

THE CHEMISTRY OF THE TETRAZOLES

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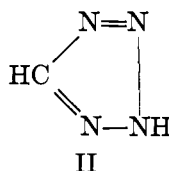
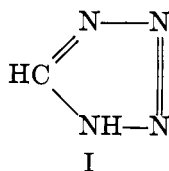
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I. INTRODUCTION

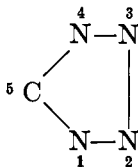
Although the tetrazoles have been extensively investigated, and well over 300 members of this class of nitrogen heterocycles have been prepared, there has been no recent comprehensive review of their chemistry. The section in the textbook by Meyer and Jacobsen (71), published in 1923, is the most complete summary of this group of compounds available. Knowledge of the tetrazoles, however, has been considerably increased since that time.

The present survey reviews the chemistry of tetrazole and its mono- and disubstituted derivatives. Tetrazolium salts and various reduced tetrazoles which have been described from time to time will not be discussed, except in so far as they may form the starting point for the synthesis of tetrazoles.

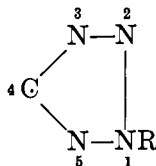
The tetrazoles are characterized by a five-membered, doubly unsaturated ring consisting of one carbon and four nitrogen atoms. Tetrazole itself may exist in the tautomeric forms I and II, the position of the hydrogen atom attached to nitrogen being indeterminate.



Mono- and di-substituted derivatives of both forms are known. Furthermore, the tetrazole ring may form part of a fused-ring system. The simplest numbering scheme for the tetrazoles is

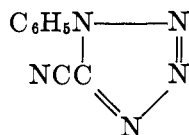


although an alternative system was used in *Chemical Abstracts* for derivatives of formula II prior to 1937.

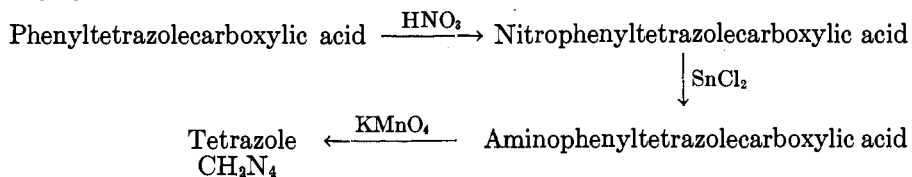


The system mentioned first will be used throughout this discussion for the sake of consistency and to avoid confusion.

The first tetrazole was prepared in 1885 by the Swedish chemist, J. A. Bladin, at the University of Upsala during the course of an investigation of the reactions of dicyanophenylhydrazine, the condensation product of cyanogen and phenylhydrazine. Bladin observed (5) that the action of nitrous acid on dicyanophenylhydrazine led to the formation of a compound, $C_8H_5N_5$, to which he ascribed the formula:



Hydrolysis, followed by decarboxylation, produced a compound having the formula $C_7H_6N_4$, the $C_6H_5CN_4$ unit remaining intact throughout these transformations (6). During his study of dicyanophenylhydrazine, Bladin had prepared numerous triazoles, and the possibility of forming a nitrogen heterocycle with one more ring nitrogen was a logical extension of his interpretations. The following year Bladin proposed the name "tetrazole" for the new ring structure (7) and in 1892 succeeded in preparing tetrazole itself by the following series of reactions (10), starting with the carboxylic acid produced from his phenylcyanotetrazole.



It thus became evident that the ring system with one carbon and four nitrogen atoms was capable of withstanding a variety of chemical agents, and was pos-

largely to Oliveri-Mandalà. The acidic dissociation constants were obtained by means of conductivity measurements, while the hydrolysis constants of the *N*-substituted tetrazole hydrochlorides were determined from the influence of these substances on the rate of acid hydrolysis of methyl acetate.

It will be seen that those tetrazoles with hydrogen in position 1 (or 2) on the ring show the usual range of strengths of organic acids. Although exact measurements are not available, other tetrazoles of this type exhibit confirmatory behavior; thus, 5-phenyltetrazole can be titrated with strong bases, using phenolphthalein as the indicator (66). It is probable that all 5-monosubstituted tetrazoles are acids with constants of 10^{-7} or larger. The K_b values of the *N*-substituted methyl- and ethyl-tetrazoles, calculated from the hydrolysis constants of the hydrochlorides, indicate these compounds to be of the same order of basicity as aniline. Consistent with this or indicating an even lower degree of basicity is the observation of Bladin (6) that 2-phenyltetrazole dissolves in concentrated acids, but is reprecipitated by the addition of water.

TABLE 1
Dissociation constants of tetrazole derivatives

COMPOUND	TEMPERATURE	K_a	HYDROLYSIS CONSTANT	K_b	REFERENCES
	°C.				
Tetrazole.....	25	1.28×10^{-5}			(76)
5-Carbethoxytetrazole.....	20	4×10^{-5}			(77)
5-Aminotetrazole.....	25	6.8×10^{-5}			(3, 4)
5-Tetrazolecarboxamide.....	20	3.3×10^{-2}			(76)
2-Methyl-5-tetrazolecarboxylic acid....	20	1.2×10^{-2}			(78)
1-Methyltetrazole hydrochloride.....			4.7×10^{-5}	2.1×10^{-10}	(74)
1-Ethyltetrazole hydrochloride.....			1.4×10^{-4}	7.1×10^{-11}	(74)
2-Methyltetrazole hydrochloride.....			2.6×10^{-4}	3.8×10^{-11}	(74)
2-Ethyltetrazole hydrochloride.....			4.9×10^{-4}	2.0×10^{-11}	(74)

The conductivity of a number of tetrazoles in water was determined by Oliveri-Mandalà (76), and the conductivity of tetrazole in liquid ammonia was determined by Strain (132).

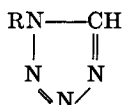
No thermochemical or spectroscopic data have been reported for tetrazole or its derivatives.

The melting or boiling points and solubilities of nearly all tetrazoles of known constitution are recorded in tables 2-7. Compounds known only as salts or those of dubious structure have been omitted. The majority of tetrazoles are crystalline solids. Some liquid tetrazoles, however, are found in each class, except for the 5-monosubstituted derivatives. It is to be noted that the three known 2-monosubstituted compounds are liquids.

The tetrazoles as a class are characterized by a considerable variation in thermal stability. Exceptional stability is found in the case of 5-guanylaminotetrazole, which does not melt at 300°C. On the other hand, most tetrazole derivatives melting above 150°C. do so with decomposition. Many tetrazoles

exhibit explosive properties. Tetrazole itself explodes when heated above its melting point, and inspection of the data in tables 2-7 reveals that several tetrazoles explode when heated. Statements are occasionally found in the

TABLE 2
Physical properties of the tetrazoles
1-Monosubstituted tetrazoles

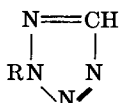


SUBSTITUENT	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Hydrogen (tetrazole)..	155; 156		es	es	ds	ds	
Methyl.....	36-37		es	es	i cold	ds	(72, 120)
Ethyl.....		162-164/30 mm.	es	es	es	es	(85)
Phenyl.....	65-66		i	es		es	(28, 39, 81)
<i>p</i> -Tolyl.....	96						(28)
<i>p</i> -Nitrophenyl.....	205 (d)†		i	s	ds	ds	(28, 39)
<i>p</i> -Aminophenyl.....	155		s hot				(39)
Hydroxy(?).....	145 (d)			s	ds	i	(86, 87)

* es = easily soluble; s = soluble; ds = difficultly soluble; i = insoluble.

† d = decomposes.

TABLE 3
Physical properties of the tetrazoles
2-Monosubstituted tetrazoles

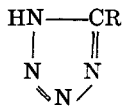


SUBSTITUENT	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Methyl.....		145-147	s	s	es		(85)
Ethyl.....		152-155; 70-71/35 mm.					(83, 85)
Phenyl.....		Explodes on heating	i	es	es		(6, 145)

* es = easily soluble; s = soluble; i = insoluble.

literature that members of this class explode when touched with a hot wire; pyridotetrazole and tetrazoloquinoline show this behavior (34). Compounds containing tetrazole rings linked to chains of nitrogen atoms, such as tetrazolyl azide or 1,6-ditetrazolyhexazdiene, are exceedingly sensitive to heat and impact.

TABLE 4
Physical properties of the tetrazoles
5-Monosubstituted tetrazoles



SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
Acetonyl.....	114		es	es			(107)
Phenyl.....	212-213 (d); 215 (d)		i cold	s	ds	ds	(66, 67, 91)
<i>p</i> -Tolyl.....	234 (d); 248		i cold	ds cold			(65, 92, 93, 123)
<i>p</i> -Cumenyl.....	189		i cold	es hot			(25)
β -Naphthyl.....	203 (d)			es	es		(91)
<i>o</i> -Chlorophenyl....	177 (d)		i	es hot	ds		(123)
Anisyl.....	228 (d)		i cold	es	ds		(64)
3-Nitrophenyl.....	145		ds cold	es	s	i	(67)
4-Nitrophenyl.....	219		ds cold	s			(91)
3-Nitro-4-methoxyphenyl..	203		ds hot		s		(64)
3-Amino-4-methoxyphenyl..	223		es hot	es hot	i		(64)
α -Furyl.....	199 (d)		ds cold	es			(92, 94)
3,6-Di(tetrazolyl-5)-1,2,4,5-tetrazine.....	Explodes on heating		es	es			(26, 63)
3,6-Di(tetrazolyl-5)-dihydro-1,2,4,5-tetrazine....			i	i	i	i	(26, 62, 63)
Ditetrazolyl.....	254-255 (d)			i	ds	i	(63, 85)
2-Hydroxybenzoyl..	172			es		s	(40)
2-Hydroxy-5-chlorobenzoyl...	180						(40)
2-Hydroxy-4-methoxy-5-bromobenzoyl...	236 (d)						(40)
Carbethoxy.....	85-86		s	s			(73)
Carboxamide.....	234 (d)		es hot	es	i	i	(85)
<i>N,N</i> -Diethyl carboxamide....	80-81						(43)
Hydrazidine.....	276 (d)						(63)
Cyano.....	99		es				(83, 85)
Chloro.....	73		es	es	es		(111)

The heavy metal salts of the 5-monosubstituted tetrazoles are particularly explosive. Probably diazotetrazole represents the extreme in explosive proper-

TABLE 4—Continued

SUBSTITUENT OR COMPOUND	MELTING POINT* °C.	BOILING POINT °C.	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
Bromo.....	156; 147-148		s; i	es hot; ds	es	i cold; s hot	(73, 111)
Iodo.....	d 190		es hot	es hot	ds		(111)
Hydroxy.....	254 (d)		s	s	s		(39, 111, 112)
Methoxy.....	159 (d)		es hot	es	ds	i	(112)
Ethoxy.....	98		es	es	es		(112)
Mercapto.....	205 (d)		es	es	es	i	(39)
Methylmercapto...	151 (d)						(39)
Methyl sulfone....	120		es	es	es	es	(39)
Sulfonic acid.....							(39)
Amino.....	203 (d)		1.17 at 18°C.	ds	i		(44, 111, 136)
Aldol imine.....	170		s	ds hot	i		(118)
Diethylacetyl- amino.....	238 (d)		ds	es hot	ds		(127)
α-Ethylcrotonyl- amino.....	240 (d)		ds hot	es hot	s		(127)
α-Bromoisovaleryl- amino.....	205 (d)		es hot	es	s		(127)
N-Tetrazolyl-5- diethylmalonic acid monoamide.	188		s	es	s		(127)
Diethylmalonyl- bis(tetrazolyl- 5-amide).....	287		ds	ds hot	i		(127)
N-Methyl-N'- tetrazolylurea...	d 265			ds			(108)
N-Phenyl-N'- tetrazolylurea...	245 (d)		i	ds hot	i		(111)
5-Tetrazolyl- urethan.....	256 (d)		ds hot	ds hot	i		(111)
Guanylamino.....	Does not melt 300°C.		s	s hot	i		(111)
Benzoylamino.....	284		i	ds hot	i	i	(120)
Anilino.....	206		s hot	es hot	ds		(117, 120)
Phenylmethyl- amino.....	139		es hot	s	s		(120)
Phenylethyl- amino.....	170		es hot	s	s		(120)
Phenylbenzyl- amino.....	144		es hot	es	s		(120)
2,4-Dinitrophe- nylamino.....	174 (d)		ds hot	ds hot	i		(128)
Picrylamino.....	224		ds	ds	i		(128)
Phenylsulfonam- ido.....	132-134						(27)

TABLE 4—Continued

SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
<i>p</i> -Tolylsulfonamido.....	146-147						(27)
<i>p</i> -Nitrobenzenesulfonamido.....	185-186 (d)		0.008 at 37°C.				(97)
Hydrazino.....	199 (d)		ds cold	i	i	i	(137, 139, 140)
Dibromoformaldehyde 5-tetrazolyldiazone..	177 (d)		ds cold	es	ds	ds	(137)
Acetone 5-tetrazolyldiazone..	181.5		ds cold	es			(139)
Benzal 5-tetrazolyldiazone..	235		i	ds hot		i	(48, 140)
Acetophenone 5-tetrazolyldiazone.....	235		i	ds			(139)
5,5'-Hydrazotetrazole.....	Explodes without melting		i hot				(137)
1-(5-Tetrazolyl) semicarbazide...	211 (slow); 218 (rapid)		ds cold				(139)
1-(5-Tetrazolyl)-3-methyl-5-pyrazolone.....	215 (d)						(140)
Tetrazole-5-azoacetoacetic acid ethyl ester.....	140-141		s hot		ds	i	(19)
Tetrazole-5-azoacetoacetic acid ethyl ester phenylhydrazone...	192-193 (d)			ds hot	i	i	(19)
Tetrazole(5-azo-4)(1-phenyl-3-methyl-5-pyrazolone).....	201 (d)						(19)
Tetrazole(5-azo-1)naphthylamine (2).....	Explodes 184		ds	ds			(136, 140)
Tetrazole-5-azo-4- <i>N,N</i> -dimethylaniline...	Explodes 155		ds		ds		(136)
Azido.....	Explodes		es	ds		ds	(47, 50, 139)
1,3-Ditetrazolyl-5-triazene.....	Deflagrates						(46, 47)

TABLE 4—*Concluded*

SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
1-Tetrazolyl-3- <i>p</i> - nitrophenyl- triazene.....	169		i	s hot	ds		(111)
<i>p</i> -Sulfamylphe- nyldiazoamino- tetrazole.....	175						(134)
3-Phenyl-1-tetra- zolyl-5-tetra- zene-1.....	d 139						(47)
4-Tetrazolyl-5- tetrazene-1- carboxamide....	122		ds				(47)
4-Tetrazolyl-5- tetrazene- guanyl-1.....	d 142		ds				(47)
4-Benzal-3-gua- nyl-1-tetra- zolyl-5-tetra- zene-1.....	d 132						(47)
1,6-Ditetrazolyl- 5-hexazdiene....	Explodes 90						(47)

* d = decomposes.

† s = soluble; i = insoluble; es = easily soluble; ds = difficultly soluble. Solubility data, when given, are in grams of solute per 100 g. of solvent.

ties; aqueous solutions of it explode at 0°C. if more concentrated than about 2 per cent (136, 140).

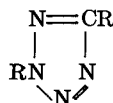
The impression should not be gained, however, that all tetrazoles are dangerous compounds. For the most part they are probably no more dangerous than the acyl azides, and may be handled safely with the precautions customarily bestowed upon organic compounds.

