THE CHEMISTRY OF THE TETRAZOLES

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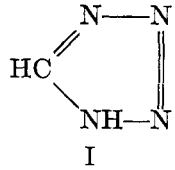
I. Introduction

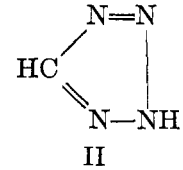
Although the tetrazoles have been extensively investigated, and well over 300 members of this class of nitrogen heterocycles have been prepared, there has been no recent comprehensive review of their chemistry. The section in the textbook by Meyer and Jacobsen (71), published in 1923, is the most complete 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.

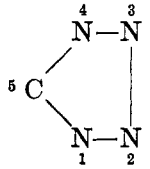


I

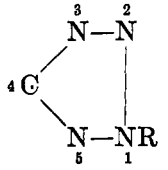


II

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

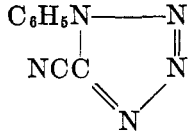


although an alternative system was used in *Chemical Abstracts* for derivatives of formula II prior to 1937.

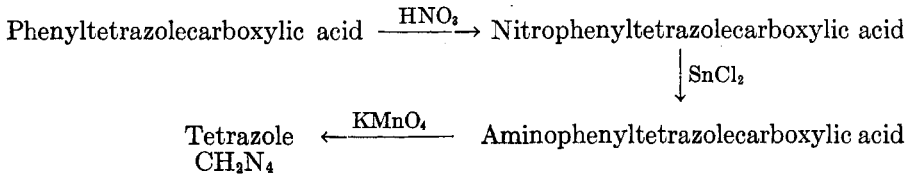


The system mentioned first will be used throughout this discussion for the sake of consistency and to avoid confusion.

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:



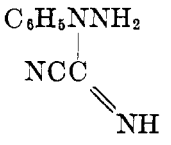
Hydrolysis, followed by decarboxylation, produced a compound having the formula $C_7H_6N_4$, the $C_6H_5CN_4$ unit remaining intact throughout these transformations (6). During his study of dicyanophenylhydrazine, Bladin had prepared numerous triazoles, and the possibility of forming a nitrogen heterocycle 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.



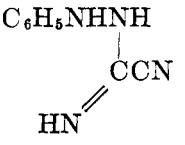
It thus became evident that the ring system with one carbon and four nitrogen atoms was capable of withstanding a variety of chemical agents, and was pos-

sessed of considerable stability. Bladin summarized his work in an extensive review (11) and thereafter discontinued his investigations in this field.

It was subsequently shown by Bamberger and De Gruyter (2) and by Widman (146) that Bladin had assigned an incorrect formula to dicyanophenylhydrazine, with resultant error in the structural formulas for many of the triazoles and tetrazoles derived therefrom. Comparison of Bladin's formula for dicyanophenylhydrazine with that shown to be correct by Bamberger and De Gruyter reveals that cyanophenyltetrazole must have the structure of a 2,5-disubstituted tetrazole.

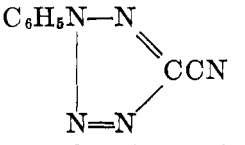


Formula of Bladin



Formula of Bamberger and De Gruyter

Dicyanophenylhydrazine



Cyanophenyltetrazole

Following Bladin's work the investigations in tetrazole chemistry became more numerous. The studies of 5-aminotetrazole by Thiele (135) and coworkers (139, 140), those on the 5-arylsubstituted tetrazoles by Pinner (91) and by Lossen and his group (64, 65, 66, 67), and those on sulfur derivatives of tetrazole by Freund and Paradies (39) were outstanding in the early period, and provided a basis for later extensions. In 1910 the simplest synthesis of tetrazole was achieved by Dimroth and Fester (30) by the direct combination of hydrogen cyanide and hydrazoic acid. The numerous papers by E. Oliveri-Mandalà and his collaborators describe a variety of tetrazoles. Oliveri-Mandalà is one of the few investigators who has studied the acidic and basic dissociation constants of tetrazole derivatives (74).

The most prolific modern investigator of tetrazoles has been R. Stollé of Heidelberg, whose studies of this class of heterocycles occupied the period 1914–1937. His investigations touched on every aspect of this field, and he filled innumerable gaps in the knowledge of these compounds. Mention should be made of the work of K. F. Schmidt (101), whose discovery of the interaction of hydrazoic acid and carbonyl compounds in the presence of acid catalysts has been widely applied to the synthesis of tetrazoles. In particular it has led to the synthesis of pentamethylenetetrazole, better known as metrazole. Although exceedingly few investigations of the tetrazoles have been made by Americans, an interesting description of these and other five-membered heterocycles in terms of the nitrogen system of compounds has been given by Franklin and Bergstrom (37).

II. Physicochemical, Physical, and Explosive Properties of the Tetrazoles

The comparatively small number of dissociation constants for tetrazole derivatives which have been measured are listed in table 1. These are due

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^{-3}			(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.

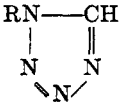
The tetrazoles as a class are characterized by a considerable variation in thermal stability. Exceptional stability is found in the case of 5-guanylaminotetrazole, which does not melt at 300°C. On the other hand, most tetrazole derivatives melting above 150°C. do so with decomposition. Many tetrazoles

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)
p-Tolyl.....	96						(28)
p-Nitrophenyl.....	205 (d)†		i	s	ds	ds	(28, 39)
p-Aminophenyl.....	155		s hot				(39)
Hydroxy(?).....	145 (d)			s	ds	i	(86, 87)

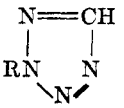
* es = easily soluble; s = soluble; ds = difficultly soluble; i = insoluble.

† 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-ditetrazolylhexazdiene, 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)
p-Tolyl	234 (d); 248		i cold	ds cold			(65, 92, 93, 123)
p-Cumenyl	189		i cold	es hot			(25)
β-Naphthyl	203 (d)			es	es		(91)
o-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)
N,*N*-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*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
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)
Diethylacetylamino	238 (d)		ds	es hot	ds		(127)
α-Ethylcrotonylamino	240 (d)		ds hot	es hot	s		(127)
α-Bromoisovalerylamino	205 (d)		es hot	es	s		(127)
N-Tetrazolyl-5-diethylmalonic acid monoamide	188		s	es	s		(127)
Diethylmalonylbis(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-Tetrazolylurethan	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)
Phenylmethylamino	139		es hot	s	s		(120)
Phenylethylamino	170		es hot	s	s		(120)
Phenylbenzylamino	144		es hot	es	s		(120)
2,4-Dinitrophenylamino	174 (d)		ds hot	ds hot	i		(128)
Picrylamino	224		ds	ds	i		(128)
Phenylsulfonamido	132–134						(27)

TABLE 4—*Continued*

SUBSTITUENT OR COMPOUND	MELTING POINT*	BOILING POINT	SOLUBILITY†				REFERENCES
			Water	Alcohol	Ether	Benzene	
	°C.	°C.					
p-Tolylsulfonamido	146–147						(27)
p-Nitrobenzenesulfonamido	185–186 (d)		0.008 at 37°C.				(97)
Hydrazino	199 (d)		ds cold	i	i	i	(137, 139, 140)
Dibromoformaldehyde 5-tetrazolylhydrazone	177 (d)		ds cold	es	ds	ds	(137)
Acetone 5-tetrazolylhydrazone	181.5		ds cold	es			(139)
Benzal 5-tetrazolylhydrazone	235		i	ds hot		i	(48, 140)
Acetophenone 5-tetrazolylhydrazone	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-*N*,*N*-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-*p*-nitrophenyl-triazene.....	169		i	s hot	ds		(111)
p-Sulfamylphenyldiazoamino-tetrazole.....	175						(134)
3-Phenyl-1-tetrazolyl-5-tetrazene-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-guanyl-1-tetrazolyl-5-tetrazene-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

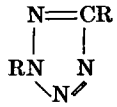
A. TETRAZOLE

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	Ethylcarbamyl	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)

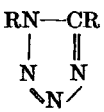
* ds = difficultly soluble; es = easily soluble; i = insoluble; s = soluble.

† 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	*p*-Tolyl	113	160/0.4 mm.					(16)
Methyl	*p*-(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)

tert-Butyl	Phenyl	102						(106)
n-Hexyl	Amino	162		ds cold	es			(15)
n-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	*p*-Tolyl	136						(16)
Phenyl	*p*-Carboxyphenyl	267						(16)
Phenyl	*o*-Nitrophenyl	168						(16)
Phenyl	*m*-Nitrophenyl	156						(16)
Phenyl	*p*-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			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
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-tetrazolyl) 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)
o-Tolyl	Mercapto	129; 131		i				(79, 110)
Bis(1-*o*-tolyltetrazolyl-5) disulfide		102		i	s	ds		(125)
o-Tolyl	*o*-Toluidino	152						(79, 110)
m-Tolyl	*m*-Toluidino	147						(110)
p-Tolyl	Methyl	106						(28)
p-Tolyl	Phenyl	132						(16)
p-Tolyl	*p*-Tolyl	148						(16)
p-Tolyl	Mercapto	150–151; 156 (d)			s	s		(75, 125)

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

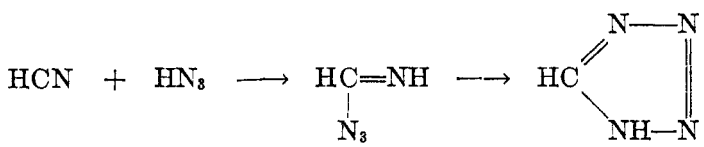
TABLE 6—*Concluded*

SUBSTITUENT OR COMPOUND		MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
1	5			Water	Alcohol	Ether	Benzene	
		°C.	°C.					
m-Nitrophenyl	*p*-Nitrophenyl	170						(16)
p-Nitrophenyl	Methyl	129						(28)
p-Nitrophenyl	Phenyl	149		i	ds			(28)
p-Nitrophenyl	*p*-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)
p-Toluenesulfonyloxy	Phenyl	91–92 (d)						(35)
β-Naphthalenesulfonyloxy	Phenyl	101 (d)			es hot			(35)
Amino	Phenyl	155		es hot	es	i		(119)
Amino	*p*-Tolyl	141		s hot	es	s		(123)
Amino	*o*-Chlorophenyl	173		ds hot	s hot	ds	ds	(123)
Amino	*p*-Nitrophenyl	154		s hot	es	s		(123)
Amino	Allylamino	94		es	es cold	ds		(114)
Amino	Anilino	210 (d)		ds hot		i	i	(114)
Phenyliminomethoxymethylamino	Phenyl	157 (d)						(122)
Phenyliminoethoxymethylamino	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-*o*-chlorophenyltetrazole		Explodes 122						(123)

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

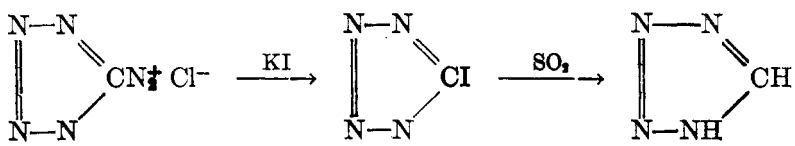
† d = decomposes.

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

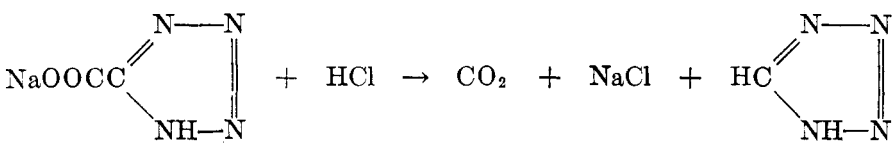


synthesis to the formation of 1,2,3-triazole from acetylene and hydrazoic acid (30) and to the synthesis of pyrazole from acetylene and diazomethane (88) is evident.

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).



