[CONTRIBUTION FROM THE INORGANIC CHEMISTRY BRANCH, CHEMISTRY DIVISION, RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE TEST STATION]

PREPARATION AND ISOMERIZATION OF 5-ALKYLAMINOTETRAZOLES

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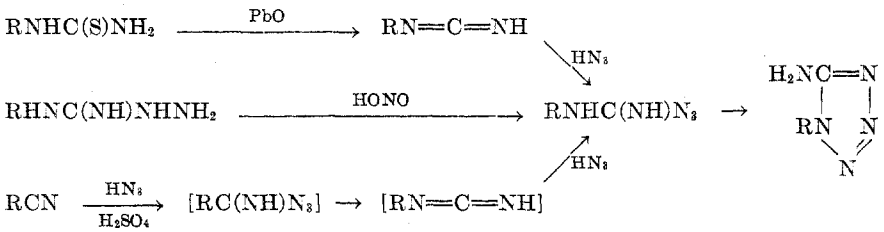
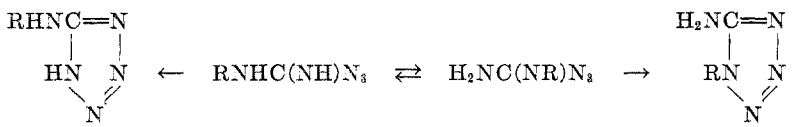
Several related syntheses for the preparation of 1-alkyl-and 1-aryl-5-aminotetrazoles have been reported in the literature. These syntheses start with monoalkyl- or aryl-substituted thioureas (1–3), cyanamides (4), or nitriles (5, 6). The same compounds can be prepared from 1-alkyl- and 1-aryl-2-aminoguanidines. Examination of the possible reaction mechanisms, in each of the methods, suggests that the formation and cyclization of an alkyl or aryl substituted guanylazide are steps common to all procedures.

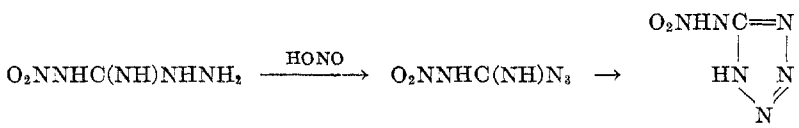


If the guanylazide is an intermediate, then ring closure should theoretically occur in two different directions and some of the isomeric 5-alkyl- or 5-arylaminotetrazole should also be formed.



Surprisingly, ring closure of the substituted guanylazide in all of these methods yields the 1-alkyl- or 1-aryl-5-aminotetrazole as the major product (as much as 95 % in certain cases). No serious consideration appears to have been given by previous workers to the isolation or detection of the other isomer, although Stollé and Heintz (7) reported the isolation of 5-anilinotetrazole in very small yield from the reaction of phenylthiourea with lead oxide and sodium azide.

When the substituent is sufficiently electronegative, ring closure to the 5-substituted aminotetrazole predominates; for example (8):

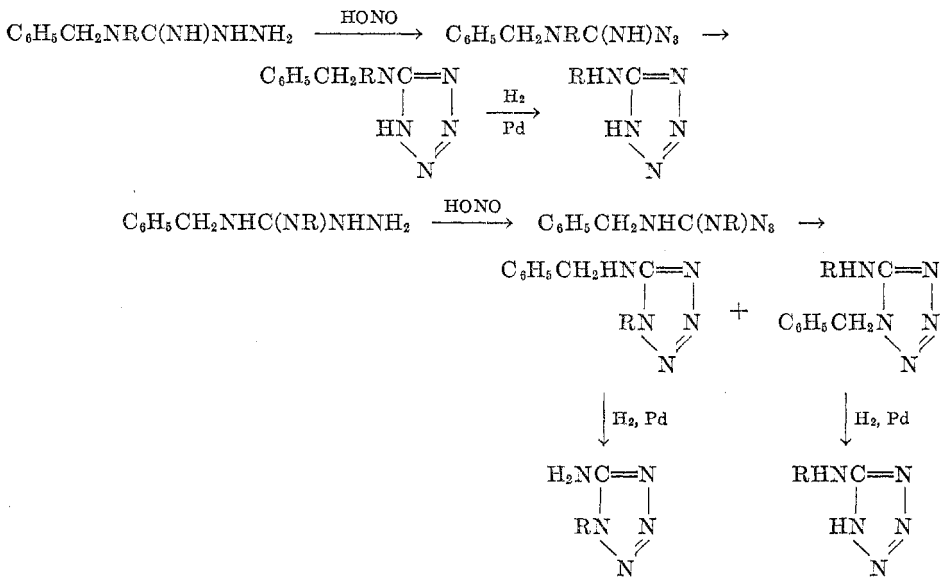


That the ring closure of the substituted guanylazides can proceed by an alternate route to yield some of the isomeric tetrazole has been confirmed by our

isolation of 5-methylamino-, 5-cyclohexylamino,- and 5-benzylamino-tetrazole in 11%, 2%, and 2.6% yields, respectively, from the reaction mother liquors after the corresponding 1-alkyl-5-aminotetrazoles had been removed. In these cases, the guanylazides, as salts, were prepared by diazotizing the aminoguanidines in aqueous acid solution and were directly isomerized, without prior isolation, by neutralizing the solutions to about *p*H 7.

The 5-alkylaminotetrazoles, which are acids, were separated from the mother liquors as their insoluble copper salts and were then regenerated from the latter by treatment with hydrogen sulfide. By applying a similar method of recovery to the compounds formed in the reaction of two moles of hydrazoic acid and one of acetonitrile in the presence of sulfuric acid, at least 0.6% of 5-methylaminotetrazole has been isolated, together with 30% of 1-methyl-5-aminotetrazole, as previously reported by Herbst, Roberts, and Harvill (6).