III. SYNTHESIS OF TETRAZOLES

A. TETRAZOLE

The synthesis of tetrazole from hydrogen cyanide and hydrogen azide has already been mentioned. This reaction, as described by Dimroth and Fester (30), requires heating a dilute alcoholic solution of hydrazoic acid with anhydrous hydrogen cyanide in a sealed tube for 2 or 3 days at 100°C. Tetrazole is said to be formed in 80 per cent yield. There is a patent claim (96) that dilute hydrogen cyanide and hydrazoic acid may be used, but whether this pertains to

TABLE 5
Physical properties of the tetrazoles
 2,5-Disubstituted tetrazoles



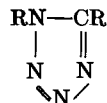
SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
2	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Methyl	Carboxylic acid	204-205 (d)†		s	s	ds	i	(85)
Methyl	Cyano		100-102/ 16 mm.	i				(85)
Ethyl	Carboxylic acid	124-125 (d)		es	ds	ds	i	(40, 83)
Ethyl	Carboxamide	125-126		ds	ds	ds	i	(83)
Ethyl	Cyano		127/45 mm.	i				(83)
Phenyl	Methyl	40	140/15 mm.			s		(32)
Phenyl	Phenyl	101.5-102		i				(31)
Phenyl	4-Hydroxyphenyl	190-191		ds cold	s	s warm	s	(145)
Phenyl	4-Aminophenyl	156		i	s	s warm	s warm	(145)
Phenyl	4-Nitrophenyl	199-200			ds	ds	s	(144)
Phenyl	Carboxylic acid	138		s	es	ds		(6, 29, 33, 145)
Phenyl	Carboxylic acid methyl ester	116		ds	es	ds		(6)
Phenyl	Carboxylic acid ethyl ester	73.5-74		ds	es	es		(6)
Phenyl	Carboxamide	167.5-168.5 (d)		ds cold	ds	ds		(6)
Phenyl	Thiocarboxamide	168-169 (d)			es			(9)
Phenyl	Carboxylic acid hydrazide	200 (d)		ds hot	s hot	i		(124)

Phenyl	Carboxylic acid azide	100 (d)	i	es	es		(124)
Phenyl	Carboxylic acid amidoxime	176-177.5 (d)	i	es warm			(8)
Phenyl	Carboxylic acid amidoxime acetate	204	i	i			(8)
Phenyl	Carboxylic acid amidoxime benzoate	205-206 (d)	i	i			(8)
Phenyl	Cyano	55.5-56	i	es	es	es	(5, 10, 146)
Phenyl	Amino	142	ds hot	es	es		(124)
Phenyl	Benzalamino	123 (d)	i	es	ds		(124)
Phenyl	Acetylamino	177 (d)	i	es	ds		(124)
Phenyl	Benzoylamino	164	i	es hot	s		(120)
Phenyl	Ethylcarbanyl	106	ds hot	es	es		(124)
Di(2-phenyl-5-tetrazolyl)urea		216 (d)	i	ds hot	i		(124)
5,5'-Hydrazodi(2-phenyltetrazole)		184 (d)	i	ds hot	ds		(124)
5,5'-Azodi(2-phenyltetrazole)		148	i	i	i		(124)
4-Bromophenyl	Phenyl	122		ds			(31)
2,4-Dibromophenyl	Phenyl	127		s hot			(21)
2-Aminophenyl	Phenyl	80	ds hot	s	s	s	(95)
4-Aminophenyl	Phenyl	164	i hot		i	ds cold	(95)
4-Aminophenyl	Carboxylic acid	196 (d)					(10)
2-Methyl-4-amino-phenyl	Phenyl	121	ds hot	s		es	(95)
2-Chloro-4-amino-phenyl	Phenyl	134	s hot	s	s	s	(95)
4-Nitrophenyl	Carboxylic acid	175 (d)					(10)

* ds = difficultly soluble; es = easily soluble; i = insoluble; s = soluble.

† d = decomposes.

TABLE 6
Physical properties of the tetrazoles
 1,5-Disubstituted tetrazoles



SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
1	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Methyl.....	Methyl	70-71						(55)
Methyl.....	Phenyl	102-103	144-146/0.3 mm.	es hot	es	ds		(16)
Methyl.....	<i>p</i> -Tolyl	113	160/0.4 mm.					(16)
Methyl.....	<i>p</i> -(Diethylaminomethyl)- phenyl	109	175/0.5 mm.					(16)
Methyl.....	Hydroxy	122		es	s	s	es hot	(120)
Methyl.....	Mercapto	126		s hot	es cold	es		(131)
Bis(1-methyltetrazolyl-5) sulfide.....		184		s hot	s hot	i		(120)
Bis(1-methyltetrazolyl-5) disulfide.....		113		es hot	ds hot	i		(120)
Methyl.....	Amino	222		es hot	s hot	i		(113)
1,1'-Dimethyl-5,5'-hydrazotetrazole.....		158 (d)†		es hot	es hot	i		(113)
1,1'-Dimethyl-5,5'-azotetrazole.....		182 (d)		es hot	s hot	i		(113)
Dimercaptomethane bis(1-methyl-5-tetrazolyl) ether.....		157		es hot	s hot	i		(121)
Diphenylenedimercaptomethane bis(1-methyl-5-tetrazolyl) ether.....		172		i	s hot	i		(126)
Allyl.....	Mercapto	69		es	es	es		(131)
Butyl.....	Phenyl		190-193/12 mm.					(16)

<i>tert</i> -Butyl.....	Phenyl	102						(106)
<i>n</i> -Hexyl.....	Amino	162		ds cold	es			(15)
<i>n</i> -Hexyl.....	Acetylamino	106		ds cold	es			(15)
Octyl.....	Phenyl		205/0.5 mm.					(16)
8-Carboxyoctyl.....	Amino	152						(15)
8-Carbethoxyoctyl.....	Amino	116						(15)
Bis(5-amino-1,1'-tetrazolyl)-1,8-octane.....		250						(15)
Benzyl.....	Methyl	50						(55)
Benzyl.....	Amino	187						(15)
Benzyl.....	Acetylamino	107						(15)
Phenyl.....	Methyl	97.5; 98-99		ds	es	es	es	(28, 56)
Phenyl.....	Phenyl	145; 146						(28, 55, 104, 105)
Phenyl.....	<i>p</i> -Tolyl	136						(16)
Phenyl.....	<i>p</i> -Carboxyphenyl	267						(16)
Phenyl.....	<i>o</i> -Nitrophenyl	168						(16)
Phenyl.....	<i>m</i> -Nitrophenyl	156						(16)
Phenyl.....	<i>p</i> -Nitrophenyl	177-178						(16, 105)
Phenyl.....	2,4-Dinitrophenyl	164						(16)
Phenyl.....	3,5-Dinitrophenyl	208						(16)
1,1'-Diphenyl-5,5'-ditetrazolyl.....		212			ds hot		s	(110, 115)
Phenyl.....	Chloro	124		s hot	es hot	ds	es hot	(113)
Phenyl.....	Bromo	151		ds hot	es hot	s		(113)
Phenyl.....	Iodo	d 140		i	es hot	s		(120)
Phenyl.....	Hydroxy	187; 188		ds hot	es			(28, 38)
Phenyl.....	Hydroxymethyl ether	74			es	es		(126)
Phenyl.....	Ethoxymethyl sulfide	56		i	s hot	i		(125)
Phenyl.....	Mercapto	150 (d); 152		s hot	es hot	es		(38, 75, 82, 110, 120, 131)
Phenyl.....	Methylmercapto	80						(38, 120)
1-Phenyl-5-tetrazolylhydroxymethyl sulfide.....		99		i cold	es	es		(125)
1-Phenyltetrazolyl-5-methyl sulfone.....		84		i	es hot	s		(120)

TABLE 6—Continued

SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
1	5			°C.	°C.	Water	Alcohol	
Bis(1,1'-diphenyl-5,5'-tetrazolyl) disulfide.....		145-148		i				(38)
Bis(1-phenyl-5-tetrazolyl)dimercaptomethane ether.....		136		i	s hot	s		(121)
Bis(1-phenyl-5-tetrazolyl)- α , α' -dimercaptoethane ether..		93		i	es hot	s		(121)
Bis(1-phenyl-5-tetrazolyl)- α , β -dimercaptoethane ether...		150		i	ds hot	i		(121)
Ethyl dimercapto acetate bis(1-phenyl-5-tetrazolyl) ether.		110		i	s hot	i		(121)
Dimercaptodiphenylenemethane bis(1-phenyl-5-tetra- zolyl) ether.....		159 (d)		i	s hot	i		(126)
Phenyl.....	Amino	158-159; 160		s hot	s	i		(15, 55, 82, 110)
Phenyl.....	Allylamino	108		i cold	es hot	s		(113)
Phenyl.....	Anilino	162-163			s warm	ds	s	(80, 110)
Phenyl.....	Acetylamino	211						(15)
Phenyl.....	Benzoylamino	157		i	es hot	ds		(120)
Phenyl.....	Hydrazino	125 (d)		es hot	es hot	i		(113)
Phenyl.....	Phenylhydrazino	190 (d)		i	es	ds	ds	(110, 113)
Phenyl.....	Benzalhydrazino	205		i	s hot	s		(113)
1,1'-Diphenyl-5,5'-hydrazotetrazole.....		190 (d)		i	es	i	i	(113)
1,1'-Diphenyl-5,5'-azotetrazole.....		228		i	i	i		(113)
1-Phenyltetrazolyl-5-azobenzene.....		168		i	es hot	ds	es hot	(113)
Phenyl.....	Azido	99		i	es hot	ds		(90, 113)
1-Phenyl-3(1-phenyltetrazolyl-5)triazene.....		d 130					s	(113)
<i>o</i> -Tolyl.....	Mercapto	129; 131		i				(79, 110)
Bis(1- <i>o</i> -tolyltetrazolyl-5) disulfide.....		102		i	s	ds		(125)
<i>o</i> -Tolyl.....	<i>o</i> -Toluidino	152						(79, 110)
<i>m</i> -Tolyl.....	<i>m</i> -Toluidino	147						(110)
<i>p</i> -Tolyl.....	Methyl	106						(28)
<i>p</i> -Tolyl.....	Phenyl	132						(16)
<i>p</i> -Tolyl.....	<i>p</i> -Tolyl	148						(16)
<i>p</i> -Tolyl.....	Mercapto	150-151; 156 (d)			s	s		(75, 125)

Bis(1- <i>p</i> -tolyltetrazolyl-5) disulfide.....		166-168 (d)			ds	ds	es	(75)
Bis(1- <i>p</i> -tolyltetrazolyl-5)dimercaptomethane ether.....		136	i		es hot	s		(121)
<i>p</i> -Tolyl.....	Amino	176; 190	ds hot		es hot	i		(15, 110)
<i>p</i> -Tolyl.....	<i>p</i> -Toluidino	207; 211			ds	ds	s hot	(79, 110)
<i>p</i> -Octadecylphenyl.....	Phenyl	80						(16)
<i>m</i> -Xylyl.....	Mercapto	141 (d)	i		es	es		(131)
Bis(1- <i>m</i> -xylyltetrazolyl-5) disulfide.....		114	i		es hot	ds		(125)
<i>m</i> -Xylyl.....	Amino	198	i		es hot	i	i	(113)
α -Naphthyl.....	Amino	194	es hot		es hot	i		(113)
1,1'-Di- α -naphthyl-5,5'-azotetrazole.....		180 (d)	i		i	i		(113)
β -Naphthyl.....	Mercapto	164	ds hot		es hot	s	es hot	(131)
β -Naphthyl.....	Amino	193	ds hot		s hot	i		(113)
1,1'-Di- β -naphthyl-5,5'-azotetrazole.....		Explodes at 204	i		i	i		(113)
<i>o</i> -Carboxyphenyl.....	Hydroxy	d 200						(79)
<i>p</i> -Carboxyphenyl.....	Hydroxy	d over 300						(75)
<i>p</i> -Carboxyphenyl.....	<i>p</i> -Carboxyphenyl	310						(16)
<i>m</i> -Chlorophenyl.....	Amino	173 (d)	i		es hot	s		(113)
<i>p</i> -Chlorophenyl.....	Amino	213 (d)	i		ds hot	i		(113)
1,1'-Di- <i>p</i> -chlorophenyl-5,5'-azotetrazole.....		228 (d)	i		ds hot	i		(113)
<i>o</i> -Methoxyphenyl.....	Amino	172	s hot		es hot	s		(113)
1,1'-Di- <i>o</i> -methoxyphenyl-5,5'-azotetrazole.....		190 (d)	i		s hot	i		(113)
<i>p</i> -Ethoxyphenyl.....	Chloro	99	s hot		es hot	s		(113)
<i>p</i> -Ethoxyphenyl.....	Amino	197	s hot		es hot	i		(113)
<i>p</i> -Ethoxyphenyl.....	<i>p</i> -Ethoxyphenylamino	197	i		ds	ds	ds	(113)
<i>p</i> -Ethoxyphenyl.....	Hydrazino	158	s hot		es hot	i		(113)
1,1'-Di- <i>p</i> -ethoxyphenyl-5,5'-hydrazotetrazole.....		167 (d)	i		es	i		(113)
1,1'-Di- <i>p</i> -ethoxyphenyl-5,5'-azotetrazole.....		223 (d)	i		ds hot	i		(113)
<i>p</i> -Ethoxyphenyl.....	Azido	72	s hot		es	es		(113)
<i>o</i> -Nitrophenyl.....	Phenyl	168						(16)
<i>o</i> -Nitrophenyl.....	<i>o</i> -Nitrophenyl	209						(16)
<i>m</i> -Nitrophenyl.....	Phenyl	133						(16)
<i>m</i> -Nitrophenyl.....	<i>m</i> -Nitrophenyl	244						(16)

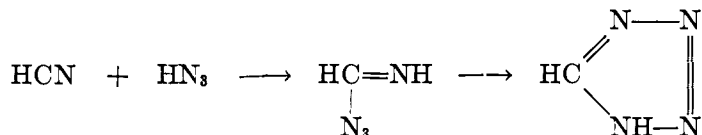
TABLE 6—Concluded

SUBSTITUENT OR COMPOUND		MELTING POINT °C.	BOILING POINT °C.	SOLUBILITY*				REFERENCES
1	5			Water	Alcohol	Ether	Benzene	
<i>m</i> -Nitrophenyl.....	<i>p</i> -Nitrophenyl	170						(16)
<i>p</i> -Nitrophenyl.....	Methyl	129						(28)
<i>p</i> -Nitrophenyl.....	Phenyl	149		i	ds			(28)
<i>p</i> -Nitrophenyl.....	<i>p</i> -Nitrophenyl	262						(16)
Hydroxy.....	Phenyl	121 (d); 124 (d)			es			(35, 147)
1,1'-Dihydroxy-5,5'-ditetrazolyl.....		Explodes	176	s hot	s			(147)
Benzoyloxy.....	Phenyl	127 (d)			ds hot			(35)
<i>p</i> -Toluenesulfonyloxy.....	Phenyl	91-92 (d)						(35)
β -Naphthalenesulfonyloxy	Phenyl	101 (d)			es hot			(35)
Amino.....	Phenyl	155		es hot	es	i		(119)
Amino.....	<i>p</i> -Tolyl	141		s hot	es	s		(123)
Amino.....	<i>o</i> -Chlorophenyl	173		ds hot	s hot	ds	ds	(123)
Amino.....	<i>p</i> -Nitrophenyl	154		s hot	es	s		(123)
Amino.....	Allylamino	94		es	es cold	ds		(114)
Amino.....	Anilino	210 (d)		ds hot		i	i	(114)
Phenyliminomethoxy- methylamino.....	Phenyl	157 (d)						(122)
Phenyliminoethoxy- methylamino.....	Phenyl	144 (d)						(122)
Isopropylideneamino.....	Anilino	136		i	es	i		(114)
Benzalamino.....	Phenyl	105		ds hot	s	s		(119, 122)
Benzalamino.....	Amino	210 (d)		i	s hot	i		(114)
Benzalamino.....	Allylamino	117		i	es hot	s		(114)
Benzalamino.....	Anilino	216		i	s hot	ds		(114)
Benzalamino.....	Benzalhydrazino	225 (d)		i	ds hot	i	ds	(114)
Anisalamino.....	Anisyl	147		i	ds hot	i		(122)
1,1'-Azo-5,5'-diphenyltetrazole.....		Explodes	141					(123)
1,1'-Azo-5,5'-di- <i>o</i> -chlorophenyltetrazole.....		Explodes	122					(123)

* ds = difficultly soluble; es = easily soluble; i = insoluble; s = soluble.

