tarring). The precipitate that formed was filtered; yield 5.5 g. (42%); m.p. around 120°. Recrystallization from a mixture of ethyl acetate and alcohol (9:1 ratio) gave needles melting at 122–125°. The material is water soluble, pH about 3. The infrared spectrum of the solid is similar to that of the known salts of carbamyldicyanomethane.

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(13) E. L. Little and H. F. Mower, U. S. Patent 2,852,552 (1958).

No well characterized material could be isolated from the mother liquors.

Anal. Calcd. for $C_9H_8N_4O$: C, 57.4; H, 4.3; N, 29.8; mol. wt., 188. Found: C, 57.3; H, 4.6; N, 29.9; mol. wt., 215, 255 (b.p. in methylene chloride).

Substitution of carbamyldicyanobromomethane for carbamyldicyanochloromethane in the above reaction gave rise to the same compound in 55% yield.

C. Pyrolysis of carbamyldicyanochloromethane with sodium cyanide. Carbamyldicyanochloromethane (40.0 g., 0.28 mole) was mixed intimately with 13.6 g. (0.28 mole) of sodium cyanide and placed in a large test tube conected to three traps, in series; the first cooled by ice brine, the other two by solid carbon dioxide–acetone. The test tube was heated with a Bunsen burner, and about 10 cc. of liquid was collected in the first trap and about 3 cc. in the next one. When the latter was allowed to warm to room temperature, an exothermic reaction occurred and the liquid solidified. The solid sintered and changed its form, without melting, in the 220–310° range and gave a strongly acid reaction with water. The acid component was extracted with water leaving a neutral fraction the infrared spectrum of which was in agreement with that of corresponding material obtained from authentic isocyanic acid.

The liquid from the first trap (combined from two runs) was distilled to yield 15 g. of dichloromalonitrile, identified by its infrared spectrum.

Pyrolysis of carbamyldicyanobromomethane. A small sample of bromodicyanoacetamide was heated at 100–105°/3 mm. Extensive decomposiion resulted. The small amount of solid that was isolated consisted of bromodicyanoacetamide and tetracyanoethylene, as shown by the infrared spectrum of the mixture and by a positive blue dimethylaniline test for tetracyanoethylene.

Hydration of tricyanomethane. An aqueous solution of pótassium tricyanomethanide was run through an Amberlite IR120 ion exchange resin and the strongly acidic eluate was collected. The solution was left standing at room temperature for 85 days. It was then boiled briefly and evaporated *in vacuo.* The colorless residue was recrystallized from acetonitrile to yield crystals identical with authentic carbamyldicyanomethane (by comparison of infrared spectra).

Reactions of aquoethereal tricyanomethane (X) *with amines.* Thirty-three grams (0.25 mole) of potassium tricyanomethanide was dissolved in 85 ml. of water with stirring. Ether (300 ml.) was added, the mixture was cooled with ice, and 25 g. (over 0.25 mole) of sulfuric acid was added dropwise. The mixture was stirred for 20 minutes and the layers were separated. The volume of the yellow middle layer was 275 ml. A portion of the middle layer was treated with an amine until the mixture was slightly basic. After standing at room temperature overnight, the solvents were removed and the residue was purified.

The amine salts of tricyanomethane are characterized by considerable solubility in water, by giving an immediate precipitate with silver nitrate solution, and by the presence of the typical tricyanomethanide band in the infrared at 4.6 μ.

The 1,1-dicyano-2-amino-2-cycloalkylamine derivatives are characterized by their low solubility in water, failure to give a precipitate with silver nitrate solution, and characteristic $-NH_2$ bands in the infrared.

Salts of tricyanomethane (XI). The salt from *t*-butylamine was obtained in 88% yield, m.p. 192–197°. Recrystallization from glyme-chloroform afforded crystals melting at 197–199° with decomposition.

Anal. Calcd. for $C_8H_{12}N_4$: C, 58.3; H, 7.4; N, 34.1. Found: C, 58.8; H, 7.6; N, 33.7.

From isopropylamine there was obtained a material (67% yield) melting at 182–185° with decomposition. Recrystallization from glyme-chloroform afforded material melting at 185–187° with decomposition.

Anal. Calcd. for $C_7H_{10}N_4$: N, 37.3. Found: N, 37.1.

Pyridine, *t*-octylamine and triethylamine also gave salts —the former two are crystalline, the latter an oil—as shown by infrared and qualitative tests. Diethylamine gave mainly a salt, although presence of $-NH_2$ bands in the infrared indicated some dicyanodiaminoethylene formation.

