THE CHEMISTRY OF 1,2,4-TRIAZOLES

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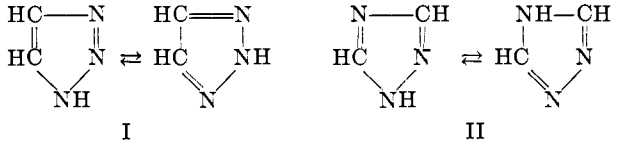
CONTENTS

I. Introduction

A. General

In five-membered ring systems the presence of three nitrogen heteroatoms defines an interesting class of compounds, the triazoles. These may be of two types, the 1,2,3-triazoles or *v*-triazoles (I) and the 1,2,4-triazoles or *s*-triazoles (II). The chemistry of the *v*-triazoles has already been reviewed (44).



I II

In this review 1,2,4-triazoles and their ring-fused derivatives are discussed, the literature having been consulted up to the end of 1959. Mention is made of the many varied uses of these compounds, in particular that of 3-aminotriazole, better known as Amizol, an important herbicide. The use of this particular agent in cranberry horticulture recently received national prominence when it was found that it could induce cancerous growth in the thyroid of rats.[1]

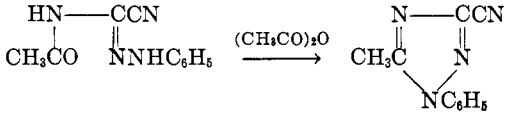
Two earlier publications (182, 235) deal briefly with the chemistry of 1,2,4-triazoles. A third, more detailed treatment (115) also includes their various oxygen- and sulfur-containing derivatives, such as urazoles and thiourazoles, an aspect of the chemistry of 1,2,4-triazoles that is not included here. Since these publications cover the earlier work on 1,2,4-triazoles, emphasis is placed on more recent work in this review.

B. Historical

The name triazole was first given to the carbon–nitrogen ring system $C_2N_3H_3$ by Bladin (55, 56), who described derivatives of it as early as 1885. This work was a direct result of Fischer's discovery that cyanogen would react with phenylhydrazine to give the so-called dicyanophenylhydrazine (119), and although the structures reported by Bladin are slightly incorrect (38,

[1] Report in *The New York Times*, International Edition, Weekly Review, November 15, 1959.

262), he should receive full credit for recognizing and establishing this ring system.



The original nomenclature and method of numbering the ring system, shown in III, are similar to those used

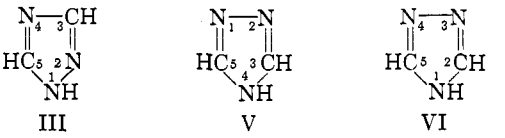
III IV

today. An alternative name for the ring system, introduced in 1889 by Andreocci (15, 16, 17, 19, 21), is pyrrodiazole, which is regarded as a member of a class of compounds analogous to pyrrole. The parent pyrrodiazole is represented by formula IV. It was first suggested that a system of nomenclature similar to that of pyrrole be used, but this was later changed to that illustrated in formula III, and the name triazole has since found general acceptance.

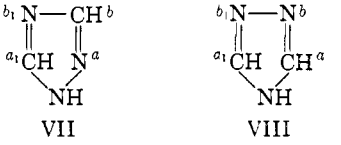
A most intensive investigation of the chemistry of 1,2,4-triazoles, especially by Andreocci's successors in Rome, followed the pioneering work of these two investigators. From about 1925 to 1946 little interest was shown in this field. The discovery that certain types of triazoles were capable of inhibiting fog formation in photographic emulsions and that others were useful herbicides and convulsants led to a renewed attention, particularly by the chemical industry, to both simple and fused triazole systems. All triazoles are of synthetic origin and there is no report of detection of this ring system in nature.

C. NOMENCLATURE

Several methods of numbering and naming the 1,2,4-triazole system are encountered in the literature. The original method is depicted in formula III (56, 357). The *Ring Index* (264) also uses the same order of numbering the ring, and III is called 1,2,4-triazole (R.I. No. 78). The tautomeric form has been numbered in two ways, represented by formulas V and VI, the former being called a 4,1,2-triazole and the latter a 1,3,4-triazole (99, 269). The *Ring Index* terms this form a 4,1,2-triazole (R.I. No. 79) and uses the same order of numbering as in formula V. Trivial names for the two tautomeric forms are pyrro(ab_1)diazole and pyrro(bb_1)diazole, the numbering of the rings being shown in formulas VII and VIII, respectively (15). The term *s*-triazole was later introduced to distinguish a *v*-triazole from a 1,2,4-triazole (374), and this description is applied to any 1,2,4-triazole with a free imino hydrogen atom.



III V VI



VII VIII

Prior to 1940 *Chemical Abstracts* distinguished between 1,2,4-triazoles, 4,1,2-triazoles, and 1,3,4-triazoles, but present practice is to treat them all as *s*-triazoles; in those compounds with *N*-substituents the relationship to the parent form is signified by describing them as 1,2,4-1*H*- or 1,2,4-4*H*-triazoles. Thus III and V are called *s*-triazole and their corresponding phenyl derivatives are called 1-phenyl-1,2,4-1*H*-triazole and 4-phenyl-1,2,4-4*H*-triazole, respectively. This nomenclature is used in this review, and minor variations of it are sometimes found in other journals.

This method conforms to the rules of nomenclature of the International Union of Pure and Applied Chemistry for heterocyclic systems (185) and enables the structure of a triazole to be seen at a glance. It is based on the assumption that 1,2,4-triazole is capable of existing as two tautomeric forms, III and V. No such isomers of 1,2,4-triazole have ever been isolated and, indeed, all experiments designed to give isomeric *C*-monosubstituted and *C*-disubstituted triazoles containing an imino hydrogen atom always yield only one product (282). However, isomeric *N*-substituted triazoles are known, and these are regarded as being derived from each of the tautomeric forms, III and V.

A more modern representation of the structure of 1,2,4-triazole (Section III) takes cognizance of the imino hydrogen atom not being attached to any of the nitrogen atoms, but rather existing as a charged atom closely bound by a negatively charged triazole nucleus stabilized by resonance. With this representation, the system of nomenclature described above is unnecessarily cumbersome but may be readily modified to a more acceptable form. Those triazoles containing a free imino hydrogen atom are still described as before, but in *N*-substituted triazoles the prefix 1*H* or 4*H* is now no longer necessary. The substitution of the nitrogen atom firmly establishes the structure of the molecule, which is completely defined by numbering the substituent group.

The univalent radical name is triazolyl and partial saturation is depicted by the use of the term "triazoline" or by the prefix dihydro-. The name triazolidine or the prefix tetrahydro- signifies complete saturation. Oxygen derivatives of dihydrotriazoles (triazolines) are called triazolones, and the corresponding compounds containing sulfur are called thiotriazolones. 3,5-

TABLE 1

Methods available for the synthesis of 1,2,4-triazole

Reactants and Mole Proportions	Conditions	Yield	References
		per cent	
1 Formhydrazide and 1 formamide	Distillation to 260°C.; atmospheric pressure	<50	(257, 258)
1 Hydrazine hydrochloride and 2 formamide	Distillation to 260°C.; atmospheric pressure	Very poor	(257, 258)
1 Hydrazine hydrochloride and 2 ammonium formate	Distillation to 260°C.; atmospheric pressure	Very poor	(257. 258)
1 Diformhydrazide and 1 formamide	Distillation to 260°C.; atmospheric pressure	Poor	(270)
1 Hydrazine hydrochloride, 2 formamide, and 2 powdered potassium hydroxide	Distillation to 260°C.; atmospheric pressure	17	(333)
1 Hydrazine hydrate and 1 formamide	Rapid distillation to 280°C.; atmospheric pressure	30	(5)
Diformhydrazide and excess ammonia	Autoclave at 200°C.; 24 hr.	70–80	(5)
1 Hydrazine, 2 formamide, and excess ammonia	Autoclave at 200°C.; 24 hr.	70–80	(5)
1 1,3,5-Triazine and 1.5 hydrazine hydrochloride	Refluxing 8 hr. in ethanol	Quantitative	(148, 149, 150)
3-Methyl-1,2,4-triazole and excess potassium permanganate	Alkaline oxidation; final decarboxylation at 120°C.	—	(20, 21, 345)
1(or 4)-Phenyl-1,2,4-triazole and excess potassium permanganate	Boiling under acid conditions	—	(20, 260)
3-Amino-1,2,4-triazole	Diazotization in the presence of hypophosphorous acid at 35°C.	75	(167)
Urazole and phosphorus pentasulfide	Heating to 180–200°C.	—	(266)

Dioxotriazolidines and the corresponding sulfur-containing compounds are also known as urazoles and dithiourazoles, respectively. The diimino compound corresponding to urazole is called guanazole.

Several 1,2,4-triazoles are known by trivial names, such as Azoman (4-cyclohexyl-3-ethyl-1,2,4-triazole), used to produce convulsions, and Amizol (3-amino-1,2,4-triazole), a herbicide.

II. Synthesis of 1,2,4-Triazoles

The many excellent methods available for the preparation and conversion of oxygen- and sulfur-containing triazoles into the parent triazoles make them important synthetic intermediates, and these are discussed fully in this section. Chlorotriazoles and triazolecarboxylic acids are usually prepared by the modification of some triazole system; these reactions are discussed in Section IV.

A. 1,2,4-Triazole

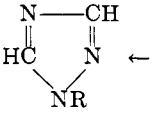
The early methods of preparation of this parent triazole were all distinguished by their simplicity and by the low yields obtained, though they made the nucleus available for study within a year of the original discovery of Bladin. These have now been replaced by later modifications (5) or by more efficient reactions (148, 149, 150, 167). Table 1 shows the methods available for the synthesis of 1,2,4-triazole.

B. Monosubstituted Triazoles

1. 1-Substituted derivatives

The fusion of an *N*-formyl-*N'*-alkyl(or aryl)hydrazine with formamide at 250–280°C. results in the formation of a 1-substituted triazole in poor yield (273). Separation of the triazole from by-products is often tedious and the reaction is of more importance in the preparation of di- and trisubstituted triazoles. The reaction may be varied by heating formamide with a substituted hydrazine hydrochloride, and this general type of reaction has become known as the Pellizzari reaction (table 2).

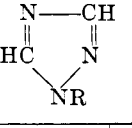
$$RNHNHCHO + HCONH_2 \rightarrow$$



$$\leftarrow HCONH_2 + RNHNH_2 \cdot HCl$$

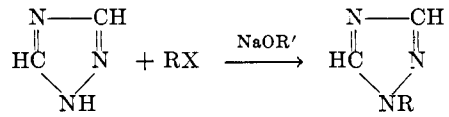
TABLE 2

1-Substituted triazoles prepared by the Pellizzari reaction



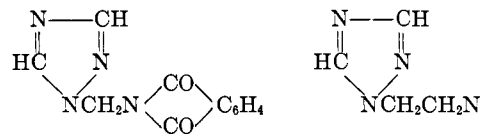
Component Heated with Formamide	R	Reaction Temperatures	Melting Point	Boiling Point at 760 mm.	References
		°C.	°C.	°C.	
N-Formyl-*N'*-methylhydrazine	CH_3—	190–200	20	178, 183	(273)
N,N'-Diformyl-*N'*-methylhydrazine	CH_3—	190–200	20	178, 183	(273)
N-Formyl-*N'*-phenylhydrazine	C_6H_5—	280	47	266	(18, 21, 257, 268, 357)
o-Tolylhydrazine hydrochloride	*o*-$CH_3C_6H_4$—	200	45	270	(269)
N-Formyl-*N'*-(*o*-tolyl)hydrazine	*o*-$CH_3C_6H_4$—	265–270			
p-Tolylhydrazine hydrochloride	*p*-$CH_3C_6H_4$—	200	67	265	(269)
N-Formyl-*N'*-(*p*-tolyl)hydrazine	*p*-$CH_3C_6H_4$—	270–280			
α-Naphthylhydrazine hydrochloride	*α*-$C_{10}H_7$—	200	99		(273)
β-Naphthylhydrazine hydrochloride	*β*-$C_{10}H_7$—	200	111		(269)

1-Alkyl-1,2,4-1*H*-triazoles are most conveniently prepared from triazole itself by alkylation with suitable reagents. The 1-substituted compound is formed almost exclusively (30). Thus 1-methyltriazole is prepared from triazole, sodium methoxide, and methyl iodide in methanol at 100°C. (30, 273); replacement of methyl iodide by ethyl bromide and allyl bromide gives the corresponding 1-ethyl- and 1-allyltriazole, respectively.



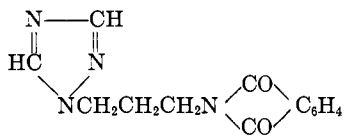
IX

The reaction of the sodium derivative of 1,2,4-triazole with alkyl halides is quite general and has been used to prepare more complex 1-substituted 1,2,4-1*H*-triazoles (5). Reaction with ethyl bromoacetate gives ethyl 1,2,4-1*H*-triazoleacetate (IX: R = $CH_2COOC_2H_5$), readily converted into the corresponding acid, amide, and alcohol (IX: R = CH_2COOH, CH_2CONH_2, and CH_2CH_2OH, respectively), and condensation with *N*-bromomethyl-, β-bromoethyl-, and γ-bromopropylphthalimides gives, respectively, 1-phthalimidomethyl-1,2,4-1*H*-triazole (IXa), 1-β-phthalimidoethyl-1,2,4-1*H*-triazole (IXb), and 1-γ-phthalimidopropyl-1,2,4-1*H*-triazole (IXc).



IXa

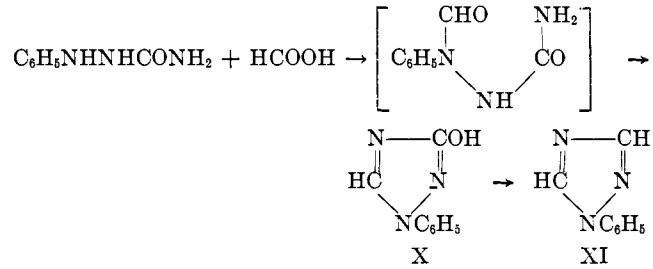
IXb



IXc

These phthalimidotriazoles can be easily hydrolyzed to the corresponding primary amines with hydrochloric acid.

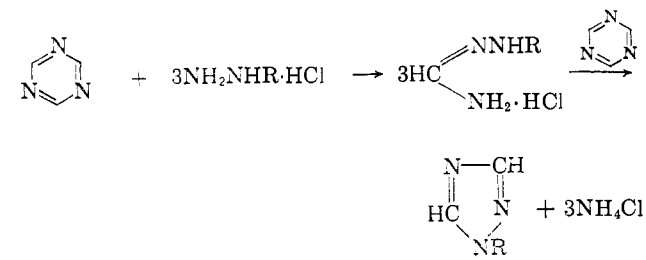
Three other methods are of practical importance, and one involves oxidative removal of a hydroxyl group from a disubstituted triazole. In this method the starting material is a 1-arylsemicarbazide; as it makes 1-aryltriazoles readily available, it is the method of choice for their preparation. This is illustrated by the formation of 3-hydroxy-1-phenyl-1,2,4-1*H*-triazole (X) from 1-phenylsemicarbazide and boiling anhydrous formic acid; the removal of the hydroxyl group is accomplished by heating X to over 200°C. with phosphorus pentasulfide (357); 1-phenyl-1,2,4-1*H*-triazole (XI) is obtained in 80 per cent yield.



X XI

Analogous to this method is the formation of 3-mercapto-4-phenyl-1,2,4-4*H*-triazole from 4-phenylthiosemicarbazide, ethyl formate, and sodium ethoxide (275), and the formation of 3-mercapto-1-(*p*-sulfamoylphenyl)-1,2,4-1*H*-triazole from 1-(*p*-sulfamoylphenyl)-thiosemicarbazide and formic acid (14). This method may also be used for the preparation of 1,5-disubstituted 1,2,4-1*H*-triazoles.

The other method involves the reaction of *s*-triazine with a substituted hydrazine salt (149). For example, from phenylhydrazine hydrochloride 1-phenyl-1,2,4-1*H*-triazole is obtained in 83 per cent yield; similarly, 1-methyl-1,2,4-1*H*-triazole results in 81 per cent yield from the use of methylhydrazine hydrochloride. This reaction may be explained simply as follows (149): A molecule of *s*-triazine undergoes ring cleavage to a substituted formamidrazone, which reacts immediately with another molecule of *s*-triazine to yield the substituted triazole and ammonia.



2. 3(or 5)-Substituted derivatives[2]

The usual way of preparing a triazole of this nature is by the cyclization of a preformed nucleus of the following types:

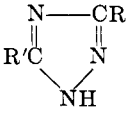
Type A Type B

The former type of ring closure has become established as the most efficient method of synthesis of *C*-monosubstituted triazoles. The preformed skeleton is such that on ring closure a triazole containing a mercapto or hydroxyl group is obtained, and this is

[2] It should be appreciated that with *C*-monosubstituted triazoles no substitution isomers exist, owing to the mobility of the hydrogen atom attached to the nitrogen atom. The convention of writing them as 3-substituted triazoles is one of convenience only.

TABLE 3

3-Substituted triazoles, 3-substituted 5-mercaptotriazoles, and some derivatives prepared by the cyclization of 1-acylthiosemicarbazides with alkali



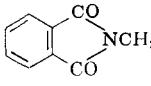
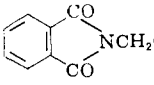
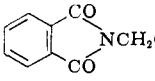
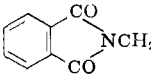
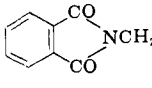
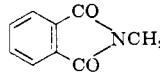
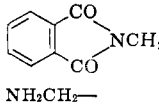
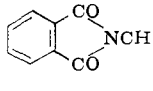
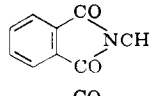
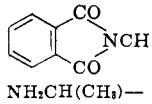
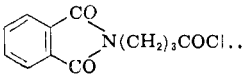
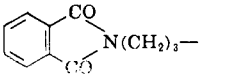
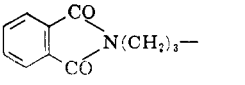
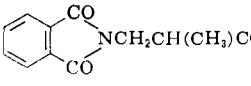
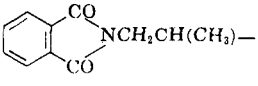
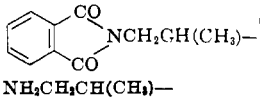
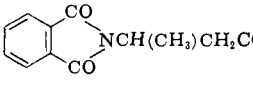
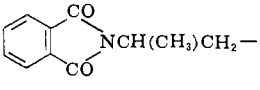
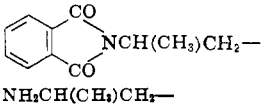
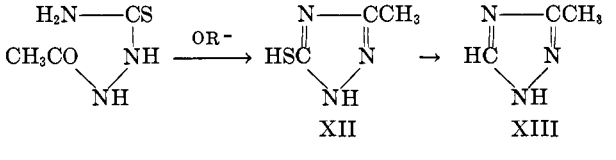
Acid Chloride Used	R	R′	Melting Point	Yield	Melting Point of Salt	References
			°C.	*per cent*	°C.	
CH_3COCl	CH_3—	SH	260–261	—	—	(191)
			282–283	83	—	(125)
—	CH_3—	H	94	61–90	—	(191)
		SH	295–297	50	—	(2, 3)
—		SCH_3	170–172	—	—	(2, 3)
—		H	215	43	245 (hydrochloride)	(2, 3)
—	$-CH_2CH_2NH_2$	H	83–85 (b.p. 160/0.1 mm.)	80	215 (d.) (dihydrochloride) 190 (dipicrate)	(2, 3)
—	$-CH_2CH_2NH_2$	SH	296–298 (d.)	61	270 (hydrochloride)	(2, 3)
—	$-CH_2CH_2NH_2$[a]	SCH_3	—	70	218 (d.) (hydrochloride)	(2, 3)
—	$-CH_2CH_2NH_2$[b]	SO_2NH_2	280–282 (d.)	40	—	(2, 3)
—	$-CH_2CH_2NHCH(CH_3)_2$[c]	H	—	—	186 (dihydrochloride)	(2, 3)
				72	142–144 (dipicrate)	
—	$-CH_2CH_2NHCH_2C_6H_5$[d]	H	—	—	220 (dihydrochloride)	(2, 3)
				70	115–117 (dipicrate)	
—	$-CH_2CH_2NHCONH_2$[e]	H	188–190	—	—	(2, 3)
—	$-CH_2CH_2NHCOC_6H_5$[f]	H	189–190	55	—	(2, 3)
—	$-CH_2CH_2NHCOCH_3$[g]	H	—	—	160 (hydrochloride)	(2, 3)
$C_6H_5OCH_2COCl$	$C_6H_5OCH_2$—	SH	224–225	65	—	(191)
—	$C_6H_5OCH_2$—	H	85	50	172–175 (hydrobromide)	(191)
CH_3OCH_2COCl	CH_3OCH_2—	SH	185–187	54	—	(191)
—	CH_3OCH_2—	H	65–66	40	—	(191)
$C_2H_5OCH_2COCl$	$C_2H_5OCH_2$—	SH	130–131	42	—	(191)
—	$C_2H_5OCH_2$—	H	54 (b.p. 118/0.5 mm.)	—	—	(191)
$C_2H_5OOCCH_2COCl$	$C_2H_5OOCCH_2$—	SH	192–194	55	—	(4)
—	$C_2H_5OOCCH_2$—[h]	H	82–83	48	—	(4)
—	NH_2COCH_2—[i]	H	148–149	—	—	(4)
—	$CH_3NHCOCH_2$—[j]	H	180	86	—	(4)
—	$(CH_3)_2NCOCH_2$—[k]	H	103–104	70	—	(4)
—	$(CH_3)_2NCH_2CH_2$—[l]	H	—	80	155–157 (dihydrochloride) 181–182 (dipicrate)	(4)
—	$CH_3NHCH_2CH_2$—[m]	H	—	26	175–178 (dihydrochloride) 159–160 (dipicrate)	(4)
$C_2H_5OCH_2CH_2COCl$	$C_2H_5OCH_2CH_2$—	SH	166–167	30	—	(4)
—	$C_2H_5OCH_2CH_2$—	H	b.p. 130/0.5 mm.	66	—	(4)
—	$ClCH_2CH_2$—[n]	H	—	42	120 (hydrochloride)	(4)
—	$C_2H_5NHCH_2CH_2$—[o]	H	—	30	158–160 (dihydrochloride) 161 (dipicrate)	(4)
—	$(C_2H_5)_2NCH_2CH_2$—	H	—	33	152–155 (dihydrochloride) 160 (dipicrate)	(4)
		SH	293–294	50	—	(4)
—		H	270–272	50	—	(4)
—	NH_2CH_2—	H	—	80	263–265 (dihydrochloride)	(4)
		SH	289–290	52	—	(4)
—		H	195–196	40	—	(4)
—	$NH_2CH(CH_3)$—	H	—	82	182–183 (dihydrochloride)	(4)

TABLE 3—*Continued*

Acid Chloride Used	R	R′	Melting Point	Yield	Melting Point of Salt	References
			°C.	*per cent*	°C.	
		SH	235–237	56	—	(4)
—		H	155–156	35	—	(4)
—	$NH_2(CH_2)_3$—	H	—	84	172–174 (dihydrochloride)	(4)
		SH	247–248	30	—	(4)
—	 [p]	H	210–212	55	—	(4)
—	$NH_2CH_2CH(CH_3)$—	H	—	20	218–220 (sulfate)	(4)
		SH	285–286	30	—	(4)
—		H	199–200	50	—	(4)
—	$NH_2CH(CH_3)CH_2$—	H	—	25	225–227 (sulfate)	(4)
C_6H_5COCl	C_6H_5—	SH	256	80	—	(175)
—	C_6H_5— [q]	H	121	75	—	(174)
p-$CH_3OC_6H_4COCl$	*p*-$CH_3OC_6H_4$—	SH	257	—	—	(175)
—	*p*-$CH_3OC_6H_4$— [q]	H	186	56	—	(174)
p-ClC_6H_4COCl	*p*-ClC_6H_4—	SH	296–298	—	—	(175)
—	*p*-ClC_6H_4— [q]	H	182	56	—	(174)
—	4-C_5H_4N—	SH	321–322 (d.)	Good	—	(371, 372)
			305–308 (d.) [r]	38		(88)
			298–299 (d.) [s, t]	—		(359)
—	4-C_5H_4N— [u]	SCH_3	165–166	—	—	(371, 372)
—	4-C_5H_4N— [v]	H	284–285	—	—	(371, 372)
—	4-(2-$CH_3C_5H_3N$—)	SH	310–320 (d.)	—	—	(359)

[a] From the mercaptan, sodium methoxide, and methyl iodide in methanol.
[b] By oxidation of the mercaptan with chlorine followed by treatment with ammonia.
[c] From the acetone Schiff base by reduction with hydrogen and platinum.
[d] From the benzaldehyde Schiff base by reduction with hydrogen and platinum.
[e] From the corresponding amine dihydrochloride and potassium cyanate.
[f] By benzoylation of the amine.
[g] From acetic anhydride and the amine.
[h] The mercapto group was removed with Raney nickel.
[i] From the ester and alcoholic ammonia.
[j] From the ester and dry methylamine.
[k] From the ester and dry dimethylamine.
[l] From the corresponding amide by reduction with lithium aluminum hydride in tetrahydrofuran solution.
[m] From the 3-β-ethoxyethyltriazole by successive reaction with hydrogen bromide and thionyl chloride.
[n] From the chloride by reaction with ethylamine.
[o] From the chloride by reaction with diethylamine.
[p] 3-β-Phthalimidoisopropyl-1,2,4-triazole.
[q] Desulfurization with Raney nickel, or with hydrogen peroxide in hot acetic acid.
[r] Prepared from isonicotinic acid hydrazide and thiourea by fusion at 160°C. for 3.5 hr.
[s] The acylthiosemicarbazide prepared from the hydrazide and thiocyanic acid at 140°C. or potassium thiocyanate and 1 *N* hydrochloric acid.
[t] Cyclization also effected by boiling in tetralin for 6 hr.
[u] Prepared from the mercaptan and methyl iodide in alcoholic sodium hydroxide.
[v] Desulfurization with Raney nickel.

then removed by oxidation. Thus, 1-acetylthiosemicarbazide may be cyclized with sodium methoxide in methanol to 5-mercapto-3-methyl-1,2,4-triazole (XII), which readily loses the mercapto group on oxidation with nitric acid (366), giving 3-methyl-1,2,4-triazole (XIII) (175, 191).

