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THE SYNTHESIS OF 5-AMINOTETRAZOLE DERIVATIVES

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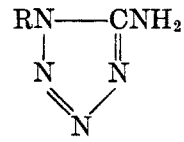
In previous communications from this laboratory the preparation of alkylated pentamethylenetetrazole derivatives (1), pentamethylenetetrazole carboxylic acids (2), and 1,5-disubstituted tetrazoles (3) was described. With few exceptions these products exhibited relatively low water solubility which limited their usefulness as potential medicinal agents. In order to circumvent this difficulty efforts were initiated to prepare simple substituted tetrazole derivatives in whose structure a salt-forming group such as the amino group was incorporated. One approach involved the synthesis of a series of 5-aminotetrazoles further substituted with an alkyl or an aryl group in the 1 position (I).



I

In addition to 5-aminotetrazole (I, R = H) a few 1-alkyl and 1-aryl-5-aminotetrazoles have been described. Since Thiele and Ingle (4) first reported the preparation of 5-aminotetrazole, it has been the subject of many investigations chiefly because of its potential value as an explosive and because of the interesting properties of certain of its derivatives. Benson (5) has included a comprehensive review of 5-aminotetrazole and its derivatives in his survey of the chemistry of tetrazoles. As is the case with all tetrazoles unsubstituted in the 1 position, 5-aminotetrazole is a moderately strongly acidic substance and readily forms metallic salts which do not decompose hydrolytically in aqueous solution. The basic properties of the amino group, however, are masked. Under anhydrous conditions a hydrochloride and a nitrate have been prepared but both are completely hydrolyzed in aqueous solution.

In view of the acidic properties of 5-aminotetrazole it might appear that a variety of 1-alkyl derivatives could be prepared by the simple expedient of alkylation under suitable conditions. Attempts at alkylation have generally led to mixtures of products including 1-alkyl- and 2-alkyl-5-aminotetrazoles together with compounds alkylated on the amino group as well. The formation of such a complex mixture of alkylation products would be anticipated upon consideration of a few of the conceivable tautomeric forms of 5-aminotetrazole.

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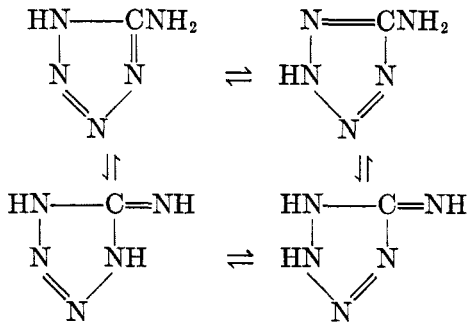
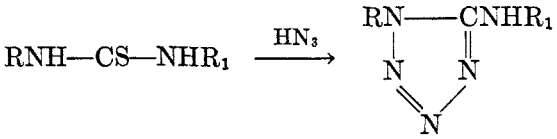
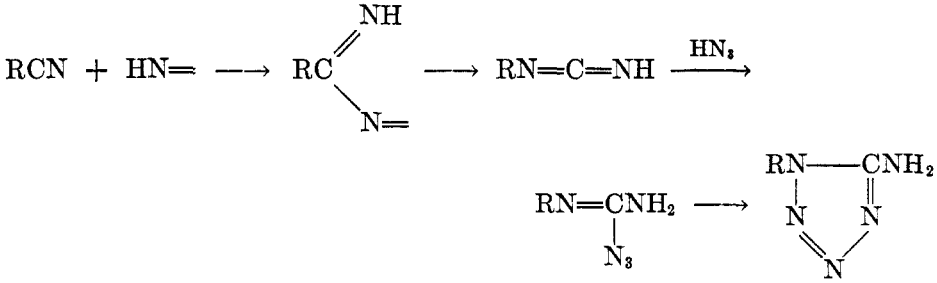


Thiele and Ingle (4) have described a variety of products resulting from attempts to methylate, ethylate, and benzylate 5-aminotetrazole, the true structures of which still require confirmation in most instances.

1-Methyl-5-aminotetrazole was first isolated by Thiele and Ingle (4) from the mixture of products formed upon methylation of 5-aminotetrazole with methyl iodide. A more clear cut preparation was described by Stollé (6), by the interaction of methyl thiourea and sodium azide in alcoholic solution in the presence of lead oxide or carbonate in a carbon dioxide atmosphere. By application of this reaction to a number of thiourea derivatives Stollé (6, 7) succeeded in synthesizing a group of 1-aryl-5-aminotetrazole derivatives as well.

