lit.[30] m.p. 98–98.5°. An infrared spectrum of a Nujol mull was superposable on a similar spectrum of authentic 1,2-diphenoxyethane.

The estimation of diphenoxyethanes was carried out by a single extraction of a 75-ml. aliquot of the diluted reaction mixture with 100 ml. of ether. The ethereal extract was washed with three 10-ml. portions of water, with three 10-ml. portions of 2% sodium hydroxide solution, and then with five 5-ml. portions of water or until the water wash was neutral to Universal Indicator paper. The ethereal solution was dried over anhydrous magnesium or calcium sulfate, filtered, and the residue washed with fresh portions of ether. The combined filtrates were evaporated under a stream of dried air, and the residue was taken up in 5 ml. of Spectro Grade carbon tetrachloride. This was evaporated to dryness and repeated once more. Finally the residue was dissolved in 0.5 ml. of the solvent for infrared examination. The extinction coefficients were determined on synthetic materials.

Polyfunctional Aliphatic Compounds. V. The Cyclization of Dinitriles by Halogen Acids. A New Synthesis of Imidazoles

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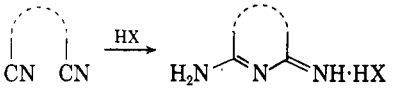
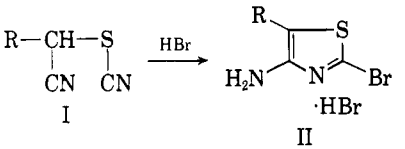
Dinitriles having the general structure, RN(CN)CH(CN)R, undergo cyclization to 2-bromo-4(5)-aminoimidazoles when treated with anhydrous hydrogen bromide. Where R and R′ are aryl groups these amino compounds are generally stable enough to be isolated as the free bases. Otherwise, the imidazoles can be obtained as their acetamino derivatives. A convenient method for the synthesis of the previously unavailable starting dinitriles utilizes the reaction of a monosubstituted cyanamide with an α-haloalkyl, or an α-[4-toluenesulfonyloxyl]alkyl cyanide in anhydrous dimethylformamide using triethylamine as an acid acceptor.

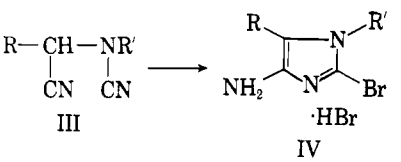
In previous publications[1-3] we have demonstrated that the halogen acid (X = Br or I) cyclization of dinitriles, *viz.*,



can be used for the synthesis of heterocyclic compounds in the pyridine,[1] isoquinoline,[2] and thiazole[3] series. The successful cyclization of α-cyanoalkyl thiocyanates (I) to 4-amino-2-bromothiazoles (II) suggested that

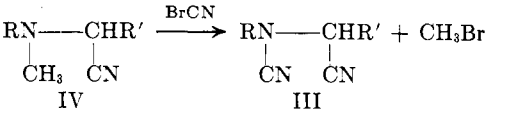


the analogous α-cyanoalkyl cyanamides (III) might lead to the corresponding imidazoles (IV).



Our findings, presented in this paper, now confirm this prediction and demonstrate, as anticipated, that the cyclization occurs in one specific direction, affording only derivatives of 4(5)-aminoimidazole.

α-Cyanoalkyl Cyanamides.—The chief difficulty in broadening the scope of the dinitrile cyclization to include imidazoles, lay in the unavailability of the precursors, namely α-cyanoalkyl cyanamides. For these aliphatic systems, only one recorded method of synthesis could be found in the literature. This, due to v. Braun,[4] involves the action of cyanogen bromide on N-alkyl-N-methylaminoacetonitriles (IV).



Where R is a simple alkyl group, selective cleavage of the methyl group occurs. Although this method proved suitable for the preparation of III, where R = alkyl and R′ = H, it was severely limited by the lack of easy methods of preparation of IV, where R = aryl or hydrogen and R′ = aryl, alkyl, or hydrogen. Therefore, a number of other approaches to III were tried, most with little success.

N-Phenyl-α-(4-methoxyphenyl)aminoacetonitrile did not react at room temperature with cyanogen bromide, and N-phenylaminoacetonitrile could only be induced to react with this reagent at temperatures above 90°. The sole product was N-(4-cyanophenyl)aminoacetonitrile.[5]

When α-phenylaminoacetonitrile (V) was treated with half an equivalent of cyanogen bromide in anhydrous ether the hydrobromide salt of V was rapidly precipitated, and from solution a sirup was obtained which could not be distilled or crystallized. Attempted chromatography only caused decomposition, and no α-cyanobenzyl cyanamide could be obtained.