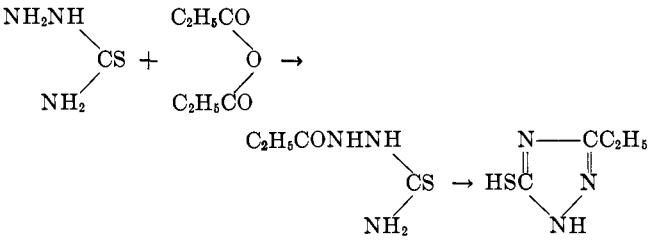


XII XIII

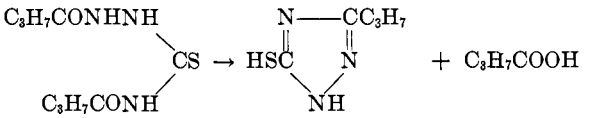
Alternatively, the cyclization can be effected by heating to about 185°C. (125, 359), although yields of the product are often inferior and sometimes much resinification occurs. By the acylation of thiosemicarbazide with appropriately substituted acid chlorides in the presence of pyridine, the necessary intermediates for this type of ring closure may be obtained. The versatility of this method is illustrated by the compounds listed in table 3.

Another route to the acylthiosemicarbazide is offered by the reaction of thiosemicarbazide with aliphatic anhydrides. With one mole of propionic anhydride, 1-propionyl-3-thiosemicarbazide is formed (367), and cyclization to 3-ethyl-5-mercapto-1,2,4-triazole is effected by boiling with 10 per cent sodium carbonate solution for 1 hr. The use of larger quantities of the

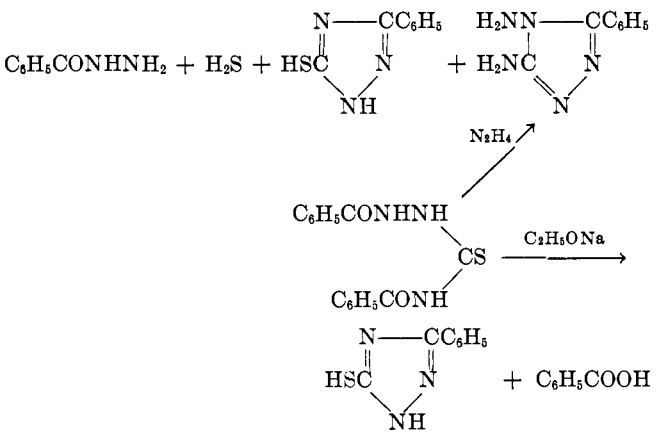
anhydride results in an intractable mixture of di- and tripropionylthiosemicarbazides.



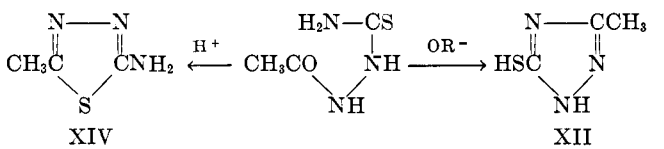
However, with an excess of butyric anhydride diacylation occurs to give the 1,4-dibutyryl-3-thiosemicarbazide, which cyclizes with 10 per cent sodium carbonate solution at 100°C., forming 5-mercapto-3-propyl-1,2,4-triazole.



This latter type of cyclization was also noted when 1,4-dibenzoylthiosemicarbazide was treated with hot sodium ethoxide solution or hydrazine in boiling ethanol (178).



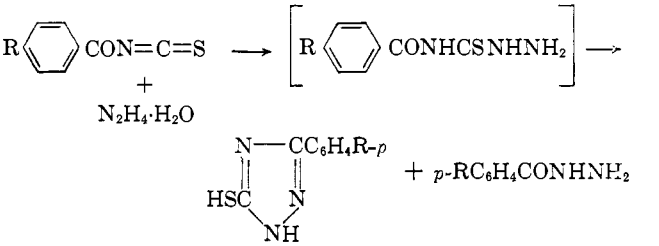
The original cyclization and dehydration were effected by allowing the acetylthiosemicarbazide to stand for several days in a 5 per cent solution of sodium hydroxide (139). After acidification the triazole (XII) was readily separated from the small amount of 2-amino-5-methyl-1,3,4-thiadiazole (XIV) also present. The use of sodium ethoxide, piperidine, or other strong bases results in the exclusive formation of the triazole but under acid dehydration conditions, such as with phosphoric acid, the thiadiazole is often the only product isolated (175).



XIV XII

The use of substituted acylthiosemicarbazides in this reaction is discussed later.

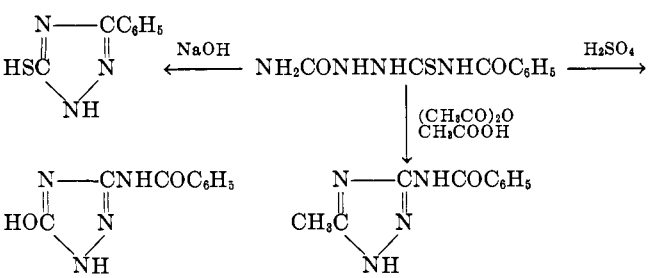
An interesting reaction that must involve a 4-acylthiosemicarbazide as an intermediate occurs when an aroyl isothiocyanate is added to an excess of hydrazine hydrate. Under the alkaline reaction conditions, spontaneous cyclization occurs with the formation of a 3-aryl-5-mercapto-1,2,4-triazole in yields varying from 23 to 37 per cent (174).



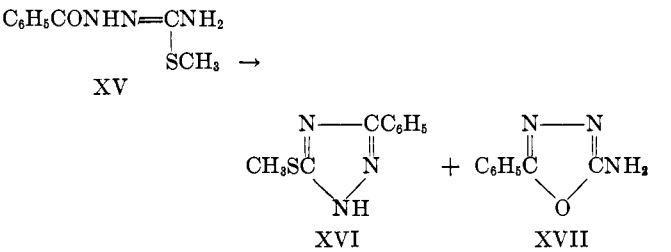
R=H, OCH_3, Cl.

The excess of hydrazine is essential for the reaction to occur; when one equivalent of hydrazine is used, 1,4-dibenzoylthiosemicarbazide and its salt with hydrazine are formed.

It is interesting to consider the products formed from 4-benzoyl-1-carbamoyl-3-thiosemicarbazide under various reaction conditions: 20 per cent sodium hydroxide solution yields 5-mercapto-3-phenyl-1,2,4-triazole, the normal product of ring closure of a 4-acylthiosemicarbazide with alkali; concentrated sulfuric acid at room temperature causes elimination of hydrogen sulfide and formation of 3-benzamido-5-hydroxy-1,2,4-triazole; a hot acetic anhydride–acetic acid mixture results in the formation of 3-benzamido-5-methyl-1,2,4-triazole (334).



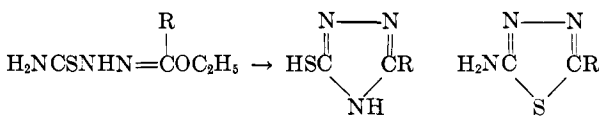
The *S*-methyl derivatives of 1-acylthiosemicarbazides are similarly readily cyclized by hot, alcoholic solutions of organic bases; e.g., 1-benzoyl-*S*-methylisothiosemicarbazide (XV) gives a mixture of 5-methylthio-3-phenyl-1,2,4-triazole (XVI) and 2-amino-5-phenyl-1,3,4-oxadiazole (XVII) (177). Ammonia and



XV XVI XVII

organic bases, such as isopropylamine, diethylamine, pyridine, and triethylamine, may be used in the reaction; in one instance where piperidine was the base used, 3-phenyl-5-piperidino-1,2,4-triazole was also isolated. Should the cyclization agent be a sodium alkoxide, then 5-alkoxy-3-phenyl-1,2,4-triazoles are formed (176). Under the influence of heat alone, methyl mercaptan is readily lost with formation of 2-amino-5-phenyl-1,3,4-oxadiazole (XVII), although it has been reported (372) that 1-(4-nicotinoyl)-*S*-methylisothiosemicarbazide is readily cyclized to the corresponding triazole in quantitative yield by heating for 5 min. at 190–200°C. In contrast to this cyclization, the 4-acyl derivatives of 1-substituted *S*-methylisothiosemicarbazides, in the presence of hot acetic anhydride, cyclize with the formation of 1,5-disubstituted 3-methylthio-1,2,4-1*H*-triazoles (46).

The facility with which thiosemicarbazide derivatives undergo cyclizations of this type is further shown by the ready ring closure of thiosemicarbazones formed from ortho esters and thiosemicarbazide. Thus the thiosemicarbazone of ethyl formate (XVIII: R = H) on treatment with a 10 per cent sodium carbonate solution for 2 hr. at 80°C. readily forms 3-mercapto-1,2,4-triazole (XIX: R = H) (198). Should the

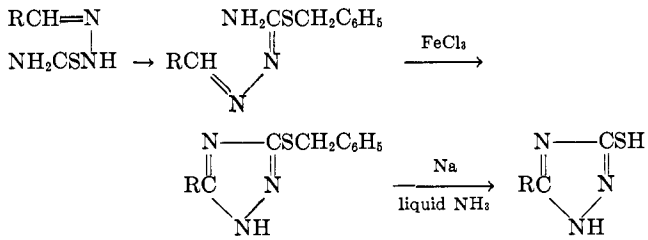


XVIII XIX XX

cyclization be effected by heat, as with the thiosemicarbazone of ethyl acetate (XVIII: R = CH_3) (1), then a mixture of 5-mercapto-3-methyl-1,2,4-triazole (XIX: R = CH_3) and 2-amino-5-methyl-1,3,4-thiadiazole (XX: R = CH_3) is formed.

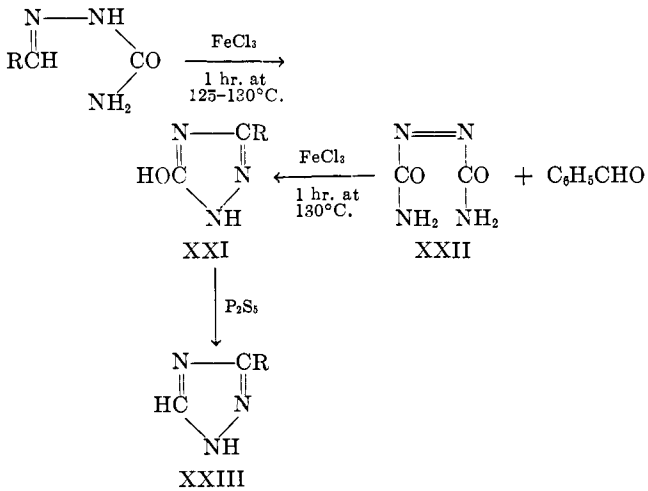
The earlier report (375) that the mild oxidation of benzalthiosemicarbazone with ferric chloride gave 2-amino-5-phenyl-1,3,4-thiadiazole (XX: R = C_6H_5) has since been substantiated (104, 175), and the claim (127) that cyclization occurred with the formation of 5-mercapto-3-phenyl-1,2,4-triazole (XIX: R = C_6H_5) must be regarded as erroneous, although this compound is formed when hydrogen peroxide is used as the oxidizing agent (104).

When the sulfur atom is protected by benzylation, then cyclization to the triazole can be achieved without formation of the thiadiazole by using ferric chloride (45, 110). Thus *p*-acetamidobenzaldehyde thiosemicarbazone is converted into the *S*-benzyl derivative and this is then oxidized with ferric chloride to 5-(*p*-acetamidophenyl)-3-benzylmercapto-1,2,4-triazole. Debenzylation is then effected with sodium and liquid ammonia.



R = *p*-$CH_3CONHC_6H_4$.

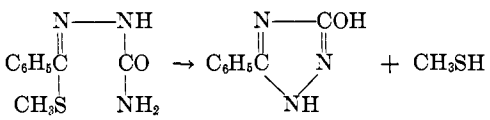
However, the similar oxidation of a benzalsemicarbazone with ferric chloride solution readily gives the 3-aryl-5-hydroxy-1,2,4-triazole (XXI), which may also be obtained by the oxidation of a mixture of benzaldehyde and azodicarbamide (XXII). On fusion of the hydroxytriazole with phosphorus pentasulfide, the hydroxyl group is removed with the formation of the 3(or 5)-substituted triazole (XXIII) (377). Though this was one of the earliest methods used for the synthesis of the triazole nucleus, it has retained its practical importance in providing a cheap route to monosubstituted aryltriazoles.



XXI XXII XXIII

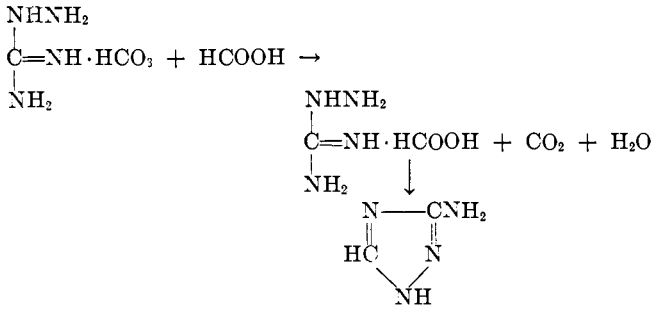
The cyclization of 1-heptoylsemicarbazide with potassium hydroxide yields 3-hexyl-5-hydroxy-1,2,4-triazole (XXI: R = C_6H_{13}) (295). This reaction is analogous to that employing a 1-acylthiosemicarbazide and appears to offer a convenient complementary route to *C*-monosubstituted triazoles (134).

A reaction that may be regarded as belonging to Type A occurs when 1-[α-(methylthio)benzylidene]-semicarbazide (XXIV) is pyrolyzed at 210°C. Methyl mercaptan is readily eliminated with the formation of 3-hydroxy-5-phenyl-1,2,4-triazole (256).

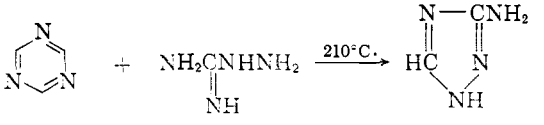


3-Amino-1,2,4-triazole is prepared in practically quantitative yield by a reaction of Type B, involving the heating of an aminoguanidine salt with formic acid in an inert solvent at 100–120°C. (12, 247). Its prepara-

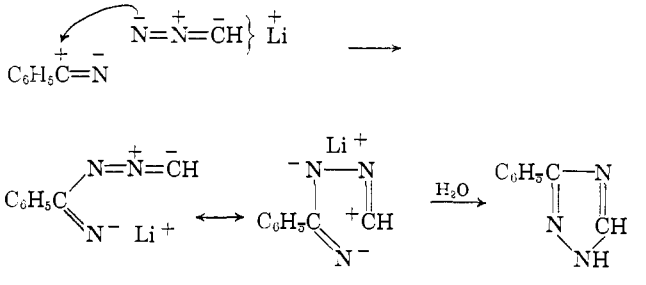
tion from formylguanidine nitrate and sodium carbonate (242, 344) is now of purely theoretical interest.



s-Triazine may be degraded to various 3-substituted 1,2,4-triazoles by heating to 120°C. with the appropriate reagent (147, 148). Thus with semicarbazide, thiosemicarbazide, and aminoguanidine it gives 3-hydroxy-, 3-mercapto-, and 3-amino-1,2,4-triazole in 19, 64, and 48 per cent yield, respectively. With hydrazine hydrochloride 1,2,4-triazole itself is obtained in quantitative yield.

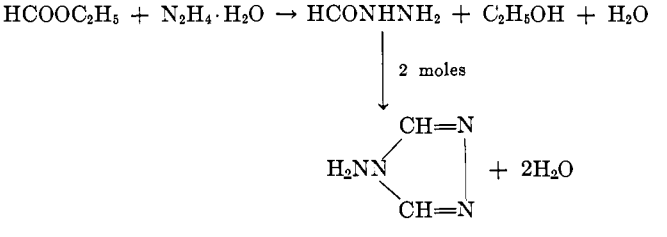


The reactions of diazomethyllithium are extremely interesting. With phenyl cyanide it yields 3-phenyl-1,2,4-triazole. The following mechanism has been proposed for this reaction (243):

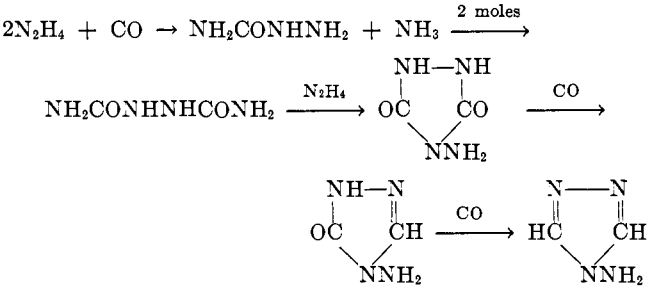


3. 4-Substituted derivatives

The simplest 4-substituted triazole, 4-amino-1,2,4-4*H*-triazole, is conveniently prepared from ethyl formate and hydrazine hydrate (11) or from formic acid and hydrazine hydrate (169).



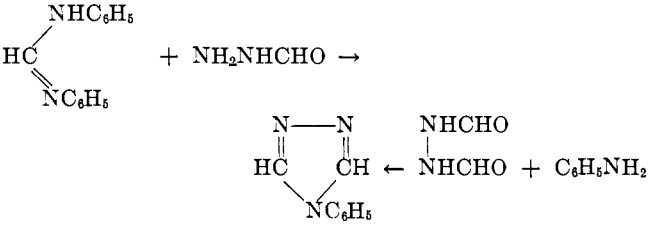
Numerous other methods, such as the reaction of orthoformic ester and hydrazine hydrate at 120°C. (322), the fusion of formhydrazide or diformhydrazide at 150–210°C. (155, 261, 297, 298), or the thermal rearrangement of 1,2-dihydro-1,2,4,5-tetrazine (99, 100), are available, but these are of no practical importance. Another method that deserves mention is the reaction of carbon monoxide with hydrazine under high pressure (69). An expected first step would be the addition of hydrazine to carbon monoxide to give formhydrazide, which would then react with itself to give cyclized products. A surprising and interesting result is that at temperatures of 20–50°C. and pressures of 500–1000 atm. the sole products are semicarbazide and ammonia; at 150°C. and 1000 atm. 4-amino-1,2,4-triazol-3-one is produced; and at 150°C. and 3000 atm. the latter is reduced to 4-amino-1,2,4-4*H*-triazole. The available evidence indicates that the reaction follows this sequence:



This reaction shows promise of being of industrial importance (70, 71).

The method of choice for the preparation of other 4-substituted 1,2,4-4*H*-triazoles is the reaction of an appropriate aliphatic, aromatic, or heterocyclic primary amine with diformhydrazide. As the latter compound is very readily available from hydrazine and 98 per cent formic acid (5), this method is economical in both time and materials. Triazoles that have been prepared in this way are listed in table 4.

An alternative method is similar to the Pellizzari reaction and involves a reaction between, for example, diphenylformamidine and formhydrazide at 150°C., 4-phenyl-1,2,4-4*H*-triazole being formed (252). This method appears to be a general one, but the one mentioned above is to be preferred.



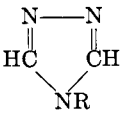
C. DISUBSTITUTED TRIAZOLES

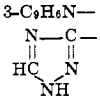
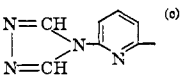
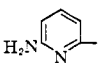
1. 1,3-Disubstituted derivatives

The disubstituted triazoles were among the first representatives of this ring system synthesized by the early Italian school. Knowing that phenylhydrazine condensed with acetoacetic ester to give methyl-

TABLE 4

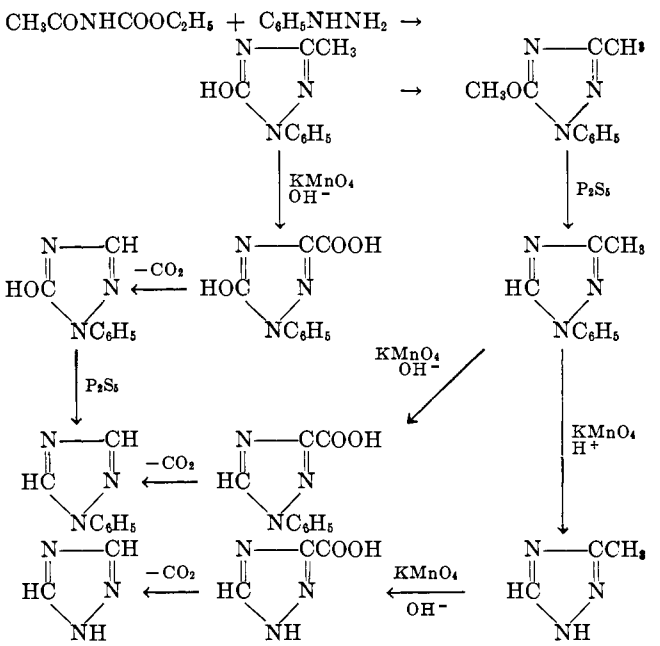
4-Substituted 1,2,4-4H-triazoles prepared by the condensation of diformhydrazide and primary amines



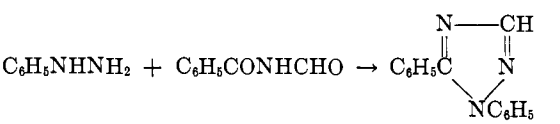
Amine Used	R	Melting Point	Yield	Reaction Conditions	Reference
		°C.	*per cent*		
Aniline	C_6H_5—	121	—	Heat at 170°C.	(271)
o-Toluidine	*o*-$CH_3C_6H_4$—	104	—	Heat at 200°C.	(265)
p-Toluidine	*p*-$CH_3C_6H_4$—	116[a]	—	Heat at 200°C.	(265)
α-Naphthylamine	α-$C_{10}H_7$—	120	—	Heat at 200°C.	(265)
β-Naphthylamine	β-$C_{10}H_7$—	160	—	Heat at 200°C.	(265)
2-Aminopyridine	2-C_5H_4N—	169	40	Heat at 165°C.	(361)
3-Aminopyridine	3-C_5H_4N—	162	42	Heat at 165–170°C.	(361)
3-Aminoquinoline	3-C_9H_6N—	202–203	80	Heat at 165°C.	(361)
3-Amino-1,2,4-triazole	 (b)	300–302 (d.)	44	Heat at 155–160°C. for 10 min.	(361)
2,6-Diaminopyridine	 (c)	325–327	13	Heat at 160–170°C.	(361)
2,6-Diaminopyridine		193–196	10	Heat at 160–170°C.[d]	(361)

[a] Crystallizes with 1.5 H_2O and melts at 83°C.; the anhydrous product melts at 116°C.
[b] 4-(1,2,4-Triazol-3-yl)-1,2,4-4*H*-triazole.
[c] Two moles of diformhydrazide used; a satisfactory name for the product is 2,6-bi(1,2,4-4*H*-triazol-4-yl)pyridine.
[d] One mole of formhydrazide used; accompanied by some of the di product.