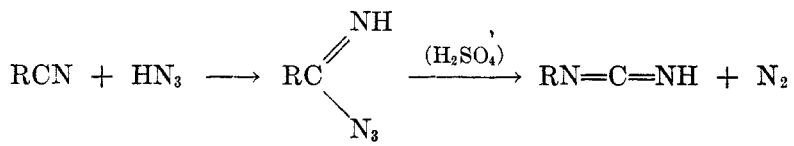


A more attractive procedure, in that it eliminated the use of lead oxide or carbonate in the presence of sodium azide or hydrazoic acid, was described by von Braun and Keller (8) in which 1-alkyl and 1-aryl-5-aminotetrazoles are formed by the interaction of nitriles and hydrazoic acid in the presence of concentrated sulfuric acid. By this technique 1-*n*-hexyl-5-aminotetrazole and the corresponding 1-benzyl, 1-phenyl, and 1-*p*-tolyl derivatives were prepared. The formation of a 5-aminotetrazole derivative requires interaction of two moles of hydrazoic acid with each mole of nitrile. Von Braun and Keller have proposed a mechanism for the reaction involving the addition of the free imine radical (HN=), whose formation from hydrazoic acid upon contact with concen-

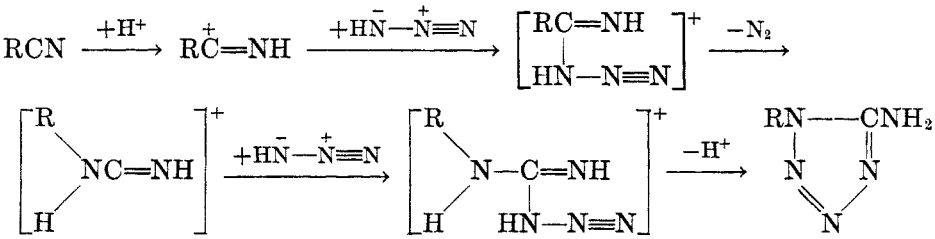


trated sulfuric acid was postulated by Schmidt (9), to the cyanide group followed by rearrangement of the addition product to a carbodiimide derivative. A second molecule of hydrazoic acid adds to the rearranged product and the resulting intermediate undergoes cyclization.

The existence of a free imine radical is doubtful, even though Schmidt has employed it extensively in formulating reactions of hydrazoic acid with various unsaturated groups. Hydrazoic acid is known to add directly to the cyanide group and in the absence of mineral acids the addition products cyclize to form tetrazole derivatives without rearrangement. For instance, tetrazole is formed by addition of hydrazoic acid to hydrocyanic acid (10), and from cyanogen bromide (11), ethyl cyanoformate (11), cyanogen (12), and cyanamide (13) are formed, respectively, 5-bromo-, 5-carbethoxy-, 5-cyano-, and 5-amino-tetrazole. It should be emphasized that these reactions do not involve a rearrangement; the substituent attached to the carbon of the cyanide group appears in the 5-position of the resulting tetrazole. The postulation by von Braun that the imine radical was essential to the reaction with alkyl and aryl cyanides was based on the belief that hydrazoic acid would not add to the cyanide group of such nitriles. Since it has recently been shown that the cyanide group of the nitriles of carboxylic acids will undergo the normal addition of hydrazoic acid and cyclization to form 5-substituted tetrazoles (14), there remains no need for the assumption of the interaction of the cyanide group with the imine radical. It seems more reasonable to assume the addition of hydrazoic acid to the cyanide group in the von Braun reaction with the formation of an imide azide. The subsequent elimination of nitrogen and rearrangement in the presence of sulfuric acid becomes closely akin to the Curtius rearrangement of acid azides. On this basis the initial phases of the von Braun reaction may be formulated as follows:



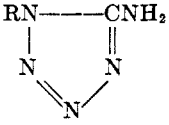
Newman and Gildenhorn (15) have shown that the Curtius rearrangement may be catalyzed by acids and have discussed the possibility of carbonium ion intermediates not only in the Curtius reaction but in the Schmidt reaction of acids with hydrazoic acid as well. It seems rather likely that the acid-catalyzed rearrangement of the imide azides may proceed by a closely analogous carbonium ion mechanism.



By the interaction of hydrazoic acid with a variety of alkyl and aryl cyanides in the presence of sulfuric acid we have prepared the series of 1-alkyl and 1-aryl-5-aminotetrazoles shown in Table I. We can confirm the observation of von Braun and Keller that the yield of tetrazole decreases as the size of the alkyl group increases. Apparently the rearrangement does not take place as readily with the