A number of reactions using cyanamide (VI) itself were tried to no avail. A combination of benzaldehyde, hydrogen cyanide, and VI in the presence of anhydrous calcium sulfate did not lead to any α-cyanobenzyl cyanamide. On the other hand the reaction of α-cyano-2-chlorobenzyl 4-toluenesulfonate (VII) in the presence of triethylamine and VI afforded only the sulfone (VIII).

(1) F. Johnson, J. P. Panella, A. A. Carlson, and D. H. Hunneman, *J. Org. Chem.*, **27**, 2473 (1962).

(2) F. Johnson and W. A. Nasutavicus, *ibid.*, **27**, 3953 (1962).

(3) Part IV: F. Johnson and W. A. Nasutavicus, *ibid.*, **28**, 1877 (1963).

(4) J. v. Braun, *Ber.*, **40**, 3933 (1907).

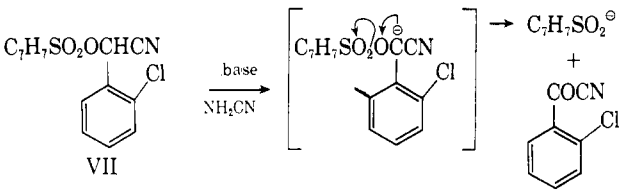
(5) Contrast N-methyl-N-phenylaminoacetonitrile which reacts with cyanogen bromide to give the bromo compound, N-methyl-N-(4-bromophenyl)aminoacetonitrile [J. v. Braun, *ibid.*, **41**, 2113 (1908)].

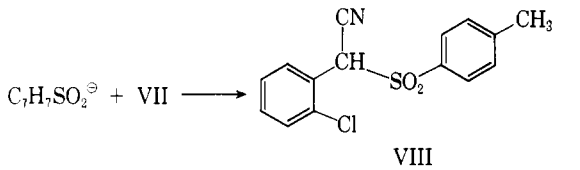
TABLE I

PREPARATION OF DINITRILES OF STRUCTURE $RCH(CN)N(CN)C_6H_5$

R	Crystd.[a] from	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	N	Cl	Found C	H	N	Cl
H	ET	50	79–81	68.8	4.5	26.7		68.7	4.7	26.7	
C_6H_5	MC/E	62	105–107	77.2	4.8	18.0		77.1	5.0	17.8	
$2\text{-}ClC_6H_4$	ET	75	107–108	67.3	3.8	15.7	13.2	67.2	4.0	15.6	13.0
$4\text{-}ClC_6H_4$	MC/E	50.5	105–106	67.3	3.8	15.7	13.2	67.1	3.8	15.6	13.3
$2,4\text{-}Cl_2C_6H_3$	ET	40	98–100	59.6	3.0	13.9	23.5	59.6	3.0	13.6	23.6
$2\text{-}CH_3OC_6H_4$	ET	84	64–65	73.0	5.0	16.0		73.0	4.9	15.9	

[a] Solvent: ET = ethanol, MC = methylene chloride, E = ether.

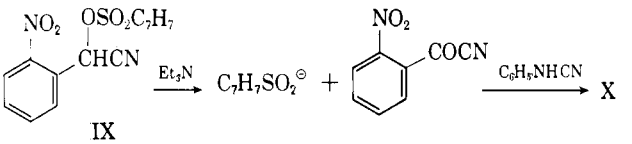




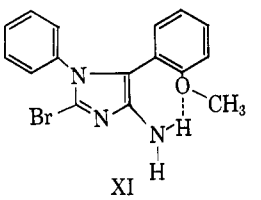
The mechanism of reactions of this type has been well documented.[3,6,7] When chloroacetonitrile was substituted for VII in the previous reaction only triethylcyanomethylammonium chloride could be isolated. Replacement of triethylamine by sodium acetate using ethanol as the solvent led to an oil, whose infrared spectrum indicated the presence of an >N–CN group but considerable absorption was present also in the 6-μ region. Attempted cyclization of this crude material in acetic acid followed by acetylation with acetic anhydride afforded only a trace of a bromine-containing material. The bulk of the product isolated by chromatography agreed well with $C_7H_{11}N_3O_4$. The n.m.r. spectrum of this substance in deuteriochloroform showed only two bands at −616 and −141 c.p.s. (with reference to tetramethylsilane at 0 c.p.s.) having relative intensities of 3:1. It exhibited bands in the infrared spectrum at 3.09, 3.16, 5.76, and 5.91 μ indicative of an imide group, but we have not been able to assign any structure to it.

