2,4-Diphenyl-s-triazine (XI).—A solution of 1.1 g. of N-carbamoylbenzamidine,[12] m.p. 130–132°, in 3 ml. of formamide was heated at 180–185° for an hour. The white solid which crystallized on cooling was extracted into petroleum ether. This solution was decanted from some insoluble oil and evaporated to give 0.10 g. (13%) of XI, m.p. 68–72°. Recrystallization from aqueous ethanol gave a sample which had m.p. 73–75° and an infrared spectrum identical with that of an authentic sample.[23]

3-Phenyl-1,2,4-triazolin-5-one (XII).—A mixture of 1.0 g. (0.007 mole) of N-cyanobenzamidine and 0.75 g. (0.007 mole) of hydrazine dihydrochloride in 15 ml. of 50% aqueous methanol and was refluxed for 3 hr. Most of the methanol was distilled. Upon cooling 0.30 g. (30%) of the starting material crystallized. A little sodium bicarbonate was added to the aqueous filtrate, from which XII slowly crystallized during 24 hr. The yield was 0.25 g. (23%), m.p. > 300°. It was recrystallized from 50% aqueous ethanol; m.p. 322–325° (lit.[24,25] m.p. 321° and 324°).

In another run, under slightly more strenuous conditions, a 15% yield of **benzoylurea**,[3] m.p. 210–212°, was isolated in addition to a lesser amount of XII.

3-Amino-5-phenyl-1,2,4-oxadiazole (XIII).—A solution composed of 1.0 g. of N-cyanobenzamidine, 0.50 g. of hydroxylamine hydrochloride, 3 ml. of ethanol, and 2 ml. of pyridine was refluxed for 30 min. and filtered hot to remove ammonium chloride. The filtrate was chilled to give 0.35 g. (31%) of XIII, m.p. 156–160°. One recrystallization from ethanol raised the m.p. to 164–165.5° (lit.[26,27] m.p. 164° and 164–165°).

(24) H. Gehlen, *Ann.*, **563**, 185 (1949).
(25) E. Hoggarth, *J. Chem. Soc.*, 1918 (1949).
(26) H. Wieland and H. Bauer, *Ber.*, **40**, 1680 (1907).
(27) P. Adams, D. W. Kaiser, and G. A. Peters, *J. Org. Chem.*, **18**, 934 (1953).

N-Cyanoimidates

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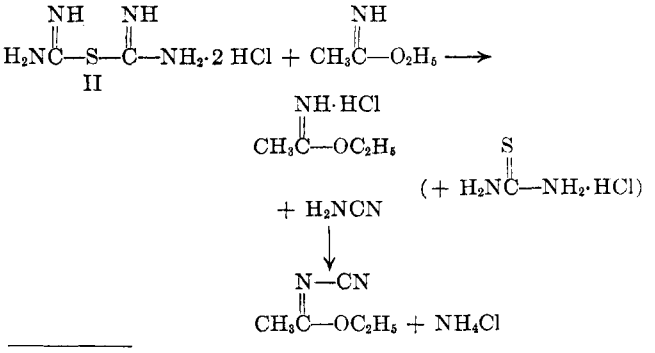
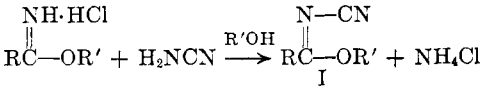
Alkyl N-cyanoimidates, a new class of reactive intermediates, have been prepared by reaction of cyanamide with ortho esters or imidate hydrochlorides. The N-cyanoimidates react with amidines to give 2-amino-*s*-triazines, with amidoximes to give 2-amino-*s*-triazine 1-oxides, with hydroxylamine to give 5-amino-1,2,4-oxadiazoles, and with hydrazine to give 3-amino-1,2,4-triazoles. Interaction of monosodium cyanamide with N-cyanoimidates gives N,N'-dicyanoamidine salts, which cyclize to 2-amino-*s*-triazines upon treatment with dry hydrogen chloride.

As an extension of the work reported in the previous paper[1] concerning the use of N-cyanoamidines as intermediates for the synthesis of certain nitrogen heterocycles, we have investigated the chemistry of the related N-cyanoimidates (I), with the expectation that the more easily displaceable alkoxy group would allow more efficient reactions with nucleophilic reagents. Although N-cyanoimidates have apparently not been reported in the literature, various N-carbamoylimidates[2] and N-acylimidates[3,4] are known. Moreover, they have been reported to react well with amines to give N-acylamidines.[2,5] An N-cyanopseudourea (I. R = NH_2) has also been prepared,[6] but its reactions were apparently not investigated.

We first obtain ethyl N-cyanoacetimidate as an unexpected product from attempted cotrimerization[7a] of ethyl acetimidate with thiodiformamidine dihydrochloride (II). Consideration of the probable mechanism of this reaction suggested that this N-cyanoimidate resulted from reaction of the imidate hydrochloride with cyanamide, the latter arising from dissociation of the starting material. Although imidates generally react with amino compounds with displacement of alcohol to give amidines, in many cases use of the imidate hydrochloride shifts the reaction to give formation of the N-substituted imidate by loss of ammonium chloride.[8] Thus, while reaction of cyanamide with imidates rapidly gave N-cyanoamidines,[1] it appeared that the corresponding reaction of the imidate salt might lead to N-cyanoimidates.





The first results were immediately encouraging when it was found that ethyl and methyl N-cyanoacetimidates (I. R = CH_3, R' = C_2H_5 or CH_3) could be prepared in 60–65% yields according to the equation shown. The procedure consisted simply of mixing the imidate hydrochloride with cyanamide in alcoholic solution, filtering the ammonium chloride after a few hours, and isolating the product by distillation. The somewhat slower reaction of imidate hydrochlorides with alcohols to give ortho esters[8] did not appear to be interfering to any appreciable extent.

