THE CHEMISTRY OF THE VICINAL TRIAZOLES

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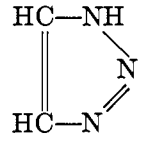
I. INTRODUCTION

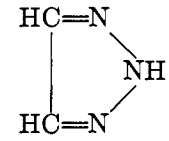
More than 1400 vicinal triazoles have been described in the chemical literature. As with so many classes of organic compounds, the only previous extensive review of these substances is the chapter in the textbook by Meyer and Jacobsen (155), which covers the accumulated knowledge of these compounds through 1915. The present survey endeavors to provide a comprehensive review of the chemistry of this group of heterocycles as currently known. To this end, the pertinent literature has been reviewed through 1947; a few articles appearing in 1948 have been inspected.

The vicinal or *v*-triazoles, also known as 1,2,3-triazoles, are five-membered, doubly unsaturated heterocycles, the ring consisting of three sequentially linked nitrogen atoms and two carbon atoms. The parent compound has one unlocated hydrogen atom, as indeed do all derivatives with hydrogen joined to a ring nitrogen. The two tautomeric forms of *v*-triazole are indicated in formulas I

and II.[1] Substitution of one or more of the hydrogen atoms in these two structures leads to the formulas of the several different classes of *v*-triazole derivatives. In addition to simple monocyclic *v*-triazoles, polycyclic fused-ring derivatives are known.



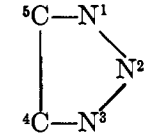
I



II

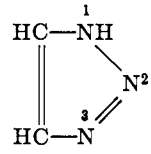
The *v*-triazoles are to be distinguished from the isomeric symmetrical or 1,2,4-triazoles, which are not included in this discussion. The present review will be confined to the aromatic type represented by *v*-triazole and its substitution products. Triazolines, triazolidines, and triazolium salts are therefore omitted. Triazole oxides, however, are included.

In accordance with the current practice of *Chemical Abstracts*, the numbering of the *v*-triazole ring in this article is as indicated. With respect to the more complicated fused-ring systems, the numbering and nomenclature practice is that prescribed by Patterson and Capell (175) and *Chemical Abstracts*. In referring to original sources it is useful to note that, particularly in the older literature, the *v*-triazoles have been called azimides and azoimines.

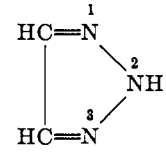


The history of the *v*-triazoles began with several isolated discoveries, the full significance of which was not apparent to the investigators. In 1860 N. Zinin (232) was investigating two isomeric compounds obtained by the nitration of azoxybenzene. One of these he called nitroazoxybenzene and the other isonitroazoxybenzene. He noted that when these materials were reduced with ammonium sulfide, the reaction with the former liberated 6 equivalents of sulfur, while the latter produced only 4 equivalents. Six equivalents of sulfur was the quantity usually obtained when nitro compounds were reduced with ammonium sulfide. The organic reduction product which Zinin obtained from his isonitroazoxybenzene was a solid melting at 85°C. Contrary to the properties of the

[1] *Chemical Abstracts* has now adopted the names given below for the tautomeric forms of *v*- or 1,2,3-triazole:



1,2,3,1*H*-Triazole



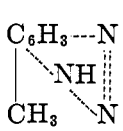
1,2,3,2*H*-Triazole

amines usually obtained by reduction of nitro compounds, the new substance formed no compounds with acids. Since Zinin was using the older atomic weights (O = 8) his empirical formulas did not enable him to make a fruitful appraisal of the nature of his compound, and his observation exerted little influence on the development of *v*-triazole chemistry. A considerable body of data and interpretation was necessary before the character of his compound became known. It remained for Werner and Stiasny (212), in 1899, to show that the product of Zinin's reduction was 2-phenylbenzotriazole 1-oxide.

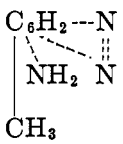
Also in 1860, A. W. Hofmann, during an investigation of the constitution of one of the nitrophenylenediamines, obtained a compound later shown to be a *v*-triazole derivative (123). When Hofmann treated his nitrophenylenediamine with nitrous acid, according to the procedure of Peter Griess, a substance resulted which differed in properties from the diazo compounds usually obtained. The new compound was found to be acid in nature and from it a silver salt was prepared. Hofmann was an advocate of the newer atomic weights (O = 16); hence his molecular formula for the product, $C_6H_4N_4O_2$, served at a later date as basis for a satisfactory structural interpretation. The state of knowledge of aromatic chemistry at the time of Hofmann's work did not enable him to perceive the positional relation of the two amino groups in his nitrophenylenediamine.

During the course of the next twenty years many similar reactions of nitrous acid with certain aromatic diamines were observed. In 1863 Kellner and Beilstein (137) treated so-called aminochrysanisic acid with nitrous acid, forming a compound which they named azoamido chrysanisic acid. Their starting material was later shown to be 3,4-diamino-5-nitrobenzoic acid. Griess (1872) similarly treated two diaminobenzoic acids, forming what he termed "azo acids" differing considerably from the usual diazo compounds in stability (107).

By 1876 the concept of positional isomerism on the benzene ring had been sufficiently well established for Ladenburg to make the generalization that these abnormal diazotizations occurred with *o*-diamines (147). Ladenburg diazotized phenylenediamine, toluylenediamine, and nitrotoluylenediamine. For the product from 3,4-toluylenediamine he proposed two structures, III and IV. Structure III, an internal diazoamino type, was the first proposal of a triazole ring. Ladenburg—oddly enough from the modern viewpoint—favored structure IV because of the stability of the compound.



III

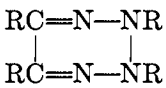


IV

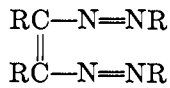
It soon became evident from the work of Griess (108), Noelting and Abt (171), and others that the "azimido" compounds were best represented by the first of Ladenburg's formulas.

Prior to 1888 all the *v*-triazoles produced were derivatives of benzotriazole.

The discovery of simple monocyclic triazoles is due to the work of H. v. Pechmann (177, 180). This investigator had earlier prepared, by oxidation of the phenylosazones of 1,2-dicarbonyl compounds, substances which he called osotetrazones and to which he ascribed the formula shown (V). Later work (201) has shown these substances to be bisazo compounds (VI), but this fact does not alter the essential validity of the logic which v. Pechmann applied to his results as far as the formation of *v*-triazoles is concerned.

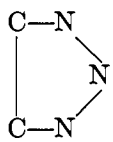


V

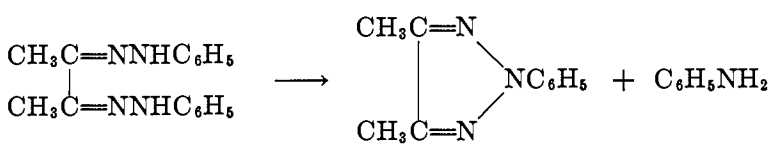


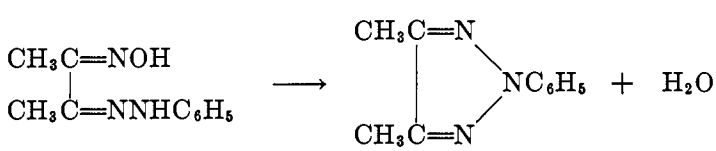
VI

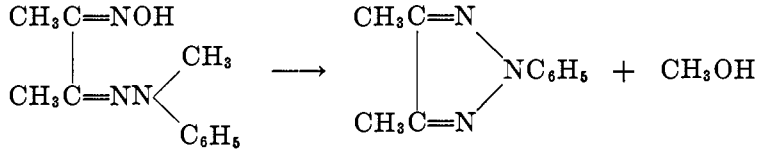
In the course of investigating the so-called osotetrazones, v. Pechmann heated the one derived from dimethylglyoxal ($C_{16}H_{16}N_4$) with acid, obtaining a neutral colorless oil, the analysis of which ($C_{10}H_{11}N_3$) showed that it differed from the starting material by the loss of C_6H_5N. The same substance, as well as aniline, was formed from dimethylphenylosazone on long heating with acid; the analytical results showed that the osazone had lost $C_6H_5NH_2$ in the formation of the new compound. In like manner, the phenylhydrazone oxime of diacetyl produced the same compound by loss of water. Similar results were obtained with the osazones and phenylhydrazone oximes of other 1,2-dicarbonyl compounds. Accordingly, v. Pechmann proposed that the products formed contained a common unsaturated ring, C_2N_3, of the structure:



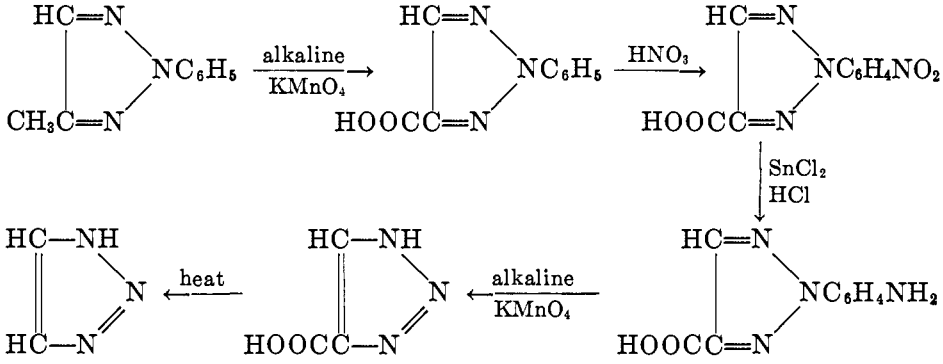
Compounds with this unit were first called osotriazones, but the name was subsequently modified to osotriazoles, a designation which is still retained for certain 2-substituted derivatives. The dimethylosotriazone of v. Pechmann was, therefore, a dimethylphenyl-*v*-triazole. It was later shown that the phenylmethylhydrazone oxime of diacetyl also yielded dimethylphenyl-*v*-triazole by loss of methyl alcohol (12). These syntheses were formulated by v. Pechmann substantially as indicated.



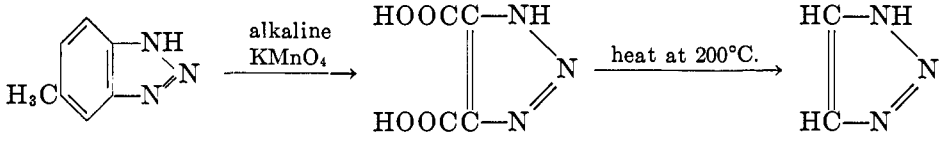




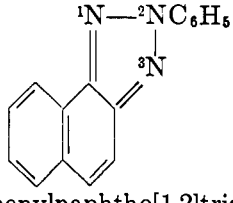
Deducing that these materials were substitution products of a substance having the formula $C_2H_3N_3$, v. Pechmann set about to prepare the parent compound by suitable degradation reactions (12). Starting with 2-phenyl-*v*-triazole-4-carboxylic acid, which he had obtained by oxidation of the 4-methyl derivative (177), he successively nitrated the phenyl group, reduced this product to an aminophenyl derivative, and obtained *v*-triazole-4-carboxylic acid by oxidizing the aminated phenyl compound. Decarboxylation led to the desired parent substance.



J. A. Bladin (27) showed that the same ring system was present in the benzotriazole (azimidobenzene) compounds. This investigator succeeded in destroying the benzene ring in 5-methylbenzotriazole by oxidation, yielding a *v*-triazole-dicarboxylic acid, which was decarboxylated to the parent compound, identical with that obtained by v. Pechmann.



Quite recently this same type of proof was furnished for a compound with a fused naphthalene and *v*-triazole ring. Ghigi and Pozzo-Balbi (101), by stepwise transformations, proceeded from 2-phenylnaphtho[1.2]triazole to *v*-triazole by a similar series involving the appropriate oxidation, nitration, reduction, and decarboxylation reactions.



2-Phenylnaphtho[1.2]triazole

After v. Pechmann's work, a large number of publications concerning the *v*-triazoles appeared. Much of the work involved extensions of Hofmann's diazotization synthesis of fused-ring *v*-triazoles and v. Pechmann's osazone synthesis. Among the important investigations was that of Dimroth and Fester (78). They effected combination of acetylene with hydrogen azide and phenyl azide, forming *v*-triazole and 1-phenyl-*v*-triazole, respectively. Dimroth made a further contribution in his study of the equilibrium between α-diazoamides and *v*-triazoles (68, 71, 72, 75), to which further reference will be made in this review. G. T. Morgan was particularly active in the synthesis of fused-ring *v*-triazoles and in the study of the behavior of acyl-substituted derivatives. Charrier's long series of publications were largely concerned with naphtho[1.2]triazoles; he demonstrated conclusively the analogous nature of this polycyclic heterocycle to phenanthrene. Probably the most notable class of *v*-triazole derivatives recently prepared is that of the sugar osotriazoles obtained by Hudson, Hann, and coworkers.

II. Physicochemical and Physical Properties of the *v*-Triazoles

Conductivities for several *v*-triazoles have been determined (68, 69, 70, 72, 112, 206). From some of these, ionization constants have been calculated and are listed in table 1. The values listed indicate that *v*-triazoles with one or no negative groups in the 4,5-positions, and having a hydrogen on a ring nitrogen, are acids of about the same strength as the first ionization of carbonic acid (4.31×10^{-7}). When, however, two negative groups are present, as with 4,5-dicyanotriazole, the dissociation constant becomes much larger. Taylor (206) assigns an important role to the possibility of several resonance structures for the dicyanotriazole anion in contributing to the relatively high acidity of this compound. Those *v*-triazoles bearing a carboxyl group attached directly to the triazole ring can be seen to be similar in strength to formic acid (1.77×10^{-4}). Of interest is the value for 1-*p*-bromophenyl-5-hydroxy-1,2,3-triazole-4-carboxylic acid ethyl ester, which shows the ionization constant of this phenolic type compound to be much greater than that of phenol (1.3×10^{-10}) or cyanuric acid (1.8×10^{-7}). The effect of negative substituents in augmenting ionization is similar to that found with picric acid (4.2×10^{-1}). Titration studies confirm the above range of constants. For example, 4-hydroxy-*v*-triazole can be titrated as a monobasic acid, using phenolphthalein as indicator (55). Using phenolphthalein, 5-hydroxy-1-*p*-tolyl-*v*-triazole-4-carboxylic acid and 1-hydroxy-5-methyl-*v*-triazole-4-carboxylic acid are found to behave as dibasic acids (69, 219).

The *v*-triazole ring also has slightly basic properties. The parent compound forms a hydrochloride which is unstable in water (12), while from 1-phenyl-*v*-triazole a platinic chloride may be prepared (157). The basicity of 1-alkylbenzotriazoles is greater than that of the 2-alkyl isomers, as shown by the solubility of the former in hydrochloric acid and the precipitation of the hydrochlorides of these from ether solution; hydrogen chloride does not precipitate the 2-alkylbenzotriazoles from ether, nor are these compounds soluble in hydrochloric acid (143).

A study of the extent of hydrogen bonding in benzotriazoles by means of

molecular weight determination in naphthalene was made by Heafield and Hunter (170). The data showed that those with a ring hydrogen were associated,

TABLE 1

Dissociation constants of the v-triazoles

COMPOUND	TEMPERATURE	K_a	REFERENCE
	°C.		
4-Phenyl-1,2,3-triazole	20	4.8×10^{-7}	(173)
4-Cyano-5-methyl-1,2,3-triazole	20	*ca.* 7.4×10^{-7}	(173)
4,5-Dicyano-1,2,3-triazole	25	3.378×10^{-2}	(206)
2-Methyl-1,2,3-triazole-4-carboxylic acid	20	*ca.* 5×10^{-4}	(173)
2-Ethyl-5-methyl-1,2,3-triazole-4-carboxylic acid	20	*ca.* 2.2×10^{-4}	(173)
2-Hydroxy-5-methyl-1,2,3-triazole-4-carboxylic acid		6.1×10^{-3}	(85)
1-*p*-Bromophenyl-5-hydroxy-1,2,3-triazole-4-carboxylic acid ethyl ester	25	1.5×10^{-2}	(69)
5-Phenyl-1,2,3-triazole-4-carboxylic acid	20	*ca.* 3.5×10^{-4}	(173)

TABLE 2

Ultraviolet absorption spectra of v-triazoles

COMPOUND	REFERENCES	COMPOUND	REFERENCES
Substituted benzotriazoles:		*Benzotriazole oxides:*	
Benzotriazole	(143, 148, 198)	1-Methyl 3-oxide	(148)
1-Methyl	(143, 148, 198)	1-Methyl-5-nitro 3-oxide	(148)
1,5-Dimethyl	(148)	1-Methyl-5-nitro-6-methyl 3-oxide	(148)
1-Methyl-5-nitro	(148)		
1-Methyl-6-nitro	(148)		
6-Nitro	(148)	*Naphtho[1.2]triazoles:*	
1-Acetyl-5-methyl	(163)	Naphtho[1.2]triazole	(4)
1-Acetyl-6-methyl	(163)	3-*p*-Tolyl	(162)
1-Phenyl	(143, 189)	3-Hydroxy-5-nitro	(148)
1-Hydroxy	(148)	2-*p*-Tolyl	(162)
1-Hydroxy-6-methyl	(148)		
1-Hydroxy-6-nitro	(148)	*v-Triazolo(d)pyrimidines:*	
1-Hydroxy-5-methyl-6-nitro	(148)	7-Hydroxy	(192)
1-Methoxy	(148)	5,7-Dihydroxy	(192, 38)
1-Methoxy-6-nitro	(148)	7-Amino	(192, 38)
1-Methoxy-5-methyl-6-nitro	(148)	5-Amino-7-hydroxy	(192, 38)
2-Methyl	(143, 198)	7-Amino-5-hydroxy	(38)
2-Phenyl	(143)	5,7-Diamino	(38)

probably chiefly through the 1 and 3 nitrogen atoms. The 1- and 2-substituted benzotriazoles were found to be substantially unimolecular.

The only heats of combustion available are those for naphtho[1.2]- and napththo[2.3]-triazoles (97). Oxidation–reduction potentials for various fused-

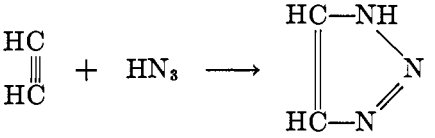
ring *v*-triazolequinones have been determined by Weygand and Henkel (213) and by Fieser (86, 87, 88, 90). Dipole moments for benzotriazole, for *v*-triazole, and for its 1- and 2-phenyl derivatives have been measured (131). Reference will be made later to these properties in connection with the structure of the *v*-triazoles.

Raman spectra have been determined for benzotriazole as well as for its 1- and 2-methyl derivatives (141). References to ultraviolet spectra are listed in table 2. It is to be noted that no spectroscopic data have been determined for simple monocyclic *v*-triazoles.

III. Synthesis of *v*-Triazoles

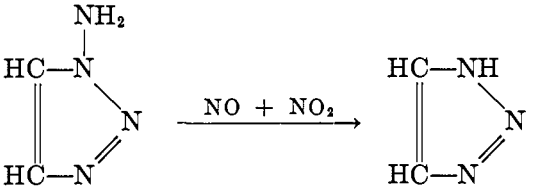
A. TRIAZOLE

Mention has already been made of the direct synthesis of *v*-triazole from acetylene and hydrogen azide. In this reaction acetylene is dissolved in acetone and hydrazoic acid in absolute alcohol; the reactants are heated in a sealed tube at 100°C. for 70 hr. (78). It is of interest that the corresponding combination of phenyl azide with acetylene under similar conditions proceeds more easily,

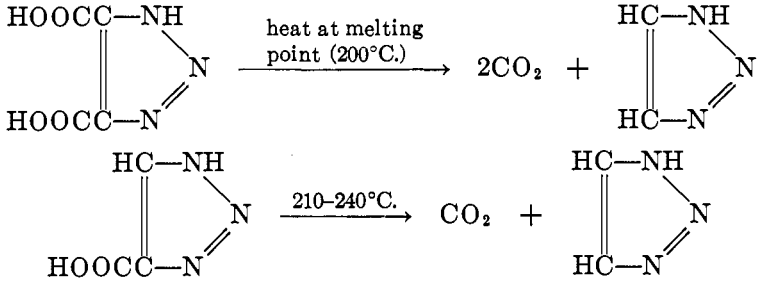


only 40 hr. of heating being required.

Other methods for preparing *v*-triazole require the use of substances already containing a triazole ring. When 1-aminotriazole is treated with oxides of nitrogen the amino group is replaced by hydrogen (179, 201).



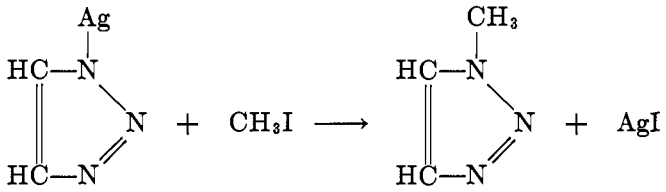
Elimination of a carboxyl group from a triazolecarboxylic acid is the remaining method for obtaining the parent compound. Either *v*-triazole-4,5-dicarboxylic acid or *v*-triazole-4-carboxylic acid loses carbon dioxide on heating. Temperatures ranging from 200° to 240°C. have been used (12, 27, 73, 101).



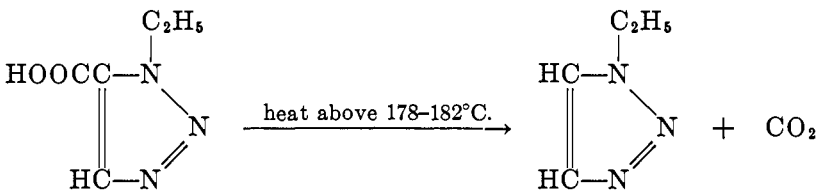
B. MONOSUBSTITUTED *v*-TRIAZOLES

1. 1-Substituted derivatives

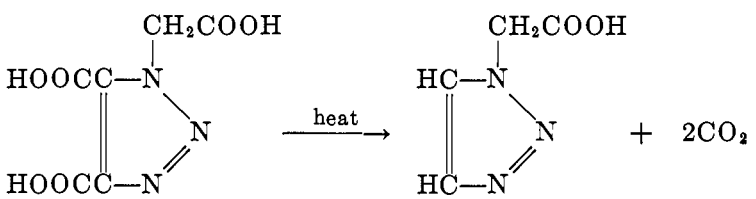
The action of methyl iodide on the silver salt of *v*-triazole leads to 1-methyl-*v*-triazole (78). This is the only alkylation reaction which has been applied to the parent compound.



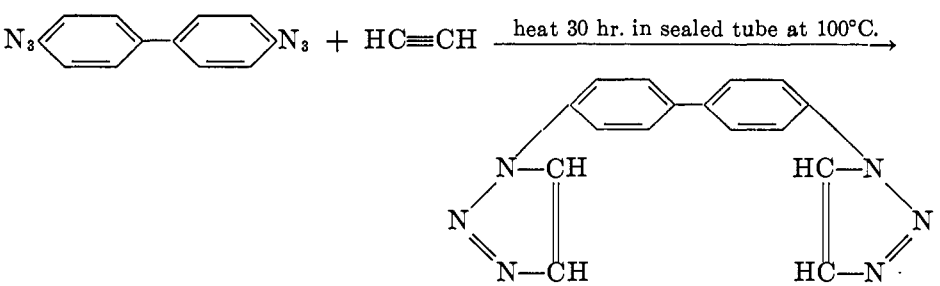
Of greater use in the synthesis of 1-substituted *v*-triazoles is the decarboxylation of *v*-triazolecarboxylic acids. Both 1-methyl- and 1-ethyl-*v*-triazoles have been obtained by heating the corresponding triazole-5-carboxylic acids above their melting points (220).



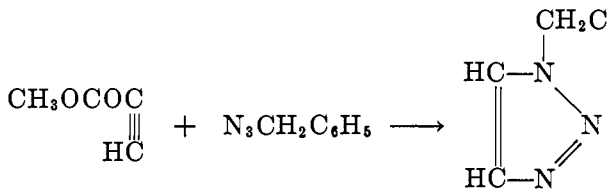
Dicarboxylic acids have also been used in this manner. 1-Benzyl- (61), phenyl- (157, 224), and *p*-nitrophenyl- (157) *v*-triazole-4,5-dicarboxylic acids have been decarboxylated to the corresponding 1-substituted *v*-triazoles. Somewhat unanticipated is the preparation of triazoleacetic acid by this procedure, where the two carboxyl groups joined to the triazole ring are preferentially eliminated, while that on the side chain is retained (59).



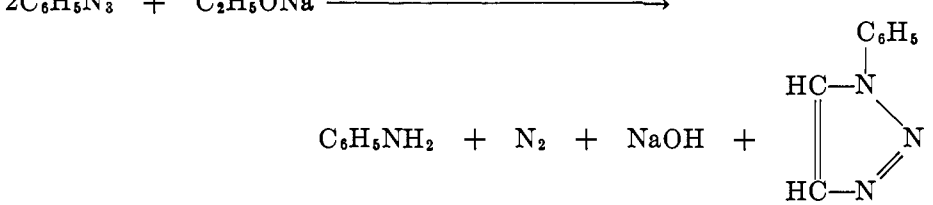
Addition of alkyl or aryl azides to acetylene leads to the formation of 1-substituted *v*-triazoles. The 1,1′-bistriazole derivative of biphenyl, for example, is



obtained from 4,4′-diazidobiphenyl (50). By means of this reaction, 1-phenyl- (138), 2,4-dichlorophenyl-, and 2,5-dichlorophenyl- (50) triazoles also have been synthesized. Similarly, methyl propiolate unites with benzyl azide on prolonged heating, with elimination of the carbomethoxyl group (61).