In order to prepare unambiguously several of these 5-substituted aminotetrazoles for comparison with those isolated from the cyclization of the guanylazides, the following reaction sequences were employed:

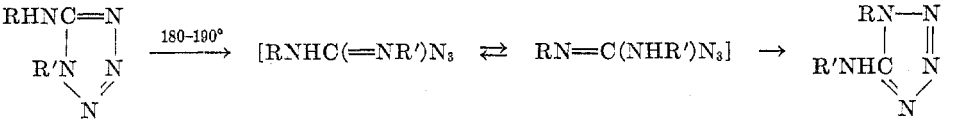


To synthesize the required substituted aminoguanidines (Table II) hydrazine and a suitably substituted S-methyl-isothiourea hydriodide were reacted according to the method of Kirsten and Smith (9).

The catalytic debenzylation of 1-benzyl-5-aminotetrazole has been reported (10) to give 5-aminotetrazole in 95% yield. In this work, 5-benzylmethylamino- and 5-benzylethylamino-tetrazole were debenzylated without complication in glacial acetic acid solution, using palladium as catalyst, to give essentially quantitative yields of 5-methylamino- and 5-ethylamino-tetrazole. 1-Benzyl-5-methylamino- and 1-methyl-5-benzylamino-tetrazole were also debenzylated to

5-methylaminotetrazole and 1-methyl-5-aminotetrazole, respectively. 1-Methyl-5-benzylethylamino- and 1-phenyl-5-benzylethylamino-tetrazole were prepared by a similar method and were debenzylated to 1-methyl-5-ethylamino- and 1-phenyl-5-ethylamino-tetrazole. In the one attempt to prepare 5-anilinotetrazole by debenzylation of 5-benzylphenylaminotetrazole, 5-cyclohexylaminotetrazole was obtained; no further effort was made to determine conditions for the preparation of 5-anilinotetrazole exclusively.

An interesting and previously unreported observation has been made that the 5-alkylaminotetrazoles, thus far prepared, are structurally unstable at elevated temperatures and smoothly isomerize to the corresponding 1-alkyl-5-aminotetrazoles when heated to 180–190°. At this temperature the isomerization is very rapid and the amount of pyrolytic decomposition is negligible. Under these conditions 1-phenyl-5-aminotetrazole isomerizes in the opposite direction and 5-anilinotetrazole is formed. Moreover, 1-phenyl-5-methylamino-, 1-phenyl-5-ethylamino-, and 1-phenyl-5-cyclohexylamino-tetrazole have also been isomerized at 180–190° to 1-methyl-, 1-ethyl- and 1-cyclohexyl-5-anilinotetrazole



where R is H or alkyl, and R′ is H or phenyl. This isomerization, which appears to be a rather general reaction for this type of tetrazole derivative, might reach an equilibrium, since 1-methyl-5-benzylaminotetrazole can only be partially isomerized to 1-benzyl-5-methylaminotetrazole and the ratio of isomers is roughly the same as that obtained when 1-benzyl-2-methyl-3-azidoguanidine is cyclized in aqueous solution. In addition, heating 1-(*o*-tolyl)-5-amino- or 1-(*p*-anisyl)-5-amino-tetrazole to 190–210° also always appears to give a mixture of the starting compound and the isomeric 5-substituted aminotetrazole. On the other hand, the isomerization of the 5-alkylamino-, the 1-phenyl-5-amino-, or the 1-phenyl-5-alkylamino-tetrazole is essentially complete, and an equilibrium, if it exists, is predominantly on the side of the other isomer. The presence of a very minor quantity of unisomerized 5-alkylaminotetrazole in the rearranged mixture can be demonstrated although this could represent incomplete reaction rather than equilibrium. More work will be necessary before the existence of an equilibrium can be conclusively established.

The isomerization is most probably due to a ring opening to the substituted guanylazide and a recyclization of the latter to the thermodynamically more stable tetrazole, or to an equilibrium in which the more stable tetrazole predominates. It is unlikely that this isomerization involves group migrations. Thermochemical studies, including differential thermal analyses, are being made with several pairs of isomers and the results will be reported later.

In all but one of the isomerizations, the product has a melting point higher than that of the starting tetrazole. 5-Ethylaminotetrazole, however, isomerizes to the lower-melting 1-ethyl-5-aminotetrazole.

To eliminate the possibility that the isomerization yielded the substituted guanylazide, several pairs of isomers were treated with hydrogen sulfide in hot aqueous solution. No reaction was noticed although known guanylazides are immediately reduced (8). Since the 5-alkyl- or arylaminotetrazoles titrate quantitatively as weak acids, whereas the 1-alkyl- or aryl-5-aminotetrazoles are very weak bases, this evidence excludes the possibility that these isomers are only polymorphic crystal forms.[1]

The behavior of the 5-alkylaminotetrazoles at elevated temperatures is consistent with the idea that the cyclization of the alkyl substituted guanylazides should take place predominately on the expected nucleophilic centers, and that the more stable isomers should be the 1-alkyl-5-aminotetrazoles. There is presently insufficient data to explain why the 1-phenyl-5-aminotetrazole is formed predominately in the low temperature cyclization in aqueous solution, whereas the thermodynamically stable form appears to be 5-anilinotetrazole. However, the tendency for 1-aryl-5-aminotetrazoles to rearrange to the 5-arylaminotetrazoles appears to decrease markedly as the electronegative character of the aromatic ring is decreased by the introduction of *ortho* or *para* alkyl or alkoxy groups and the behavior is more in agreement with that observed with the monoalkyl substituted aminotetrazoles. The effect of temperature, solvent and *p*H on the cyclization of arylguanylazides will be studied in order to gain additional data.