Unfortunately, this method failed to give pure isolable N-cyanoimidates when the group R was made more complex than alkyl. The use in this reaction of alkyl imidates containing α- or β-chloro, α-hydroxy, or α-cyano groups led to complex mixtures or different products.

(1) K. R. Huffman and F. C. Schaefer, *J. Org. Chem.*, **28**, 1812 (1963).
(2) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **77**, 5872 (1955).
(3) H. L. Wheeler and P. T. Walden, *Am. Chem. J.*, **19**, 129 (1897).
(4) H. L. Wheeler, P. T. Walden, and H. F. Metcalf, *ibid.*, **20**, 64 (1898).
(5) H. L. Wheeler and P. T. Walden, *ibid.*, **20**, 568 (1898).
(6) W. Madelung and E. Kern, *Ann.*, **427**, 1 (1922).
(7) (a) F. C. Schaefer, *J. Org. Chem.*, **27**, 3608 (1962); (b) F. C. Schaefer and G. A. Peters, *ibid.*, **26**, 2778 (1961).
(8) For examples, see R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

TABLE I

PREPARATION OF N-CYANOIMIDATES FROM CYANAMIDE AND ORTHO ESTERS

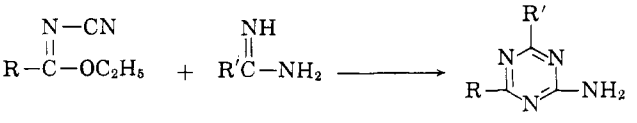
$$RC(OR')_3 + H_2NCN \xrightarrow{2Ac_2O} \underset{\displaystyle RC(=N-CN)-OR'}{}$$

R	R'	Temp., °C.	Time	Yield, %	B.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	C_2H_5	140	1 hr.	90	90–95 (20 mm.)	$C_5H_8N_2O$	53.55	7.19	24.99	53.56	7.52	24.61
H	C_2H_5	140	1 hr.	90	58–63 (0.1 mm.)	$C_4H_6N_2O$	48.97	6.17	28.56	49.26	6.18	28.37
$C_2H_5O_2CCH_2$[a]	C_2H_5	150	15 min.	74	103–106 (0.2 mm.)	$C_8H_{12}N_2O_3$	52.16	6.57	15.21	52.22	6.39	14.85
C_6H_5	CH_3	150	20 min.	61	115–125 (0.3 mm.)	$C_9H_8N_2O$	67.48	5.03	17.49	67.18	4.99	17.34
$ClCH_2$	CH_3	130	30 min.	75	76–80 (0.3 mm.)	$C_4H_5N_2OCl$[b]	36.24	3.80	...	36.54	3.88	...
$ClCH_2$	C_2H_5	145	30 min.	65	87–90 (0.2 mm.)	$C_5H_7N_4OCl$[c]	34.40	4.04	32.09	34.36	4.01	32.25

[a] The ketene acetal (III) was used with one equivalent of acetic anhydride. [b] Calcd.: Cl, 26.75. Found: Cl, 26.46. [c] Calcd.: Cl, 20.31. Found: Cl, 20.43.

TABLE II

PREPARATION OF 2-AMINO-*s*-TRIAZINES IN METHANOL AT 25°



R	R'	Reaction time (hr.)	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3[a]	CH_3	3	84	170–171[b]	$C_5H_8N_4$	...	...	...	...	...	...
CH_3[a]	C_6H_5	3	76	156.5–158	$C_{10}H_{10}N_4$	64.50	64.32	5.41	5.39	30.09	30.26
CH_3	NH_2	0.5	77	276–277	$C_4H_7N_5$	...	...	...	...	...	...
CH_3	$CH_3O_2CCH_2$[c]	2[d]	38[e]	117.5–119.5	$C_7H_{10}N_4O_2$	46.15	46.04	5.52	5.41	30.76	30.22
CH_3	$C_2H_5O_2CCH_2$	18[f]	27	125–126	$C_8H_{12}N_4O_2$	48.97	48.92	6.17	6.16	28.56	28.62
CH_3	CH_3O	2	45	257–259[g]	$C_5H_8N_4O$	42.85	43.00	5.75	6.00	39.98	39.77
CH_3	*p*-NO_2-C_6H_5	2[d]	60	267–268	$C_{10}H_9N_5O_2$	51.94	52.24	3.92	4.32	30.29	30.50
H	NH_2	1	...[h]	>300[h]	$C_3H_5N_5$	...	...	...	...	...	...
H	C_6H_5	0.5	29	203.5–204.5[i]	$C_9H_8N_4$	...	...	...	...	...	...
$ClCH_2$	C_6H_5	0.5	23	145–147	$C_{10}H_9N_4Cl$[j]	54.43	54.66	4.11	4.16	25.39	25.46
$ClCH_2$	CH_3O	0.25	63	164–165	$C_5H_7N_4OCl$[k]	34.40	34.36	4.04	4.01	32.09	32.25
C_6H_5[l]	CH_3	1	54[e]	156–158	$C_{10}H_{10}N_4$[m]	...	...	...	...	...	...

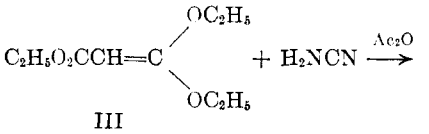
[a] Starting material was *methyl* N-cyanoacetamidate. [b] N. Tscherven-Iwanoff, *J. prakt. Chem.*, [2] **46**, 147 (1892), reports m.p. 170°. [c] Ethyl ester was used as starting material. Ester interchange occurred during course of reaction. [d] At 50°. [e] Yield of crude product. [f] In ethanol. [g] Purified by trituration with hot water. [h] See Experimental. [i] Ref. 1 gives m.p. 203–204°. [j] Calcd.: Cl, 16.07. Found: Cl, 15.83. [k] Calcd.: Cl, 20.31. Found: Cl, 20.43. [l] Starting material was methyl N-cyanobenzimidate. [m] Identical with second entry in this table.