1,1-Diamino-2,2-dicyanoethylenes (XII) *from tricyanomethane.* A slight excess of piperidine was added to aquoethereal tricyanomethane solution. The solvents were removed yielding an oil which could not be distilled at 200°/1 mm. The residue was triturated with ethyl acetate to yield 2.4 g (28%) of a solid melting at 161–164°. This was shown to be identical with 1,1-dicyano-2-amino-2-piperidinoethylene[6] by mixed melting point determination and by comparison of infrared spectra.

Under similar conditions, pyrrolidine gave rise to 2.4 g. (20%) of a product melting at 176–177° after recrystallization from glyme and chloroform.

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.2; H, 6.2. Found: C, 59.4; H, 6.0.

The infrared spectrum is similar to the piperidine derivative; the compound is therefore 1,1-dicyano-2-amino-2-pyrrolidinoethylene.

Benzamidinium tricyanomethanide.[14] A solution of 12.9 g. (0.1 mole) of potassium tricyanomethanide in 100 ml. of cold water was mixed with a solution of 15.7 g. (0.1 mole) of benzamidine hydrochloride in 100 ml. of cold water. The crystalline precipitate that formed was collected on a filter and recrystallized twice from water to give 10.1 g. of benzamidinium tricyanomethanide as off-white needles, m.p. 148–149°. The salt has infrared absorption bands for $C\equiv N$ at 4.60 μ with a weak side band at 4.68 μ and additional weak bands at 7.82, 8.05, and 8.10 μ. All of these bands are characteristic of the tricyanomethanide ion.

Benzamidinium tricyanomethanide is identical in all respects, including infrared spectrum and melting point, with a compound incorrectly identified previously as the isomeric 5-cyano-4,6-diamino-2-phenylpyrimidine.[15] This pyrimidine has now been obtained from the salt by heating 285 mg. of it at 155°/0.1 mm. for 28 hours; this caused sublimation of 61 mg. (21%) of the pyrimidine, identified by comparison of its infrared spectrum with that of an authentic sample prepared as described below.

5-Cyano-4,6-diamino-2-phenylpyrimidine.[16] A mixture of 2.16 g. (0.020 mole) of 1,1-diamino-2,2-dicyanoethylene, 2.06 g. (0.020 mole) of benzonitrile, and 8 ml. of a solution of 1.0 g. of potassium hydroxide in 40 ml. of 2-ethoxyethanol was stirred under reflux; these are conditions under which cyanoguanidine (in one of its tautomeric forms an aza analog of 1,1-diamino-2,2-dicyanoethylene) condenses with benzonitrile to give benzoguanamine.[17] After 15 minutes the mixture was cooled to 25° and filtered to separate 1.48 g. of cream-colored solid. The solid was an insoluble polymeric material, infusible at 350°, mixed with 0.28 g. of colorless 5-cyano-4,6-diamino-2-methylpyrimidine that was separated by sublimation at 170°/0.1 mm. The filtrate was poured into 60 ml. of ice water, and the precipitate was separated and dried; weight 1.42 g. It was shown to be mainly 5-cyano-4,6-diamino-2-methylpyrimidine by infrared analysis. Sublimation at 170°/0.1 mm. gave 0.96 g. of the pyrimidine, so that the total yield of sublimed pyrimidine was 1.24 g. (39%). A sample recrystallized from toluene melted at 240–241°.

Anal. Calcd. for $C_{11}H_9N_5$: C, 62.6; H, 4.3; N, 33.2. Found: C, 62.5; H, 4.4; N, 33.3.

The infrared spectrum supports the assigned structure, with bands at 3.0 mμ and 3.15 mμ (NH_2), 4.55 mμ (conjugated CN), and 12.9 mμ and 14.2 mμ (monosubstituted

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[14] Dr. W. J. Middleton did this experiment.

[15] W. J. Middleton and V. A. Engelhardt, *J. Am. Chem. Soc.*, **80**, 2831 (1958).

[16] Dr. B. C. McKusick performed this experiment.

[17] J. K. Simons and M. R. Saxton, *Org. Syntheses*, **33**, 13 (1953).

phenyl). Further support for the pyrimidine structure was furnished by running the reaction with acetonitrile in place of benzonitrile to give a known pyrimidine (see next section).