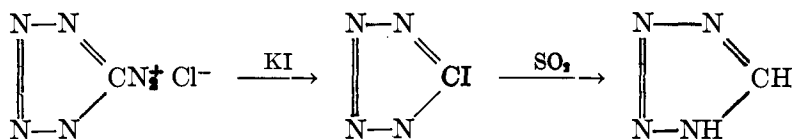
† d = decomposes.

aqueous solution is not mentioned, nor are experimental details given.¹ It would be of interest to determine the mechanism and limiting conditions for this reaction. Dimroth and Fester suggested that formimidazide is formed first and subsequently rearranges to tetrazole, but no experimental evidence to support this mechanism was presented. The similarity of this direct tetrazole

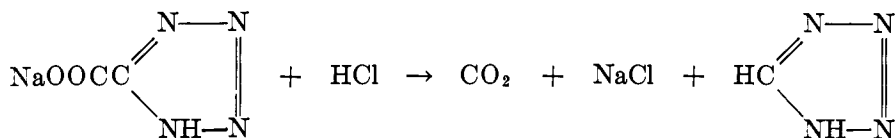


synthesis to the formation of 1,2,3-triazole from acetylene and hydrazoic acid (30) and to the synthesis of pyrazole from acetylene and diazomethane (88) is evident.

Tetrazole may be obtained from diazotized 5-aminotetrazole by several procedures. The sodium salt of diazotized 5-aminotetrazole may be treated with alcohol in the presence of carbon dioxide (139), or diazotetrazole may be reduced with stannous chloride and hydrochloric acid (139) or by hypophosphorous acid (111). An indirect method involves the formation of 5-iodotetrazole from diazotetrazole, and the subsequent reduction of this compound with sulfur dioxide or sodium ethylate (111).



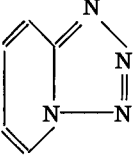
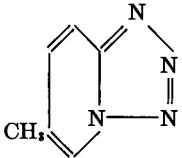
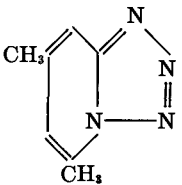
5-Tetrazolecarboxylic acid is not stable in the free state, and tetrazole can be obtained from its salts upon acidification (73, 84, 107).



The formation of tetrazole can be achieved by the oxidation of all classes of substituted tetrazoles. Thus, 5-mercaptotetrazole, when treated with nitric

¹ The following improved directions for the preparation of tetrazole are included by the courtesy of Dr. R. M. Herbst of E. Bilhuber, Inc., Orange, New Jersey: Anhydrous hydrogen cyanide (5.4 g.) and 40 cc. of a 13.4 per cent benzene solution of hydrazoic acid are heated in a sealed tube for 96 hr. at 110°C. ± 5°. On completion of the reaction, the supernatant benzene solution is decanted from the deposit of crystals. The crystals are dissolved in warm methanol and this solution added to the benzene mother liquor. After removal of the solvents under reduced pressure on a water bath, the residue is recrystallized from 150 cc. of ethyl acetate, the tetrazole separating as small needles, melting at 156–157°C., uncorr. Yield: 6.6 g. or 75 per cent.

TABLE 7
Physical properties of the tetrazoles
 Fused-ring 1,5-disubstituted tetrazoles

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
Pyridotetrazole		°C. 159	°C.	i	s	i		(16, 34)
6-Methylpyridotetrazole		152-153						(23)
5,7-Dimethylpyridotetrazole		128-129						(23)

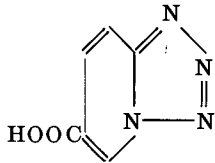
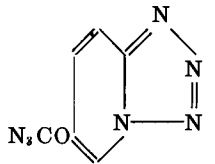
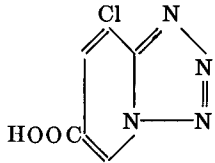
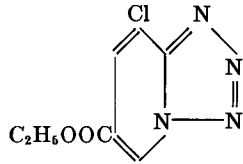
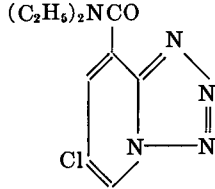
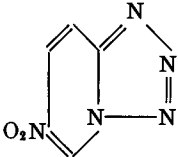
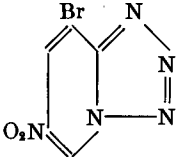
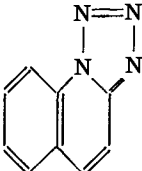
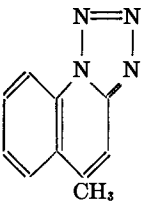
6-Carboxypyridotetrazole		Explodes over 338	s hot				(70)
6-Carboxylic acid azide pyridotetra- zole		103-104	ds hot	ds cold			(70)
8-Chloropyridotetrazole-6-carboxylic acid		195-196					(41)
8-Chloro-6-carbethoxypyridotetrazole		95-96					(41)
6-Chloropyridotetrazole-8- <i>N,N</i> - diethylcarboxamide		(C ₂ H ₅) ₂ NCO 113-115				s	(42)

TABLE 7—Continued

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
6-Nitropyridotetrazole		°C. 142-143 (d)	°C.					(17)
8-Bromo-6-nitropyridotetrazole		125						(17)
Tetrazolo[a]quinoline		157						(16, 69)
5-Methyltetrazolo[a]quinoline		207		ds hot	es			(68)

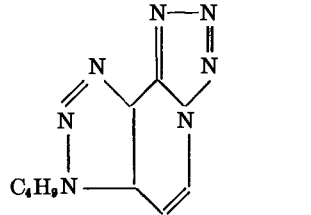
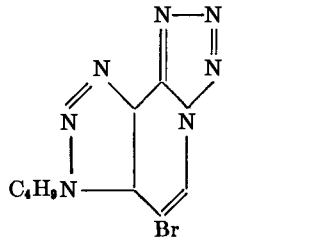
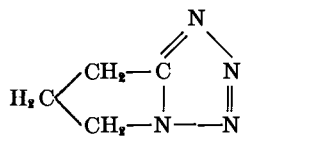
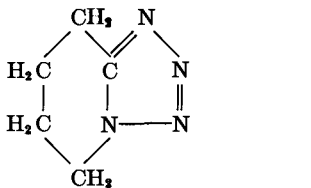
7-Butyltetrazolo[1,5- α]triazolo[c]-pyridine		157-158					(17)
7-Butyl-6-bromotetrazolo[1,5- α]triazolo[c]pyridine		114					(17)
6,7-Dihydro-5-pyrrolotetrazole (trimethylenetetrazole)		110					(22)
5,6,7,8-Tetrahydropyridotetrazole (tetramethylenetetrazole)		115-116					(23)

TABLE 7—Continued

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
6-Methyl-5,6,7,8-tetrahydropyridotetrazole		°C. 92-94	°C.					(23)
5,7-Dimethyl-5,6,7,8-tetrahydropyridotetrazole		95-97						(23)
1,3-Dioxotetramethylenetetrazole-2-carboxylic acid		d 195						(107)

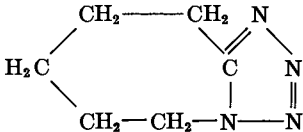
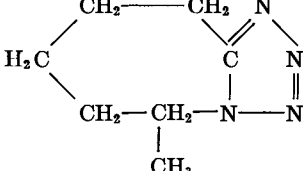
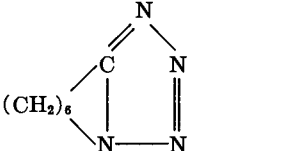
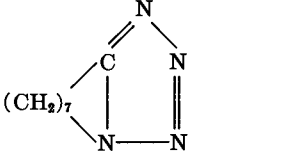
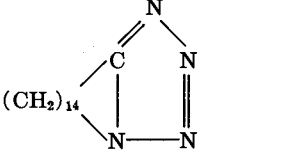
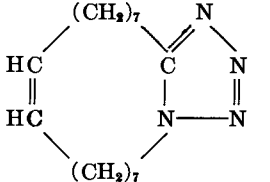
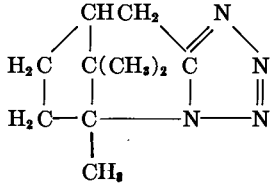
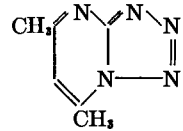
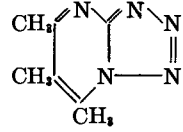
6,7,8,9-Tetrahydro-5-azepotetrazole (pentamethylenetetrazole, metra- zole)		59		s		(54)
5-Methyl-6,7,8,9-tetrahydro-5-azepo- tetrazole		32	185/15 mm.			(14)
5,6,7,8,9,10-Hexahydrotetrazolo- azocine		66-68	135-140/ 0.1 mm.			(98)
6,7,8,9,10,11-Hexahydro-5-tetrazolo- azonine			145-146/ 0.1 mm.			(98)
"Cyclotetradecamethylenetetrazole"		97-98	180-185/ 0.1 mm.	i		(98)

TABLE 7—Continued

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				°C.	°C.	Water	Alcohol	
"Civetonetetrazole"		90-91	225-235/ 0.4 mm.					(99)
5,10,10-Trimethyl-6,7,8,9-tetrahydro-5,8-methano-5-azepotetrazole, "camphortetrazole"		242-243						(60, 103)
" α and β -Thujonetetrazoles"		86						(60, 103)
" β -Thujonetetrazole"		93-95						(103)
5,7-Dimethyltetrazolo[<i>a</i>]pyrimidine		151-152			es hot	i	es	(19)
5,6,7-Trimethyltetrazolo[<i>a</i>]pyrimidine		123-123.5		s hot		i	es	(19)

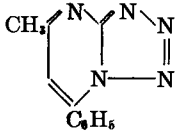
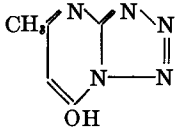
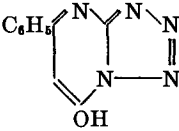
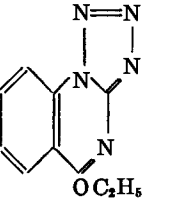
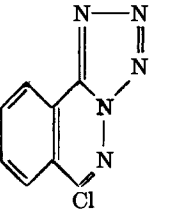
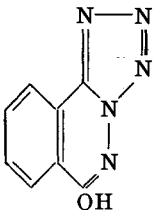
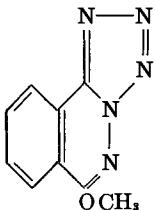
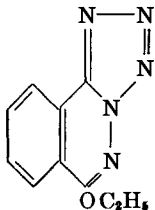
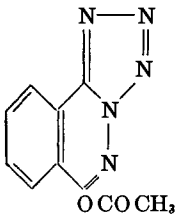
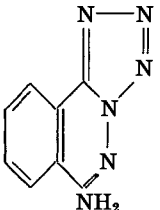
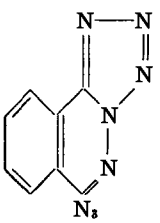
5-Phenyl-7-methyltetrazolo[a]pyrimidine		185			ds	ds	(19)
5-Hydroxy-7-methyltetrazolo[a]pyrimidine		246-247	es hot	es	ds	ds	(19)
5-Hydroxy-7-phenyltetrazolo[a]pyrimidine		261 (d)					(19)
Tetrazolo[a]-5-ethoxyquinazoline		165	i	s hot	s		(116)
Tetrazolo[a]-6-chlorophthalazine		195 (d)	i	ds hot	ds		(130)

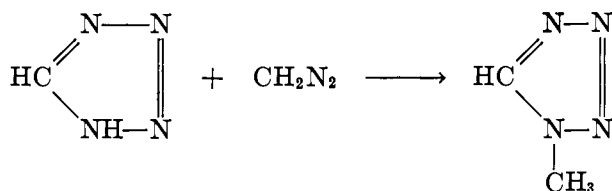
TABLE 7—Concluded

COMPOUND	FORMULA	MELTING POINT °C.	BOILING POINT °C.	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
Tetrazolo[<i>a</i>]-6-hydroxyphthalazine		258 (d)		ds hot	ds hot	i		(130)
Tetrazolo[<i>a</i>]-6-methoxyphthalazine		211		i	s hot	ds		(130)
Tetrazolo[<i>a</i>]-6-ethoxyphthalazine		187		i	es hot	ds		(130)

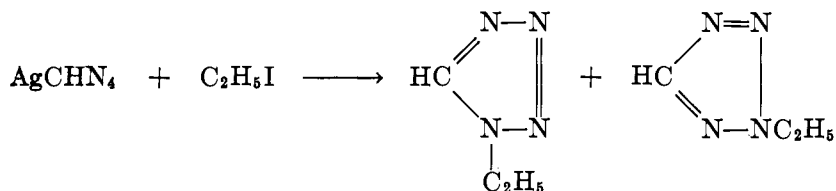
Tetrazolo[a]-6-acetoxypthalazine		165					(130)
Tetrazolo[a]-6-aminophthalazine		305	i	s hot	i	i	(130)
Tetrazolo[a]-6-azidophthalazine		152	i	es	ds		(130)

* ds =difficultly soluble; es = easily soluble; i = insoluble; s = soluble.

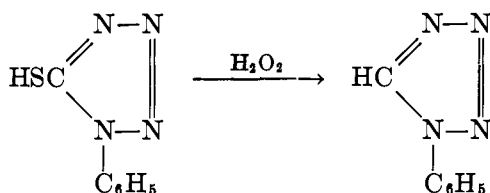
† d = decomposes.



A mixture of 1- and 2-ethyltetrazoles is produced by the action of ethyl iodide on silver tetrazole in benzene (85).



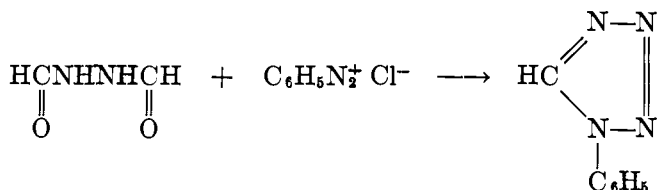
Stollé prepared 1-methyl- and 1-phenyl-tetrazoles by the action of hydrogen peroxide on the appropriate 5-mercaptotetrazole in the presence of ammonium hydroxide (120).



This reaction recalls the formation of tetrazole from 5-mercaptotetrazole by oxidation with nitric acid.

Oliveri-Mandalà observed that heating 1-phenyl-5-anilinetetrazole above its melting point (162°C.) gave rise to some 1-phenyltetrazole (80).

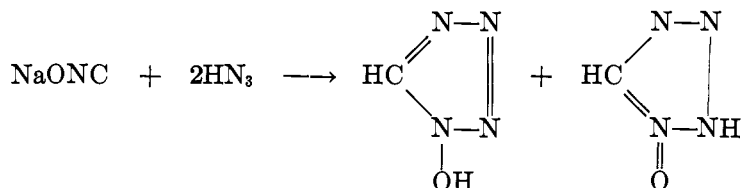
Certain 1-aryltetrazoles may be prepared by an interesting reaction, which involves the interaction of diazonium salts and *sym*-diformylhydrazine in the



presence of dilute sodium hydroxide. The loss of a formyl group and of a molecule of water is involved. (Further applications of this synthesis are discussed in the section on 1,5-disubstituted tetrazoles.) Dimroth and De Montmollin synthesized the phenyl, *p*-tolyl, and *p*-nitrophenyl derivatives in this way (28).

The interaction of aqueous sodium fulminate and hydrazoic acid leads to the

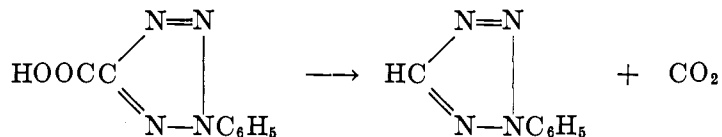
formation of two compounds; one of these was assigned the structure of 1-hydroxytetrazole and the other 1-tetrazole oxide (86, 87). Justification for



their structures appears to be meager, being based on the behavior of the methylated derivatives obtained by interaction with diazomethane. The methyl derivative of the so-called 1-hydroxytetrazole gave results indicating the presence of a methoxyl group by the Zeisel technique, while treatment of the methyl derivative of the isomer with dilute sulfuric acid gave methylamine.

2. 2-Substituted derivatives

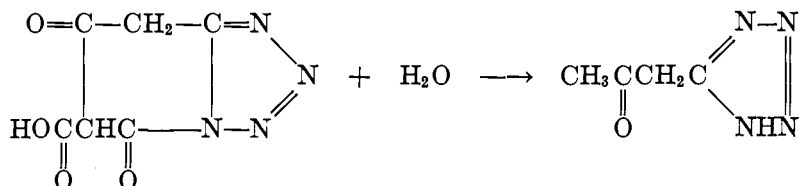
Decarboxylation of 5-carboxy-2-substituted tetrazoles has been used to obtain each of the three known 2-monosubstituted tetrazoles: namely, the methyl (85), ethyl (83), and phenyl (6, 145) derivatives.