1-Methyl-5-ethylamino-, 1-methyl-5-benzylamino-, 1-ethyl-5-ethylamino-, 1-phenyl-5-methylamino-, 1-phenyl-5-dimethylamino-, and 1-phenyl-5-ethylaminotetrazole, prepared by straightforward methods and described in Table III, were previously reported by Herbst, Roberts, and Harvill (6) to have been formed by alkylation of suitable 1-substituted-5-aminotetrazoles. However, the very marked differences in physical properties and reactivities between the two series of compounds casts considerable doubt on the structures of the compounds obtained in the very drastic alkylation methods employed by these authors. This problem is currently being investigated.

EXPERIMENTAL[2]

Substituted thioureas and S-methylisothiourea hydriodides. The necessary substituted thioureas, most of which have been previously reported in the literature, were prepared by conventional procedures: (a) an appropriate mustard oil and a suitable amine were reacted, or (b) an appropriately substituted ammonium thiocyanate was isomerized by heating at 140–160°. The preparation of the previously unreported *1-methyl-1-benzylthiourea* is typical of the latter method.

A suspension of 121 g. (1.0 mole) of benzylmethylamine in 100 ml. of water was cooled in an ice-water bath and neutralized to the Bromphenol Blue endpoint with concentrated hydrochloric acid (approximately 90 ml.). A solution of 81 g. (1.0 mole) of sodium thio-

[1] X-ray powder diagrams for many of these compounds are included in a paper by D. Moore and L. Burkardt, Physical Chemistry Branch, Chemistry Division, U. S. Naval Ordnance Test Station, accepted for publication by Analytical Chemistry.

[2] All melting points were obtained in capillary tubes and are corrected. The analyses were performed by Margaret M. Mayfield, Analytical Branch, Chemistry Division, NOTS, and by Dr. Adelbert Elek, Elek Micro Analytical Laboratory, Los Angeles, California.

cyanate in 100 ml. of water was added, and the resulting solution was evaporated to dryness on a steam-bath with the aid of an air jet. The methylbenzylammonium thiocyanate was extracted from the residue with several portions of boiling 95% ethanol. Evaporation of the alcohol solution at reduced pressure on a steam-bath left a quantitative yield of benzylmethylammonium thiocyanate. The dry thiocyanate salt was heated to 150–160° for 3 hours and then poured into 250 ml. of cold water. The precipitate of 1-methyl-1-benzylthiourea was removed and washed on the filter with several portions of water. The combined filtrates were reconcentrated to dryness at reduced pressure on a steam-bath and the recovered thiocyanate salt reheated as before. After five cycles the total yield of 1-methyl-1-benzylthiourea amounted to 137.6 g. (76.4%). After one crystallization from 600 ml. of 1:2 water-ethanol the yield was 127.6 g., (70.9%) and the product melted at 147.5–148.5°.

Anal. Calc'd for $C_9H_{12}N_2S$: N, 15.54. Found: N, 15.27.

1-Ethyl-1-benzylthiourea was similarly prepared in 41.4% yield; m.p. 122.5–123.5° after recrystallization from 50% ethanol.

Anal. Calc'd for $C_{10}H_{14}N_2S$: C, 61.81; H, 7.26.
Found: C, 61.75; H, 7.25.

1-Cyclohexyl-3-benzylthiourea was prepared from cyclohexyl isothiocyanate and benzylamine; flat needles from 60% ethanol; m.p. 93–94°.

Anal Calc'd for $C_{14}H_{20}N_2S$: C, 67.69; H, 8.15.
Found: C, 67.60; H, 7.85.

The substituted S-methylisothiourea hydriodides were made in the conventional manner by reacting the substituted thiourea (1 equivalent) and methyl iodide (1.05 equivalents) in absolute ethanol The salts were recrystallized from absolute ethanol, or from mixtures of the latter and diethyl ether; the yields were essentially quantitative. A detailed example is the preparation of *1,S-dimethyl-1-benzylisothiourea hydriodide:*

A slurry of 127.6 g. (0.71 mole) of 1-methyl-1-benzylthiourea in 300 ml. of absolute ethanol was cooled to 5° and treated with 106.5 g. (0.75 mole) of methyl iodide in one portion. The resulting mixture was allowed to stand for 48 hours at room temperature, then heated to reflux for 1 hour, and finally concentrated to a syrup at reduced pressure on a steam-bath. By seeding, the syrup could be made to crystallize; the yield was 228 g. Recrystallization from ethanol-diethyl ether gave a product melting at 123–125°.

Compounds prepared in this manner are listed in Table I together with pertinent analytical data.

Substituted aminoguanidines. These compounds (Table II) were all prepared in essentially quantitative yield from the substituted S-methylisothiourea hydriodides by the method of Kirsten and Smith (9). If the products could be induced to solidify, they were recrystallized from absolute ethanol or mixtures of ethanol and diethyl ether. Occasionally it was necessary to convert the hydriodide to a nitrate or a picrate in order to obtain a solid derivative; these non-crystallizable syrups were generally used without purification for the preparation of the substituted aminotetrazoles. The synthesis of *1-benzyl-2-methyl-3-aminoguanidinium iodide* affords a detailed example of the procedure:

A solution of 81.1 g. (0.25 mole) of 1-benzyl-2,3-dimethylisothiourea hydriodide, 8.5 g. (0.25 mole) of 95% hydrazine, and 200 ml. of absolute ethanol was refluxed until the evolution of methyl mercaptan ceased (*ca.* 1 hour). Evaporation of the solution to dryness under reduced pressure left the theoretical weight of white crystalline product, which melted at 121–122° after one recrystallization from the minimum volume of absolute ethanol.