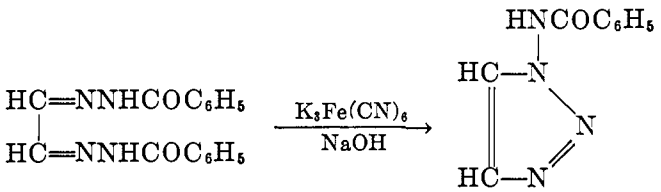


The formation of 1-phenyl-*v*-triazole may also be effected by the reaction of phenyl azide with sodium ethoxide in alcohol (23). Two moles of azide are required, one being converted to aniline. Preliminary formation of a phenyl



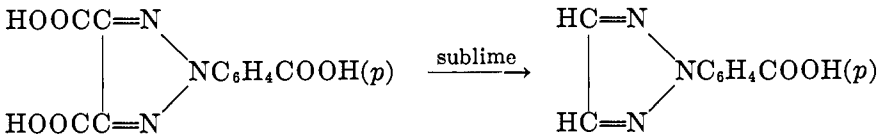
imide radical, which then removes hydrogen from the alkoxide to yield sodium vinylate, followed by condensation with the second mole of phenyl azide, was suggested as the mechanism of this reaction. It is also conceivable that an intermediate formation of acetylene may be involved, depending on whether sodium hydroxide is eliminated before, after, or simultaneously with the addition of phenyl azide. In the section on 1,4-disubstituted derivatives further applications of this synthesis are mentioned.

Formation of 1-benzoylamino-*v*-triazole is attained by oxidizing the benzoylosazone of glyoxal (179). Originally the product of this reaction was formulated as 2-benzoylamino-*v*-triazole, but subsequent work has shown it to be the 1-isomer (201).

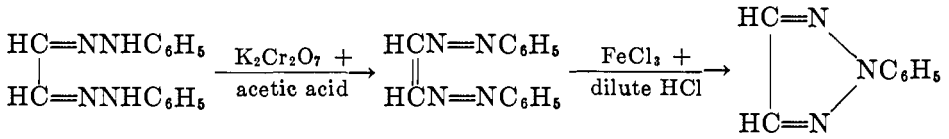


2. 2-Substituted derivatives

Decarboxylation of the 4,5-dicarboxylic acids has been used to prepare 2-phenyl- and 2-*p*-carboxyphenyl-*v*-triazoles (92, 133).

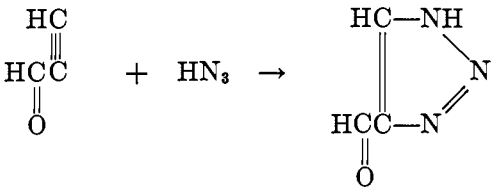


The 2-phenyl derivative has also been prepared from α,β-bis(benzeneazo)-ethylene by oxidation with ferric chloride. This starting material is prepared by the oxidation of glyoxal phenylhydrazone (133, 177, 201).

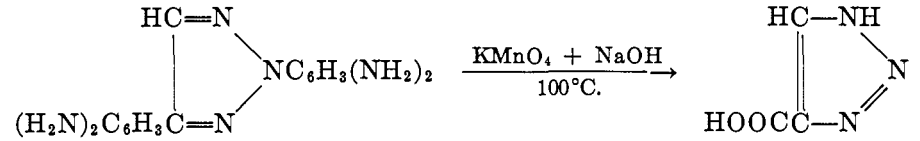


3. 4-Substituted derivatives

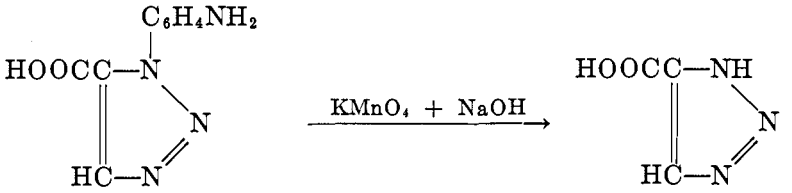
The reaction of acetylene derivatives and hydrazoic acid is applicable to the synthesis of *v*-triazoles substituted in the 4-position. Formyltriazole (124) and *v*-triazolecarboxylic acid (174) have both been prepared using this reaction. In view of the current availability of acetylenic compounds, this synthesis should find more extensive application.



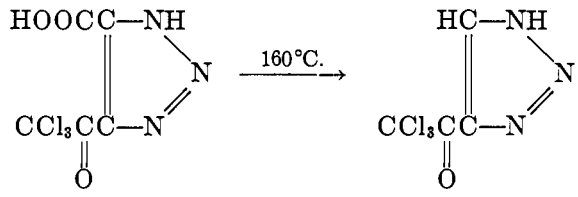
Triazolecarboxylic acid is one of the end products of the oxidation of 2,4-bis-(diaminophenyl)-*v*-triazole (101); this reaction is the penultimate step in the stepwise degradation of 2-phenylnaphtho[1.2]triazole to *v*-triazole carried out by Ghigi and Pozzo-Balbi. The complete elimination of the aromatic group



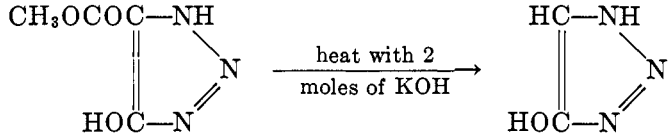
attached to nitrogen is to be noted. Likewise, 1-aminophenyl-*v*-triazole-5-carboxylic acid yields the same compound by permanganate oxidation (73).



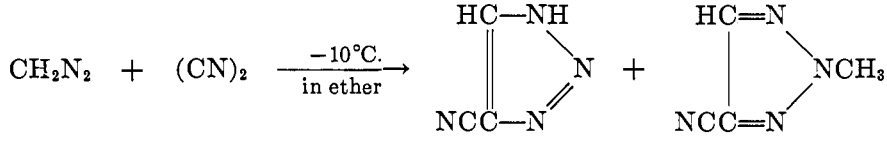
As with the other classes of monosubstituted *v*-triazoles, the decarboxylation reaction has been of value in obtaining members of this subdivision. The 4-phenyl (174), trichloroacetyl (223), and anilino (74) compounds have been prepared in this manner.



In similar fashion the alkaline saponification of 4-hydroxy-*v*-triazole-5-carboxylic acid methyl ester leads to the 4-hydroxy derivative (71).

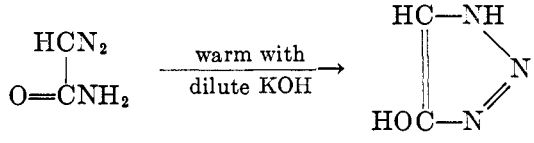


The interaction of diazomethane and cyanogen results in the formation of 4-cyano-*v*-triazole (181), the reaction being analogous to the synthesis of 5-cyanotetrazole from cyanogen and hydrogen azide; some 4-cyano-2-methyl-*v*-triazole is formed at the same time. Hydrolysis of this material, through the amide,

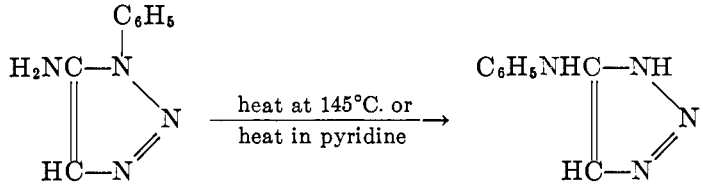


leads to *v*-triazole-4-carboxylic acid, identical with that prepared by other methods.

A triazole preparation also involving an aliphatic diazo compound is the rearrangement of diazoacetamide to 4-hydroxy-*v*-triazole (63). Many other applications of this reaction are described in the sections on simple 4,5-disubstituted and 1,4,5-trisubstituted *v*-triazoles.



Another rearrangement, leading to a 4-substituted derivative, is the thermal transposition of 5-amino-1-phenyl-*v*-triazole to 4-anilino-*v*-triazole (70).[2] The



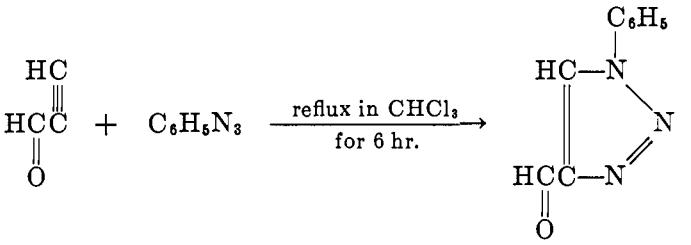
same compound is obtained if 5-chloro-1-phenyl-*v*-triazole is heated with alcoholic ammonia in a sealed tube, or when 5-amino-1-phenyl-*v*-triazole-4-carboxylic acid is decarboxylated.

[2] The formula of 4-anilino-*v*-triazole is shown in the inverted position; the equivalence of positions 4 and 5 in the *v*-triazoles monosubstituted on carbon is to be noted.

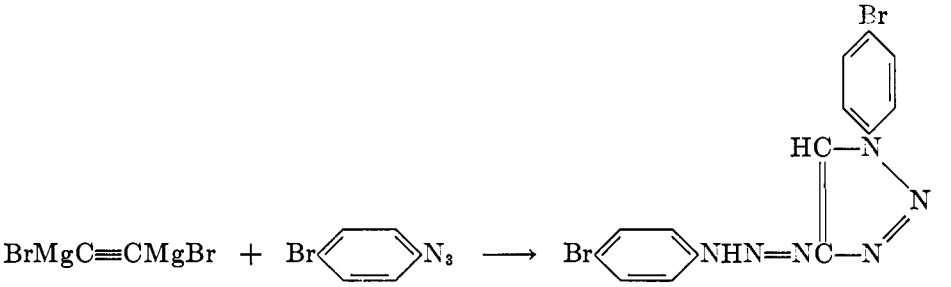
C. SIMPLE DISUBSTITUTED *v*-TRIAZOLES

1. 1,4-Disubstituted derivatives

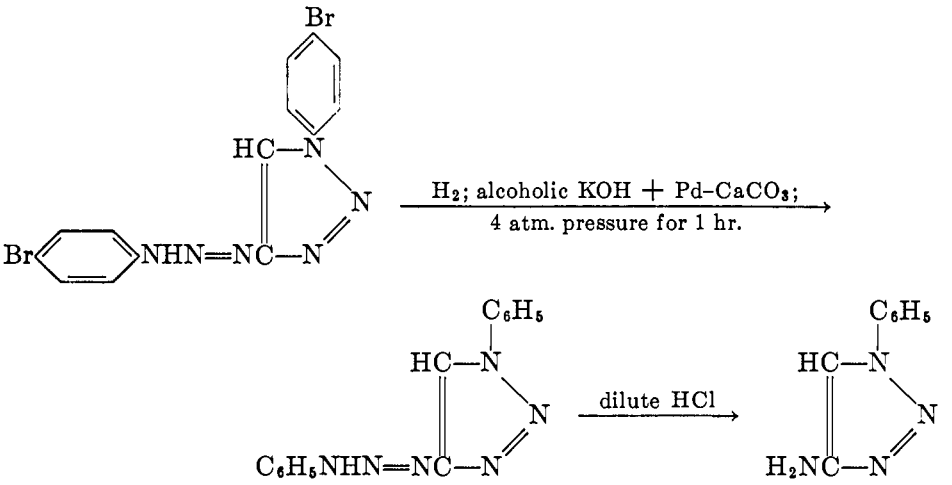
Interaction of azides with acetylenic compounds has been used in two instances to prepare 1,4-disubstituted triazoles. Propargyl aldehyde and phenyl azide combine to form 4-formyl-1-phenyl-*v*-triazole (124), from which the corresponding acid and hydroxymethyl derivatives were prepared by means of the Cannizzaro reaction.



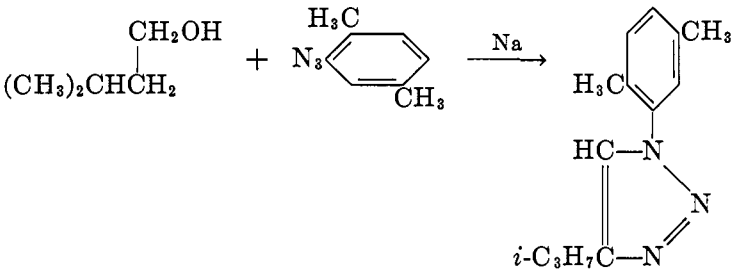
The other reaction using an acetylene derivative is the combination of *p*-bromophenyl azide with the Grignard derivative of acetylene. When an ether solution of these materials is allowed to stand out of contact with the air for 2–3 days and is finally decomposed with ammoniacal ammonium chloride, a diazoamino derivative of *v*-triazole is formed (138). After selective reduction has removed



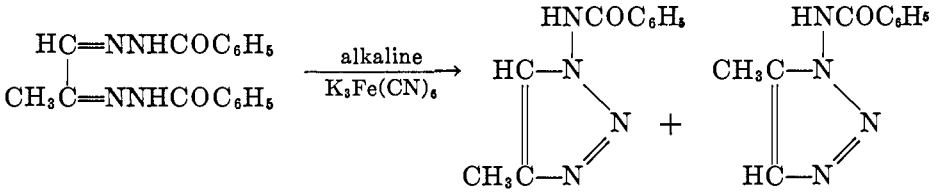
the bromine atoms, acid hydrolysis leads to 4-amino-1-phenyl-*v*-triazole.



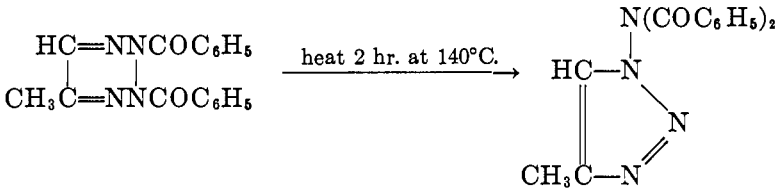
The azide–alkoxide procedure mentioned previously has been of considerable use in the synthesis of 1,4-disubstituted *v*-triazoles. Thus, *p*-xylyl azide and isoamyl alcohol combine to form 4-isopropyl-1-*p*-xylyl-*v*-triazole (24). In addition, the 4-methyl-1-*p*-xylyl and 4-phenyl derivatives (24), as well as the 4-methyl-1-phenyl, ethyl, and isopropyl (23) compounds have been prepared by this method.



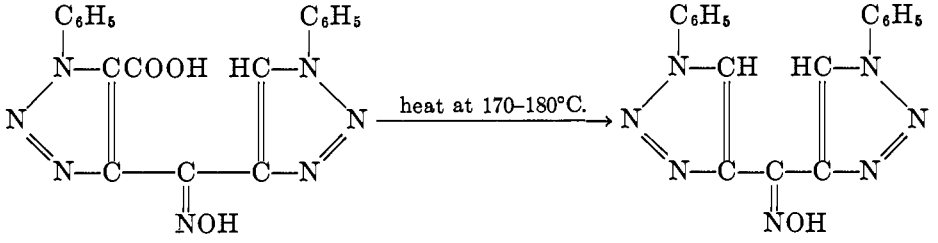
Oxidation of the benzoylosazone of methylglyoxal leads to the formation of both 1-benzoylamino-4-methyl-*v*-triazole and 1-benzoylamino-5-methyl-*v*-triazole by elimination of a benzoyl group (201). It is of interest that heating the closely related starting material, methyldibenzoyl osotetrazine, leads to the formation



of 1-dibenzoylamino-4-methyl-*v*-triazole by rearrangement (201).

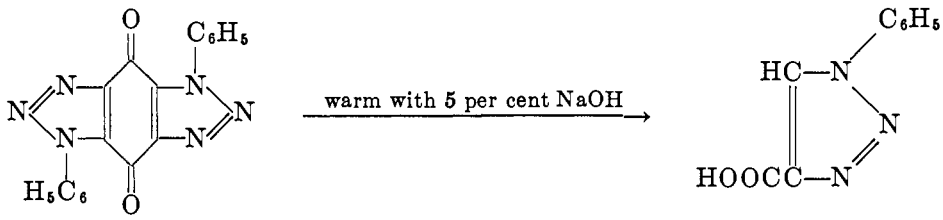


The usual decarboxylation reactions also have been applied in this series. For example, (1-phenyl-5-carboxy-1,2,3-triazolyl-4) (1-phenyl-1,2,3-triazolyl-4) ketoxime loses carbon dioxide at 170–180°C. (220). Similarly, 1-phenyl-*v*-

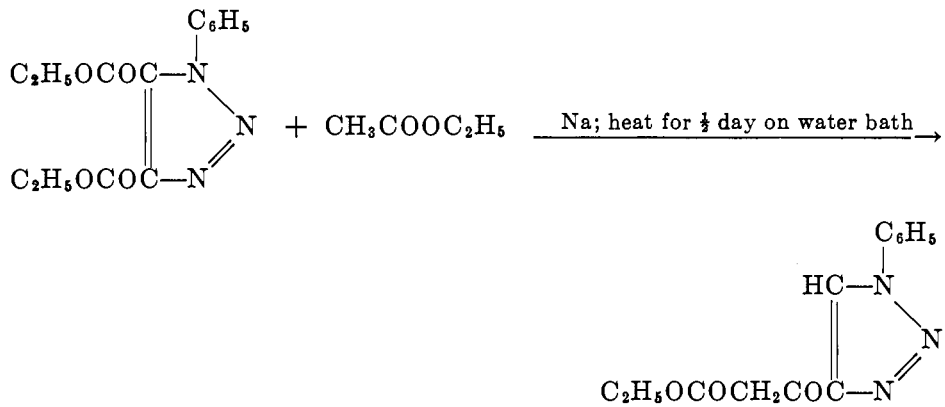


triazole-4,5-dicarboxylic acid preferentially decarboxylates to form the 1-phenyl-*v*-triazole-4-carboxylic acid (73).

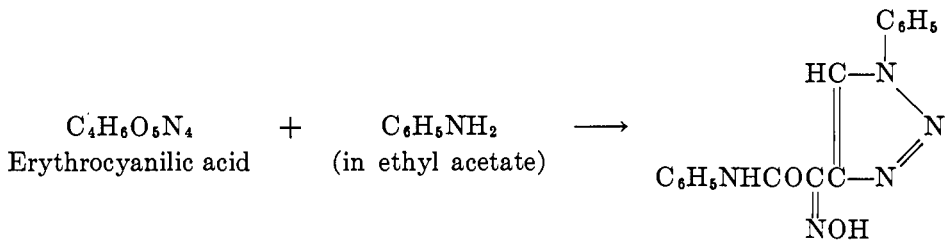
The latter substance is obtained also by alkaline treatment of 1,5-diphenylbenzo[1.2.4.5]bistriazolequinone (220).



When a Claisen-type condensation is carried out with 1-phenyl-*v*-triazole-4,5-dicarboxylic acid diethyl ester, the carbethoxyl group at position 5 is eliminated (30).

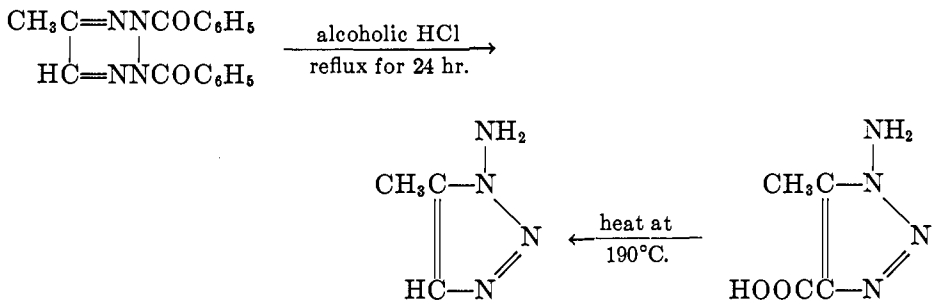


In the course of the work on the polymers of fulminic acid, Wieland and coworkers treated the tetramer, isocyanilic acid, with strong potassium hydroxide forming erythrocyanilic acid. The latter material on reaction with aniline was transformed to (1-phenyltriazolyl-4)isonitrosoacetanilide (215). The structure of this substance was shown by its reaction with thionyl chloride, forming 4-cyano-1-phenyl-*v*-triazole, which is easily hydrolyzed to the known carboxylic acid.

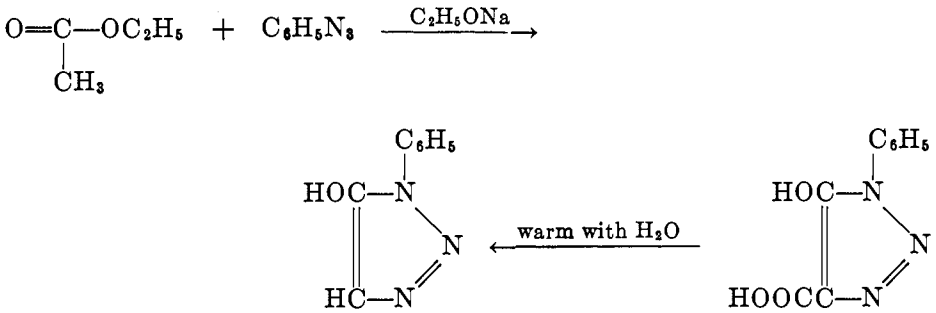


2. 1,5-Disubstituted derivatives

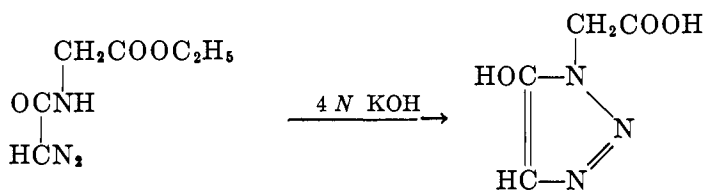
As indicated in the previous section, mild oxidation of the benzoylosazone of methylglyoxal leads to the formation of both 1,4- and 1,5-(benzoylamino)-methyl-*v*-triazoles. Heating methyldibenzoylosotetrazine with alcoholic hydrogen chloride leads to the formation of 1-amino-5-methyl-*v*-triazole (201). This same triazole has been obtained by decarboxylating 1-amino-5-methyl-*v*-triazole-4-carboxylic acid (221).



The interaction of ethyl acetate and phenyl azide in the presence of sodium ethoxide results in the synthesis of 5-hydroxy-1-phenyl-*v*-triazole (68, 74), the structure being confirmed by the preparation of the same substance from 5-hydroxy-1-phenyl-*v*-triazole-4-carboxylic acid.

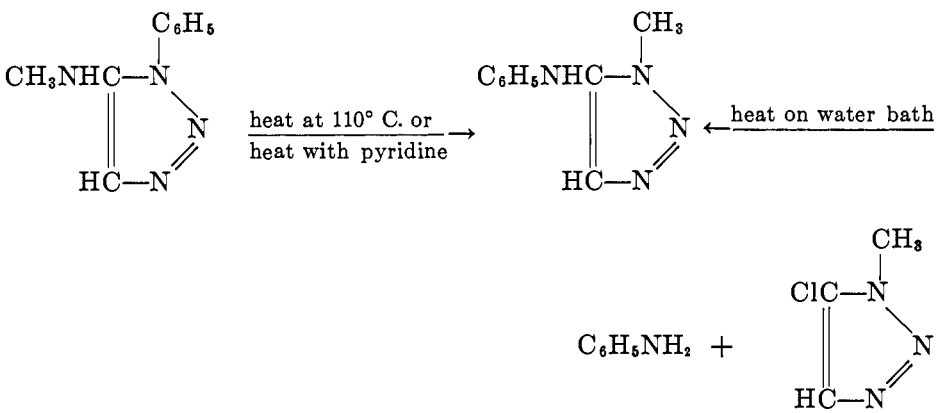


When the ethyl ester of diazoacetylglycine is heated with dilute alkali, the usual ring closure occurs, yielding 5-hydroxy-*v*-triazole-1-acetic acid (62, 64).

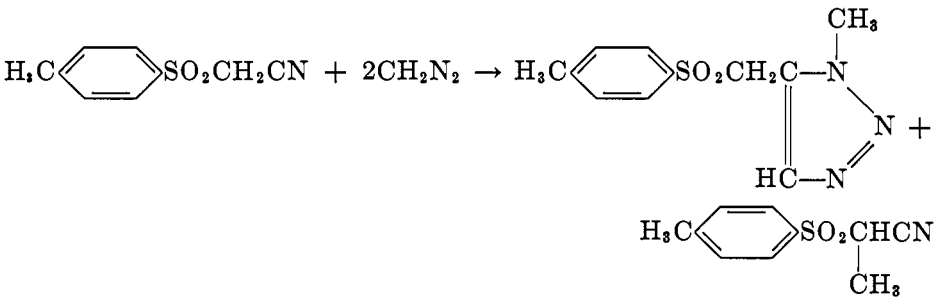


If concentrated ammonium hydroxide is employed as reagent in this reaction, the corresponding amide is formed (62), while the use of hydrazine hydrate leads to the hydrazide (64).