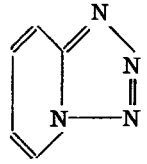
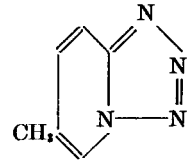
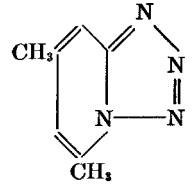
The formation of tetrazole can be achieved by the oxidation of all classes of substituted tetrazoles. Thus, 5-mercaptotetrazole, when treated with nitric

[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 presssure 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	
		°C.	°C.					
Pyridotetrazole		159		i	s	i		(16, 34)
6-Methylpyridotetrazole		152–153						(23)
5,7-Dimethylpyridotetrazole		128–129						(23)

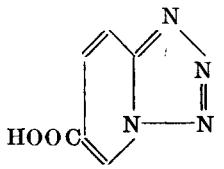
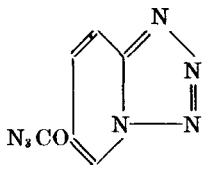
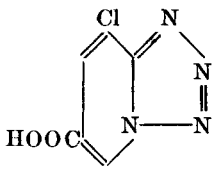
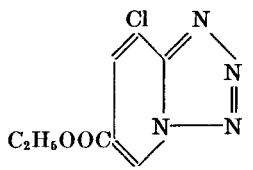
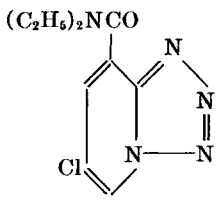
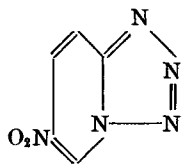
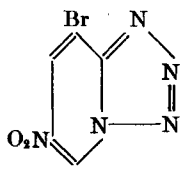
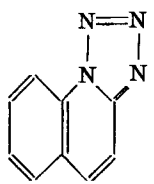
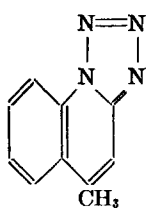
6-Carboxypyridotetrazole		Explodes over 338		s hot				(70)
6-Carboxylic acid azide pyridotetrazole		103–104		ds hot	ds cold			(70)
8-Chloropyridotetrazole-6-carboxylic acid		195–196						(41)
8-Chloro-6-carbethoxypyridotetrazole		95–96						(41)
6-Chloropyridotetrazole-8-*N*,*N*-diethylcarboxamide		113–115					s	(42)

TABLE 7—*Continued*

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

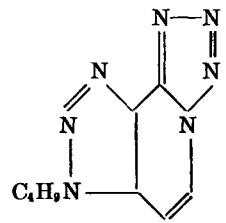
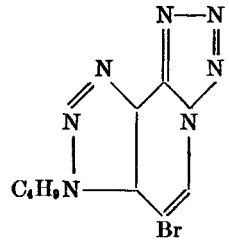
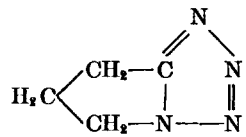
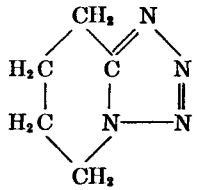
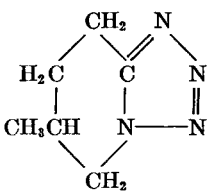
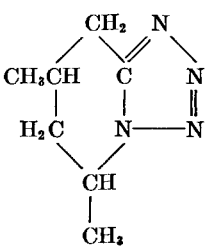
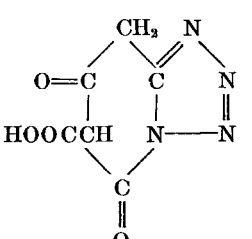
7-Butyltetrazolo[1,5-*a*]triazolo[*c*]-pyridine		157–158						(17)
7-Butyl-6-bromotetrazolo[1,5-*a*]-triazolo[*c*]pyridine		114						(17)
6,7-Dihydro-5-pyrrolotetrazole (trimethylenetetrazole)		110						(22)
5,6,7,8-Tetrahydropyridotetrazole (tetramethylenetetrazole)		115–116						(23)

TABLE 7—*Continued*

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

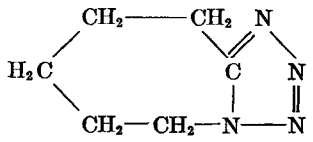
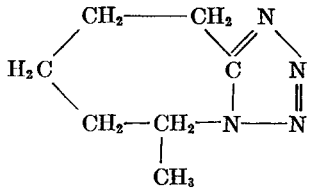
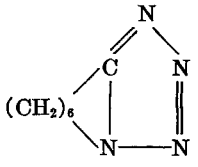
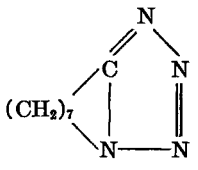
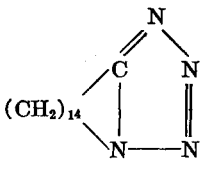
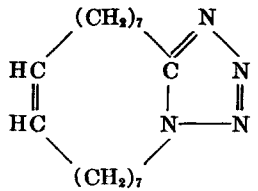
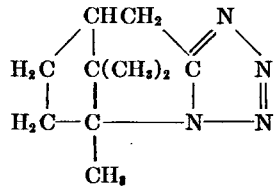
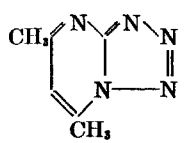
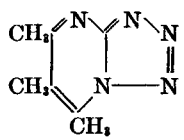
6,7,8,9-Tetrahydro-5-azepotetrazole (pentamethylenetetrazole, metrazole)		59		s				(54)
5-Methyl-6,7,8,9-tetrahydro-5-azepotetrazole		32	185/15 mm.					(14)
5,6,7,8,9,10-Hexahydrotetrazoloazocine		66–68	135–140/0.1 mm.					(98)
6,7,8,9,10,11-Hexahydro-5-tetrazoloazonine			145–146/0.1 mm.					(98)
"Cyclotetradecamethylenetetrazole"		97–98	180–185/0.1 mm.		i			(98)

TABLE 7—*Continued*

COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
"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[*a*]pyrimidine		151–152			es hot	i	es	(19)
5,6,7-Trimethyltetrazolo[*a*]pyrimidine		123–123.5		s hot		i	es	(19)

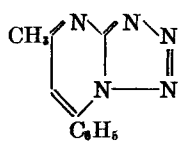
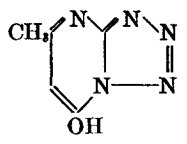
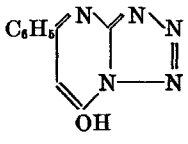
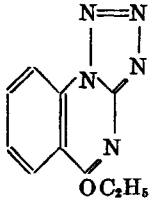
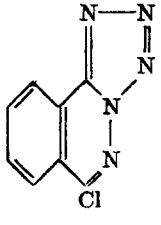
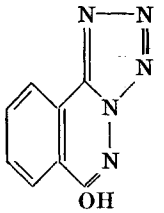
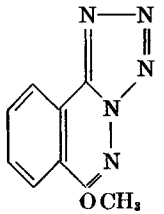
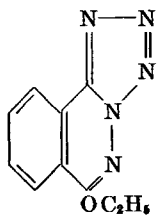
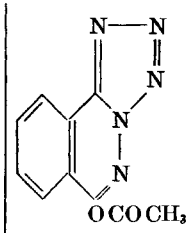
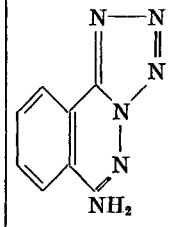
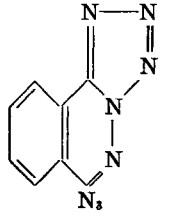
5-Phenyl-7-methyltetrazolo[*a*]pyrimidine		185				ds	ds	(19)
5-Hydroxy-7-methyltetrazolo[*a*]pyrimidine		246–247		es hot	es	ds	ds	(19)
5-Hydroxy-7-phenyltetrazolo[*a*]pyrimidine		261 (d)						(19)
Tetrazolo[*a*]-5-ethoxyquinazoline		165		i	s hot	s		(116)
Tetrazolo[*a*]-6-chlorophthalazine		195 (d)		i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

TABLE 7—*Concluded*

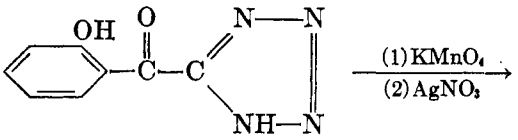
COMPOUND	FORMULA	MELTING POINT	BOILING POINT	SOLUBILITY*				REFERENCES
				Water	Alcohol	Ether	Benzene	
		°C.	°C.					
Tetrazolo[*a*]-6-hydroxyphthalazine		258 (d)		ds hot	ds hot	i		(130)
Tetrazolo[*a*]-6-methoxyphthalazine		211		i	s hot	ds		(130)
Tetrazolo[*a*]-6-ethoxyphthalazine		187		i	es hot	ds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

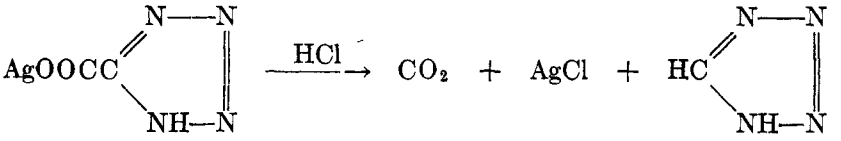
Tetrazolo[*a*]-6-acetoxyphthalazine		165						(130)
Tetrazolo[*a*]-6-aminophthalazine		305		i	s hot	i	i	(130)
Tetrazolo[*a*]-6-azidophthalazine		152		i	es	ds		(130)

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

† d = decomposes.

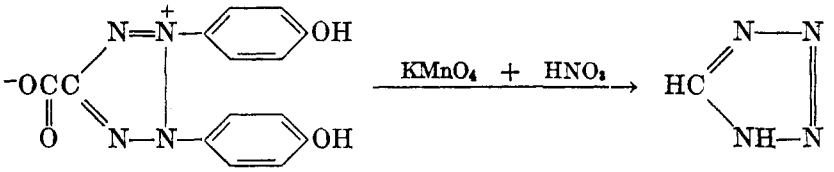
acid, is converted to tetrazole (39), as is 5-(2′-hydroxybenzoyl)tetrazole when oxidized with potassium permanganate (40).





Tetrazoles substituted in the 1-position, such as 1-(*p*-aminophenyl)tetrazole (39), and fused-ring compounds such as tetrazoloquinoline (69), may be oxidized with potassium permanganate to the parent compound. In the latter example, a 97 per cent yield of tetrazole is obtained. The oxidation of 2-(*p*-aminophenyl)-5-carboxytetrazole was mentioned previously as the method used by Bladin in the first synthesis of tetrazole (10).

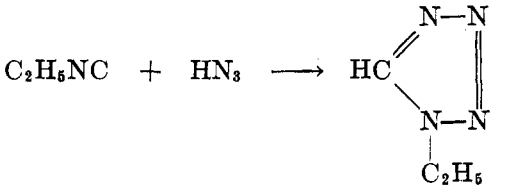
Tetrazolium salts can be oxidized similarly, as in the case of 2,3-di(*p*-hydroxyphenyl)-5-carboxytetrazolium betaine (89):



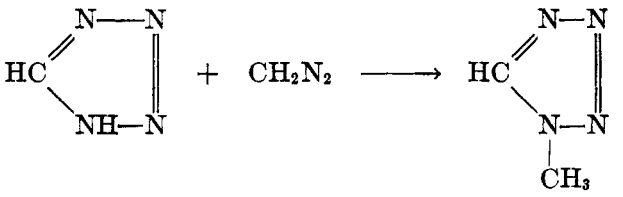
B. MONOSUBSTITUTED TETRAZOLES

1. 1-Substituted derivatives

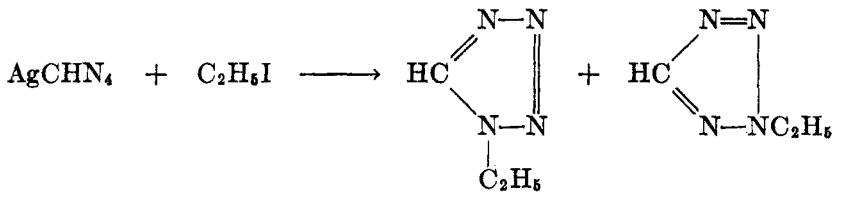
Tetrazoles substituted in the 1-position with alkyl and aryl groups may be prepared by the interaction of isocyanides and hydrazoic acid in ether solution. This synthesis of 1-substituted tetrazoles is the one most generally applicable, the methyl- (72), ethyl-, and phenyl- (81) substituted tetrazoles having been prepared by this procedure.



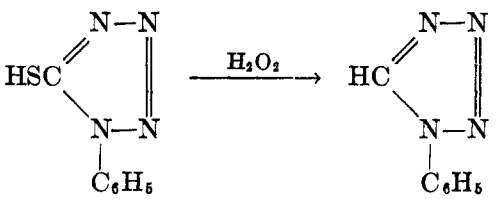
The preparation of 1-methyltetrazole has also been accomplished by the action of diazomethane on tetrazole (120), but the use of higher diazoalkanes has not been investigated.