The nitrate salts reported in Table II were prepared by a metathetical reaction with silver nitrate in water, and after their recovery, were recrystallized from absolute ethanol. The picrates were prepared by treating the aminoguanidinium iodide with an equivalent amount of picric acid in water; recrystallization was from water, ethanol, or aqueous ethanol. The picrates of the benzal hydrazone were made by first condensing equivalent quantities of the aminoguanidinium iodide and benzaldehyde in a hot aqueous ethanol solution and then adding an equivalent quantity of picric acid; the sparingly soluble hydrazones were recrystallized from aqueous methanol or ethanol.

Substituted 5-aminotetrazoles. Three examples of the methods employed for converting the substituted aminoguanidines into tetrazole derivatives are outlined below. The compounds prepared in this manner are listed in Table III.

5-Methylbenzylaminotetrazole. A solution of 220 g. (0.71 mole) of 1-methyl-1-benzyl-2-aminoguanidinium iodide in 700 ml. of water was warmed to 50° and acidified with 9.0 g. (0.1 mole) of concentrated nitric acid. A solution of 120.6 g. (0.71 mole) of silver nitrate in 150 ml. of water was then added dropwise with stirring. After 30 minutes any excess silver ion was precipitated by the addition of 8.5 ml. (0.1 mole) of concentrated hydrochloric acid. The silver iodide was removed and washed with two 50-ml. portions of hot water. Concentrated hydrochloric acid (51 ml., 0.6 mole) was added to the combined filtrates which were cooled to 5° in an ice-bath. A solution of sodium nitrite (49.0 g., 0.7 mole) in 150 ml. of water was added with stirring and continued cooling so that the temperature did not exceed 10°. Nitrite was consumed very rapidly; after a starch-iodide endpoint was reached, the

TABLE I

SUBSTITUTED S-METHYLISOTHIOUREA HYDRIODIDES

$R_1R_2NC(SCH_3)NR_3 \cdot HI$

R_1	R_2	R_3	M.P., °C.[a]	ANALYSIS					
				C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_2=$CHCH_2$	H	H	68.5–69.5	23.26	23.28	4.30	4.40	10.85	10.66
C_6H_{11}	H	H	143–144	32.00	31.94	5.71	5.76	—	—
C_6H_5	H	H	145–146	32.66	32.84	3.77	3.97	9.53	9.82
p-$CH_3OC_6H_4$	H	H	162–163	33.34	33.68	4.04	4.27	—	—
CH_3	$C_6H_5CH_2$	H	123–125	37.16	37.41	4.99	4.72	—	—
CH_3	H	C_6H_5	156.5–157.5	35.07	35.26	4.25	4.19	9.09	8.53
CH_3	H	$C_6H_5CH_2$	109.5–110.5	37.27	37.63	4.69	5.01	8.70	8.87
C_2H_5	H	C_2H_5	75.5–76.5	26.28	26.38	5.51	5.56	—	—
C_6H_{11}	H	$C_6H_5CH_2$	172.5–173.5	46.15	46.20	5.94	6.17	7.18	7.27
C_6H_{11}	H	C_6H_5	185–187	44.68	44.99	5.63	5.65	7.45	7.11
CH_3	CH_3	C_6H_5	132–133.5	37.27	37.87	4.69	4.87	8.69	8.95

[a] The melting points are corrected.

solution was stirred for an additional 15 minutes. The portionwise addition of solid, anhydrous sodium carbonate (85 g., 0.80 mole) produced a gummy precipitate of 1-methyl-1-benzyl-2-azidoguanidine which spontaneously cyclized. The resulting tetrazole partially dissolved in the sodium carbonate solution. The mixture was stirred for 30 minutes, reacidified with concentrated hydrochloric acid (acid to litmus and basic to Congo Red indicators), and then recooled to 5° (caution; some evolution of hydrazoic acid frequently occurs on acidification). The precipitate of 5-methylbenzylaminotetrazole was removed, washed on the filter with cold water, and dried; yield, 116.3 g. (86.8%). After one recrystallization from 10:1 benzene-ethanol, the product melted at 136–137°.

1-Cyclohexyl-5-aminotetrazole and 5-cyclohexylaminotetrazole. Silver nitrate (20.6 g., 0.12 mole) in 30 ml. of water was added with agitation to a solution of 34.4 g. of 1-cyclohexyl-2-aminoguanidinium iodide in 125 ml. of water and 2 ml. of concentrated nitric acid. Then 5 ml. of conc'd hydrochloric acid was added to precipitate any excess silver ion. The silver iodide was removed and washed with 25 ml. of cold water. After another 5 ml. of hydrochloric acid was added to the combined filtrates which were cooled to 10°, 8.4 g. (0.12 mole) of sodium nitrite in 20 ml. of water was introduced. The temperature was maintained between 8 and 13°. As soon as the diazotization was completed, the solution was neutralized

to *p*H 8 with solid, anhydrous potassium carbonate and stirred for one hour at 10–15°. In order to complete the cyclization of the guanylazide, the reaction mixture was warmed to 50° and then recooled to 5°. The solid 1-cyclohexyl-5-aminotetrazole was removed and washed twice with ice-cold water, and air-dried. The yield was 15.6 g. (76.8%); m.p. 210–216°. One recrystallization from 87% isopropyl alcohol gave long, flat needles, m.p. 221–222°.