As mentioned previously, treatment of the silver salt of tetrazole with ethyl iodide yields a mixture of 1- and 2-ethyltetrazoles.

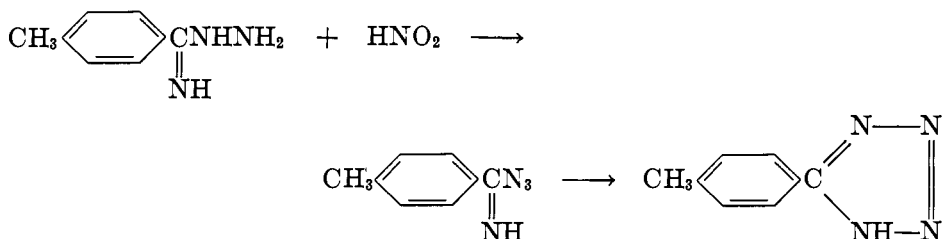
3. 5-Substituted derivatives

No 5-alkyltetrazoles have been reported, although there appears to be no reason why their synthesis should present undue difficulty. The preparation of 5-acetyltetrazole has been effected by heating 1,3-dioxotetramethylene-tetrazole-2-carboxylic acid with water, 2 moles of carbon dioxide being eliminated (107).

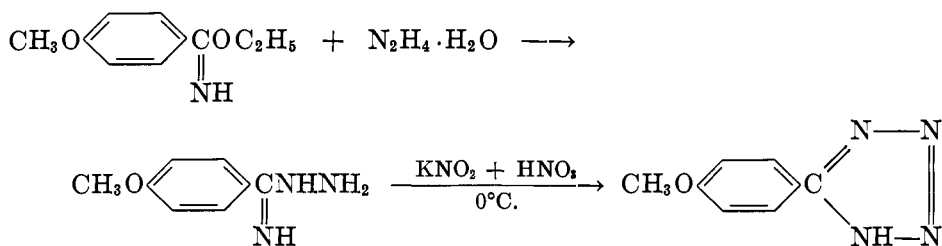


Numerous 5-aryltetrazoles have been made, the most general procedure involving the diazotization of hydrazidines. This synthesis is also useful in preparing 5-substituted tetrazoles other than aryl derivatives, and these applications will be indicated in the appropriate place. It is generally assumed that the mechanism of this synthesis involves the preliminary formation of an imide azide which subsequently rearranges to a tetrazole, either with or without the

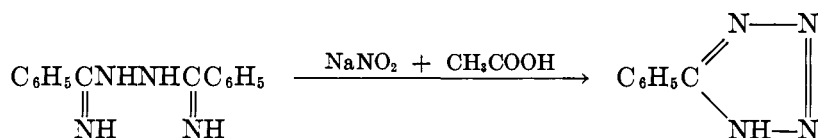
aid of a catalyst. In most cases it is impossible to isolate the intermediate imide azide. Aryltetrazoles substituted in the 5-position which have been



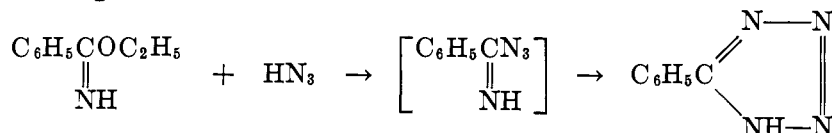
obtained by this process include phenyl (91), *p*-tolyl (92, 93), *p*-cumenyl (25), *p*-anisyl (64), *p*-nitrophenyl, and β -naphthyl (91). The diazotization of furoic acid hydrazidine similarly leads to 5- α -furyltetrazole (94). In practice, it is not always necessary to isolate the hydrazidine; these are frequently made by the interaction of imino ethers and hydrazine, and the acidified solution so obtained may be treated with a metal nitrite. This procedure was followed in the synthesis of 5-anisyltetrazole:



Another reaction leading to 5-aryltetrazoles consists in heating diaroyl imino hydrazides with sodium nitrite in acetic acid solution (91, 93). This method has been used to make 5-phenyl- and 5-*p*-tolyl-tetrazoles.

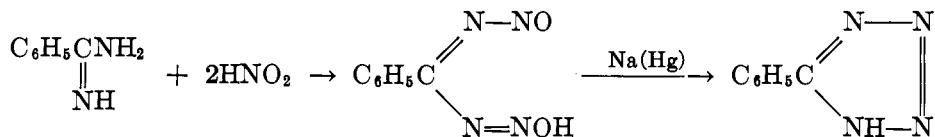


The interaction of benzimido ethyl ester and hydrazoic acid is claimed in a patent (53) to lead to 5-phenyltetrazole. Presumably this reaction also proceeds through the imide azide.

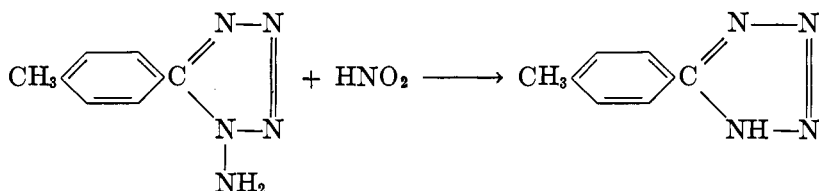


An interesting synthesis discovered by Lossen involves treating an amidine with nitrous acid to form a so-called dioxytetrazotic acid; the potassium salt of this substance is reduced in aqueous solution to a tetrazole by sodium amalgam.

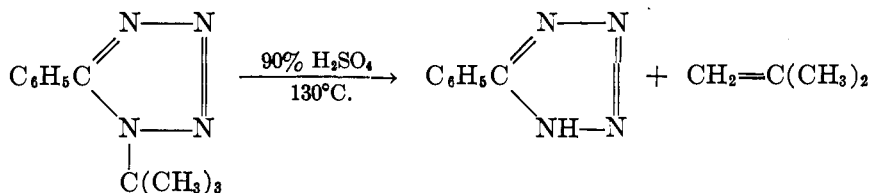
The yields obtained by this method are poor. The 5-phenyl- (66, 67) and 5-*p*-tolyl- (65) tetrazoles have been synthesized in this manner. The structure of the dioxytetrazotic acid is in doubt, but may be that indicated in the equation. This tetrazole synthesis is of particular interest, since it is the only one known which does not start with a derivative of hydrazine or hydrazoic acid.



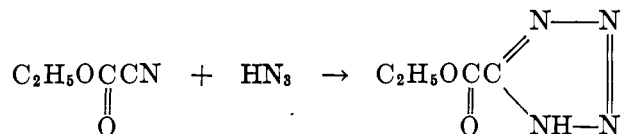
The reaction of nitrous acid and 5-aryl-1-aminotetrazoles effects replacement of the amino group with hydrogen (123). This method has been used in the preparation of 5-*p*-tolyl- and 5-*o*-chlorophenyl-tetrazoles.



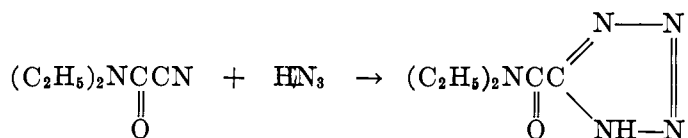
Another method of converting certain 1,5-disubstituted tetrazoles into 5-monosubstituted compounds is due to Schroeter (106), who treated 1-*tert*-butyl-5-phenyltetrazole with sulfuric acid, thereby causing elimination of 2-methylpropene.



Free 5-tetrazolecarboxylic acid does not exist, but is known in the form of its salts, ester, amides, and nitrile. The salts are obtained by alkaline hydrolysis of the nitrile or in the oxidative degradation of 5-substituted tetrazoles. In the latter case the oxidation is sometimes effected in neutral solution in the presence of silver nitrate, the insoluble silver salt of 5-tetrazolecarboxylic acid being formed (40, 107). The ethyl ester of 5-tetrazolecarboxylic acid is prepared by the combination of ethyl cyanofornate and hydrazoic acid (73):

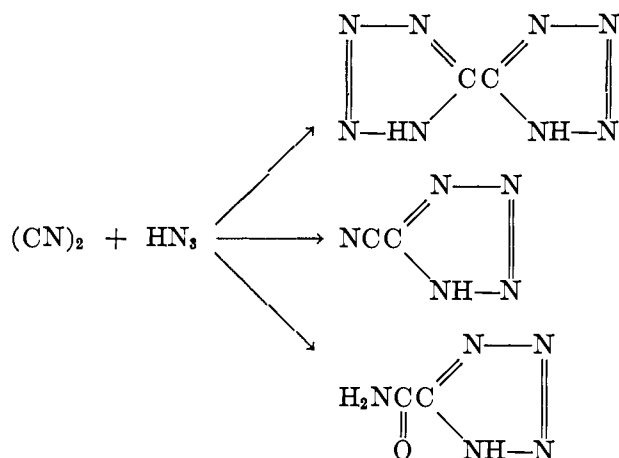


In like manner the nitrile of diethyloxamic acid and hydrazoic acid produce *N,N*-diethyl-5-tetrazolecarboxamide when heated in a sealed tube at 115–120°C. for 25–30 hr. (43).



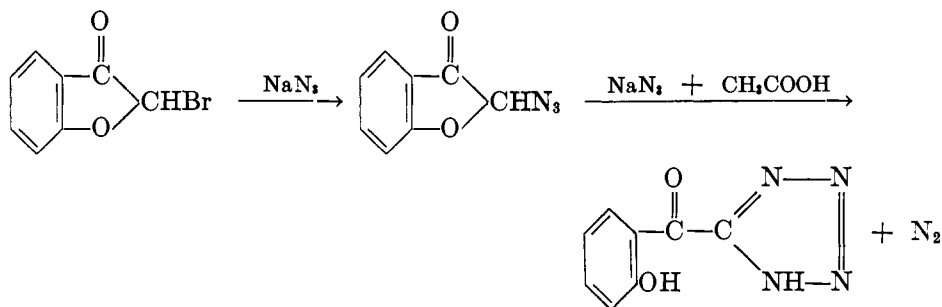
In general, the combination of hydrazoic acid with cyanides linked to a sufficiently negative group leads to 5-substituted tetrazoles. This is a reaction of considerable utility, as will be seen.

The interaction of cyanogen and concentrated aqueous hydrazoic acid in the cold results in three different compounds, depending upon the experimental conditions. Ditetrazolyl (84), 5-cyanotetrazole (62, 63, 84, 87), and 5-tetrazolecarboxamide (84) may be formed.



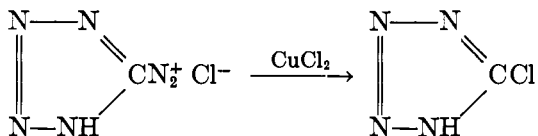
Ditetrazolyl has also been prepared from 5-tetrazolehydrazidine by diazotization (63).

Some 5-(*o*-hydroxybenzoyl)tetrazoles have been prepared from 2-azido-3-coumaranones by the action of excess sodium azide in glacial acetic acid. The azides are prepared from the bromo compounds and need not be isolated prior to conversion to the tetrazoles. It is to be noted that the formation of the tetrazole ring involves the introduction of an NH group, derived from excess hydrazoic acid, accompanied by the loss of a molecule of nitrogen. Besides the 2'-hydroxybenzoyl derivative, the 5'-bromo-2'-hydroxy-4'-methoxybenzoyl-

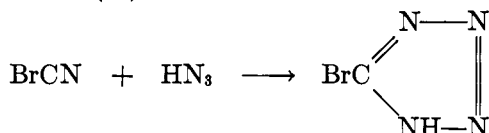


and 5'-chloro-2'-hydroxybenzoyl-tetrazoles have been synthesized by this method (40).

Stollé prepared 5-chloro-, 5-bromo-, and 5-iodo-tetrazoles from diazotized 5-aminotetrazole (111). In the case of the chloro and bromo compounds the use of cupric salts was required, while potassium iodide sufficed for the preparation of 5-iodotetrazole. These procedures in the tetrazole series thus parallel those employed in the case of diazotized aniline.

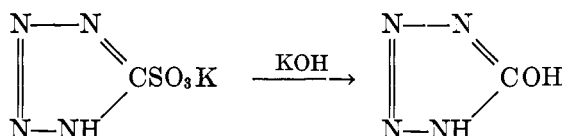


The preparation of 5-bromotetrazole has also been effected by Oliveri-Mandalà by the interaction of cyanogen bromide and hydrazoic acid in ether for several days at 50-60°C. (73).

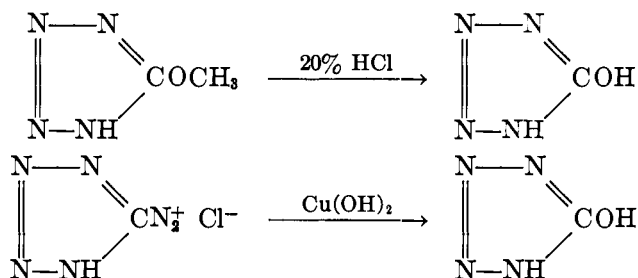


An unexplained discrepancy exists between the melting point of the 5-bromotetrazole obtained by Stollé (156°C.) and that obtained by Oliveri-Mandalà (147-148°C.).

Just as alkaline fusion of benzene- and naphthalene-sulfonic acids leads to phenols and naphthols, similarly fusion of the potassium salt of 5-tetrazole-sulfonic acid with potassium hydroxide results in a small yield of 5-hydroxytetrazole (39). This compound may also be obtained by the hydrolysis of

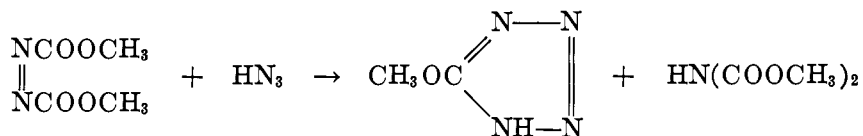


5-methoxytetrazole with 20 per cent hydrochloric acid (112), or by treatment of diazotized 5-aminotetrazole with cupric hydroxide at 60°C. (111). Although

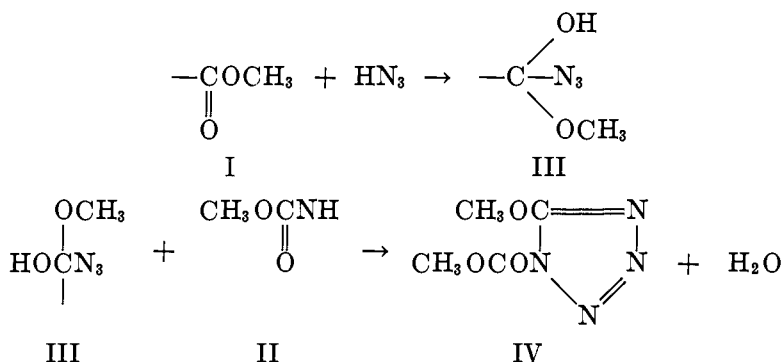


hydrolysis of 5-chloro- or 5-bromo-tetrazole is not effected by 60 per cent sodium hydroxide, 5-iodotetrazole is converted by this reagent to 5-hydroxytetrazole (111).

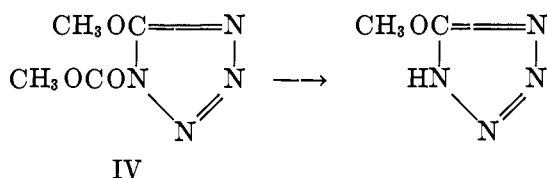
The only method by which 5-methoxytetrazole has been prepared involves a reaction discovered by Stollé and Adam (112), in which azodicarboxylic acid dimethyl ester and excess hydrazoic acid react in ether solution. Besides methoxytetrazole some iminodicarboxylic acid dimethyl ester is obtained. The mechanism suggested by Stollé for this curious reaction involves splitting



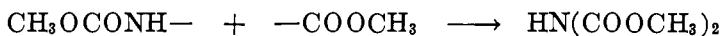
the azodicarboxylic ester under the influence of hydrazoic acid with evolution of 2 moles of nitrogen to form two residues, $-\text{COOCH}_3$ (I) and $-\text{NHCOOCH}_3$ (II). It is assumed that I combines with HN_3 to form III, which in turn unites with II to form 1-carbomethoxy-5-methoxytetrazole (IV).