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



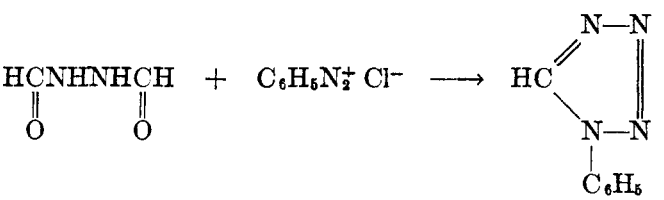
Stollé prepared 1-methyl- and 1-phenyl-tetrazoles by the action of hydrogen peroxide on the appropriate 5-mercaptotetrazole in the presence of ammonium hydroxide (120).



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

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

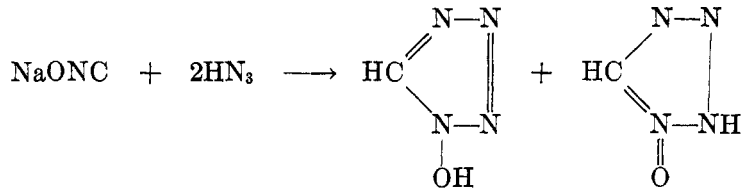
Certain 1-aryltetrazoles may be prepared by an interesting reaction, which involves the interaction of diazonium salts and *sym*-diformylhydrazine in the



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

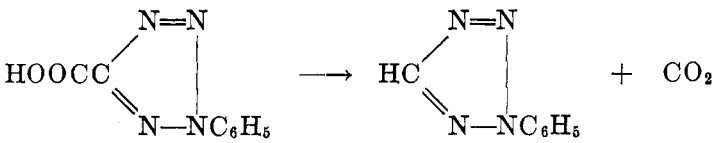
formation of two compounds; one of these was assigned the structure of 1-hydroxytetrazole and the other 1-tetrazole oxide (86, 87). Justification for



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

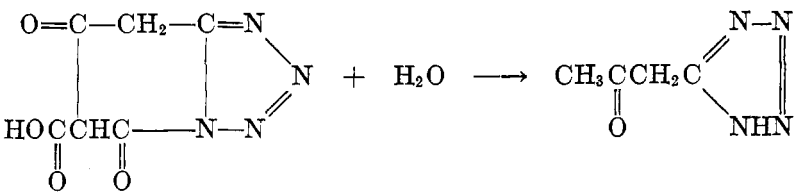
Decarboxylation of 5-carboxy-2-substituted tetrazoles has been used to obtain each of the three known 2-monosubstituted tetrazoles: namely, the methyl (85), ethyl (83), and phenyl (6, 145) derivatives.



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

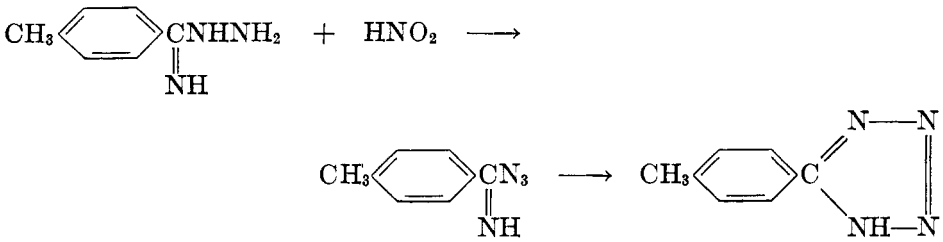
3. 5-Substituted derivatives

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

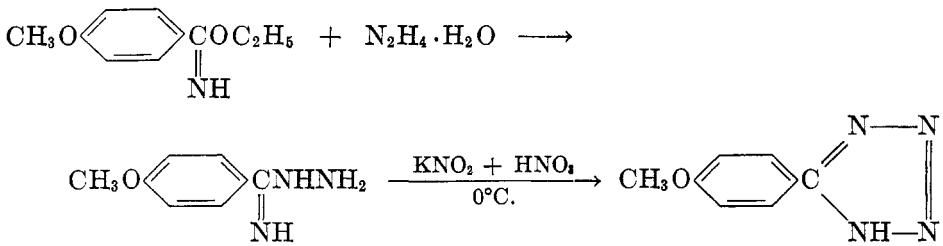


Numerous 5-aryltetrazoles have been made, the most general procedure involving the diazotization of hydrazidines. This synthesis is also useful in preparing 5-substituted tetrazoles other than aryl derivatives, and these applications will be indicated in the appropriate place. It is generally assumed 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

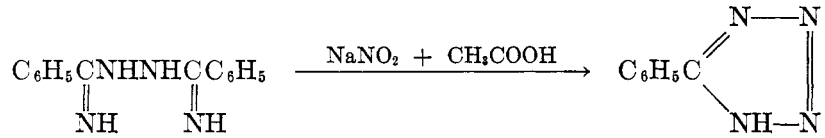
aid of a catalyst. In most cases it is impossible to isolate the intermediate imide azide. Aryltetrazoles substituted in the 5-position which have been



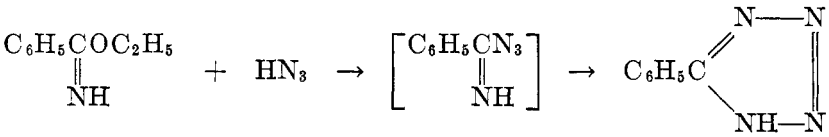
obtained by this process include phenyl (91), *p*-tolyl (92, 93), *p*-cumenyl (25), *p*-anisyl (64), *p*-nitrophenyl, and β-naphthyl (91). The diazotization of furoic acid hydrazidine similarly leads to 5-α-furyltetrazole (94). In practice, it is not always necessary to isolate the hydrazidine; these 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.

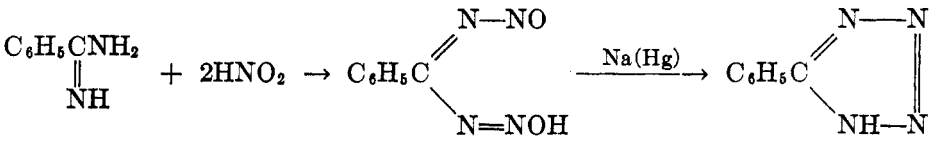


The interaction of benzimido ethyl ester and hydrazoic acid is claimed in a patent (53) to lead to 5-phenyltetrazole. Presumably this reaction also proceeds through the imide azide.

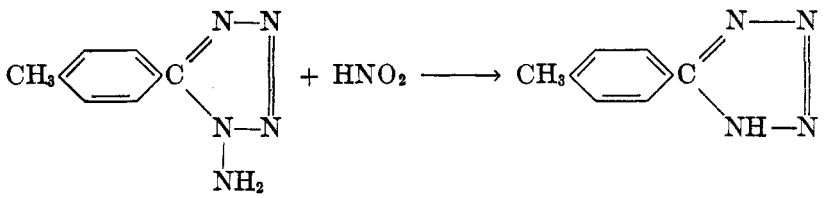


An interesting synthesis discovered by Lossen involves treating an amidine with nitrous acid to form a so-called dioxytetrazotic acid; the potassium salt of this substance is reduced in aqueous solution to a tetrazole by sodium amalgam.

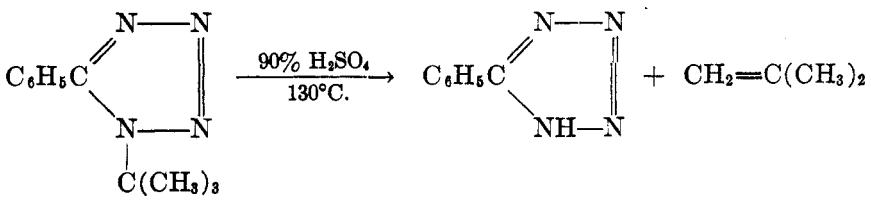
The yields obtained by this method are poor. The 5-phenyl- (66, 67) and 5-*p*-tolyl- (65) tetrazoles have been synthesized in this manner. The structure of the dioxytetrazotic acid is in doubt, but may be that indicated in the equation. This tetrazole synthesis is of particular interest, since it is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



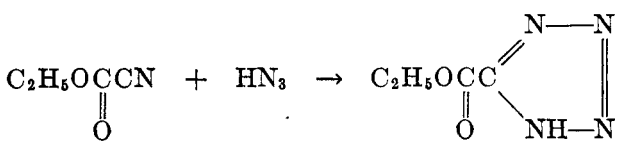
The reaction of nitrous acid and 5-aryl-1-aminotetrazoles effects replacement of the amino group with hydrogen (123). This method has been used in the preparation of 5-*p*-tolyl- and 5-*o*-chlorophenyl-tetrazoles.



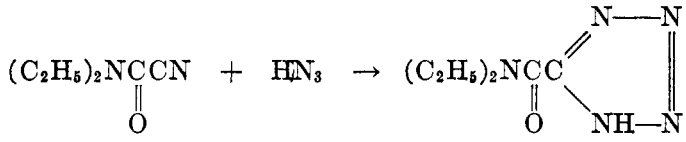
Another method of converting certain 1,5-disubstituted tetrazoles into 5-monosubstituted compounds is due to Schroeter (106), who treated 1-*tert*-butyl-5-phenyltetrazole with sulfuric acid, thereby causing elimination of 2-methylpropene.



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 cyanoformate and hydrazoic acid (73):

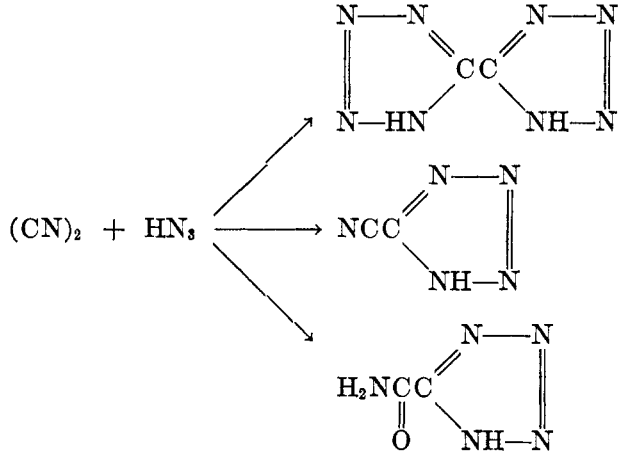


In like manner the nitrile of diethyloxamic acid and hydrazoic acid produce *N*,*N*-diethyl-5-tetrazolecarboxamide when heated in a sealed tube at 115–120°C. for 25–30 hr. (43).



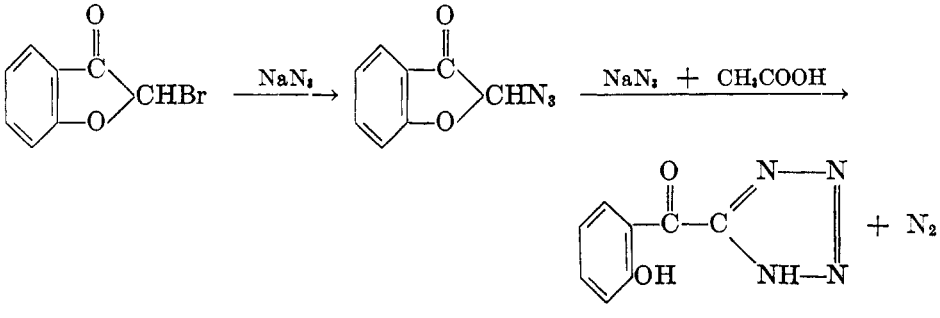
In general, the combination of hydrazoic acid with cyanides linked to a sufficiently negative group leads to 5-substituted tetrazoles. This is a reaction of considerable utility, as will be seen.

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.



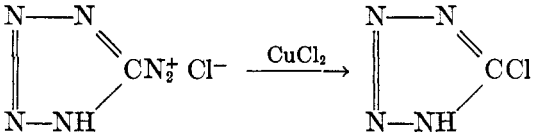
Ditetrazolyl has also been prepared from 5-tetrazolehydrazidine by diazotization (63).

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-

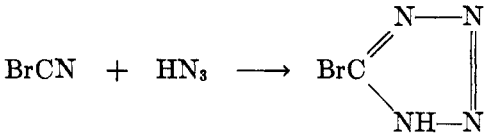


and 5′-chloro-2′-hydroxybenzoyl-tetrazoles have been synthesized by this method (40).

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.

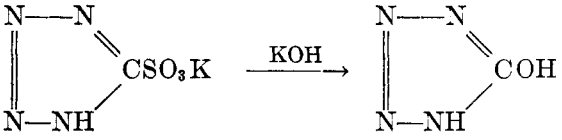


The preparation of 5-bromotetrazole has also been effected by Oliveri-Mandalà by the interaction of cyanogen bromide and hydrazoic acid in ether for several days at 50–60°C. (73).