The reaction mixture of phenyl cyanamide and chloroacetonitrile in ethanol in the presence of sodium ethoxide darkened quickly and only tarry products could be obtained. Nevertheless when this reaction was carried out at room temperature in anhydrous dimethylformamide using triethylamine in place of sodium ethoxide, a good yield of N-cyano-N-phenylaminoacetonitrile was obtained. Using this procedure, phenyl cyanamide reacted with a range of α-chloroalkyl and α-[4-toluenesulfonyloxy]alkyl cyanides[3] to produce a number of the required dinitriles (III). These are listed in Table I. In only one case was a failure recorded. This involved α-cyano-2-nitrobenzyl 4-toluenesulfonate (IX), the only product that could be isolated being N-cyano-N-phenyl-2-nitrobenzamide (X). The latter was identified by comparison with an authentic specimen prepared from phenyl cyanamide and 2-nitrobenzoyl chloride.

Although phenyl cyanamide was the only monosubstituted cyanamide used in the preparation of III, we envisage that other aryl cyanamides could be utilized with equal success. However, attempts to extend the scope of this synthesis by using sodium dicyanamide in place of phenyl cyanamide met with uniform failure.



Imidazoles.—When the α-cyanoalkyl cyanamides were treated with hydrogen bromide in an inert medium, reaction occurred rapidly in most instances, and the salt of the bromoaminoimidazole separated from solution. These materials were usually unstable to moisture and underwent a fast decomposition when added to mild base. The salts, however, could be converted easily to the corresponding acetamino compounds and most of the imidazoles were characterized as these derivatives. Where both 1- and 5-positions of the imidazoles were unsubstituted by aryl groups, the free amines could be isolated. The most stable was XI perhaps due to hydrogen bonding between the methoxyl and amino groups. The imidazoles prepared by hydrogen bromide induced cyclization are listed in Table II.



Debromination of these compounds was accomplished easily as shown by the facile conversion of 4-acetamino-2-bromo-1-methylimidazole to 4-acetamino-1-methylimidazole when the former was shaken in solution with hydrogen and a palladium catalyst.

The constitution of these compounds as the 4-amino-2-bromoimidazoles and not the isomeric 2-amino-4-bromo compounds is suggested (a) by the instability of the free amines, a characteristic of 4(5)-aminoimidazoles[8] but not of 2-aminoimidazoles; and (b) by analogy with the cyclization of α-cyanoalkyl thiocyanates. The

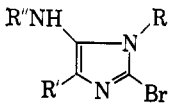
(6) E. C. Taylor, G. A. Berchtold, N. A. Goeckner, and F. G. Stroehmann, *J. Org. Chem.*, **26**, 2715 (1961).

(7) J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1780 (1959).

(8) K. Hofmann, "Imidazole and Its Derivatives," Part I, Interscience Publishers, Inc., New York, N. Y., 1953, pp. 142–143.