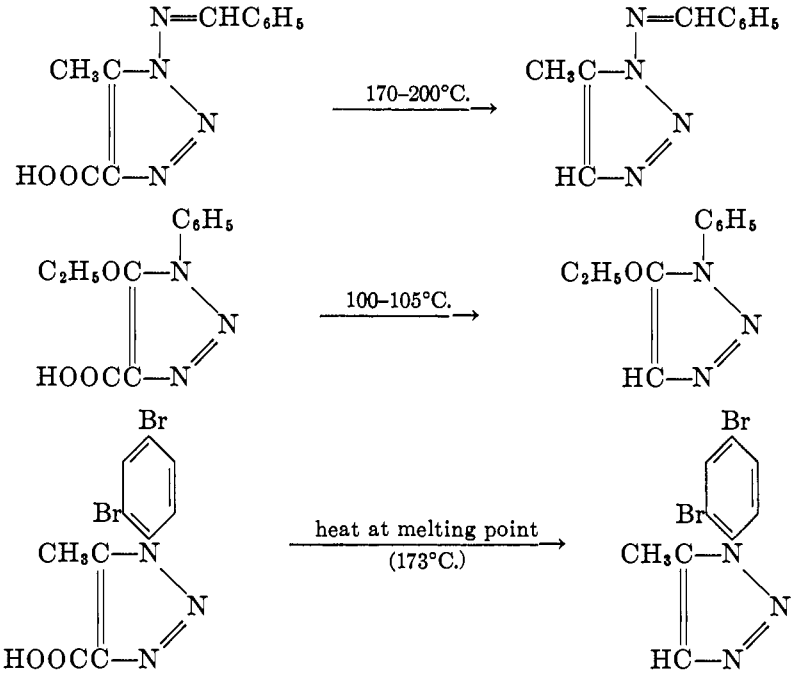
The same type of rearrangement noted for 5-amino-1-phenyl-*v*-triazole has been used to prepare 5-anilino-1-methyl-*v*-triazole (70). In this instance, the net effect is the interchange of positions by the methyl and phenyl radicals. Direct reaction of 5-chloro-1-methyl-*v*-triazole with aniline yields the same compound.



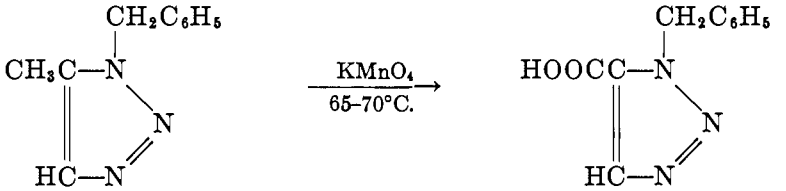
Two moles of diazomethane combine with *p*-toluenesulfonylacetonitrile to form 1-methyl-5-(*p*-toluenesulfonylmethyl)-*v*-triazole (6); one mole of diazomethane is utilized in forming the triazole ring, while the other effects methylation. Some α-*p*-toluenesulfonylpropionitrile is formed at the same time.



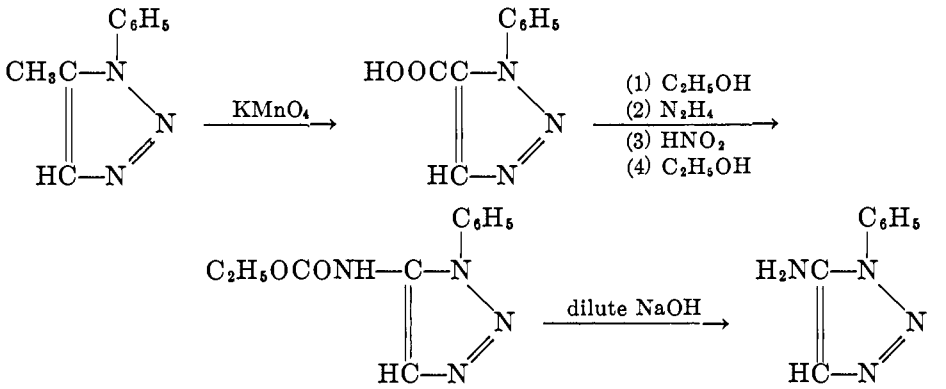
Decarboxylation is the principal method used to obtain 1,5-disubstituted *v*-triazoles. In addition to the examples already given, some other applications of this method include the formation of such diverse types as 1-benzalamino-5-methyl- (221), 5-ethoxy-1-phenyl- (68), and 1-(2′,4′-dibromophenyl)-5-methyl-*v*-triazoles (50).



Triazoles with a carboxyl group in the 5-position and a 1-alkyl or 1-aryl group are easily obtained by the oxidation of 1-alkyl- or 1-aryl-5-methyl-*v*-triazoles. By means of this reaction, the 1-methyl-, 1-ethyl-, 1-benzyl- (220), and 1-phenyl-



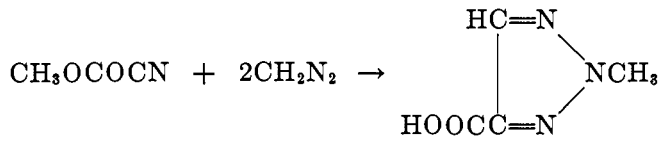
(73) *v*-triazole-5-carboxylic acids have been obtained. The resistance to oxidation of the groups substituted on nitrogen, compared to that of the methyl group



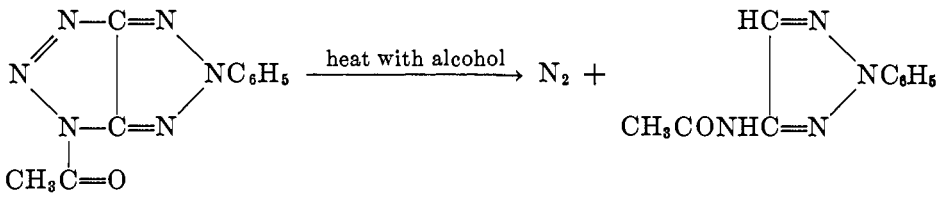
attached to carbon, is noteworthy. This reaction is the first step in the synthesis of 5-amino-1-phenyl-*v*-triazole starting with 5-methyl-1-phenyl-*v*-triazole. The sequence proceeds through the carboxylic acid, ester, hydrazide, azide, and urethan to the amine (70, 73).

3. 2,4-Disubstituted derivatives

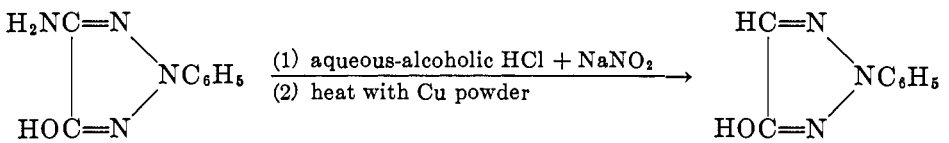
The formation of 4-cyano-2-methyl-*v*-triazole by the reaction of cyanogen and diazomethane was indicated previously (181). Similarly, diazomethane converts other negatively substituted nitriles to the 2-methyl-4-substituted *v*-triazoles, the 4-chloro, 4-bromo (205), and 4-carboxy (172) derivatives having been prepared by this method.



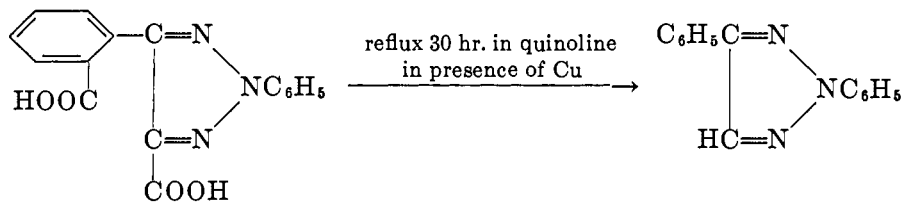
Thiele and Schleussner (207) succeeded in preparing 4-acetamino-2-phenyl-*v*-triazole by heating 1-acetyl-1,5-dihydro-5-phenyl-*v*-triazolo-[*d*]-*v*-triazole with alcohol. In the same article, these investigators reported the preparation of



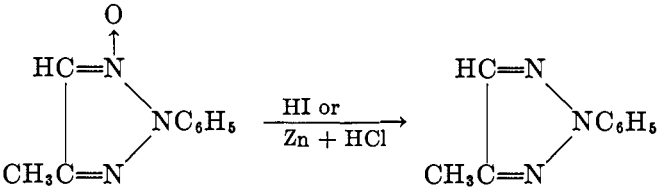
4-hydroxy-2-phenyl-*v*-triazole by deamination of 5-amino-4-hydroxy-2-phenyl-*v*-triazole.



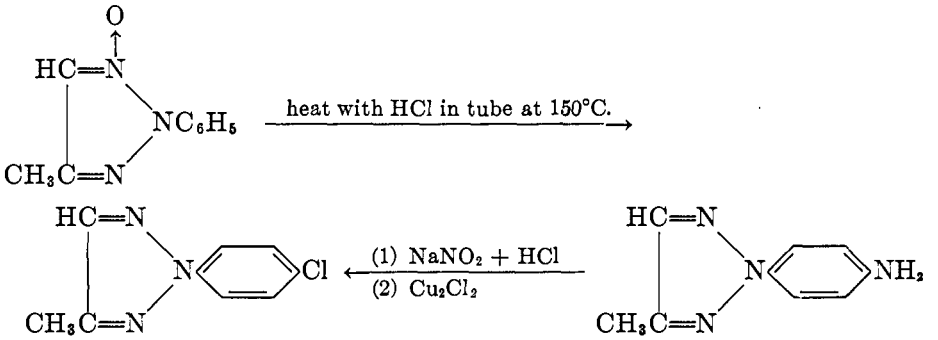
Decarboxylation of 5-(*o*-carboxyphenyl)-2-phenyl-*v*-triazole-4-carboxylic acid leads to the formation of 2,4-diphenyl-*v*-triazole (101). By similar treatment, 2-*p*-arsonophenyl-*v*-triazole-4,5-dicarboxylic acid loses one carboxyl group to yield 2-*p*-arsonophenyl-*v*-triazole-4-carboxylic acid (51).



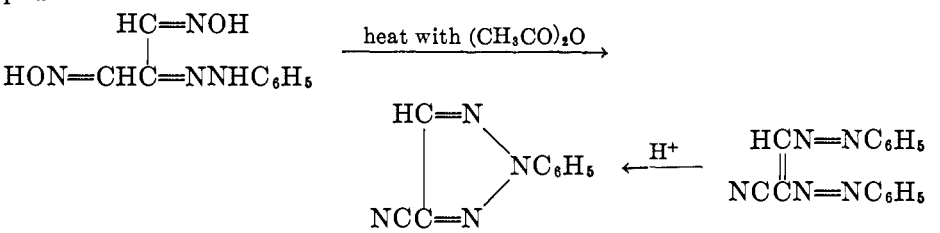
Reduction of 2,4-disubstituted *v*-triazole oxides results in the formation of 2,4-disubstituted *v*-triazoles, as in the preparation of 4-methyl-2-phenyl-*v*-triazole from 4-methyl-2-phenyl-*v*-triazole 1-oxide (182, 185). The same oxide on heating with hydrochloric acid under pressure is converted to 2-*p*-chlorophenyl-4-methyl-



v-triazole; evidently the oxide acts to form chlorine which then enters the phenyl group. The position of the chlorine was proven by the preparation of the same compound from 2-*p*-aminophenyl-4-methyl-*v*-triazole by means of the Sandmeyer reaction. Besides these substances, 2-*p*-iodophenyl- and 2-*p*-aminophenyl-4-methyl-*v*-triazoles (182, 185) have been obtained by reduction of the oxides.

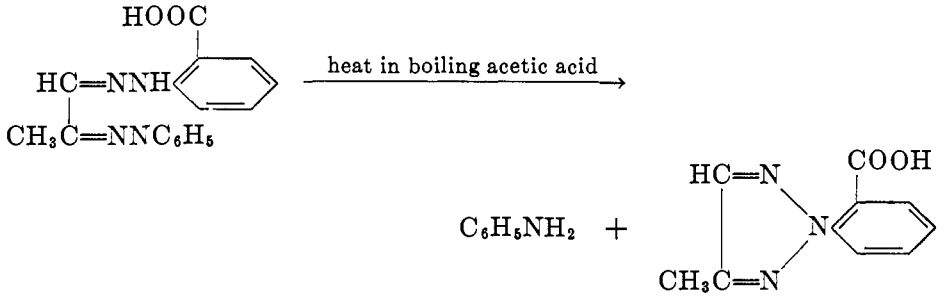


As mentioned in the introduction, conversion of α-phenylhydrazone oximes or their acetate derivatives to *v*-triazoles in this class can be effected by loss of a mole of water or acetic acid. Thus, by heating the phenylhydrazone of diisonitrosoacetone with acetic anhydride 5-cyano-2-phenyl-*v*-triazole is formed (133). Treatment of α,β-di(benzeneazo)acrylonitrile with acid leads to the same compound.

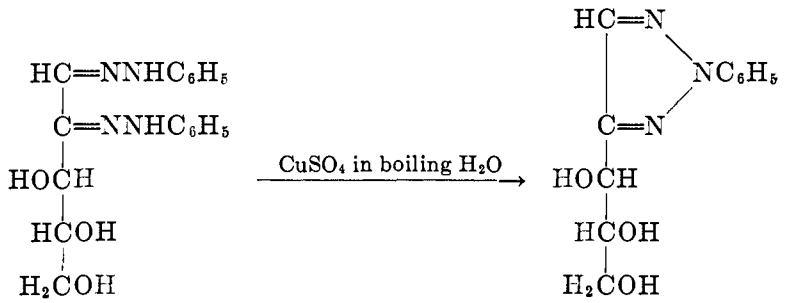


The reaction of diarylazoölefins is also used in the preparation of 4-methyl-2-phenyl-*v*-triazole from α,β-di(benzeneazo)-α-propylene (177). Osazones, however, are more easily accessible starting materials for obtaining 2,4-disubstituted *v*-triazoles by what is essentially the same type of reaction. For example, 2-(*o*-

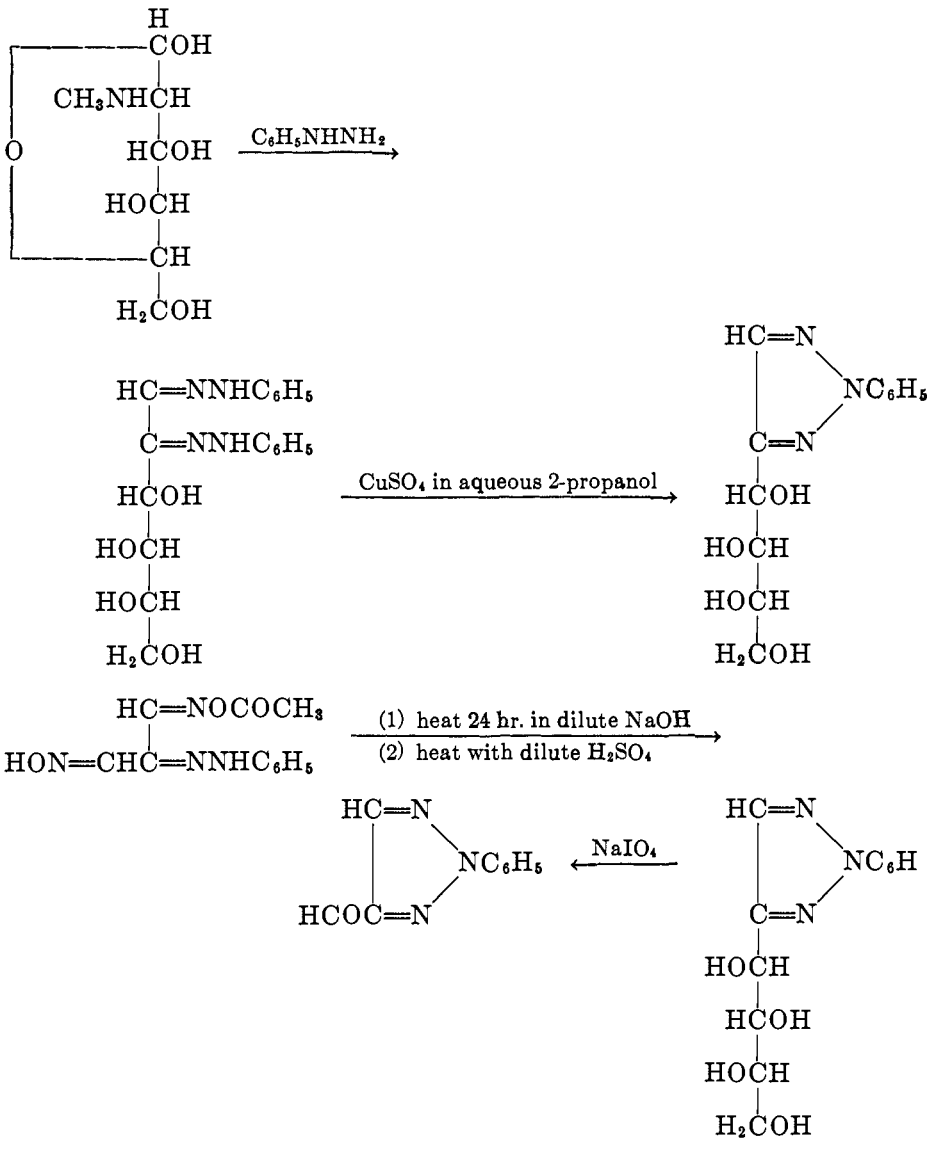
carboxyphenyl)-4-methyl-*v*-triazole is synthesized from the mixed phenyl(*o*-carboxyphenyl)osazone of methylglyoxal (139), aniline being eliminated. The major application of this reaction has been in the formation of the sugar osotriazoles.



A considerable improvement in technique was introduced by Hudson and coworkers in the use of copper sulfate to promote the elimination of aniline (111, 116, 118). The phenylosazones of the sugars are simply heated with this material in boiling water for 1 hr. to form the triazole derivative. The reaction is illustrated with xylose phenylosazone (116). Recently Hardegger and El Khadem have prepared the *p*-tolylosotriazoles of several sugars (113).

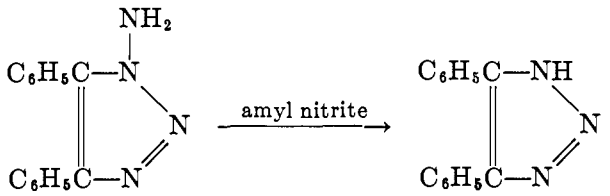


The sugar osotriazoles constitute another type of derivative useful in the characterization of reducing saccharides. These readily prepared compounds are usually easily crystallized and have definite melting points and characteristic optical rotations. An interesting application of a sugar osotriazole derivative was in the identification of the optical configuration of the *N*-methyl-L-glucosamine formed in the degradation of streptomycin. This substance was converted to its phenylosazone and then to the phenylosotriazole (145). The latter was found to have the same melting point, and an equal but opposite rotation to the phenylosotriazole derivative of D-glucose. The ready preparation of sugar osotriazoles makes available 4-formyl-2-phenyl-*v*-triazole. This substance was first prepared by v. Pechmann (133, 180) from the monoacetate of diisonitrosoacetone phenylhydrazone by treatment with alkalies, followed by hydrolysis of the intermediate oxime. It may now be obtained by sodium periodate (111, 116, 117, 118, 119) or lead tetraacetate (191) oxidation of the various sugar phenylosotriazoles; the oxidation of L-sorbose osotriazole is given as illustration.

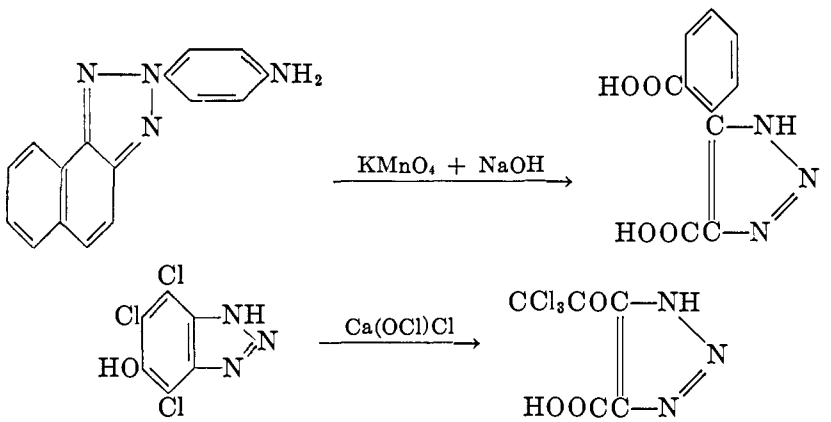


4. 4,5-Disubstituted derivatives

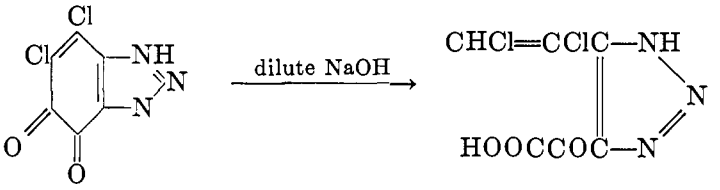
A variety of reactions have been used to prepare members of this series from compounds already containing a *v*-triazole ring. Thus, the amino group of 1-amino-4,5-diphenyl-*v*-triazole is replaced by hydrogen when this material is diazotized (202, 204). The reaction is typical of *N*-aminoazoles. In like manner, 4,5-dimethyl-*v*-triazole is obtained by treating the *N*-amino derivative with oxides of nitrogen (179).



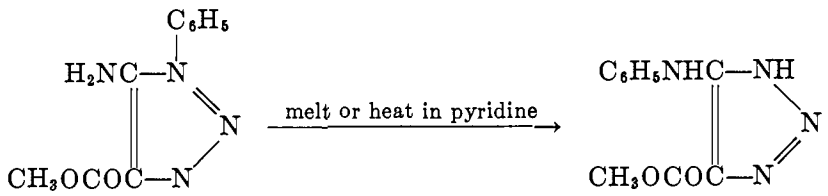
Oxidation of certain polycyclic *v*-triazoles leads to substances of this class. Alkaline permanganate, for example, effected the degradation of 2-*p*-aminophenylnaphtho[1.2]triazole or its acetyl derivative to 5-*o*-carboxyphenyl-*v*-triazole-4-carboxylic acid (47). The action of bleaching powder on 4,6,7-trichloro-5-hydroxybenzotriazole results in 5-trichloroacetyl-*v*-triazole-4-carboxylic acid (223).



Triazole-4,5-dicarboxylic acid has been obtained by oxidizing 5-methylbenzotriazole (27, 222), 6-chloro-5-hydroxy-benzotriazole-4,7-quinone (223), and 1-*p*-aminophenyl-*v*-triazole-4,5-dicarboxylic acid (157). A nonoxidative conversion of a fused-ring triazole to a simple 4,5-disubstituted derivative results from the alkaline hydrolytic splitting of 6,7-dichlorobenzotriazole-4,5-quinone to 5-((α,β-dichlorovinyl)-*v*-triazolyl-4)glyoxylic acid (223).

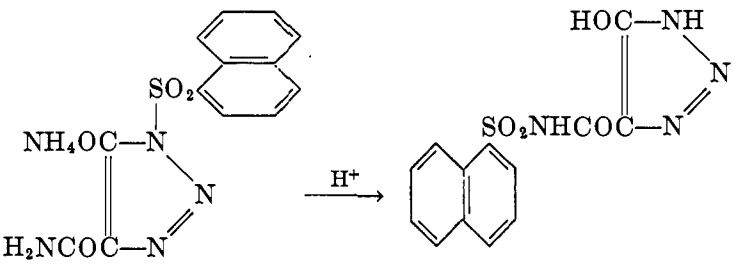


The rearrangement of 5-amino-1-aryl-*v*-triazoles mentioned in an earlier portion of this article is applicable to the synthesis of 4,5-disubstituted derivatives. Melting or heating in pyridine converts 5-amino-1-phenyl-*v*-triazole-4-carboxylic acid methyl ester to 5-anilino-*v*-triazole-4-carboxylic acid methyl ester (70). In like manner, 5-anilino-*v*-triazole-4-carboxylic acid ethyl ester and 5-anilino-4-

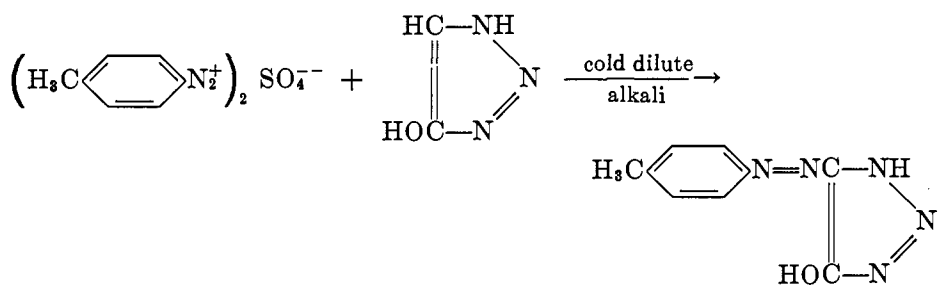


phenyl-*v*-triazole (70) have been obtained. The velocity and equilibrium data for these transformations have been determined (72).

