[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

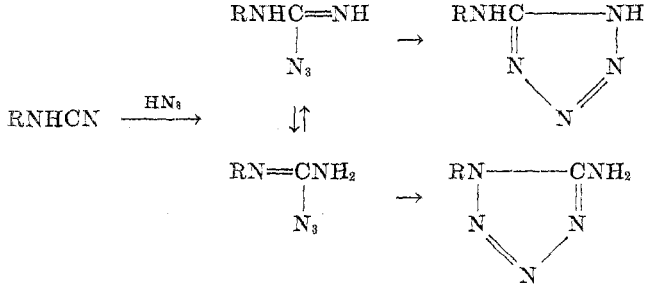
THE SYNTHESIS OF CERTAIN 5-AMINOTETRAZOLE DERIVATIVES. II. THE ACTION OF HYDRAZOIC ACID ON MONOALKYLCYANAMIDES[1]

WILLIAM L. GARBRECHT[2,3] AND ROBERT M. HERBST

Received February 19, 1953

In a previous communication the formation of 5-dialkylaminotetrazoles by the interaction of dialkylcyanamides and hydrazoic acid was described (1). Since Hantzsch and Vagt had shown that cyanamide and hydrazoic acid react readily to form 5-aminotetrazole (2), it was of interest to investigate the behavior of the monosubstituted cyanamides toward hydrazoic acid.

It has been postulated that guanyl azide occurs as an intermediate during the formation of 5-aminotetrazole from cyanamide and hydrazoic acid. Although guanyl azide may exist in two tautomeric forms, they are indistinguishable and both could cyclize to give the same tetrazole. However, when the same type of reaction was applied to the dialkylcyanamides, tautomerism of the substituted guanyl azide was precluded by the replacement of both hydrogens of the amino group with alkyl groups. Consequently cyclization could take place in one direction only. The addition of hydrazoic acid to a monoalkylcyanamide would be expected to lead to an intermediate guanyl azide which could again exist in two tautomeric modifications. Cyclization in this case could result in two distinctly different 5-aminotetrazole derivatives. If cyclization were to involve the nitrogen carrying the alkyl substituent, a 1-alkyl-5-aminotetrazole would result. On the other hand, involvement of the unsubstituted nitrogen in the cyclization would result in a 5-alkylaminotetrazole.



Since the formation of two products was to be anticipated in the reaction of monoalkylcyanamides with hydrazoic acid, benzylcyanamide was selected for exploratory work. Both 1-benzyl-5-aminotetrazole and 5-benzylaminotetrazole,

[1] Based on a thesis submitted to the School of Graduate Studies at Michigan State College in 1952 by William L. Garbrecht in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Parke-Davis Fellow in Organic Chemistry, 1951–1952.

[3] Present address: Eli Lilly and Company, Indianapolis, Indiana.

the probable products, were known. The former had been obtained by von Braun and Keller (3) by interaction of hydrazoic acid and benzyl cyanide in the presence of sulfuric acid and by Thiele and Ingle (4) as a benzylation product of 5-aminotetrazole. 5-Benzylaminotetrazole had also been observed by Thiele and Ingle among the benzylation products of 5-aminotetrazole. These two isomeric products are almost insoluble in cold water but can be separated easily and quantitatively by virtue of the acidic character of 5-benzylaminotetrazole and its consequent solubility in dilute aqueous alkali. Treatment of benzylcyanamide with hydrazoic acid in ethereal solution led to the essentially exclusive formation of 1-benzyl-5-aminotetrazole.