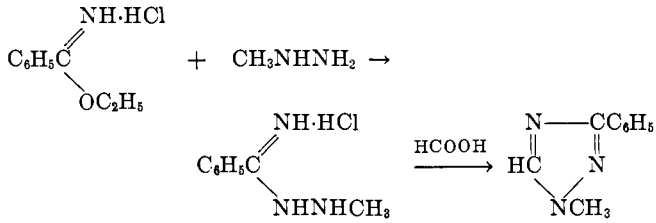
phenylpyrazolone (212), Andreocci condensed phenylhydrazine with acetylurethan and obtained 5-hydroxy-3-methyl-1-phenyl-1,2,4-1*H*-triazole (15, 16), which is converted into 3-methyl-1-phenyl-1,2,4-1*H*-triazole (17, 19), 1-phenyl-1,2,4-1*H*-triazole (17, 19), 3-methyl-1,2,4-triazole (21), and 1,2,4-triazole itself (21) by the reactions shown. Other hydrazines may be used in this condensation (138).



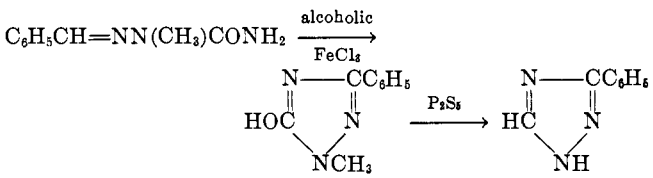
The reaction of phenylhydrazine with *N*-formylbenzamide was originally thought to yield 1,3-diphenyl-1,2,4-1*H*-triazole (113), since shown to be the isomeric 1,5-diphenyl-1,2,4-1*H*-triazole (347). From the carbonyl properties of the formyl group of *N*-formylbenzamide, one would expect the condensation to occur in this way.



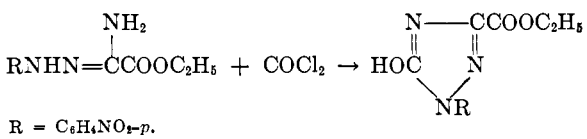
However, 1,3-disubstituted 1,2,4-1*H*-triazoles may be prepared in an unambiguous manner by cyclization of amidrazones with formic acid (32, 278). This cyclization is of Type B. It is illustrated by the formation of benzimidoylmethylhydrazine hydrochloride, from ethylbenzimidoate hydrochloride and methylhydrazine, and cyclization by boiling with 95 per cent formic acid to 1-methyl-3-phenyl-1,2,4-1*H*-triazole in 69 per cent yield. Replacement of methylhydrazine with phenylhydrazine gives 1,3-diphenyl-1,2,4-1*H*-triazole (29). This method is only limited by the availability of the hydrazine used and is the most efficient for the synthesis of these triazoles. It is interesting that only poor yields of the triazoles are obtained when the cyclization is carried out using the free base.



An adaptation of the method used to prepare 3-substituted triazoles by the ferric chloride oxidation of benzal semicarbazones should lead to 1,3-disubstituted triazoles by using 2-substituted semicarbazones. Indeed, oxidation to 5-hydroxy-1-methyl-3-phenyl-1,2,4-1*H*-triazole proceeds smoothly, but on fusion with phosphorus pentasulfide the 1-methyl group is lost with formation of 3-phenyl-1,2,4-triazole (376). This interesting property of *N*-substituted triazoles is discussed in Section IV.



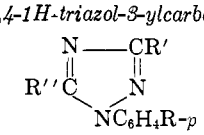
The action of carbonyl chloride on ethyl α-aminoglyoxylate *p*-nitrophenylhydrazone readily leads to ring closure with the formation of ethyl 5-hydroxy-1-(*p*-nitrophenyl)-1,2,4-1*H*-triazol-3-ylcarboxylate (308). Table 5 lists the products formed by modifications of these substituent groups.



R = $C_6H_4NO_2$-*p*.

TABLE 5

Substituted triazoles prepared from ethyl 5-hydroxy-1-(p-nitrophenyl)-1,2,4-1H-triazol-3-ylcarboxylate (308)

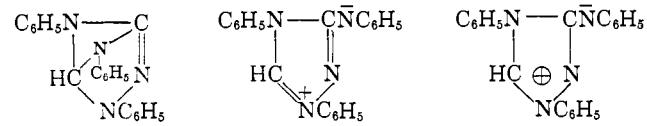


R	R′	R″	Melting Point
			°C.
NO_2	$COOC_2H_5$	OH	243-244
NO_2	$COOCH_3$	OH	254-255
NH_2	$COOC_2H_5$	OH	211-212
AsO_3H_2	$COOC_2H_5$	OH	—
NO_2	COOH	OH	316-319[a]
NO_2	$CONHNH_2$	OH	290-291
NO_2	CON_3	OH	163-164 (explodes)
NO_2	$COOC_2H_5$	Cl	160-162
NO_2	H		165-166

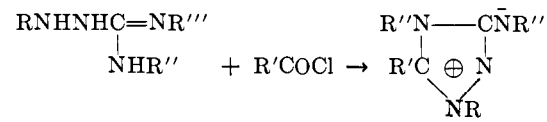
[a] See also reference 132.

2. 1,4-Disubstituted derivatives

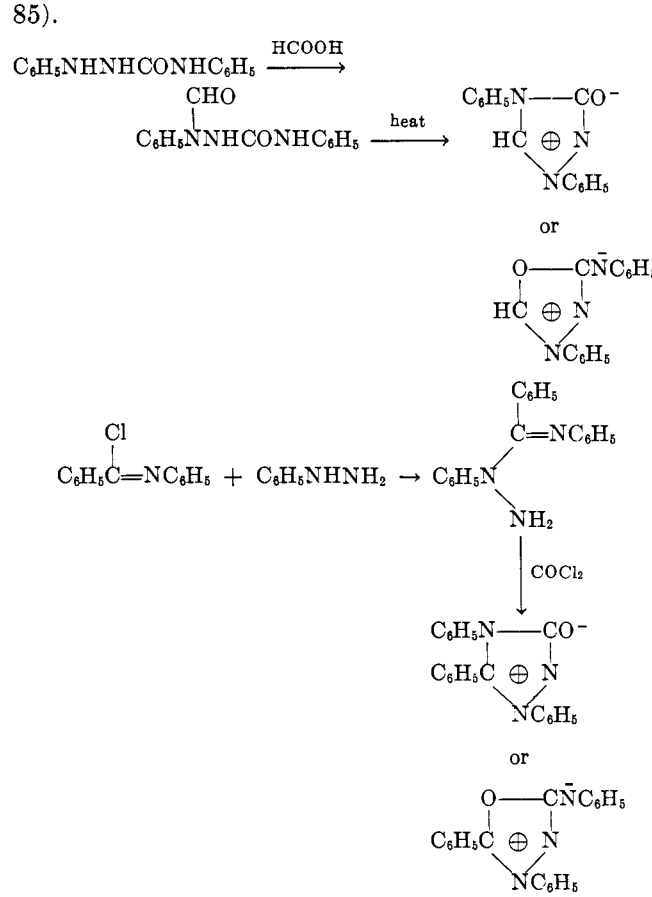
Compounds belonging to this group, the endoimino- and endoxytriazolines, are of great theoretical interest. For many years they have been regarded as containing a sterically prohibited bridged triazole ring (79). The nitric acid precipitant, nitron, is the best known and was originally given the structure triphenylendoiminodihydro-1,2,4-triazole. They all have high dipole moments, and the suggestion that this can be accounted for by a hybrid zwitterion structure (188, 355) has since been modified to a more acceptable meso-ionic formula (36).



The endoiminotriazoles are readily prepared from substituted guanidines and acid chlorides or, where R′ = H, by using formic acid (82, 83). These compounds are yellow, basic substances whose nitrates are very insoluble in water.

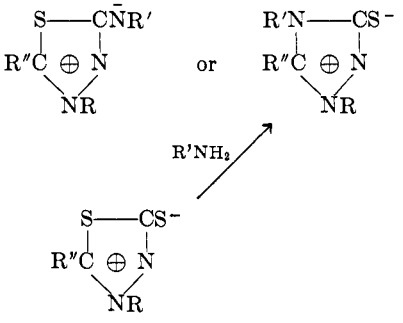


The endoxytriazolines are similarly now represented by a meso-ionic structure and are prepared from a 1-formyl-1,4-dialkylsemicarbazide or arylsemicarbazide by strong heating or by the action of carbonyl chloride on an *N*-(*N*′-arylbenzimidoyl)-*as*-*N*-arylhydrazine (84, 85).



A third type of meso-ionic compound is the endothiotriazoline that is obtained by the action of primary amines on endothiodihydrothiodiazoles (77, 78, 79). The original representation as a bridged-ring compound has been replaced by the meso-ionic structure for which two isomers are also possible. They are formed by the action of acid chlorides or anhydrides on 1,4-diarylthiosemicarbazides (108).

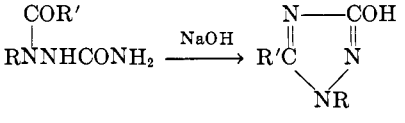
$$RNHNHCSNHR' + R''COCl \rightarrow$$



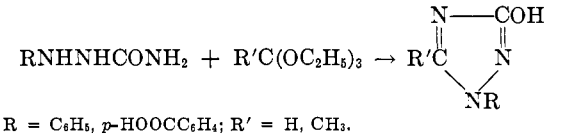
3. 1,5-Disubstituted derivatives

1-Acyl-1-phenylsemicarbazides on treatment with warm, dilute alkali readily cyclize to 1,5-disubstituted 3-hydroxytriazoles and offer the most convenient route to these substances (358). The hydroxyl group may then be removed by heating with phosphorus pentasulfide. Heat or formic acid may also be used as the cyclization agent (357). Table 6 lists 1,5-disubstituted 3-hydroxy-1,2,4-1*H*-triazoles prepared by this method.

$$RNHNHCONH_2 + R'COCl \rightarrow$$



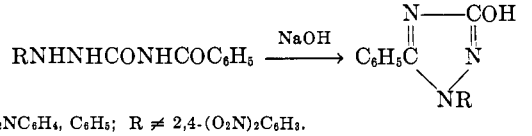
An interesting reaction occurs when the 1-arylsemicarbazide is treated with an ortho ester, such as triethyl orthoformate or triethyl orthoacetate. Cyclization occurs with the formation of 1,5-disubstituted 3-hydroxy-1,2,4-1*H*-triazoles (356), making this method a useful variation of that mentioned above.



R = C_6H_5, *p*-$HOOCC_6H_4$; R' = H, CH_3.

Similarly, 1-aryl-4-benzoylsemicarbazides obtained by the addition of an arylhydrazine to benzoyl isocyanate are cyclized with dilute alkali to 1-aryl-3-hydroxy-5-phenyl-1,2,4-1*H*-triazoles (25). Polyphosphoric acid may also be used as the cyclization agent.

$$C_6H_5CON{=}C{=}O + RNHNH_2 \rightarrow$$



R = *p*-$O_2NC_6H_4$, C_6H_5; R ≠ 2,4-$(O_2N)_2C_6H_3$.

4. 3,4-Disubstituted derivatives

The majority of 3,4-disubstituted 1,2,4-4*H*-triazoles have been prepared through the intermediate 5-mercaptans and by methods that involve the use of thiosemicarbazide or its derivatives.

The simplest method (327), that of treating thiophosgene with hydrazine in ether to give thiocarbohydrazide and heating this in a sealed tube at 100°C., gives 4-amino-3-mercapto-1,2,4-4*H*-triazole and is of no importance for the synthesis of the corresponding 4-aminotriazole. Replacement of the thiophosgene with tetrachlorodimethyl sulfide (117) offers a more direct route to the 4-amino-3-mercapto-1,2,4-4*H*-triazole.

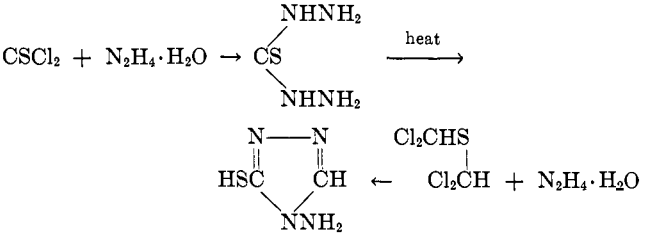
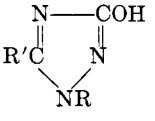


TABLE 6

1,5-Disubstituted 3-hydroxy-1,2,4-1H-triazoles prepared by alkaline cyclization of 1-acyl-1-phenylsemicarbazides



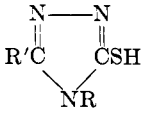
Acylation Agent	R	R'	Melting Point	Reference
			°C.	
CH_3CH_2COCl	C_6H_5—	CH_3CH_2—	191–192	(358)
$(CH_3)_2CHCOCl$	C_6H_5—	$(CH_3)_2CH$—	242	(358)
$CH_3CH_2CH_2COCl$	C_6H_5—	$CH_3CH_2CH_2$—	160	(358)
$(CH_3)_2CHCH_2COCl$	C_6H_5—	$(CH_3)_2CHCH_2$—	164–165	(358)
C_6H_5COCl	C_6H_5—	C_6H_5—	290	(358)
$C_6H_5CH{=}CHCOCl$	C_6H_5—	$C_6H_5CH{=}CH$—[a]	287	(358)
HCOOH	C_6H_5—	H	147–148	(300)
$(CH_3CO)_2O$	3,4-$(CH_2O_2)C_6H_3CH_2$—	CH_3—	190	(300)
$(CH_3CO)_2O$	$C_6H_5CH(CH_3)$—	CH_3—	146–147	(300)

[a] Alkaline oxidation with potassium permanganate gives 3-hydroxy-1-phenyl-1,2,4-1*H*-triazole.

The cyclization of 1-acyl-4-substituted-thiosemicarbazides with alkali or by heat has been thoroughly studied and developed as one of the most efficient routes to these triazoles (281, 376). The thiosemicarbazides are readily available in quantitative yield from an acid hydrazide and an isothiocyanate. Table 7 shows the usefulness of this particular method.

TABLE 7

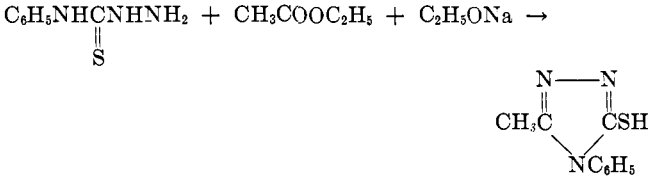
3,4-Disubstituted 5-mercapto-1,2,4-4H-triazoles prepared from 1-acyl-4-substituted-thiosemicarbazides



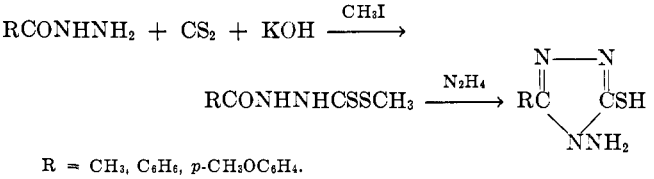
R	R′	Method of Cyclization*	Yield	Melting Point	Reference
			per cent	°C.	
CH_3—	C_6H_5—	A†	—	163–164	(376)
p-ClC_6H_4—	4-C_5H_4N—	B	87	269–271	(281)
p-$C_2H_5OC_6H_4$—	4-C_5H_4N—	B	90	223–224	(281)
p-$CH_3OC_6H_4$—	4-C_5H_4N—	B	87	238–239	(281)
p-$C_2H_5OC_6H_4$—	3-C_5H_4N—	B	87	238–240	(281)
p-$C_2H_5OC_6H_4$—	C_6H_5—	B	87	264–265	(281)
p-$C_2H_5OC_6H_4$—	*p*-$NH_2C_6H_4$—	B	80	268–269	(281)
C_6H_5—	C_6H_5—	C‡	—	287	(112)
p-$CH_3C_6H_4$—	*p*-$CH_3C_6H_4$—	C	—	223–225	(112)
H	CH_3—	A	—	260–261	(126)

* A: Heating above the melting point.
B: 2 *N* NaOH at the boiling point for 15 min.
C: Heating with the appropriate aromatic primary amine above 200°C.
† Oxidation with hydrogen peroxide gives 4-methyl-3-phenyl-1,2,4-4*H*-triazole, melting point 112–113°C.
‡ This is accompanied by a small amount of 5-anilino-3,4-diphenyl-1,2,4-4*H*-triazole, melting point 210–212°C.

A further useful variation of this method simply involves the reaction of a 4-alkyl- or 4-arylthiosemicarbazide with aliphatic or aromatic acid esters in the presence of a sodium alkoxide. Thus from 4-phenylthiosemicarbazide and ethyl acetate, 5-mercapto-3-methyl-4-phenyl-1,2,4-4*H*-triazole is obtained. Using ethyl carbonate as the ester component, 3-hydroxy-5-mercapto-4-phenyl-1,2,4-4*H*-triazole is obtained (275). This method enables the 3-substituent to be varied almost at will.

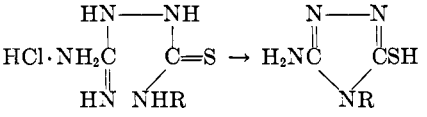


The second important method involves the reaction of an acid hydrazide with carbon disulfide and potassium hydroxide, giving the potassium salt of a 2-acyldithiocarbazic acid, which is converted into its methyl ester with methyl iodide. This reacts readily with hydrazine to form the 4-amino-5-mercapto-3-substituted-1,2,4-4*H*-triazole (180, 199, 373).



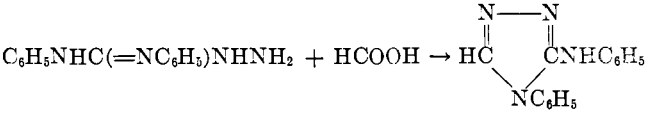
R = CH_3, C_6H_5, *p*-$CH_3OC_6H_4$.

The isomeric products are formed when an *N*-substituted *N′*-guanidinothiourea hydrochloride is treated with 10 per cent sodium hydroxide solution at 100°C. for 1 hr. (130).



R = CH_3, C_2H_5, iso-C_3H_7, allyl, C_6H_5, $C_6H_5CH_2$, C_6H_{11}.

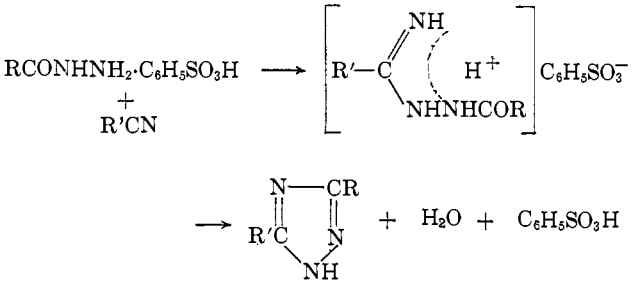
A somewhat similar method is the cyclization of *N″*-amino-*N*,*N′*-diphenylguanidine with formic acid to 3-anilino-4-phenyl-1,2,4-4*H*-triazole (81). Several variations of this general type of reaction have been reported (87, 181, 286).



5. 3,5-Disubstituted derivatives

The 3,5-disubstituted 1,2,4-triazoles comprise the greatest number of the disubstituted triazoles. In cases where the two substituent groups are different, only one product has ever been isolated, showing the mobility of the hydrogen atom attached to the nitrogen atoms.

The simplest method of preparation involves the fusion of an aromatic cyanide with an acid hydrazide benzenesulfonate or *p*-toluenesulfonate at 200–250°C. (282). The scope of the reaction is limited to the use of aromatic cyanides but the acid hydrazide moiety may be alkyl, aromatic, or heterocyclic (284). The most probable course of the reaction appears to be that shown:

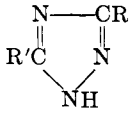


In table 8 are included triazoles that have been prepared by this reaction.

A similar reaction, that in which an acid hydrazide is distilled with an acid amide (223, 262), is known as the Pellizzari reaction. The yields are variable and by-

TABLE 8

3,5-Disubstituted 1,2,4-triazoles



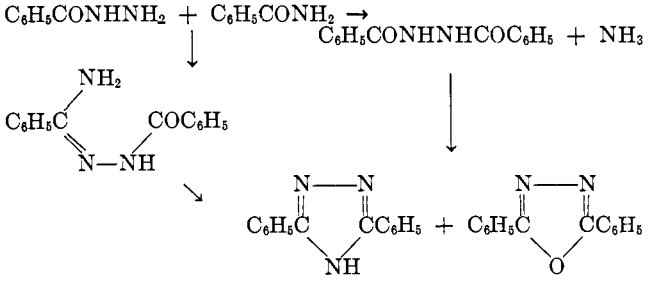
R	R′	Melting Point	Yield	Method*	References
		°C.	*per cent*		
C_6H_5—	C_6H_5—	190, 192	92, —	A, B, E	(262, 282, 368)
C_6H_5—	*p*-$CH_3C_6H_4$—	189	Quantitative	A	(282)
C_6H_5—	*o*-$CH_3C_6H_4$—	176	—†	A	(282)
C_6H_5—	α-$C_{10}H_7$—	118	88	A	(282)
C_6H_5—	*p*-$O_2NC_6H_4$—	239	Quantitative	A	(282)
p-$O_2NC_6H_4$—	C_6H_5—	240	86	A	(282)
p-$O_2NC_6H_4$—	*p*-$CH_3C_6H_4$—	244	Quantitative	A	(282)
p-$O_2NC_6H_4$—	$C_6H_5CH_2$—	212	84	A	(282)
p-$O_2NC_6H_4$—	*p*-$O_2NC_6H_4$—	250–251	58	A, D	(282, 326)
p-$O_2NC_6H_4$—	α-$C_{10}H_7$—	192	80	A	(282)
2-C_5H_4N—	C_6H_5—	212	86	A	(282)
2-C_5H_4N—	*p*-$CH_3C_6H_4$—	202	77	A	(282)
CH_3—	C_6H_5—	166	25‡	A	(284)
C_2H_5—	C_6H_5—	103–104	18‡	A	(284)
CH_3—	CH_3—	142 (b.p., 258)	—	B, C, E	(67, 262, 311, 321, 323)
C_2H_5—	C_2H_5—	61–62 (b.p., 267)	—	E	(151)
4-C_5H_4N—	4-C_5H_4N—	283	5, 27§	B	(223)
CH_3—	C_6H_5—	164.5	Poor	B	(164)
$(CH_3)_2CH$—	$(CH_3)_2CH$—	146	—	C, E	(151, 329)
C_3H_7—	C_3H_7—	67.5, 70	—	C, E	(237, 332)
m-ClC_6H_4—	*m*-ClC_6H_4—	220	—	C	(328)
p-$CH_3C_6H_4$—	*p*-$CH_3C_6H_4$—	246	—	E	(370)

* A: Fusion of an aromatic cyanide with an acid hydrazide benzenesulfonate.
B: Fusion of an acid hydrazide with an acid amide.
C: Treatment of an *s*-diacylhydrazine with ammonia and zinc chloride.
D: Treatment of an *s*-diacylhydrazine with phosphorus pentachloride and then ammonia.
E: From diacylamines and semicarbazide in the presence of sodium acetate.
† Isolated as the picrate.
‡ Some 3,5-diphenyl-1,2,4-triazole was also present.
§ The use of pyridine-4-thiocarboxyamide results in a better yield.