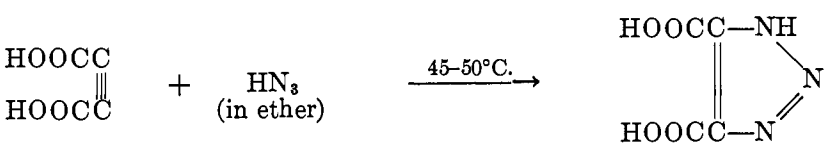
A second rearrangement which leads to 4-arylsulfonylcarboxamido-5-hydroxy-*v*-triazoles starts with the corresponding 1-arylsulfonyl derivatives. The ammonium salt of 5-hydroxy-1-α-naphthalenesulfonyl-*v*-triazole-4-carboxamide undergoes this transformation when acidified (54). The 4-*p*-toluenesulfonyl- (58), 4-β-naphthalenesulfonyl-, and 4-bis(1′,5′-naphthalenedisulfonyl)- (54) carboxamido-5-hydroxy-*v*-triazoles also were obtained in this way.



Diazotized *p*-toluidine couples with 4-hydroxy-*v*-triazole in the 5-position (63, 76). The 5-position of this triazole is similarly substituted by the action of nitrous acid, to form 4-hydroxy-5-nitroso-*v*-triazole, known only in the form of its salts (71).

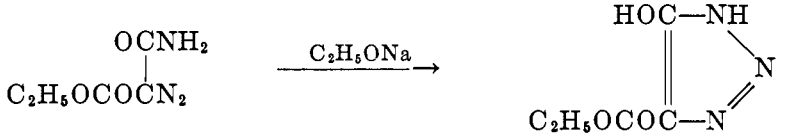


Treatment of phenylpropiolic acid and acetylenedicarboxylic acid with hydrogen azide (174) leads to the corresponding 4,5-disubstututed *v*-triazoles.

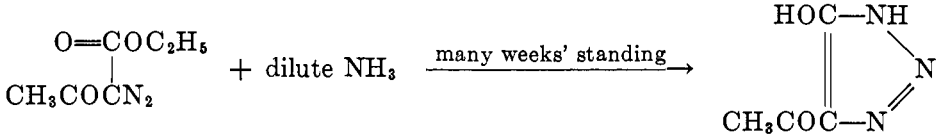


Another reaction involving an azide by which a member of this class has been prepared is the reaction of malonamide and phenyl azide in the presence of sodium ethoxide (71). The phenyl azide serves to introduce two ring nitrogen atoms.

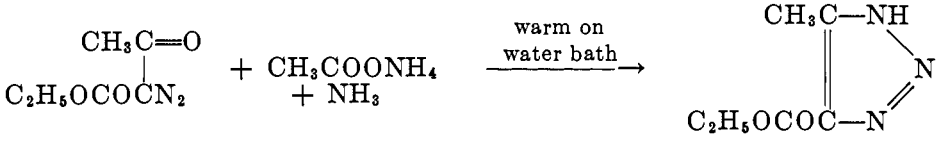
If the ester amide of diazomalonic acid is treated with sodium ethoxide cyclization to 5-hydroxy-*v*-triazole-4-carboxylic acid ethyl ester occurs (71). Substantially the same reaction is involved in the interaction of diazo diketones or



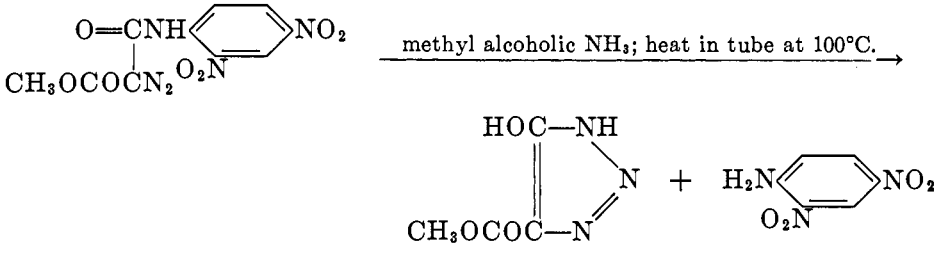
ketone esters with ammonia (220). It seems likely that imides or amides are intermediates.



Thus, diazoacetoacetic ester on standing with dilute ammonia for several weeks forms 4-acetyl-5-hydroxy-*v*-triazole (219). If, instead, this same compound is warmed with aqueous-alcoholic ammonium acetate with occasional addition of ammonia, the ethyl ester of 5-methyl-*v*-triazole-4-carboxylic acid is obtained (219).

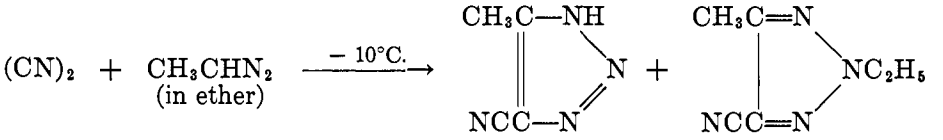


Essentially the same process occurs with the half-methyl ester, half-dinitroanilide of diazomalonic acid, dinitroaniline being eliminated (71, 76).

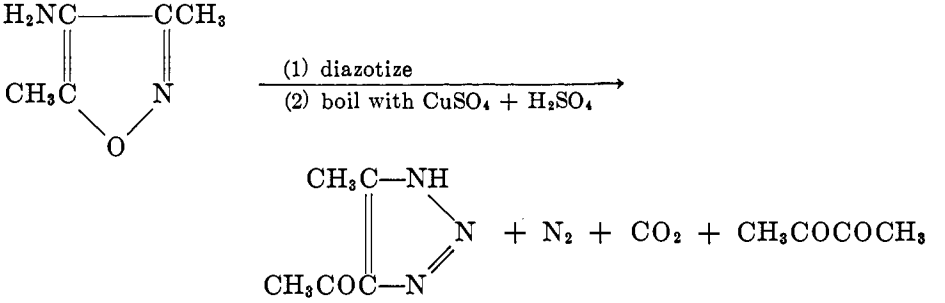


Diazoethane reacts with cyanogen (181) and cyanogen chloride (205) in the

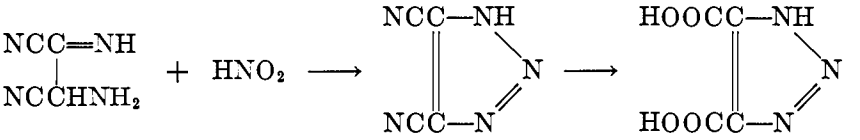
same way as diazomethane. Some ring ethylation occurs, as similarly noted in the comparable reaction leading to 2-methyl-4-substituted *v*-triazoles.



A curious reaction of 4-amino-3,5-dimethylisoxazole leads to the formation of 4-acetyl-5-methyl-*v*-triazole. Diazotization of the isoxazole derivative, followed by boiling with acidified copper sulfate, effects the transformation (187).



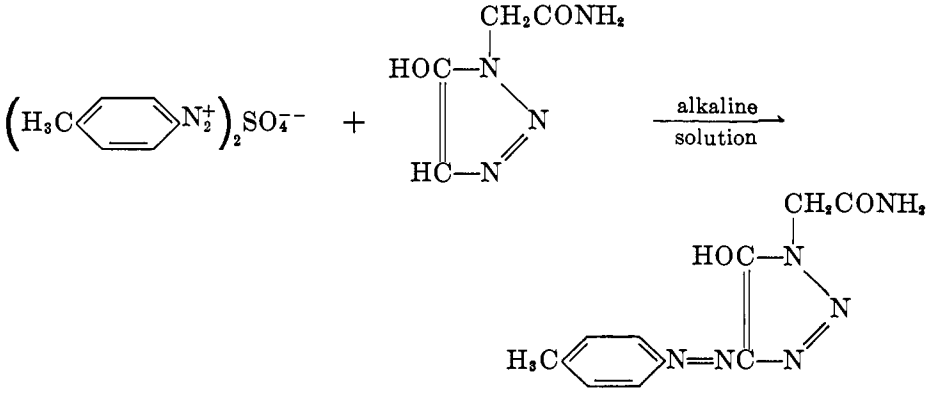
After considerable investigation the tetramer of hydrogen cyanide has been shown to be aminoiminosuccinonitrile (122). Treatment of this compound with nitrous acid leads to 4,5-dicyano-*v*-triazole, identified by hydrolysis to the known dicarboxylic acid.



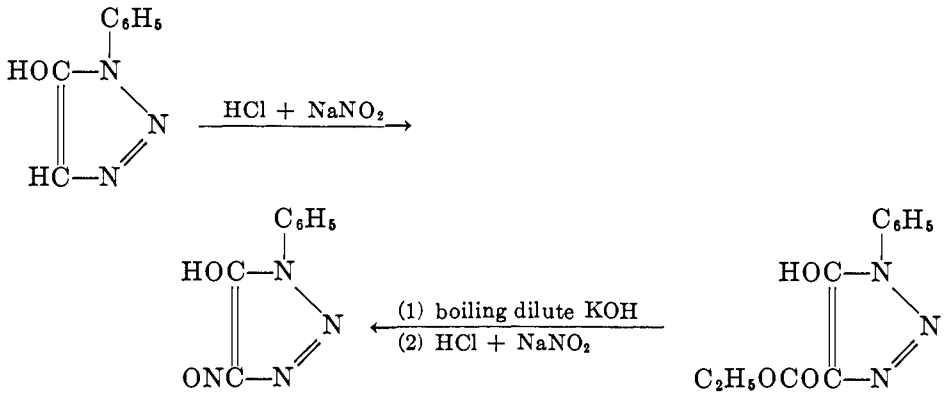
D. SIMPLE TRISUBSTITUTED *v*-TRIAZOLES

1. 1,4,5-Trisubstituted derivatives

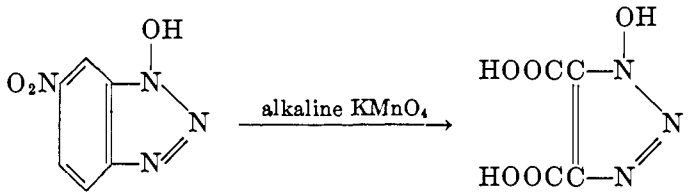
The 1,5-disubstituted *v*-triazoles with a hydroxyl group at position 5 couple with diazo compounds to yield azo derivatives. Thus, 1-acetamido-5-hydroxy-*v*-triazole combines with diazotized *p*-toluidine in the indicated manner (63). In like manner the corresponding 1-acetic acid (63), 1-acetylbenzalhydrazide,



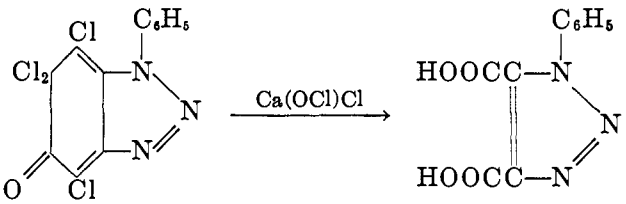
and 1-acetylglycylbenzalhydrazide (56) derivatives of 5-hydroxy-4-*p*-tolueneazo-*v*-triazole as well as 4-benzeneazo-5-hydroxy-1-phenyl-*v*-triazole (68) have been prepared. Nitrosation of 5-hydroxy-1-phenyl-*v*-triazole results in the formation of the 4-nitroso derivative (82); the same substance is better obtained by the action of nitrous acid on 5-hydroxy-1-phenyl-*v*-triazole-4-carboxylic acid, prepared *in situ* by saponification of the ethyl ester (77, 82).



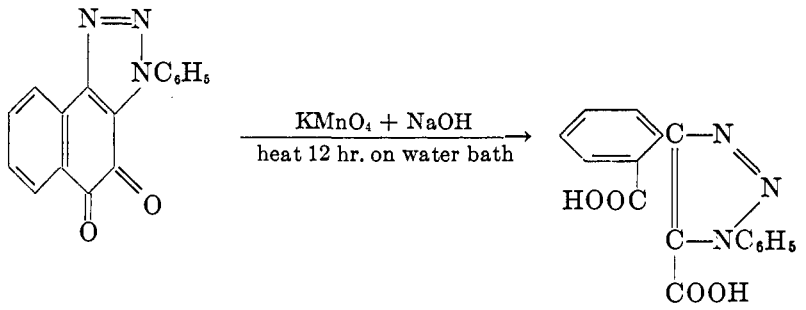
Oxidation of some 1-substituted fused-ring *v*-triazoles leads to 1-substituted *v*-triazole-4,5-dicarboxylic acids. For example, the fused benzene ring in both 1-hydroxy-6-nitro- and 1-hydroxy-benzotriazole is destroyed by permanganate with the formation of 1-hydroxy-*v*-triazole-4,5-dicarboxylic acid (60, 231). Treat-



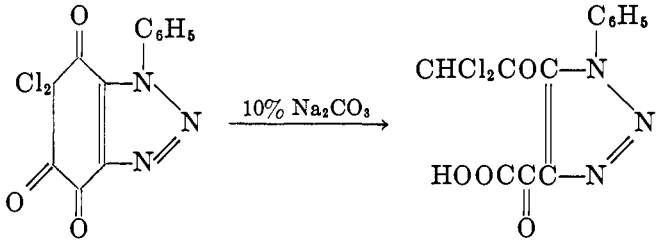
ment of various chlorinated 1-phenylbenzotriazoles, such as the 4,6,6,7-tetrachloro-5,6-dihydro-5-oxo derivative, with bleaching powder produces 1-phenyl-*v*-triazole-4,5-dicarboxylic acid (224, 230). This acid is also formed in the



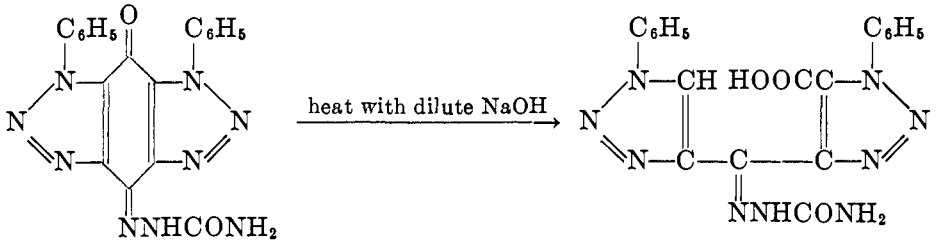
hypobromite oxidation of benzotriazole-4,7-quinone (220). An oxidative rupture, more frequently employed to obtain simple 2,4,5-trisubstituted *v*-triazoles, finds one application in the 1,4,5 series. Thus, alkaline permanganate opens the middle ring of 3-phenylnaphtho[1.2]triazole-4,5-quinone, with the formation of 4-*o*-carboxyphenyl-1-phenyl-*v*-triazole-5-carboxylic acid (42).



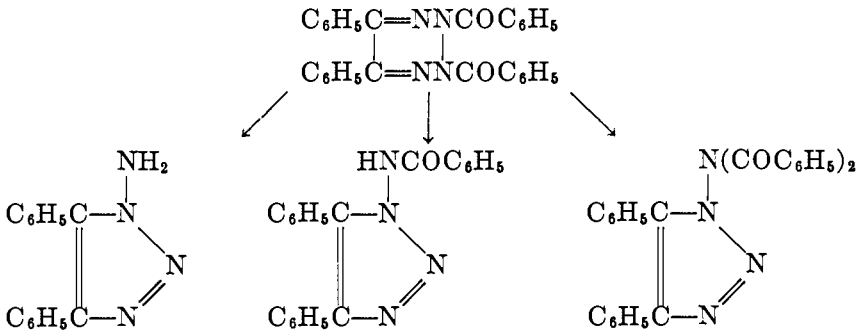
The hydrolytic action of alkaline media on certain fused-ring *v*-triazoles leads to the formation of simple 1,4,5-trisubstituted derivatives. When 6,6-dichloro-4,5,6,7-tetrahydro-4,5,7-trioxo-1-phenylbenzotriazole is treated with sodium carbonate, (5-dichloroacetyl-1-phenyl-*v*-triazolyl-4)glyoxylic acid results (224).



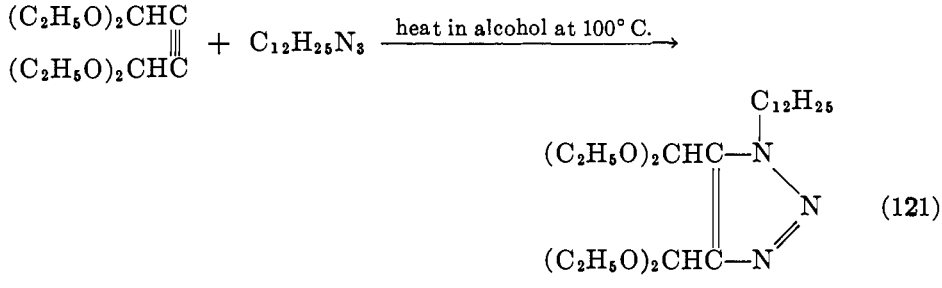
Likewise, 1,7-diphenylbenzo[1.2.4.5]bistriazolequinone and its monosemicarbazone are opened by the action of sodium hydroxide (220).



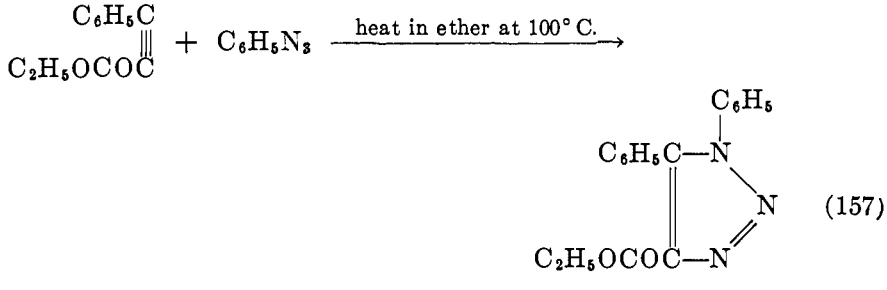
Diphenyl- or dimethyl-dibenzoylosotetrazines are converted to *v*-triazoles by treatment with acid (178, 179, 201, 203, 204). Depending on experimental conditions the 1-amino, 1-benzoylamino, or 1-dibenzoylamino compounds are formed.



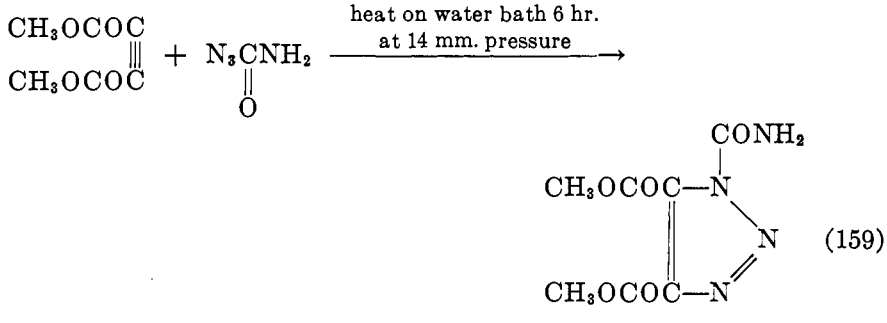
Combination of alkyl, aryl, or acyl azides with disubstituted acetylenes leads to 1,4,5-trisubstituted *v*-triazoles (25, 61, 156). A few examples will serve to illustrate the application of this general reaction to the synthesis of *v*-triazoles of this class.



(121)



(157)

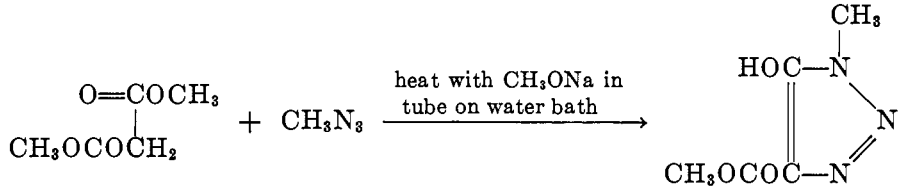


(159)

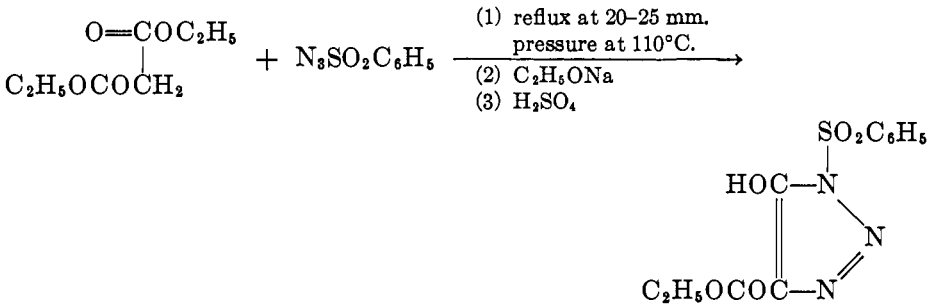
As might be anticipated in the last reaction illustrated and with acyl azides generally, poor yields are obtained; with alkyl and aryl azides the yields are usually good. Since ethyl phenylpropiolate (second example above) is the only unsymmetrical acetylene which has been investigated in this reaction, no general conclusions can be drawn concerning the direction of addition of the azide.

Apparently closely related to the acetylene azide synthesis is the interaction of azides and malonic esters or β-keto esters in the presence of sodium alkoxide (54, 68, 69, 71, 73, 74, 79, 80, 81, 100, 134). In this case alkyl, aryl, and acyl azides also may be employed. The use of malonates leads to compounds with a hydroxyl in position 5. Methyl azide reacts with dimethyl malonate to form the

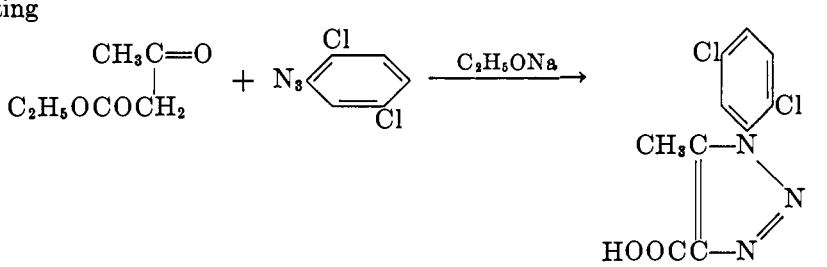
methyl ester of 5-hydroxy-1-methyl-*v*-triazole-4-carboxylic acid (70). Benzenesulfonyl azide unites with diethyl malonate to produce 1-benzenesulfonyl-5-



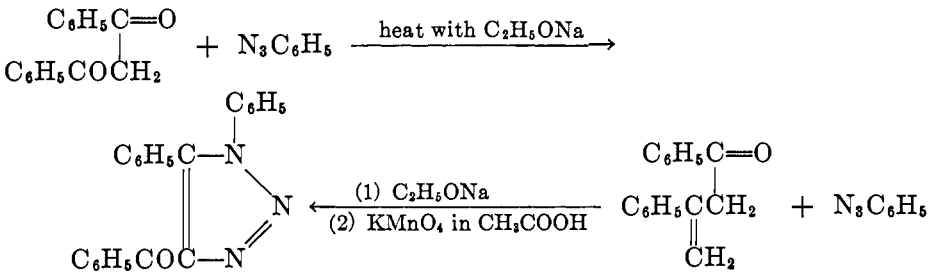
hydroxy-*v*-triazole-4-carboxylic acid ethyl ester (57), it being necessary to work rapidly after the introduction of sodium ethoxide to avoid alkaline decomposition. When β-keto esters are employed, *v*-triazoles with 5-alkyl or aryl groups are



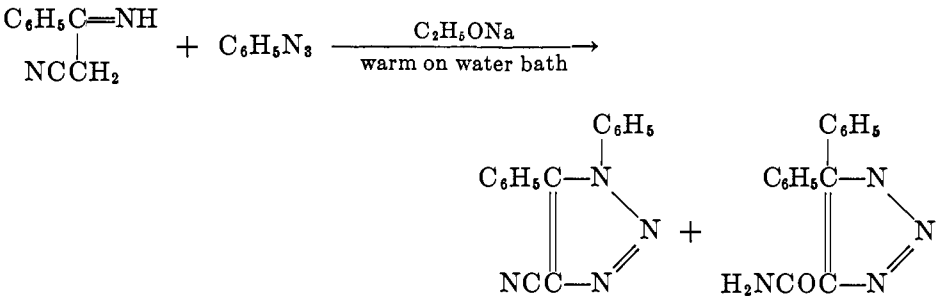
formed. Thus, use of acetoacetic ester and 2 5-dichloroazidobenzene leads to 1-(2,5-dichlorophenyl)-5-methyl-*v*-triazole-4-carboxylic acid (50). Use of a diketone is illustrated by the reaction of dibenzoylmethane with phenyl azide to form 4-benzoyl-1,5-diphenyl-*v*-triazole (79). The effect of an olefin linkage in complementing



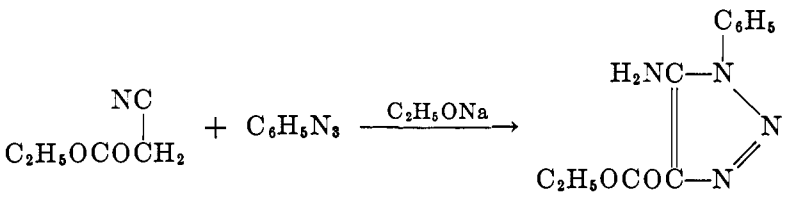
the activating function of a carbonyl group toward a methylene group is shown by dypnone, which reacts with phenyl azide to produce a substance capable of oxidation to the same diphenylbenzoyltriazole (79). Essentially the same reaction



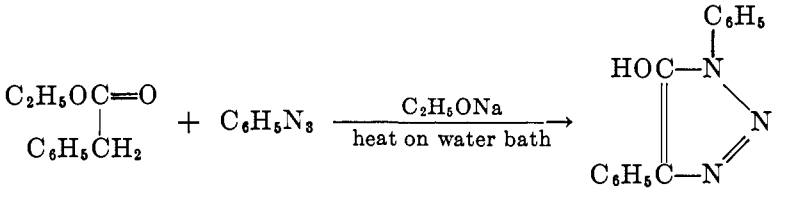
is involved in the conversion of β-imino-β-phenylpropionitrile (benzoacetodinitrile) to a mixture of 4-cyano-1,5-diphenyl-*v*-triazole and the corresponding amide (154). The analogous β-imino-β-methylpropionitrile undergoes a similar



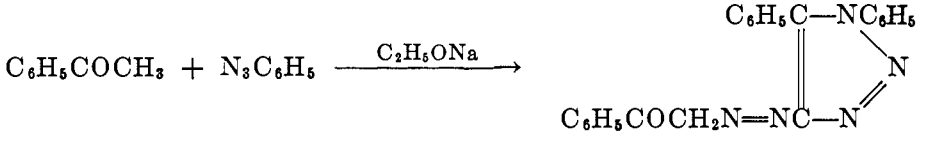
condensation. When esters of cyanoacetic acid are treated with phenyl azide, 5-amino-1-phenyl derivatives are formed (70).