TABLE I

1-SUBSTITUTED-5-AMINOTETRAZOLES



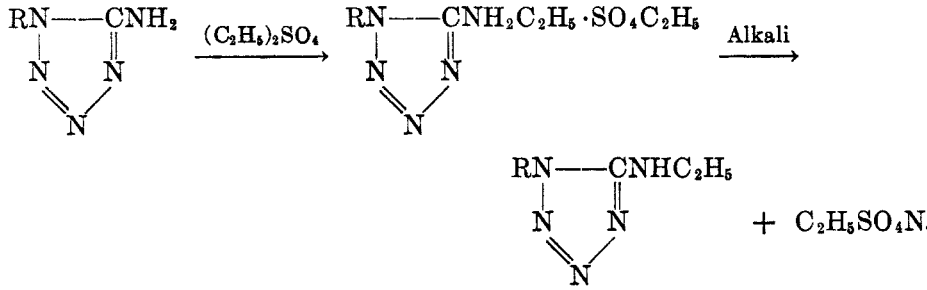
R	FORMULA	M.P., °C.	YIELD, %	CRYSTALLIZED FROM	ANALYSIS, N	
					Calc'd	Found
CH_3 (Ref. 4, 6)	$C_2H_5N_5$	222.5–223.5	30	Water	—	—
C_2H_5	$C_3H_7N_5$	148–148.5	51	Water	61.9	62.1
n-C_3H_7	$C_4H_9N_5$	153–153.5	31	Aqueous isopropyl alcohol	55.1	55.5
iso-C_3H_7	$C_4H_9N_5$	161.5–162	28	Isopropyl alcohol-benzene	55.1	55.4
n-C_4H_9	$C_5H_{11}N_5$	149–149.5	46	Aqueous isopropyl alcohol	49.6	49.8
iso-C_4H_9	$C_5H_{11}N_5$	204	55	Water	49.6	49.9
n-C_5H_{11}	$C_6H_{13}N_5$	161–162	54	Aqueous methanol	45.2	45.1
iso-C_5H_{11}	$C_6H_{13}N_5$	186–187	47	Aqueous isopropyl alcohol	45.2	45.1
$(C_2H_5)_2CH$	$C_6H_{13}N_5$	190–190.5	37	99% Isopropyl alcohol	45.2	44.7
n-C_7H_{15}	$C_8H_{17}N_5$	162.5–163	60	99% Isopropyl alcohol	38.2	38.2
$(C_2H_5)(C_4H_9)CH$	$C_8H_{17}N_5$	146–146.5	32	Heptane	38.2	38.4
n-C_9H_{19}	$C_{10}H_{21}N_5$	162.5–163	28	Aqueous methanol	33.1	33.0
n-$C_{11}H_{23}$	$C_{12}H_{25}N_5$	161.5–162	19	Methanol	29.3	28.9
C_6H_{11}(cyclo)	$C_7H_{13}N_5$	216.5–217.5	40	87% Isopropyl alcohol	41.9	42.0
C_6H_5 (Ref. 7, 8, 18)	$C_7H_7N_5$	159.5–160	46	Water	—	—
$C_6H_5CH_2$ (Ref. 8)	$C_8H_9N_5$	186.5–187.5	23	Aqueous isopropyl alcohol	40.0	40.2
$C_6H_5CH_2CH_2$	$C_9H_{11}N_5$	176	26	99% Isopropyl alcohol	37.0	37.1
$ClCH_2CH_2$—	$C_3H_6ClN_5$	151.5–152	15	Heptane	47.5	47.8

higher alkyl cyanides since the product is usually contaminated with rather large amounts of the simple amide.

Although the 5-aminotetrazole derivatives are usually represented structurally as primary amines, the basic properties of the amino group are masked, perhaps by the unsaturated character of the nitrogen heterocycle. They are all relatively high melting solids, a property that is difficult to reconcile with their molecular weight and structure as primary amines. Only the lower members of the series are moderately soluble in hot water, but all of the compounds exhibit at least a slight solubility in cold water. The aqueous solutions are usually neutral or

slightly acidic. On prolonged boiling with acetic anhydride, however, acetyl derivatives are formed (6), while condensation with benzaldehyde to form Schiff bases takes place only slowly on heating in the presence of piperidine (6). Stable nitroso derivatives are formed with sodium nitrite in acid solution (6), and hydrochlorides are said to be obtained on crystallization from concentrated hydrochloric acid but they decompose hydrolytically in aqueous or alcoholic solution (6). 1-Phenyl-5-dibenzylaminotetrazole was prepared by Stollé by prolonged heating of an alcoholic solution of the corresponding primary amine with benzyl chloride and potassium hydroxide, and it is interesting to note that Stollé (6) found this compound to have a considerably lower melting point than the primary amine from which it is derived and solubility properties more in keeping with its character as a tertiary amine. Thiele and Ingle (4) have also described products which are probably 1-methyl-5-methylaminotetrazole and 1-ethyl-5-ethylaminotetrazole obtained by the alkylation of 5-aminotetrazole with methyl iodide and ethyl iodide, respectively. Both compounds are basic liquids that form hydrochlorides which are stable in aqueous and alcoholic solutions.