Hydrolysis and decarboxylation of IV produces 5-methoxytetrazole.

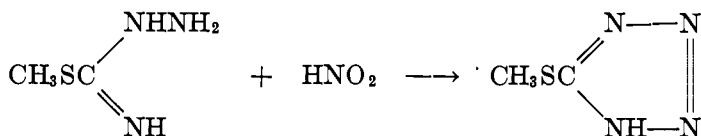


The iminodicarboxylic acid dimethyl ester arises according to this hypothesis from the combination of I and II. In the absence of more adequate proof, this mechanism must be regarded as highly speculative. Azodicarboxylic

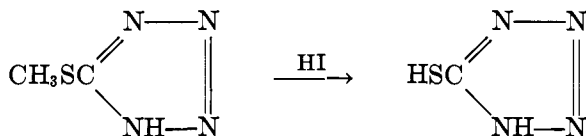


acid diethyl ester on treatment with hydrazoic acid yields 5-ethoxytetrazole in analogous fashion.

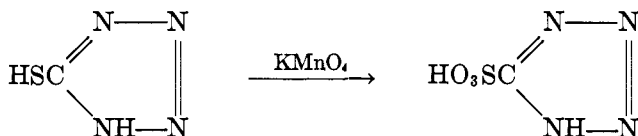
The 5-methylmercapto derivative of tetrazole was prepared by Freund and Paradies (39) from *S*-methylthiosemicarbazide by the diazotization method.



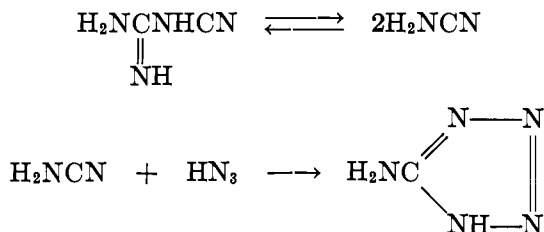
Hydrolysis of this compound with concentrated hydriodic acid in glacial acetic acid produces 5-mercaptotetrazole (39).



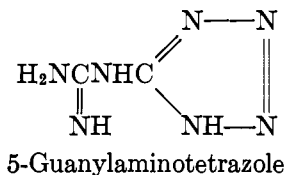
By oxidizing 5-mercaptotetrazole with 2.5 per cent potassium permanganate 5-tetrazolesulfonic acid is formed (39).



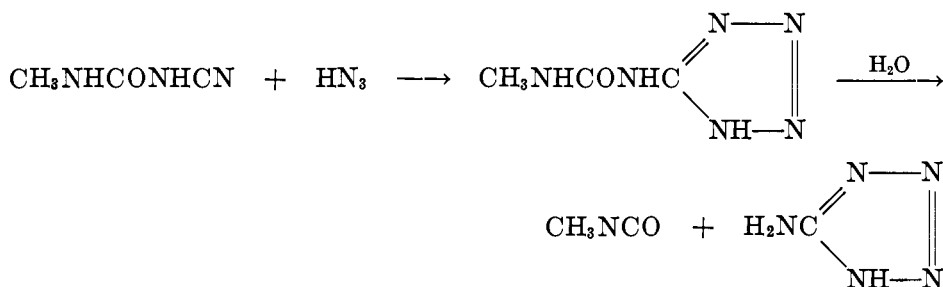
By far the most important 5-monosubstituted tetrazole is 5-aminotetrazole, since it may be used to prepare a wide variety of tetrazoles. It may be obtained by the same type of methods used in the preparation of other 5-monosubstituted derivatives. Cyanamide (44) or dicyandiamide (111, 129) may be treated with hydrazoic acid to form this compound. It is highly probable that when dicyandiamide is used, the species actually reacting is cyanamide, derived by depolymerization. This contention is supported by the fact that 5-guanyl-



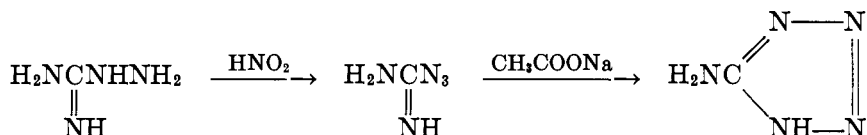
aminotetrazole, which would be formed if dicyandiamide united directly with hydrazoic acid, is stable under the conditions obtaining in this synthesis of 5-aminotetrazole (111).



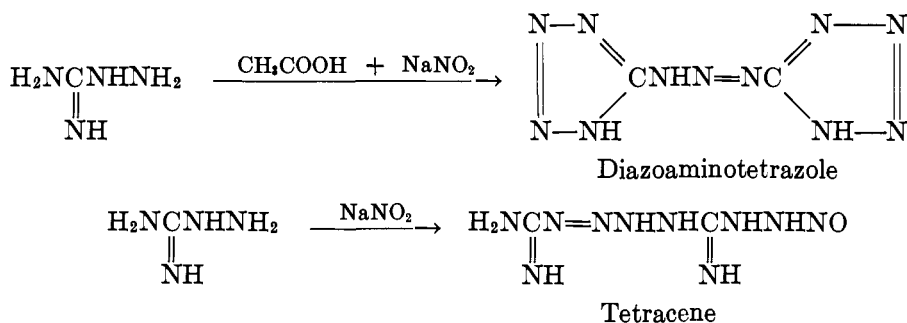
Interaction of *N*-methyl-*N'*-cyanourea with hydrazoic acid leads to *N*-methyl-*N'*-tetrazolyurea, which dissolves in hot water with decomposition to yield 5-aminotetrazole (108).



The diazotization method is applicable to the preparation of 5-aminotetrazole, and indeed was the method used by Thiele in the first synthesis of this compound. The starting material is aminoguanidine (44, 136, 138). In this case the intermediate imide azide, guanyl azide, is sufficiently stable to be isolated, and the rearrangement to 5-aminotetrazole is effected by heating with sodium acetate or carbonate. Dilute acids or merely heating with water will also effect the rearrangement. This diazotization, leading to guanyl azide, is



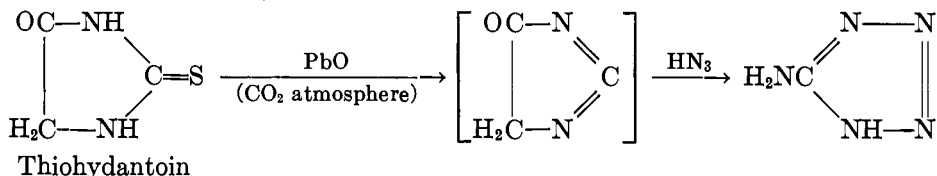
effected by using nitric acid and sodium nitrite; aminoguanidine treated with acetic acid and sodium nitrite yields 1,3-ditetrazolyltriazene (diazoaminotetrazole), while the action of sodium nitrite alone yields 1-guanyl-4-nitrosoaminoguanilyltetrazene, better known as tetracene.



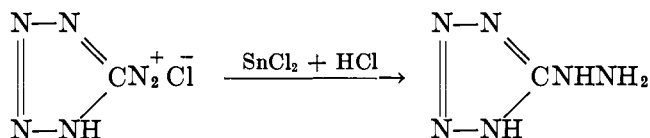
It is of interest that both of these compounds, as well as 1-guanyl-4-tetrazolyltriazene, may be converted to 5-aminotetrazole by treatment with acids (46, 47, 49). An excellent discussion of these transformations of aminoguanidine and related compounds is to be found in the article by Lieber and Smith (61).

In a different category is the preparation of 5-aminotetrazole from thiohydantoin by treatment with sodium azide and lead oxide in an atmosphere of carbon dioxide (127). The mechanism of this reaction is obscure, but, by

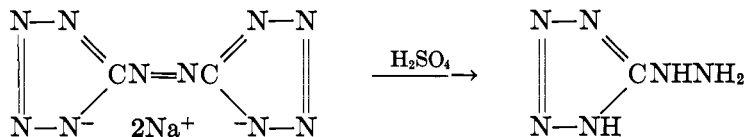
analogy with a preparative method to be discussed under 1,5-disubstituted tetrazoles, it presumably involves the formation of a cyclic carbodiimide, followed by addition of hydrazoic acid and rearrangement.



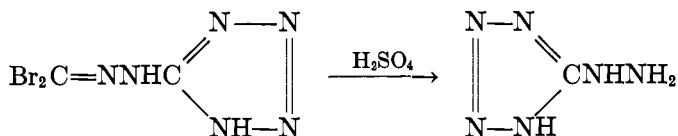
Another 5-substituted tetrazole of importance is 5-hydrazinotetrazole, which is best obtained by reduction of tetrazolediazonium salts with stannous chloride and hydrochloric acid (139, 140). Similar treatment of tetracene (48) and 1,3-ditetrazolyltriazene (46) also leads to 5-hydrazinotetrazole. In the case of



tetracene it is to be noted that ring closure occurs here, just as in the formation of 5-aminotetrazole from this material, under the influence of acid. Treatment of the sodium salt of 5-azotetrazole with acid results in the formation of



5-hydrazinotetrazole, as is also the case with dibromoformaldehyde 5-tetrazoly-hydrazone (137). It should be mentioned that 5-hydrazinotetrazole is usually

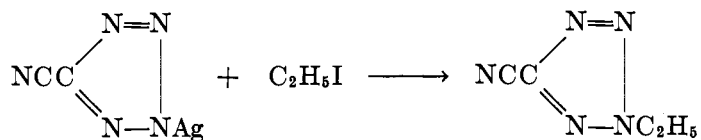


isolated as the insoluble benzal derivative, owing to its tendency to oxidize in air.

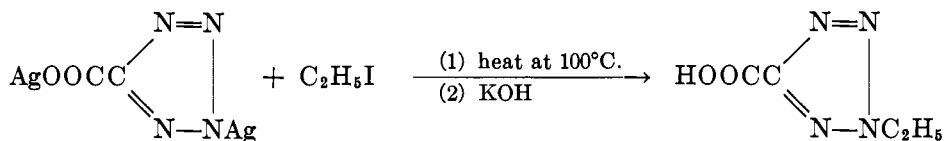
C. DISUBSTITUTED TETRAZOLES

1. 2,5-Disubstituted derivatives

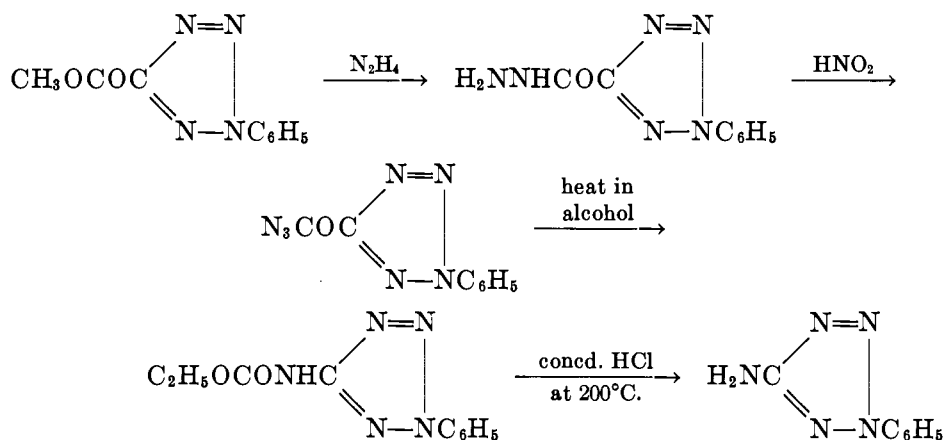
A few 2,5-disubstituted tetrazoles may be prepared from 5-monosubstituted compounds. Thus 2-methyl- or 2-ethyl-5-cyanotetrazole results from the interaction of silver cyanotetrazole with the appropriate alkyl iodide (83, 85).



Hydrolysis of the cyanide group leads to the carboxylic acids. Fries and Saftien also prepared 2-ethyl-5-tetrazolecarboxylic acid by heating silver 5-tetrazolecarboxylate and ethyl iodide at 100°C., followed by saponification with potassium hydroxide (40).

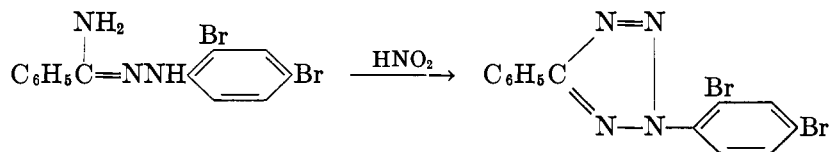


Most 2,5-disubstituted derivatives are obtained by starting with acyclic compounds. The synthesis by Bladin of 2-phenyl-5-cyanotetrazole from dicyanophenylhydrazine and nitrous acid has already been mentioned. It has not been prepared by any other method. Using this compound Bladin prepared a variety of acid derivatives by the usual methods of organic chemistry, no new syntheses of the tetrazole ring being involved. More recently Stollé and Orth (124), starting with the methyl ester of 2-phenyl-5-tetrazolecarboxylic acid prepared according to Bladin, obtained 2-phenyl-5-aminotetrazole by proceeding through the hydrazide, azide, and urethan.

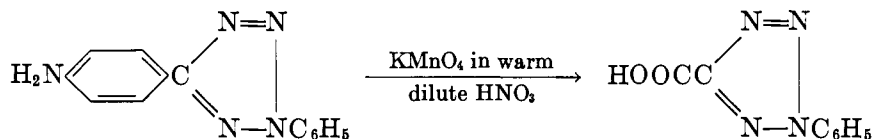


From 2-phenyl-5-aminotetrazole, or compounds intermediate in its synthesis, the corresponding urea, azo, hydrazo, acetyl, benzoyl, and benzal derivatives were prepared.

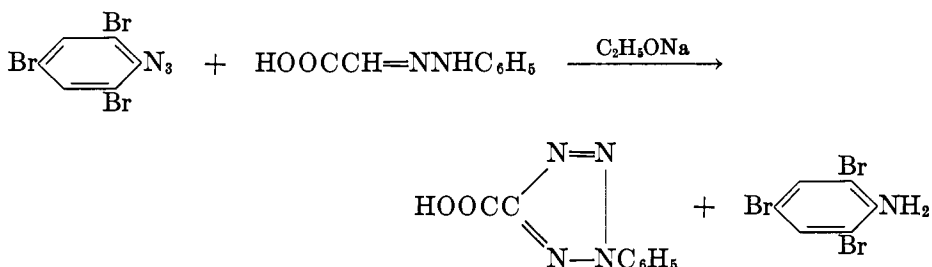
A reaction closely related to that of Bladin was used by Chattaway and Parkes (21) in the preparation of 2-(2',4'-dibromophenyl)-5-phenyltetrazole from ω -aminobenzaldehyde 2,4-dibromophenylhydrazone and nitrous acid.



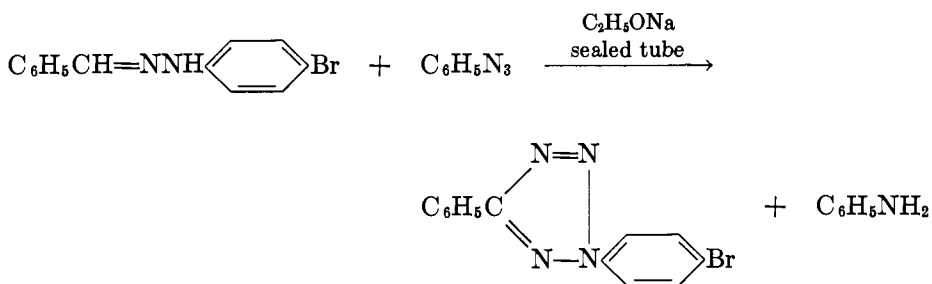
The preparation of 2-phenyl-5-tetrazolecarboxylic acid has been effected by methods other than the hydrolysis of the nitrile used by Bladin (6). Wedekind obtained it by oxidation of 2-phenyl-5-*p*-aminophenyltetrazole (145).



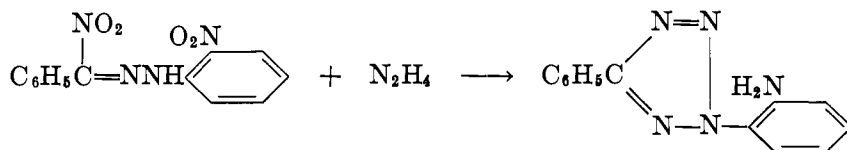
Another synthesis of this compound involves the interaction of 2,4,6-tribromoazidobenzene with the phenylhydrazone of glyoxalic acid in sodium ethylate solution (32), tribromoaniline being formed simultaneously.