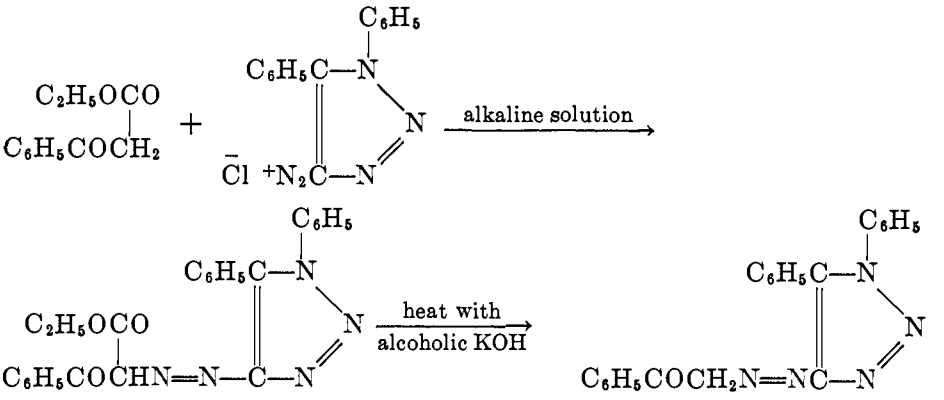
It is not necessary, however, that a methylene group be activated by two groups such as ester, imide, or cyanide. Compounds with one ester or cyanide radical linked to methylene have been found to undergo this reaction. Thus, benzyl cyanide and ethyl phenylacetate combine with phenyl azide (80, 81). The formation of ω-(1,5-diphenyl-1,2,3-triazole-4-azo)acetophenone from acetophenone and phenyl azide is closely similar (79); the azo group obviously is derived from



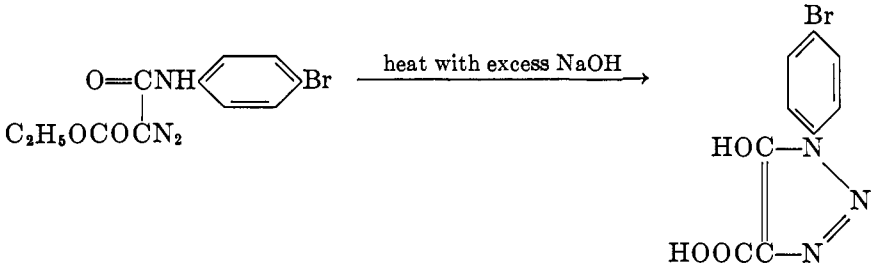
the azide, but the mechanism remains obscure. Proof of structure of this compound was secured by preparing the same substance by the following reaction



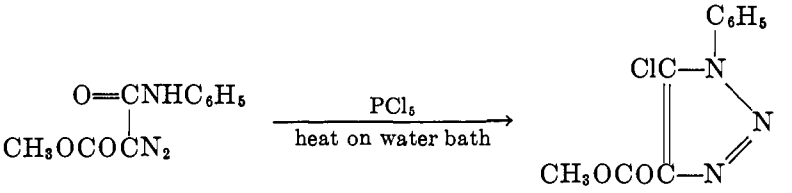
sequence:



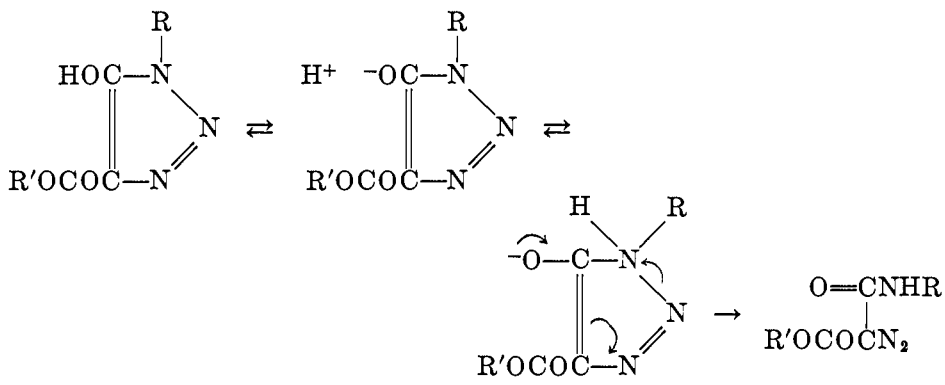
The cyclization of α-diazo amides constitutes another method for obtaining 1,4,5-trisubstituted *v*-triazoles. The discovery and development of this reaction are due largely to Dimroth (68, 69, 70, 72, 74). The half-ester, half-*N*-*p*-bromophenyl amide of diazomalonic acid is converted to 1-*p*-bromophenyl-5-hydroxy-*v*-triazole-4-carboxylic acid by heating with alkali (69). Alkaline materials are not the only cyclizing agents; heating methyl diazomalonanilide with phosphorus



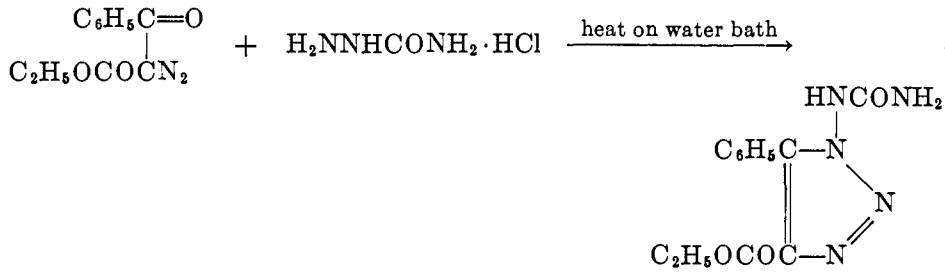
pentachloride results in the formation (70) of methyl 5-chloro-1-phenyl-*v*-triazole-4-carboxylate.



Dimroth believed, on the basis of his studies of the equilibrium between the triazole and diazo amide forms, that this conversion was unimolecular with respect to the enol. A recent reinterpretation of his data leads to the conclusion that this tautomeric change is bimolecular and ionic in nature, a proton attacking the substituted nitrogen to initiate the indicated change (34).

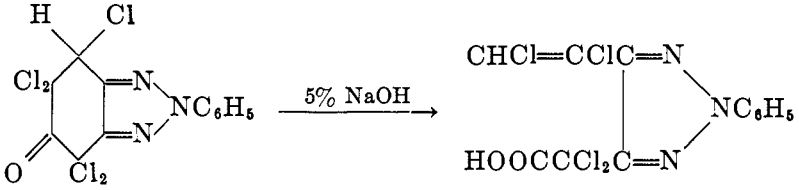


By means of a closely related reaction *v*-triazoles may be obtained from the interaction of compounds containing an α-diazoketone structure with substances with an amino group. Semicarbazide, for example, combines with diazobenzoylacetic ester to form 5-phenyl-1-ureido-*v*-triazole-4-carboxylic acid ethyl ester (221). Hydroxylamine, phenylhydrazine, methylphenylhydrazine (219), aniline (199), benzylamine, ethylamine, and methylamine (220) have been used in this manner.

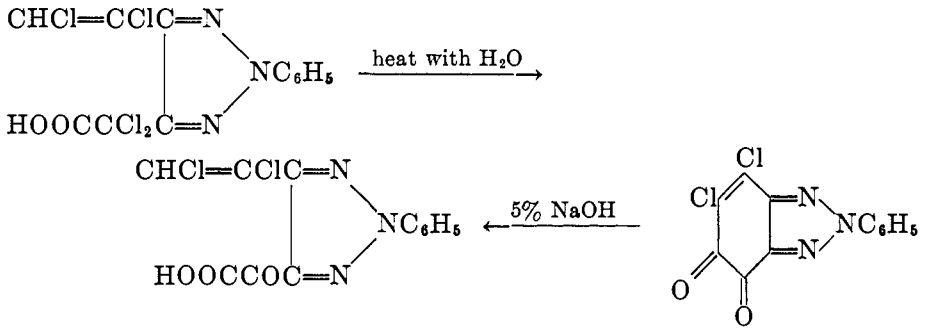


2. 2,4,5-Trisubstituted derivatives

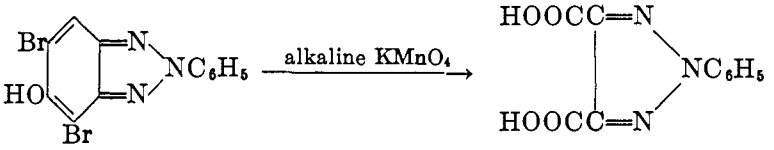
Alkaline hydrolysis of 4,4,6,6,7-pentachloro-4,5,6,7-tetrahydro-5-oxo-2-phenylbenzotriazole opens the six-membered ring, accompanied by loss of one mole of hydrogen chloride (225). On heating the sodium salt of the product of this reaction, [5-(α,β-dichlorovinyl)-2-phenyl-*v*-triazolyl-4]glyoxylic acid is ob-



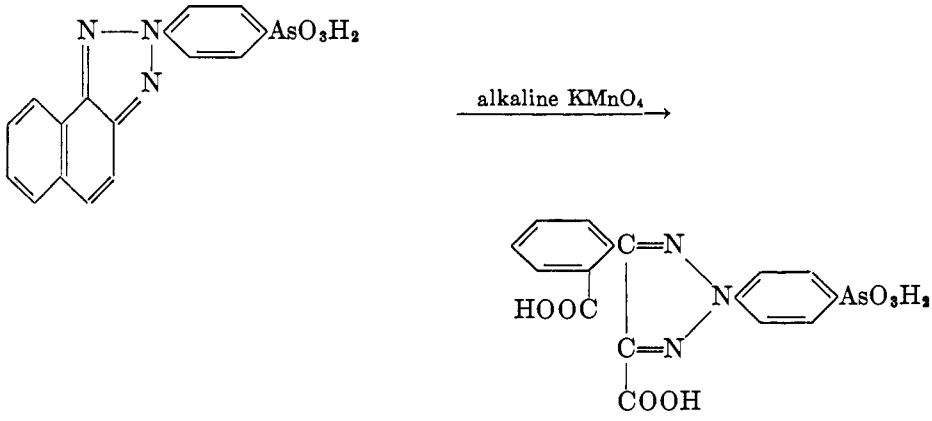
tained. The latter compound is also formed by the hydrolytic splitting of 6,7-dichloro-2-phenylbenzotriazole-4,5-quinone (225).



A considerable number of simple 2,4,5-trisubstituted *v*-triazoles have been obtained by oxidative rupture of fused-ring *v*-triazoles. Alkaline permanganate oxidation of 4,6-dibromo-5-hydroxy-2-phenylbenzotriazole cleaves the benzene ring with the formation of 2-phenyl-*v*-triazole-4,5-dicarboxylic acid (94); the same compound is formed also by oxidation of 5-amino-2-phenyl (and 5-amino-6-methyl) benzotriazoles (20, 92).

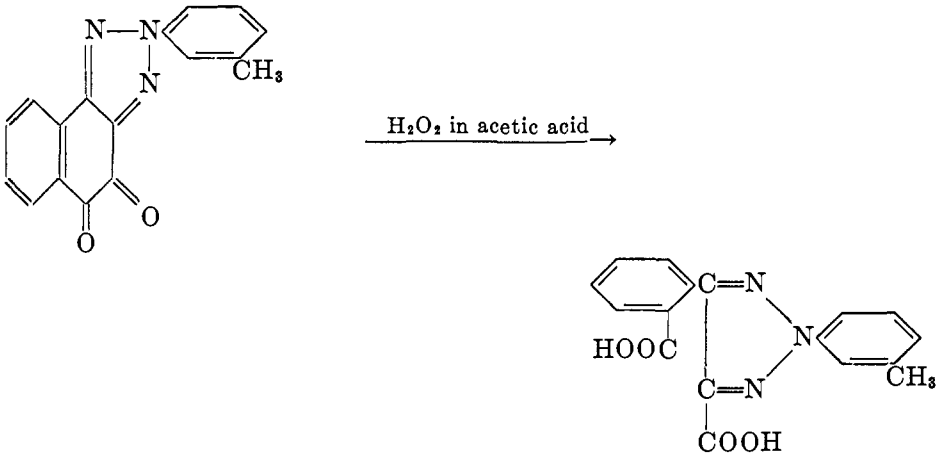


Charrier noted the structural similarity between naphtho[1.2]triazole and phenanthrene, and drew the conclusion that dicarboxylic acids, analogous to diphenic acid, would be formed on oxidation of either the naphtho[1.2]triazoles or their 4,5-quinones. This was found to be the case. For example, 2-(*p*-arsonophenyl)naphtho[1.2] triazole is converted to 2-(*p*-arsonophenyl)-5-*o*-carboxyphenyl-*v*-triazole-4-carboxylic acid (49). The reagent usually employed with quinones in the phrenanthrene series, hydrogen peroxide in glacial acetic acid,

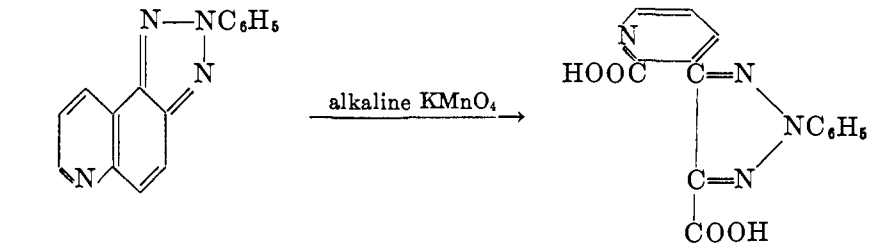


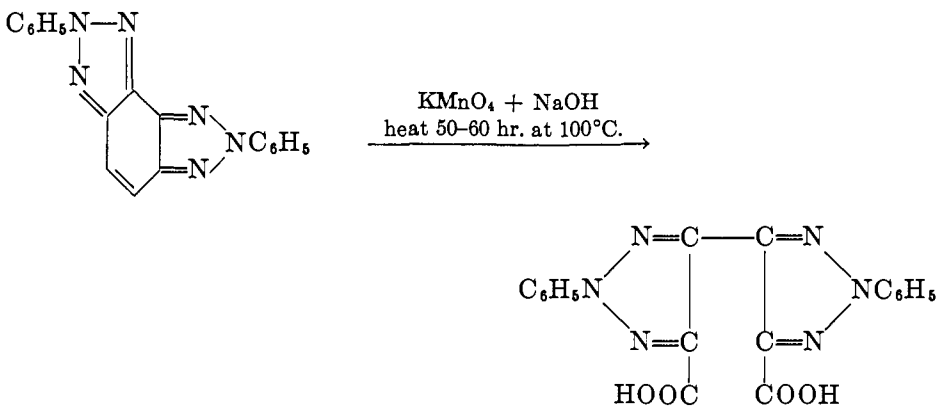
converts 2-(*m*-tolyl)naphtho[1.2]triazole-4,5-quinone to a dicarboxylic acid (40). Several other 2-substituted naphtho[1.2]triazoles or the corresponding quinones

have been treated in this fashion (39, 45, 46, 48, 99, 101). In like manner, 5-(2′-carboxypyridyl-3)-2-phenyl-*v*-triazole-4-carboxylic acid is formed from 2-

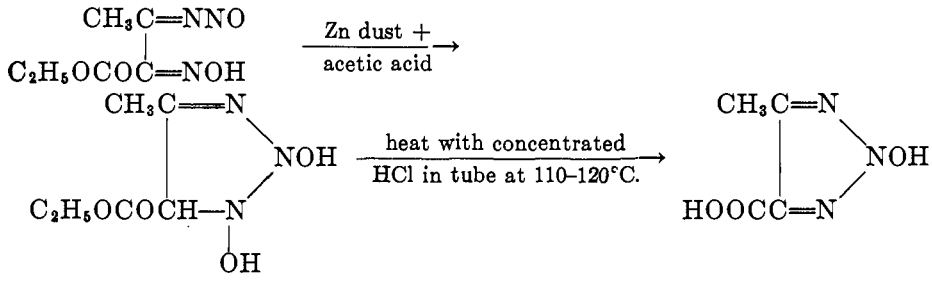


phenyltriazolo[*f*]quinoline (22). Even 2,7-diphenylbenzo[1.2.3.4]bistriazole behaves analogously to phenanthrene on oxidation (19).

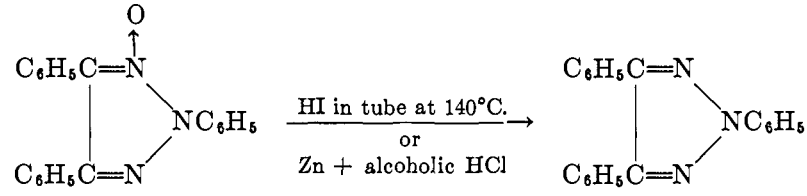




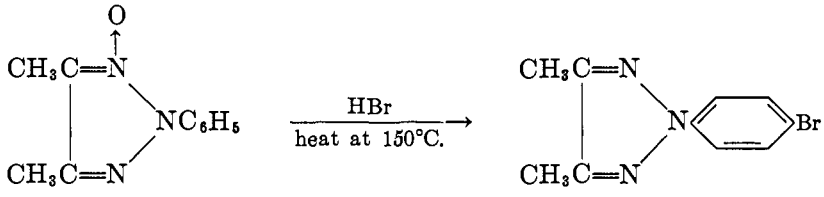
Preparation of 2-hydroxy-5-methyl-*v*-triazole-4-carboxylic acid is achieved from the triazoline obtained by the reduction of ethyl α-oximino-β-nitrosiminobutyrate as indicated (85).



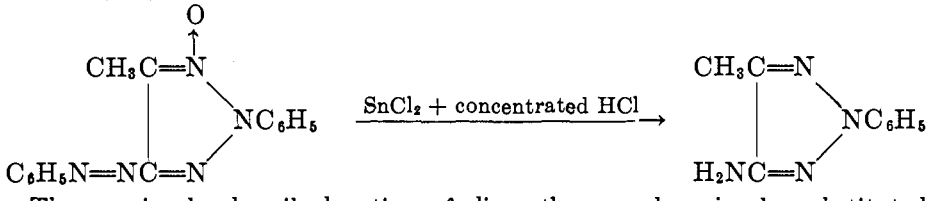
Appropriately substituted triazole oxides may be reduced to simple 2,4,5-trisubstituted *v*-triazoles (51, 183). Triphenyl-*v*-triazole oxide thus forms 2,4,5-triphenyl-*v*-triazole (184). As noted in the section on 2,4-disubstituted triazoles,



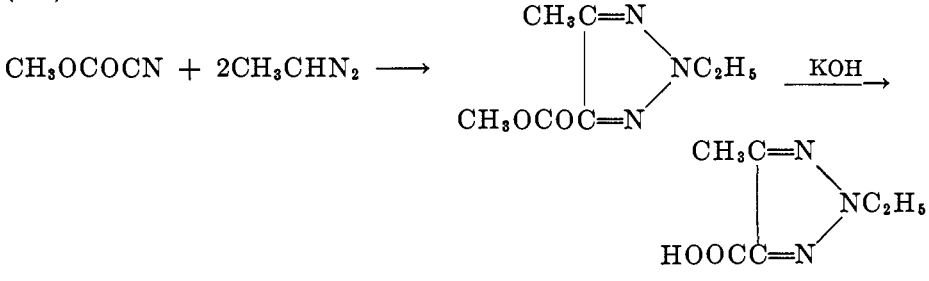
hydrogen halides reduce 2-aryltriazole oxides, thereby releasing halogen which then substitutes in the aryl group (182, 185). Stannous chloride converts 4-ben-



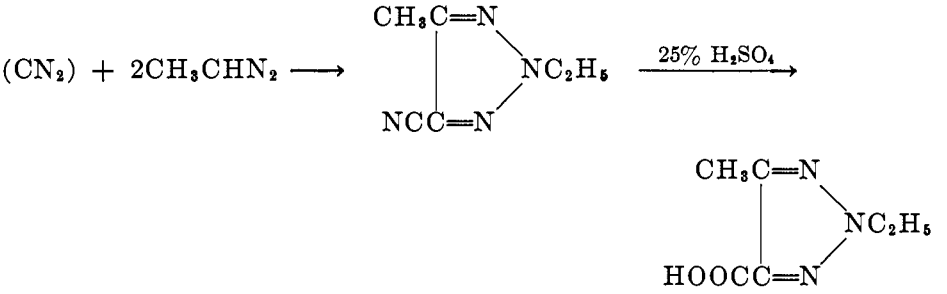
zeneazo-5-methyl-2-phenyl-*v*-triazole 1-oxide to 4-amino-5-methyl-2-phenyl-*v*-triazole (188).



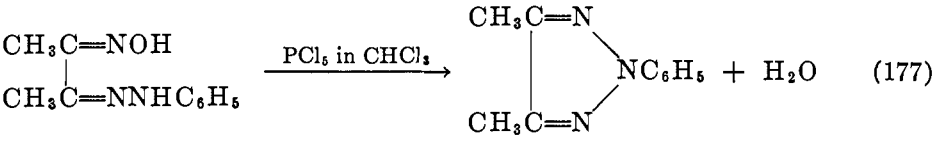
The previously described action of diazoethane and variously substituted nitriles brings about the formation of 2-ethyl-5-methyl-4-substituted *v*-triazoles. The following steps thus lead to 2-ethyl-5-methyl-*v*-triazole-4-carboxylic acid (172).



Similarly, cyanogen combines with diazoethane to yield 4-cyano-2-ethyl-5-methyl-*v*-triazole, which can be hydrolyzed to the same 4-carboxylic acid (181). Cyanogen chloride and bromide (205) undergo similar combination with diazoethane.