The combined filtrate and washings were heated to boiling, acidified with concentrated hydrochloric acid to about *p*H 3, and recooled to 50°. A saturated solution of copper acetate was added slowly until a definite excess was evident. When the solution had cooled to room temperature, the green colored precipitate was removed, washed carefully with cold water, resuspended in 40–50 ml. of boiling water, and treated with hydrogen sulfide. The copper sulfide was removed and washed with a small volume of hot water. When the filtrates were cooled, there was obtained 0.4 g. (2%) of 5-cyclohexylaminotetrazole, melting at 191–192°. One recrystallization from water raised the melting point to 193–194°; after melting, the compound resolidified and then remelted at 217–220°. Similar procedures were used to isolate 5-methylamino- and 5-benzylamino-tetrazole.

1-Benzyl-5-methylaminotetrazole and 1-methyl-5-benzylaminotetrazole. The conversion of 73.5 g. (0.22 mole) of 1-benzyl-2-methyl-3-aminoguanidinium iodide into the nitrate, its subsequent diazotization, and the cyclization of the azide were performed in the same manner as outlined in the two previous experiments. The yield of mixed isomers was 38.7 g. (85.1%); m.p. 97–98°. By repeated recrystallization from 95% ethanol there was finally recovered 21.1 g. of 1-methyl-5-benzylaminotetrazole as coarse prisms, melting at 99°, and 11.0 g. of 1-benzyl-5-methylaminotetrazole as rosettes of fine needles, melting at 117–118°.

5-Methylaminotetrazole. 5-Methylbenzylaminotetrazole (18.9 g., 0.1 mole), which was carefully purified by recrystallization, was dissolved in 100 ml. of glacial acetic acid in a 300-ml. Parr hydrogenation bottle, and 0.2 g. of palladium oxide was added. The hydrogenation was begun at an initial pressure of 50 p.s.i. and was allowed to continue until the theoretical absorption of hydrogen was attained. After the catalyst had been removed and washed with acetic acid, the filtrate was concentrated to dryness at reduced pressure on a steam-bath. The residue (m.p. *ca.* 185°) was recrystallized from absolute ethanol. The yield of 9.9 g. was quantitative. The pK_a, as determined by potentiometric titration in 50% ethanol, was 6.7.

Anal. Calc'd for $C_2H_5N_5$: Equiv. weight, 99.10. Found: Equiv. weight, 98.7.

5-Methylaminotetrazole from acetonitrile and hydrazoic acid. Acetonitrile (0.1 mole) and hydrazoic acid (0.24 mole) were reacted according to the detailed procedure described in Reference 6. After the quenched sulfuric acid layer had been neutralized with a 50% solution of sodium hydroxide (acid to litmus, basic to Congo Red paper), the solution was evaporated to dryness. The residue was extracted three times with 100-ml. portions of hot 95% ethanol, and the combined filtrates were evaporated to dryness at reduced pressure on a steam-bath. The mixture of 1-methyl-5-aminotetrazole and 5-methylaminotetrazole was dissolved in 25 ml. of warm water and a solution of 3 g. of cupric acetate monohydrate in 20 ml. of hot water was added. The precipitate of copper 5-methylaminotetrazole was removed, washed with several portions of warm water, and then suspended in 25 ml. of warm water. A stream of hydrogen sulfide was introduced until the precipitation of copper sulfide was complete. The copper sulfide was removed and washed several times with hot water. Evaporation of the filtrates at reduced pressure left 0.06 g. (0.61%) of impure 5-methylaminotetrazole; m.p. 176–184°, with resolidification and remelting at 222–225°. A mixture melting point with an authentic sample of 5-methylaminotetrazole was about 180–185°.

Isomerization of substituted 5-aminotetrazoles. The isomerizations were all performed in essentially the same manner; the following two experiments are typical:

1-Methyl-5-aminotetrazole. 5-Methylaminotetrazole (1.0 g. $\sim$ 0.01 mole) was heated to and maintained at 180–190° for about three minutes. The melt was seeded with 1-methyl-5-aminotetrazole or, alternatively, removed from the heating bath and allowed to solidify.