Methyl benzimidate hydrochloride also did not react smoothly with cyanamide, although a small amount of methyl N-cyanobenzimidate was obtained.

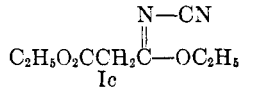
Investigation of a second method for synthesis of N-cyanoimidates was based on the known reaction of amino compounds with ortho esters to give alkoxymethylene derivatives. Such a reaction has been used successfully by Whitehead and Traverso[2] to convert substituted ureas to N-carbamoylimidates, but there is no report of the use of cyanamide as the amine component. Accordingly, this route to N-cyanoimidates was tried and was found to work quite well in most cases. Table I lists the compounds prepared by this procedure, which consisted simply of heating the reagents in two equivalents of acetic anhydride at 130–150° for periods of fifteen minutes to one hour, while distilling the by-products, acetic acid and alkyl acetate. The pure N-cyanoimidates were then isolated by distillation.

$$RC(OR')_3 + H_2NCN + 2Ac_2O \longrightarrow \underset{\displaystyle RC(=N-CN)-OR'}{\text{I}} + 2\,R'OAc + 2HOAc$$

In order to obtain an example of an N-cyanoimidate containing a potentially active methylene group, the ketene acetal III was prepared and treated with cyanamide in the presence of one equivalent of acetic anhydride. This variation of the usual procedure produced the N-cyanoimidate Ic in 74% yield.

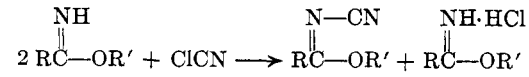


III



Ic

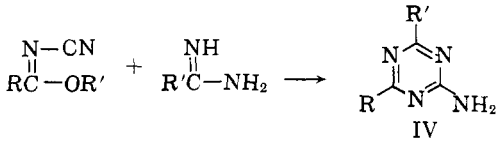
A few experiments directed at the preparation of N-cyanoimidates by reaction of imidates with cyanogen chloride were also carried out. Although it has long been known that imidates could be acylated with acid chlorides,[3,4] addition of cyanogen chloride to two equivalents of methyl benzimidate in ether gave little or no reaction, while the same procedure applied to methyl acetimidate afforded only a 23% yield of methyl N-cyanoacetimidate. In the latter case the major product was 2,4,6-trimethyl-*s*-triazine, resulting from acid-catalyzed trimerization of the imidate.[7b] Low yields of crude methyl N-cyanobenzimidate and methyl N-cyanoacetimidate were obtained by treatment of the imidates with cyanogen chloride in aqueous solution in the presence of calcium hydroxide.



The N-cyanoimidates prepared during this investigation were all colorless liquids characterized primarily by analyses and by infrared absorption spectra. These compounds exhibit strong nitrile bands near 4.5 μ and strong C=N bands near 6.2 μ, with no absorption in the N—H or carbonyl region. Chemical confirmation of the assigned structures was obtained by their reaction with amino compounds resulting, in most cases, in ready displacement of the alkoxyl group.

In contrast to the strenuous conditions required to convert N-cyanoamidines to aminotriazines,[1] N-cyanoimidates were found to react smoothly with amidines in alcoholic solution to give 2-amino-*s*-triazines (IV).

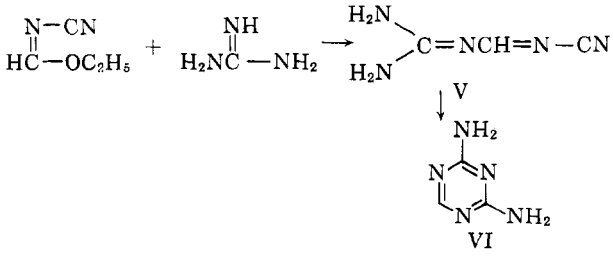
Compounds of type IV prepared by this method are listed in Table II. The R′ group of the amidine was



IV

varied successfully among such groups as methyl, phenyl, *p*-nitrophenyl, amino, methoxy, and carbethoxymethyl. While the best yields were obtained with N-cyanoacetimidates, the other N-cyanoimidates, with the exception of compound Ic, were also converted to triazines by this procedure. This new method appears to be the best available for synthesis[9] of monoamino-*s*-triazines containing dissimilar R groups.

In one case, the reaction of guanidine with an excess of ethyl N-cyanoformimidate, an open chain intermediate V was isolated. This compound was identified by analysis, infrared spectrum (strong nitrile band, absence of ring band at 12.4 μ), and by its quantitative conversion to the isomeric 2,4-diamino-*s*-triazine (VI) upon recrystallization from water. Equivalent amounts of the starting materials produced a mixture of V and VI in high conversion. Intermediates similar to V are probably formed in the other cases also, but are normally too soluble and too reactive to be isolated.

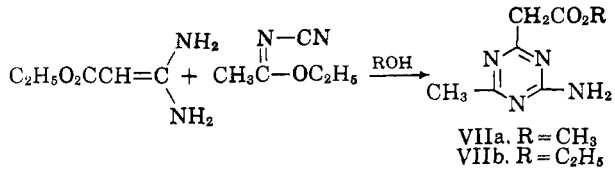


VI

The reaction of 2-carbethoxyacetamidine with ethyl N-cyanoacetimidate in methanol was accompanied by interchange with the solvent to afford the methyl ester VIIa.