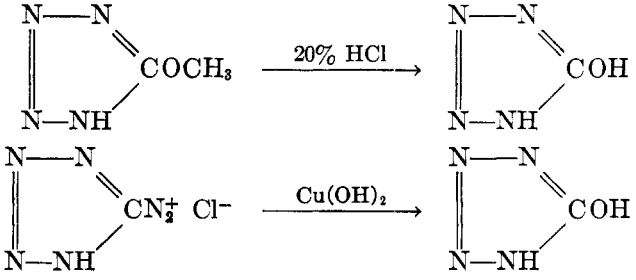


An unexplained discrepancy exists between the melting point of the 5-bromotetrazole obtained by Stollé (156°C.) and that obtained by Oliveri-Mandalà (147–148°C.).

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

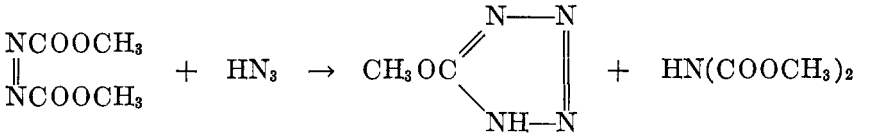


5-methoxytetrazole with 20 per cent hydrochloric acid (112), or by treatment of diazotized 5-aminotetrazole with cupric hydroxide at 60°C. (111). Although

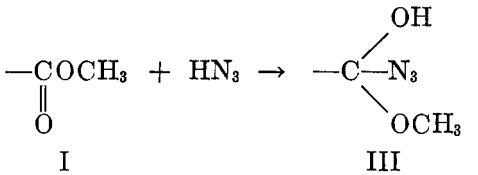


hydrolysis of 5-chloro- or 5-bromo-tetrazole is not effected by 60 per cent sodium hydroxide, 5-iodotetrazole is converted by this reagent to 5-hydroxytetrazole (111).

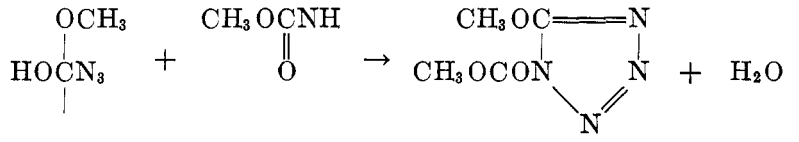
The only method by which 5-methoxytetrazole has been prepared involves a reaction discovered by Stollé and Adam (112), in which azodicarboxylic acid dimethyl ester and excess hydrazoic acid react in ether solution. Besides methoxytetrazole some iminodicarboxylic acid dimethyl ester is obtained. The mechanism 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, $-COOCH_3$ (I) and $-NHCOOCH_3$ (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).

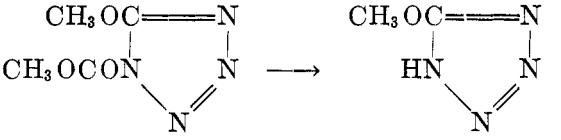


I III



III II IV

Hydrolysis and decarboxylation of IV produces 5-methoxytetrazole.



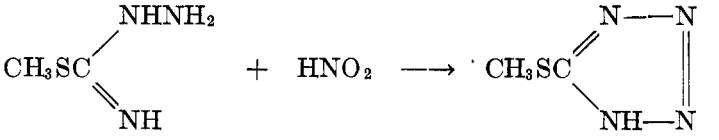
IV

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

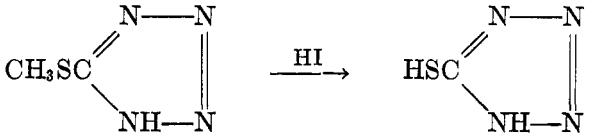
$$CH_3OCONH- \; + \; -COOCH_3 \longrightarrow HN(COOCH_3)_2$$

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

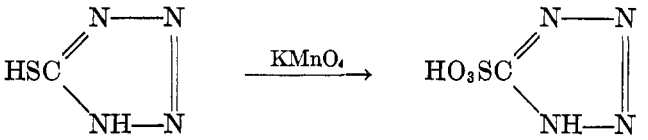
The 5-methylmercapto derivative of tetrazole was prepared by Freund and Paradies (39) from *S*-methylthiosemicarbazide by the diazotization method.



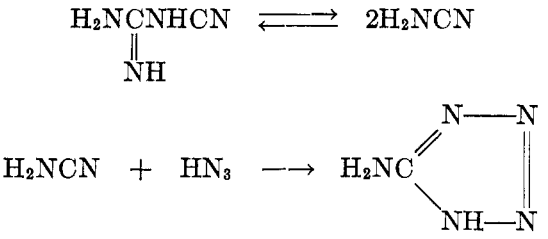
Hydrolysis of this compound with concentrated hydriodic acid in glacial acetic acid produces 5-mercaptotetrazole (39).



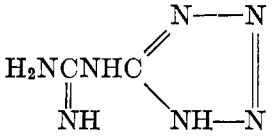
By oxidizing 5-mercaptotetrazole with 2.5 per cent potassium permanganate 5-tetrazolesulfonic acid is formed (39).



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-

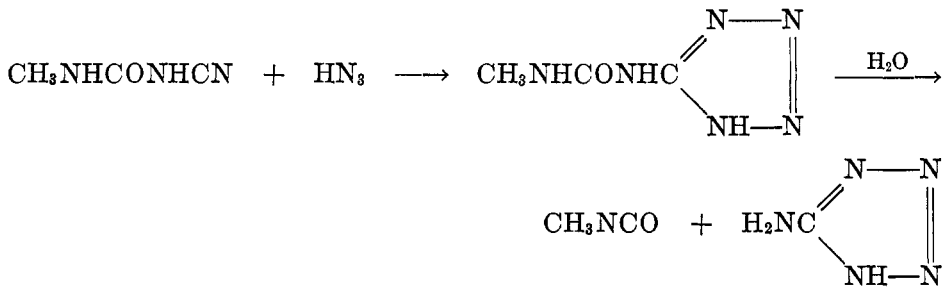


aminotetrazole, which would be formed if dicyandiamide united directly with hydrazoic acid, is stable under the conditions obtaining in this synthesis of 5-aminotetrazole (111).

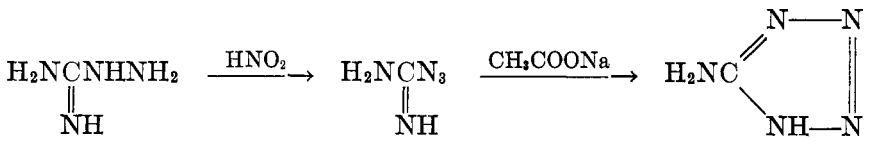


5-Guanylaminotetrazole

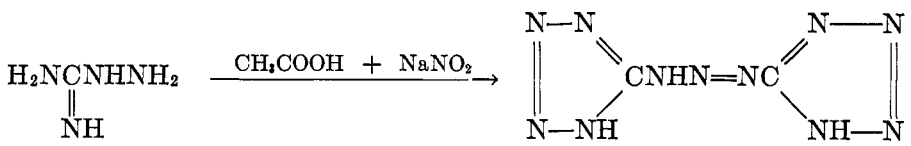
Interaction of *N*-methyl-*N'*-cyanourea with hydrazoic acid leads to *N*-methyl-*N'*-tetrazolylurea, which dissolves in hot water with decomposition to yield 5-aminotetrazole (108).



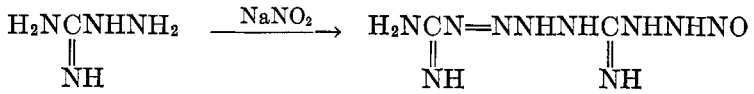
The diazotization method is applicable to the preparation of 5-aminotetrazole, and indeed was the method used by Thiele in the first synthesis of this compound. The starting material is aminoguanidine (44, 136, 138). In this case the intermediate imide azide, guanyl azide, is sufficiently stable to be 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-nitrosoaminoguanyltetrazene, better known as tetracene.



Diazoaminotetrazole

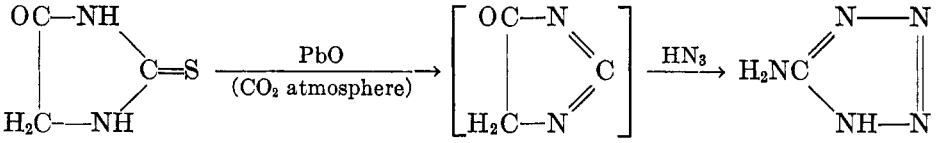


Tetracene

It is of interest that both of these compounds, as well as 1-guanyl-4-tetrazolyltetrazene, 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).

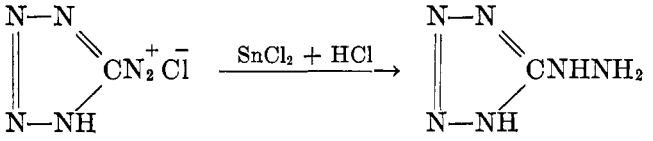
In a different category is the preparation of 5-aminotetrazole from thiohydantoin by treatment with sodium azide and lead oxide in an atmosphere of carbon dioxide (127). The mechanism of this reaction is obscure, but, by

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.

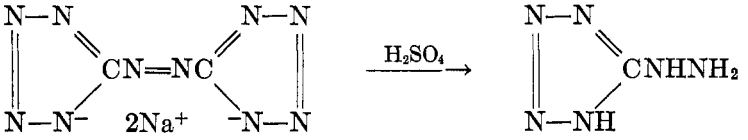


Thiohydantoin

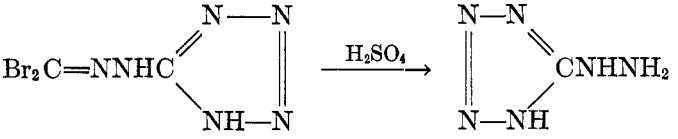
Another 5-substituted tetrazole of importance is 5-hydrazinotetrazole, which is best obtained by reduction of tetrazolediazonium salts with stannous chloride and hydrochloric acid (139, 140). Similar treatment of tetracene (48) and 1,3-ditetrazolyltriazene (46) also leads to 5-hydrazinotetrazole. In 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-tetrazolylhydrazone (137). It should be mentioned that 5-hydrazinotetrazole is usually

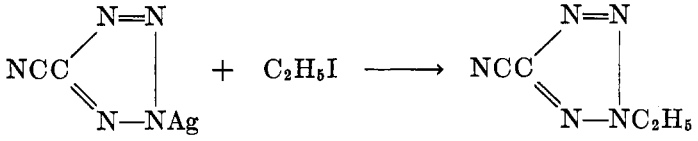


isolated as the insoluble benzal derivative, owing to its tendency to oxidize in air.

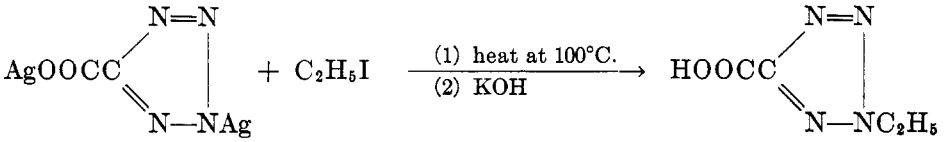
C. DISUBSTITUTED TETRAZOLES

1. 2,5-Disubstituted derivatives

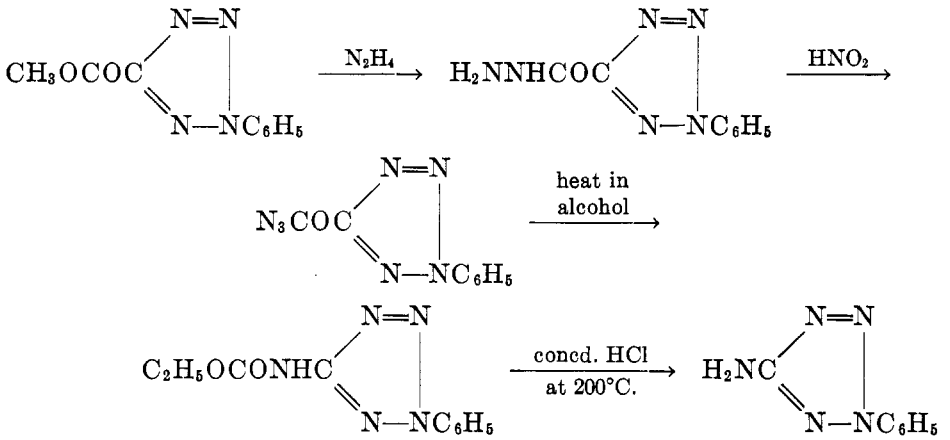
A few 2,5-disubstituted tetrazoles may be prepared from 5-monosubstituted compounds. Thus 2-methyl- or 2-ethyl-5-cyanotetrazole results from the interaction of silver cyanotetrazole with the appropriate alkyl iodide (83, 85).