TABLE II

PREPARATION OF IMIDAZOLES FROM DINITRILES OF STRUCTURE $RN(CN)CH_2R'CN$

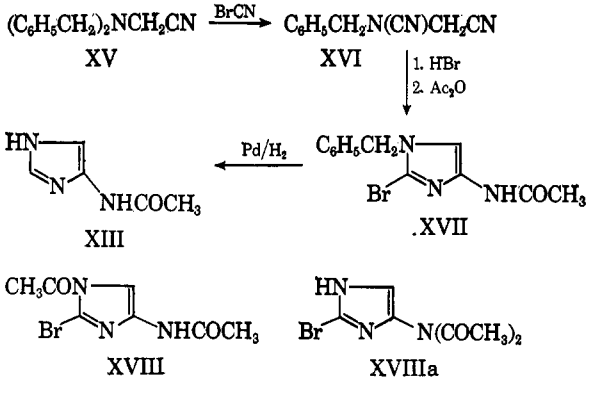


R	R′	R″	Method	Crystd.[a] from	Yield, %	M.p., °C.	Analyses, % Calcd. C	H	Br	N	Cl	Found C	H	Br	N	Cl
CH_3	H	CH_3CO	B	M	33	223–224	33.0	3.7	36.6	19.3		33.1	3.7	36.5	19.0	
C_2H_5	H	CH_3CO	B	MC/E	53	175–176.5	36.2	4.3	34.4	18.1		36.4	4.5	34.5	18.2	
C_4H_9	H	CH_3CO	B	MC/EA	47	138–140	41.6	5.4	30.7	16.2		41.6	5.2	30.8	16.0	
C_6H_5	H	CH_3CO	C	MC/E	82	200–202	47.2	3.6	28.5	15.0		47.0	3.5	28.4	14.9	
C_6H_5	C_6H_5	H	A	MC	82	195–210 dec.	57.3	3.9	25.4	13.4		57.3	3.9	25.7	13.2	
C_6H_5	2-ClC_6H_4	H	B[b]	M/E	10	249–252 dec.	51.7	3.2	22.9	12.0	10.2	51.5	3.4	22.7	11.9	10.1
C_6H_5	2-ClC_6H_4	CH_3CO	C	M	55	219–220	52.3	3.4	20.5	10.8	9.1	52.3	3.2	20.7	10.7	9.2
C_6H_5	4-ClC_6H_4	CH_3CO	C	MC	50	187–189	52.3	3.4	20.5	10.8	9.1	52.0	3.4	20.3	10.9	9.0
C_6H_5	2,4-$Cl_2C_6H_3$	H	A	MC/E	68	154–156	47.0	2.6	20.9	11.0	18.5	46.9	2.4	20.9	10.8	18.6
C_6H_5	2-$CH_3OC_6H_4$	H	A	MC	82.5	187–192 dec.	55.8	4.1	23.2	12.2		55.8	4.0	23.3	12.1	
$C_6H_5CH_2$	H	CH_3CO	B	MC/E	68	184–185	49.0	4.1	27.2	14.3		49.2	3.9	27.3	14.1	

[a] Solvent: M = methanol, MC = methylene chloride, EA = ethyl acetate. [b] Isolated by chromatography.

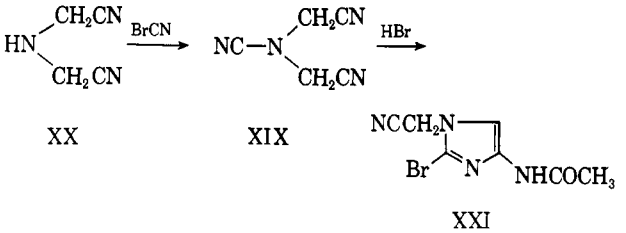
latter lead to 4-amino-2-bromothiazoles when treated with hydrogen bromide.[3] However, chemical evidence seemed desirable and an attempt was made to prepare 4(5)-acetamino-2-bromoimidazole (XII) with a view to converting it to the known 4(5)-acetaminoimidazole (XIII).

Treatment of aminoacetonitrile (XIV) with cyanogen bromide at 0° led to the rapid deposition of the hydrobromide of XIV together with a considerable quantity of highly colored gum. The liquid phase was removed and as attempted isolation of material from this led to further decomposition, it was treated directly with hydrogen bromide followed by acetic anhydride. The only product that could be isolated from this reaction was what appears to be the diacetylated imidazole (XVIII), and this only in very small amount. This structure is supported not only by a good elemental analysis but by its infrared spectrum which shows weak bands at 3.12 and 3.28 μ characteristic of a 4(5)-acetamino group in this series. Again imidazoles that we have examined having no substituent at the 1-position show a strong absorption at 3.10 μ. In addition strong bands are apparent at 5.75 (ring N-acetyl group) and 6.01 μ, the latter again characteristic of a 4(5)-acetaminoimidazole. Structure XVIIIa can be eliminated as a possibility because the 4(5)-diacetamino group could, by analogy with known examples in the thiazole series,[3] be expected to have only one absorption band at approximately 5.82 μ. However, the sequence of reactions shown finally led to the desired compound.



N,N-Dibenzylaminoacetonitrile (XV) was prepared[9] best by the action of chloroacetonitrile on dibenzylamine in the presence of triethylamine in anhydrous dimethylformamide. Cleavage of XV by cyanogen bromide occurred smoothly as did the subsequent cyclization and acetylation of XVI to give XVII. Hydrogenation of the latter to XVII, however, could not be accomplished in one step. It appears that the presence of bromide ion in solution inhibits the debenzylation reaction, for when this was removed, debenzylation occurred smoothly. The final product XIII had m.p. 225° in close agreement with that recorded (226°) for 4(5)-acetaminoimidazole,[10] but not with that (287°) of 2-acetaminoimidazole.[11] The infrared spectrum of XIII exhibited strong bands at 3.10 and 6.01 μ, in good agreement with what might be expected for a compound with this structure. The structures of the other imidazoles prepared were assigned by analogy with the direction of cyclization of XVI.

A number of other systems also were examined. N-Cyanoiminodiacetonitrile (XIX) prepared by the action of cyanogen bromide on XX underwent immediate reaction with hydrogen bromide. After acetylation the imidazole XXI could be obtained but the yield varied capriciously from 5–65%.