5-Cyano-4,6-diamino-2-methylpyrimidine.[18] A heavy-walled polymer tube (25 mm. × 21 cm.) was charged with 2.0 g. (18.5 mmoles) of 1,1-diamino-2,2-dicyanoethylene, 5.0 g. (120 mmoles) of acetonitrile, and 0.29 g. (3.7 mmoles) of piperidine. The mixture was frozen, the air was replaced by nitrogen, and the tube was sealed. It was heated in a Carius furnace at 180–190° for 1 hr. The tube was then cooled and opened and its contents removed with the aid of a few ml. of absolute alcohol. The pyrimidine, obtained as pale yellow crystals, was separated by filtration and air-dried; wt. 1.65 g. (60%); m.p. 397–398° on a block.[19] Recrystallization from acetic acid gave a colorless product of unchanged melting point. The infrared spectrum is similar to that of the 2-phenyl analog.

Anal. Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.7; N, 47.0 Found: C, 48.4; H, 4.8; N, 45.7.

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[18] Dr. J. R. Roland did this experiment.

[19] Z. Budesinsky and J. Kopecky [*Collection Czechoslov. Communs.*, 20, 52 (1955)], who prepared this pyrimidine by a 3-step synthesis, report m.p. > 360°.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS, UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE, AND THE DEPARTMENT OF CHEMISTRY, OHIO STATE UNIVERSITY]

Synthesis and Properties of Isoserine. A Novel Bromhydrination Method

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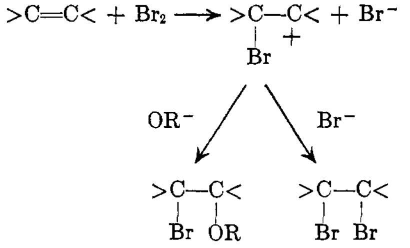
The bromination of methyl acrylate was carried out in the presence of silver nitrate, which prevented formation of methyl dibromopropionate as a byproduct. Isoserine was synthesized by hydrolysis of the product of amination of methyl bromohydroxypropionate. The copper-catalyzed oxidative deamination of isoserine yielded tartronic acid semialdehyde; under these conditions, hydroxypyruvic acid was produced from serine. Other chemical properties of isoserine are described.

Isoserine inhibits several enzymes of serine metabolism in mammals[1] and interferes with pantothenic acid synthesis from β-alanine in yeast.[2] The compound was first synthesized by Melikoff[3] by treatment of α-chloro-β-hydroxypropionic acid with aqueous ammonia. The apparent rearrangement of the hydroxyl group was explained by postulating that glycidic acid is the intermediate, as amination of glycidic and α-hydroxy-β-chloropropionic acids also led to the same product. Mattocks and Hartung,[4] however, obtained the methyl ester of *N*-benzylserine by treatment of methyl α-bromo-β-hydroxypropionate with anhydrous benzylamine. Since the base strengths of benzylamine and ammonia are similar,[5] it was of interest to study the reaction of the same ester with anhydrous ammonia.

When the preparation of methyl α-bromo-β-hydroxypropionate by treatment of methyl acrylate with alkaline bromine water[4] was attempted, a large proportion of the product proved to be methyl α,β-dibromopropionate. Bartlett and Tarbell[6] concluded from kinetic studies that the reaction of olefins with bromine in alcohols occurs with the following mechanism:



Although the predominant product early in the reaction is the bromoalkoxy adduct, more of the dibromo derivative is formed as the first reaction proceeds and bromide ion concentration is increased. Bromide ion also reacts with the halogen molecule to form the tribromide ion, thus diminishing the bromine concentration and slowing the first reaction.

If the reaction of olefins with halogens in water is similar to that in alcohols, the addition of silver nitrate to precipitate the bromide ions as formed should greatly increase the proportion of bromhydrin among the products. It was found that when methyl acrylate was treated with bromine in an aqueous silver nitrate solution in the cold, a yield of over 80% of crude bromhydrin was afforded. Distillation of the product at reduced pressure caused great losses by decomposition, but a small amount of methyl bromohydroxypropionate was obtained.

Treatment of the bromohydroxy ester with aqueous ammonium hydroxide (analogous to Meli-

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[1] (a) S. K. Fellner and K. C. Leibman, *Federation Proc.*, 19, 9 (1960); (b) K. C. Leibman, *Federation Proc.*, 20, 235 (1961).

[2] N. Nielson and G. Johansen, *Naturwiss.*, 31, 235 (1943).

[3] P. Melikoff, *Ber.*, 13, 1265 (1880).

[4] A. M. Mattocks and W. H. Hartung, *J. Biol. Chem.*, 165, 501 (1946).

[5] pK_b in water at 25°: ammonia, 4.74; benzylamine, 4.70. Calculated from data in *Internat. Critical Tables*, 6, 281 (1929); 7, 240 (1930).

[6] P. D. Bartlett and D. S. Tarbell, *J. Am. Chem. Soc.*, 58, 466 (1936).