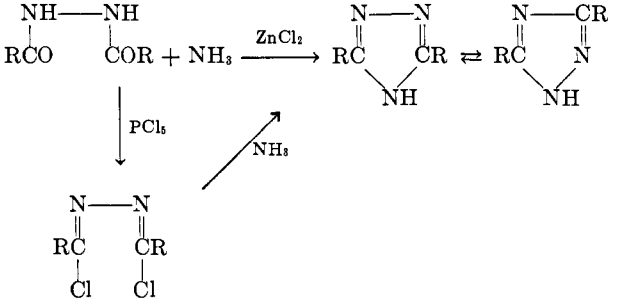
products are often formed, owing to a transamination of the following type:

$$RCONHNH_2 + R'CONH_2 \rightleftharpoons R'CONHNH_2 + RCONH_2$$

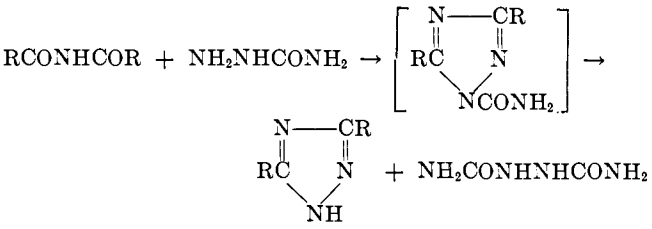
This type of side reaction is more prone to occur when aliphatic acid hydrazides are used (284, 294). It was originally thought that the reaction path involved the formation of a diacylhydrazine with elimination of ammonia, since some 2,5-disubstituted 1,3,4-oxadiazole is formed as a by-product (262). A more likely course for the reaction would be through an intermediate acylhydrazidine, which can then cyclize in two ways.



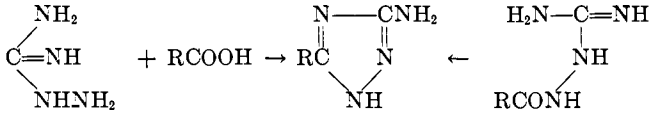
Just as β-diketones react with ammonia and a dehydrating agent to form pyrroles, *s*-diacylhydrazines react with ammonia and zinc chloride to form 3,5-disubstituted 1,2,4-triazoles (321). Poor yields of the products are usually obtained. A necessary improvement of this method was developed by first treating the diacylhydrazine with phosphorus pentachloride and then causing the dichloroazine formed to react with ammonia. This modification requires lower reaction temperatures and better yields are obtained (331), making it one of the more important methods for the preparation of these triazoles.



The other major method for the synthesis of this type of 3,5-disubstituted triazole involves the reaction of semicarbazide hydrochloride with a diacylamine in aqueous sodium acetate solution (67). An intermediate *N*-carbamyltriazole reacts with the excess of semicarbazide present, the carbamyl group being readily removed owing to the electrophilic nature of the carbonyl carbon atom (Section IV). This reaction is particularly useful for the synthesis of 1,3,5-trisubstituted triazoles by replacement of the semicarbazide with a substituted hydrazine (this is discussed later).

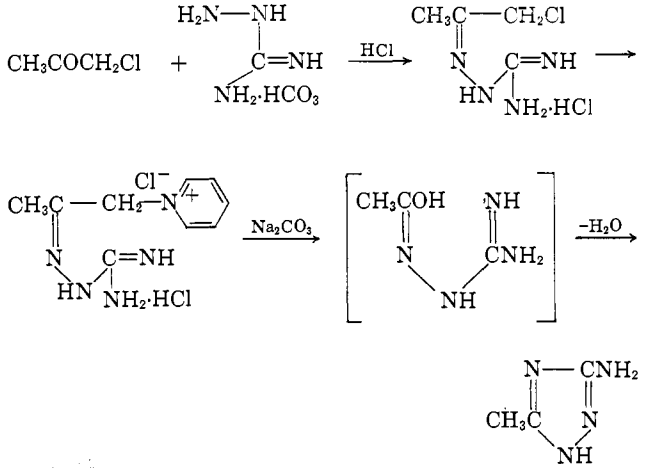


The methods discussed up to now have always given 3,5-disubstituted triazoles with either alkyl or aryl substituents. 3-Amino-5-alkyl- or 3-amino-5-aryltriazoles may be obtained from an aminoguanidine salt and the appropriate organic acid (26, 228, 288, 289), an extension of the original method used to prepare 3-amino-1,2,4-triazole (344). In several instances, the reaction was found to proceed in good yield only in concentrated mineral acid (26).

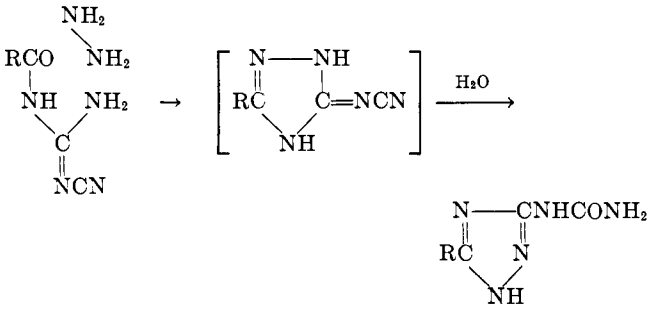


A variation of this reaction involves a prior acylation of the aminoguanidine and then ring closure with alkali (49, 341, 342) or heat (140, 177), the acylaminoguanidine being readily available by acylation of aminoguanidine with an acid chloride, or from an acid hydrazide, *S*-methylisothiourea sulfate, and alkali. Table 9 lists triazoles prepared from aminoguanidine and substituted aminoguanidines.

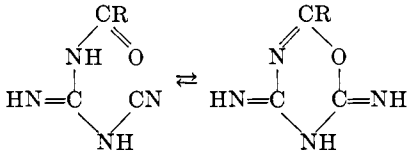
Though the prior acetylation and subsequent ring closure of aminoguanidine to 3-amino-5-methyl-1,2,4-triazole described above offers the more direct route, that in which the aminoguanidine reacts with chloroacetone to form an initial chloroacetone guanylhydrazone is quite interesting (47). Use is made of the reactivity of the chlorine atom to form with pyridine in absolute alcohol the acetonylpyridinium chloride–guanylhydrazone hydrochloride, which reacts with dilute alkali in the same way as a β-acylpyridinium salt (208, 215) to form an intermediate hydroxy compound which undergoes spontaneous ring closure to the triazole.



The reactions leading to an aminotriazole discussed above have involved a system containing an arrangement of atoms such as C—N—N—C—N. There is one more arrangement possible and this is C—N—C—N, that is, an acyldicyandiamide, the other two nitrogen atoms being supplied by a hydrazine residue. Indeed, these were found to react readily with hydrazine salts, giving 5-alkyl-3-ureido-1,2,4-triazoles (193, 194, 196) in practically quantitative yields.



The course of this reaction has been interpreted (196) as involving an elimination of water and subsequent hydrolysis of the cyano group, before or after ring closure by elimination of ammonia. As the same product could not be obtained from the reaction of acylguanylurea and hydrazine, it was suggested that the acyldicyandiamides could exist in an isomeric form, shown below, and that reaction then occurred by the opening of the six-membered ring.



A simpler mechanism, involving an intermediate similar to that described above, is as follows: The cyano group, in contrast to the amido group, supplies the initial activation for addition of the hydrazino amino group across the C=N, with subsequent elimination of ammonia. A canonical form of the intermediate would be a highly reactive carbodiimide, which is known to react with water very readily, forming a substituted urea.

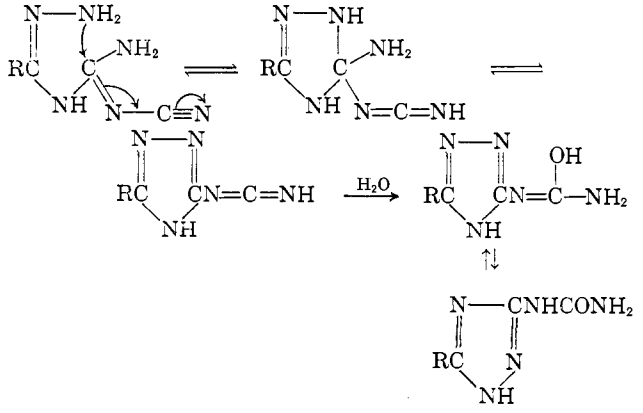
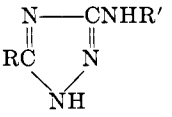


TABLE 9

3-Amino-5-substituted-1,2,4-triazoles prepared from aminoguanidine and substituted aminoguanidine salts



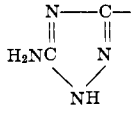
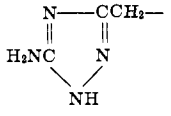
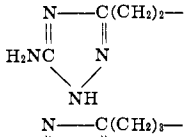
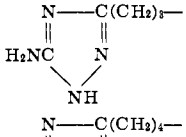
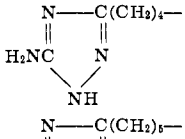
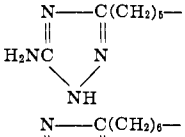
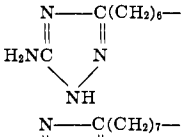
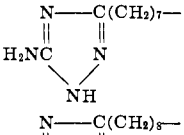
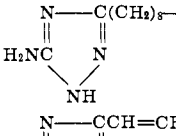
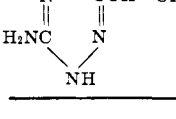
R	R′	Conditions	Yield	Melting Point	References
			per cent	°C.	
CH_3—	H	Acetic acid; heat	Quantitative	148	(242)
CH_3—	NO_2	1-Acetamido-3-nitroguanidine; aqueous sodium carbonate at 100°C.	97	212–213 (d.)	(165)
C_2H_5—	H	Propionic acid; heat	36	152	(289)
C_3H_7	H	Butyric acid; heat	34	143	(288, 289)
$(CH_3)_2CH$—	H	Isobutyric acid; at boiling point for 6 hr.	45	112	(288)
$CH_3(CH_2)_5$—	H	Heptanoic acid; 180°C. for 2 hr.	40	131.5	(26)
C_6H_5—	H	Benzoic acid; 120°C. for 4 hr.	14	188	(26)
C_6H_5—	H	Benzoic acid; reflux temperature of 40 per cent hydrobromic acid for 24 hr.	Quantitative	188	(26)
C_6H_5—	H	Heating benzoyl chloride and aminoguanide carbonate	Poor	186–187	(43)
C_6H_5—	H	Benzamidoguanidine; heat at 220°C. or sodium ethoxide	85	186–187	(177)
C_6H_5—	$C_5H_{10}N$—	Benzhydrazide, *S*-methyl-*N*,*N*-pentamethyleneisothiourea and sodium hydroxide at room temperature	74	196–198	(177)
3-C_5H_4N—	H	Pyridine-3-carboxylic acid; reflux in 40 per cent hydrobromic acid for 40 hr.	44	233	(26)
2-C_5H_4N—	H	Pyridine-2-carboxylic acid, hydrochloric acid; reflux in 40 per cent hydrobromic acid for 40 hr.	42	217	(26)
	H	Oxalic acid; boil in water, then with potassium carbonate	—	>350	(310)[a]
	H	Malonic acid; boil in water, then with potassium carbonate	34	293	(310)
	H	Succinic acid; boil in water, then with potassium carbonate	40	310–312	(310)
	H	Glutaric acid; boil in water, then with potassium carbonate	20	243–244	(310)
	H	Adipic acid; boil in water, then with potassium carbonate	—	278–280	(310)[b]
	H	Pimelic acid; boil in water. then with potassium carbonate	43	224–270	(310)
	H	Suberic acid; boil in water, then with potassium carbonate	57	270–273	(310)
	H	Azelaic acid; boil in water, then with potassium carbonate	50	217–219	(310)
	H	Sebacic acid; boil in water, then with potassium carbonate	49	238–241	(310)
	H	Crotonic acid; boil in water, then with potassium carbonate	25	>350	(310)

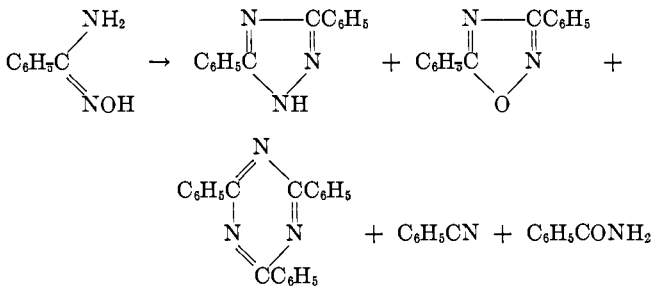
TABLE 9—*Continued*

R	R'	Conditions	Yield	Melting Point	References
			per cent	°C.	
$C_2H_5OCH_2CH_2$—	H	Ethyl 3-ethoxypropionate; reflux with 48 per cent hydrobromic acid for 14 hr.	70	132–133	(34)
o-HOC_6H_4—	H	*o*-Hydroxybenzamidoguanidine; heat at 200°C.	—	162	(140)
4-C_5H_4N—	H	4-Pyridamidoguanidine; heat at 250°C.	—	273–274	(49, 140)
3-C_5H_4N—	H	3-Pyridamidoguanidine; heat at 250°C.	—	223	(140)
p-$CH_3OC_6H_4$—	H	*p*-Anisamidoguanidine; heat at 220°C.	—	224–226	(177)
p-ClC_6H_4—	H	*p*-Chlorobenzamidoguanidine; heat at 220°C.	—	227–229	(177)
p-$CH_3OC_6H_4$—	$C_5H_{10}N$—	*p*-Anishydrazide, *S*-methyl-*N*,*N*-pentamethyleneisothiourea, and sodium hydroxide at room temperature	—	206–208	(177)
$C_6H_5CONHCH_2$—	H	Hippuric acid hydrazide, *S*-methylisothiourea sulfate, and alkali at room temperature	58	228–233	(49)
$C_6H_5CONHCH_2CH_2$—	H	Benzoyl-β-alanine hydrazide, *S*-methylisothiourea sulfate, and alkali at room temperature	54	201–203	(49)
$CH_3CONHCH(CH_2C_6H_5)$—	H	*N*-Acetylphenylalanine hydrazide, *S*-methylisothiourea sulfate, and alkali at room temperature	66	220–224	(49)

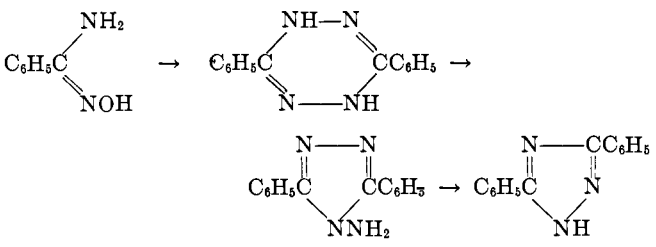
[a] 5,5′-Diamino-3,3′-bi(1,2,4-triazole).
[b] 1,4-Di(5-amino-1,2,4-triazol-3-yl)butane.

Other methods that are essentially variations of those discussed above are available and lead to 3-amino-5-mercapto- (129, 131), 3,5-diamino- (95, 103, 168, 350), and 3,5-dinitramino-1,2,4-triazoles (168).

The isolation of several unusual products, including 3,5-diphenyl-1,2,4-triazole, by heating benzamidoxime at 170°C. has been reported (218). Associated with this triazole were 3,5-diphenyl-1,2,4-oxadiazole, 2,4,6-triphenyl-1,3,5-triazine, phenyl cyanide, benzamide, and various gases. The triazole is probably formed by the condensation of two molecules of benzamidoxime.



One possible route would be through an initial 1,4-dihydro-3,6-diphenyl-1,2,4,5-tetrazine, known to isomerize under the influence of heat to 4-amino-3,5-diphenyl-1,2,4-4*H*-triazole (74). These *N*-aminotriazoles have been known to lose the amino group on strong heating (330). It is also possible that mechanisms involving an initial rearrangement of the amidoxime might be involved.

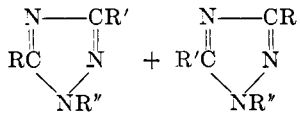


D. TRISUBSTITUTED TRIAZOLES

1. 1,3,5-Trisubstituted derivatives

The most satisfactory method of preparation of the trisubstituted triazoles is from a diacylamine and a substituted hydrazine (67). This has been called the Einhorn–Brunner reaction (28), a variation of it having been mentioned earlier for the synthesis of 1,5-disubstituted 1,2,4-1*H*-triazoles. Satisfactory yields are obtained. Some triazoles prepared by this method are listed in table 10.

$RCONHCOR' + R''NHNH_2HX \rightarrow$

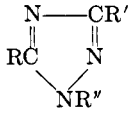


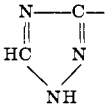
When the groups R and R′ in the diacylamine are different, the formation of two isomeric triazoles would be expected. It was found, however, that the substituent in the diacylamine derived from the stronger acid appears in the 3-position of the resulting triazole (28). This would appear to indicate that the reaction is initiated by an attack of the more basic unsubstituted hydrazine amino group on the more electrophilic carbonyl carbon atom of the acyl group of the stronger acid moiety.

Just as the Pellizzari reaction can be used to prepare mono- and disubstituted triazoles, then by the choice of suitable reactants it can be utilized for the preparation of 1,3,5-trisubstituted 1,2,4-1*H*-triazoles (262). High reaction temperatures are usually involved and yields are often far from satisfactory. The most usual form of the reaction is the fusion at over 250°C. of an amide and an acid hydrazide of an acid higher than formic. The actual reagents may be varied in several ways, as shown below. Pellizzari has found that the second of these methods is the most suitable.

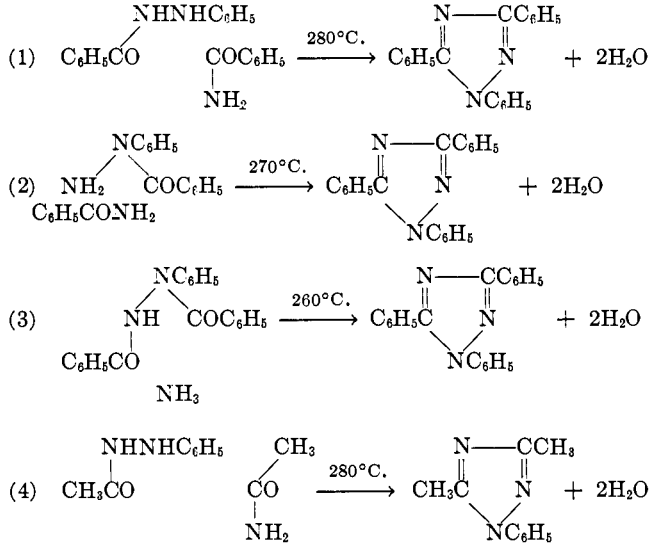
TABLE 10

1,3,5-Trisubstituted 1,2,4-1H-triazoles prepared by the Einhorn-Brunner method



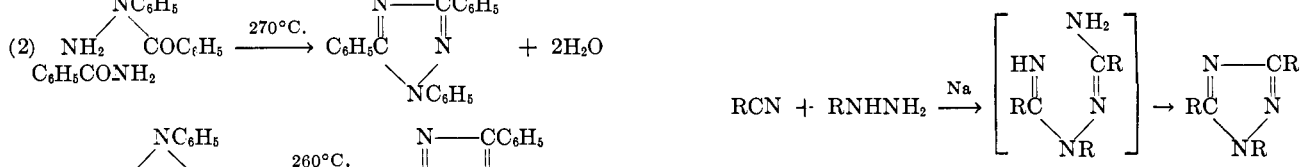
R	R′	R″	Yield	Melting Point	References
			per cent	°C.	
CH_3—	CH_3—	CH_3—	57	193/755 mm.[a] 72–74/11 mm.	(30)
C_6H_5—	C_6H_5—	CH_3—	40	85	(30)
C_2H_5—	CH_3—	C_6H_5—	48	122/2 mm.[a]	(28)
C_6H_5—	H	C_6H_5—	52	90–90.5	(28)
C_6H_5—	CH_3—	C_6H_5—	78	80–81	(28)
C_6H_5—	CH_3—	CH_3—	65	72	(32)
CH_3—	CH_3—		9	191	(26)
CH_3—	CH_3—	C_6H_5—	—	46–46.5	(68, 133)
CH_3—	CH_3—	*p*-BrC_6H_4—	—	93.5–94	(171)
CH_3—	CH_3—	*m*-$NO_2C_6H_4$—	—	128	(171)
CH_3—	CH_3—	*o*-$CH_3C_6H_4$—	—	24.5–25[b]	(170)
CH_3—	CH_3—	*m*-$CH_3C_6H_4$—	—	147–149/11 mm.[a]	(170)
CH_3—	CH_3—	*p*-$CH_3C_6H_4$—	—	47–49	(170)
CH_3—	CH_3—	α-$C_{10}H_7$—	—	69	(152)
CH_3—	CH_3—	β-$C_{10}H_7$—	—	104	(152)
C_2H_5—	C_6H_5—	C_6H_5—	—	37–38	(152)
C_6H_5—	C_6H_5—	C_6H_5—	—	104–105	(369)
p-$CH_3C_6H_4$—	*p*-$CH_3C_6H_4$—	C_6H_5—	—	115	(369)
$C_6H_5CH{=}CH$—	CH_3—	C_6H_5—	—	74[c]	(27)

[a] Boiling point.
[b] Boiling point, 141–143°C./11 mm.
[c] Sublimes at 145°C./0.1 mm.

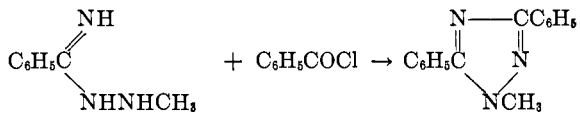


When the acyl groups of the amide and acylhydrazine are different, transamination may occur, particularly if the acyl group of the hydrazine is aliphatic. A mixture of isomeric triazoles is often obtained. It appears that there is less tendency for this transacylation reaction to occur if the reaction temperature is kept to ca. 200°C.; below this temperature condensation often does not occur. Some triazoles prepared by this particular method are listed in table 11.

1,3,5-Triaryltriazoles may also be obtained from aryl cyanides and arylhydrazines in the presence of sodium, a reaction that must involve the formation of an intermediate hydrazidine (114, 223, 354). This method is of little practical importance.



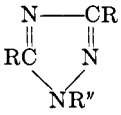
A method of obtaining 1,3,5-trisubstituted triazoles with no possibility of the formation of isomers involves the ring closure of amidrazones with acylation reagents (32, 320). Thus when benzimidoylmethylhydrazine is heated with benzoyl chloride, ring closure to 1-methyl-3,5-diphenyl-1,2,4-1*H*-triazole occurs in over 90 per cent yield (32). Substituted benzimidoylphenylhydrazines have also been used (189); indeed, the ring closure has provided evidence that amidrazones have been obtained as reaction products (190, 287).