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).

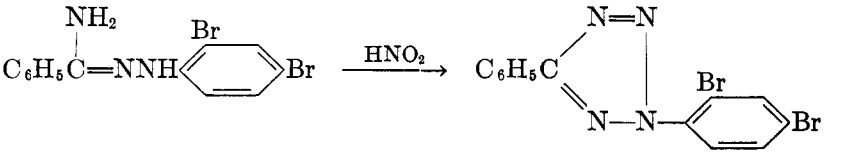


Most 2,5-disubstituted derivatives are obtained by starting with acyclic compounds. The synthesis by Bladin of 2-phenyl-5-cyanotetrazole from dicyanophenylhydrazine and nitrous acid has already been mentioned. It has not been prepared by any other method. Using this compound Bladin prepared a variety 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.

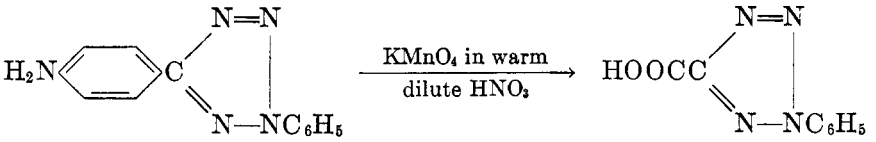


From 2-phenyl-5-aminotetrazole, or compounds intermediate in its synthesis, the corresponding urea, azo, hydrazo, acetyl, benzoyl, and benzal derivatives were prepared.

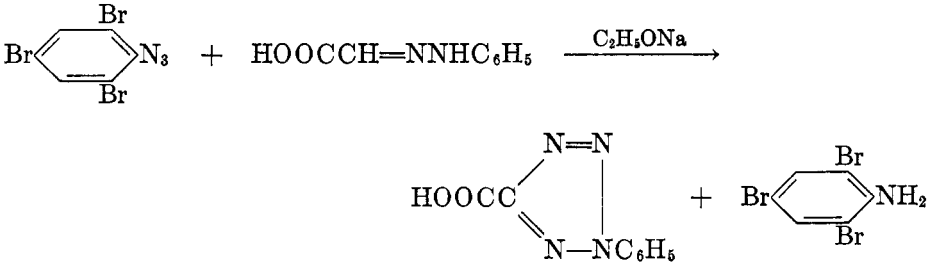
A reaction closely related to that of Bladin was used by Chattaway and Parkes (21) in the preparation of 2-(2′,4′-dibromophenyl)-5-phenyltetrazole from ω-aminobenzaldehyde 2,4-dibromophenylhydrazone and nitrous acid.



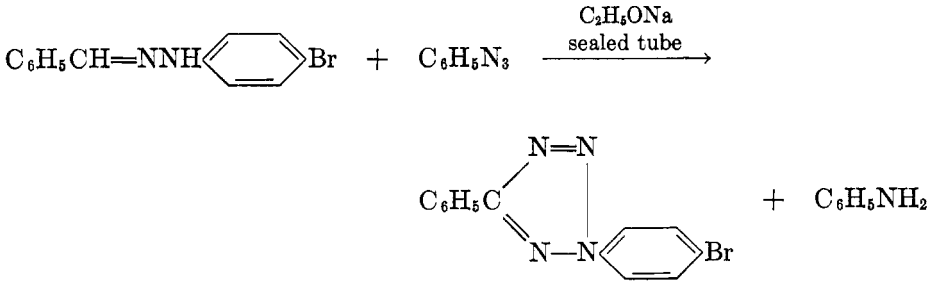
The preparation of 2-phenyl-5-tetrazolecarboxylic acid has been effected by methods other than the hydrolysis of the nitrile used by Bladin (6). Wedekind obtained it by oxidation of 2-phenyl-5-*p*-aminophenyltetrazole (145).



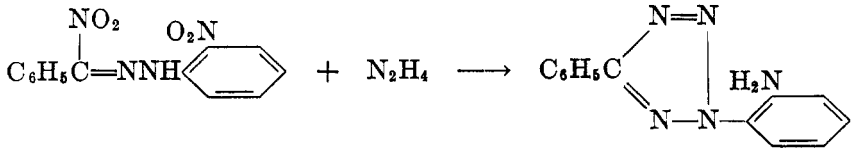
Another synthesis of this compound involves the interaction of 2,4,6-tribromoazidobenzene with the phenylhydrazone of glyoxalic acid in sodium ethylate solution (32), tribromoaniline being formed simultaneously.



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.

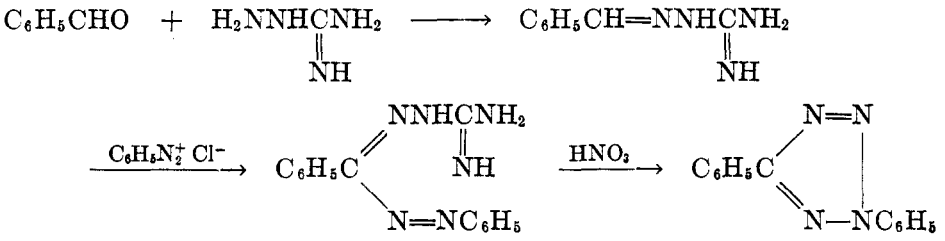


By means of the reaction of hydrazine with the *o*-nitrophenylhydrazone of phenylnitroformaldehyde, 2-*o*-aminophenyl-5-phenyltetrazole has been prepared (95).

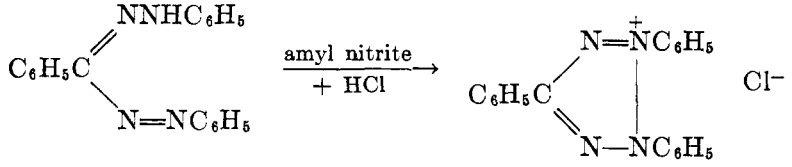


This reaction involves a displacement of the nitro group on the aldehyde moiety, and reduction of the one on the aromatic ring. The 2-*p*-aminophenyl-, *o*-methyl-*p*-aminophenyl-, and *o*-chloro-*p*-aminophenyl-5-phenyltetrazoles were obtained by this reaction.

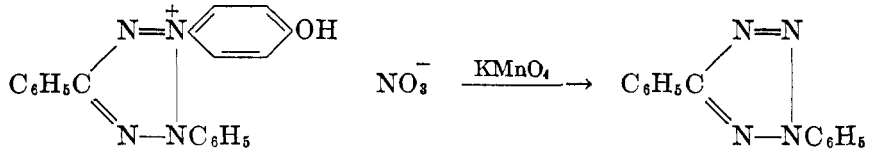
Another synthesis of 2,5-diaryltetrazoles involves use of the coupling product of a guanylhydrazone and diazobenzene. Warming with concentrated nitric acid or with a chloroform solution of nitrogen trioxide effects ring closure. Starting with aminoguanidine and benzaldehyde, the synthesis of 2,5-diphenyltetrazole involves the following sequence:



This scheme, which is due to Wedekind (143, 144), was also used to prepare 2-phenyl-5-*p*-nitrophenyltetrazole. Because of the ready availability of the starting materials, this method appears to be the best for the synthesis of 2,5-diaryltetrazoles. The structure of the intermediate "guanazyl benzene" is quite similar to that of the formazyl compounds, which may be oxidized by acidified amyl nitrite to the tetrazolium compounds. Suitably substituted tetrazolium compounds—e.g., those containing one hydroxylated phenyl group



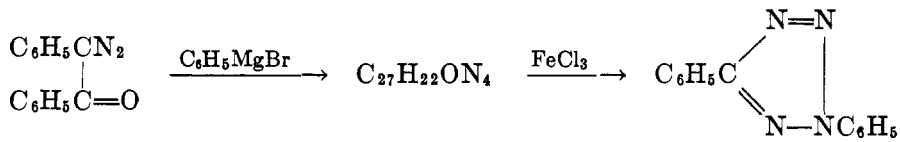
attached to nitrogen—are oxidized to 2,5-disubstituted tetrazoles. Wedekind obtained the same tetrazole derivatives in this manner that he obtained from the guanazyl derivatives (142, 144). It appears reasonable to suggest that the



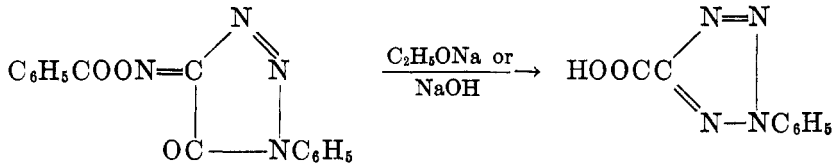
conversion of "guanazyl benzene" to 2,5-diphenyltetrazole proceeds through an intermediate tetrazolium compound.

The formation of 2,5-diphenyltetrazole has also been accomplished starting with azibenzil. When this compound is condensed with phenylmagnesium

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

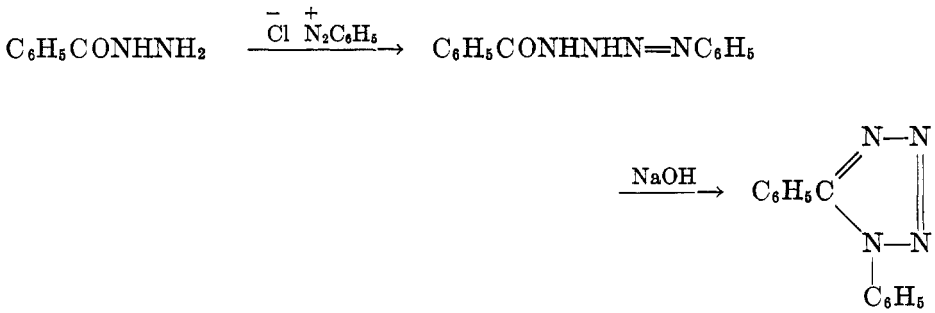


The conversion of a triazole derivative into a tetrazole has been observed in one instance. Rearrangement of the benzoyl or *m*-nitrobenzoyl derivative of 1-phenyl-5-keto-4-isonitroso-1,2,3-triazoline in alkaline solution at −10°C. gives rise to 2-phenyl-5-tetrazolecarboxylic acid (29, 33).

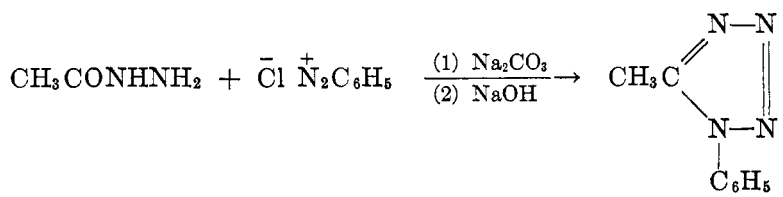


2. Simple 1,5-disubstituted derivatives

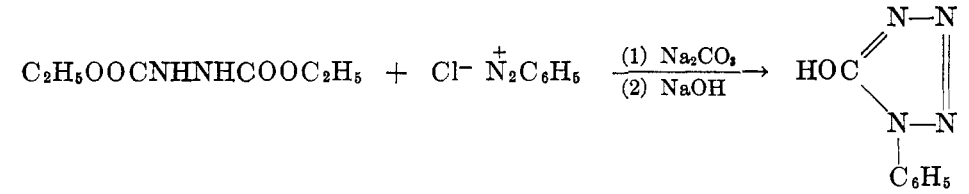
The cyclization of 1-aryl-4-acyltetrazenes to 1,5-disubstituted tetrazoles may be accomplished by use of dilute alkali. Such tetrazenes are prepared by coupling diazo compounds with acyl hydrazides. Thus 1,5-diphenyltetrazole is obtained from benzohydrazide and benzenediazonium chloride by the sequence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

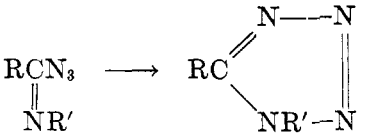


1-*p*-nitrophenyl-5-phenyl-, and 1-(phenyl-*p*-sulfonic acid)-5-methyltetrazoles. In some cases a symmetrical diacylated hydrazide is used in place of the monoacyl hydrazide, the second acyl group being eliminated during the reaction. An interesting application of this modification involves the use of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

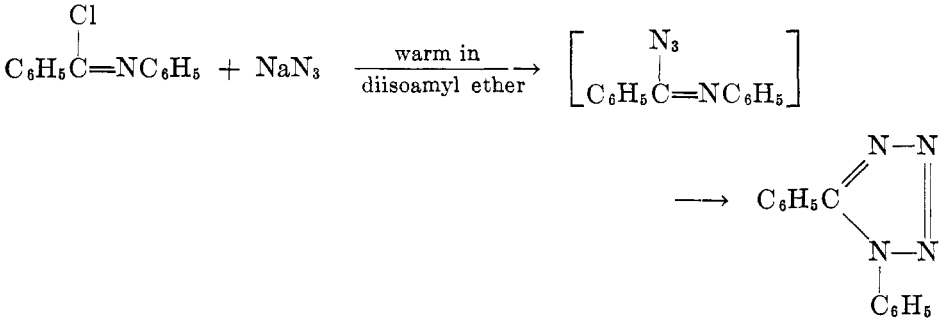


1-monosubstituted tetrazoles from diazonium compounds and symmetrical diformylhydrazine which was mentioned previously.