The structure assigned to XXI is supported by an elemental analysis and its infrared spectrum which exhibits a band at 5.95 (acetamino group) and a doublet at 6.34 and 6.44 μ characteristic of this type of imidazole. This spectrum, also, is strikingly similar to that

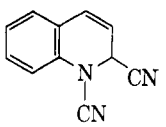
(9) The method described by R. A. Turner and C. Djerassi [*J. Am. Chem. Soc.*, **72**, 3081 (1950)] for the preparation of XV gave lower yields than the present procedure, and was often complicated by the appearance of N,N,N′,N′-tetrabenzylmethylenediamine.

(10) G. Hunter and J. A. Nelson, *Can. J. Research*, **19B**, 296 (1941).

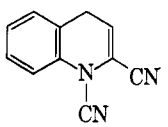
(11) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, 217 (1919).

of 4-acetamino-2-bromo-1-methylimidazole, having corresponding bands at approximately 7.1, 7.2, 7.9, 10.0, and 13.5 μ. The lack of nitrile absorption in the spectrum of XXI was at first sight surprising but the complete absence of nitrile absorption in compounds such 2-acetoxy-2-cyanopropane has been noted previously.[12] This, however, appears to be the first reported occasion where an imidazole ring on the carbon atom bearing the nitrile group quenches the absorption of the latter. In addition the n.m.r. spectrum of XXI in trifluoroacetic acid shows absorptions at 473, 327, and 146.5 c.p.s. which integrated for proton ratios of 1:2:3. The positions of these bands are in good agreement with what might be expected for an imidazole proton, a methylene group flanked by an aromatic nucleus and a cyano group, and the hydrogens of an acetyl function. By way of comparison 4-acetamino-2-bromo-1-ethylimidazole showed n.m.r. absorption bands at 462 (proton at the 5-position), 265 (methylene quadruplet), 148 (acetyl methyl), and 98 c.p.s. (methyl triplet) in trifluoroacetic acid. However, no further chemical work on XXI has been attempted.

N,2-Dicyano-1,2-dihydroquinoline XXII prepared according to v. Braun[13] also was treated with hydrogen bromide. Reaction occurred immediately and a dark green muddy precipitate was deposited, but no crystalline product could be isolated. The isomeric dinitrile (XXIII) exhibited the same behavior.

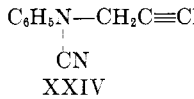


XXII

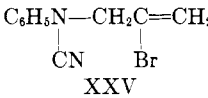


XXIII

In an attempt to determine if the cyclization procedure could be applied to groups isoelectronic with nitriles, N-phenyl-N-propargylcyanamide (XXIV), prepared by the action of propargyl bromide on phenylcyanamide in dimethylformamide, was treated with hydrogen bromide. A heavy white precipitate ap-



XXIV



XXV

peared but neutralization of this with mild base afforded only the hydrogen bromide addition product XXV which showed vinyl CH_2 absorption at 10.82 μ in its infrared spectrum.

Further work on the application of this dinitrile cyclization synthesis to other heterocyclic systems will be reported in subsequent publications.

Experimental

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded on a Baird spectrophotometer Model No. A-55 as films or as Nujol mulls, and n.m.r. spectra were taken using a Varian A-60 instrument. Tetramethylsilane absorption was taken as the reference point of 0 c.p.s. in the n.m.r. spectra from the spectrophotometer. Hydrogen bromide in acetic acid was used as supplied by Eastman Kodak.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 266.

(13) O. Mumm and E. Herrendorfer, *Ber.*, **47**, 758 (1914).

Preparation of α-Cyanoalkyl Phenyl Cyanamides.—Phenyl cyanamide (0.02 to 0.04 mole) was dissolved in dry dimethylformamide (6 ml.) and triethylamine (0.2 to 0.4 mole) added. This mixture was then treated with a solution of the requisite halide or 4-toluenesulfonate. After a few minutes a precipitate of triethylamine salt began to appear. As soon as salt separation appeared complete (no more than 2 hr.) the total reaction mixture was poured into crushed ice. The solid which separated was rubbed until crystalline and then removed by filtration, dried, and recrystallized from the appropriate solvent.

N-Butyl-N-cyanomethyl Cyanamide.—Cyanogen bromide (10.6 g.) and N-butyl-N-methylaminoacetonitrile (12.6 g.) were combined and heated gently at 40° for 1.5 hr. The mixture was diluted with ether and the solid removed by filtration. The filtrate was heated to remove ether and the residual liquid (9.3 g.) distilled under reduced pressure. The fraction distilling at 95–115° (0.8 mm.) was collected (4.5 g.) and redistilled at 0.45 mm. to give the pure product (3 g.), b.p. 110°, $n^{25}D$ 1.4482.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.3; H, 8.1; N, 30.6. Found: C, 61.2; H, 8.0; N, 30.7.