The preparation of *v*-triazoles substituted in the 2-position starting with osazones, or α-hydrazone oximes, was discussed in the section covering 2,4-disubstituted derivatives. The method is, of course, applicable to the preparation of 2,4,5-trisubstituted *v*-triazoles (9, 10, 11, 12, 17, 26, 110, 130, 140, 160, 166, 182, 185, 186, 207). A few representative examples are listed:



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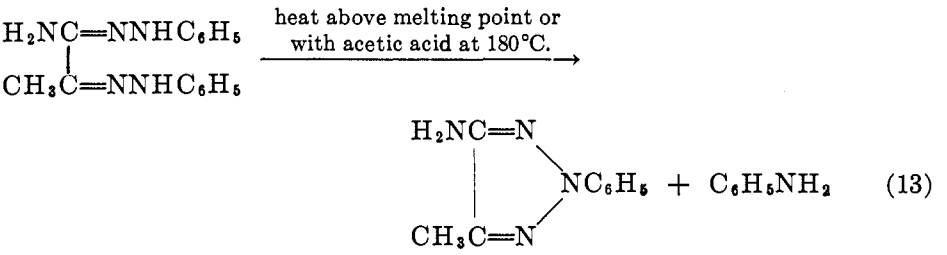

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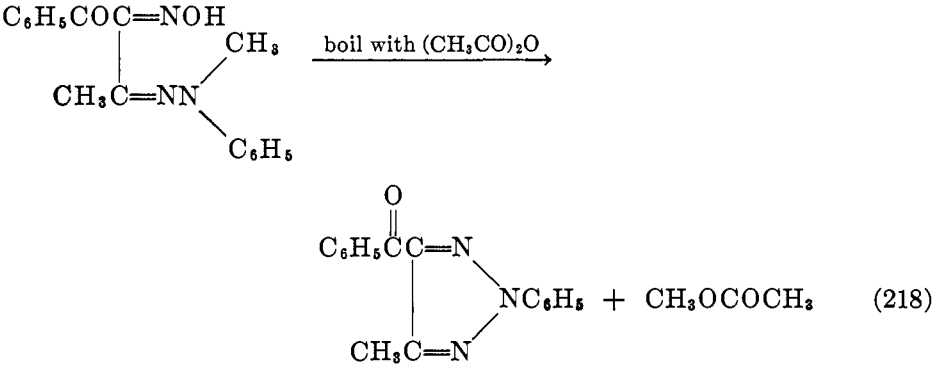
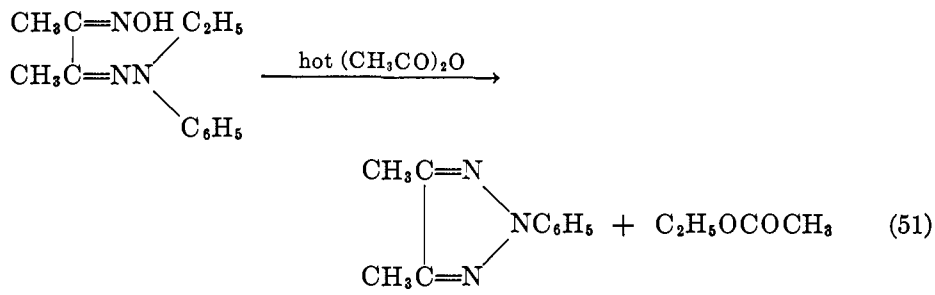
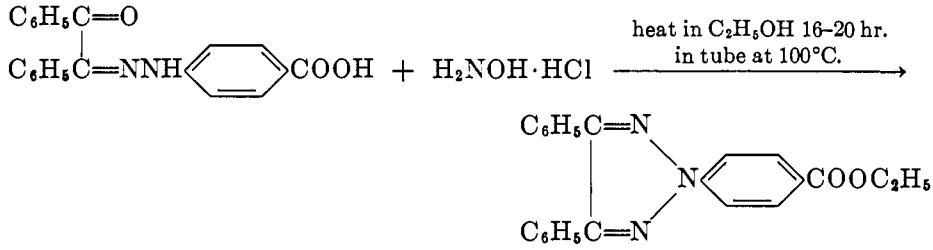


(218)

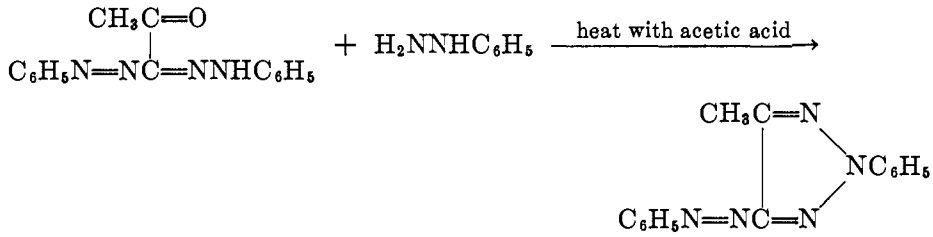


(51)

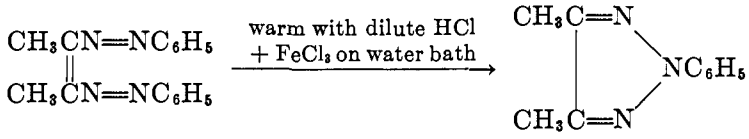
It is not always necessary to isolate the α-oxime hydrazone or osazone. In the case of the mono-*p*-carboxyphenylhydrazone of benzil, heating with hydroxylamine hydrochloride effects conversion to the triazole, the reaction presumably proceeding through the intermediate oxime (9). Likewise heating acetyldiphenylformazan in acetic acid with phenylhydrazine results in the formation of 4-ben-



zeneazo-5-methyl-2-phenyl-*v*-triazole (14, 16).

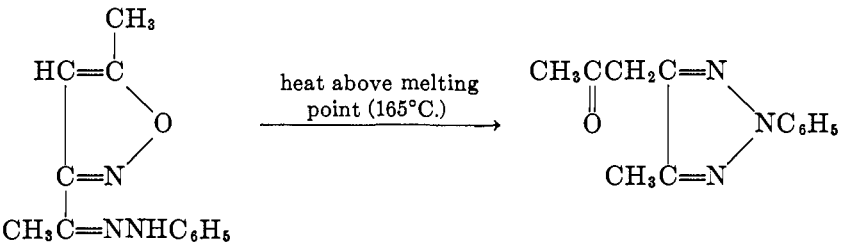


Compounds in the state of oxidation next higher than the osazones—namely, the bisazo olefins—are converted to *v*-triazoles on treatment with acid. This is illustrated by the formation of 4,5-dimethyl-2-phenyl-*v*-triazole from β,γ-bis-(benzeneazo)-2-butene mentioned in the introduction (177).

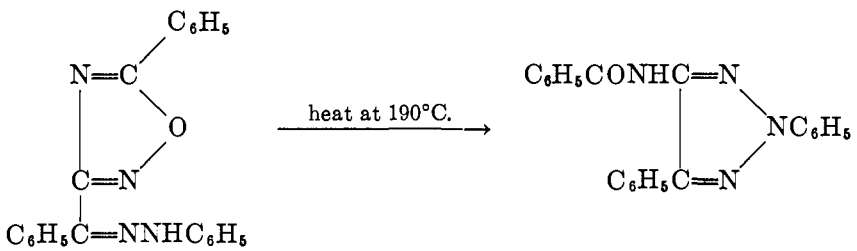


Since isoxazoles may be regarded as cyclic *O*-substituted oximes, it is not surprising that a compound of this class having an appropriately located hydrazone group undergoes rearrangement to a *v*-triazole with simultaneous fission of the isoxazole ring. Such a substance is 3-acetyl-5-methylisoxazole phenylhydra-

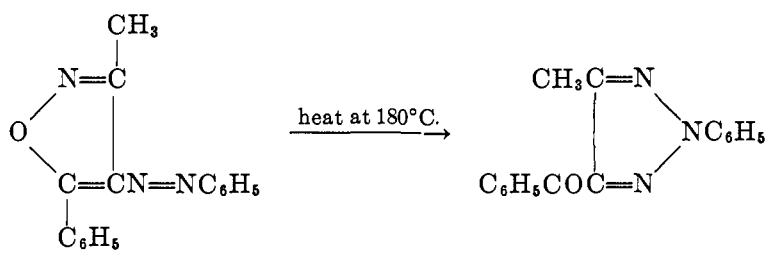
zone, which forms 5-acetonyl-4-methyl-2-phenyl-*v*-triazole (1). Hydrazones of 3-acyl-1,2,4-oxadiazoles are converted to 5-acylamino-*v*-triazole derivatives in



like manner. Thus, the phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole is changed to 5-benzamino-2,4-diphenyl-*v*-triazole on heating (105). 5-Benzamino-2-phenyl-4-(*p*-tolyl)-*v*-triazole and 5-benzamino-2-(*p*-bromophenyl)-4-phenyl-*v*-triazole also have been obtained by this transformation.



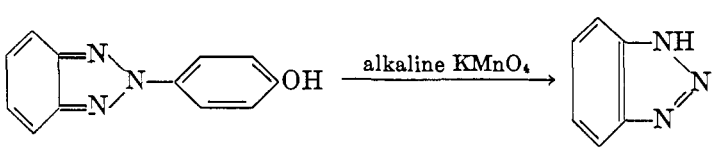
A similar rearrangement occurs when 4-benzeneazo-3-methyl-5-phenylisoxazole is heated. Copper powder or sand is admixed with the isoxazole to moderate a possible explosive reaction (218).



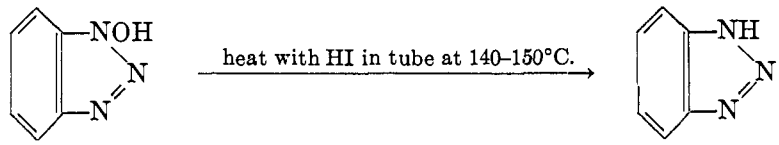
E. FUSED-RING *v*-TRIAZOLES

1. Fused-ring 4,5-disubstituted derivatives

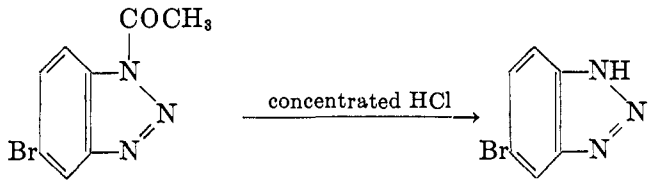
Oxidation of certain substituted benzotriazoles leads to the formation of benzotriazole. The 2-*p*-hydroxyphenyl derivative is converted to the unsubstituted compound (84), as also is the 1-vinyl derivative (143).



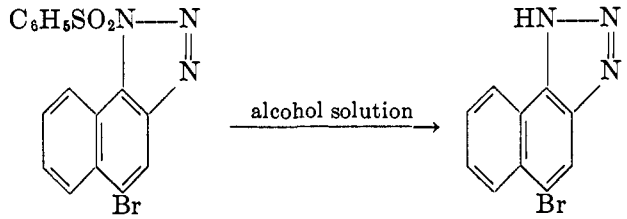
On the other hand, benzotriazole is formed by reduction of 1-hydroxybenzotriazole (231).



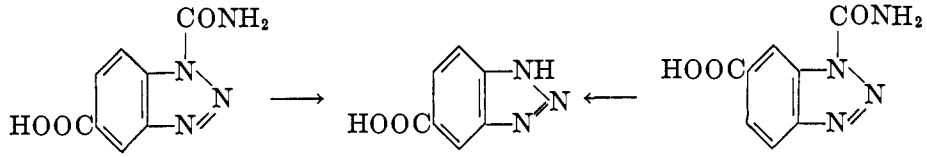
Polycyclic *v*-triazoles with acyl groups attached to a ring nitrogen are hydrolyzed to 4,5-disubstituted derivatives (18, 28, 35, 41, 88, 146, 163, 171). Thus, 1-acetyl-5-bromobenzotriazole is converted to 5-bromobenzotriazole (226).



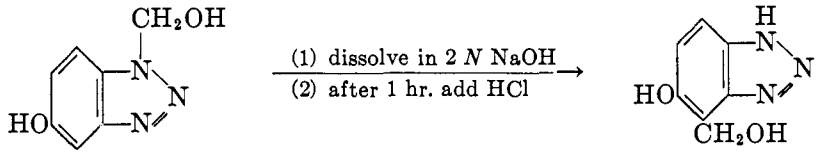
By merely keeping a solution of 1-benzenesulfonyl-5-bromonaphtho[1.2]triazole in alcohol, splitting to the deacylated derivative occurs (161). Similarly, 1-carbamylbenzotriazole-5(or 6)-carboxylic acid is hydrolyzed by heating with water,



alcohol, or acetic acid (108, 222). The fact that the same benzotriazolecarboxylic acid is obtained from both these substances shows the tautomeric nature of the hydrogen linked to nitrogen.

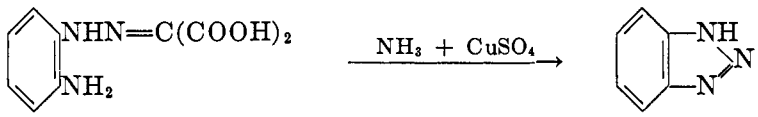


The rearrangement of 5-hydroxy-1-hydroxymethylbenzotriazole involves exchange of the methylol group on the triazole cycle for a hydrogen on the benzene ring (95).

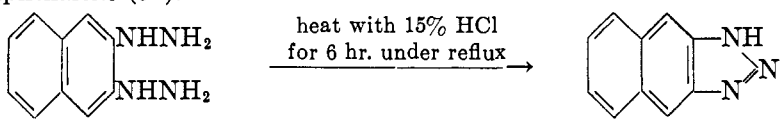


Two reactions leading to the formation of a *v*-triazole ring in this series are known in which ring closure is accompanied by expulsion of an attached group.

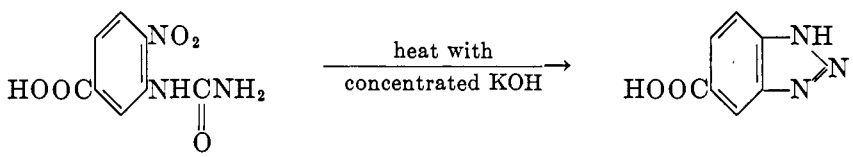
In the first of these, the *o*-aminophenylhydrazone of oxomalonic acid, on treatment with ammoniacal copper sulfate, produces benzotriazole (94). The other



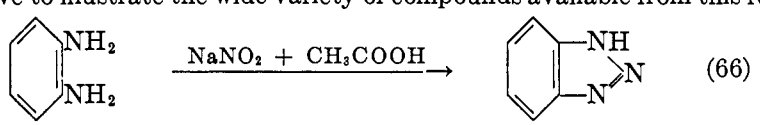
reaction of this type is the formation of naphtho[2.3]triazole from 2,3-dihydrazinonaphthalene (91).



Through the influence of strong alkali *p*-nitro-*m*-ureidobenzoic acid forms benzotriazole-5-carboxylic acid (108). It is evident that the loss of a molecule of carbon dioxide and one of water, as well as a rearrangement, are involved.

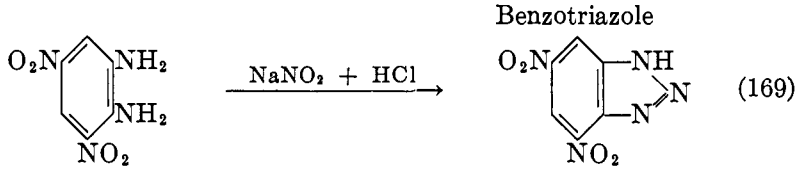


By far the most important method for preparing fused-ring 4,5-disubstituted *v*-triazoles is the reaction of *o*-diamines with nitrous acid. The majority of the members of this series have been obtained in this way. A few specific examples will serve to illustrate the wide variety of compounds available from this reaction.



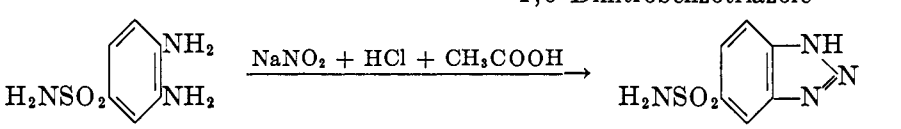
(66)

Benzotriazole



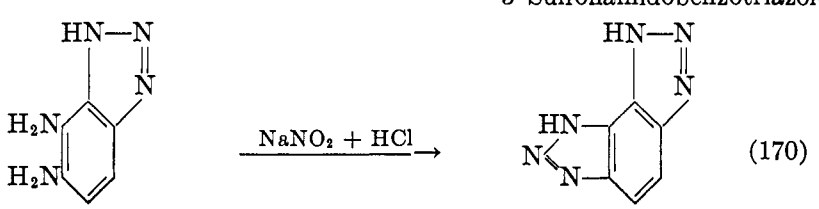
(169)

4,6-Dinitrobenzotriazole



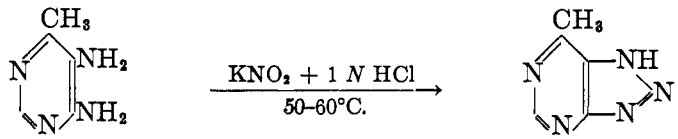
(3)

5-Sulfonamidobenzotriazole



(170)

Benzo[1.2.3.4]bistriazole

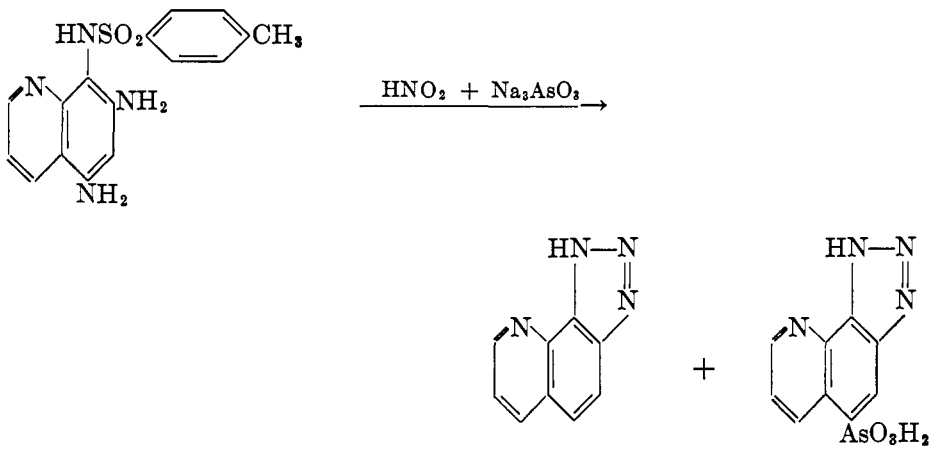


(98)

7-Methyl-*v*-triazolo[*d*]pyrimidine

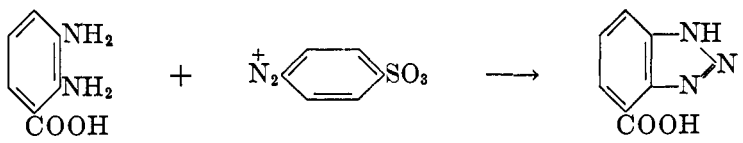
The essential problem in the synthesis of fused-ring *v*-triazoles of this class is the preparation of the appropriate *o*-diamines.

In some cases a monoacylated *o*-diamine is employed, the acyl group being lost during the diazotization. Thus 5,7-diamino-8-(*p*-toluenesulfonamido)quinoline on treatment with nitrous acid and sodium arsenite yields two triazolo[*h*]-quinolines with no substituents on the triazole ring (195). It will be noted that,

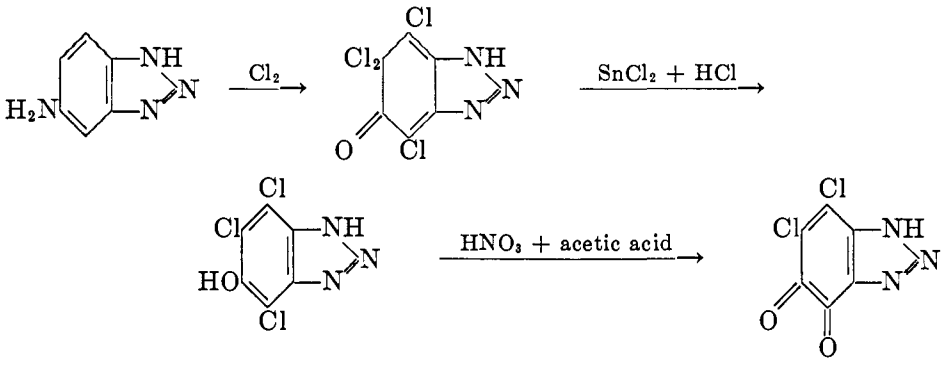


with respect to the 5-amino group, a portion of the starting material has undergone the Bart reaction, whereas in the remainder hydrogen has replaced this amino group.

Instead of using nitrous acid to introduce the middle *v*-triazole nitrogen, diazonium salts may be used for the same purpose. For example, 2,3-diaminobenzoic acid is converted to benzotriazole-4-carboxylic acid on treatment with diazotized sulfanilic acid (109).

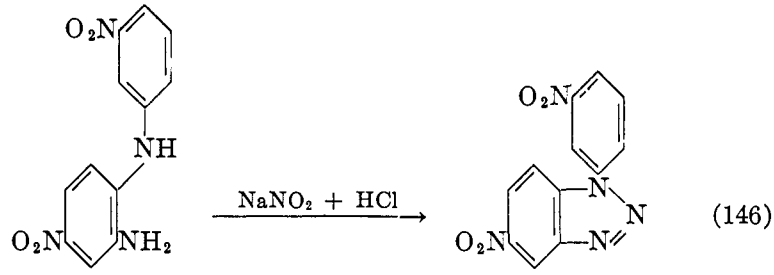


A considerable number of benzotriazole derivatives were obtained by Zincke and Fries by chlorinating hydroxy- and amino-benzotriazoles. The chlorinated derivatives first formed may be subjected to various further transformations. In particular, various quinones are obtained in this manner; the synthesis of 6,7-dichlorobenzotriazole-4,5-quinone is shown for illustration (223).

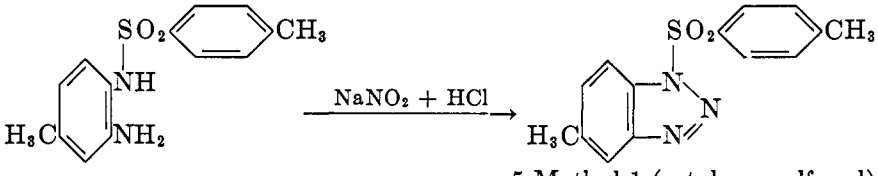


2. Fused-ring 1,4,5-trisubstituted derivatives

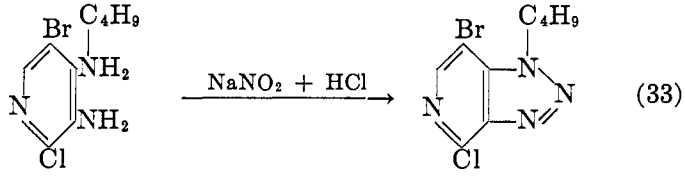
The action of nitrous acid on *o*-diamines is also applicable to the synthesis of 1,4,5-trisubstituted *v*-triazoles. For this group monoalkyl, monoaryl, or monoacyl *o*-diamines are the requisite starting materials. As with the 4,5-disubstituted derivatives, this reaction is the one most frequently used to obtain compounds in this series. Indeed, proof of structure of a polycyclic 1,4,5-*v*-triazole, made by another method, is usually secured by preparing the same substance *via* the diazotization procedure. A few examples will suffice to indicate the utility of the reaction.



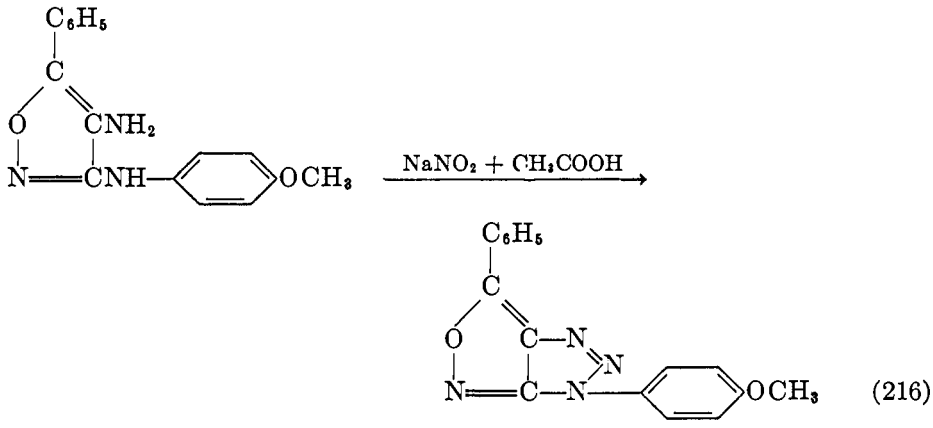
5-Nitro-1-(*m*-nitrophenyl)-benzotriazole (146)



5-Methyl-1-(*p*-toluenesulfonyl)-benzotriazole (208)



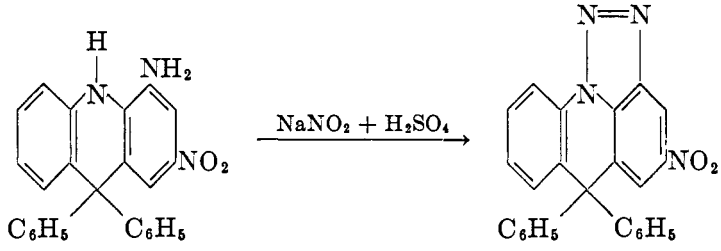
1-Butyl-7-bromo-4-chloro-pyrido[3.4-*d*]-*v*-triazole (33)



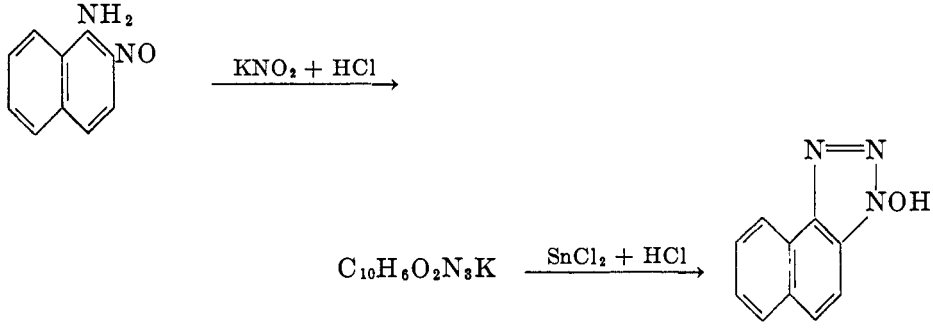
(216)

3-(*p*-Anisyl)-6-phenyl-*v*-triazolo[*c*]isoxazole

Compounds in which two sides of the *v*-triazole ring are fused to other rings—substances which might be called angular *v*-triazoles—are formed when one of the two amino groups is part of a ring system. Thus, diazotization of the aminonitrodiphenyl-5-acridine shown leads to 4-nitro-6,6-diphenyl-6-triazolo[*de*]acridine (136). This is the only synthetic method for this type of triazole so far described.