These methods all give alkyl or aryl substituents in the 3- and 5-positions. To obtain other substituent groups, such as amino groups, it is necessary to use a

TABLE 11

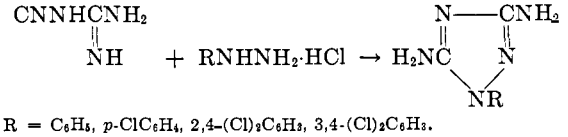
Some 1,3,5-trisubstituted 1,2,4-1H-triazoles prepared by the Pellizzari reaction



R	R′	R″	Reactants and Reaction Temperature	Melting Point	Reference
				°C.	
C_6H_5—	C_6H_5—	C_6H_5—	s-Benzoylphenylhydrazine and benzamide; 280°C.	104	(262)
C_6H_5—	C_6H_5—	C_6H_5—	as-Benzoylphenylhydrazine and benzamide; 270°C.	104	(262)
C_6H_5—	C_6H_5—	C_6H_5—	1-Phenyl-1,2-dibenzoylhydrazine and ammonia; 260°C.	104	(262)
CH_3—	CH_3—	C_6H_5—	s-Acetylphenylhydrazine and acetamide; 280°C.	43	(262)
CH_3—	C_2H_5—	C_6H_5—	s-Propionylphenylhydrazine and acetamide; 210°C.	278/755 mm.[a]	(28)
CH_3—	CH_3—	C_6H_5—	s-Acetylphenylhydrazine and benzamide; 225°C.	155–157[b]	(28)
C_6H_5—	CH_3—	C_6H_5—	s-Acetylphenylhydrazine and benzamide; 225°C.	79–80	(28)
CH_3—	C_6H_5—	C_6H_5—	s-Benzoylphenylhydrazine and acetamide; 250°C.	80–85	(28)
CH_3—	CH_3—	C_6H_5—	s-Benzoylphenylhydrazine and acetamide; 260–280°C.	134–138/3 mm.[a]	(28)
CH_3—	CH_3—	o-$CH_3C_6H_4$—	s-Diacetylhydrazine and acet-o-toluidide; 200°C.	168	(264)
CH_3—	CH_3—	p-$CH_3C_6H_4$—	s-Diacetylhydrazine and acet-p-toluidide; 250°C.	228	(264)

[a] Boiling point.
[b] Isolated and identified as the picrate.

molecule that contains potential amino groups or amino groups as such. Dicyandiamide is the one of choice, and when it is heated with an appropriate arylhydrazine hydrochloride in aqueous solution, 3,5-diamino-1-aryl-1,2,4-1*H*-triazoles are obtained in excellent yields (93, 348).

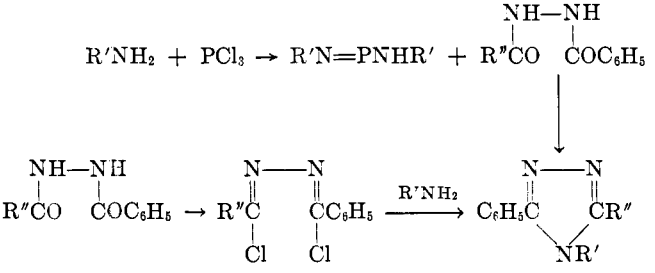


R = C_6H_5, p-ClC_6H_4, 2,4-$(Cl)_2C_6H_3$, 3,4-$(Cl)_2C_6H_3$.

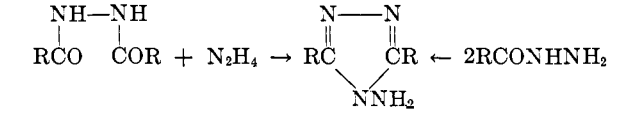
In a similar way, 1-aryl-3,5-di(*N*-substituted amino)-1,2,4-1*H*-triazoles are obtained from 2,4-dialkyl-1,5-diaryl-2,4-diisodithiobiurets by reaction with arylhydrazines at temperatures over 100°C. (351). Reaction of the hydrazine with an unsaturated disulfide, such as perthiocyanic acid, gives a 3-amino-1-aryl-5-mercapto-1,2,4-1*H*-triazole (61).

2. 3,4,5-Trisubstituted derivatives

A logical extension of the dehydration of *s*-diacylhydrazines in the presence of ammonia to form 3,5-disubstituted 1,2,4-triazoles is to effect the dehydration in the presence of a primary amine and so obtain 3,4,5-trisubstituted 1,2,4-4*H*-triazoles. This was the first method used to obtain *s*-triazoles with alkyl or aryl substituents in the 4-position, and the reaction has since been improved by the development of more efficient methods for carrying out the dehydration. Phosphorus pentoxide was the agent originally chosen but the yields were of the order of 20 per cent (80); anhydrous zinc chloride was effective but also gave low yields (48). These practical difficulties are overcome by the use of *N,N′*-diphenylphosphenimidous amide[3] as the dehydrating agent (210), or by the conversion of the *s*-diacylhydrazine into a dichloroaldazine, followed by reaction with a primary amine (211, 324, 325). Table 12 illustrates the general usefulness of this method.



The replacement of the primary amine in the reaction with *s*-diacylhydrazines by hydrazine hydrate and heating this mixture in a sealed tube gives 4-amino-3,5-disubstituted-1,2,4-4*H*-triazoles (169). These may be prepared directly by a simple fusion of acylhydrazines at atmospheric pressure (98, 262), a reaction that can give only symmetrically substituted triazoles. This method has been modified for the preparation of the lower 3,5-dialkyl-4-amino-1,2,4-4*H*-triazoles (96, 169). In this process the carboxylic acid and hydrazine hydrate are heated at 200°C. in an apparatus that permits the continuous, slow removal of water.

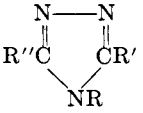


What is essentially a variation of the above methods is the reaction of a chloroimide, such as *N*-phenyl-

[3] This nomenclature is based on the rules of nomenclature of the International Union of Pure and Applied Chemistry for compounds containing one phosphorus atom.

TABLE 12

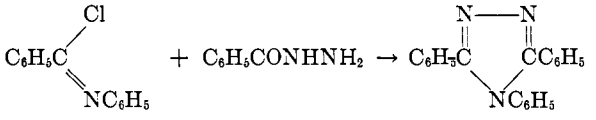
3,4,5-Trisubstituted 1,2,4-4H-triazoles prepared by the dehydration of s-diacylhydrazines and primary amines



R	R′	R″	Dehydration Agent*	Yield	Melting Point	References
				per cent	°C.	
C_6H_5—	C_6H_5—	C_6H_5—	A, B, D	95 (A), 20	292	(80, 210, 324, 325)
p-$CH_3C_6H_4$—	C_6H_5—	C_6H_5—	A, C	88, poor	296–297	(48, 210)
o-$CH_3C_6H_4$—	C_6H_5—	C_6H_5—	A	88	301–302	(210)
m-$CH_3C_6H_4$—	C_6H_5—	C_6H_5—	A, C	83, poor	256–257	(48, 210)
p-ClC_6H_4—	C_6H_5—	C_6H_5—	A	88	261.5–262	(210)
C_6H_5—	4-C_5H_4N—	C_6H_5—	A	95	268–269	(210)
β-$C_{10}H_7$—	C_6H_5—	C_6H_5—	A	52	275.5–276.5	(210)
C_6H_5—	CH_3—	CH_3—	B	Poor	236	(164)
C_6H_5—	C_6H_5—	CH_3—	B	Poor	161	(164)
o-$CH_3C_6H_4$—	C_6H_5—	CH_3—	B	—	177.5	(164)
p-$CH_3C_6H_4$—	C_6H_5—	CH_3—	B	—	162.5	(164)
C_6H_5—	C_6H_5—	2-Anthraquinonyl	D	ca. 90	275–276	(211)

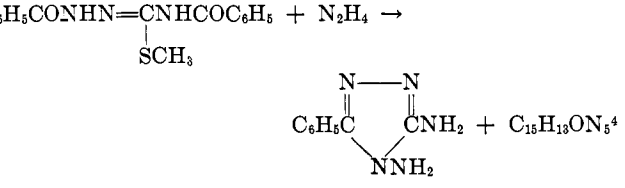
* A: *N,N′*-Diarylphosphenimidous amide.
B: Phosphorus pentoxide.
C: Zinc chloride.
D: Conversion of the *s*-diacylhydrazine into the dichloroaldazine and reaction with aniline.

benzimidoyl chloride, with benzhydrazide to give 3,4,5-triphenyl-1,2,4-4*H*-triazole (86, 115). A hydrazide anil may also be used in this condensation (211).



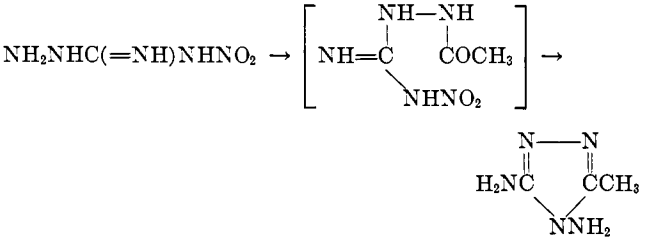
A further method of preparation involving the rearrangement of dihydro-1,2,4,5-tetrazines is discussed in the next section.

Variation of the 3,5-substituents can only be achieved by using an appropriately substituted starting material (306). Thus, 1,4-dibenzoyl-*S*-methylisothiosemicarbazide, on treatment with hydrazine hydrate, readily gives 4,5-diamino-3-phenyl-1,2,4-4*H*-triazole, benzhydrazide, and a compound of the empirical formula $C_{15}H_{13}ON_5$ (179).



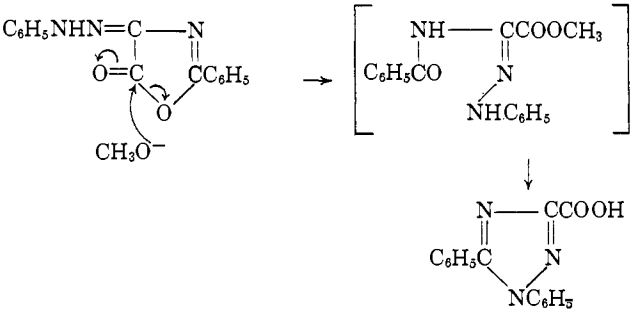
The diaminotriazole is also obtained in small amounts from 1-benzoylthiosemicarbazide and hydrazine hydrate.

In the reduction by zinc and acetic acid of nitroaminoguanidine no diaminoguanidine is obtained; instead ring closure occurs to yield 4,5-diamino-3-methyl-1,2,4-4*H*-triazole (224, 307). The formation of the triazole arises from a prior acetylation of nitroaminoguanidine which immediately undergoes ring closure on reduction.



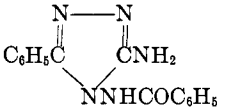
E. SYNTHESES FROM OTHER RING SYSTEMS

Under the influence of alcoholic potassium hydroxide, 4-phenylazo-2-phenyloxazolin-5-one readily rearranges in quantitative yield to 1,5-diphenyl-1,2,4-1*H*-triazol-3-ylcarboxylic acid. In alcoholic ammonia the corresponding amide is obtained (304). This rearrangement is very similar to that involved in the alkaline transformation of β-methylglutaconic anhydrides to pyridazones (362).

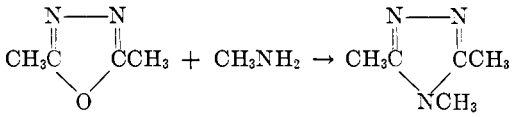


Just as pyrroles are obtained from furans and amines

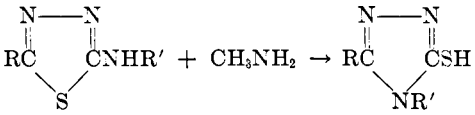
[4] The most likely structure for this product is that of 3-amino-4-benzamido-5-phenyl-1,2,4-4*H*-triazole:



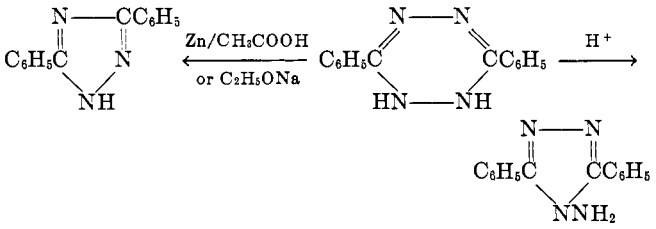
at elevated temperatures (192), so are triazoles obtained from furodiazoles (234). Thus, when 2,5-dimethylfurodiazole is treated with alcoholic methylamine at 110°C., 3,4,5-trimethyl-1,2,4-4*H*-triazole is formed. Aliphatic, aromatic, or heterocyclic primary amines may be used.



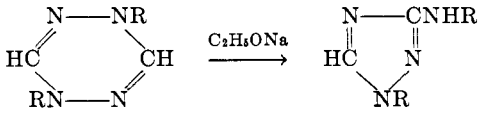
Methylamine at 150°C. is also able to effect the rearrangement of 2-amino-5-substituted-1,3,4-thiadiazoles to 3,4-disubstituted 5-mercapto-1,2,4-4*H*-triazoles in excellent yields (141). It is interesting to note that sodium ethoxide cannot bring about this rearrangement.



1,2-Dihydro- and 1,4-dihydro-1,2,4,5-tetrazines are readily isomerized to triazole derivatives. The early literature on 1,2,4,5-tetrazines is remarkably confused because of this ready isomerization and has been adequately covered elsewhere (360). One of the characteristic reactions of 3,6-diaryl-1,2-dihydro-1,2,4,5-tetrazines is their ready isomerization with 25 per cent hydrochloric acid (223, 276, 277, 279) to 4-amino-3,5-diaryl-1,2,4-4*H*-triazoles. With reducing agents, such as zinc and acetic acid, or by isomerization with sodium alkoxides (223) triazoles with the 4-amino group removed are formed.

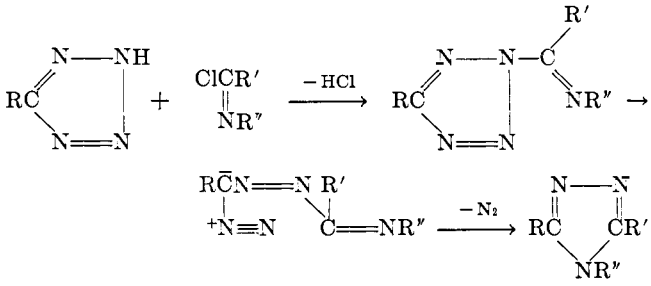


In contrast to the above isomerization that occurs with rupture of a carbon–nitrogen bond, 1,4-diaryl-1,4-dihydro-1,2,4,5-tetrazines isomerize under the influence of sodium alkoxides (37) with rupture of a nitrogen–nitrogen bond to give 1-aryl-3-arylamino-1,2,4-1*H*-triazoles.



5-Substituted tetrazoles have also given 1,2,4-4*H*-triazoles in excellent yield on reaction with imino chlorides or iminobenzenesulfonates in pyridine (183).

A likely mechanism for the reaction is shown:

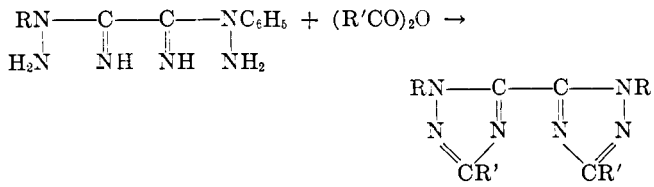


The rearrangement of the *s*-triazine ring system has been discussed in Section II.

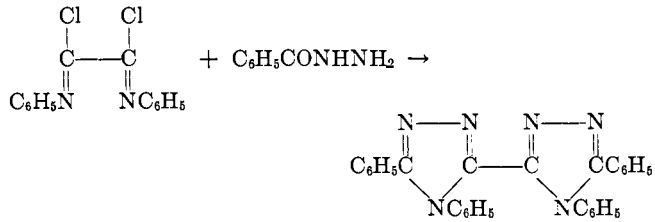
F. BITRIAZOLES

Several bitriazoles are known, and those joined by a carbon–carbon bond are prepared by methods that involve a reactant containing an N—C—C—N chain. The direct coupling of two preformed nuclei, as in the biphenyl series, has not yet been accomplished.

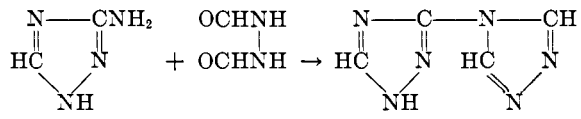
Cyanophenylhydrazine, obtained from cyanogen and an alcoholic solution of phenylhydrazine, reacts with acid anhydrides, giving 5,5′-bi-1,2,4-1*H*-triazoles (57, 120, 292). Cyanohydrazine itself and substituted cyanohydrazines may be used (58).



3,3′-Bitriazoles may be obtained, though in poor yield, from a disubstituted oximidyl chloride and an acid hydrazide. Thus from diphenyloximidyl chloride and benzhydrazide, 4,4′,5,5′-tetraphenyl-3,3′-bi-1,2,4-4*H*-triazole is obtained (211). The ultraviolet spectrum of this compound indicates that the conjugation between the nuclei is not as pronounced as in the biphenyl series.



3,4′-Bitriazoles are prepared from 3-amino-1,2,4-triazoles and diformhydrazide, as in the formation of 3,4′-bitriazole [also called 4-(1,2,4-triazol-3-yl)-1,2,4-4*H*-triazole] from 3-amino-1,2,4-triazole itself and diformhydrazide (361).



The use of 4-amino-1,2,4-4*H*-triazole in this type of

condensation should give the isomeric 4,4′-bitriazoles.

III. Structure and Physical Properties

An acceptable representation of the structure of a 1,2,4-triazole must take into consideration its amphoteric nature; the mobility of the imino hydrogen atom; the great stability, aromatic character, and substitution pattern of the nucleus; and the physical evidence that suggests its considerably polar nature. This last point is emphasized for azoles in general on comparison of their melting points and dipole moments (188) with those of other five-membered heterocycles, such as furan, thiophene, and pyrrole. Table 13 lists these

TABLE 13

Physical constants of a number of five-membered heterocycles

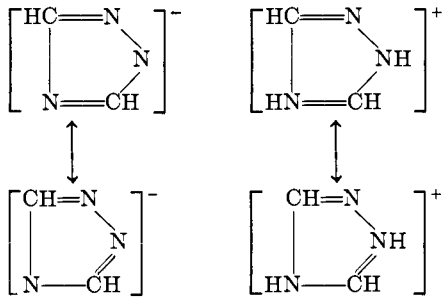
Compound	Melting Point	Boiling Point at 760 mm.	Dipole Moment	pK_a
	°C.	°C.	D	
Furan	—	32	0.63	—
Pyrrole	—	131	1.80	—
Thiophene	—	84	0.54	—
Thiazole	—	117	1.64	2.53
Pyrazole	70	187	1.57	2.53
1,2,3-Triazole	23	204	1.77	—
Imidazole	90	256	3.84	6.95
1,2,4-Triazole	121	260	3.17	2.55, 10.1
Tetrazole	155	Sublimes	5.11	—
1-Methyl-1,2,4-1*H*-triazole	20	178	—	—
4-Methyl-1,2,4-4*H*-triazole	90	—	—	—
1-Phenyl-1,2,4-1*H*-triazole	47	266	2.88	—
4-Phenyl-1,2,4-4*H*-triazole	121	—	5.63	—
3-Methyl-1,2,4-triazole	95	265	—	—
3-Phenyl-1,2,4-triazole	119	—	—	—
3-Anilino-1-phenyl-1,2,4-1*H*-triazole	114.5–115	—	3.54	—

constants. The boiling point of 1,2,4-triazole is unusually high in comparison with those of furan and pyrrole, though there is only a slight difference in molecular weights. The introduction of a methyl group into the 1-position of 1,2,4-triazole lowers the boiling point by 82°C., whereas the introduction of a 3-methyl substituent makes no appreciable difference. The effect upon the melting points of 1-substituted derivatives is even more striking, the melting point of 1-methyl-1,2,4-1*H*-triazole being nearly 100°C. lower and that of 1-phenyl-1,2,4-1*H*-triazole 77°C. lower than those of the parent compounds. Again, the melting points of the 3-substituted derivatives are not altered greatly.

1,2,4-Triazole is readily soluble in polar solvents and only slightly soluble in nonpolar solvents, the solubility in the latter being increased by substitution on the nitrogen atom. Molecular-weight determinations by the Rast method give results that deviate only slightly from the normal. The infrared spectra of triazole and its derivatives containing an unsubstituted

group indicate the presence of an associated

group in the solid state (282, 283), a fact that is also suggested by the above physical properties. This has recently been interpreted as an intermolecular association in which the hydrogen atom of the imino group protonates an unsaturated nitrogen of an adjacent molecule, the two charged particles being stabilized by resonance (251):



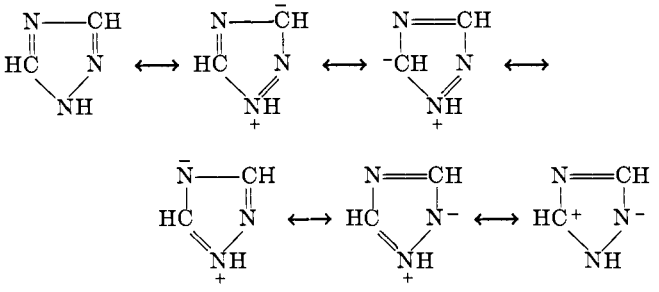
This suggestion was made because of the presence of two bands in the infrared spectrum of 1,2,4-triazole: a broad ammonium-type band at 3.5–4.0 μ and the other at 5.5 μ—the so-called immonium bands (365) of the structural element

These bands are not present in the gas-phase spectrum nor in the spectra of those substituted triazoles that contain an imino hydrogen atom and that are sufficiently soluble in chloroform for the spectra to be measured in solution (284). The intensity of the 5.5 μ band is very low, particularly in comparison with the intensities of the bands to which the original assignment was made and, as the spectrum was determined in the solid state, it is possible that this band might be due to orientation effects. However, a similar band does occur in the spectrum of imidazole and of tetrazole (251). Also, in those triazoles with a heteroatom adjacent to the

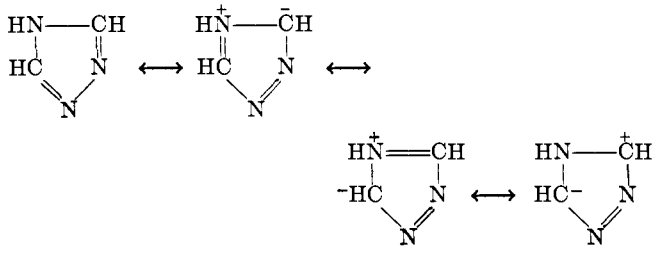
group this absorption band does not appear (283), and it is possible that this diminution in intensity is due to a similar effect being exerted by a neighboring heteroatom. This effect has also been observed in 1,3-benzoxazines. From the dipole moment and electron density data, it appears that the 4-nitrogen atom would be the one most likely involved in the protonation. This association may be represented in various ways, from the classical hydrogen bonding of two molecules to one where the triazole nuclei are associated by the sharing of a hydrogen atom between two adjacent mole-

cules. Before any definite conclusions can be made, an x-ray structural analysis of 1,2,4-triazole will be necessary.

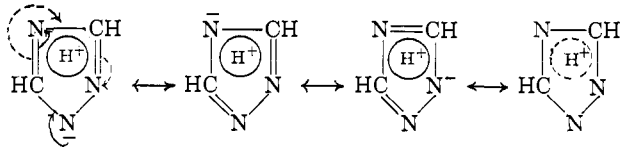
Various chemical reactions show that 1,2,4-triazole possesses an extremely stable nucleus which may be regarded as aromatic in nature. An aromatic sextet can be formed by contributions of one π electron from each atom joined by the double bonds and of two electrons from a nitrogen atom. Such a system is stabilized by resonance and, though the triazole nucleus may be represented by tautomeric forms, each tautomer is capable of extended resonance, and its structure is more correctly represented as a hybrid to which the following canonical forms contribute:



It is also necessary to consider the tautomeric form where the imino hydrogen atom is at the 4-position. The canonical forms that contribute to this resonance hybrid are:

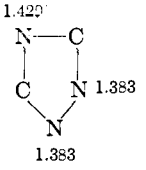


This representation is not particularly satisfactory. It makes the assumption that the triazole nucleus actually consists of two hybrid structures, each representing an individual tautomeric form. In modern theories such a view is incorrect. A more suitable expression is to regard 1,2,4-triazole as a true aromatic system, stabilized by resonance, and represented below.