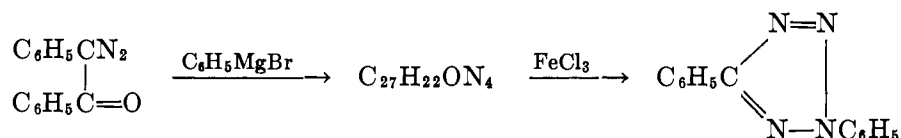
This type of reaction has been extended, and other 2,5-disubstituted tetrazoles may be prepared from hydrazones by means of several reagents. Acetaldehyde phenylhydrazone and 2,4,6-tribromoazidobenzene yield 2-phenyl-5-methyltetrazole. Phenyl azide, under the more vigorous conditions of a sealed-tube reaction, is used to prepare 2,5-diphenyltetrazole, 2-*p*-bromophenyl-5-phenyltetrazole (31), and 2-(2',4'-dibromophenyl)-5-phenyltetrazole (21) in this type reaction. The phenyl group of the phenyl azide reappears in the form of aniline.



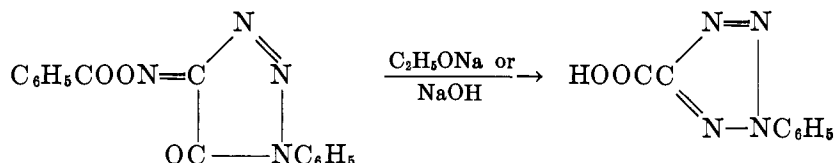
By means of the reaction of hydrazine with the *o*-nitrophenylhydrazone of phenylnitroformaldehyde, 2-*o*-aminophenyl-5-phenyltetrazole has been prepared (95).



bromide, an intermediate product of unknown constitution is formed, from which the tetrazole is obtained by oxidation with ferric chloride (36).

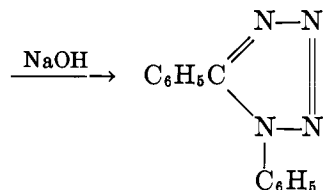
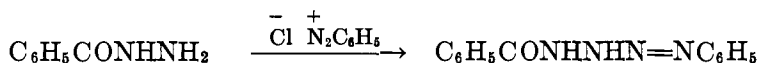


The conversion of a triazole derivative into a tetrazole has been observed in one instance. Rearrangement of the benzoyl or *m*-nitrobenzoyl derivative of 1-phenyl-5-keto-4-isonitroso-1,2,3-triazoline in alkaline solution at -10°C . gives rise to 2-phenyl-5-tetrazolecarboxylic acid (29, 33).

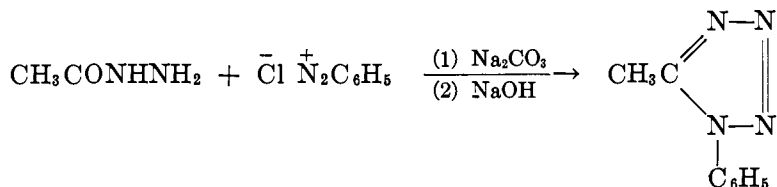


2. Simple 1,5-disubstituted derivatives

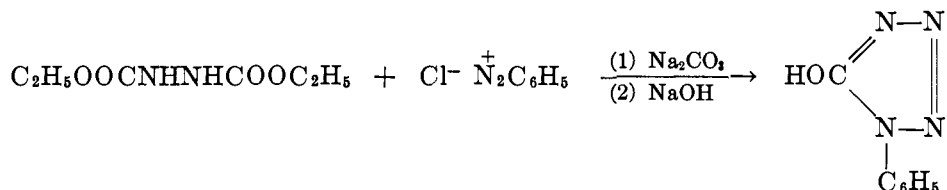
The cyclization of 1-aryl-4-acyltetrazenes to 1,5-disubstituted tetrazoles may be accomplished by use of dilute alkali. Such tetrazenes are prepared by coupling diazo compounds with acyl hydrazides. Thus 1,5-diphenyltetrazole is obtained from benzohydrazide and benzenediazonium chloride by the sequence (28):



In practice it is not necessary to isolate the intermediate tetrazene; in the case of 1-phenyl-5-methyltetrazole, sodium hydroxide is added to the reaction mixture after coupling to cyclize the intermediate. Other compounds obtained by this technique include 1-*p*-tolyl-5-methyl-, 1-*p*-nitrophenyl-5-methyl-,

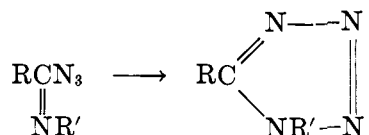


1-*p*-nitrophenyl-5-phenyl-, and 1-(phenyl-*p*-sulfonic acid)-5-methyltetrazoles. In some cases a symmetrical diacylated hydrazide is used in place of the mono-acyl hydrazide, the second acyl group being eliminated during the reaction. An interesting application of this modification involves the use of diethyl hydrazinedicarboxylate and benzenediazonium chloride to prepare 1-phenyl-5-hydroxy-tetrazole (28). This reaction sequence is an extension of the synthesis of

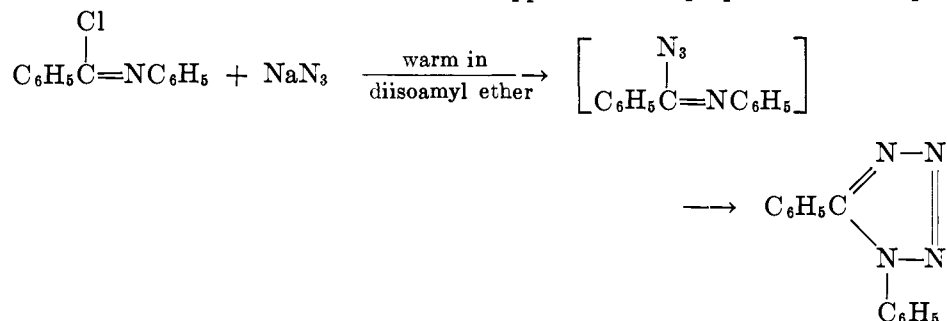


1-monosubstituted tetrazoles from diazonium compounds and symmetrical diformylhydrazine which was mentioned previously.

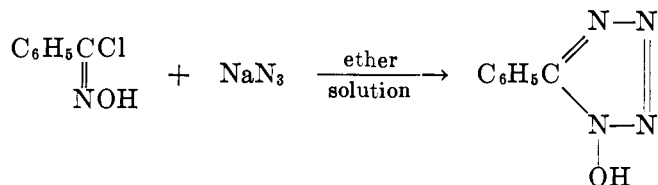
The essential step in a large number of syntheses of 1,5-disubstituted tetrazoles involves the cyclization of a substituted imide azide.



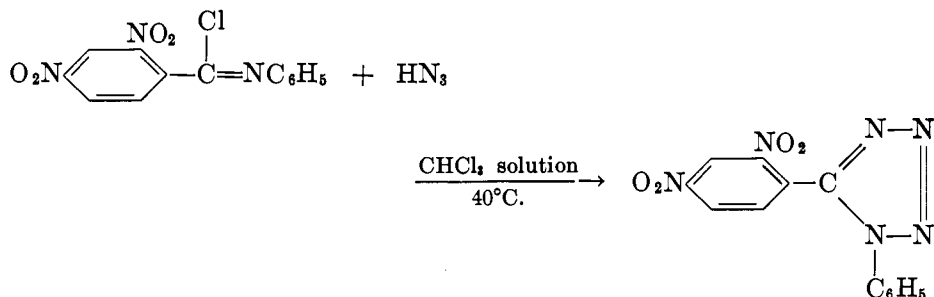
As in the case of the analogous synthesis of 5-monosubstituted tetrazoles, it is unnecessary and also frequently impossible to isolate the intermediate imide azide. The most direct method involving this type reaction starts with an imide chloride. The reaction was first applied to the preparation of simple



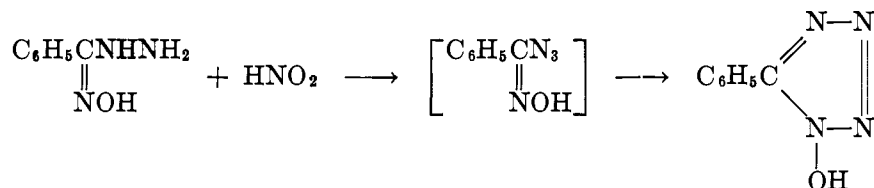
diaryl or alkyl-aryl 1,5-disubstituted tetrazoles by Schroeter (104), but was originated by Forster (35) in his synthesis of 1-hydroxy-5-phenyltetrazole from benzohydroxamic acid chloride and sodium azide.



Quite recently this method has been used by von Braun and Rudolph (16) to prepare a long series of 1,5-diaryl- or alkylaryl-tetrazoles. These investigators found that many imide chlorides which do not react with sodium azide yield tetrazole derivatives if free hydrazoic acid is used in chloroform or benzene solution. Thus, nitroaromatic derivatives, which are stable to sodium azide, may be transposed by this technique.

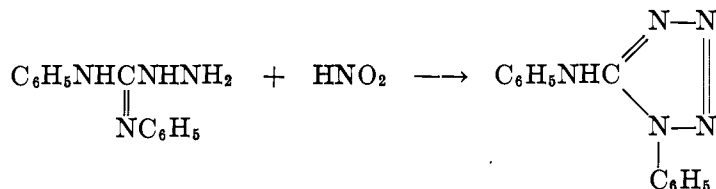


Tetrazoles of this class may also be obtained by diazotization of the appropriate hydrazide, this synthesis also proceeding through the imide azide. Wieland obtained 1-hydroxy-5-phenyltetrazole, identical with that prepared by Forster, by diazotization of benzohydrazide oxime (147). Similarly, Wieland



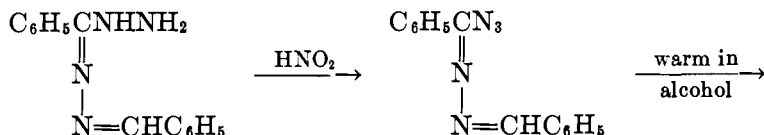
prepared 1,1'-dihydroxy-5,5'-ditetrazolyl by the diazotization of oxalic acid dihydrazide dioxime.

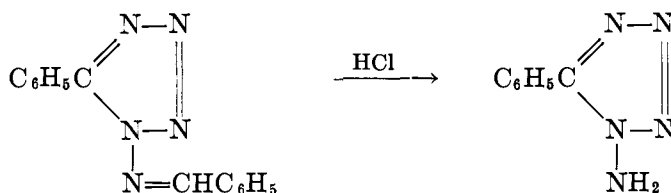
Busch and Bauer (20) obtained 1-aryl-5-arylamino-tetrazoles using substituted aminoguanidines. Compounds prepared in this manner include



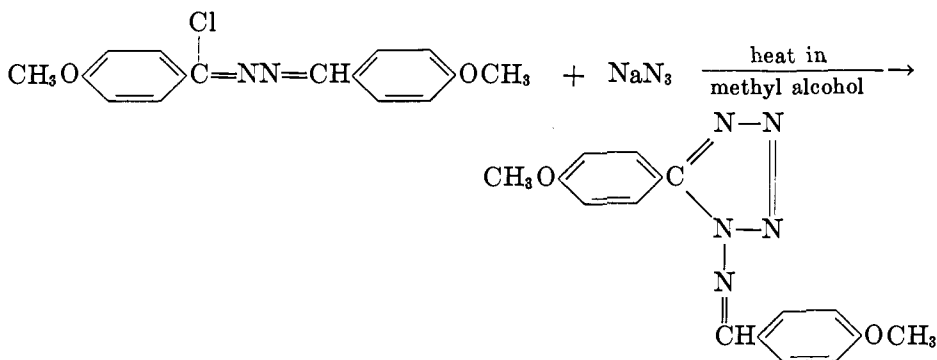
1-phenyl-5-anilino-, 1-*o*-tolyl-5-toluidino-, and 1-*p*-tolyl-5-*p*-toluidino-tetrazoles.

This technique enabled Stollé and Helworth (119) to obtain 1-amino-5-phenyltetrazole as indicated in the equations. In this case the intermediate

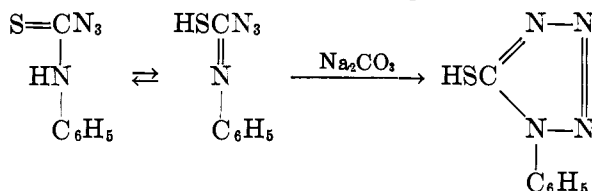




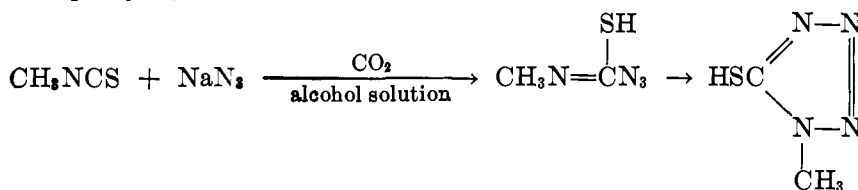
azide was stable enough to be isolated. Subsequently this azide and tetrazole were also prepared from benzal benzohydrazide chloride and sodium azide; in like manner 1-anisylideneamino-5-anisyltetrazole was prepared (122):



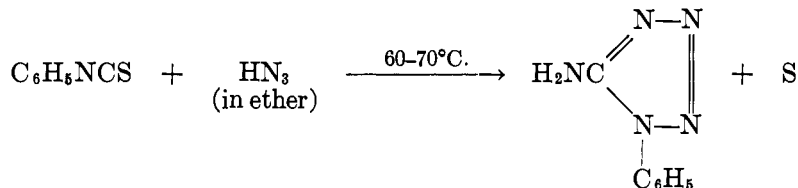
An extension of this reaction to the synthesis of 1-aryl-5-mercaptotetrazoles involves the use of compounds of the type of thiocarbamic azide. Probably the tautomeric mercapto form is the species undergoing reaction. The rearrangement is effected by the use of alkaline reagents such as sodium carbonate or ammoniacal silver solution (38, 75). The required thiocarbamic acid azide



can be obtained from isothiocyanates and hydrazoic acid under the proper conditions, and in some cases cyclization to the tetrazole may be effected merely by further heating. Thus, heating methyl isothiocyanate and sodium azide in a carbon dioxide atmosphere leads to 1-methyl-5-mercaptotetrazole (120). In like manner the 1-allyl- (131), phenyl-, *p*-tolyl- (75), *o*-tolyl- (79), *m*-xylyl, and β -naphthyl- (131) 5-mercaptotetrazoles have been prepared.

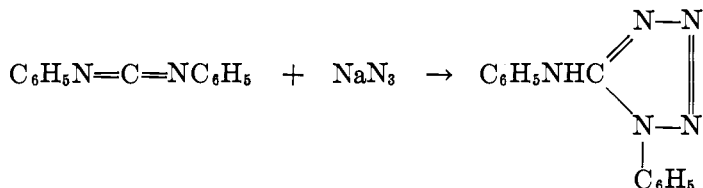


It is interesting that heating phenyl isothiocyanate with hydrazoic acid in ether under pressure results in an elimination of sulfur and formation of 1-phenyl-5-aminotetrazole (82, 110). This reaction was first performed by Oliveri-

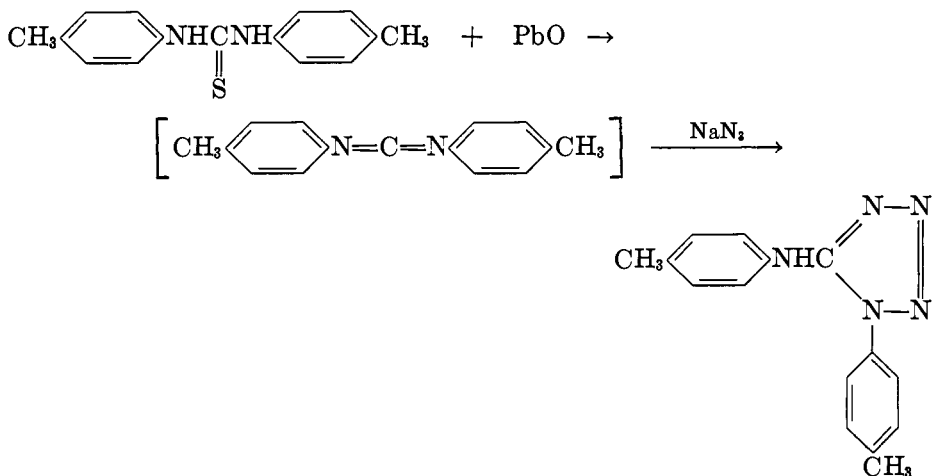


Mandalà and Noto, who believed their product to be an addition compound of hydrazoic acid and phenyl isothiocyanate. It was subsequently shown by Stollé to be sulfur free and identical with 1-phenyl-5-aminotetrazole prepared by a different method.