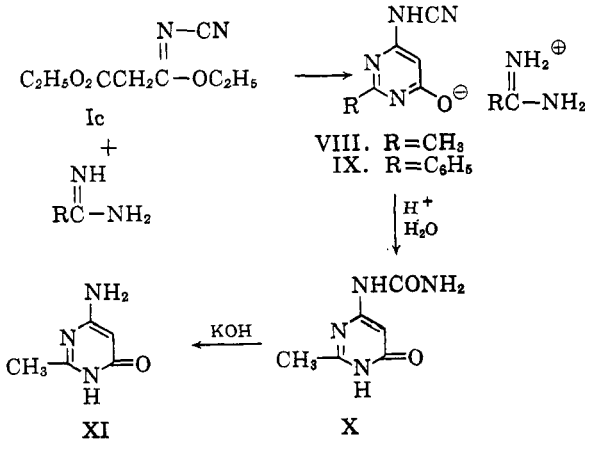
The similar product VIIb was not formed, however, upon reaction of acetamidine with ethyl 2-carbethoxy-N-cyanoacetimidate. Instead, the product was a high

(9) For previous syntheses of monoamino-*s*-triazines see E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers Inc., New York, N. Y., 1959, p. 217.



VIIa. R = CH_3
VIIb. R = C_2H_5

melting solid which still contained a nitrile group but no ester group, indicating that ring closure had occurred in an alternative manner to give a pyrimidine derivative. Structure VIII was assigned to this material on the basis of the infrared spectrum and rather erratic analytical data. This structure was confirmed by acid hydrolysis to the ureido derivative X, which upon treatment with strong base gave the known 4-amino-6-hydroxy-2-methylpyrimidine (XI). Treatment of Ic with benzamidine similarly led to the phenyl derivative IX.



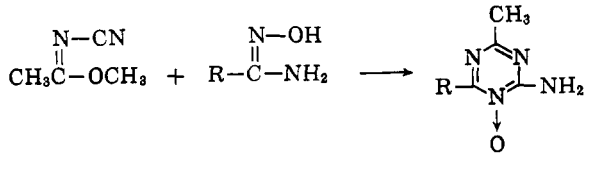
Ic

VIII. R = CH_3
IX. R = C_6H_5

XI X

Methyl N-cyanoacetimidate reacted with benzamidoxime and lactamidoxime to give the 2-amino-*s*-triazine 1-oxides XII and XIII, respectively.

These products were characterized by analysis, for-



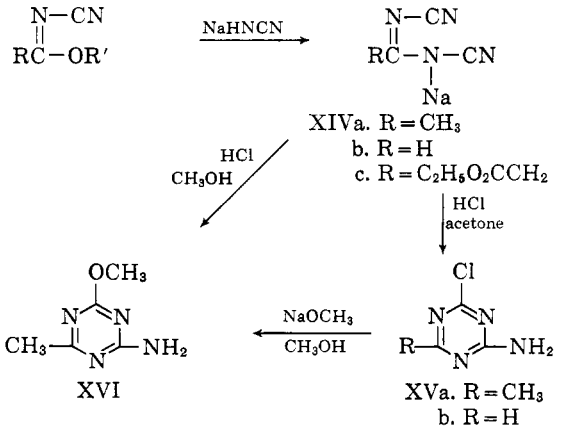
XII. R = C_6H_5
XIII. R = $CH_3CH(OH)$

mation of a red color with ferric chloride,[10] and, in the case of the phenyl derivative XII, by reduction with phosphorus trichloride to 2-amino-4-methyl-6-phenyl-*s*-triazine. Although these results establish the presence of the triazine N-oxide system, they do not rule out the isomeric 4-amino 1-oxide structure. The assignment of structures XII and XIII is based primarily on the infrared spectral correlation with 2-aminopyridine N-oxide, in which one of the N—H stretching bands and the N—O band are shifted to appreciably longer wave lengths than normal, presumably due to hydrogen bonding between the adjacent groups. Similar shifts to longer wave lengths were shown by the two triazine derivatives, in which the N—O band ap-

(10) J. T. Shaw, *J. Org. Chem.*, **27**, 3890 (1962).

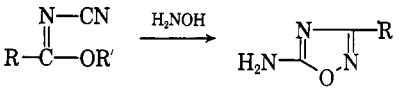
peared near 8.75 μ, well outside the normal range of 7.7–8.3 μ quoted for normal heterocyclic N-oxides.[11]

Treatment of N-cyanoimidates with monosodium cyanamide led to the formation of N,N′-dicyanoamidine sodium salts (XIV) in excellent yields, although the products were not obtained analytically pure in all cases. Compounds of type XIV have been prepared previously by reaction of amidines with cyanogen chloride.[10] Cyclization of the dicyanoamidines XIVa and XIVb to 2-amino-4-chloro-*s*-triazines (XV) was effected by treatment with dry hydrogen chloride in acetone. Alternatively, when the dicyanoacetamidine salt XIVa was cyclized in methanol, the product was the methoxytriazine XVI. The latter was also prepared by displacement of the chlorine of XVa with sodium methoxide in methanol.



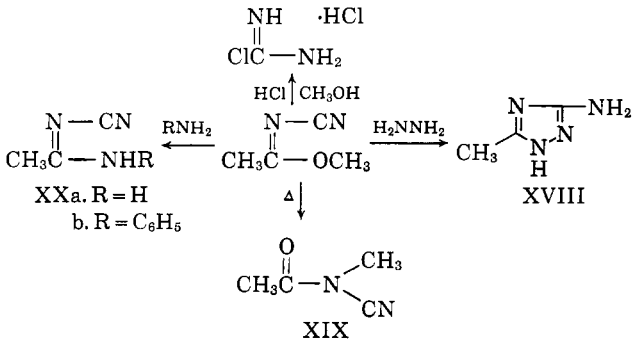
This new route to the *s*-triazine system is analogous to the known cyclization of potassium dicyanoguanidine to 2,4-diamino-6-chloro-*s*-triazine.[12] In view of the ease of displacement of the chlorine atom, compounds of type XV should be useful as intermediates for the synthesis of a variety of monoamino-*s*-triazines.