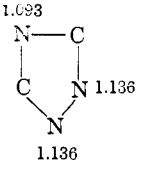
The six electrons required to form a stable aromatic sextet are made up of four from the double bonds and two from a nitrogen atom. It is not intended to represent the charges on a nitrogen atom and on the hydrogen atom as separate, complete charges but merely as a slight, overall negative charge on the ring, balanced by a corresponding positive charge on the hydrogen atom. The question arises as to whether the three resonance forms are of equal importance in what actually represents the resonance hybrid. Dipole moment data indicate that there is an appreciable contribution from the resonance form that has the negative charge more closely associated with the nitrogen atom in the 4-position. This interpretation is supported by experimental evidence, such as salt formation on this nitrogen atom, but it must be remembered that the permanent charge distribution in a molecule by itself would not be expected to determine the relative reactivities of different positions, although it may have an effect in orienting them into a suitable configuration for reaction to occur.

It is interesting that the π-electron densities for 1,2,4-triazole are in accord with the above ideas, although unfortunately there is a difference of opinion as to what these values are. This is due to the different parameters chosen. Those used for the calculations shown immediately below are more reliable.



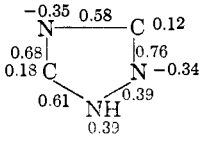
1.383

π-electron densities, neutral molecule (32)[5]

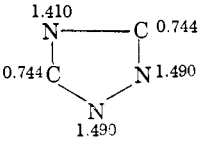


1.136

π-electron densities, anion (32)[6]



π-electron densities and bond orders (249)[7]



π-electron densities (39)[7]

From this representation of the structure of 1,2,4-triazole, one would expect it to be largely dissociated in ionizing solvents and to form a stable anion and metallic salts. Such salts are prepared in liquid ammonia solution (333) and are readily hydrolyzed in water to the triazole and the metal hydroxide, although the preparation of cupric triazole by the addition of triazole to a neutral or slightly alkaline solution of a copper salt has been reported (267). Table 14 lists metallic salts of 1,2,4-triazole.

Excellent evidence that a pair of electrons from a nitrogen atom of 1,2,4-triazole enters into the molecular orbital is obtained from the study of the infrared spectra of 1,2,4-triazole and suitable substituted derivatives. 3-Aminotriazole behaves chemically like a typical

[5] Parameters, $h = +1$. This calculation includes overlap integrals.

[6] Parameters, $h = -(1/3)$. This calculation includes overlap integrals.

[7] The relationship between these different sets of parameters and their influence on the nature of the results obtained is discussed in Quarterly Reviews of the Chemical Society 6, 63 (1952).

TABLE 14

Salts of 1,2,4-triazole (333)

Metal	Formula	Color	Crystalline Form
Na	$NaC_2H_2N_3$	Colorless	
Ag	$AgC_2H_2N_3 \cdot NH_3$	Colorless	Tetrahedra
	$AgC_2H_2N_3$	Gray	Powder
Mg	$Mg(C_2H_2N_3)_2 \cdot 4NH_3$	White	Small prisms
	$Mg(C_2H_2N_3)_2$		
Ca	$Ca(C_2H_2N_3)_2 \cdot xNH_3$	White	Small prisms
	$Ca(C_2H_2N_3)_2$		
Cu(I)	$CuC_2H_2N_3 \cdot xNH_3$	White	Microcrystalline
	$CuC_2H_2N_3$		

aromatic amine and its infrared spectrum, as well as that of 4-aminotriazole, shows the characteristic, strong NH deformation frequency of a primary amine at 1642 cm.$^{-1}$ (6.09 μ) and the various aromatic CH absorptions (283). In *N*-acyltriazoles[8] the involvement of the lone pair of electrons of the nitrogen atom in the aromatic sextet is dramatically emphasized by the position of the carbonyl absorption bands (250, 282, 291). In *N*-acetyltriazole (250) (other acyl compounds are listed in table 15) this absorption occurs at 1765 cm.$^{-1}$ (5.67 μ)—a slightly higher frequency than the absorption of the normal, open-chain, saturated ketone at 1725–1705 cm.$^{-1}$ (5.85–5.87 μ)—whereas that of an *N*,*N*-disubstituted amide occurs at 1650 cm.$^{-1}$ (6.06 μ). This indicates that there is no contribution from the dipolar form of an amide:

Another significant feature of these spectra is the presence of very intense absorption bands at 1420–1370 cm.$^{-1}$ (7.04–7.30 μ), associated with methyl ketones, and at 1330–1250 cm.$^{-1}$ (7.50–8.00 μ). The latter may be due to a C—N stretching absorption.

[8] The position of the acyl group has not been established.

N-Triazolylcarbonic acid anilide shows a similar carbonyl absorption frequency (252).

The conclusions drawn from physical measurements are amply supported by chemical data. One consequence of the involvement of the electrons of the nitrogen atom in the aromatic sextet is that the conjugate acid of the *N*-acyltriazole is a relatively strong acid and the carbonyl carbon atom becomes much more strongly electrophilic. Thus the *N*-acyltriazoles are rapidly hydrolyzed in water to the triazole and the corresponding acid (30, 50, 252, 312, 314, 315, 317). A similar situation exists in other five-membered heterocycles where the electrons of the nitrogen atom form part of the aromatic sextet. The kinetics of these and related reactions have been investigated and are discussed in the next section.

The ultraviolet absorption spectra of several 1,2,4-triazoles have been examined and found to obey Beer's law in concentrations not exceeding 2×10^{-4} *M*. These data are recorded in table 16. 1,2,4-Triazole itself shows very weak absorption ($\epsilon = 200$) at 205 mμ and in *N*-acetyl-1,2,4-triazole bathochromic and hyperchromic shifts occur with the absorption band being located at 221.5 mμ ($\epsilon = 7800$). A similar shift in the absorption maximum also occurs on conversion of 3,5-dimethyltriazole into the *N*-acetyl-3,5-dimethyltriazole. Cyclopentadiene has an absorption maximum at 238.5 mμ ($\epsilon = 3400$) and with the known hypsochromic effect of replacing carbon–carbon unsaturation with carbon–nitrogen unsaturation, the low values obtained for 1,2,4-triazole are understandable. Though the large hyperchromic shift occurring on the acetylation of triazole and its derivatives may be compared qualitatively to the similar effect observed in passing from benzene to acetophenone, profitable speculation can result only with the accumulation of more data. The effect of substituent groups and the variation in absorption maxima produced by various combinations may be ascertained from the table.

TABLE 15

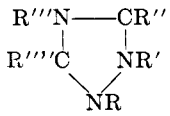
Characteristic absorption frequencies of N-acyl-1,2,4-triazoles and related five-membered heterocycles (250, 252, 283)

Compound	C=O absorption		$COCH_3$ absorption		C—N Absorption			
	ν	λ	ν	λ	ν	λ	ν	λ
	cm.$^{-1}$	μ	cm.$^{-1}$	μ	cm.$^{-1}$	μ	cm.$^{-1}$	μ
N-Acetyltriazole	1765	5.67[a]	1282	7.80	1245	8.03	1212	8.25
N-Acetyl-3,5-diphenyltriazole	1748	5.72[b]	1290	7.75	1266	7.90	1208	8.28
N-Acetyl-3-phenyl-5-(*o*-tolyl)triazole	1748	5.72[b]	1290	7.75	1266	7.90	1208	8.30
N-Acetylpyrrole	1732	5.78[c]	1325	7.55	—	—	1305	7.66
N-Acetylimidazole	1747	5.73[a]	1294	7.73	—	—	1258	7.95
N-Acetyltetrazole	1779	5.62[a]	1205	8.30	—	—	1198	8.35
N-Butyrylimidazole	1748	5.72[d, e]	—	—	—	—	—	—
N-Triazolylcarbonic acid anilide	1733	5.79[a]	1282	7.8	1250	8.0	1212	8.25
	1752	5.71[d]						

[a] Potassium bromide disc.
[b] Nujol.
[c] Liquid film.
[d] Chloroform solution.
[e] Other data not available.

TABLE 16

The ultraviolet absorption spectra of some 1,2,4-triazoles



R	R′	R″	R‴	R⁗	Neutral		Anion		References
					$\lambda_{max.}$	ϵ	$\lambda_{max.}$	ϵ	
					mμ		mμ		
H	—	H	—	H	205	200[a]	—	—	(312)
CH_3CO—[b]	—	H	—	H	221.5	7,800[a]	—	—	(312)
CH_3CO—[b]	—	CH_3—	—	CH_3—	222	6,900[c]	—	—	(27)
H[b]	—	C_6H_5—	—	H	241.5	14,100[d]	257	13,500	(27)
C_6H_5—	—	H	—	H	239	10,900[d]	—	—	(27)
—	—	H	C_6H_5—	H	224.5	10,900[d]	—	—	(27)
C_6H_5—	—	CH_3—	—	H	244	15,400[d]	—	—	(27)
C_6H_5—	—	H	—	CH_3—	224.5	7,600[d]	—	—	(27)
C_6H_5—	—	CH_3—	—	CH_3—	230	9,000[d]	—	—	(27)
C_6H_5—	—	C_2H_5—	—	CH_3—	230	9,400[d]	—	—	(27)
C_6H_5—	—	CH_3—	—	C_2H_5—	230	10,600[d]	—	—	(27)
CH_3—	—	C_6H_5—	—	H	243	15,000[d]	—	—	(27)
CH_3—	—	H	—	C_6H_5—	235	11,900[d]	—	—	(27)
—	—	C_6H_5—	CH_3—	H	270	550[d]	—	—	(27)
—	—	CH_3—	C_6H_5—	H	272; 267	400[d]	—	—	(27)
—	—	CH_3—	C_6H_5—	CH_3—	259	300[d]	—	—	(27)
CH_3—	—	C_6H_5—	—	CH_3—	245	15,300[d]	—	—	(27)
CH_3—	—	CH_3—	—	C_6H_5—	239	12,700[d]	—	—	(27)
C_6H_5—	—	CH_3—	—	C_6H_5—	252	10,500[d]	—	—	(27)
C_6H_5—	—	C_6H_5—	—	CH_3—	253	22,100[d]	—	—	(27)
C_6H_5—	—	C_6H_5—	—	H	265	23,400[d]	—	—	(27)
C_6H_5—	—	H	—	C_6H_5—	248	13,600[d]	—	—	(27)
—	—	C_6H_5—	C_6H_5—	H	235.5	14,700[d]	—	—	(27)
—	—	CH_3—	CH_3—	C_6H_5—	235.5	11,500[d]	—	—	(27)
—	—	C_6H_5—	C_6H_5—	CH_3—	232	14,700[d]	—	—	(27)
H[b]	—	C_6H_5—	—	C_6H_5—	255	22,700[d]	276	21,900	(27, 49)
					234	21,800[d]			(27)
—	—	C_6H_5—	C_6H_5—	C_6H_5—	256.5	8,000[d]	—	—	(27)
H[b]	—	CH_3—	—	C_6H_5—	244	15,600[d]	261	15,100	(27)
CH_3—	—	C_6H_5—	—	C_6H_5—	247	19,400	—	—	(27)
—	—	C_6H_5—	CH_3—	C_6H_5—	251	24,400	—	—	(27)
C_6H_5—	—	C_6H_5—	—	C_6H_1—	244	29,200	—	—	(27)
C_6H_5—	—	CH_3—	—	C_6H_5CH=CH—	300	52,300	—	—	(27)
C_6H_5—	—	HO—	—	H	282	9,100[d]	284	11,500	(27)
C_6H_5—	CH_3—	=O	—	—	280	7,400[d]	—	—	(27)
C_6H_5—	—	—OH	—	C_6H_5—	294	5,700[d]	302	6,700	(27)
					226	15,600[d]	230	15,500	
C_6H_5—	—	CH_3—	—	HO—	249	16,800[d]	261	14,600	(27)
H	H	—OH	H	C_6H_5—	264	10,900[d]	273	6,700	(27)
							223.5	13,800	
CH_3—	—	C_6H_5—	—	HO—	269.5	12,800[d]	267	8,700[d]	(27)
							223.5	13,800	
H[b]	—	—NH_2	—	2-C_5H_4N—	283	8,100[d]	—	—	(26)
H[b]	—	NH_2—	—	4-C_5H_4N—	271	7,850[e]	—	—	(49)
					284	10,200[e]			
					298	10,100[f]			
3-Triazolyl	—	CH_3—	—	CH_3—	218	6,100[d]	—	—	(26)
	—								
—	—	C_6H_5—	—$NHCOCH_3$	HS—	220	11,500[d]	—	—	(199)
					260	16,400			
—	—	C_6H_5—	—$NHCOC_2H_5$	HS—	220	10,960[d]	—	—	(199)
					260	16,600			
—	—	C_6H_5—	—NH_2	C_6H_5—	261.1	17,780[d]	—	—	(144)
—	—	C_6H_5—	—$NHCOCH_3$	C_6H_5—	256.7	17,780[d]	—	—	(144)
—	—	C_6H_5—	—$N(COCH_3)_2$	C_6H_5—	256.7	17,780[d]	—	—	(144)
—	—	*p*-$CH_3C_6H_4$—	—NH_2	*p*-$CH_3C_6H_4$—	261.1	17,780[d]	—	—	(144)
—	—	*m*-$CH_3C_6H_4$—	—NH_2	*m*-$CH_3C_6H_4$—	261.1	17,780[d]	—	—	(144)
H	—	CH_3—	—	H_2N—	ca. 210	5,620[d]	—	—	(142)

[a] Anhydrous tetrahydrofuran.
[b] The location of this substituent may be either 1 or 4.
[c] Hexane.
[d] Alcohol.
[e] Water.
[f] 5 *N* hydrochloric acid.

Very little attention has been paid to the physical properties of 1,2,4-triazole and its derivatives. In a study of the heats of combustion of compounds containing a high percentage of nitrogen, several triazole derivatives were studied. The values obtained are shown in table 17.

TABLE 17

Heats of combustion of some triazoles (364)

Compound	Heat of Combustion
	kcal./mole
3-Amino-1,2,4-triazole	−343.10
3-Amino-1,2,4-triazole nitrate	−318.01
3-Amino-5-methyl-1,2,4-triazole nitrate	−466.68
5-Methyl-3-nitramino-1,2,4-triazole	−465.67
3-Nitramino-1,2,4-triazole	−317.45
3-Benzylidenehydrazino-5-methyl-1,2,4-triazole	−1377.87

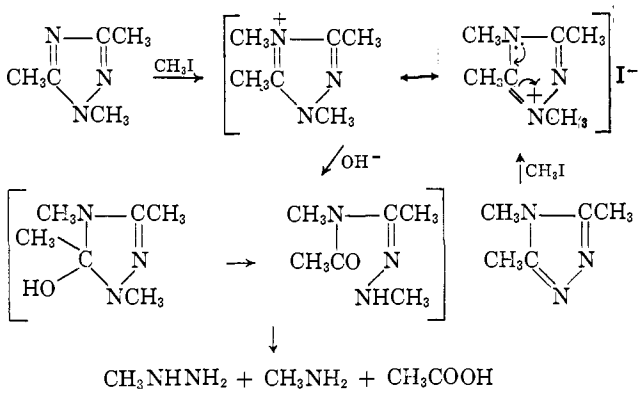
Polymorphism occasionally occurs with 1,2,4-triazoles, as with 3,5-dimethyl-1-phenyl-1,2,4-1*H*-triazole, which has two melting points, 46°C. and 37.5°C., corresponding to two different modifications of the triazole (60).

IV. Reactions of 1,2,4-Triazoles

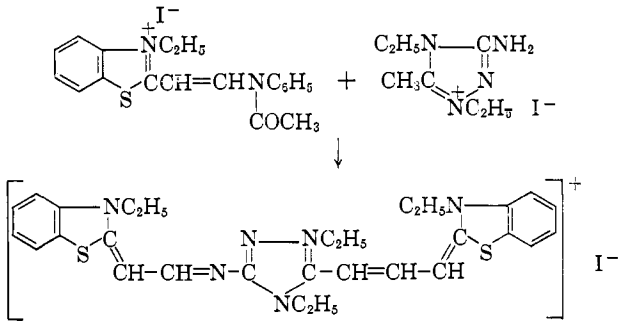
1,2,4-Triazoles are amphoteric in nature, forming salts with acids and with bases. They are such weak bases that the salts with mineral acids are usually completely dissociated in aqueous solution, although in the early literature hydrochlorides and nitrates were used for identification purposes. Alkali metal salts, i.e., those formed by replacement of the imino hydrogen atom, are unstable in aqueous solution. Picrates are useful derivatives for the identification of 1,2,4-triazoles and are best prepared in benzene solution, although the recent use of disulfimides (299) for the characterization of amines offers another excellent method. Mercurichlorides are also useful for identification. It has been claimed that triazoles are often difficult to analyze, but failure to obtain satisfactory analytical figures can be attributed to contamination with small amounts of by-products having the same chemical properties (283). Fortunately, a large number of triazoles may be sublimed *in vacuo* and this offers an excellent method of purification.

The characteristic feature of 1,2,4-triazoles is the stability of the nucleus, an inherent property of its aromatic nature. The claim (163) that 1,2,4-triazole was cleaved to 1,4-dibenzoylhydrazine on heating with benzoyl chloride has been shown to be incorrect (31); it could be that the original 1,2,4-triazole used was contaminated with diformylhydrazine, known to form 1,4-dibenzoylhydrazine on heating with benzoyl chloride.

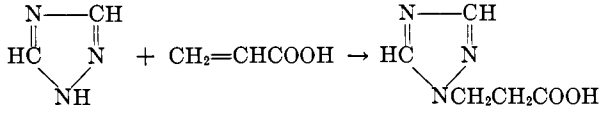
Heterocycles containing a heteroatom that is capable of forming a quaternary salt usually undergo ring opening with alkali (216). Thus in both 1,3,5-trimethyl-1,2,4-1*H*-triazole and 3,4,5-trimethyl-1,2,4-4*H*-triazole there is a nitrogen atom that can form a quaternary salt with methyl iodide, and treatment of this quaternary salt with alkali should provide a means of opening the 1,2,4-triazole ring. This method of ring fission has been successful (31, 107, 108), and from 1,3,5-trimethyl-1,2,4-1*H*-triazole, after formation of the methiodide and treatment with alkali, methylhydrazine and methylamine were obtained. It is interesting to note that the same methiodide was formed from 1,3,5-trimethyl-1,2,4-1*H*-triazole and 3,4,5-trimethyl-1,2,4-4*H*-triazole, indicating that salt formation had occurred on the 4-position of the former and in agreement with theoretical considerations. Similarly, phenylhydrazine and methylamine were obtained from 3,4,5-trimethyl-1-phenyl-1,2,4-1*H*-triazolium iodide and alkali (107, 108).



Quaternary salt formation in triazole derivatives of the above type has been used to activate the adjacent C—CH_3 group so that it will condense with heterocyclic dye salts of the type used in cyanine dyes (24, 108, 201, 202). Thus condensation of 3-amino-1,4-diethyl-5-methyl-1,2,4-4*H*-triazolium iodide with 2-[2-(*N*-acetylanilino)vinyl]-3-ethylbenzothiazolium iodide gives a tricyanine dye with excellent photographic sensitizing properties: 1,4-diethyl-2-[2-(3-ethyl-2-benzothiazolylidene)ethylideneamino]-5-[3-(3-ethyl-2-benzothiazolylidene)propenyl]-1,2,4-4*H*-triazolium iodide.



The stability of the 1,2,4-triazole nucleus is reflected in its inertness to lithium aluminum hydride (191), sodium and liquid ammonia (110), and oxidizing agents in general. It shows no dienic character and reaction with acrylic acid results in *N*-substitution with the formation of β-(1,2,4-1*H*-triazol-1-yl)propionic acid. Similarly, with benzalacetophenone β-phenyl-β-(1,2,4-1*H*-triazol-1-yl)propiophenone is formed (363).

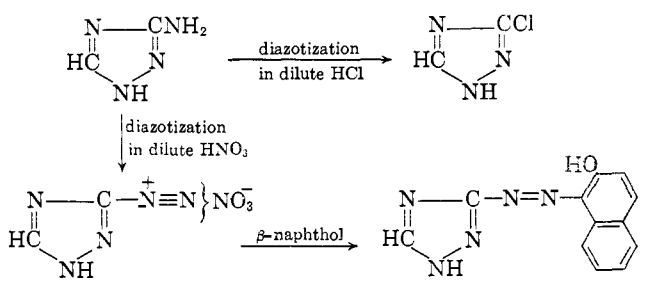


It is interesting to note also that the open-chain analog, benzalazine, does not form a normal adduct with maleic anhydride (352).

Thus the majority of reactions of 1,2,4-triazoles are the reactions of the substituent groups, and these reactions are as fully diversified as those found in benzene chemistry. Only a brief discussion of the more important reactions is included here.

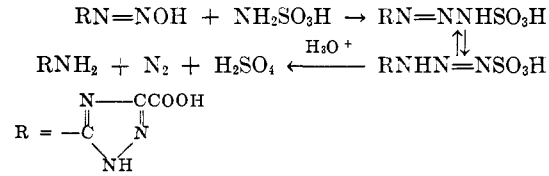
C-Aminotriazoles behave as normal aromatic amines and are diazotized in aqueous mineral acid with nitrous acid, forming diazonium salts which couple with aromatic bases, such as β-naphthylamine (33, 34, 242, 289, 343). The detection of 3-amino-1,2,4-triazole in plant extracts depends on this property. It is separated by paper chromatography, using ethanol:water:butanol (1:1:4, volume/volume) as solvent, and the spot is developed by diazotization and coupling with a phenol (6).

These diazonium salts are very unstable in the presence of hydrochloric acid, decomposing rapidly even in ice-cold solution with evolution of nitrogen and formation of the corresponding chlorotriazole (242). Substitution of the nucleus with alkyl groups tends to stabilize the diazonium salt (289) and a more favorable result is obtained by diazotization in the presence of an oxy acid, such as nitric acid. The normal reactions of the diazonium group, such as reduction to the hydrazine and oxidation to an azo compound (229, 288, 343), are shown by these compounds.



C-Halotriazoles are most efficiently synthesized from these diazonium salts (33, 229), and treatment of the diazonium salt with 50 per cent hypophosphorous acid is the most effective way of achieving *C*-deamination (34, 167). On the other hand, *N*-amino groups are very readily removed as nitrous oxide by treatment with nitrous acid (99, 180), by heating in a vacuum at 250°C. (330), or by reaction with alkaline Raney nickel catalysts (283).

Sulfamic acid has long been used to remove excess nitrous acid following the diazotization of amines but it reacts with 5-diazo-1,2,4-triazol-3-ylcarboxylic acid regenerating the amine (145). It is possible that the reaction follows this route.

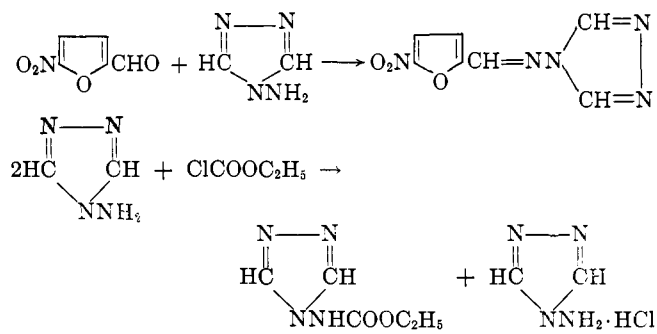


Both *C*- and *N*-aminotriazoles undergo the other reactions characteristic of a primary amine. Besides salt formation with mineral acids, 3-amino-1,2,4-triazole forms salts with pentachlorophenol (346) and several phytotoxic acids, such as *p*-chlorophenoxyacetic acid (219). These salts may be titrated to a sharp end-point in ethanol, using phenolphthalein as indicator, and the alkali used is equivalent to the acid content. All these compounds are of interest as herbicides.