TABLE II

SUBSTITUTED AMINOGUANIDINES

$R_1R_2NC(NR_3)NHNH_2$

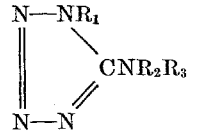
R_1	R_2	R_3	SALT OR DERIVATIVE	M.P., °C.[a]	FORMULA	ANALYSIS					
						C		H		N	
						Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_2=CH—CH_2	H	H	Picrate	114–115	$C_{10}H_{13}N_7O_7$	34.99	34.38	3.82	3.76	28.57	28.70
CH_2=CH—CH_2	H	H	Picrate of benzalhydrazone	206–207	$C_{17}H_{17}N_7O_7$	47.33	47.41	3.97	4.14	—	—
C_6H_{11}	H	H	Picrate	149–150	$C_{13}H_{19}N_7O_7$	—	—	—	—	25.45	25.47
$C_6H_5CH_2$	H	H	Hydriodide	127–128	$C_8H_{13}IN_4$	32.89	33.04	4.48	4.31	—	—
$C_6H_5CH_2$	H	H	Picrate	148.5–149.5	$C_{14}H_{15}N_7O_7$	42.75	42.51	3.84	3.83	24.93	24.58
$C_6H_5CH_2$	H	H	Picrate of benzalhydrazone	215–216 (dec)	$C_{21}H_{19}N_7O_7$	52.39	52.16	3.98	4.13	—	—
C_6H_5	H	H	Nitrate	121–122	$C_7H_{11}N_5O_3$	39.43	39.46	5.20	5.18	32.85	33.16
C_6H_5	H	H	Picrate	165.5–166.5	$C_{13}H_{13}N_7O_7$	41.16	41.12	3.45	3.35	25.86	25.80
C_6H_5	H	H	Picrate of benzalhydrazone	225–227	$C_{20}H_{17}N_7O_7$	51.39	51.54	3.67	3.71	20.98	21.04
4-$CH_3OC_6H_4$	H	H	Hydriodide	150–151	$C_8H_{14}IN_4O$	31.08	31.22	4.56	4.23	18.12	18.35
2-$CH_3C_6H_4$	H	H	Hydriodide	153–154	$C_8H_{14}IN_4$	32.78	33.01	4.81	4.50	19.11	19.31
CH_3	CH_3	H	Hydriodide	188–189	$C_3H_{11}IN_4$	15.66	16.77	4.82	4.80	24.35	24.52
CH_3	CH_3	H	Picrate	162–163	$C_9H_{12}N_7O_7$	—	—	—	—	8.46[b]	8.34[b]
CH_3	CH_3	H	Hydriodide of benzalhydrazone	245–247 (dec)	$C_{10}H_{15}IN_4$	37.75	37.78	4.75	4.26	17.61	17.77
CH_3	CH_3	H	Picrate of benzalhydrazone	207–208.5 (dec)	$C_{16}H_{17}N_7O_7$	—	—	—	—	6.68[b]	6.67[b]
CH_3	H	$C_6H_5CH_2$	Hydriodide	121–122	$C_9H_{15}IN_4$	35.31	35.65	4.94	5.07	—	—
CH_3	H	$C_6H_5CH_2$	Picrate	132–133	$C_{15}H_{17}N_7O_7$	44.22	44.34	4.21	4.48	24.07	24.11
CH_3	H	$C_6H_5CH_2$	Picrate of benzalhydrazone	147.5–148.5	$C_{22}H_{21}N_7O_7$	—	—	—	—	19.79	19.76
CH_3	H	C_6H_5	Hydriodide	139.5–140	$C_8H_{13}IN_4$	32.89	33.04	4.48	4.33	19.18	19.40
CH_3	H	C_6H_5	Picrate	126–127	$C_{14}H_{15}N_7O_7$	42.75	42.83	3.84	3.87	24.93	25.14
CH_3	H	C_6H_5	Picrate of benzalhydrazone	177–178	$C_{21}H_{19}N_7O_7$	52.39	52.83	3.98	4.27	20.37	20.42
C_2H_5	H	C_2H_5	Hydriodide	85.5–86.5	$C_5H_{15}IN_4$	23.26	23.46	5.86	5.80	21.71	21.38
C_2H_5	H	C_2H_5	Picrate of benzalhydrazone	158–159	$C_{18}H_{21}N_7O_7$	48.32	48.24	4.73	4.53	—	—

C_6H_{11}	H	$C_6H_5CH_2$	Hydriodide	139.5–140.5	$C_{14}H_{23}IN_4$	44.93	44.91	6.19	6.57	14.97	14.88
CH_3	CH_3	CH_3	Picrate	155–156	$C_{10}H_{15}N_7O_7$	34.78	35.22	4.38	4.43	28.23	28.56[c]
CH_3	CH_3	CH_3	Hydriodide of benzalhydrazone	165–166	$C_{11}H_{17}IN_4$	39.77	40.22	5.16	4.73	16.87	17.05
CH_3	CH_3	CH_3	Picrate of benzalhydrazone	154–155	$C_{17}H_{19}N_7O_7$	—	—	—	—	6.47[b]	6.45[b]

[a] The melting points are corrected. [b] Hydrazine nitrogen as determined by titration with potassium iodate in acid solution [Jamieson, *Am. J. Sci.*, **33**, 352 (1912)]. Also see Fuller, Lieber, and Smith, *J. Am. Chem. Soc.*, **59**, 1150 (1937); and Keim, Henry, and Smith, *J. Am. Chem. Soc.*, **72**, 4944 (1950). [c] Calc'd Hydrazine N, 8.12. Found, Hydrazine N, 8.07.

TABLE III

5-Aminotetrazole Derivatives



R_1	R_2	R_3	M.P., °C.[a]	YIELD, %	METHOD[b]	CRYSTALLIZED FROM	ANALYSIS					
							C		H		N	
							Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_3	H	H	228	65.5	A	Water	24.23	24.46	5.09	5.01	—	—
				Ca. 100	C							
C_2H_5	H	H	147–148[d]	68.5	A	Water	—	—	—	—	61.91	61.40
				Ca. 100	C							
CH_2=$CHCH_2$	H	H	129.5–130.5	72.8	A	Water	38.39	38.54	5.64	5.48	55.97	56.24
C_6H_{11}	H	H	221–222[e]	76.8	A	Isopropyl alcohol, 87%	—	—	—	—	41.89	41.47
				Ca. 100	C							
$C_6H_5CH_2$	H	H	191–192[f]	58.5	A	Methanol	54.84	54.98	5.18	4.59	—	—
				Ca. 100	C							
C_6H_5	H	H	160.5–161.5[g]	95.2	A	Water	52.16	52.41	4.38	4.76	—	—
4-$CH_3OC_6H_4$	H	H	209–210	81.8	A	Ethanol, 95%	50.25	50.28	4.74	4.71	36.63	36.42
2-$CH_3C_6H_5$	H	H	191–192	87	A	Ethanol, 50%	54.84	54.98	5.18	5.43	39.98	40.20
H	CH_3	H	185–187	11	A	Ethanol, 95%	24.23	24.48	5.09	4.92	70.67	71.25
				Ca. 100	B							
H	C_2H_5	H	174–175	*Ca.* 100	B	Acetonitrile	31.85	31.96	6.24	6.25	61.91	61.55
H	$C_6H_5CH_2$	H	180.5–181.5	2.6	A	Water	54.84	55.02	5.18	5.11	39.98	39.83