N-Cyanoimidates were also found to be useful as precursors of 1,2,4-oxadiazoles and 1,2,4-triazoles. When N-cyanoimidates were mixed with hydroxylamine hydrochloride in methanol, in the presence of triethylamine, an exothermic reaction occurred with formation of a 5-amino-1,2,4-oxadiazole (XVII). The isomeric 3-amino-1,2,4-oxadiazoles could be ruled out as possible structures for these products as the 3-amino-5-methyl-[13] and 3-amino-5-phenyl-1,2,4-oxadiazole[1,14,15] are known compounds having melting points different from our products. Moreover, the phenyl derivative, XVIId, had properties in agreement with the known material.[16,17]



XVIIa. R = CH_3
c. R = $C_2H_5OCCH_2$-
d. R = C_6H_5
e. R = $ClCH_2$

Methyl N-cyanoacetimidate reacted vigorously with hydrazine to give 3-amino-5-methyl-1,2,4-triazole (XVIII). Additional reactions tried with this N-cyanoimidate included treatment with dry hydrogen chloride in methanol, which led to cleavage of the molecule with formation of 1-chloroformamidine hydrochloride, and displacement of the methoxy group with ammonia and aniline to form the N-cyanoamidines XXa and XXb. N-Cyano-N′-substituted amidines have been obtained previously by reaction of the N-substituted imidate with cyanamide.[18,19]



Methyl N-cyanoacetimidate was stable to distillation at reduced pressure, as were the other compounds of type I, but upon heating at 165° at atmospheric pressure it slowly underwent the Chapman rearrangement[8] to give the isomeric N-cyano-N-methylacetamide (XIX).

Experimental[20]

Reagents.—Cyanamide was obtained and purified as before.[1] Monosodium cyanamide[21] was purified by extracting the crude material with boiling methanol, filtering the insoluble impurities, and evaporating to dryness at reduced pressure. All amidine salts were prepared by standard methods.

Trimethyl orthobenzoate was prepared by a literature procedure.[22] Trimethyl and triethyl 2-chloroorthoacetates[23] were prepared by allowing the corresponding imidate hydrochlorides to stand in methanol or ethanol at 25° for 1–3 days. 2-Carbethoxyketene diethyl acetal[24,25] was obtained following the procedure of McElvain and Schroeder[26] for the preparation of triethyl 2-carbethoxyorthoacetate and redistilling the product from *p*-toluenesulfonic acid.

N-Cyanoimidates from Ortho Esters and Cyanamide. General Procedure.—In general, equivalent amounts of cyanamide and ortho ester were dissolved in 2 equivalents of acetic anhydride and the resulting solution was heated to 130–140°, at which point the alkyl acetate began to distil rapidly. The oil bath was removed until the initial vigorous reaction subsided and then heating was continued at 135–150°, until most of the alkyl acetate and acetic acid had distilled. The residual liquid was then distilled under vacuum. The N-cyanoimidates prepared by this procedure are listed in Table I.

Reaction of Thiodiformamidine Dihydrochloride with Ethyl Acetimidate.—A suspension of 20.0 g. (0.10 mole) of thiodiformamidine dihydrochloride[27] in 20 ml. of methanol at 55–60° was treated dropwise with 29.0 g. of ethyl acetimidate (0.31 mole) during 20 min. The reaction mixture was heated at 65° for an

(11) A. R. Katritzky, *Quart. Rev.*, **13**, 353 (1959).
(12) J. J. Roemer and D. W. Kaiser, U. S. Patent 2,658,893 (November 10, 1953); *Chem. Abstr.*, **48**, 12813 (1954).
(13) G. W. Anderson, *et al.*, *J. Am. Chem. Soc.*, **64**, 2902 (1942).
(14) H. Wieland and H. Bauer, *Ber.*, **40**, 1680 (1907).
(15) P. Adams, D. W. Kaiser, and G. A. Peters, *J. Org. Chem.*, **18**, 934 (1953).
(16) G. Ponzio, *Gazz. chim. ital.*, **62**, 854 (1932).
(17) G. Palazzo and G. Strani, *ibid.*, **90**, 1290 (1960).
(18) W. J. Comstock and H. L. Wheeler, *Am. Chem. J.*, **13**, 514 (1891).
(19) G. Pellizzari, *Gazz. chim. ital.*, **41**, 93 (1911).
(20) Melting points and boiling points are uncorrected. Microanalyses were by J. Deonarine and associates.
(21) R. A. Vingee and L. J. Christmann, U. S. Patent 2,656,246 (October 29, 1953); *Chem. Abstr.*, **48**, 2996 (1954).
(22) S. M. McElvain and J. T. Venerable, *J. Am. Chem. Soc.*, **72**, 1661 (1950).
(23) F. Beyerstedt and S. M. McElvain, *ibid.*, **59**, 1273 (1937).
(24) H. Reitter and A. Weindel, *Ber.*, **40**, 3358 (1907).
(25) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).
(26) S. M. McElvain and J. P. Schroeder, *ibid.*, **71**, 40 (1949).
(27) B. H. Chase and J. Walker, *J. Chem. Soc.*, 4443 (1955).

additional hour at which point it was cooled and diluted with ether. The ethereal solution was decanted from insoluble material and distilled to give 12.0 g. of liquid, b.p. 120–130° (40 mm.). This crude product was shown to contain approximately 65% ethyl N-cyanoacetimidate and 18% methyl N-cyanoacetimidate by infrared and mass spectroscopic comparison with samples obtained as before. The combined yield was approximately 85%.

Methyl N-Cyanoacetimidate.—To a solution of 19.6 g. (0.47 mole) of freshly purified cyanamide in 70 ml. of dry methanol was added 51.1 g. (0.47 mole) of methyl acetimidate hydrochloride.[28] The resulting mixture was shaken for a few minutes and allowed to stand at room temperature for 3 hr. After filtration of the ammonium chloride the methanol was stripped from the filtrate and the product was distilled rapidly. Redistillation gave 30.1 g. (66%) of methyl N-cyanoacetimidate, b.p. 98–99° (25 mm.).