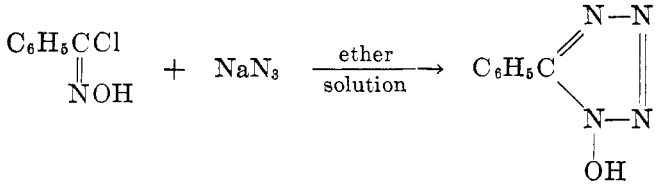
The essential step in a large number of syntheses of 1,5-disubstituted tetrazoles involves the cyclization of a substituted imide azide.



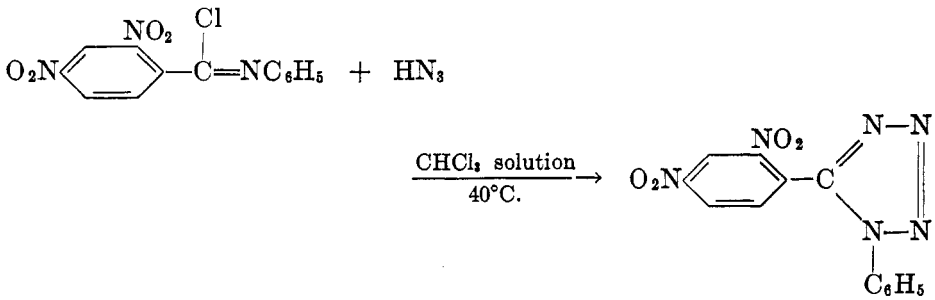
As in the case of the analogous synthesis of 5-monosubstituted tetrazoles, it is unnecessary and also frequently impossible to isolate the intermediate imide azide. The most direct method involving this type reaction starts with an imide chloride. The reaction was first applied to the preparation of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



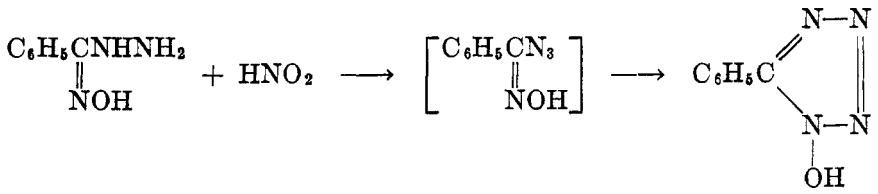
diaryl or alkyl-aryl 1,5-disubstituted tetrazoles by Schroeter (104), but was originated by Forster (35) in his synthesis of 1-hydroxy-5-phenyltetrazole from benzohydroxamic acid chloride and sodium azide.



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.

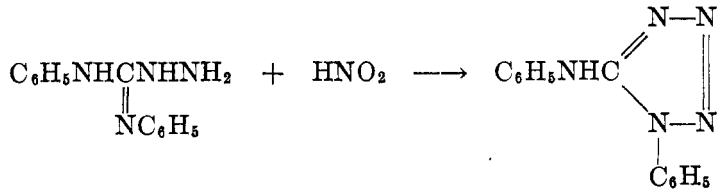


Tetrazoles of this class may also be obtained by diazotization of the appropriate hydrazide, this synthesis also proceeding through the imide azide. Wieland obtained 1-hydroxy-5-phenyltetrazole, identical with that prepared by Forster, by diazotization of benzohydrazide oxime (147). Similarly, Wieland



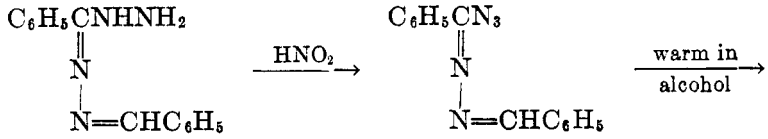
prepared 1,1′-dihydroxy-5,5′-ditetrazolyl by the diazotization of oxalic acid dihydrazide dioxime.

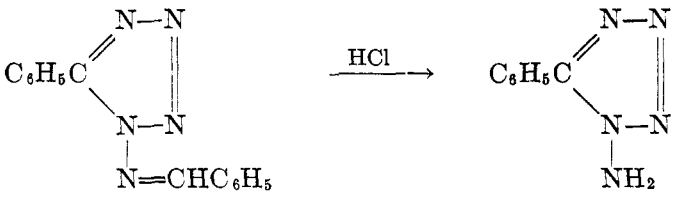
Busch and Bauer (20) obtained 1-aryl-5-arylaminotetrazoles using substituted aminoguanidines. Compounds prepared in this manner include



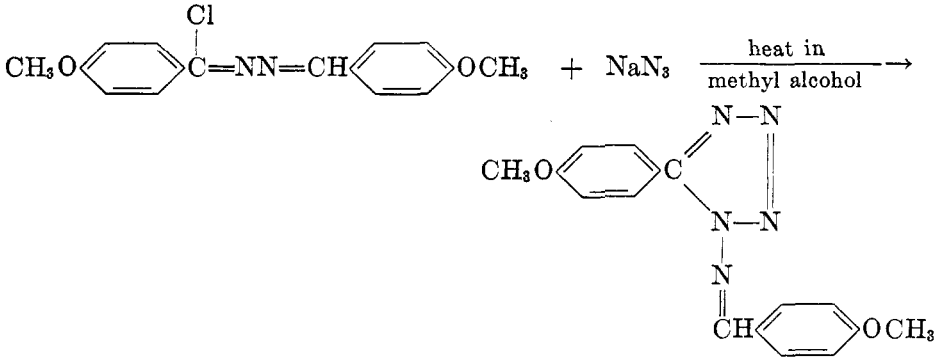
1-phenyl-5-anilino-, 1-*o*-tolyl-5-toluidino-, and 1-*p*-tolyl-5-*p*-toluidino-tetrazoles.

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

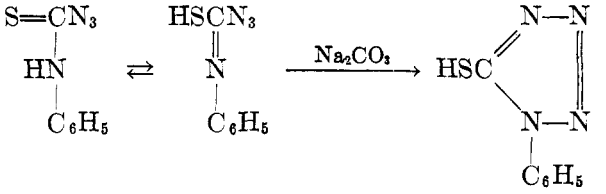




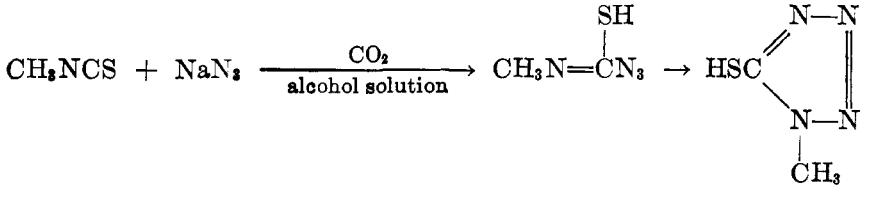
azide was stable enough to be isolated. Subsequently this azide and tetrazole were also prepared from benzal benzohydrazide chloride and sodium azide; in like manner 1-anisylideneamino-5-anisyltetrazole was prepared (122):



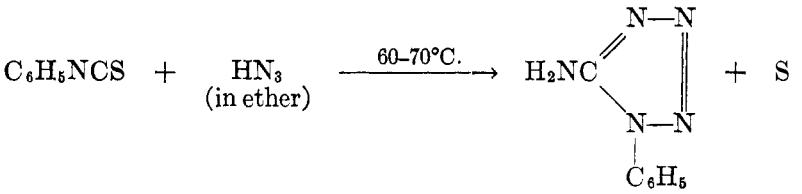
An extension of this reaction to the synthesis of 1-aryl-5-mercaptotetrazoles involves the use of compounds of the type of thiocarbanilic azide. Probably the tautomeric mercapto form is the species undergoing reaction. The rearrangement is effected by the use of alkaline reagents such as sodium carbonate 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.

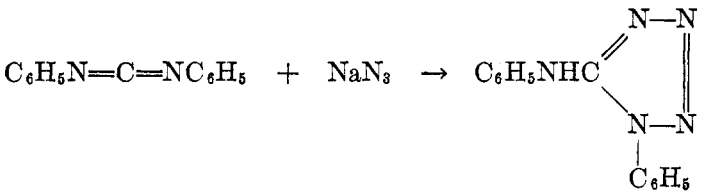


It is interesting that heating phenyl isothiocyanate with hydrazoic acid in ether under pressure results in an elimination of sulfur and formation of 1-phenyl-5-aminotetrazole (82, 110). This reaction was first performed by Oliveri-

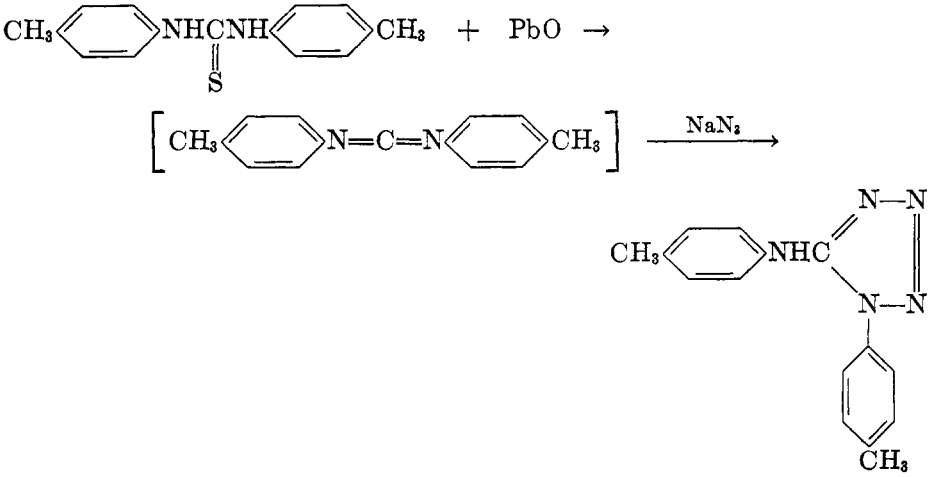


Mandalà and Noto, who believed their product to be an addition compound of hydrazoic acid and phenyl isothiocyanate. It was subsequently shown by Stollé to be sulfur free and identical with 1-phenyl-5-aminotetrazole prepared by a different method.