Reaction of 3-aminotriazole with acyl chlorides (187, 199) gives the usual substituted amides and, with sulfonyl chlorides, sulfonamides of therapeutic interest (105, 184). It also forms precipitates with ferric and cupric ions (223).

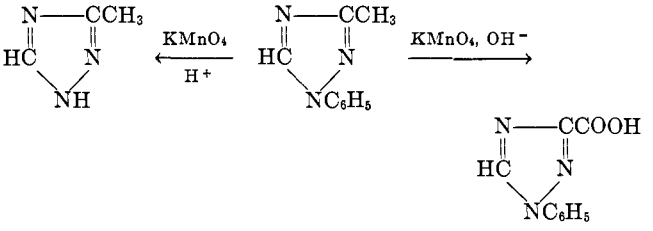
The *C*-primary amino group may be converted into a secondary one by reductive alkylation in which a mixture of an aldehyde and a 30–50 per cent excess of 3-aminotriazole is heated in alcohol with hydrogen under pressure in the presence of Raney nickel (274).

The amino group of 4-amino-1,2,4-4*H*-triazole also reacts in a similar manner and with aldehydes readily forms the corresponding Schiff base. Those from 5-nitrofurfural and 5-nitrofurylacrylic aldehyde compare favorably with Furacin (5-nitrofurfural semicarbazone) in bacteriostatic properties (303). As expected, ethyl chloroformate readily forms ethyl *N*-(1,2,4-4*H*-triazol-4-yl)carbamate with 4-amino-1,2,4-4*H*-triazole (97).

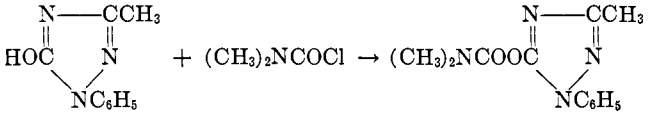


C-Alkyl-substituted triazoles are readily oxidized to the carboxylic acids by oxidizing agents, such as alkaline potassium permanganate (21, 23, 228, 342), and this is the standard method used for the degradation of side chains containing a point of unsaturation. The carboxylic acid is readily decarboxylated to the triazole itself on heating above its melting point. However, oxidation with potassium permanganate under acid conditions oxidizes a *C*-alkyl group only to a very small extent but it is very effective in removing an *N*-aryl substituent (21, 23). This interesting oxidation probably proceeds through a free-radical mech-

anism involving oxidation by Mn(III).

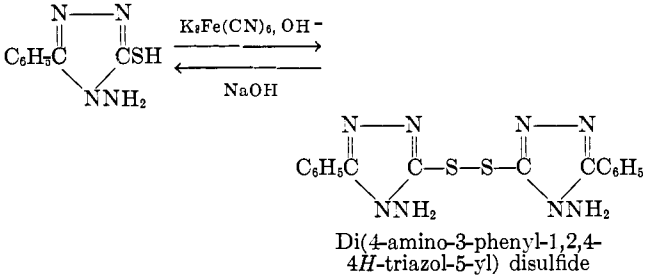


Oxygen- and sulfur-containing triazoles are obtained by the methods discussed earlier. The presence of a hydroxyl or mercapto group in the molecule practically removes all basic character, and no definite decision can yet be made as to which tautomeric form is actually present. Those compounds containing hydroxyl groups form ethers with diazoalkanes, and alkyl sulfates and alkali, and the hydroxyl group may be removed by heating with phosphorus sulfides. With acid chlorides, such as dimethylcarbamoyl chloride, they form esters which are useful as insecticides (136, 137).



3-Methyl-1-phenyl-1,2,4-1*H*-triazol-5-yl dimethylcarbamate

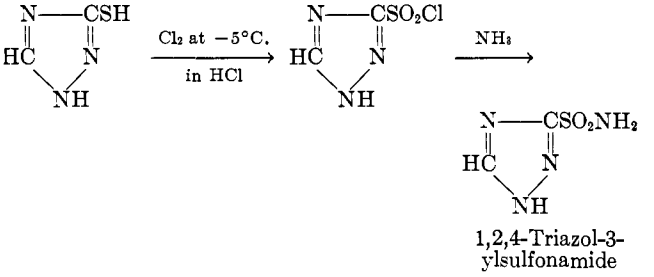
Mercapto groups are easily converted into their methyl ethers with sodium hydroxide and methyl iodide, and these ethers have a slight tendency to lose methanethiol on standing. The mercapto group may be oxidized to a disulfide linkage with alkaline potassium ferricyanide, a reaction that is reversed by dissolution of the disulfide in alkali (180).



Di(4-amino-3-phenyl-1,2,4-4*H*-triazol-5-yl) disulfide

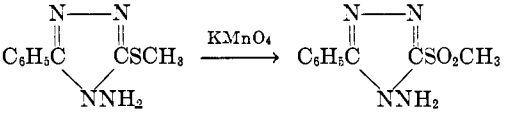
At low temperatures oxidative chlorination of a mercaptotriazole is an excellent method of obtaining the corresponding sulfonyl chloride, which readily forms a sulfonamide where the sulfur is joined directly to the nucleus (91, 92). This method of oxidation is successful with triazoles containing one or two mercapto groups, or a hydroxyl group, but is not satisfactory when an amino group is present.

The sulfur may also be oxidized in a methylthio ether to a sulfone with potassium permanganate (180)



1,2,4-Triazol-3-ylsulfonamide

or by any of the oxidizing agents used for the aliphatic analogs.

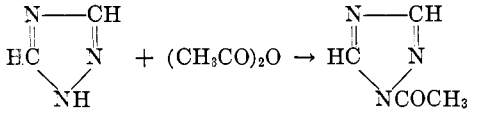


4-Amino-5-methanesulfonyl-3-phenyl-1,2,4-4*H*-triazole

The elimination of the mercapto group is readily achieved with such reagents as Raney nickel, dilute nitric acid, or hydrogen peroxide (125, 174).

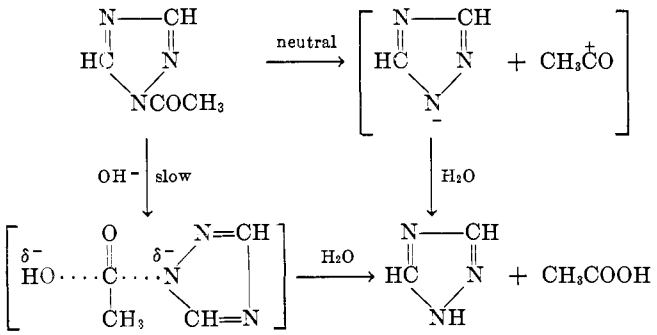
The other main reactions of the triazole nucleus are those associated with the imino hydrogen atom. Its replacement by alkali metals has been mentioned earlier, but more interesting are those reactions in which it is replaced by an acyl or some similar group. These reactions all involve a reagent with a strongly electrophilic carbon atom and are probably best represented as nucleophilic displacements on carbon where the entering group is the triazole nucleus. The fact that these reactions do proceed so readily and are even more readily reversed by the presence of a trace of moisture is further evidence in support of representing the triazole nucleus as a resonance-stabilized, aromatic system with an overall negative charge on the ring.

Acetylation of 1,2,4-tirazole, or its derivatives containing an imino hydrogen atom, with acetic anhydride gives the *N*-acetyltriazole very readily, but there is insufficient evidence available to confirm that acetylation occurs on the nitrogen atom in the 1-position (30, 312). The same acetyl compounds are also obtained from the sodium salt of the triazole and acetyl chloride or from two moles of the triazole and one of acetyl chloride.

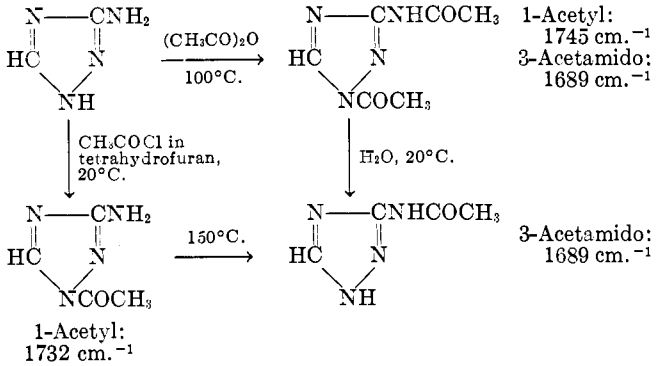


The kinetics of neutral, basic, and acid-catalyzed hydrolysis, and also of aminolysis, have been investigated (312, 313, 316) and interpreted in the following way. In neutral solution the reactive *N*-acetyltriazole undergoes a monomolecular dissociation into an acetyl cation and a triazolyl anion which then react further with the solvent, whereas in the presence of strongly nucleophilic amines or hydroxyl ions the hydrolysis is of

a bimolecular S_N2 type, both being illustrated below.



The acetyl derivatives of 3-amino-1,2,4-triazole undergo the interesting series of transformations shown, and the infrared absorption frequencies of the carbonyl bands are an excellent means of following these reactions (317). The most probable course of the acetyl group rearrangement is an intermolecular one.



Other acyl and diacyl derivatives of 3-amino- and 5-amino-3-methyl-1,2,4-triazole have been described (50) and are shown in table 18. These are striking

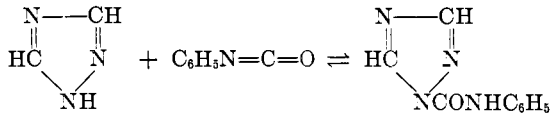
TABLE 18

Melting points of monoacyl and diacyl derivatives of 3-amino- and 5-amino-3-methyl-1,2,4-triazoles (50)

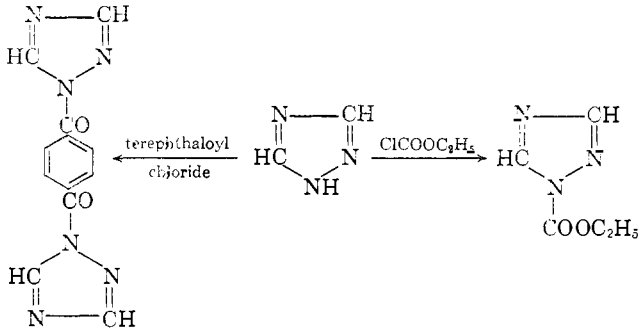
Acyl Group	3-Amino		5-Amino-3-methyl	
	Monoacyl	Diacyl	Monoacyl	Diacyl
	°C.	°C.	°C.	°C.
Acetyl	295–300	190–191	284	203
Propionyl	268–271	130	265	134
Butyryl	233–234	107–114	258	86

examples of the effect that substitution on the imino nitrogen atom has on the melting points of 1,2,4-triazoles.

Phenyl isocyanate reacts with 1,2,4-triazole forming *N*-1,2,4-triazolylcarbonic acid anilide, which also has the property of being readily hydrolyzed (166, 252). Indeed, at 80°C. in benzene or chloroform solution, it is largely dissociated into 1,2,4-triazole and phenyl isocyanate, a reaction that can be followed by the presence of an infrared absorption band at 4.4 μ due to phenyl isocyanate. It is of interest to note that a similar reaction with pyrroles always gives α-substitution (72), a fact that is in agreement with the differences that one would expect between the structure of pyrrole and that suggested earlier for 1,2,4-triazole.



Reaction of 1,2,4-triazole with ethyl chloroformate gives the corresponding *N*-carbonic acid ester (315); similarly, reaction with a diacid chloride in tetrahydrofuran gives the corresponding di(*N*-triazolyl) compounds (314). Both these types of *N*-acyl derivatives are readily hydrolyzed.



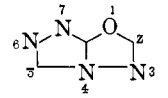
Alkylation of 1,2,4-triazole and 3,5-disubstituted 1,2,4-triazoles affords mainly the 1-alkyltriazole, whether the alkylating agent is a diazoalkane, or an alkyl halide and the sodium salt of the triazole (30). With a 3-substituted 1,2,4-triazole, both 1-alkyl-3-substituted and 1-alkyl-5-substituted 1,2,4-1*H*-triazoles are formed in a ratio of about 1:2 (5).

V. Fused 1,2,4-Triazole Systems

1,2,4-Triazole does not contain two adjacent carbon atoms, and a fused triazole ring system is possible only when one of the nitrogen atoms of the triazole ring is also one of the heteroatoms of the other ring system. Fused triazole systems that have not been well authenticated, or about which only very little information is available, are not included in this discussion. All names are based on the *Ring Index* method (254) and are the same as those used in *Chemical Abstracts*.

A. C_2N_3–C_2N_2O system

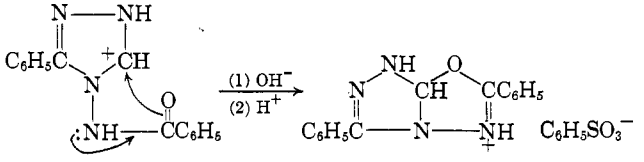
Only one fused triazole of this particular type is known; using the *Ring Index* system, it is named as a derivative of the parent compound, *s*-triazolo[3,4-*b*]-1,3,4-oxadiazole, shown below.



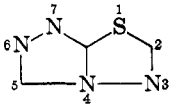
s-Triazolo[3,4-*b*]-1,3,4-oxadiazole

Its preparation involves an alkali-catalyzed cyclization of a benzamido group on to a tertiary carbon

atom that in acid solution exists as a carbonium ion and isolation of the product, after acidification, as the benzenesulfonate salt. Thus, alkali treatment of the reaction intermediate, formed from benzhydrazide benzenesulfonate and dimethylformamide on long heating, results in the formation of 7,8-dihydro-2,5-diphenyl-*s*-triazolo[3,4-*b*]-1,3,4-oxadiazolium benzenesulfonate (284).

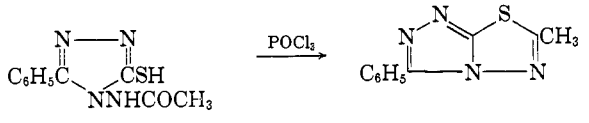


B. C_2N_3–C_2N_2S SYSTEM



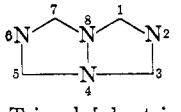
s-Triazolo[3,4-*b*]-1,3,4-thiadiazole

The parent system is represented by the *Ring Index* name *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole and is analogous to the oxadiazole type mentioned above. Representatives of this system are prepared by the action of phosphoryl chloride on the acyl derivatives of 4-amino-5-mercapto-3-phenyl-1,2,4-4*H*-triazole, and in the case of the acetyl compound the final product is 2-methyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (199). These compounds exhibit an ultraviolet absorption maximum at 275 mμ (ϵ = 25,120) and a shoulder at 245 mμ (ϵ = 9550).



C. C_2N_3–C_2N_3 SYSTEM

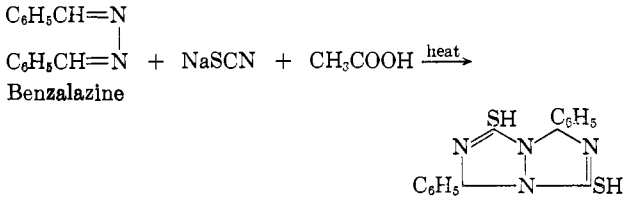
The simplest system of this kind is that named 1,5-*s*-triazolo[*a*]-*s*-triazole and numbered as shown. In the early literature it is also referred to as 1,2-triazolotriazole or bitriazole (35, 272).



1,5-*s*-Triazolo[*a*]-*s*-triazole
(R.I. No. 581)

The parent product itself is unknown, but substituted derivatives are conveniently prepared by the reaction of an aldehyde- or ketoazine with sodium thiocyanate and acetic acid. Thus 3,7-dimercapto-1,5-diphenyl-1,5-*s*-triazolo[*a*]-*s*-triazole is obtained from benzalazine (239, 240).

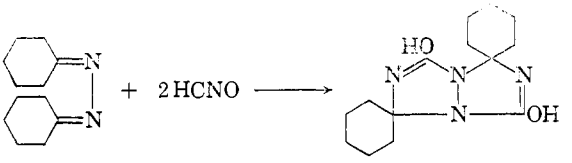
Variations of this reaction are possible, such as the alternative use of thiocyanic acid and water (241, 335)



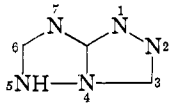
Benzalazine

or the direct combination of an aldehyde with a hydrazine thiocyanate (89).

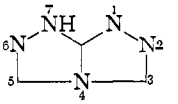
Cyanic acid may also be used in this type of reaction with azines, with the formation of the corresponding 3,7-dihydroxy compounds (35). When an azine of a hydroaromatic ketone, such as cyclohexanone, is used, an interesting type of spiro-fused 1,5-*s*-triazolo[*a*]-*s*-triazole results (111).



The alternative method of fusion of the two rings with a carbon and nitrogen atom forming the two common atoms has been reported, but on the evidence available no decision as to which of the isomers is formed can be made. The two isomeric parent ring systems are:

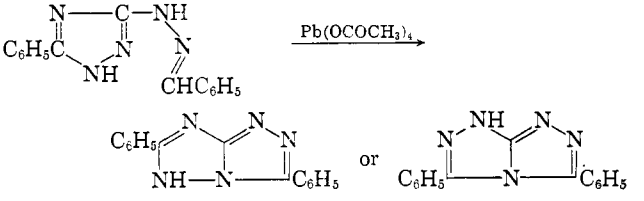


5-*s*-Triazolo[3,2-*c*]-*s*-triazole



7-*s*-Triazolo[3,4-*c*]-*s*-triazole

The method of preparation involves the lead tetraacetate dehydrogenation and ring closure of benzaldehyde 5-phenyl-1,2,4-triazol-3-ylhydrazone (59). It can be readily seen that either 3,6-diphenyl-5-*s*-triazolo[3,2-*c*]-*s*-triazole or 3,5-diphenyl-7-*s*-triazolo[3,4-*c*]-*s*-triazole can be formed, depending on the direction of ring closure (59).

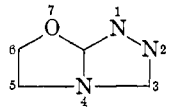


However, from the action of an excess of benzoyl chloride followed by hydrolysis on 4,5-diamino-3-phenyl-1,2,4-4*H*-triazole, a compound, $C_{15}H_{11}N_5$, is obtained which appears to be 3,6-diphenyl-5-*s*-triazolo[3,2-*c*]-*s*-triazole (178). The physical constants of these two compounds are in general agreement, so it is possible that this is the isomer obtained in the above dehydrogenative ring closure.

D. C_2N_3–C_3NO SYSTEM

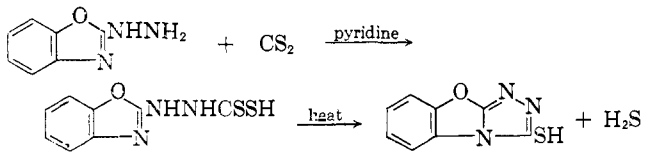
The parent compounds of all the possible members of

this ring system are unknown and only a benzoxazolo[2,3-*c*]-*s*-triazole has been synthesized.



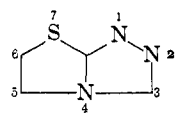
Oxazolo[2,3-*c*]-*s*-triazole

3-Mercaptobenzoxazolo[2,3-*c*]-*s*-triazole is prepared from 2-hydrazinobenzoxazole through the intermediate dithiocarbazic acid, which readily loses hydrogen sulfide on heating to form the triazole (213).

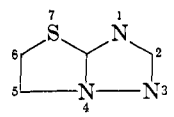


E. C_2N_3–C_3NS SYSTEM

Two members only of this system are known and are shown below.

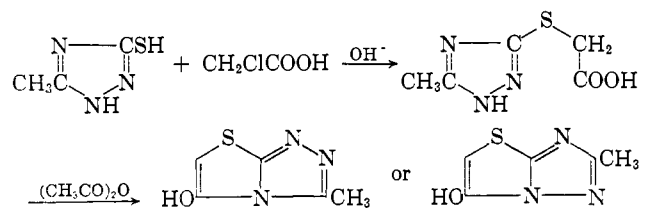


Thiazolo[2,3-*c*]-*s*-triazole



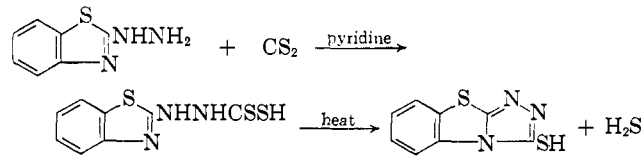
Thiazolo[3,2-*b*]-*s*-triazole (R.I. No. 583)

Derivatives of thiazolo[2,3-*c*]-*s*-triazole are claimed to be prepared by heating a 3-triazolylglycolic acid in the presence of a dehydrating solvent, such as acetic anhydride, to effect ring closure. Thus, from 3-mercapto-5-methyl-1,2,4-triazole and chloroacetic acid in the presence of alkali, the intermediate *S*-(5-methyl-1,2,4-triazol-3-yl)thioglycolic acid is obtained and this is cyclized to 5-hydroxy-3-methylthiazolo[2,3-*c*]-*s*-triazole (203). However, cyclization may occur in the alternative way to give 5-hydroxy-2-methylthiazolo-[3,2-*b*]-*s*-triazole and it seems most likely that the latter compound would predominate in such a reaction mixture.

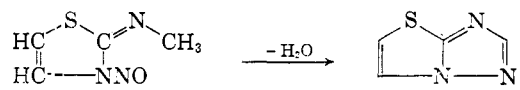


A more efficient method of synthesis has been used for benzo ring-fused members of this system, such as 3-mercaptobenzothiazolo[2,3-*c*]-*s*-triazole. 2-Hydrazinobenzothiazole is converted into the dithiocarbazic acid which, on heating, loses hydrogen sulfide with cyclization to the triazole (213).

The parent thiazolo[3,2-*b*]-*s*-triazole itself has been synthesized by intramolecular elimination of water

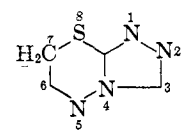


from 2-(*N*-methylimino)-3-nitroso-2,3-dihydrothiazole (245).



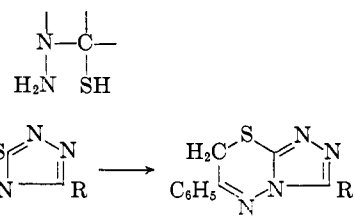
F. C_2N_3–C_3N_2S SYSTEM

This system is represented by 7-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazine and only 3,6-disubstituted derivatives are known.



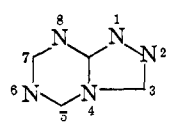
7-*s*-Triazolo[3,4-*b*]-1,3,4-thiadiazine

They are prepared from 4-amino-5-mercapto-3-phenyl- and 3-methyl-1,2,4-4*H*-triazoles and phenacyl bromide, the formation of a 1,3,4-thiadiazine in this reaction being characteristic of the grouping (180):

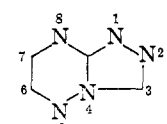


G. C_2N_3–C_3N_3 SYSTEM

It is theoretically possible to have nine isomeric triazolotriazines derived from *s*-triazine, *as*-triazine, and *v*-triazine. Of these, only two are known, *s*-triazolo-[4,3-*a*]-*s*-triazine and *s*-triazolo[4,3-*b*]-*as*-triazine, numbered as shown.

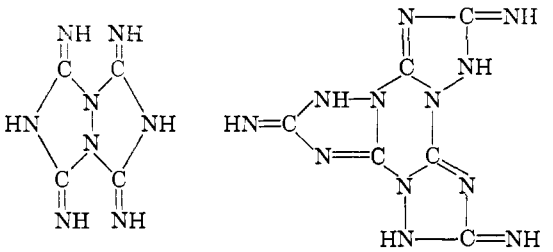


s-Triazolo[4,3-*a*]-*s*-triazine

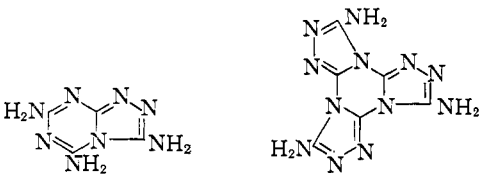


s-Triazolo[4,3-*b*]-*as*-triazine

It has been known for many years that guanazole, from hydrazine hydrochloride and dicyandiamide (259), when fused with two moles of dicyandiamide gives guanazoguanazole (172, 173, 263), and this when heated to high temperatures gives pyroguanazole. These have been regarded as derivatives of *s*-triazolo[*a*]-*s*-triazole and tris-*s*-triazolo[2,3-*a*, 2,3-*c*, 2,3-*e*]-*s*-triazine (*s*-triazolo[2,3-*a*]-*s*-triazine, R.I. No. 701, also referred to as 1,3,4,6-tetrazaindolizine), respectively.