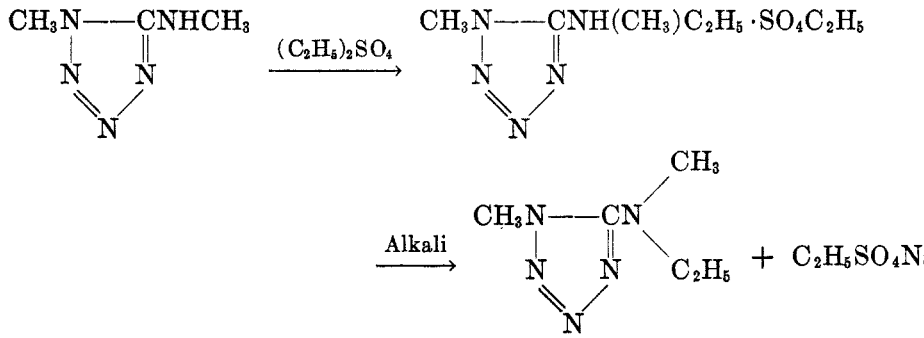
In view of our experience with the effect of alkylating agents on pentamethylenetetrazoles (1), it was of interest to investigate the possibility of alkylating the amino group of the 1-substituted 5-aminotetrazoles. When 1-phenyl-5-aminotetrazole was warmed with an equimolar amount of methyl benzenesulfonate, an exothermic reaction was initiated and 1-phenyl-5-methylaminotetrazole could be isolated from the reaction mixture in 73% yield. In contrast to the primary amine the methylated product was a low melting solid that could be distilled under reduced pressure. It exhibited basic porperties, formed salts with acids that were stable in aqeuous solution, reacted readily with alkylating agents to form tertiary amines, and reacted readily with reagents used to characterize amines, such as acid chlorides and the isothiocyanates. Similar reactions took place on warming other 1-substituted 5-aminotetrazoles with methyl benzenesulfonate, methyl sulfate or ethyl sulfate.



The possibility that alkylation of the ring nitrogen had taken place was considered. In this case a quaternary ammonium compound would have been formed. It is rather unlikely that the quaternary base liberated from the salt would be easily extractable from aqueous medium by organic solvents such as benzene or ether, nor could such a base be distilled without extensive decomposition. Since the bases formed upon alkylation were readily soluble in benzene or

ether, insoluble in water when the molecular weight was moderately large, and could all be distilled without apparent decomposition, it seems reasonable to assume that alkylation of the amino group was the principal reaction. The formation of thiourea derivatives with phenyl isothiocyanate, a reaction not exhibited by the primary amines of this group, and the possibility of further alkylation to form tertiary amines substantiated the conclusion that alkylation of the amino group predominated over ring alkylation in this series of compounds.

Several of the simple secondary amines were subjected to further alkylation with methyl benzenesulfonate or ethyl sulfate. In each case a spontaneous, rapid, exothermic reaction followed immediately upon mixing the amine with an equimolar quantity of alkylating agent. The tertiary amines exhibited the anticipated normal characteristics; they were liquids, distillable under reduced pressure, formed stable salts with acids, and were soluble in solvents such as ether, benzene, and chloroform. Aqueous solutions of the tertiary amines had an alkaline reaction.

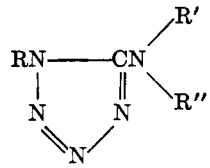


Particularly noteworthy is the fact that further alkylation with small alkyl groups generally caused a lowering of the boiling point although the molecular weight increased. For example, 1-ethyl-5-methylaminotetrazole distilled at 118–120° at 19 mm., and 1-ethyl-5-ethylaminotetrazole distilled at 121–122° at 21 mm., but 1-ethyl-5-methylethylaminotetrazole distilled at 113–115° at 24 mm.

A comparison of the properties of the primary and secondary amines is most interesting. As noted before, the primary amines are relatively high melting solids that fail to exhibit basic properties; their salts are stable only under anhydrous condition, they react with the usual reagents for amines only under drastic conditions, and their solubilities are not those usually associated with primary amines. The secondary amines are liquids or low melting solids that can be distilled under reduced pressure and which exhibit apparently normal characteristics; they are soluble in solvents such as ether, benzene, acetone, chloroform, and the lower alcohols, their aqueous solutions are alkaline in reaction, they form readily crystallizable salts with acids that are stable in aqueous solution, and they react readily with alkylating agents and other characteristic amine reagents under normal conditions. The profound change from the almost amidic character of the primary amines to the apparently normal character of the secondary amines, as well as the further lowering of the boiling point associated with the conversion of the secondary to tertiary amines will probably