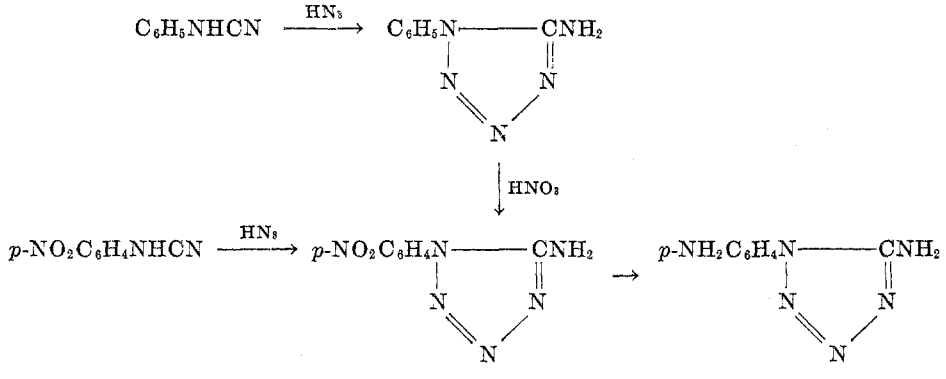
The formation of a single product in the reaction of benzylcyanamide with hydrazoic acid was rather surprising and suggested that the character of the group substituted on the cyanamide might influence the nature and distribution of the products. In the reaction of phenylthiourea with sodium azide in the presence of lead oxide, which has also been assumed to involve a guanyl azide as an intermediate, Stollé observed the formation of 1-phenyl-5-aminotetrazole accompanied by a trace of a product which he assumed to be 5-phenylaminotetrazole on the basis of its acidic character and an elementary analysis (5). More recently the cyclization of a nitroguanyl azide, formed upon treatment of N-nitro-N′-aminoguanidine with nitrous acid, has been described as leading exclusively to the formation of 5-nitraminotetrazole (6).

In order to include a reasonable range of electrical and steric effects the monosubstituted cyanamides studied included methyl-, ethyl-, isobutyl-, *n*-amyl-, *n*-hexyl-, *n*-heptyl-, *n*-octyl-, benzyl-, phenyl-, and *p*-nitrophenyl-cyanamide. The cyanamides were prepared by treating the appropriate primary amines with cyanogen bromide in ethereal solution, but aqueous alcohol functions equally well as the solvent. *p*-Nitrophenylcyanamide was prepared according to Pierron (7). While several of the monoalkylcyanamides have been described in the older literature (8), their characterization leaves much to be desired. These materials trimerize readily into triazines as well as other less well defined polymeric substances. In an effort to place the nature of the intermediate cyanamides on a firmer basis, in view of the difficulties accompanying attempts to isolate them in pure form, several were converted in excellent yield into the corresponding alkylureas. When a molar equivalent of alkali was used, the hydrolysis did not proceed appreciably; when a five-fold excess of alkali was employed, the hydrolysis to the urea was rapid and nearly complete. These results are in accord with work on the hydrolysis of the parent substance, cyanamide, which is converted into urea quantitatively in alkaline solutions of *p*H greater than 12; in solutions of lower *p*H dicyandiamide is formed (9).

All of the monosubstituted cyanamides listed above were treated with hydrazoic acid. Excepting *p*-nitrophenylcyanamide which could be isolated in pure form, an ethereal solution of the cyanamide was prepared by adding cyanogen bromide to the appropriate primary amine dissolved in ether. Without separating the precipitated amine hydrobromide, a solution of hydrazoic acid in ether was added and the mixture was stirred at room temperature for several

hours. After evaporation of the solvent and excess hydrazoic acid the product was separated from the residue. The possible presence of alkali-soluble products was investigated in each instance. In every case only the 1-alkyl- or 1-aryl-5-aminotetrazole could be isolated in yields of 50–80% based on the amount of primary amine used for the preparation of the cyanamide. No alkali-soluble products were observed. The 1-alkyl- and 1-aryl-5-aminotetrazoles were characterized by analysis and comparison with samples obtained by the von Braun technique (10). These data are summarized in Table II.

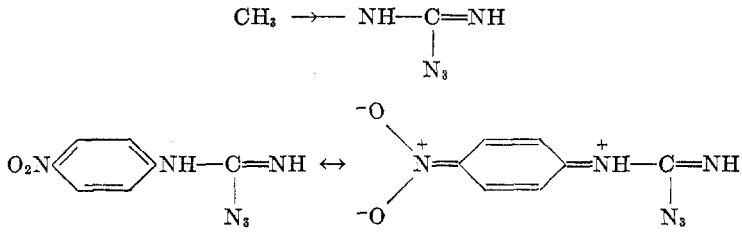
Of the compounds prepared only 1-*p*-nitrophenyl-5-aminotetrazole has not been previously described. Structure assignment was based on the analogy of the method of its formation from *p*-nitrophenylcyanamide and elementary analysis. To provide an independent synthesis, 1-phenyl-5-aminotetrazole was subjected to nitration. The 1-*p*-nitrophenyl-5-aminotetrazole obtained in this way was identical in all respects with the product obtained from *p*-nitrophenylcyanamide. It is interesting to note that the tetrazole ring system, when attached to the phenyl group through the nitrogen in position 1, exerts a *para* orienting influence. Catalytic reduction of samples of the 1-*p*-nitrophenyl-5-aminotetrazole prepared by both methods resulted in identical 1-*p*-aminophenyl-5-aminotetrazoles.