The Action of Cyanamide and Triethylamine on α-Cyano-2-chlorobenzyl 4-Toluenesulfonate.—A solution of α-cyano-2-chlorobenzyl 4-toluenesulfonate (6.4 g.) in anhydrous dimethylformamide (10 ml.) was added to cyanamide (0.9 g.) and triethylamine (2.1 g.) in the same solvent (5 ml.). After 5 hr. the bronze-colored solution was poured into ice–water. The product, isolated by extraction with methylene chloride, was a colorless crystalline solid (2.7 g. 71%) and after recrystallization from methanol afforded pure α-cyano-2-chlorobenzyl 4-tolyl sulfone, m.p. 110–112°, lit.[7] m.p. 112°. Its infrared spectrum showed bands at 7.51 and 8.66 μ characteristic of a sulfone group.

Anal. Calcd. for $C_{15}H_{12}ClNO_2S$: C, 58.9; H, 4.0; Cl, 11.6; N, 4.6. Found: C, 58.9; H, 3.8; Cl, 11.6; N, 4.9.

N-Cyano-N-phenyl-2-nitrobenzamide. A.—Phenyl cyanamide (2.4 g.) in dry dimethylformamide (5 ml.) was treated with triethylamine (2 g.) followed by a solution of α-cyano-2-nitrobenzyl 4-toluenesulfonate (6.6 g.) in dimethylformamide (20 ml.). The mixture immediately became deep blue in color but changed to red within 3 hr. Addition of the solution to ice–water resulted in a partially crystalline red precipitate. This was removed by extraction with ether. Isolation of the product in the usual way followed by crystallization from ethanol led to the title compound (2.1 g., 40%), m.p. 116–118°. Its melting point was not depressed when mixed with the sample prepared later. Its infrared spectrum showed bands at 4.47, 5.81, and 6.56 μ.

Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.9; H, 3.4; N, 15.7. Found: C, 63.3; H, 3.3; N, 16.0.

B.—Phenyl cyanamide (1.2 g.) in dry dimethylformamide (10 ml.) was treated successively with triethylamine (1.0 g. and 2-nitrobenzoyl chloride (1.9 g.). After 45 min. the solid precipitate was removed by filtration and recrystallized from ethanol to give the desired material, m.p. 116–117°. A mixture melting point with the specimen prepared as in a showed no depression.

Cyclization of Cyanoalkyl Cyanamides. A.—The dinitrile (0.01 mole) in methylene chloride (25–50 ml.) was treated with hydrogen bromide at 0° for 1.5 hr. The solvent and excess hydrogen bromide were removed at 30° under reduced pressure and the resulting solid added to saturated sodium hydrogen carbonate. After the subsidence of effervescence, the solid was removed, dried, and recrystallized from the appropriate solvent.

B.—The dinitrile (0.02 mole) if liquid, or dissolved in a minimum of acetic acid if solid, was added with cooling to a saturated solution (10 ml.) of hydrogen bromide in acetic acid. After stirring for 1 hr. an excess of a mixture of acetic anhydride and pyridine (3:1) was added. One and a half hours later the mixture was poured into saturated sodium hydrogen carbonate solution and the product isolated by methylene chloride extraction.

C.—This was the same as method A, except that the product was acetylated as in B.

4-Acetamino-1-methylimidazole.—4-Acetamino-2-bromo-1-methylimidazole (0.545 g.) and sodium acetate (0.205 g.) in ethanol (50 ml.) were stirred with hydrogen in the presence of a palladium-on-charcoal catalyst (90 mg., 10% Pd) at atmospheric pressure and room temperature. Hydrogen absorption ceased after 20 min. and the catalyst and solvent were then removed by the usual procedures. The residue was extracted with methylene chloride and the solution concentrated, then diluted with methanol to give 4-acetamino-1-methylimidazole (0.309 g., 89.5%), m.p. 249–252° dec.

Anal. Calcd. for $C_6H_9N_3O$: C, 51.7; H, 6.5; N, 30.2. Found: C, 51.7; H, 6.7; N, 30.5.