TABLE II

1-SUBSTITUTED-5-ALKYLAMINOTETRAZOLES



R	R′	R″	BASE			HYDROCHLORIDE			
			B.P., °C.	MM.	YIELD, %	M.P., °C.	FORMULA	ANALYSIS, N	
								Calc'd	Found
CH_3	C_2H_5	H	117–119	20	60	202–203 d.	$C_4H_{10}ClN_5$	42.8	42.4
CH_3	$C_6H_5CH_2$	H	—	—	—	217–218 d.	$C_9H_{12}ClN_5$	31.0	31.2
C_2H_5	CH_3	H	118–120	19	71	201–202 d.	$C_4H_{10}ClN_5$	42.8	42.3
C_2H_5	C_2H_5	H	121–122	21	60	228–229 d.	$C_5H_{12}ClN_5$	39.4	39.0
C_2H_5[b]	CH_3	C_2H_5	113–115	24	74	143–145	$C_6H_{14}ClN_5$	36.5	36.1
C_2H_5	iso-C_4H_9	H	[a]	—	—	201 d.	$C_7H_{16}BrN_5$	28.0	27.7
C_2H_5	$C_6H_5CH_2$	H	—	—	—	224 d.	$C_{10}H_{14}ClN_5$	29.2	29.4
C_2H_5	$C_6H_5CH_2CH_2$	H	[a]	—	—	203–204 d.	$C_{11}H_{16}BrN_5$	23.5	23.6
n-C_3H_7	C_2H_5	H	94–95	4.5	71	187	$C_6H_{14}ClN_5$	36.5	36.6
iso-C_3H_7	C_2H_5	H	100–102	5	71	226 d.	$C_6H_{14}ClN_5$	36.5	36.4
n-C_4H_9	C_2H_5	H	108–109	3.5	74	196–197	$C_7N_{16}ClN_5$	34.1	33.7
iso-C_4H_9	CH_3	H	130–132	20	75	243–244 d.	$C_6H_{14}ClN_5$	36.5	36.7
iso-C_4H_9	C_2H_5	H	135–137	19	65	239 d.	$C_7H_{16}ClN_5$	34.1	33.9
n-C_5H_{11}	C_2H_5	H	117–119	3.5	71	188–189	$C_8H_{18}ClN_5$	31.9	31.9
iso-C_5H_{11}	C_2H_5	H	115–117	3.5	76	221–222 d.	$C_8H_{18}ClN_5$	31.9	32.0
$(C_2H_5)_2CH$	C_2H_5	H	107–109	6	67	216 d.	$C_8H_{18}ClN_5$	31.9	32.2
n-C_7H_{15}	CH_3	H	145–148	7	81	198–199	$C_9H_{20}ClN_5$	30.0	30.3
n-C_7H_{15}	C_2H_5	H	134–136	4.5	75	162–163	$C_{10}H_{22}ClN_5$	28.3	28.3
cyclo-C_6H_{11}	CH_3	H	140–142	5	80	264 d.	$C_8H_{16}ClN_5$	32.2	32.1
cyclo-C_6H_{11}	C_2H_5	H	138–140	6.5	67	248 d.	$C_9H_{18}ClN_5$	30.2	30.0
cyclo-C_6H_{11}	C_2H_5	C_2H_5	123–125	2.5	84	161–162	$C_{11}H_{22}ClN_5$	27.0	26.7
cyclo-C_6H_{11}	$C_6H_5CH_2$	H	—	—	—	240 d.	$C_{14}H_{20}ClN_5$	23.8	24.1
cyclo-C_6H_{11}	$C_6H_5CH_2CH_2$	H	[a]	—	—	208–209	$C_{15}H_{22}BrN_5$	19.9	20.1
C_6H_5	CH_3	H	139–141	3	73	225 d.	$C_8H_{10}ClN_5$	33.1	32.7
C_6H_5	CH_3	CH_3	136–138	3.5	66	210 d.	$C_9H_{12}ClN_5$	31.0	30.8
C_6H_5	C_2H_5	H	146–148	5	61	239 d.	$C_9H_{12}ClN_5$	31.0	31.3
$C_6H_5CH_2$	C_2H_5	H	155–156	3	70	226 d.	$C_{10}H_{14}ClN_5$	29.2	29.4
$C_6H_5CH_2$-CH_2	C_2H_5	H	172–173	7	67	217–218 d.	$C_{11}H_{16}ClN_5$	27.6	27.5
cyclo-C_6H_{11}	$C_6H_4(CO)_2NCH_2CH_2$	H	[a]	—	—	270 d.	$C_{17}H_{21}BrN_6O_2$	20.0	20.2

[a] Isolated and analyzed as the hydrobromide.

[b] Prepared both by methylation of 1-ethyl-5-ethylaminotetrazole and by ethylation of 1-ethyl-5-methylaminotetrazole.

find an explanation in the elucidation of the true structure of these compounds, a development requiring further investigation.