Anal. Calcd. for $C_4H_6N_2O$: C, 48.97; H, 6.17; N, 28.56. Found: C, 49.23; H, 6.50; N, 28.60.

Ethyl N-cyanoacetimidate was prepared according to the previous procedure using ethyl acetimidate hydrochloride[7b] in ethanol. The yield was 65%, b.p. 95–96° (15 mm.). The infrared spectrum was identical with that of the sample prepared as in Table I.

Reaction of Methyl Acetimidate with Cyanogen Chloride.—A solution of 14.6 g. (0.20 mole) of methyl acetimidate[29] in 100 ml. of ether was stirred in an ice bath while 6.2 g. (0.10 mole) of cyanogen chloride was distilled into the solution. The flask was stoppered and kept at 0° for 6 hr. and then at room temperature overnight. Filtration at this point yielded 3.5 g. (32%) of methyl acetimidate hydrochloride. Removal of the ether and distillation afforded 3.5 g. (43%) of **2,4,6-trimethyl-s-triazine**,[7b] b.p. to 63° (20 mm.), which solidified in the condenser, and 2.3 g. (23%) of **methyl N-cyanoacetimidate**, b.p. 90–92° (20 mm.).

Preparation of 2-Amino-s-triazines. General Procedure.—The 2-amino-s-triazines listed in Table II were prepared by the following procedure. A solution of 0.020 mole of sodium methoxide in 20 ml. of methanol was treated with 0.021 mole of the amidine hydrochloride. The mixture was shaken for a few minutes and then filtered into 0.020 mole of the N-cyanoimidate while stirring and cooling the reaction mixture in an ice bath, if necessary. In most cases the product crystallized directly from the reaction mixture. If crystallization did not occur, the solvent was evaporated after an appropriate length of time and the residue was crystallized from ethyl acetate and then recrystallized from ethanol.

N-Cyano-N′-guanylformamidine (V).—A solution of guanidine in 15 ml. of methyl alcohol was prepared from 1.90 g. of guanidine hydrochloride (0.020 mole) and 1.1 g. of sodium methoxide (0.020 mole). This was filtered and 2.20 g. (0.022 mole) of ethyl N-cyanoformimidate was added. The solution became warm with crystallization of a white solid, which after an hour was filtered and washed with ethanol. This was the open chain product V, 0.95 g. (43%), m.p. >300°.

Anal. Calcd. for $C_3H_5N_5$: C, 32.43; H, 4.54; N, 63.04. Found: C, 32.17; H, 4.42; N, 62.76.

The infrared spectrum of this material showed a strong nitrile band near 4.55 μ. Recrystallization from water resulted in near-quantitative conversion to the isomeric 2,4-diamino-s-triazine (VI), m.p. >300°, which could not be detected in the spectrum of the original material.

In another run using the standard procedure for reaction of N-cyanoimidates with amidines a mixture of V and VI crystallized from the solution in a combined yield of 87%. Pure VI was then obtained by recrystallization of this mixture from water.

4-Cyanoamino-6-hydroxy-2-methylpyrimidine, Acetamidine Salt (VIII).—A solution of 0.021 mole of acetamidine, prepared from 2.15 g. of the hydrochloride and 1.15 g. of sodium methoxide in 20 ml. of methanol, was filtered into 2.0 g. (0.011 mole) of ethyl 2-carbethoxy-N-cyanoacetimidate and the resulting solution was heated at 50° for 3 hr. while a pale yellow solid slowly crystallized. The solid was filtered and triturated with fresh methanol to give 1.20 g. (53%) of VIII, m.p. >250 dec.

Anal. Calcd. for $C_6H_6N_4O \cdot C_2H_6N_2$: C, 46.14; H, 5.81; N, 40.36. Found: C, 45.57; H, 5.71; N, 39.80.

Reaction of acetamidine with the N-cyanoimidate in a 1:1 ratio also gave VIII as the only solid product.

A 0.25-g. sample of VIII was heated with 3 ml. of 6 *N* hydrochloric acid for 30 min. on the steam bath. The resulting hydrochloride salt was neutralized with aqueous bicarbonate to give **4-hydroxy-2-methyl-6-ureidopyrimidine (X)**, m.p. >275°, which upon treatment with aqueous potassium hydroxide for 2 hr. at 90° was converted to **4-amino-6-hydroxy-2-methylpyrimidine (XI)**, m.p. 298–300° dec. The infrared spectrum of this material was identical with that of an authentic sample prepared by a literature procedure.[30] Lit.[30] m.p. 295–297°.)

4-Cyanoamino-6-hydroxy-2-phenylpyrimidine, Benzamidine Salt (IX).—A solution of 1.85 g. (0.010 mole) of ethyl 2-carbethoxy-N-cyanoacetimidate and an equivalent amount of benzamidine in 15 ml. of methanol was warmed at 35–40° for 3 hr. Evaporation of the solvent gave a gum which was crystallized from ethanol–ethyl acetate. The yield of IX, m.p. 191–192° dec., was 1.1 g. (66% based on the amidine). Recrystallization from water afforded off-white crystals, m.p. 192–193° dec.

Anal. Calcd. for $C_{11}H_8N_4O \cdot C_7H_8N_2$: C, 65.04; H, 4.85; N, 25.29. Found: C, 64.53; H, 4.60; N, 25.91.

2-Amino-4-methyl-6-phenyl-s-triazine 1-Oxide (XII).—A solution of 1.0 g. (0.010 mole) of methyl N-cyanoacetimidate and 1.4 g. (0.010 mole) of benzamidoxime[31] in 5 ml. of ethanol was refluxed for 4 hr. and chilled. The white crystalline product was filtered and washed with ether, 0.65 g., m.p. 209–215°. After standing for a week the filtrate had deposited another 0.30 g., m.p. 216–219°, for a total of 0.95 g. (45%). Trituration with ethanol raised the m.p. to 219–221°.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 58.99; H, 5.02; N, 27.47.