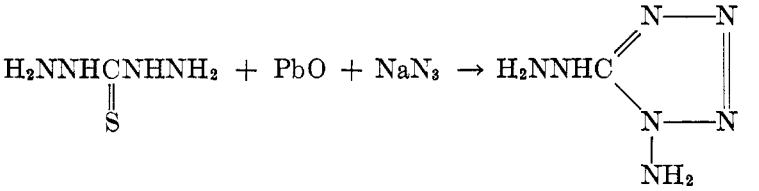
A somewhat similar reaction which has been utilized extensively by Stollé and his collaborators involves the use of carbodiimide derivatives and sodium azide or hydrazoic acid. This reaction, which was discovered independently by Oliveri-Mandalà and Stollé (80, 110), leads to 1-aryl-5-amino- or substituted amino-tetrazoles. Thus, diphenyl carbodiimide and sodium azide heated in absolute alcohol form 1-phenyl-5-anilinotetrazole. 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*-toluidinotetrazole, identical with that obtained from di-*p*-tolylcarbodiimide. Mono-



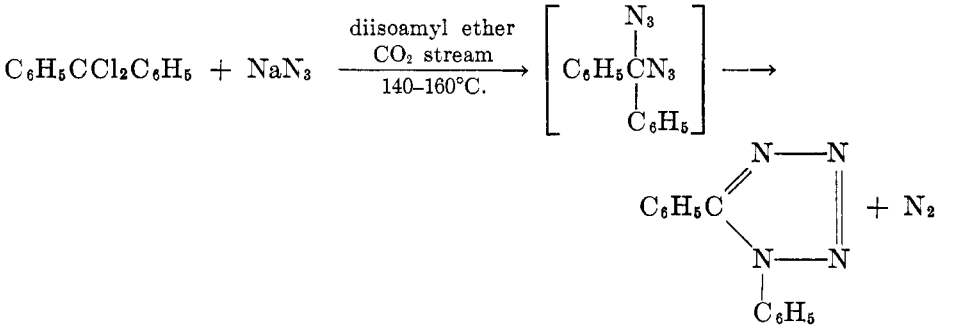
substituted thioureas may also be used; monophenylthiourea in this reaction is converted to 1-phenyl-5-aminotetrazole. This procedure may be used to prepare 1,5-diaminotetrazole by starting with thiosemicarbazide, and 1-amino-5-hydrazinotetrazole by starting with thiocarbohydrazide, both being isolated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



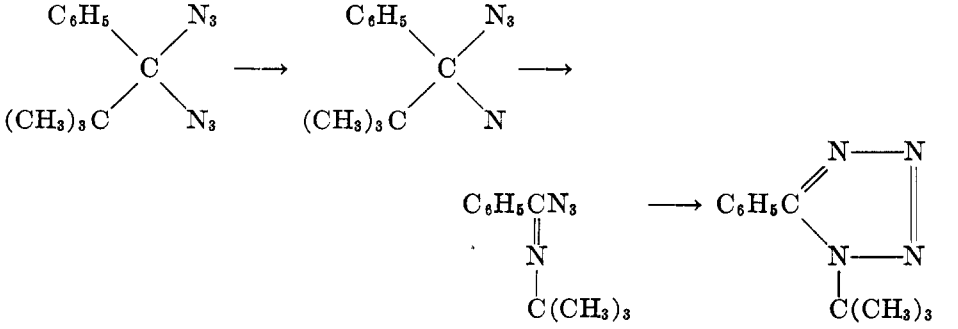
zoles linked to nitrogen in the 5-position this method is probably the most convenient.

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).

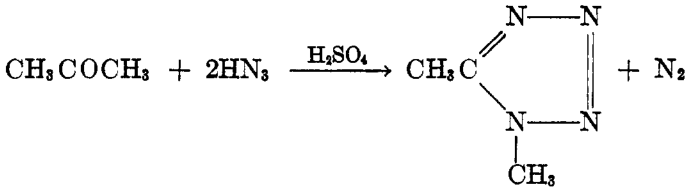


It is of interest that in these cases phenyl migrates in preference to *p*-nitrophenyl, and *tert*-butyl in preference to phenyl. Schroeter considers this synthesis to involve the intermediate formation of monovalent nitrogen, followed by rearrangement to the imide azide, analogous to one view of the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

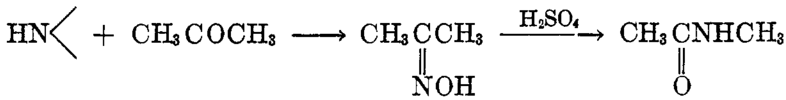
$$CH_3COCH_3 + HN_3 \xrightarrow{H_2SO_4} CH_3CONHCH_3 + N_2$$



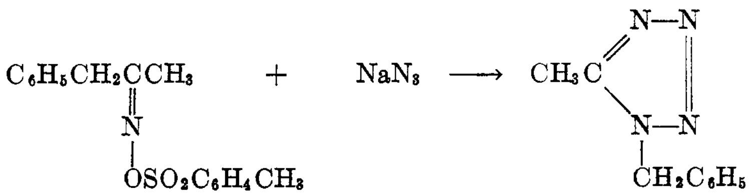
amide under the conditions of the reaction; hence the formation of the tetrazole must involve addition to an intermediate of some sort. The mechanism offered by Schmidt to explain this and other reactions of hydrazoic acid in the presence of acid catalysts assumes the formation of the imide or imine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

$$HN_3 \longrightarrow N_2 + HN\langle$$

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



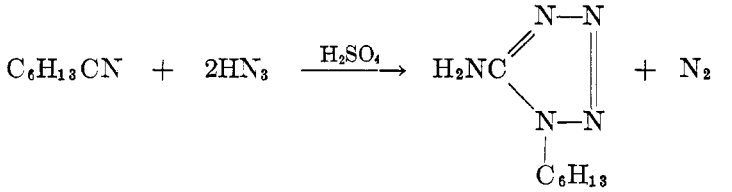
such as the sulfonic, benzenesulfonic, or phosphoric do undergo such reaction. Thus the *p*-toluenesulfonic ester of benzyl methyl ketoxime yields 1-benzyl-5-



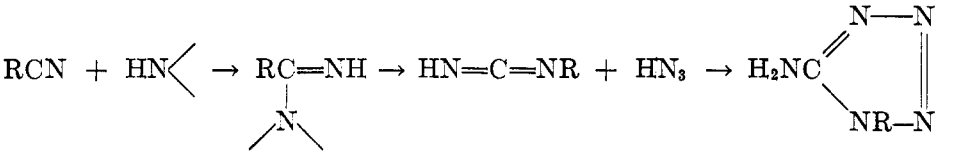
methyltetrazole (12). It appears reasonable to suppose that the formation of a tetrazole from a ketone involves the intermediate formation of the precursor of the oxime, possibly the oxime sulfonic ester, which further reacts with hydrazoic acid to complete the ring. There is some doubt whether the imide 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-,



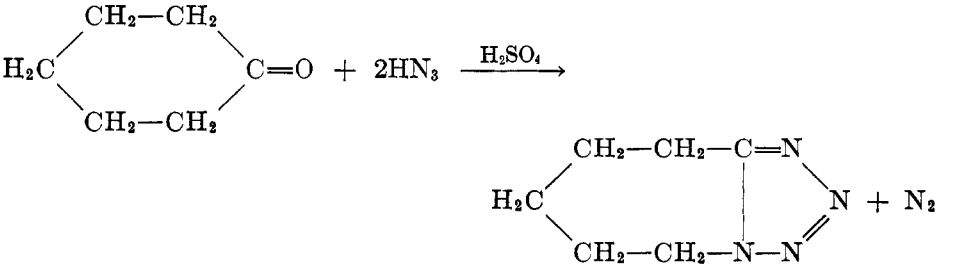
and benzyl-5-aminotetrazoles, as well as the bisaminotetrazole from sebaconitrile, have been prepared in this manner. The mechanism proposed by von Braun and Keller for this reaction involves the formation of a carbodiimide derivative by the agency of the imide radical derived from hydrazoic acid, followed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

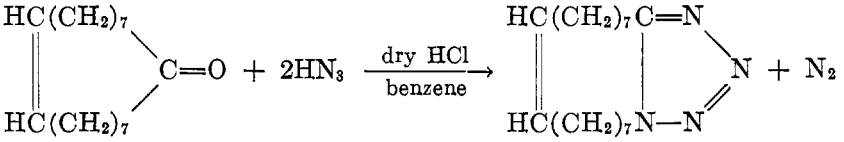
3. Fused-ring 1,5-disubstituted tetrazoles

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.

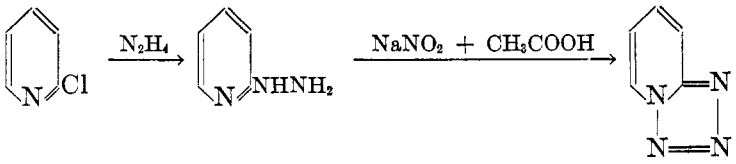


In addition the corresponding tetrazoles from cycloheptanone, cycloöctanone, and cyclopentadecanone were synthesized. Both sulfuric acid and dry hydrogen chloride were used as condensing agents. In the course of this work Ruzicka checked the patent claims of Schmidt and others concerning this reaction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

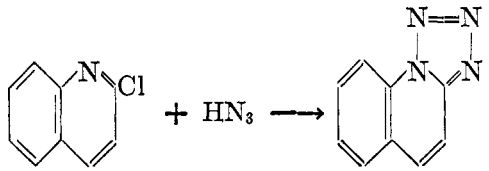
During the preparation of methyl-ε-leucine lactam from methylcyclohexanone and hydrazoic acid, von Braun and Heymons (14) obtained a small amount of a methylmetrazole.

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

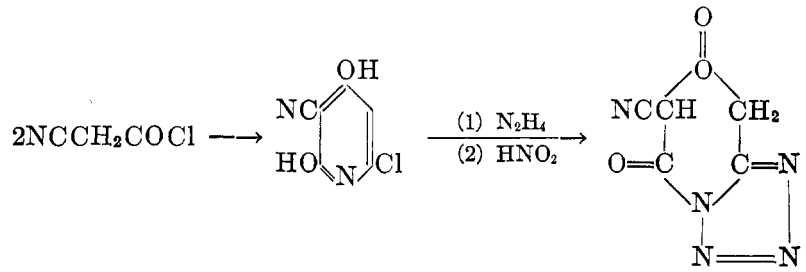
The synthesis of 1,5-disubstituted tetrazoles through the imide azide is as important in the fused-ring series as with the simple derivatives. Both the interaction of a cyclic imide chloride with hydrazine, followed by diazotization, as well as the direct action of hydrazoic acid or sodium azide on the 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



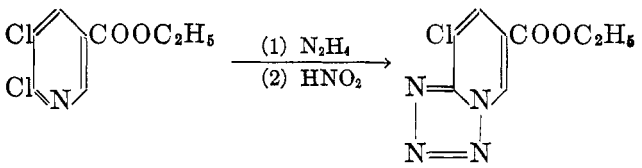
compound, it being formed easily from 2-chloropyridine and hydrazoic acid. Tetrazolo[*a*]quinoline was similarly prepared. Sodium azide could not be used in these syntheses.



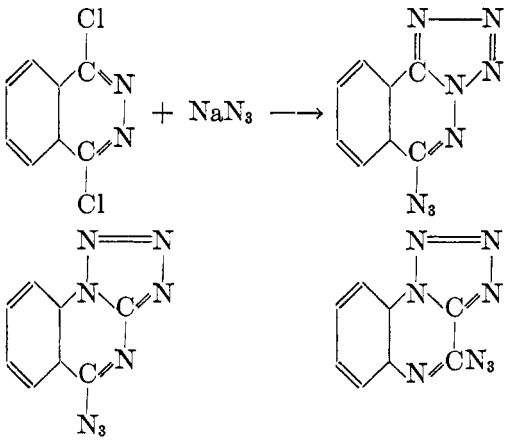
Schroeter and Finck (107), in their study of the spontaneous polymerization of cyanoacetyl chloride, prepared several tetrazole derivatives. This substance undergoes self-condensation with loss of a molecule of hydrogen chloride to form 6-chloronorricinine. Treatment of the latter with hydrazine, followed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

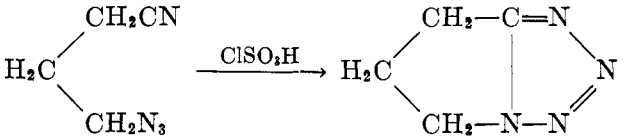


Tetrazolo[*a*]-5-azido-quinazoline

Tetrazolo[*a*]-4-azido-quinoxaline

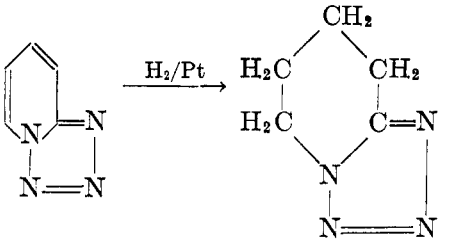
chlorides, but was able to effect ring closure in but one position. When dichlorophthalazine was treated with sodium azide in absolute alcohol tetrazolo[*a*]-6-azidophthalazine was formed (130). In like manner, only one tetrazole ring could be formed in the compounds derived from dichloroquinazoline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



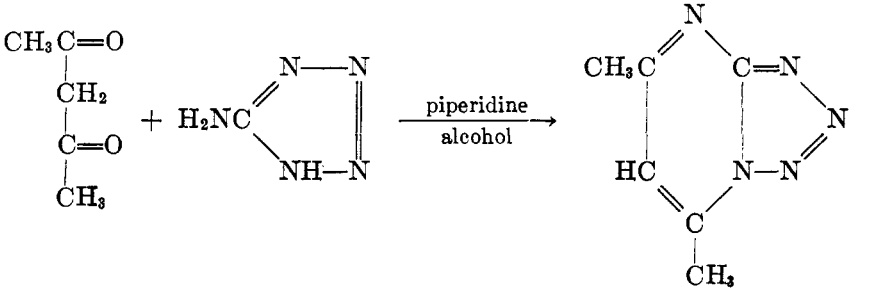
methylenetetrazole. Syntheses of tetramethylenetetrazole, dimethyltetramethylenetetrazole, and the ethyl ester of tetramethylenetetrazolecarboxylic acid also are claimed to be feasible by this procedure.