Perhaps the most remarkable feature of the reaction of the monosubstituted cyanamides with hydrazoic acid is the unidirectional character of the cyclization. The nature of the substituent appears to play at best a minor role in directing the course of the reaction. Substituents as different in their electrical effects as the methyl group and the *p*-nitrophenyl group permit the formation of the same type of compound. Usually the inductive effect of an alkyl group such as methyl is assumed to make the atom to which it is attached more negative. On the other hand, the pronounced resonance effects of the *p*-nitrophenyl group might be assumed to cause the atom to which it is attached to become more positive.

Since the electrical effects of the alkyl and the aryl substituents would appear to have opposite effects on the nitrogen involved in the cyclization, other factors which overbalance these effects must be operative in determining the course of the reaction. Furthermore, the nature of the solvent does not seem to be

important since 1-*n*-octyl-5-aminotetrazole could be prepared in equally good yield and under similar conditions either in ethereal or in aqueous-alcoholic solution.



The possibility immediately arises that the guanyl azide structure does not represent the correct intermediate in the reaction. It may be recalled that Thiele (11) had succeeded in preparing 5-aminotetrazole by treatment of aminoguanidine with nitrous acid and that it was possible to isolate the guanyl azide formed as an intermediate in this instance. The application of this sequence of reactions to an N-alkyl-N′-aminoguanidine should help to clarify the nature of the intermediate. N-Methyl-N′-aminoguanidine (12) on treatment with nitrous acid gave an insoluble, gummy product, presumably the guanyl azide, which was converted into the high-melting and crystalline 1-methyl-5-aminotetrazole on warming in aqueous suspension. No 5-methylaminotetrazole was observed among the products of the reaction. Although this sequence of reactions has not been applied to other compounds, this observation supports the assumption of guanyl azides as intermediates in the reaction of the cyanamides with hydrazoic acid.

Other effects, such as the relative stability of the two products that might arise through cyclization of the guanyl azides, the relative rates of the two cyclizations, and the stability of the tautomeric forms could profoundly influence the course of the reaction. Unfortunately, the available data do not permit evaluation of these effects.

In general, the ease with which hydrazoic acid reacts with a carbon-nitrogen unsaturation to form tetrazole derivatives varies widely. Negatively substituted cyanides, such as cyanogen bromide, cyanogen, and ethyl cyanoformate react under mild conditions (13), while the alkyl and aryl cyanides require much more drastic conditions of temperature and longer reaction time (14). These differences may be attributed to the relative electrophilic nature of the cyanide carbon, enhancement of which by negative substituents would be expected to facilitate formation of the intermediate imide azide. The cyanamides appear to fall into this latter group, but their reactivity toward hydrazoic acid, as reflected by the ease of tetrazole formation, decreases as the number of substituents is increased. Thus the monoalkylcyanamides react readily at room temperature while the dialkylcyanamides require higher temperature and longer reaction periods (1). On the other hand, *p*-nitrophenylcyanamide does not react as readily as the monoalkylcyanamides and requires much higher reaction temperatures. These differences may be closely related to, and may possibly be explained by, the factors which cause the preferential cyclization.

EXPERIMENTAL[4, 5]

PREPARATION OF ALKYLUREAS FROM ALKYLCYANAMIDES

Several alkylcyanamides were converted into the corresponding alkylureas by alkaline hydrolysis. The alkylcyanamides were prepared by treating an ethereal solution of the appropriate primary amine with cyanogen bromide. Extraction of the ether solution with aqueous alkali and warming the alkaline solution of the alkylcyanamide on the steam-bath sufficed to convert the cyanamide into the urea. A typical example of the conversion is described below. The alkylureas prepared in this way are listed in Table I.