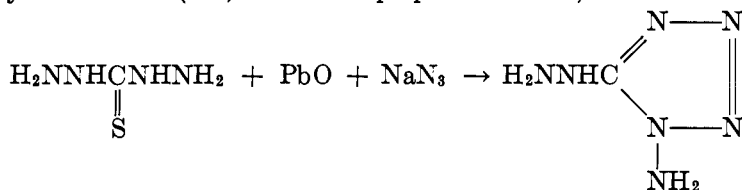
A somewhat similar reaction which has been utilized extensively by Stollé and his collaborators involves the use of carbodiimide derivatives and sodium azide or hydrazoic acid. This reaction, which was discovered independently by Oliveri-Mandalà and Stollé (80, 110), leads to 1-aryl-5-amino- or substituted amino-tetrazoles. Thus, diphenyl carbodiimide and sodium azide heated in absolute alcohol form 1-phenyl-5-anilinetetrazole. Carbodiimides are most conveniently prepared from thiourea derivatives and lead oxide; in practice it



is convenient to obtain tetrazoles without isolating the intermediate by treating the thiourea derivative with lead oxide and sodium azide. It was found that interaction of di-*p*-tolylthiourea with these reagents led to 1-*p*-tolyl-5-*p*-toluidinetetrazole, identical with that obtained from di-*p*-tolylcarbodiimide. Mono-



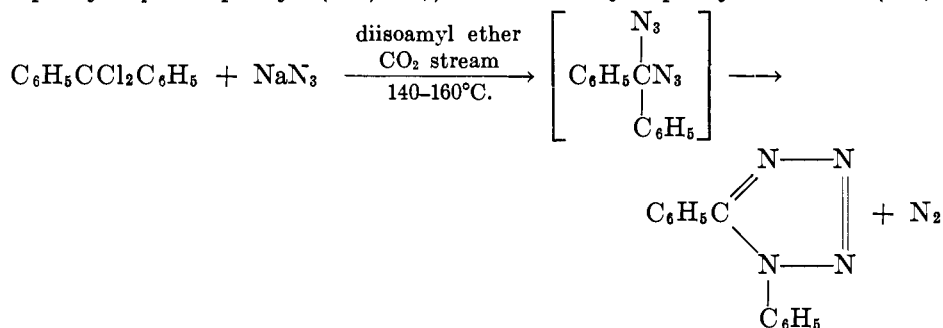
substituted thioureas may also be used; monophenylthiourea in this reaction is converted to 1-phenyl-5-aminotetrazole. This procedure may be used to prepare 1,5-diaminotetrazole by starting with thiosemicarbazide, and 1-amino-5-hydrazinotetrazole by starting with thiocarbonylhydrazide, both being isolated as the hydrochlorides (114). For the preparation of 1,5-disubstituted tetra-



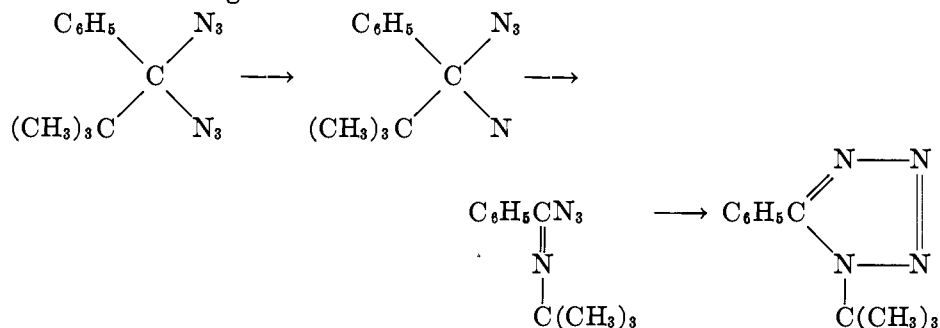
zoles linked to nitrogen in the 5-position this method is probably the most convenient.

The foregoing synthetic methods have involved cyclizations without migration of alkyl or aryl radicals. Several syntheses are known in which a carbon-to-carbon link is broken and a carbon-to-nitrogen bond is established. All of these involve the use of 2 moles of inorganic azide or hydrazoic acid per mole of substrate.

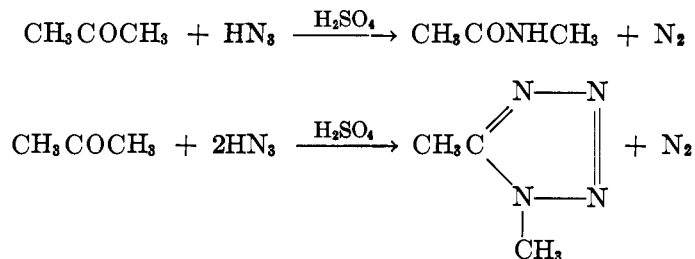
The first method involves the rearrangement of the product derived from the dichloro derivatives of ketones and sodium or silver azide. Presumably the intermediate is the diazide. This method was used to obtain 1,5-diphenyl-, 1-phenyl-5-*p*-nitrophenyl- (104, 105), and 1-*tert*-butyl-5-phenyl-tetrazoles (106).



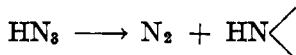
It is of interest that in these cases phenyl migrates in preference to *p*-nitrophenyl, and *tert*-butyl in preference to phenyl. Schroeter considers this synthesis to involve the intermediate formation of monovalent nitrogen, followed by rearrangement to the imide azide, analogous to one view of the Curtius and Beckmann rearrangements.



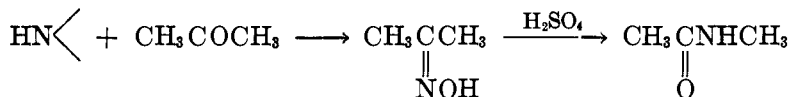
Another procedure for the synthesis of 1,5-disubstituted tetrazoles involving a rearrangement of this type is the reaction of hydrazoic acid and ketones in the presence of sulfuric acid, discovered by Schmidt (101). When 1 mole of hydrazoic acid is used per mole of ketone, *N*-substituted amides are produced; if 2 moles of hydrazoic acid are used, a 1,5-disubstituted tetrazole is formed. According to Schmidt, no tetrazole is obtained if hydrazoic acid is added to the



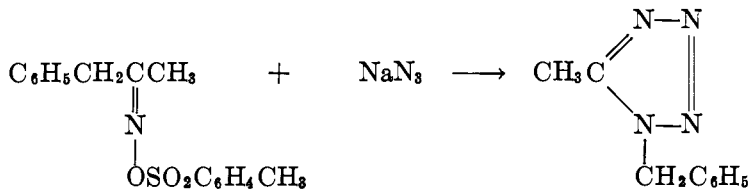
amide under the conditions of the reaction; hence the formation of the tetrazole must involve addition to an intermediate of some sort. The mechanism offered by Schmidt to explain this and other reactions of hydrazoic acid in the presence of acid catalysts assumes the formation of the imide or imine radical, which subsequently reacts with the substrate.



Further discussion of this decomposition of hydrazoic acid is given by Audrieth (1). Interaction with ketones leads to oximes which, under the influence of the acid, undergo the Beckmann rearrangement to yield the substituted amide. While oximes do not react with hydrazoic acid to yield tetrazoles, oxime esters



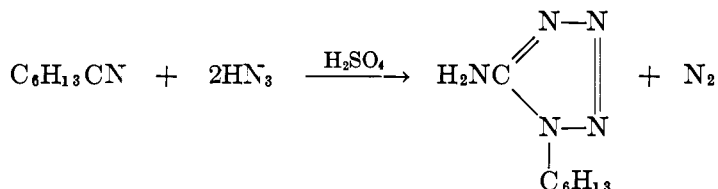
such as the sulfonic, benzenesulfonic, or phosphoric do undergo such reaction. Thus the *p*-toluenesulfonic ester of benzyl methyl ketoxime yields 1-benzyl-5-



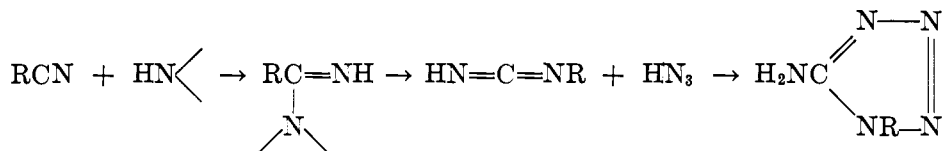
methyltetrazole (12). It appears reasonable to suppose that the formation of a tetrazole from a ketone involves the intermediate formation of the precursor of the oxime, possibly the oxime sulfonic ester, which further reacts with hydrazoic acid to complete the ring. There is some doubt whether the imide radical is the active entity in the initial reaction (109); since the reaction occurs in the presence

of sulfuric acid or other acid catalysts, it may be that NH_2^+ or H_2N_3^+ is involved. The Schmidt synthesis of tetrazoles will be considered further in connection with the fused-ring tetrazoles.

Another synthesis involving fission of a carbon-to-carbon link in the presence of sulfuric acid consists in the interaction of nitriles and hydrazoic acid. Although compounds containing a negative group joined to the cyanide radical react with hydrazoic acid to yield 5-monosubstituted tetrazoles, alkyl and aryl cyanides undergo a different reaction with this reagent. Enanthonitrile is converted to 1-hexyl-5-aminotetrazole by excess hydrazoic acid under the influence of concentrated sulfuric acid (15). In addition the 1-phenyl-, *p*-tolyl-,



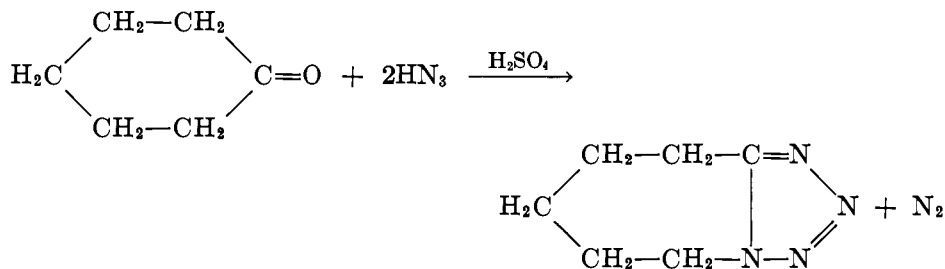
and benzyl-5-aminotetrazoles, as well as the bisaminotetrazole from sebaconitrile, have been prepared in this manner. The mechanism proposed by von Braun and Keller for this reaction involves the formation of a carbodiimide derivative by the agency of the imide radical derived from hydrazoic acid, followed by the addition of another molecule of hydrazoic acid. It is evident



that a considerable similarity exists between this reaction and that of Schmidt; both involve the insertion of a nitrogen between two carbon atoms, one of which carries a negative group and the other of which is in an alkyl or aryl group.

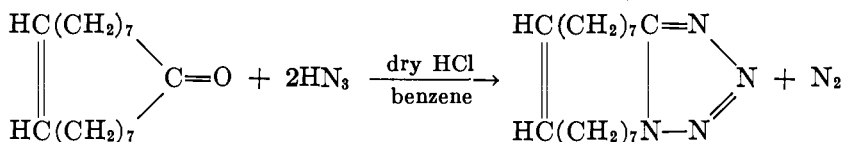
3. Fused-ring 1,5-disubstituted tetrazoles

The Schmidt reaction may be applied to cyclic as well as acyclic ketones, fused-ring tetrazoles being formed in this instance. Metrazole, also known as cardiazole and 1,5-pentamethylenetetrazole, is obtained from cyclohexanone and a benzene solution of hydrazoic acid in the presence of an acid catalyst (101). This reaction forms the subject of a considerable number of patents



(12, 57, 58, 59, 102) and several variants in the procedure are employed. As with the simple 1,5-disubstituted tetrazoles, the interaction of ketoxime esters, or the necessary reactants for their formation, and azides may be used to obtain fused-ring tetrazoles (13, 55). Thus, cyclohexanone oxime, phosphorus oxychloride, piperidine, and sodium azide are claimed in one patent (12) to react producing metrazole. In another instance, the *p*-toluenesulfonic ester of cyclohexanone oxime is treated with hydrazine, followed by diazotization to yield metrazole (54). Since hydrazoic acid is obtained by the action of nitrous acid on hydrazine, this reaction is nearly equivalent to that of Schmidt. A further extension of this procedure is the use of azidosulfonic acid in the reaction with ketoximes (24).

Ruzicka and coworkers have applied the Schmidt reaction to higher cyclic ketones, and have prepared the expected tetrazoles (98, 99). These investigators converted civetone into a tetrazole fused to an eighteen-membered ring.

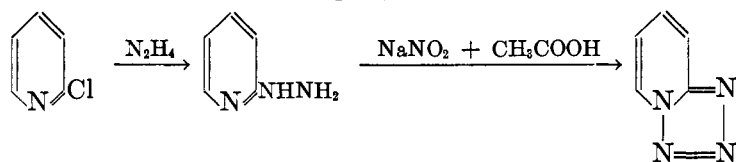


In addition the corresponding tetrazoles from cycloheptanone, cycloöctanone, and cyclopentadecanone were synthesized. Both sulfuric acid and dry hydrogen chloride were used as condensing agents. In the course of this work Ruzicka checked the patent claims of Schmidt and others concerning this reaction and found them to be valid.

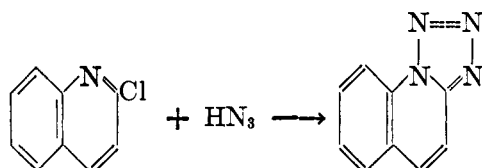
During the preparation of methyl- ϵ -leucine lactam from methylcyclohexanone and hydrazoic acid, von Braun and Heymons (14) obtained a small amount of a methylmetrazole.

Camphor and thujone have also been employed in this reaction, yielding the corresponding tetrazoles (60, 103).

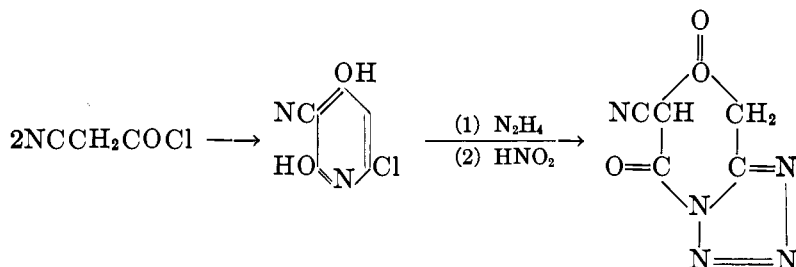
The synthesis of 1,5-disubstituted tetrazoles through the imide azide is as important in the fused-ring series as with the simple derivatives. Both the interaction of a cyclic imide chloride with hydrazine, followed by diazotization, as well as the direct action of hydrazoic acid or sodium azide on the imide chloride have been used. Pyridotetrazole was first prepared by Fargher and Furness from 2-hydrazinopyridine, which had been obtained from the chloride (34). It is to be noted that 2-chloropyridine may be considered to be an imide chloride. The work of von Braun and Rudolph (16) also included the synthesis of this



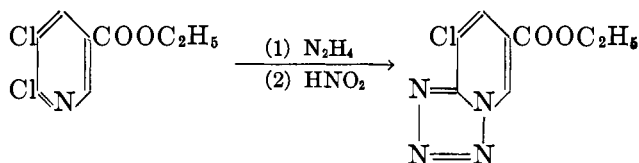
compound, it being formed easily from 2-chloropyridine and hydrazoic acid. Tetrazolo[*a*]quinoline was similarly prepared. Sodium azide could not be used in these syntheses.