4-Acetamino-2-bromo-1-acetylimidazole.—Aminoacetonitrile (5.6 g.) in dry ether (30 ml.) was cooled to −60° and a solution of cyanogen bromide (5.3 g.) in the same solvent (30 ml.) added dropwise. The colorless solution was allowed to come to room temperature slowly and during this period it gradually darkened and an almost black gummy solid separated. The liquid phase was decanted and hydrogen bromide bubbled through it at ice bath temperatures. A copious yellow precipitate appeared and this was removed by filtration and added to acetic anhydride (10 ml.) and pyridine (2 ml.). Warming on the steam bath for 2 hr. followed by adding to sodium acetate solution led to a crude solid (0.5 g.). Repeated crystallization from ethyl acetate–ethanol gave the pure material, m.p. 192–193°.

Anal. Calcd. for $C_7H_8BrN_3O_2$: C, 34.2; H, 3.3; N, 17.1. Found: C, 33.9; H, 3.3; N, 17.0.

The Reaction of Chloroacetonitrile with Cyanamide.—Cyanamide (4.2 g.) was dissolved in ethanol (50 ml.) containing sodium acetate (8.2 g.) in suspension and the mixture stirred while chloroacetonitrile (7.5 g.) in ethanol (20 ml.) was added. Stirring was continued at room temperature until the aqueous phase gave only a slight test for organic chlorine (4 days). The precipitate (6.5 g.) was removed by filtration and the solvent evaporated to small bulk below 40°, and ethyl acetate added. After filtration to remove a small amount of suspended solid, the ethyl acetate and volatile materials were removed under reduced pressure. This afforded a sirup (5.3 g.) whose infrared spectrum showed bands at 4.44 and 5.90 μ. A sample of this material (3.4 g.) was added to a solution of hydrogen bromide (5.4 g., 30% hydrogen bromide) in acetic acid. After stirring for 1.5 hr., acetic anhydride (11.0 g.) was added and the mixture heated for 30 min. to effect solution of the precipitated solid. The liquid was then poured into saturated sodium acetate solution and, after stirring for a short period, the product was isolated by ethyl acetate extraction. This afforded brown crystals (1.9 g.) whose color was removed by percolation through a silica gel (15 g.) column in a 1:1 mixture of ethyl acetate methylene chloride. Two recrystallizations from acetone–ether gave the pure product (0.6 g.), m.p. 153–154°. It gave a negative Beilstein test.

Anal. Calcd. for $C_7H_{11}N_3O_4$: C, 41.8; H, 5.5; N, 20.9. Found: C, 41.8; H, 5.5; N, 21.0.

N,N-Dibenzylglycinonitrile.—Dibenzylamine (25 g.) and triethylamine (13.0 g.) were dissolved in anhydrous dimethylformamide (50 ml.), and chloroacetonitrile (10.5 g.) then added dropwise with stirring. Within 15 min. a precipitate began to appear and heat was evolved, but the solution was allowed to stand overnight. The dimethylformamide was removed under reduced pressure using a vacuum pump and the residue triturated with ice–water. The solid which formed was removed by filtration, dissolved in ether, and the ether solution stirred with magnesium sulfate and decolorizing charcoal. Filtration followed by concentration of the filtrate and dilution with petroleum ether afforded N,N-dibenzylglycinonitrile (21 g., 70%), m.p. 45–46°, lit.[9] m.p. 46–48°.

Using the procedure of Turner and Djerassi[9] the same product could be obtained in only 50% yield and isolation was more difficult.

N-Cyano-N-benzylglycinonitrile.—N,N-Dibenzylglycinonitrile (8.0 g.) in dry 1,2-dimethoxyethane (10 ml.) was treated with a solution of cyanogen bromide (4.24 g.) in the same solvent (20 ml.). The system was closed and the mixture heated for 48 hr. at 60–70°. The reaction solution was then added to a mixture of water and ethyl acetate. The organic layer was separated, dried over magnesium sulfate, and ethyl acetate and most of the benzyl bromide removed under reduced pressure. The resulting syrup was dissolved in benzene and chromatographed over silica gel (80 g.). Elution of the column with benzene afforded some benzyl bromide whereas benzene containing 10% methylene chloride gave starting material (about 1 g.). Further elution with the same solvents up to 100% methylene chloride removed unwanted materials (about 0.6 g.) which were discarded. Finally methylene chloride containing 10% ethyl acetate eluted the desired compound. Recrystallization from acetone–ether–petroleum ether (b.p. 30–60°) afforded pure N-cyano-N-benzylglycinonitrile (2.8 g., 48%), m.p. 63–64°. Its infrared spectrum showed a strong band at 4.46 μ.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.2; H, 5.3; N, 24.5. Found: C, 70.3; H, 5.2; N, 24.2.