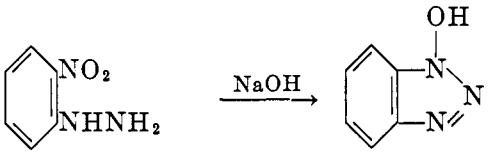


A modification of the diazotization reaction which has been used to prepare both 1- and 3-hydroxynaphtho[1,2]triazoles involves the use of an aminonitrosonaphthalene. Subsequent to reaction with nitrous acid, the hydroxytriazole is formed by reduction (114, 115).

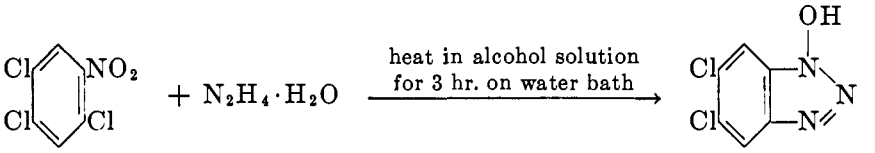


Fused-ring *v*-triazoles with a hydroxyl group in the 1-position are usually prepared by the cyclization of *o*-nitrohydrazino compounds. For example, 1-hy-

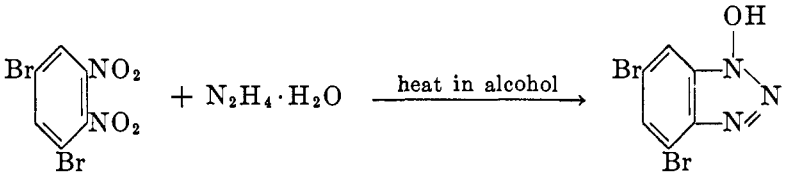
droxybenzotriazole, also known as benzazimidole, is formed by treatment of *o*-nitrohydrazinobenzene with alkali (168, 231). It is not necessary to start with



the preformed *o*-nitrohydrazine derivatives; these may be prepared *in situ* by reaction of hydrazine with aromatic derivatives having a suitably labile substituent adjacent to the nitro group. The hydrazine salts obtained first are decomposed to the free 1-hydroxytriazole by treatment with acid. Thus the interaction of 2,4,5-trichloronitrobenzene and hydrazine hydrate leads to 5,6-dichloro-1-hydroxybenzotriazole, the chlorine ortho to the nitro group being replaced (165). Similarly, a nitro group is replaced when 3,5-dibromo-1,2-dini-

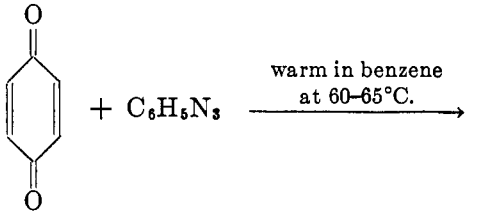


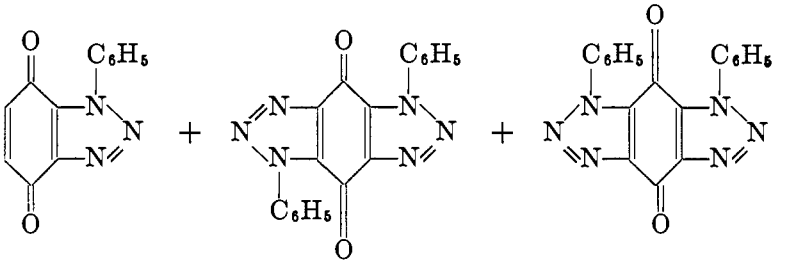
trobenzene is treated with hydrazine hydrate (210).



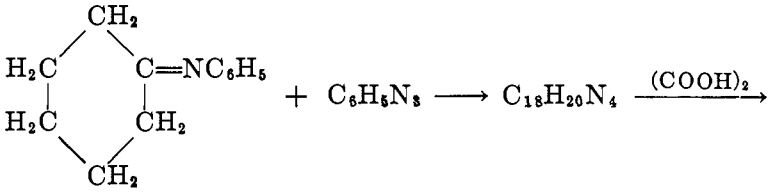
Mention is made of the fact that most of the 1-hydroxybenzotriazoles are somewhat explosive in character (104, 151, 210).

Phenyl azide reacts with quinone to produce three different fused-ring *v*-triazoles (220).

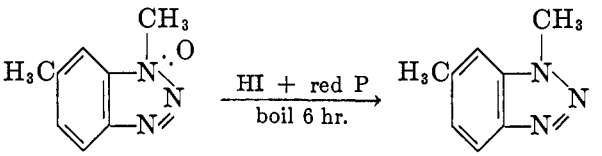




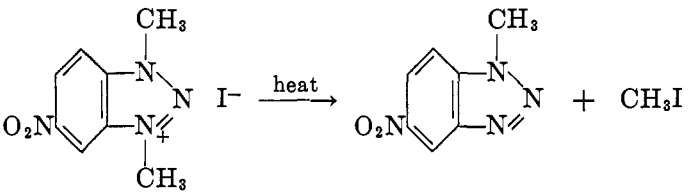
Another formation of a *v*-triazole of this class using phenyl azide is the synthesis of 4,5,6,7-tetrahydro-1-phenylbenzotriazole. The azide and cyclohexanone anil condense to form an intermediate of unknown structure, from which the reduced triazole is obtained on elimination of aniline (2). Formation of 1,6-dimethyl-



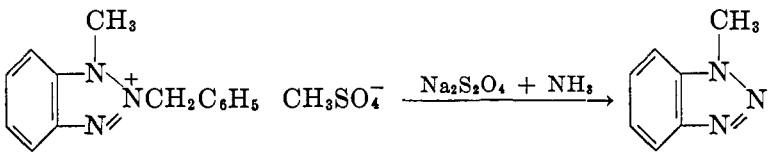
benzotriazole is achieved by reduction of the corresponding 1-oxide (31). The synthesis of the same substance by diazotizing *p*-amino-*m*-methylaminotoluene



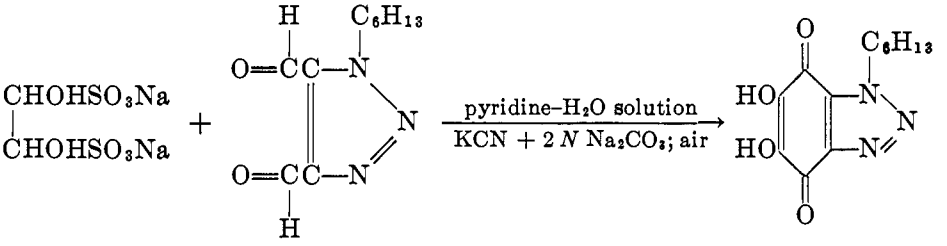
constitutes proof of structure. Decomposition of certain benzotriazolium salts leads to the formation of 1-substituted derivatives. Thus, 1,3-dimethyl-5-nitrobenzotriazolium iodide decomposes on heating to methyl iodide and 1-methyl-5-nitrobenzotriazole (32). In like manner 2-benzyl-1-methylbenzotriazolium methosulfate is converted to 1-methylbenzotriazole by reduction with ammoniacal sodium hydrosulfite in almost quantitative yield (143). Discussion



of the closely allied reaction of substitution in the nitrogen portion of 4,5-disubstituted fused-ring triazoles will be deferred until the section covering reactions. Some benzotriazole derivatives have been obtained by building the benzene

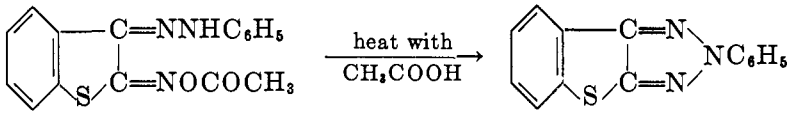


ring from 4,5-diformyltriazoles and glyoxal bisulfite (213). Condensation was effected by means of potassium cyanide and sodium carbonate; owing to the insolubility of some of the dialdehydes, the use of a wetting agent was found to be efficacious.

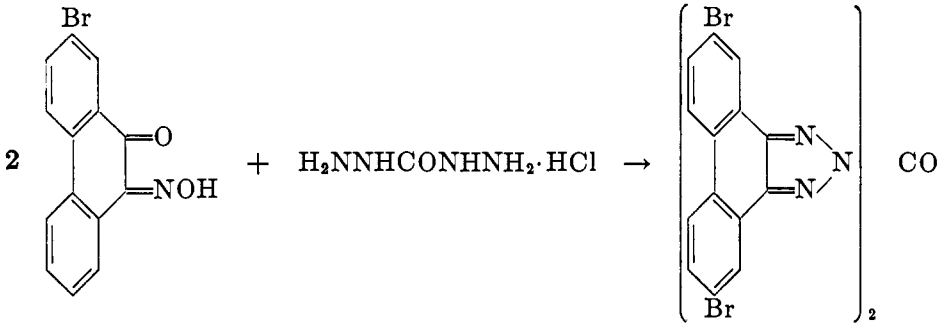


3. Fused-ring 2,4,5-trisubstituted derivatives

A few syntheses of fused-ring 2,4,5-trisubstituted *v*-triazoles have been accomplished by the use of α-hydrazone oxime esters. Thus, 2-phenylthianaphtheno[2.3]triazole was prepared from the indicated thianaphthene derivative (7).

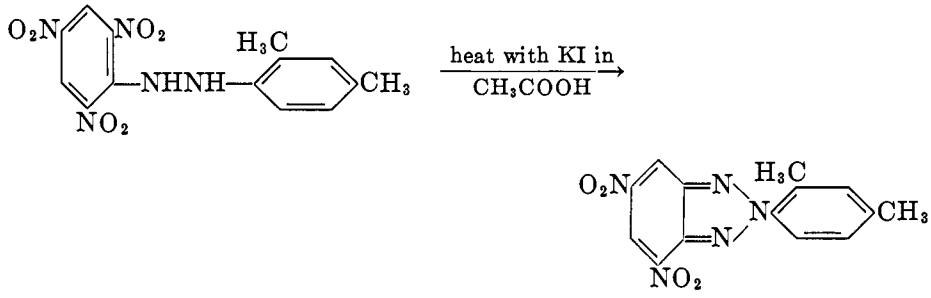


In like manner various carbonyl- and thiocarbonyl-bisphenanthro[9.10]triazoles have been obtained by the interaction of the phenanthrenequinone monoximes with carbohydrazide or thiocarbohydrazide (67). Carbohydrazone formation is undoubtedly an intermediate phase in this reaction. The example given is the formation of 2,2′-carbonylbis(5,10-dibromophenanthro[9.10]triazole).

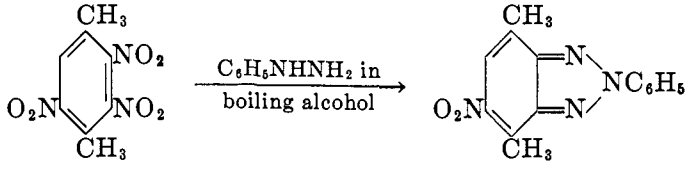


A preparative method of wide application is the treatment of *o*-nitroarylhydrazine derivatives with reducing agents. When 2,4,6-trinitro-(2′,4′-dimethylphenylhydrazino)benzene is heated with potassium iodide in glacial acetic acid the dinitroaryltriazole shown is formed (217). It is not necessary, however, to use either a preformed *o*-nitrohydrazine derivative or an auxiliary reducing agent.

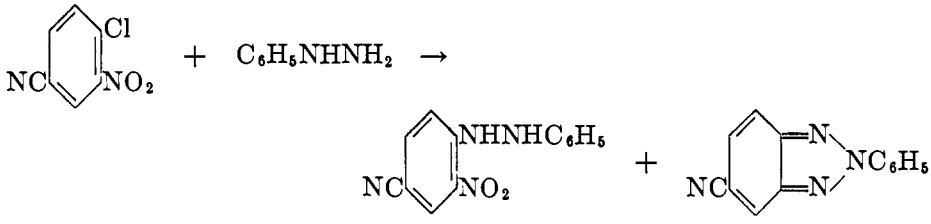
As in the synthesis of 1-hydroxybenzotriazoles from hydrazine and nitrobenzene derivatives with a replaceable radical ortho to the nitro group, a suitably sub-



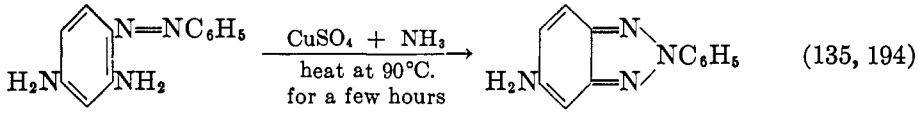
stituted nitro aromatic compound may serve as starting material. An excess of the hydrazine component (e.g., phenylhydrazine) will suffice as reducing agent. For instance, 4,7-dimethyl-5-nitro-2-phenylbenzotriazole is prepared from trinitro-*p*-xylene and phenylhydrazine (102). One of the two adjacent nitro groups is displaced by phenylhydrazine. When *p*-chloro-*m*-nitrobenzonitrile is similarly



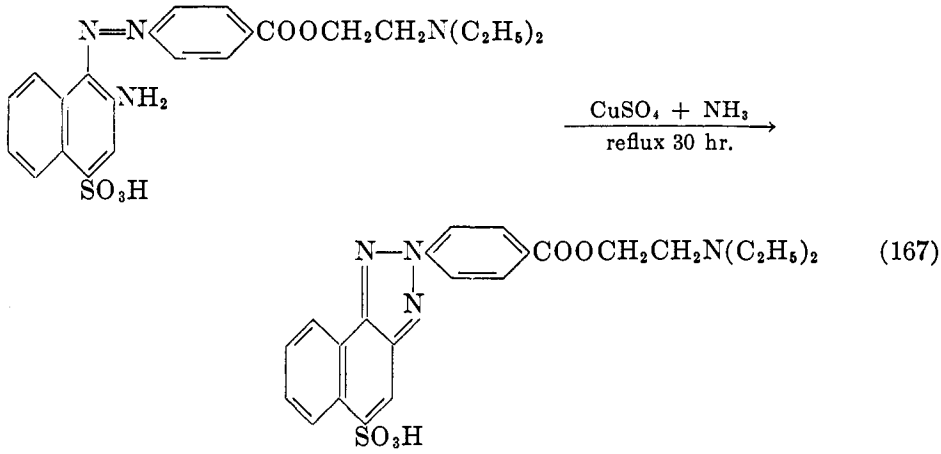
treated with phenylhydrazine, a mixture of the triazole and the phenylhydrazino nitro compound is produced (152).



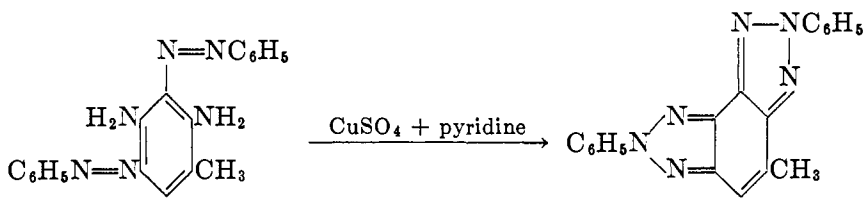
Probably the synthesis of widest application for this class of substances is the cyclication of *o*-azoamino or negatively substituted amino compounds. The azo compounds are usually obtained by standard coupling reactions. The conversion can be effected by heat alone or by oxidation with chromic acid, ammoniacal copper sulfate, or hydrogen peroxide. The following are typical examples of this reaction:



(135, 194)



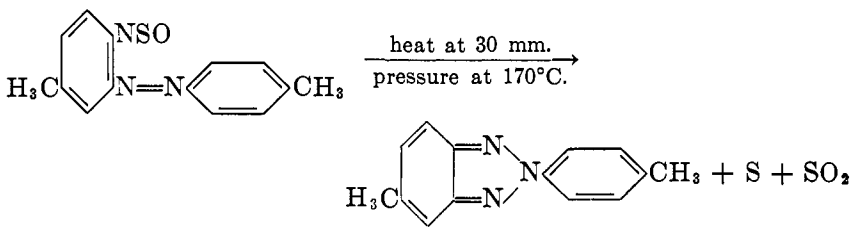
(167)



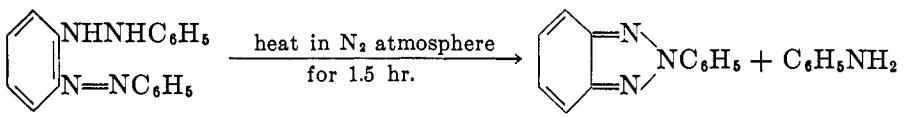
(194)

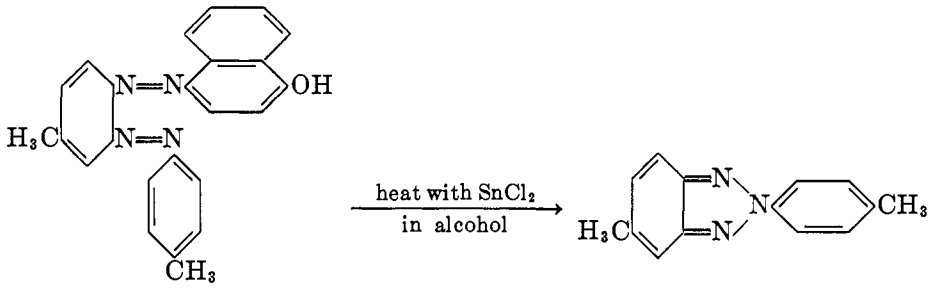
The formation of 2-phenylbenzotriazole by the action of ammonium sulfide or sodium hydrosulfite on *o*-nitroazobenzene (106) in all probability involves a preliminary reduction of the nitro group.

The tendency toward the formation of the triazole ring from azo compounds is likewise evident with *o*-phenylhydrazino, azido, and thionylamino substituents. Thus, heating 4-thionylamino-3-(*p*-tolueneazo)toluene leads to the formation of 5-methyl-2-*p*-tolylbenzotriazole (158). Similarly, *o*-azo azides lose nitrogen (228) and *o*-benzeneazophenylhydrazinobenzene loses aniline (193) with resulting

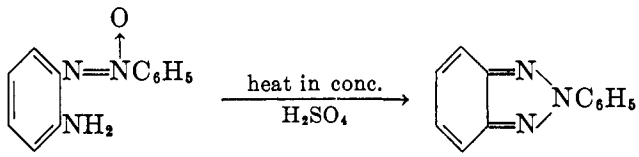


triazole formation. Bisazo compounds may form triazoles under reducing conditions, reduction of one of the azo linkages presumably being involved (229).

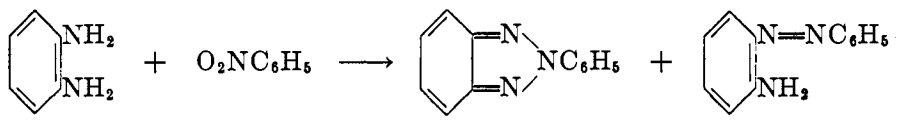




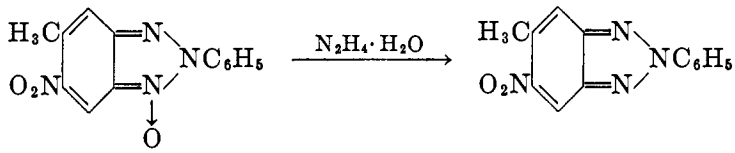
When *o*-aminoazoxybenzene is treated with concentrated sulfuric acid, water is eliminated and 2-phenylbenzotriazole results (65).



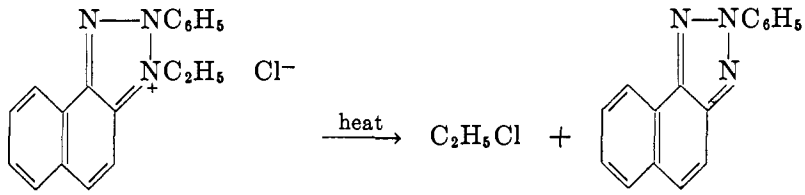
Another method of formation of 2-phenylbenzotriazole, which would appear to be worthy of further investigation, is the interaction of *o*-phenylenediamine and nitrobenzene. Some *o*-aminoazobenzene is also obtained at the same time (52).



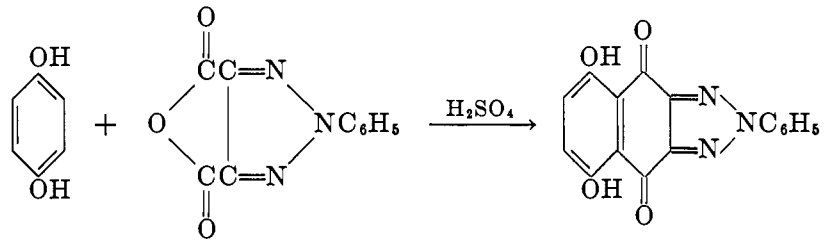
Appropriate triazole oxides are easily reduced to triazoles. For example, 6-methyl-5-nitro-2-phenyl-benzotriazole 3-oxide is readily converted to the corresponding benzotriazole by hydrazine (5). The syntheses of fused-ring 2,4,5-trisubstituted triazoles from phenylhydrazine and compounds with a nitro group ortho to a labile substituent undoubtedly proceed through the oxide.



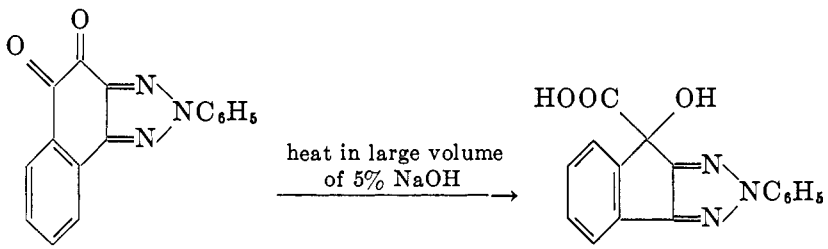
As with the 1,4,5-derivatives, triazolium compounds may be employed in some instances to prepare fused-ring 2,4,5-trisubstituted *v*-triazoles. Thus, 3-ethyl-2-phenylnaphtho[1.2]triazolium chloride on heating yields 2-phenylnaphtho[1.2]-triazole (144).



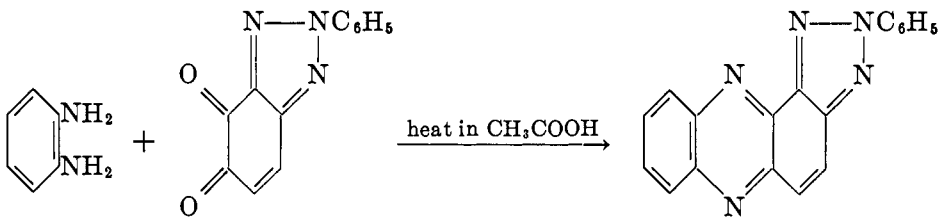
A considerable number of polycyclic *v*-triazoles in this series are prepared by methods standard for the synthesis of non-triazole analogs. A few such syntheses are given to indicate the methods of choice for several of these more complicated fused-ring *v*-triazoles. The anhydride of 2-phenyl-*v*-triazole-4,5-dicarboxylic acid condenses with hydroquinone to form 2-phenyl-5,8-dihydroxynaphtho[2.3]triazole-4,9-quinone, analogous to similar reactions of phthalic anhydride (21).



The indeno[1.2]triazoles are obtained by benzilic acid rearrangement of naphtho[1.2]triazole-4,5-quinones, as shown by the reaction of the 2-phenyl derivative (190). This reaction is, of course, strictly analogous to the conversion of phenanthrenequinone to hydroxyfluorenecarboxylic acid.



Lastly, numerous phenazine- and quinoxaline-triazole derivatives are prepared by means of the condensation of *o*-quinones and *o*-phenylenediamine. The preparation of 2-phenyltriazolo[*a*]phenazine (96) will serve to illustrate this type of reaction.