In Table II are recorded pertinent data regarding the properties of the secondary amines and their hydrochlorides. Data relative to a few tertiary amines are also included.

The pharmacologic properties of this group of compounds have been reported by Gross and Featherstone (16). In general, the secondary and tertiary amines exerted a convulsant action upon white rats. The potency of the compounds could be enhanced by increasing the size of the substituent in position 1 of the tetrazole nucleus or by increasing the size of the substituent on the amino group. Thus 1-ethyl-5-benzylaminotetrazole and 1-benzyl-5-ethylaminotetrazole had comparable convulsant action. The tertiary amines were usually more potent than the closely related secondary amines.

EXPERIMENTAL[4]

Nitriles. Excepting those alkyl cyanides which are available commercially, the nitriles were prepared by the dehydration of the appropriate amides by heating with phosphorus pentoxide. Phenyl cyanide was prepared both by the Sandmeyer reaction from diazotized aniline and by the fusion of sodium benzene sulfonate with potassium cyanide in an electrically-heated retort. The latter method was found to be the more convenient.

1-Alkyl-5-aminotetrazoles. These compounds were prepared by the method of von Braun and Keller (8). The preparation of 1-*n*-amyl-5-aminotetrazole affords an example. A solution of 60 g. (0.62 mole) of *n*-capronitrile in 1 liter of a 6.8% solution of hydrazoic acid in benzene[5] (68 g. of HN_3, 1.63 moles) was warmed with continuous mechanical stirring to 35–40°. To the warm solution 400 g. of concentrated sulfuric acid was added dropwise[6] with continued vigorous stirring during about two hours at such a rate that the temperature of the reaction mixture was maintained between 45–50°. Addition of the sulfuric acid was accompanied by vigorous evolution of nitrogen. Stirring was continued for 4–5 hours after complete addition of the sulfuric acid before the reaction mixture was allowed to stand overnight. After separation from the benzene, the acid layer was poured onto 400–500 g. of ice and neutralized to litmus by the addition of 50% caustic soda solution. The product separated as a solid and was recrystallized from aqueous methanol; yield, 52 g. of 1-*n*-amyl-5-aminotetrazole, m.p. 161–162°.

In general the 5-aminotetrazoles could be recrystallized from water or aqueous alcohols. The compounds prepared in this manner are listed in Table I together with pertinent analytical and descriptive data.

ALKYLATION OF 5-AMINOTETRAZOLES

Since several procedures were employed for the alkylation of 1-alkyl-5-aminotetrazoles, typical examples with several alkylating agents will be described.

1-Phenyl-5-methylaminotetrazole. A mixture of 41 g. (0.25 mole) of 1-phenyl-5-aminotetrazole and 45 g. (0.26 mole) of methyl benzenesulfonate was heated on a boiling water-bath with occasional stirring. When the temperature of the mixture approached 100° a rapid exothermic reaction set in causing the temperature to rise to about 160° with the formation of a clear, homogeneous melt. Heating was continued for 30 minutes after which the reaction mixture was allowed to cool to room temperature. The mixture solidified on cooling. The methylated product was isolated by adding a warm solution of the crude benzene sulfonate in 100 ml. of absolute methanol to a warm solution of 6 g. of sodium in

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[4] Microanalyses were carried out on all compounds by Mr. William Saschek.

[5] Solutions of hydrazoic acid in benzene are conveniently prepared by the method of von Braun (17). Because of its toxic character reactions involving hydrazoic acid should always be caried out in a good hood.

[6] It is advisable to introduce the sulfuric acid below the surface of the liquid since dropping the concentrated sulfuric acid through hydrazoic acid has been said to cause occasional, explosive decomposition of the latter. Observing this precaution we have never suffered any untoward experiences.

85 ml. of absolute methanol. After boiling the resulting mixture a few minutes, the methanol was removed by distillation on a water-bath, finally under reduced pressure. The residue was suspended in about 50 ml. of water and after addition of 40–50 g. of anhydrous potassium carbonate, the base was extracted from the sludge with four or five 200-ml. portions of benzene. The combined benzene extracts were dried over potassium carbonate, after which the residue left upon evaporation of the solvent was distilled under reduced pressure. The yield of product distilling at 139–141° at 3 mm. (bath at 160°) was 33 g. The hydrochloride was prepared by dissolving the entire quantity of base in 100 ml. of 87% isopropyl alcohol and adding a slight excess of dry hydrogen chloride. The hydrochloride separated on cooling as a coarse, granular, colorless crystalline product. After recrystallization from 87% isopropyl alcohol, 29.5 g. of pure hydrochloride, m.p. 225° with decomposition was obtained.