1-Benzyl-4-acetaminoimidazole.—1-Benzyl-2-bromo-4-acetaminoimidazole (1.8 g.) in ethanol (50 ml.) containing sodium acetate (0.65 g.) was shaken with hydrogen in the presence of a 10% palladium-on-charcoal catalyst (0.1 g.) at room temperature and pressure. Gas absorption ceased after 1 hr. and the catalyst and solvent were then removed. Water and methylene chloride were added and the organic layer separated and dried over magnesium sulfate. Evaporation of the solvent led to a solid which was recrystallized from methanol to give the pure product (1.15 g., 87%), m.p. 180–181°. Its infrared spectrum showed bands at 3.12, 3.17, 5.94, and 6.35 μ.

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 67.0; H, 6.1; N, 19.5. Found: C, 66.9; H, 5.9; N, 19.3.

4(5)-Acetaminoimidazole.—1-Benzyl-4-acetaminoimidazole (0.6 g.) in glacial acetic acid (15 ml.) was stirred with a 10% palladium-on-charcoal catalyst (0.6 g.) in a hydrogen atmosphere overnight at room temperature and pressure. After the solution was filtered, the acetic acid was removed under reduced pressure and the solid product crystallized from methanol to give 4(5)-acetaminoimidazole (0.2 g.), m.p. 225° dec., lit.[10] 226°. For analysis, a sample was twice recrystallized from ethyl acetate.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 48.0; H, 5.6; N, 33.5.

N-Cyanoiminodiacetonitrile.—A solution of iminodiacetonitrile (9.5 g.) and dry cyanogen bromide (5.8 g.) in monoglyme (100 ml.) was heated at 60° for 10 hr. The precipitated solid was removed by filtration and discarded. The filtrate was taken to dryness under reduced pressure and the residue crystallized from acetone–methylene chloride to give the pure product, m.p. 76–78° (2.7 g., 45%). The infrared spectrum showed a strong band at 4.45 μ.

Anal. Calcd. for $C_5H_4N_4$: C, 50.0; H, 3.16; N, 46.6. Found: C, 50.1; H, 3.4; N, 46.4.

4-Acetamino-2-bromo-1-cyanomethylimidazole.—To a cooled solution of N-cyanoiminodiacetonitrile (0.6 g.) in glacial acetic acid (10 ml.) there was added a 30% solution (11 g.) of hydrogen bromide in the same solvent. A heavy white precipitate formed immediately. After stirring for 1 hr., excess acetic anhydride (5 ml.) was added, and the solution heated for a further hour in a steam bath. The cooled solution was then poured into aqueous sodium acetate, and the precipitate removed by filtration. Recrystallization of this solid from methanol gave the desired compound (0.4 g.), m.p. 234–236°.

Anal. Calcd. for $C_7H_7BrN_4O$: C, 34.6; H, 2.9; Br, 32.9; N, 23.1. Found: C, 34.5; H, 3.0; Br, 32.9; N, 23.2.

N-Phenyl-N-propargyl Cyanamide.—To a cooled solution of phenyl cyanamide (2.4 g.) and triethylamine (2 g.) in anhydrous dimethylformamide (100 ml.), there was added dropwise propargyl chloride (1.6 g.) in the same solvent (10 ml.). The mixture was allowed to warm to room temperature and stood for 18 hr. The solution was poured into water and the gummy precipitate removed by filtration, dissolved in ethyl acetate, and this solution dried over anhydrous magnesium sulfate. Removal of the solvent led to a syrup which was dissolved in benzene and percolated through a silica gel (20 g.) column. Elution with methylene chloride–benzene (1:10) led to a solid (1.2 g.) which on crystallization from ether–petroleum ether (b.p. 30–60°) afforded the product, m.p. 46–47°. This material previously prepared[14] by the reaction of N-propargylaniline with cyanogen bromide was reported to have m.p. 48–49°.

Action of Hydrogen Bromide on N-Phenyl-N-Propargyl Cyanamide.—N-Phenyl-N-propargyl cyanamide (0.4 g.) was added to a 30–33% solution of hydrogen bromide in acetic acid (15 g.) and the mixture stirred for 20 hr. at room temperature. The reaction mixture was poured into an excess sodium hydrogen carbonate solution and the whole extracted with ethyl acetate. Isolation of the product in the usual way led to a sirup which crystallized. Recrystallization from ether–petroleum ether (b.p. 30–60°) afforded pure N-(2-bromoallyl)-N-phenyl cyanamide, m.p. 72–73°. Its infrared spectrum showed bands at 4.48 and 10.82 μ.

Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.7; H, 3.8; Br, 33.7; N, 11.8. Found: C, 50.4; H, 3.8; Br, 33.9; N, 11.6.

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(14) J. v. Braun and L. Tauber, *Ann.*, **458**, 102 (1927).