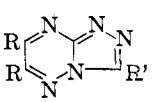
Both cyanuric acid and nitrogen were isolated from the oxidation of pyroguanazole, an observation that is not in agreement with the above structure. These have been modified recently (197) and guanazoguanazole is now represented as 3,5,7-triamino-*s*-triazolo[4,3-*a*]-*s*-triazine or its isomer derived by possible ring closure at the 2-nitrogen atom of the triazole nucleus. This reaction has also been found to be general for 3-amino-5-alkyl(or aryl)-1,2,4-triazoles (195, 197). Similarly, by assuming that an intramolecular condensation of three moles of guanazole, better represented as 3,5-diamino-1,2,4-triazole, occurs, a more satisfactory expression for the structure of pyroguanazole results. This is now regarded as being 3,7,11-triamino-tris-*s*-triazolo[4,3-*a*, 4,3-*c*, 4,3-*e*]-*s*-triazine.



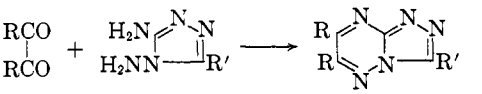
Derivatives of *s*-triazolo[4,3-*b*]-*as*-triazine, also called 1,2,4,7,9-pentaazaindene, are readily available by two methods. The first is analogous to the condensation of an α-diketone with an *o*-diaminobenzene to form a quinoxaline. The aromatic *o*-diamino compound in this case is a 3,4-diamino-1,2,4-triazole and this readily condenses with an aliphatic or aromatic α-diketone (178, 179, 181, 340). *s*-Triazolo[4,3-*b*]-*as*-triazines prepared by this method are shown in table 19.

TABLE 19

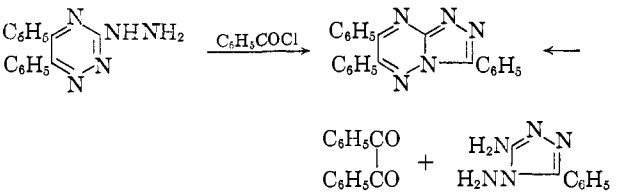
3,6,7-Trisubstituted-s-triazolo[4,3-b]-as-triazines



R	R′	Melting Point	References
		°C.	
C_6H_5—	NH_2—	263-264	(340)
CH_3—	NH_2—	299-300	(340)
p-ClC_6H_4—	NH_2—	229-231	(340)
9,10-Phenanthro-	NH_2—	334-336 (d.)	(340)
C_6H_5—	SH—	305-306	(340)
C_6H_5—	SCH_3—	201-203	(181, 340)
C_6H_5—	C_6H_5—	250	(178)
C_6H_5—	H	182-183	(181)
CH_3—	C_6H_5—	203	(178)
C_6H_5—	*p*-$CH_3OC_6H_4$—	247	(179)
CH_3—	*p*-$CH_3OC_6H_4$—	215	(179)

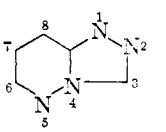


The alternative method involves the familiar reaction of a 3-hydrazino-*as*-triazine with a dehydrating agent, with ring closure occurring in the direction shown (116, 301).

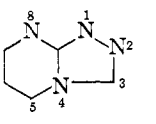


H. C_2N_3–C_4N_2 SYSTEM

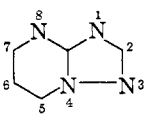
There are nine possible isomers of a C_2N_3–C_4N_2 system and at present only four are known: *s*-triazolo[4,3-*b*]pyridazine, *s*-triazolo[3,4-*b*]pyrimidine, *s*-triazolo[2,3-*a*]pyrimidine, and *s*-triazolo[4,3-*c*]pyrimidine.



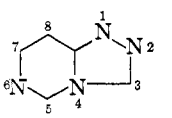
s-Triazolo[4,3-*b*]pyridazine (R.I. No. 706)



s-Triazolo[4,3-*a*]pyrimidine

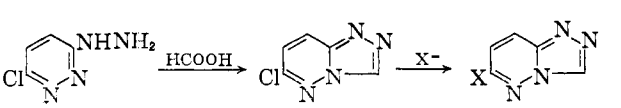


s-Triazolo[2,3-*a*]pyrimidine (R.I. No. 707)



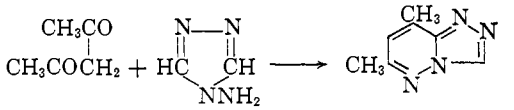
s-Triazolo[4,3-*c*]pyrimidine

The *s*-triazolo[4,3-*b*]pyridazine system is referred to in the literature as a 2,3,7-triazaindolizine (244) or a 2,3-triazo-7,0′-pyridazine (75, 336). These names are not as descriptive as the *Ring Index* names. The most direct route to this ring system involves the cyclization of a 3-hydrazinopyridazine and most investigations have been mainly concerned with the various ways of effecting this ring closure. This is usually done with 80 per cent formic acid (336, 338) or ethyl orthoformate (336), and the use of acetic anhydride gives the corresponding 3-methyl compound (336). It has been claimed that 3-acylhydrazino-6-chloropyridazines undergo cyclization in alkaline solution but not in neutral or acid solution (337), an observation that seems to contradict evidence obtained in similar systems.



The original method (75, 76) of obtaining this ring system was from the condensation of 4-amino-1,2,4-4*H*-triazole and a β-dicarbonyl compound, such as acetylacetone, in the presence of piperidine. Substituted acetoacetic esters, like ethyl α-ethylacetoacetate, have

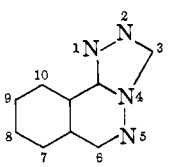
been used more recently, the condensation being effected by heat and 7-ethyl-8-hydroxy-6-methyl-*s*-triazolo-[4,3-*b*]pyridazine being formed in moderate yield (214, 319). Replacement of the hydroxyl group with chlorine gives a reactive chloro compound that reacts with amines, forming *s*-triazolo[4,3-*b*]pyridazines with basic substituents in the 8-position (319).



Triazolopyridazines substituted in the 6-position are prepared by making use of the reactivity of the 6-chloro compound in nucleophilic displacement reactions (338), and the chlorine atom is readily replaced with hydrogen by catalytic reduction.

This system has a characteristic ultraviolet absorption with maximum absorption at 240 mμ (ϵ = 16,600) and 305 mμ (ϵ = 6460) (337, 338) and is of interest in photography as a stabilizer (217, 290).

It is also convenient to consider here those fused triazoles that can be obtained from the two possible condensed bicyclic systems of pyridazine, cinnoline, and phthalazine. Derivatives of the latter only are known and are called *s*-triazolo[3,4-*a*]phthalazine, with the numbering of the ring system as shown (106). It has also been called in the literature a 1,2,3*a*,4-tetrazabenz[*E*]indene (291), a name that offers no advantages over that used by *Chemical Abstracts*.



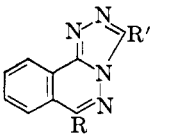
s-Triazolo[3,4-*a*]phthalazine

As with the triazolopyridazines, this system is obtained by ring closure of a 1-hydrazinophthalazine with formic acid (157, 291), or by the action of an acid chloride in pyridine (106, 293), or by essentially similar methods involving modification of the hydrazine group. Table 20 shows some *s*-triazolo[3,4-*a*]phthalazines of pharmacological interest prepared by these various methods.

The first preparation of a compound containing a triazole and a pyrimidine ring fused together involved the reaction of 3-amino-1,2,4-triazole with a compound having two reactive groups in the β-positions, such as keto, aldehyde, cyano, or ester groups (73). Thus with ethyl acetoacetate, condensation of the amino group can occur with either the keto group or the ester group, and cyclization on to the triazole nucleus is possible at both positions 2 and 4, leading to the formation of four isomers (A, B, C, and D)

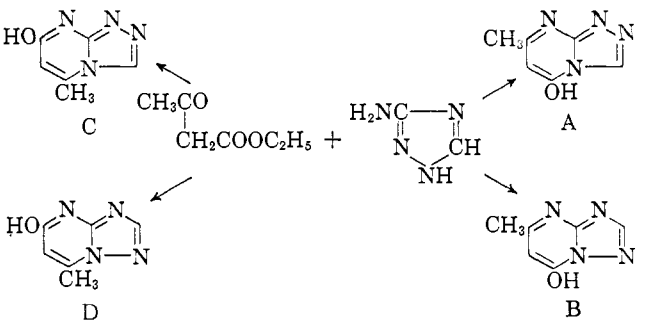
TABLE 20

s-Triazolo[3,4-a]phthalazines



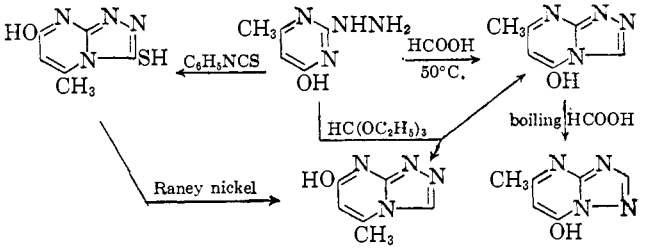
R	R′	Melting Point	Method*	References
		°C.		
H	H	190-191	A	(106, 157)
H	CH_3—	171-172	B, C, D	(106, 157)
CH_3—	C_6H_5—	212	C	(157)
H	—NHNHCHO	300 (d.)	A	(291)
H	4-(2,6-$Cl_2C_6H_2N$—)	292-295	C	(293)
H	4-[2,6-$(C_2H_5O)_2C_5H_2N$—]	207-211	C	(293)
H	C_4H_9—	101-102	C	(106)
H	iso-C_4H_9—	91-92	C	(106)
H	C_6H_{13}—	71-73	C	(106)
H	C_6H_5—	208-209	C	(106)
H	—CH_2Cl	188-189	E	(106)
H	—$CHCl_2$	213-215	E	(106)
H	—Cl	205	F	(106)
H	—OH	275-277	C	(106)
CH_3—	—SH	ca. 300	G	(106)
CH_3—	—NHC_6H_5	139-140	G	(106)

* A: Heating with 85 per cent formic acid.
B: Heating with acetic anhydride.
C: With the acid chloride and pyridine.
D: Heating with a methyl ketone or acetoacetic ester.
E: Heating with an acid.
F: Action of phosphoryl chloride and phosphorus pentachloride on the hydroxy compound.
G: From the allylthiosemicarbazide and acetic acid.

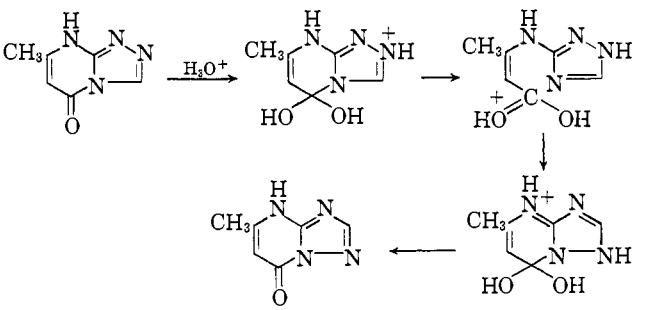


It was originally assumed that condensation occurred between the keto and the amino groups and cyclization at the 2-nitrogen atom was involved (73). This would result in the formation of an *s*-triazolo[2,3-*a*]-pyrimidine (B), R.I. No. 707, also known by such trivial names as 1,3,4-triazaindolizine, pyrimidotriazole, 1,3-triazo-7,0′-pyrimidine, and 1,2,3*a*,7-tetrazaindene. An attempt was made to resolve this ambiguity by cyclization of 4-hydroxy-6-methyl-2-pyrimidylhydrazine with formic acid. As the product obtained is identical with that obtained from 3-aminotriazole and ethyl acetoacetate, the original cyclization was assumed to occur at the 4-nitrogen atom, giving an *s*-triazolo[4,3-*a*]-pyrimidine derivative (A) (51, 52, 54, 59). In an excellent series of papers, this has been shown to be an oversimplification of the problem (291). When 4-hydroxy-6-methyl-2-pyrimidylhydrazine is treated with

formic acid under milder conditions than those used above, an isomeric triazolopyrimidine is formed, and this is isomerized with boiling formic acid to the triazolopyrimidine obtained in the initial ring closure (248, 291). Both these isomers are obtained in effecting the ring closure with ethyl orthoformate, and the 7-oxo-*s*-triazolo[4,3-*a*]pyrimidine is also available by reaction of the hydrazine with phenyl isothiocyanate and desulfurization of the intermediate mercapto compound with Raney nickel (291). Although these syntheses are not unequivocal in themselves the spectral and chemical evidence considered in this more recent work (291) strongly supports these assignments.

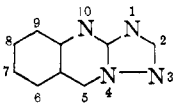


The rearrangement of the *s*-triazolo[4,3-*a*]pyrimidine to the [2,3-*a*] isomer is further evidence for the nonamidic nature of this carbonyl group (the infrared absorption band of the carbonyl group is well below 6.0 μ) and of the aromatic character of the triazole nucleus in the oxo derivatives of this ring system. It is interesting that the ultraviolet spectral data also indicate that these derivatives exist in the oxo form (291), which is more stable here than in an *N*-acyltriazole. A mechanism for this rearrangement is as follows (291):

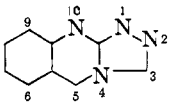


Other workers (94, 128, 161, 162) have also assumed that this particular type of cyclization occurred at the 2-nitrogen atom. The structures assigned to these compounds should be reëvaluated in view of this new evidence, e.g., substituted *s*-triazolo[3,2-*b*]quinazolines, formed by condensation of cyclic β-keto esters and 3-aminotriazole, might possibly have the isomeric *s*-triazolo[3,4-*b*]quinazoline (also known as 1,2,4-triazol-4,5-quinazoline) structure (138). The verification of these structures must await further study.

It is possible for an unsymmetrical 2-pyrimidylhydrazine to undergo cyclization in two ways on treatment with formic acid, and it has been established that in



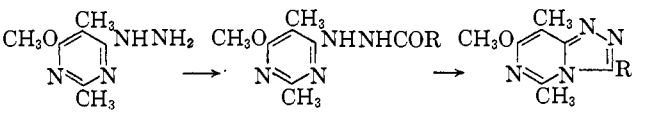
s-Triazolo[3,2-*b*]quinazoline



s-Triazolo[3,4-*b*]quinazoline (R.I. No. 1498)

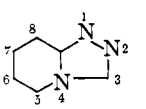
the case of 4-hydroxy-6-methyl-2-pyrimidylhydrazine, both isomers have been isolated by a small change in reaction conditions (291). When this same hydrazine is treated with benzoyl chloride, followed by phosphoryl chloride, formation of the triazole ring is also accompanied by replacement of the hydroxyl group with chlorine; the same compound is obtained by replacement of the hydroxyl group with chlorine in the product isolated by cyclization of the corresponding hydrazone with lead tetraacetate (59). These products are regarded as derivatives of *s*-triazolo[4,3-*a*]pyrimidine, but as acidic reaction conditions are involved, they might have the alternative *s*-triazolo[2,3-*a*]pyrimidine structure, as described above. Unfortunately, a detailed consideration of this interesting and complex problem is outside the scope of this review.

Cyclization of a 4-pyrimidylhydrazine can occur in only one way, with the formation of an *s*-triazolo[4,3-*c*]pyrimidine (309). The acyl compound is first formed from the hydrazine and an acid, acid chloride, or ester, and this is then cyclized with phosphoryl chloride. An alternative method of cyclization is to treat the hydrazine with an acid anhydride and a trace of sulfuric acid.

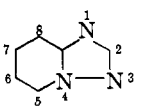


I. C_2N_3–C_5N SYSTEM

The two fused triazoles shown below represent this system but derivatives of the former only are known.



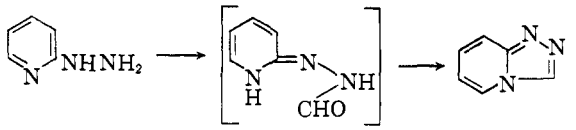
Pyrido[2,1-*c*]-*s*-triazole (R.I. No. 712)



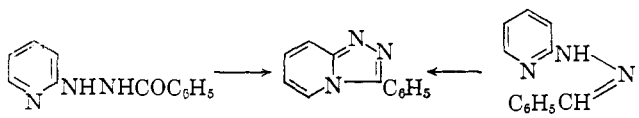
Pyrido[1,2-*b*]-*s*-triazole

In the early literature pyrido[2,1-*c*]-*s*-triazole has erroneously been called benztriazole (143, 232), and other equally undesirable names are triazolopyridine, 2,3-diazapyrrocoline (42), 1,2,9-benzisotriazole (116), and for those fused triazoles derived from quinoline, naphthtriazole (231).

The original and most efficient method of synthesis involves the cyclization of a 2-pyridylhydrazine, and later syntheses are variations in the way of effecting the ring closure. When formic acid or acetic anhydride is used as the dehydrating agent, it also supplies the carbon atom necessary for ring formation (116, 232)



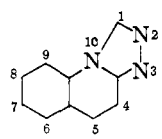
A prior acylation of the hydrazine to form, for example, the benzoyl derivative of 2-pyridylhydrazine and then heating this with phosphoryl chloride to effect ring closure is a satisfactory alternative method. The same result is also obtained by the dehydrogenation of benzaldehyde 2-pyridylhydrazone with lead tetraacetate (59).



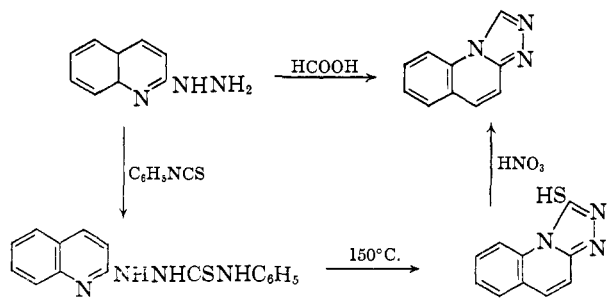
The reaction of 2-pyridylhydrazine with one equivalent of carbon disulfide results in ring closure to a pyrido[2,1-*c*]-*s*-triazole substituted with a mercapto group in the 3-position (339). This same fused triazole is also obtained by the use of potassium dithiocarbonate and acetic acid in this reaction (238).

With alkaline potassium permanganate, the ring system is oxidized to a 1,2,4-triazole.

It is convenient to consider here the corresponding system derived from 2-quinolylhydrazine, *s*-triazolo-[4,3-*a*]quinoline. It may be prepared by cyclization of the corresponding hydrazine with formic acid (231), or with acetic anhydride which gives the 1-methyl derivative (66), but an interesting alternative involves the reaction of the hydrazine with phenyl isothiocyanate. The disubstituted thiosemicarbazide formed, on being heated above 150°C., loses aniline, forming 1-mercapto-*s*-triazolo[4,3-*a*]quinoline. Heating with dilute nitric acid readily removes the mercapto group (230, 231).



s-Triazolo[4,3-*a*]quinoline
(R.I. No. 1504)



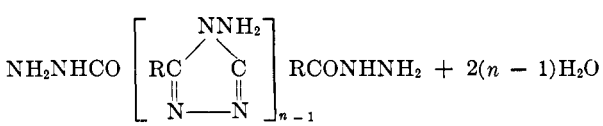
Condensation of substituted *s*-triazolo[4,3-*a*]quinolinium iodides with suitably substituted heterocyclic salts gives cyanine dyes, which are of great interest in photography (66).

VI. Uses

The uses proposed for triazole derivatives have been many and varied and this wide range of applications has been covered by more than sixty papers in the literature, many in the form of patents. The more important uses are discussed only briefly here and may be regarded as falling into one of four classes: polymers, agricultural chemicals, pharmaceuticals, and photographic chemicals and dyestuffs.

A new series of condensation polymers, the polyaminotriazoles, which are rather similar to nylon, have been studied extensively in the United States (285), Great Britain (62, 63), Germany (10, 225), and France (7, 8, 9). In the initial work, the conditions of preparation did not lead to constancy of composition and formation of suitable polymers, but these difficulties have been largely overcome with the production of polymers that are fiber-forming and that can be melt-spun to give filaments that, after drawing, possess high strength and good affinity for dyestuffs (40, 41, 121).

These polyaminotriazoles are condensation polymers, produced most readily by heating dihydrazides in the presence of a small amount of hydrazine. The name refers to the recurring linkage, the 4-amino-1,2,4-4*H*-triazole ring. The condensation may also be effected by heating a molar quantity of a suitable dibasic acid, such as sebacic acid, with more than two moles of hydrazine.



The chemical behavior of the polymers is largely similar to that of the aminotriazole structure, since they are resistant to hot aqueous alkalis but are attacked by acids and bleaching powder. However, fabrics or other textiles made from these polymers are unaffected by the ordinary acidic media with which they come into contact in textile processing or ordinary wear.

Various improvements (124), modifications (122, 123, 209), and fabrications (302) of these polyaminotriazoles have been described.

Triazole derivatives prepared from biguanides, i.e., 3,5-diamino-1,2,4-triazoles, on condensation with aldehydes give resinous products that are used for the production of moulding compounds or as coating materials for cloth and paper (102, 103). The intermediate compounds were also reported as being useful as fungicides and insecticides (101).

3-Amino-1,2,4-triazole, under its trade name Amizol, has been used as a commercial defoliant for a number of years, particularly in the cotton industry (13, 154). The phototoxic effect appears to be due to chlorophyll

destruction and inhibition of chlorophyll synthesis (227), together with an interference with the carbohydrate metabolism. It has been used successfully in the control of Canada thistle (220) and other perennial weeds (159, 255, 296), various woody plants, including poison ivy, black cherry, etc. (236), and in the respiration of sugar beets (246). In small concentrations it was found to have growth-promoting properties, though not of the same order as indole-3-acetonitrile (226). It has been claimed that 3-furfurylideneamino-1,2,4-triazole is a better defoliant than Amizol (305). A recent investigation has shown that Amizol protects mice against 650 r. of x-irradiation and significantly prolongs the survival of animals receiving 750 or 850 r. No protection is noted when Amizol is administered after irradiation (118).

Various triazole derivatives have been shown to inhibit cholinesterase activity (280), and δ-aminolevulinic acid dehydrase activity in liver (349); to have mitotic action (186); to have a slight hypotensive effect in dogs (353); and to be stimulants of the central nervous system (153, 200, 221). Several other pharmacological uses for triazole derivatives have been described (109, 158, 222).

Triazoles and condensed triazole systems have found considerable use in the photographic industry. The tendency to fog formation in silver halide emulsions is reduced by incorporating in the emulsion or developer a triazole derivative, such as *N*,*N*′-bi(5-methyl-1,2,4-triazol-3-yl)formamidine (206), and the addition of 5-mercaptotriazoles or their soluble salts to the emulsion after development produces a greater maximum image density and prevents a bronzing effect (90, 318). Condensed triazole systems, such as *s*-triazolo[3,4-*b*]quinazoline have been particularly effective as toning agents and stabilizers for silver images (53, 156, 161, 207). Cyanine dyes containing, as one of the heterocyclic nuclei, a 1,3,4-trisubstituted 1,2,4-1*H*-triazole derivative sensitize silver halide emulsions (204, 205), and a similar effect has been obtained with those dyes containing a fused triazole system (64, 65, 160).

The sodium salt of a sulfonated triazole derivative possesses good detergent action and is useful in textiles (135); in the same industry it has been found that *N*-benzylated aminotriazoles have useful properties in inhibiting the acid-fading of dyestuffs (146).

The literature on the uses and potential uses of various triazole derivatives is quite voluminous and that mentioned above is a representative sample only.

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