1-Ethyl-5-ethylaminotetrazole. A mixture of 28.3 g. (0.25 mole) of 1-ethyl-5-aminotetrazole and 38.5 g. (0.25 mole) of ethyl sulfate was heated on a boiling water-bath. After the reaction was initiated the temperature rose rapidly to about 150° with the formation of an homogeneous melt. Heating was continued for half an hour after the temperature started to fall. The product remained as a thick, viscous mass on cooling. The base was isolated by adding a warm solution of the crude ethosulfate in 50 ml. of absolute methanol to a warm solution of 5.6 g. of sodium in 50 ml. of absolute methanol. Evaporation of the methanol and extraction of the base followed the preceding example. The 1-ethyl-5-ethylaminotetrazole was obtained as a mobile liquid of ammoniacal odor distilling at 122–123° at 21 mm.; yield, 20.5 g. The hydrochloride was prepared from 13 g. of the base by treating its solution in 50 ml. of absolute isopropyl alcohol with a slight excess of dry hydrogen chloride. After recrystallization from absolute isopropyl alcohol, 11 g. of pure hydrochloride was obtained as long, colorless, rectangular prisms, m.p. 228–229° with decomposition.

Thiele and Ingle (4) described the hydrochloride of a product obtained by heating 5-aminotetrazole with ethyl iodide in a sealed tube and to which they assigned the structure of 1-ethyl-5-ethylaminotetrazole as colorless needles, m.p. 232–233°. We have not attempted to repeat their preparation but it is probable that the two products are identical.

1-Ethyl-5-methylaminotetrazole. From a mixture of 28.3 g. (0.25 mole) of 1-ethyl-5-aminotetrazole and 31.5 g. (0.25 mole) of methyl sulfate, 22.5 g. (71%) of 1-ethyl-5-methylaminotetrazole, b.p. 118–120° at 19 mm., was obtained by a procedure analogous to the immediately preceding one. The reaction mixture was warmed slowly on a water-bath; exothermic interaction was initiated when the bath temperature reached 70°.

1-Ethyl-5-benzylaminotetrazole. A mixture of 5.7 g. (0.05 mole) of 1-ethyl-5-aminotetrazole and 6.3 g. (0.05 mole) of benzyl chloride[7] was heated to 150° in an oil-bath. Formation of an homogeneous melt was followed by an exothermic reaction. The bath was kept at 150° for half an hour after apparent interaction ceased. The crude hydrochloride was taken up in 100 ml. of boiling 87% isopropyl alcohol from which it crystallized as colorless needles on cooling. Recrystallization from 75 ml. of 80% isopropyl alcohol gave 6 g. of pure hydrochloride, m.p. 224° with decomposition.

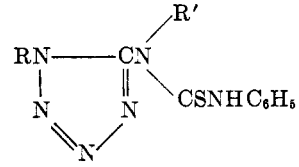
1-Cyclohexyl-5-diethylaminotetrazole. A mixture of 27 g. (0.14 mole) of crude 1-cyclohexyl-5-ethylaminotetrazole, obtained by ethylation of 1-cyclohexyl-5-aminotetrazole with ethyl sulfate, and 21.5 g. (0.14 mole) of ethyl sulfate was warmed carefully on a water-bath. When the temperature of the mixture reached 50° a vigorous, exothermic reaction set in. Heating was continued for a half an hour on a boiling water-bath after the initial reaction subsided. The reaction mixture remained as a viscous syrup on cooling to room temperature. The base was liberated by adding a warm solution of the crude ethosulfate in 40 ml. of absolute methanol to a warm solution of 3.2 g. of sodium in absolute methanol. Removal of the solvent and extraction of the base followed the procedure pre-

[7] When isobutyl bromide was used as the alkylating agent, the reactions were carried out in a sealed tube at 130–140°.

viously described. The base was obtained as a viscous liquid which distilled at 123–125° at 2.5 mm. and solidified to a colorless solid on chilling. The entire quantity of base (26 g.) was converted into the hydrochloride by treatment of its solution in 50 ml. of absolute isopropyl alcohol with a slight excess of dry hydrogen chloride. After removal of the isopropyl alcohol under reduced pressure, the hydrochloride remained as a gum which