Benzylurea. A solution of 21.4 g. (0.2 mole) of benzylamine in ether, was treated dropwise while stirring and cooling in an ice-water bath, with an ether solution of 10.6 g. (0.1 mole) of cyanogen bromide. After removing the precipitate of benzylamine hydrobromide by filtration the filtrate was extracted with a solution of 28 g. (0.5 mole) of potassium hydroxide

TABLE I

MONOALKYLUREAS FORMED BY HYDROLYSIS OF MONOALKYLCYANAMIDES

SUBSTITUTED UREA	YIELD,[a] %	M.P., °C.	FORMULA	N		REF.
				Calc'd	Found	
Isobutyl	77	141.5–142	$C_5H_{12}N_2O$	24.1	23.9	18
n-Amyl	52	99–100	$C_6H_{14}N_2O$	21.5	21.5	19
n-Hexyl	81	108.5–109	$C_7H_{16}N_2O$	19.4	19.2	19
n-Heptyl	91	111.5–112.5	$C_8H_{18}N_2O$	17.7	17.6	19
n-Octyl	33	101–102	$C_9H_{20}N_2O$	16.3	15.9	19
Benzyl	68	150–150.5	$C_8H_{10}N_2O$	18.7	18.8	20

[a] The yield is based on the amount of primary amine used in the preparation of the cyanamide.

in 100 ml. of water. The alkaline extract was warmed on the steam-bath for three hours. On chilling benzylurea separated as long, lustrous needles, crude yield 10.2 g. The analytical sample was recrystallized from acetone.

In some instances the crude alkylurea separated from the hot alkaline solution as an immiscible liquid that solidified on cooling.

REACTIONS OF HYDRAZOIC ACID WITH MONOALKYLCYANAMIDES

The reactions between hydrazoic acid and the monoalkylcyanamides and phenylcyanamide were carried out in essentially the same manner. The appropriate primary amine, usually in ethereal solution, was treated in the cold with an ethereal solution of cyanogen bromide. An ethereal solution of hydrazoic acid (1) was added to the crude alkylcyanamide and the mixture was stirred at room temperature for several hours. In the first experiments the amine hydrobromide was removed by filtration before adding the hydrazoic acid solution but this was found to be unnecessary. The use of ethyl acetate and aqueous ethanol as solvents did not appear to alter the course of the reaction or the yield.

Since one of the anticipated products, a 5-alkylaminotetrazole, would be expected to possess acidic character, an effort to establish its presence was made by extracting with aqueous alkali the residue obtained after evaporation of the solvent from the reaction mixture. In general, the water-solubility of substituted tetrazoles is low and any appreciable amount of the 5-alkylaminotetrazole, if formed, would be detected on careful neutralization of the alkaline extract. The 1-alkyl-5-aminotetrazoles were then isolated from the residue by crystallization from appropriate solvents.

[4] Micro-analyses were done by Micro-Tech Laboratories, Skokie, Illinois.

[5] Melting points were taken in open capillaries; temperatures are corrected unless otherwise indicated.

p-Nitrophenylcyanamide would react with hydrazoic acid only in boiling xylene-ethanol solution in sharp contrast to the other reactions which were carried out at room temperature. Descriptions of several typical examples follow; all compounds are listed in Table II.

1-Methyl-5-aminotetrazole. A solution of 15.5 g. (0.5 mole) of methylamine in 200 ml. of ethyl acetate was treated dropwise, while stirring and cooling in an ice-water bath, with 26.5 g. (0.25 mole) of cyanogen bromide dissolved in 100 ml. of ether. The amine salt was removed by filtration and the methylcyanamide solution was combined rapidly with an ether solution containing approximately a mole of hydrazoic acid and stirred at room temperature for an hour. After allowing the solvent to evaporate 20 g. of crude colorless product remained from which no acidic material was extracted by cold aqueous alkali. The crude material gave 12 g. of fine, colorless needles after one crystallization from water. The product was identical in all respects with a sample of 1-methyl-5-aminotetrazole prepared according to von Braun and Keller (3).

TABLE II

1-SUBSTITUTED 5-AMINOTETRAZOLES FROM MONOALKYLCYANAMIDES

1-SUBSTITUTED 5-AMINOTETRAZOLE	YIELD,[a] %	M.P., °C.	FORMULA	N		REF.
				Calc'd	Found	
Methyl	49	228–229	$C_2H_5N_5$	70.7	70.7	10
Ethyl	53	147.5–148.5	$C_3H_7N_5$	61.9	62.0	10
Isobutyl	50	212–212.5	$C_5H_{11}N_5$	49.6	49.9	10
n-Amyl	52	165–166	$C_6H_{13}N_5$	45.1	45.6	10
n-Hexyl	54	165.5–166.5	$C_7H_{15}N_5$	41.4	41.7	3
n-Heptyl	74	165.5–166.5	$C_8H_{17}N_5$	38.2	38.5	10
n-Octyl	82	163.5–164.5	$C_9H_{19}N_5$	35.5	35.5	15
Benzyl	69	191–192	$C_8H_9N_5$	40.0	39.9	3
Phenyl	32	163–163.5	$C_7H_7N_5$	43.5	44.0	3

[a] Yields are based on the amount of amine used in the preparation of the alkylcyanamide.