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

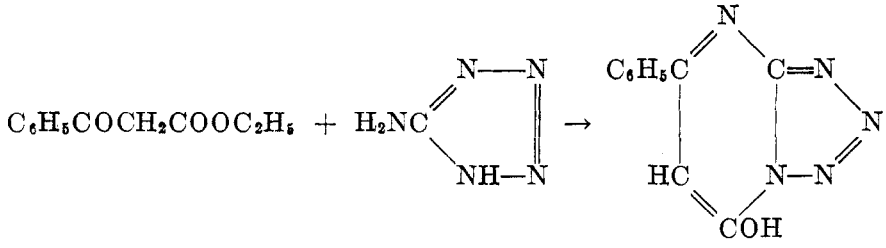


should be mentioned in this connection that Roblin and coworkers (97) were unable to reduce 5-*p*-nitrobenzenesulfonamidotetrazole without splitting the tetrazole ring, although a variety of methods, including hydrogenation in the presence of palladium, were employed.

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. Acetoacetic ester led to the 7-methyl derivative and benzoylacetic ester to the 7-phenyl compound.



IV. Reactions

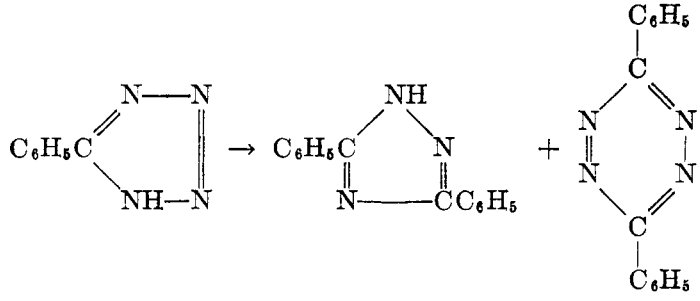
In the foregoing discussion numerous reactions of substituted tetrazoles have been recorded. It is apparent that the several organic radicals linked to the tetrazole ring can undergo the customary transformations. It is also evident that the tetrazole ring exhibits a chemical stability wholly comparable 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:

$$2CN_6 \rightarrow (CN)_2 + 5N_2$$

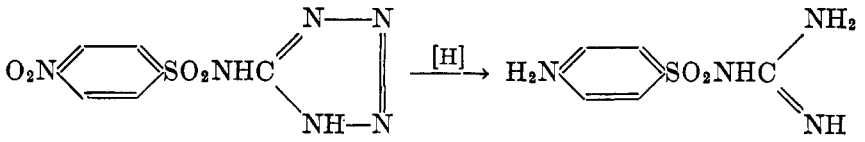
A small amount of a solid substance thought to be oxytetrazole was also formed.

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



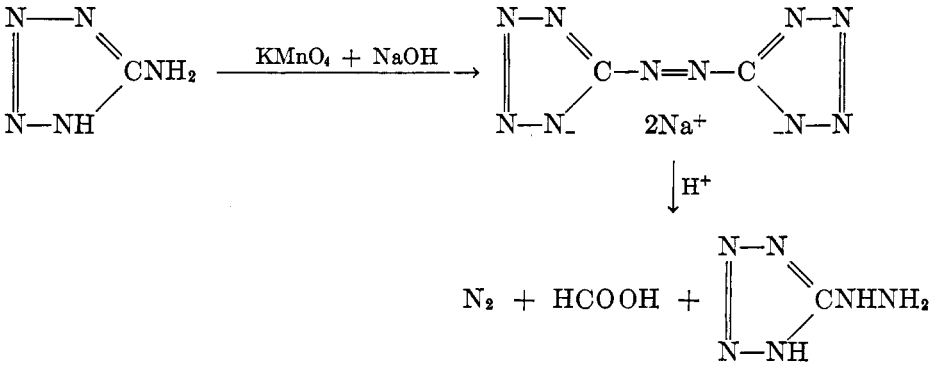
to be a type of dismutation. Similarly the extended heating of 5-*p*-anisyltetrazole at 218°C. leads to the formation of 3,5-bis(*p*-anisyl)-1,2,4-triazole (64). No other studies of the purely thermal decomposition of tetrazoles are recorded.

Mention has already been made of the disruption of the tetrazole ring in 5-*p*-nitrobenzenesulfonamidotetrazole during attempted reduction of the nitro group (97). Sulfanilylguanidine was formed even with such a mild reducing agent as iron and acetic acid in alcohol. On the other hand, the reported



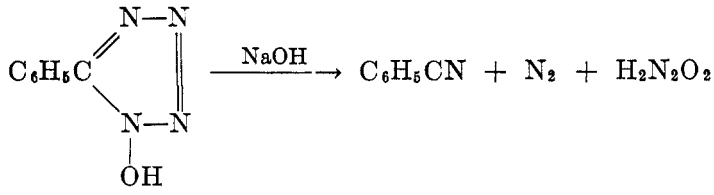
catalytic reduction of pyridotetrazole (23) reduced only the pyridine ring. The difference may lie in the greater negativity of the *p*-nitrobenzenesulfonamido group compared to that of the fused pyridine ring. Reductions of various nitrosubstituted phenyltetrazoles, however, have been carried out without splitting the heterocyclic ring. Thus, stannous chloride converts 1-(*p*-nitrophenyl)tetrazole (39) and 5-(*o*-nitro-*p*-anisyl)tetrazole (64) to the corresponding amino derivatives without ring fission.

That the tetrazole ring is stable toward strenuous oxidizing agents is indicated by the various conditions under which the parent compound is formed from substituted derivatives. These were mentioned in the discussion of the synthesis of tetrazole. In the case of 5-aminotetrazole, however, treatment with weakly alkaline permanganate results in the formation of hydrogen cyanide and carbon dioxide (136). Strongly alkaline permanganate converts 5-aminotetrazole to the salt of 5-azotetrazole. When this salt is neutralized, nitrogen

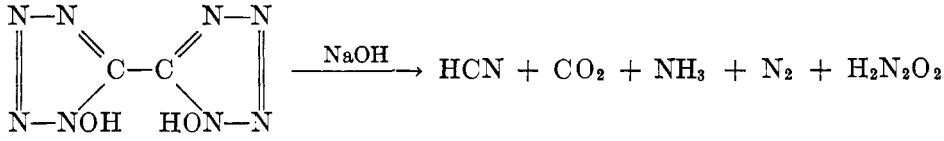


is liberated and formic acid and tetrazolylhydrazine are formed. It is evident that the decomposition of azotetrazole does not proceed by the same mechanism as the oxidative decomposition of 5-aminotetrazole.

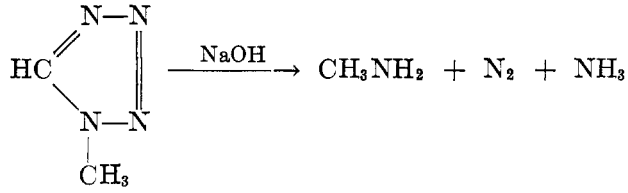
In the case of the alkaline decomposition of tetrazoles, the effect of negative substituents linked to the ring nitrogen atoms is to weaken the ring. While 5-phenyltetrazole is unchanged on heating with potassium hydroxide at 240°C. (91), 1-hydroxy-5-phenyltetrazole is ruptured by dilute alkali on warming (147).



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

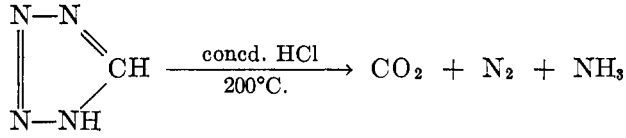


Heating 1-methyltetrazole with alkalies leads to the formation of nitrogen,

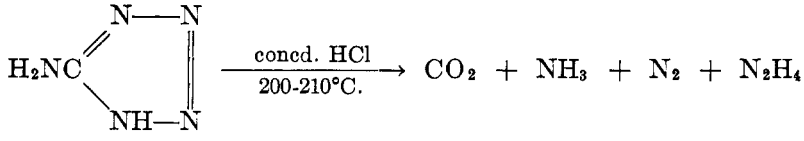


ammonia, and methylamine (81). Not enough compounds have been investigated to generalize concerning the limits of resistance of the tetrazole cycle toward alkali.

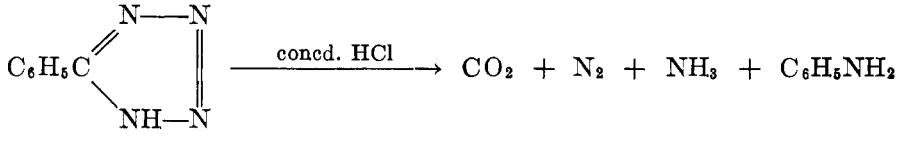
Most tetrazoles are stable toward acids at moderately elevated temperatures, but are decomposed by them above 200°C. Heating tetrazole at this temperature with hydrochloric or sulfuric acid results in the formation of carbon



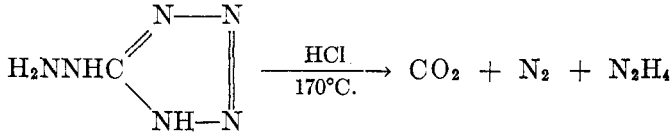
dioxide, ammonia, and nitrogen. If 5-aminotetrazole is heated with hydrochloric acid at 160-170°C., no splitting occurs; with the same reagent at 200–210°C. it is completely decomposed (139).



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

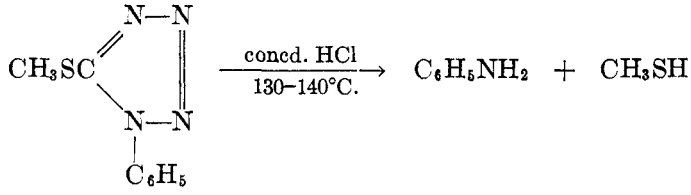


shows that a rearrangement has occurred, the group in the 5-position having become separated from carbon and attached to nitrogen. From the evidence it is impossible to indicate a satisfactory mechanism, but the similarity to the Beckmann rearrangement is apparent. Although 5-hydrazinotetrazole yields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



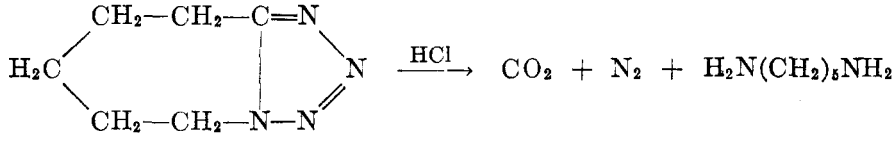
acid (139), it is possible that it decomposes in the same manner, since the product expected, triazane, would undoubtedly immediately decompose. Ditetrazolyl on warming with concentrated sulfuric acid yields nitrogen, ammonia, and carbon dioxide (85). The absence of cyanogen or other compound with linked 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



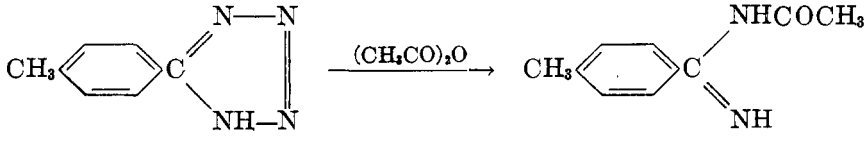
(38) does not lead to a clear indication of the mode of decomposition. It does not appear, however, to be inconsistent with a mechanism involving preliminary separation of the CH_3S group.

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

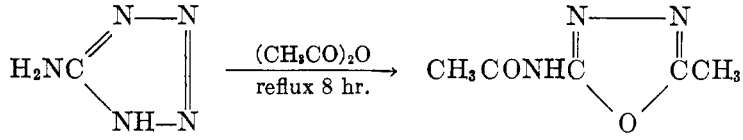


by Schmidt for this decomposition involves preliminary formation of nitrogen and a pentamethyleneamine isocyanate, followed by hydrolysis of the cyanate group. In this case the group linked to the carbon of the tetrazole ring is also detached under the influence of acid.

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*-toluamidine 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-acetylamino-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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