This compound exhibited a bright red color with ethanolic ferric chloride. Treatment of a small sample with refluxing phosphorus trichloride gave 2-amino-4-methyl-6-phenyl-s-triazine, m.p. 155.5–156.5°, identical with the sample prepared as in Table II.

2-Amino-4-methyl-6-(1-hydroxyethyl)-s-triazine 1-Oxide (XIII).—A solution of 1.95 g. (0.020 mole) of methyl N-cyanoacetimidate and 2.10 g. (0.020 mole) of lactamidoxime[32] in 5 ml. of methanol was refluxed for 2.5 hr. and evaporated to dryness. Recrystallization of the solid residue from acetonitrile gave 1.05 g. of tan solid, m.p. 153–158°. Two further recrystallizations from methanol gave an analytical sample of XIII, m.p. 172–173°.

Anal. Calcd. for $C_5H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.44; H, 6.22; N, 32.66.

The yield of crude product was 31%. This compound also gave a bright red color test with ferric chloride in ethanol.

Sodium N,N′-Dicyanoacetamidine (XIVa).—To a solution of 10.0 g. (0.10 mole) of methyl N-cyanoacetimidate in 50 ml. of methanol was added 6.5 g. (0.10 mole) of purified monosodium cyanamide. Upon shaking a clear warm solution formed. After an hour at 40° the methanol was removed at reduced pressure and the pale yellow solid residue was washed with cold ethanol. The yield of crude XIVa was 10.45 g. (79%), m.p. 244–245° dec. Lit.[10] m.p. 262–263°).

Anal. Calcd. for $C_4H_3N_4Na$: C, 36.93; H, 2.32; N, 43.07. Found: C, 36.34; H, 2.31; N, 42.12.

Sodium N,N′-Dicyanoformamidine (XIVb).—A solution of 1.0 g. of ethyl N-cyanoformimidate in 10 ml. of methanol was treated with 0.65 g. of monosodium cyanamide and worked up as before. This gave 1.10 g. (93%) of crude XIVb, m.p. 253–255° dec.

Anal. Calcd. for C_3HN_4Na: C, 31.05; H, 0.87; N, 48.28. Found: C, 30.33; H, 2.22; N, 46.07.

Sodium 2-Carbethoxy-N,N′-dicyanoacetamidine (XIVc).—To a solution of 0.70 g. of 90% monosodium cyanamide (0.010 mole) in 10 ml. of methanol was added 1.8 g. of ethyl 2-carbethoxy-N-cyanoacetimidate. The solution was kept at 45–50° for 10 min. and then evaporated under vacuum. The resulting gum crystallized upon prolonged scratching with a glass rod. The solid was washed with ether, dissolved in acetonitrile, filtered to remove a small amount of insoluble material, and again evaporated to a gum. The latter crystallized upon treatment with hot benzene giving 1.60 g. (80%) of XIVc, m.p. 155–165° dec.

(28) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, 1892.

(29) Prepared according to procedure for ethyl acetimidate in ref. 7b.

(30) A. Maggiolo, A. P. Phillips, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 106 (1951).

(31) F. Tiemann and P. Kruger, *Ber.*, **17**, 1685 (1884).

(32) H. Schiff, *Ann.*, **321**, 357 (1902).

Anal. Calcd. for $C_7H_7N_4O_2Na$: C, 41.59; H, 3.49; N, 27.72. Found: C, 41.84; H, 3.28; N, 27.75.

2-Amino-4-chloro-6-methyl-s-triazine (XVa).—A suspension of 6.5 g. of sodium N,N′-dicyanoacetamidine in 100 ml. of acetone was treated with a large excess of dry hydrogen chloride while cooling occasionally in an ice bath. The white insoluble solid was filtered, washed with ether, and added in portions with stirring to 75 ml. of cold 5% sodium bicarbonate. The aqueous mixture was filtered and the solid product was washed with a little cold water. The yield of XVa was 6.5 g. (90%), m.p. 202–203° dec. The analytical sample was recrystallized from ethylene dichloride, raising the m.p. to 206–207°.

Anal. Calcd. for $C_4H_5N_4Cl$: C, 33.23; H, 3.49; Cl, 24.53. Found: C, 33.34; H, 3.59; Cl, 24.69.

2-Amino-4-chloro-s-triazine (XVb).—Application of the above procedure to 0.90 g. of sodium N,N′-dicyanoformamidine gave 0.60 g. (60%) of 2-amino-4-chloro-s-triazine, m.p. >300°, which could not be recrystallized.

Anal. Calcd. for $C_3H_3N_4Cl$: C, 27.60; H, 2.32; N, 42.92; Cl, 27.16. Found: C, 27.73; H, 2.72; N, 42.60; Cl, 26.95.

2-Amino-4-methoxy-6-methyl-s-triazine (XVI). A.— A solution of 1.0 g. of sodium N,N′-dicyanoacetamidine in 10 ml. of methanol was treated with excess dry hydrogen chloride while cooling in an ice bath. The reaction mixture was worked up as before to give 0.70 g. (65%) of XVI, m.p. 259–261°, identical with a sample prepared from methyl N-cyanoacetimidate and methylpseudourea (Table II).

B.—To 0.30 g. (0.0055 mole) of sodium methoxide in 10 ml. of dry methanol was added 0.72 g. (0.0050 mole) of 2-amino-4-chloro-6-methyl-s-triazine. The reaction mixture was shaken for 10 min., warmed gently on the steam bath for 5 min., and then chilled and filtered. The resulting white solid was extracted with cold water leaving 0.57 g. (81%) of XV, m.p. 258–260°, identical with the sample described previously.