TABLE III

PHENYL THIOUREA DERIVATIVES OF THE 1-SUBSTITUTED-5-ALKYLAMINOTETRAZOLES



R	R'	M.P., °C.	FORMULA	ANALYSIS, N	
				Calc'd	Found
CH_3	C_2H_5	148.5–149.5	$C_{11}H_{14}N_6S$	32.0	31.9
CH_3	$C_6H_5CH_2$	123–124	$C_{16}H_{16}N_6S$	25.9	26.1
C_2H_5	CH_3	149–150	$C_{11}H_{14}N_6S$	32.0	32.4
C_2H_5	C_2H_5	109–110	$C_{12}H_{16}N_6S$	30.4	30.4
C_2H_5	iso-C_4H_9	75–77	$C_{14}H_{20}N_6S$	27.6	27.9
C_2H_5	$C_6H_5CH_2$	117–118	$C_{17}H_{18}N_6S$	24.8	25.1
C_2H_5	$C_6H_5CH_2CH_2$	80–81	$C_{18}H_{20}N_6S$	23.9	23.7
n-C_3H_7	C_2H_5	77–78	$C_{13}H_{18}N_6S$	28.9	29.0
iso-C_3H_7	C_2H_5	109–110	$C_{13}H_{18}N_6S$	28.9	28.8
n-C_4H_9	C_2H_5	71–73	$C_{14}H_{20}N_6S$	27.6	27.5
iso-C_4H_9	CH_3	111–112	$C_{13}H_{18}N_6S$	28.9	28.5
iso-C_4H_9	C_2H_5	77–78	$C_{14}H_{20}N_6S$	27.6	27.5
n-C_5H_{11}	C_2H_5	77–78	$C_{15}H_{22}N_6S$	26.4	26.6
iso-C_5H_{11}	C_2H_5	82–83	$C_{15}H_{22}N_6S$	26.4	26.8
$(C_2H_5)_2CH$	C_2H_5	120–121	$C_{15}H_{22}N_6S$	26.4	26.6
n-C_7H_{15}	CH_3	76–77	$C_{16}H_{24}N_6S$	25.3	25.2
n-C_7H_{15}	C_2H_5	50–51	$C_{17}H_{26}N_6S$	24.3	24.2
cyclo-C_6H_{11}	CH_3	172–173	$C_{15}H_{20}N_6S$	26.6	26.6
cyclo-C_6H_{11}	C_2H_5	143–144	$C_{16}H_{22}N_6S$	25.4	25.4
cyclo-C_6H_{11}	$C_6H_5CH_2$	150–151	$C_{21}H_{24}N_6S$	21.4	21.5
cyclo-C_6H_{11}	$C_6H_5CH_2CH_2$	120–121	$C_{22}H_{26}N_6S$	20.7	20.9
C_6H_5	CH_3	181–182	$C_{15}H_{14}N_6S$	27.1	27.2
C_6H_5	C_2H_5	93–94	$C_{16}H_{16}N_6S$	25.9	26.2
$C_6H_5CH_2$	C_2H_5	117–118	$C_{17}H_{18}N_6S$	24.8	25.0
$C_6H_5CH_2CH_2$	C_2H_5	81–82	$C_{18}H_{20}N_6S$	23.9	23.9

crystallized from propylene dichloride. After recrystallization from a mixture of equal volumes of propylene dichloride and heptane, 12.2 g. of pure hydrochloride, m.p. 161–162° was obtained as colorless needles.

By application of the procedures just described to the appropriate 1-alkyl-5-aminotetrazoles all of the compounds listed in Table II were prepared.

All of the secondary amines were further characterized as phenyl thiourea derivatives by treatment of the bases with phenyl isothiocyanate in the usual manner. The thiourea derivatives were recrystallized from either isopropyl alcohol, aqueous isopropyl alcohol

toluene, benzene-heptane, ether-petroleum ether or petroleum ether. The derivatives containing large alkyl groups were most easily crystallized from ether-petroleum ether or petroleum ether alone. Physical constants and other pertinent data for the phenyl thiourea derivatives are summarized in Table III.

SUMMARY

1. A series of new 1-alkyl-5-aminotetrazoles was prepared by the interaction of alkyl cyanides with hydrazoic acid in benzene solution in the presence of concentrated sulfuric acid.

2. The mechanism suggested by von Braun for the formation of 5-aminotetrazoles from alkyl cyanides has been modified so as to obviate the postulation of a free imine radical, HN=, as a participant in the reaction. A carbonium ion mechanism for the reaction is suggested.

3. A method for the preparation of 1-alkyl-5-alkylaminotetrazoles and 1-alkyl-5-dialkylaminotetrazoles which consists of heating the corresponding 1-alkyl-5-aminotetrazoles with alkylating agents such as methyl benzenesulfonate, methyl sulfate, ethyl sulfate or alkyl halides has been developed.

4. Alkylation of the amino group of the 5-aminotetrazoles led to basic compounds which exhibited the typical characteristics of secondary and tertiary amines. The products were characterized as hydrochlorides or hydrobromides and the secondary amines were further characterized by the formation of phenyl thiourea derivatives with phenyl isothiocyanate.

5. Attention has been directed toward the anomalous character of the 5-aminotetrazoles as primary amines as compared with the relatively normal behavior of the corresponding secondary and tertiary aminotetrazoles.

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