1-n-Octyl-5-aminotetrazole. To 32.3 g. (0.25 mole) of *n*-octylamine in 200 ml. of ether there was added dropwise, with stirring and cooling, 13 g. (0.12 mole) of cyanogen bromide in 50 ml. of ether. Without removal of the amine salt, an ether solution containing approximately half a mole of hydrazoic acid was added rapidly and the resulting mixture was stirred for several hours at room temperature. On removal of the solvent an almost colorless solid residue remained which was leached with cold water to remove the amine salt, extracted with dilute, aqueous alkali to separate any acidic products, and finally crystallized from ethyl acetate, yield 20 g. The product was identical in all respects with a sample of 1-*n*-octyl-5-aminotetrazole prepared by the von Braun method (15). No 5-*n*-octylaminotetrazole was obtained on neutralization of the alkaline extract.

Duplication of the above experiment except for the substitution of aqueous ethanol as the solvent resulted in the formation of 20 g. of 1-*n*-octyl-5-aminotetrazole as before. Again, no acidic product could be found.

1-Phenyl-5-aminotetrazole. A solution of 93 g. (1 mole) of aniline in 200 ml. of ether was treated dropwise, with stirring and cooling, with 53 g. (0.5 mole) of cyanogen bromide in 200 ml. of ether over a period of 1½ hours. An ether solution containing about two moles of hydrazoic acid was added rapidly and the mixture was stirred at room temperature for several hours. Aniline hydrobromide was removed by filtration before the reaction mixture was concentrated on the steam-bath. The red, oily residue was digested for several minutes on the steam-bath with dilute, aqueous alkali, then chilled and the resulting solid was collected. Any 5-phenylaminotetrazole formed would be in the alkaline filtrate. That no appreciable amount of this product was formed was evident since no solid material precipitated on neutralization of the alkaline filtrate.

A rather large amount of oily contaminant was removed from the crude, alkali-insoluble material by extraction with ether. The ether-insoluble solid was recrystallied from water from which it separated as faintly pink plates, yield 26 g., which showed the following behavior on heating: melted at 163–163.5°, solidified at 165° and then remelted with decomposition at 205–206°. The higher melting point is that reported by Stollé (5) for the presumed 5-phenylaminotetrazole. The significance of this behavior will be discussed in a later paper.

A small amount of material that was not soluble in boiling water was recrystallized from 50% ethanol to give 1 g. of colorless micro-crystals which were soluble in dilute aqueous acid and insoluble in dilute aqueous alkali, m.p. 163.5–164.5° (uncorrected).[6]

The oily material obtained by evaporation of the ether extract of the crude material was extracted with hot 50% ethanol. On cooling the ethanol solution fine, colorless plates separated, yield 12.6 g., m.p. 146–147° (uncorrected). The product was soluble in dilute aqueous hydrochloric acid but insoluble in dilute aqueous alkalies. *s*-Diphenylguanidine is reported to melt at 147° (17).

1-p-Nitrophenyl-5-aminotetrazole. (From p-nitrophenylcyanamide). A solution of 6.0 g. of *p*-nitrophenylcyanamide (7), 50 ml. of absolute ethanol, and 100 ml. of xylene containing 16 g. of hydrazoic acid was heated under reflux for two hours. On cooling fine, tan-colored needles separated, yield 3.6 g. The crude product was recrystallized from a 1:1 mixture of acetonitrile and dioxane from which it separated as pale yellow plates, yield 3.5 g. On heating in a capillary tube the product began to darken at about 170°, shrank suddenly at about 176° and melted with frothing at 221–223°. The compound was identical with the nitration product of 1-phenyl-5-aminotetrazole described in a subsequent section. The significance of the changes observed on heating will be discussed in a later paper.

Anal. Calc'd for $C_7H_6N_6O_2$: C, 40.8; H, 2.93; N, 40.8.

Found: C, 40.7; H, 2.97; N, 40.6.

From the xylene-ethanol mother liquor 2.8 g. of *p*-nitrophenylcyanamide was recovered by evaporation of the solvent in an air-stream.