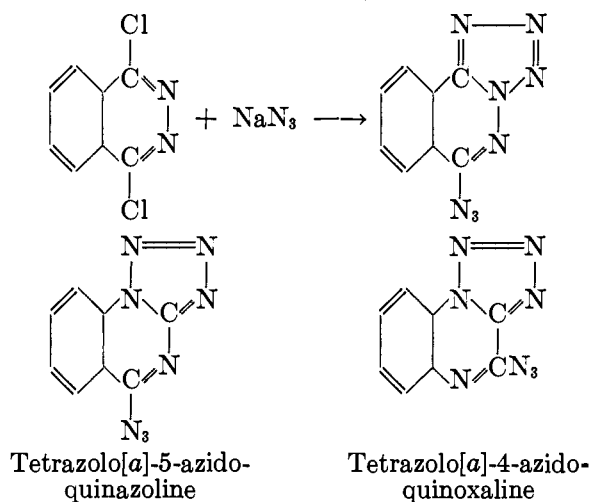
Schroeter and Finck (107), in their study of the spontaneous polymerization of cyanoacetyl chloride, prepared several tetrazole derivatives. This substance undergoes self-condensation with loss of a molecule of hydrogen chloride to form 6-chloronorricinine. Treatment of the latter with hydrazine, followed by diazotization, leads to a tetrazole, from which other derivatives were prepared.



Other 2-chloropyridine derivatives were used by Graf and coworkers to obtain tetrazoles of this series (41, 42). Thus ethyl 2,3-dichloronicotinate was converted to a tetrazole by the same series of reactions:

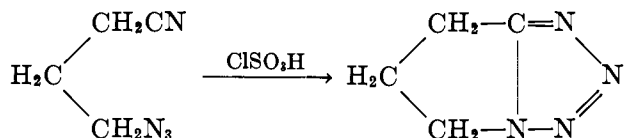


Stollé attempted to prepare bis fused-ring tetrazoles from various diimide



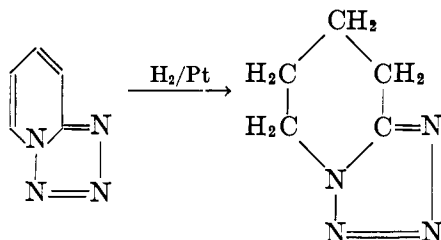
chlorides, but was able to effect ring closure in but one position. When dichlorophthalazine was treated with sodium azide in absolute alcohol tetrazolo[*a*]-6-azidophthalazine was formed (130). In like manner, only one tetrazole ring could be formed in the compounds derived from dichloroquinazoline or dichloroquinoxaline. The azide group in these compounds was easily replaced by hydroxyl or alkoxy, or could be reduced to amino (115, 116).

An interesting internal condensation leading to a fused-ring tetrazole is described in a patent (22): γ -azidobutyronitrile when treated with chlorosulfonic acid yields 6,7-dihydro-5-pyrrolotetrazole, otherwise known as tri-



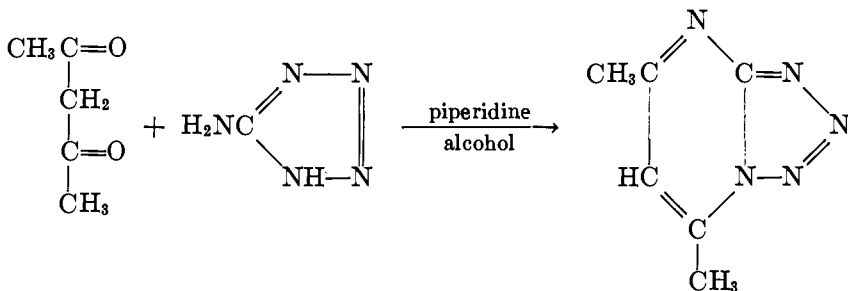
methylenetetrazole. Syntheses of tetramethylenetetrazole, dimethyltetramethylenetetrazole, and the ethyl ester of tetramethylenetetrazolecarboxylic acid also are claimed to be feasible by this procedure.

Catalytic reduction of pyridotetrazole and its alkyl derivatives is claimed in another patent to lead to tetramethylenetetrazole and derivatives (23). It

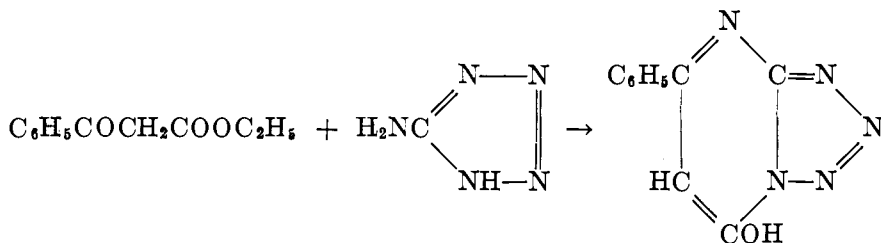


should be mentioned in this connection that Roblin and coworkers (97) were unable to reduce 5-*p*-nitrobenzenesulfonamidotetrazole without splitting the tetrazole ring, although a variety of methods, including hydrogenation in the presence of palladium, were employed.

The only syntheses of fused-ring tetrazoles which have been effected starting with a monocyclic tetrazole are those of Bülow (19). This investigator condensed 5-aminotetrazole with β -diketones such as acetylacetone in alcoholic solution in the presence of piperidine to form tetrazolo[*a*]pyrimidines. Di-



methyl-, trimethyl-, and phenylmethyl-tetrazolo[*a*]pyrimidines were obtained in this fashion. Bülow also condensed β -ketonic esters with 5-aminotetrazole in glacial acetic acid solution to form hydroxytetrazolo[*a*]pyrimidines. Aceto-acetic ester led to the 7-methyl derivative and benzoylacetic ester to the 7-phenyl compound.



IV. REACTIONS

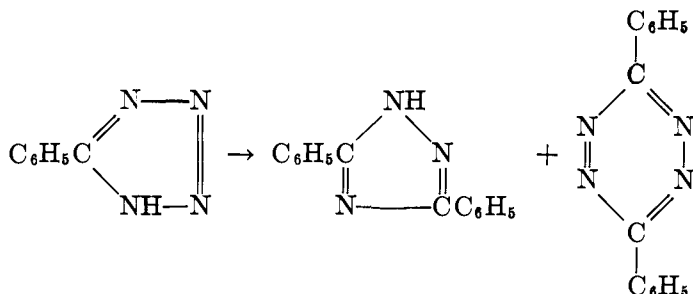
In the foregoing discussion numerous reactions of substituted tetrazoles have been recorded. It is apparent that the several organic radicals linked to the tetrazole ring can undergo the customary transformations. It is also evident that the tetrazole ring exhibits a chemical stability wholly comparable to other aromatic cycles. The material in this section, therefore, will not detail the usual organic reactions, but will indicate conditions under which the tetrazole ring is stable and by which it is broken, and the products of decomposition when ruptured.

The thermal decomposition in aqueous solution of one of the least stable tetrazoles, diazotetrazole, was studied by Thiele and Marais (139). These investigators found that 94.9 per cent of the compound decomposed to form nitrogen and cyanogen according to the equation:

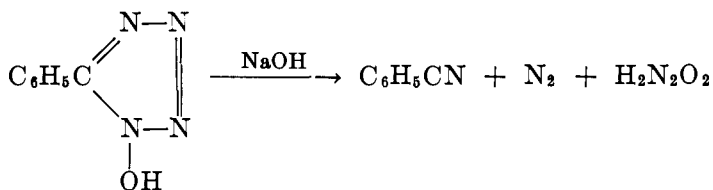


A small amount of a solid substance thought to be oxytetrazole was also formed.

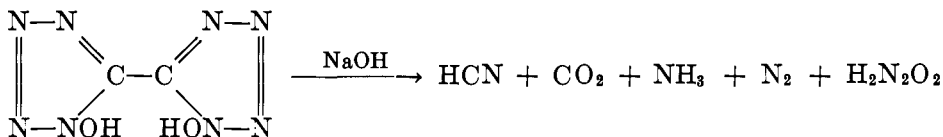
The simultaneous formation of a triazole and a tetrazine occurs when 5-phenyl-tetrazole is heated above its melting point (91). This reaction may be considered



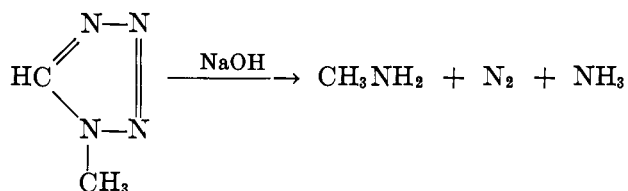
to be a type of dismutation. Similarly the extended heating of 5-*p*-anisyl-tetrazole at 218°C. leads to the formation of 3,5-bis(*p*-anisyl)-1,2,4-triazole (64). No other studies of the purely thermal decomposition of tetrazoles are recorded.



Under the same conditions 1,1'-dihydroxyditetrazolyl-5,5' is also decomposed.

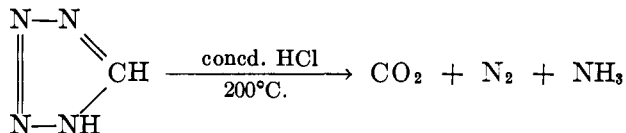


Heating 1-methyltetrazole with alkalis leads to the formation of nitrogen,

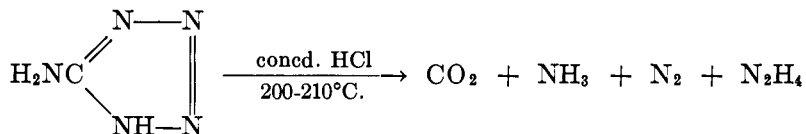


ammonia, and methylamine (81). Not enough compounds have been investigated to generalize concerning the limits of resistance of the tetrazole cycle toward alkali.

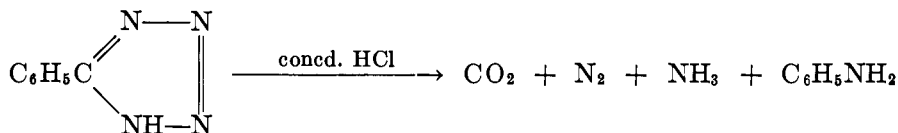
Most tetrazoles are stable toward acids at moderately elevated temperatures, but are decomposed by them above 200°C. Heating tetrazole at this temperature with hydrochloric or sulfuric acid results in the formation of carbon



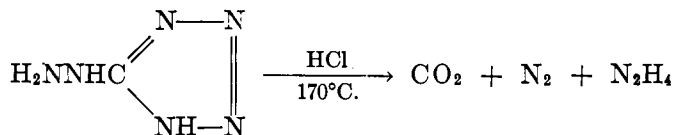
dioxide, ammonia, and nitrogen. If 5-aminotetrazole is heated with hydrochloric acid at 160-170°C., no splitting occurs; with the same reagent at 200-210°C. it is completely decomposed (139).



A similar decomposition is found in the case of 5-phenyltetrazole (91). The formation of hydrazine from 5-aminotetrazole and aniline from 5-phenyltetrazole

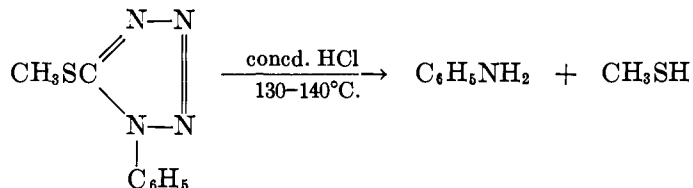


shows that a rearrangement has occurred, the group in the 5-position having become separated from carbon and attached to nitrogen. From the evidence it is impossible to indicate a satisfactory mechanism, but the similarity to the Beckmann rearrangement is apparent. Although 5-hydrazinotetrazole yields carbon dioxide, nitrogen, and hydrazine on heating at 170°C. with hydrochloric



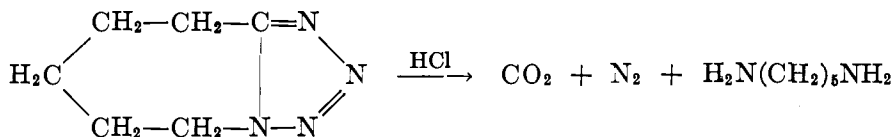
acid (139), it is possible that it decomposes in the same manner, since the product expected, triazane, would undoubtedly immediately decompose. Ditetrazolyl on warming with concentrated sulfuric acid yields nitrogen, ammonia, and carbon dioxide (85). The absence of cyanogen or other compound with linked carbon atoms from among the products of decomposition of ditetrazolyl constitutes further confirmation that the decomposition of 5-substituted tetrazoles by acid involves a separation of this group from the tetrazole carbon atom.

The observation that aniline and methyl mercaptan are formed from 1-phenyl-5-methylmercaptotetrazole by heating with concentrated hydrochloric acid



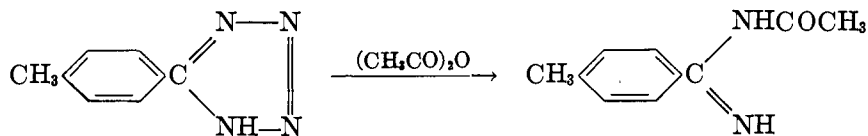
(38) does not lead to a clear indication of the mode of decomposition. It does not appear, however, to be inconsistent with a mechanism involving preliminary separation of the CH_3S group.

Heating metrazole with hydrochloric acid in a sealed tube gives rise to nitrogen, carbon dioxide, and pentamethylenediamine (101). The mechanism proposed

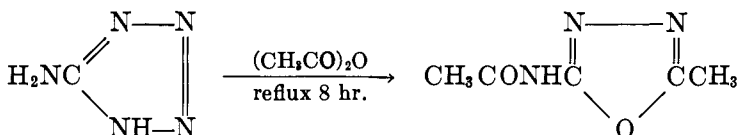


by Schmidt for this decomposition involves preliminary formation of nitrogen and a pentamethyleneamine isocyanate, followed by hydrolysis of the cyanate group. In this case the group linked to the carbon of the tetrazole ring is also detached under the influence of acid.

Of considerable interest are the decompositions effected by acetic anhydride.



When 5-*p*-tolyltetrazole is heated with this reagent for half an hour, *N*-acetyl-*p*-toluamid is produced (92, 93). Warming 5-aminotetrazole with acetic anhydride gently for a short time leads to the monoacetyl derivative; if instead, heating is continued for 8 hr., profound disintegration of the tetrazole ring occurs and 2-methyl-5-acetyl-amino-1,3,4-furodiazole is formed (111).



V. USES

Several patents have been issued covering the use of tetrazoles as explosives, either as initiators or as ingredients of initiating compositions. Thus Rathsburg described the use of salts of tetrazole, tetrazolyl azide, azotetrazole, diazoaminotetrazole, diazotetrazole, bistetrazole, and others for the purpose of replacing mercury fulminate in whole or in part in initiating explosives (96). The preparation of the copper salt of 5-nitrotetrazole for use in priming compositions is mentioned by Hertz (45), and the copper salt of diazoaminotetrazole is advocated by Brun (18).

The pharmacological uses of tetrazoles of the metrazole type depend on their ability to stimulate the central nervous system. Metrazole is extensively employed as a general cardiac and respiratory stimulant. Its use in the treatment of dementia praecox by shock therapy is also well known. Apparently metrazole is the best compound in this series for these purposes discovered to date, although others such as camphortetrazole (103) and trimethylenetetrazole (51) are claimed to have valuable properties.

Considerable doubt exists as to whether 5-sulfanilamidotetrazole has actually been prepared (52, 133, 141). No data appear to have been published on the bacteriostatic activity of the supposed sulfanilamidotetrazole. As an intermediate in an attempted preparation of this compound, Roblin and coworkers (97) prepared 5-*p*-nitrobenzenesulfonamidotetrazole. This compound attained a rather high blood level in spite of low water solubility, but was inactive as a bacteriostatic agent.

The author wishes to acknowledge his great debt to Dr. L. F. Audrieth for his encouragement and guidance at the inception of this work. Dr. Audrieth's stimulating enthusiasm for nitrogen chemistry was most infectious.

To Dr. R. M. Herbst and to Dr. G. B. L. Smith is extended the deepest appreciation for reviewing and criticizing this article and for their kindly encouragement.

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