H	C_6H_{11}	H	196–198	2	A	Water	50.28	49.98	7.83	7.56	41.89	41.48
				Ca. 100	B							
H	C_6H_5	H	211–212[h]	*Ca.* 100	C	Water	52.16	52.82	4.38	4.54	—	—
H	CH_3	CH_3	244–246	79.6	A	Water	31.85	31.95	6.24	5.98	61.91	62.23
H	CH_3	$C_6H_5CH_2$	136–137	86.8[i]	A	10:1 Benzene-Ethanol	57.12	57.41	5.86	5.61	37.02	37.14
H	C_2H_5	$C_6H_5CH_2$	134–136	38[i]	A	Benzene	59.09	59.34	6.45	6.28	34.46	34.41
H	C_6H_5	$C_6H_5CH_2$	145–147	46.9	*i*	Benzene	—	—	—	—	27.88	27.43
CH_3	CH_3	H	172–173[k]	100	A	Ethanol	31.85	31.75	6.24	6.31	61.91	61.97
CH_3	C_2H_5	H	87–88	*Ca.* 100	B	7:2 Benzene-Ligroin	37.78	37.94	7.13	7.21	55.09	55.63
C_2H_5	C_2H_5	H	96–97	86.5	A	1:1 Benzene-Ligroin	42.53	42.83	7.85	7.88	49.61	50.11
CH_3	C_6H_5	H	185.5–186.5	*Ca.* 100	C	Ethanol, 95%	54.84	55.26	5.18	5.31	39.98	39.52
C_6H_5	CH_3	H	133.5–136.5	*Ca.* 100	A	Ethanol, 95%	54.84	54.67	5.18	5.35	39.98	40.64
C_2H_5	C_6H_5	H	164.5–165.5	*Ca.* 100	C	Benzene	—	—	—	—	37.02	36.83
C_6H_5	C_2H_5	H	118.5–119.5	*Ca.* 100	B	Benzene	57.12	56.75	5.86	5.76	37.02	36.74
CH_3	$C_6H_5CH_2$	H	99	*Ca.* 57	A	Ethanol, 95%	57.12	57.38	5.86	5.70	37.02	37.75
$C_6H_5CH_2$	CH_3	H	117–118	*Ca.* 27	A	Ethanol, 95%	57.12	57.41	5.86	5.71	37.02	36.54
C_6H_{11}	$C_6H_5CH_2$	H	197–198	(*l*)	A	Ethanol, 95%	65.34	65.50	7.44	7.56	27.22	27.41
C_6H_{11}	C_6H_5	H	223.5–224.5	*Ca.* 100	C	4:1 Benzene-Ethanol	64.17	64.49	7.04	6.80	28.79	28.24
C_6H_5	C_6H_{11}	H	120.5–121.5	80	A	Ethanol, 65%	64.17	64.45	7.04	7.05	28.79	28.91
CH_3	CH_3	CH_3	43–44[m]	54.2	A	2:3 Benzene-Ligroin	37.78	37.76	7.13	7.41	55.08	55.01
C_6H_5	CH_3	CH_3	110–111[n]	68.6	A	Methanol	57.12	57.03	5.86	6.09	37.02	37.70
CH_3	$C_6H_5CH_2$	C_2H_5	[o]	80	A	—	—	—	—	—	—	—
C_6H_5	$C_6H_5CH_2$	C_2H_5	81–82	78.5	A	Isopropyl alcohol–Diethyl ether	68.78	68.77	6.14	6.07	25.08	25.23

[a] The melting points are corrected. [b] The methods of synthesis are: A—Diazotization of an aminoguanidine and cyclization of the azide. B—Catalytic debenzylation. C—Isomerization by heat. [c] Ref. (3) reported 222°; ref. (6) reported 222.5–223.5°. [d] Ref. (6) reported 148–148.5°. [e] Ref. (6) reported 216.5–217.5°. [f] Ref. (5) reported 187°; ref. (6) 186.5–187.5°. [g] Ref. (6) reported 159.5–160°. [h] Ref. (4) reported 206°. [i] The yield is based on the weight of starting thiourea. [j] Prepared from benzylphenylcyanamide and hydrazoic acid, following the procedure of Stolle and Henke-Stark, *J. prakt. Chem.*, **124**, 261 (1930). [k] The *picrate* crystallized from 1:4 ethanol-diethyl ether as bright yellow needles, m.p. 119–120°. A mixture melting point with picric acid was 105–110°. Calc'd for $C_9H_{10}N_8O_7$: N, 32.74. Found: N, 32.61. [l] The yield of mixed isomers amounted to 92.2% of theory. The yields of the individual isomers were not determined because of the difficulty of separation. [m] The *hydrochloride*, after recrystallization from ethanol and diethyl ether, melted at 150.5–151.5°. Calc'd for $C_4H_{10}ClN_5$: C, 29.38; H, 6.16. Found: C, 30.16; H, 6.30. The *picrate* after recrystallization from 95% ethanol melted at 97–97.5°. Calc'd for $C_{10}H_{12}N_8O_7$: C, 33.71; H, 3.40. Found: C, 33.78; H, 3.15. [n] The *hydrochloride*, after recrystallization from methanol and diethyl ether, decomposed at 157.5–159.5°. Calc'd for $C_9H_{12}ClN_5$: C, 47.89; H, 5.36. Found: C, 48.10; H, 5.54. [o] B.p. 207–207.5° at *ca.* 3 mm (uncorr.). The *hydrochloride* after recrystallization from isopropyl alcohol and diethyl ether, melted at 74–77°. Calc'd for $C_{11}H_{16}ClN_5$: N, 27.61. Found: N, 27.36.