5-Amino-3-methyl-1,2,4-oxadiazole (XVIIa).—A stirred mixture of 1.40 g. (0.020 mole) of hydroxylamine hydrochloride and 2.0 g. of triethylamine (0.020 mole) in 10 ml. of ethanol was treated dropwise with 1.95 g. (0.020 mole) of methyl N-cyanoacetimidate. Toward the end of the addition the reaction mixture was cooled to keep the temperature below 40°. After 30 min. the now clear solution was evaporated to dryness and the residue was recrystallized from water to give 1.35 g. (69%) of XVIIa as white needles, m.p. 153–157°. Two additional recrystallizations raised the m.p. to 159–160.5°.

Anal. Calcd. for $C_3H_5N_3O$: C, 36.36; H, 5.09; N, 42.41. Found: C, 36.23; H, 5.28; N, 42.62.

5-Amino-3-phenyl-1,2,4-oxadiazole (XVIId).—To 3 ml. of methanol was added 0.40 g. of methyl N-cyanobenzimidate, 0.18 g. of hydroxylamine hydrochloride, and 0.25 g. of triethylamine. The mixture became warm and a clear solution formed on shaking. After an hour the methanol was removed and the residue was recrystallized from water to give 0.35 g. (88%) of XVIId, m.p. 146–147°. After a second recrystallization from benzene the m.p. was 147–148° (lit.[16,17] m.p. 153–154°).

5-Amino-3-chloromethyl-1,2,4-oxadiazole (XVIIe).—The procedure used for preparation of the 3-methyl compound, when applied to 2.65 g. of methyl 2-chloro-N-cyanoacetimidate (0.020 mole), gave an oily residue which was crystallized from water to give 1.20 g., m.p. 110–120°. Extraction of the mother liquor with ether yielded more product, which after two recrystallizations from benzene weighed 0.40 g., m.p. 116–121°; total yield of crude product, 1.60 g. (60%). Two additional recrystallizations from benzene afforded colorless prisms, m.p. 125.5–127.5°.

Anal. Calcd. for $C_3H_4ClN_3O$: C, 26.98; H, 3.02; N, 31.47; Cl, 26.55. Found: C, 27.41; H, 2.95; N, 31.13; Cl, 26.34.

This compound is a strong vesicant and should be handled cautiously.

5-Amino-1,2,4-oxadiazole-3-acetic Acid, Ethyl Ester (XVIIc).—Ethyl 2-carbethoxy-N-cyanoacetimidate, 1.85 g., was treated with hydroxylamine as before. After the methanol had been removed, the mushy residue was dissolved in water and extracted twice with ether. Evaporation of the dried extracts afforded an oil which crystallized on standing overnight. The yield of XVIIc was 1.20 g. (70%), m.p. 61–65°. This material was recrystallized once from water and once from benzene–petroleum ether; m.p. 68–70°.

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.09; H, 5.08; N, 24.33.

3-Amino-5-methyl-1,2,4-triazole (XVIII).—A solution of 1.95 g. of methyl N-cyanoacetimidate in 5 ml. of methanol was treated dropwise with 0.65 g. of 98% hydrazine while stirring and cooling in an ice bath. After the addition, during which a vigorous reaction occurred, the solution was allowed to warm to room temperature and then evaporated to dryness. The solid residue was recrystallized from acetonitrile to give 1.30 g. (67%) of the triazole as a white solid, m.p. 147–148° (lit.[33] m.p. 148°).

N-Cyanoacetamidine (XXa).—A solution of 4.2 g. of methyl N-cyanoacetimidate in 10 ml. of methanol was cooled in an ice bath while 1.5 g. of gaseous ammonia was added. After an hour at room temperature the solvent was removed. Recrystallization of the residue from ethanol gave 2.4 g. of N-cyanoacetamidine,[1] m.p. 132–135°. A second crop of 0.35 g., m.p. 122–130°, made a total of 2.75 g. (77% yield).

N-Cyano-N′-phenylacetamidine (XXb).—A solution of 2.0 g. of methyl N-cyanoacetimidate and 1.9 g. of aniline in 5 ml. of ethanol was refluxed for 12 hr. and chilled. The white crystalline product was filtered and washed with ether. The yield was 2.25 g. (70%), m.p. 189.5–192°. Upon recrystallization from ethanol the melting point was increased to 191.5–193.5° (lit.[19] m.p. 193°).

N-Cyano-N-methylacetamide (XIX).—Methyl N-cyanoacetimidate was heated in an oil bath at 160–165° for 5 hr. and then distilled. Two fractions were collected: A, b.p. 87–91° (25 mm.), and B, b.p. 95–97° (25 mm.). Fraction A partially crystallized on being chilled. The crystalline material was filtered, washed with a 2:1 petroleum ether–ether mixture, and then recrystallized twice from ether–petroleum ether to give a pure sample of XIX, m.p. 51.5–52.5°.

Anal. Calcd. for $C_4H_6N_2O$: C, 48.97; H, 6.17. Found: C, 49.16; H, 6.13.

This compound was quite unstable in storage and decomposed after a few days in a closed vial.

Fraction B was identified as unchanged starting material by its infrared spectrum.

Reaction of Methyl N-Cyanoacetimidate with Hydrogen Chloride.—A cold solution of 0.70 g. of methyl N-cyanoacetimidate in 5 ml. of ethanol was treated with an excess of dry hydrogen chloride. The white solid which formed weighed 0.50 g., m.p. 177–179° dec. It was identified as chloroformamidine hydrochloride (61% yield) by infrared comparison with an authentic sample.[34]

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(33) J. Thiele and K. Hedenreich, *Ber.*, **26**, 2598 (1893).

(34) H. Z. Lecher and C. L. Kosloski, U. S. Patent 2,727,922 (December 20, 1955); *Chem. Abstr.*, **50**, 15578 (1956).