Reduction of 1-p-nitrophenyl-5-aminotetrazole. A solution of 4.1 g. of 1-*p*-nitrophenyl-5-aminotetrazole (from *p*-nitrophenylcyanamide) in 200 ml. of absolute ethanol was shaken with 5% palladium-charcoal under three atmospheres of hydrogen pressure until the calculated amount of hydrogen for reduction of the nitro group had been absorbed. The catalyst was removed by filtration and the residue remaining after evaporation of the solvent crystallized from acetonitrile as transparent, diamond-shaped plates, m.p. 200–201°. The product, 1-*p*-aminophenyl-5-aminotetrazole, was readily soluble in dilute aqueous acids, insoluble in dilute aqueous alkalies, and gave a typical coupling product with β-naphthol after treatment with nitrous acid.

Anal. Calc'd for $C_7H_8N_6$: C, 47.7; H, 4.58; N, 47.7.

Found: C, 47.8, 48.0; H, 4.73, 4.65; N, 47.8, 47.8.

1-p-Nitrophenyl-5-aminotetrazole. (From 1-phenyl-5-aminotetrazole). 1-Phenyl-5-aminotetrazole (12 g.) was dissolved in 50 ml. of concentrated sulfuric acid and, while stirring and cooling in an ice-water bath, 50 ml. of concentrated nitric acid was added during two hours. The reaction mixture was poured onto ice and the nearly colorless, granular solid that separated was collected, washed repeatedly with water, and air-dried, yield 15 g. The product was soluble in dilute, warm hydrochloric acid, insoluble in cold, dilute hydrochloric acid and dilute aqueous alkalies, and crystallized as pale yellow plates from 1:1 acetonitrile-dioxane. Its behavior on heating and all other properties were identical with those of the 1-*p*-nitrophenyl-5-aminotetrazole obtained from *p*-nitrophenylcyanamide.

Anal. Calc'd for $C_7H_6N_6O_2$: C, 40.8; H, 2.93; N, 40.8.

Found: C, 41.1, 41.1; H, 3.00, 3.00; N, 41.4, 41.4.

Catalytic hydrogenation of this material gave 1-*p*-aminophenyl-5-aminotetrazole identical in all respects with the product obtained by reduction of the 1-*p*-nitrophenyl-5-aminotetrazole from *p*-nitrophenylcyanamide.

[6] The product was not characterized further. It may be the addition product of phenylcyanamide and triphenylisomelamine, m.p. 162–163° later given as 185°, described by Hofmann (16). Triphenylisomelamine, m.p. 210°, has been characterized by Arndt (21).

Anal. Calc'd for $C_7H_8N_6$: C, 47.7; H, 4.58; N, 47.7.
Found: C, 48.0, 47.7; H, 4.68, 4.63; N, 47.8, 48.0.

THE ACTION OF NITROUS ACID ON N-METHYL-N'-AMINOGUANIDINE

A solution of 1.5 g. (0.01 mole) of N-methyl-N'-aminoguanidine nitrate (12) in 10 ml. of water was treated in the cold with a solution of 1.4 g. (0.02 mole) of sodium nitrite in 10 ml. of water. The cloudy mixture was warmed gently on the steam-bath for 15 minutes during which period a red, gummy material separated. Continued heating transformed the red material into a colorless, crystalline solid which was collected and recrystallized from a small amount of water. The colorless needles so obtained melted at 228–229° and were identical in all respects with 1-methyl-5-aminotetrazole prepared according to von Braun and Keller (3) or from methylcyanamide with hydrazoic acid.

SUMMARY

The interaction of monosubstituted cyanamides and hydrazoic acid has been shown to give 1-substituted 5-aminotetrazoles. This constitutes a new and superior method for the preparation of these tetrazole derivatives. A group of eleven 1-substituted 5-aminotetrazoles, two of which are new compounds, has been prepared. Although a monosubstituted guanyl azide is assumed as an intermediate in the reaction, its cyclization appears to be unidirectional and is not influenced extensively by the nature of the alkyl or aryl substituent.

It has been shown that the tetrazole ring, when attached to a phenyl group through the nitrogen in the 1-position, exerts an *ortho-para* orienting influence. Nitration of 1-phenyl-5-aminotetrazole resulted in the formation of 1-*p*-nitrophenyl-5-aminotetrazole.

A number of monoalkylcyanamides have been characterized by alkaline hydrolysis to the corresponding alkylureas.

EAST LANSING, MICHIGAN

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