Recrystallization of the product from water gave 1-methyl-5-aminotetrazole, m.p. 226–227°, in quantitative yield.

5-Anilinotetrazole. 1-Phenyl-5-aminotetrazole, m.p. 160–161° (3 g.), was heated for five minutes at 185° in an oil-bath; the melt was cooled momentarily, allowed to resolidify, and then heated for ten minutes more. The product remained solid during the second heating period. The cooled product was recrystallized from 600 ml. of water; m.p. 211–212°. An aqueous solution of the isomerized product gave a white precipitate with silver nitrate, whereas the starting compound did not. The pK_a as determined by potentiometric titration in water, was 6.3; the measured equivalent weight was 158.9 (theory, 161.17).

Attempted isomerization of 1-(p-anisyl)-5-aminotetrazole. When 0.77 g. of 1-(*p*-anisyl)-5-aminotetrazole was heated for ten minutes at 200°, a melt was obtained which remained liquid at this temperature. Titration of the mixture with standard base solution indicated the presence of about 26–27% of 5-(*p*-anisylamino)tetrazole. Heating for a longer period of time at 200°, or at a higher temperature (210–215°) did not increase the amount of acidic isomer. The partially isomerized mixture would also give a precipitate with silver nitrate whereas the pure starting compound would not. Limited attempts to isolate 5-(*p*-anisylamino)tetrazole from the mixture by fractional crystallization were not successful.

Similar results were obtained when 1-(*o*-tolyl)-5-aminotetrazole was heated at 190 or 200°.

2-Hydrazino-4,5-dihydroimidazole hydriodide. This compound was prepared in 94.7% yield by the hydrazinolysis of 2-methylmercapto-4,5-dihydroimidazole hydriodide (11) in aqueous solution using the general procedure outlined above for the preparation of substituted aminoguanidine derivatives. After recrystallization from 95% ethanol the compound melted at 142–143°.

Anal. Calc'd for $C_3H_9IN_4$: N, 24.57. Found: N, 24.17.

The *picrate* was obtained as rosettes of flat, orange needles from 95% ethanol; m.p. 182–182.5°.

Anal. Calc'd for $C_9H_{11}N_7O_7$: Hydrazine N, 8.8. Found: Hydrazine N, 8.5.

The *hydriodide* of the *benzal hydrazone* melted at 194–195° after recrystallization from water.

Anal. Calc'd for $C_{10}H_{13}IN_4$: N, 17.72. Found: N, 17.52.

The *picrate* of the *benzal hydrazone* crystallized as fine needles from 95% ethanol; m.p. 256–257° (dec.; uncorr.).

Anal. Calc'd for $C_{16}H_{14}N_7O_7$: N, 23.55. Found: N, 23.33.

5,6-Dihydro-7-imidazo[1,2]tetrazole. 2-Hydrazino-4,5-dihydroimidazole hydriodide was converted to the nitrate, treated with nitrous acid, and the resulting azide was cyclized in the same manner outlined previously for the preparation of substituted aminotetrazole from substituted aminoguanidines. The yield of tetrazole derivatives from 46.3 g. of starting hydriodide was 16.8 g. (74.5%); m.p. 159–162°. Two recrystallizations from absolute ethanol raised the melting point to 163–164° (dec.). The compound can also be recrystallized from water.

Anal. Calc'd for $C_3H_5N_5$: C, 32.43; H, 4.54; N, 63.04.
Found: C, 32.65; H, 4.38; N, 62.65.

The *picrate* was recrystallized from 50–50 absolute ethanol-diethyl ether; m.p. 122–123° (dec.). A mixture melting point with picric acid was 110–115°.

Anal. Calc'd for $C_9H_8N_8O_7$: C, 31.77; H, 2.37.
Found: C, 31.78; H, 2.26.

SUMMARY

5-Cyclohexylamino-, 5-benzylamino-, and 5-methylamino-tetrazole are formed in 2–11% yield by the cyclization of the respective guanylazides; the principal product is the isomeric 1-substituted-5-aminotetrazole. 5-Methylaminotetrazole is also formed in about 0.6% yield by the reaction of hydrazoic acid and acetoni-

trile in the presence of sulfuric acid. 5-Methylamino- and 5-ethylamino-tetrazole have been prepared in good yield by the catalytic debenzylation of the appropriate 5-benzylalkylaminotetrazoles. All of the 5-alkylaminotetrazoles that have been prepared isomerize at 170–190° to the isomeric 1-alkyl-5-aminotetrazoles. On the other hand, 1-phenyl-5-aminotetrazole and 1-phenyl-5-alkylaminotetrazoles can be isomerized in the same temperature range to 5-anilinotetrazole and 1-alkyl-5-anilinotetrazoles, respectively. This isomerization appears to be rather general and probably reaches an equilibrium state since 1-methyl-5-benzylaminotetrazole can be partially isomerized to 1-benzyl-5-methylaminotetrazole.

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