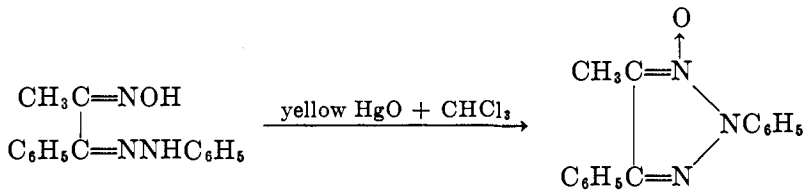


F. TRIAZOLE OXIDES

The methods for preparing triazole oxides involve substantially the same reactions that are used to prepare 2-substituted triazoles, except that more highly oxidizing or less highly reducing conditions are used.

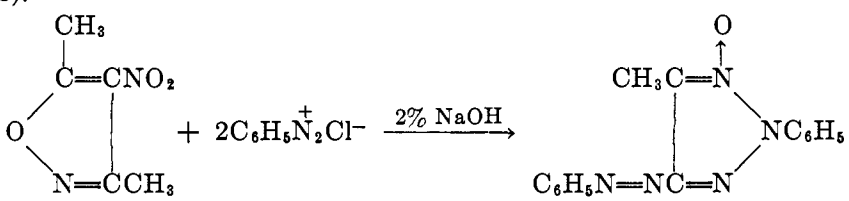
When α-phenylhydrazone oximes are heated for prolonged periods with yellow mercuric oxide, 2-phenyltriazole 1-oxides are produced. The 4-methyl (182),

4,5-dimethyl (185), 5-ethyl-4-methyl, 4-ethyl-5-methyl (183), 5-methyl-4-phenyl, and 4,5-diphenyl (184) derivatives have been prepared by this reaction. In the

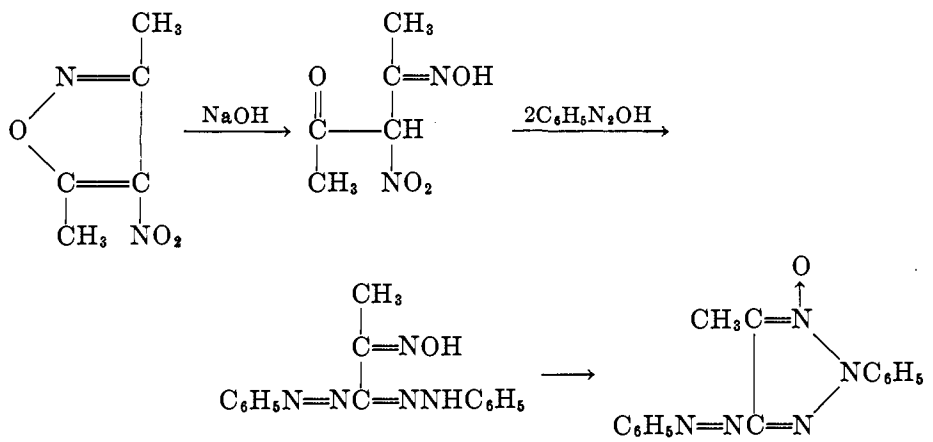


case of the 4,5-dimethyl derivative, nitrogen tetroxide in ether also was found to be capable of converting the α-hydrazone oxime to the triazole oxide.

Another method of preparing triazole oxides involves the use of nitroisoxazoles and diazo compounds. Thus, benzenediazonium chloride and 3,5-dimethyl-4-nitroisoxazole combine to form 4-benzeneazo-5-methyl-2-phenyl-*v*-triazole 1-oxide (188).

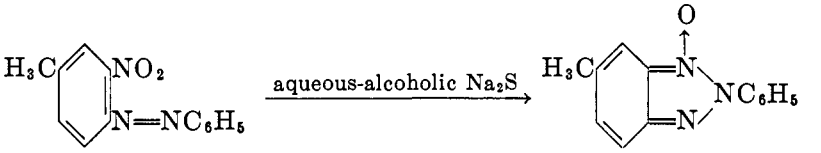


The mechanism suggested by Quilico and Musante required opening of the isoxazole ring and coupling with two moles of diazo compound, accompanied by loss of an acetyl and a nitro group. The relationship of this synthesis to the formation

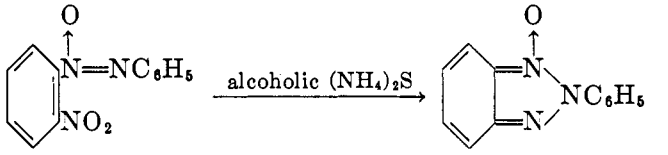


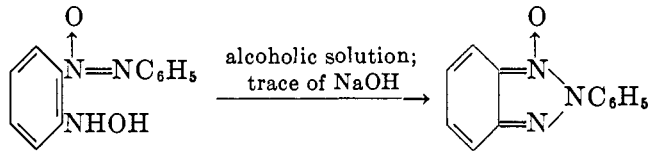
of 2,4,5-trisubstituted *v*-triazoles from isoxazole phenylhydrazones is somewhat obscure. It seems likely, however, that the ultimate source of the oxide oxygen atom is the nitro group.

The action of such reducing agents as sodium hydrosulfite, sodium or ammonium sulfide, or hydrazine on *o*-nitro azo compounds leads to benzotriazole oxides. The preparation of 6-methyl-2-phenylbenzotriazole 1-oxide is given as an example (15). More extensive reducing action would, of course, lead to 6-methyl-2-phenylbenzotriazole.

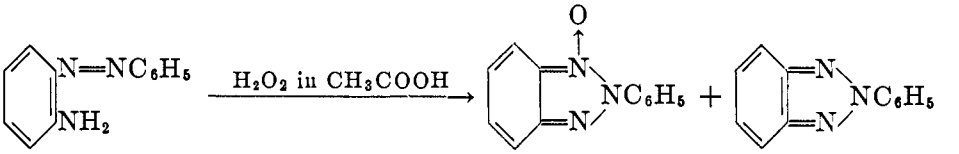


Zinin's synthesis of a triazole oxide, mentioned in the introduction, involves reduction of *o*-nitroazoxybenzene (212, 232). Whereas the mechanism of this reaction is not known with certainty, it is of interest that *o*-hydroxyaminoazoxybenzene is converted to 2-phenylbenzotriazole 1-oxide by treatment with a trace of alkali (65). It is possible that Zinin's synthesis proceeded through the intermediate formation of the hydroxyamino compound.

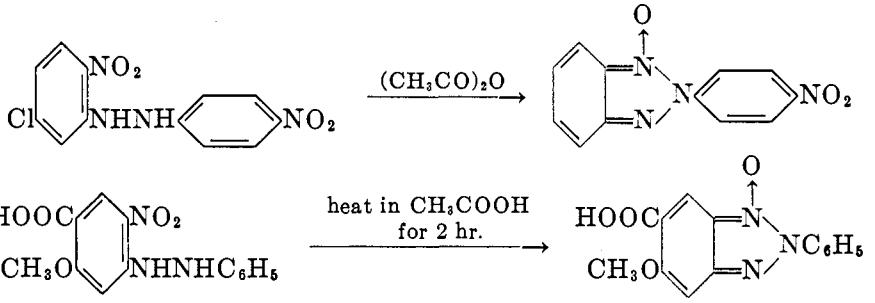




Undoubtedly, the formation of the same oxide, together with some 2-phenylbenzotriazole, from *o*-aminoazobenzene by treatment with hydrogen peroxide involves a similar mechanism (43, 44).

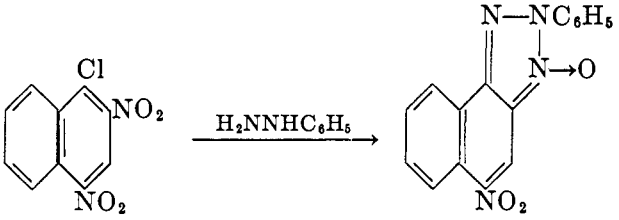


By far the majority of the fused-ring triazole oxides have been prepared from *o*-nitroarylhydrazine compounds. This reaction consists of an intramolecular dehydration. Illustration is made with 5-chloro-2-nitro-1-(*p*-nitrophenylhydrazino)benzene (150), and 4-carboxy-5-methoxy-2-nitro-1-phenylhydrazinobenzene (103).



As with the corresponding synthesis of fused-ring 2,4,5-trisubstituted *v*-triazoles, the use of separate hydrazine and nitro components is feasible. Thus, 1-chloro-

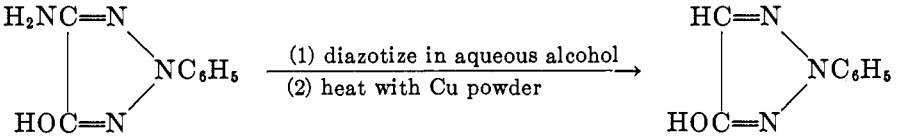
2,4-dinitronaphthalene reacts with phenylhydrazine to form 5-nitro-2-phenylnaphtho[1.2]triazole 3-oxide (149).



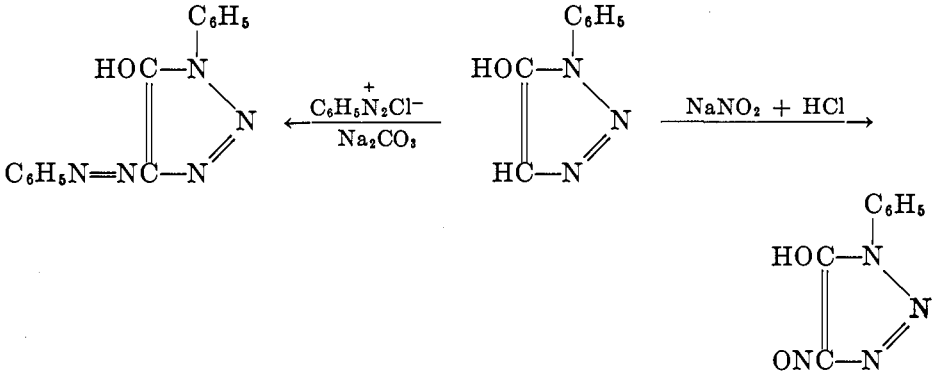
IV. Structure of the *v*-Triazoles

This section is concerned with the aromaticity of the *v*-triazoles, and with the disposition of the valences in the *v*-triazole ring, particularly in the 2-substituted polycyclic derivatives. Insofar as the question has an answer, the location of the hydrogen atom in *v*-triazoles not substituted on the ring nitrogen also will be considered.

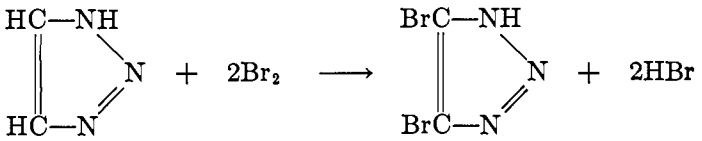
There is little doubt concerning the bond structure of the simple 1- or 2-substituted derivatives. Their aromatic nature is attested by the characteristic diazotization reactions of compounds with an amino group on the 4- or 5-position. Thus, 5-amino-1,4-diphenyl-*v*-triazole, when subjected to the Sandmeyer reaction in the presence of cuprous chloride, yields 5-chloro-1,4-diphenyl-*v*-triazole (81). Heating the diazo derivative of 5-amino-4-hydroxy-2-phenyl-*v*-triazole with copper powder in the presence of alcohol effects replacement of the amino group with hydrogen (207). Similarly, diazotized 5-amino-1-phenyl-*v*-triazole couples with β-naphthol to form an azo compound (70). When 5-acetamino-4-amino-2-



phenyl-*v*-triazole is diazotized and coupled with R-salt, an intense blue-red color is formed (207). As with phenols having a free ortho position, 4- or 5-hydroxy-*v*-triazoles can couple or nitrosate in the unsubstituted position. This is illustrated with 5-hydroxy-1-phenyl-*v*-triazole (68, 82). Another indication of aromaticity is the typical phenolic reaction with ferric chloride, which carbon-substituted

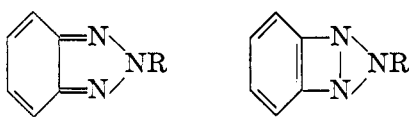


hydroxy-*v*-triazoles also can undergo. Although substitution reactions are not as readily accomplished with *v*-triazoles as with benzene derivatives, such reactions are known. Thus, bromination of *v*-triazole leads to 4,5-dibromo-*v*-triazole (125).



These examples illustrate the parallelism of the *v*-triazoles with aromatic substances such as benzene with respect to certain chemical behavior. It appears reasonable to correlate the conjugated double-bond arrangement, associated with aromatic properties in other five-membered heterocycles such as furan or thiophene, with its presence in *v*-triazole.

The mode of formation of the 1-substituted benzotriazoles clearly establishes their structure. With respect to the 2-substituted benzotriazoles, however, there has been considerable dispute as to the disposition of the bonds. Two formulas have been proposed for this type of compound (I and II). Structure I has been questioned, because it was felt that such a compound should be colored and should otherwise exhibit quinoid properties. The 2-substituted benzotriazoles are colorless.



I II

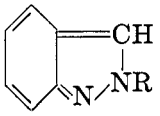
While the ultraviolet absorption spectra of the 2-methyl- and 2-phenyl-benzotriazoles (143, 198) do not enable a choice between formulas I and II, it is to be noted that the maxima of both the 2-isomers are somewhat closer to the visible than those of the corresponding 1-isomers. Further, the extent of absorption at the maxima is greater with the 2-derivatives than with the 1-substituted compounds.

Although the valence requirements of the atoms are formally satisfied in formula II, consideration of the geometry of such a molecule raises a doubt concerning its validity. If the three nitrogen atoms in structure II are assumed to be equidistant from each other, then the bond angles of the three-membered ring are necessarily 60°. The consequence of such an arrangement renders such a formulation improbable, owing to the strain involved. No other compound with a three-membered nitrogen ring is known; in this connection the establishment of the linear nature of the azide group is to be recalled. Any three-membered ring where the atoms are not equidistant would involve still greater strain. Unfortunately, no x-ray or electron diffraction studies of 2-substituted benzotriazoles or other *v*-triazoles have been made; hence no experimental interatomic distances are available. It does not seem unreasonable, however, to assume that the length of the carbon-to-carbon bond common to the two fused rings is similar to that in naphthalene (1.41 Å.) (214) or that of dibromohydrindene (1.42 Å.) (142). If the transannular nitrogen-to-nitrogen link in structure II has the normal single-bond

length (1.40 Å.) (214), then the tetragon described by the two carbon and two nitrogen atoms will be essentially a rectangle. Consequently, the bond angles of the four-membered ring will all be close to 90°. The cyclic system of structure II, then, requires that two of the valence angles of each nitrogen (1 and 3) be 60° and 90°, an extremely strained arrangement. The normal valence angles of nitrogen in ammonia and trimethylamine are approximately 108° (176). Thus, from geometric considerations structure II appears quite improbable.

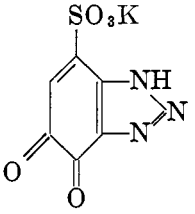
On the other hand, structure I lends itself readily to the construction of a diagram for the fused *v*-triazole ring with acceptable interatomic distances (214) for the C—C (1.40 Å.), C=N (1.28 Å.), and N—N (1.40 Å.) bonds. If the internal valence angles are 108°—a reasonable assumption—the distance between nitrogen atoms 1 and 3 will be of the order of magnitude of 2.2 Å. If the C—C=N angles are 112.5°, as shown to be probable for the C—C—CH_2 angle in dibromohydrindene (142), the distance between nitrogens 1 and 3 will be 2.39 Å. Just as the postulate of a 9,10-bond in anthracene was shown to be untenable, owing to the distance between these atoms, so the calculated distance between the 1 and 3 nitrogen atoms renders the probability of a bond between them unlikely.

The structure of the 2-substituted benzotriazoles was investigated by v. Auwers by means of spectrochemical (refractive index) studies (8). He found the exaltations of the 2-alkylbenzotriazoles were similar to those of the 2-alkylindazoles, for which the *o*-quinoid form has been shown to be highly probable (129). Similarly, as with the indazoles, the 2-isomers have greater molar refractions and dispersions than do the corresponding 1-derivatives.

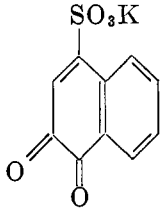


2-Substituted indazole

The relationship of the reduction potentials of benzo- and naphtho-triazolequinones have been employed in an attempt to indicate the degree of aromaticity of the *v*-triazole ring. The lowering of the potential of benzotriazole-4,7-quinone and its 1- and 2-phenyl derivatives from that of α-naphthoquinone is not as pronounced as the lowering of the values for the quinolinequinones or thianaphthenequinone. Hence, the conclusion is drawn that the *v*-triazole ring is closer to benzene in its aromaticity than pyridine or thiophene (86, 89). Similarly, the reduction potentials of the potassium salts of 7-sulfobenzotriazole-4,5-quinone and 4-sulfo-1,2-naphthoquinone are quite close (88). Between naphtho[2.3]triazole-4,9-quinone and its 1-derivatives (methyl and phenyl) there is a considerable difference in the reduction potential (86, 90). This difference is

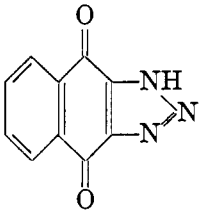


E_0 = 0.672 v.



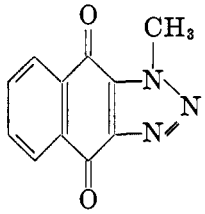
E_0 = 0.630 v.

not found between benzotriazole-4,7-quinone and its 1-phenyl derivative (89).

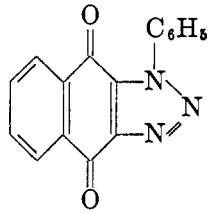


E_0 = 0.435 v. (50% alcohol, 0.1 *N* HCl, and 0.2% *N* LiCl)

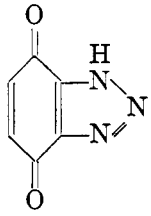
E_0 = 0.345 v. (37% alcohol, 0.047 *M* KH_2PO_4, and 0.047 *M* Na_2HPO_4)



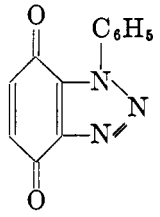
E_0 = 0.235 v. (50% alcohol, 0.1 *N* HCl)



E_0 = 0.256 v. (50% alcohol)

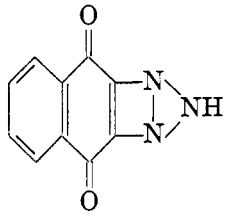


E_0 = 0.526 v. [3]



E_0 = 0.539 v. [3]

Fieser suggested that the larger value found for naphtho[2.3]triazole-4,9-quinone compared to its 1-derivatives might be explained on the basis of the following constitution:



Since, however, comparison of the potentials of the benzotriazolequinones does not show such a difference, it is doubtful that any conclusion concerning structure can be drawn therefrom.

It might be suggested that the higher value of the unsubstituted compound is indicative of a greater degree of aromaticity. Likewise, the value for 2-phenylbenzotriazole-4,7-quinone (E_0=0.487 v.) (86) could be interpreted to mean that this substance is less capable of becoming aromatic than the corresponding 1-phenyl or the unsubstituted quinone. A conclusion from these data concerning the structure of 2-substituted derivatives does not seem possible. It is to be borne in mind that the reduction operation involved in the measurement of the potentials of these compounds is concerned with the transformation of another

[3] Calculated from data in reference 89.

ring from the quinone state to an aromatic state, and does not operate directly on the triazole nucleus.

Fries determined the heats of combustion of naphtho[1.2]triazole and naphtho-[2.3]triazole (97). These substances are structurally analogous to phenanthrene and anthracene, respectively. The linear [2.3] compound had a molal heat of combustion 3.4 Cal. higher than the angular [1.2] isomer. Since anthracene similarly has a higher (7 Cal.) heat of combustion than phenanthrene, it was thereby indicated that the triazole ring was similar to benzene.

There are several data which suggest that benzotriazoles not substituted on the ring nitrogens exist mainly with the hydrogen atom on the 1-nitrogen. For example, in basicity benzotriazole is similar to the 1-alkyl derivatives, in that it also dissolves in dilute hydrochloric acid (143). As mentioned earlier in this article, the 2-alkylbenzotriazoles are not basic toward dilute hydrochloric acid. The ultraviolet absorption spectrum of benzotriazole more closely resembles that of the 1-methyl and 1-phenyl derivatives than it does the 2-isomers (143,

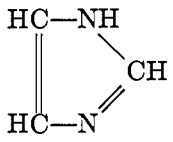
TABLE 3

Dipole moments of some triazoles

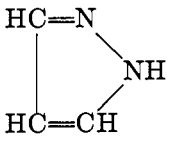
COMPOUND	SOLVENT	μ
		$\times 10^{-18}$ E.S.U.
v-Triazole	Benzene	1.77
Benzotriazole	Dioxane	4.07
1-Phenylbenzotriazole	Benzene	4.08
2-Phenylbenzotriazole	Benzene	0.97

198). Probably the most convincing evidence on this point, however, is that of the dipole moments (131) listed in table 3.

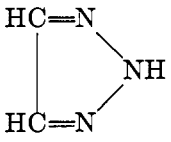
The close correspondence of values for 1-phenylbenzotriazole and benzotriazole, and the divergent figure for 2-phenylbenzotriazole, were taken as implying that hydrogen is attached to position 1 in the unsubstituted compound (131). The fact of association of benzotriazole and other of its derivatives with a hydrogen on nitrogen through intermolecular hydrogen bonds (120), mentioned previously, is probably of significance in the creation of the unsymmetrical structure indicated by the high dipole moment. On the other hand, comparison of the moments found for *v*-triazole with those of imidazole and pyrazole, in which the nitrogen-substituted hydrogens have unequivocal positions, is suggestive that the parent compound is predominantly of the structure shown with hydrogen in position 2.



Imidazole
$\mu = 3.84$



Pyrazole
$\mu = 1.57$



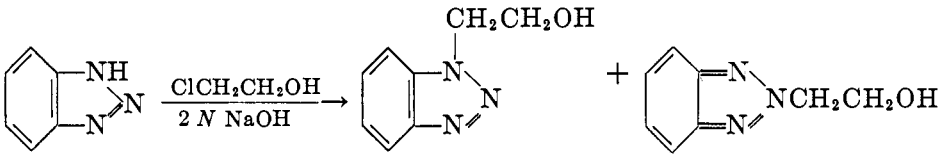
v-Triazole
$\mu = 1.77$

V. Reactions

Of the several reactions of *v*-triazoles, some have already been mentioned in connection with the synthesis and structure of these compounds. Standard organic reactions of substituent groups have no place in the present discussion. Decomposition of 1-arylbenzotriazoles to form carbazole derivatives is described elsewhere (36). The orientation of entering substituents, however, to form 1- and 2-substituted *v*-triazoles is a phase which demands consideration. Unfortunately, the simple monocyclic *v*-triazoles have been investigated but slightly in this connection. This section, therefore, will be concerned with the substitution of fused-ring 4,5-substituted *v*-triazoles. This topic has been the subject of several investigations and in a general way the results of alkylation and acylation can be predicted.

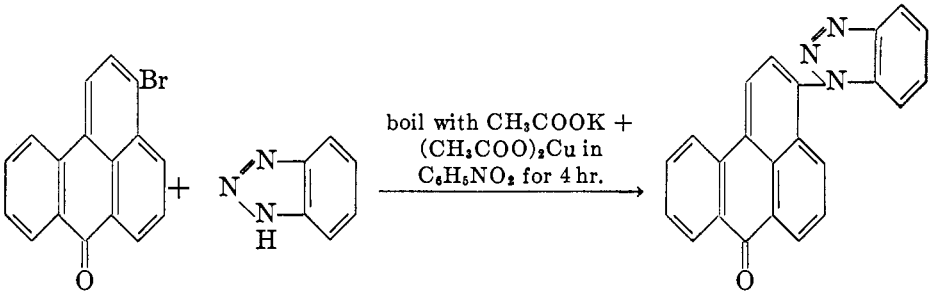
The results of studies of the alkylation of benzotriazole with alkyl sulfates or halides show that substitution in the 1-position is the chief reaction. When methylation is effected with dimethyl sulfate and dilute sodium hydroxide a 30.6 per cent yield of 1-methylbenzotriazole and 20.4 per cent of the 2-isomer is obtained. If methyl iodide in methyl alcohol is used, 55 per cent of the 1-isomer and 33 per cent of the 2-derivative are formed (144). On the other hand, methylation of benzotriazole with diazomethane afforded 15 per cent of 1-methyl- and 51 per cent of 2-methyl-benzotriazoles (37). The investigations of Krollpfeiffer and his collaborators included determination of orientation in the formation of the ethyl-, *n*-propyl-, *n*-butyl-, benzyl-, and allyl-benzotriazoles, using the alkyl sulfates in the presence of dilute sodium hydroxide (143, 144). The results may be summarized by stating that the 1-alkylbenzotriazoles were obtained in yields of 37–65 per cent and 2-alkyl compounds in yields of 23–33 per cent. In the case of allylation, the products were not homogeneous, some propenyl derivatives being formed.

The interaction of ethylene chlorohydrin and benzotriazole results in the formation of 60 per cent of the 1-isomer and 32 per cent of the 2-isomer (143). Similarly, both benzotriazoleacetic acids are obtained when sodium monochloroacetate is heated with benzotriazole.

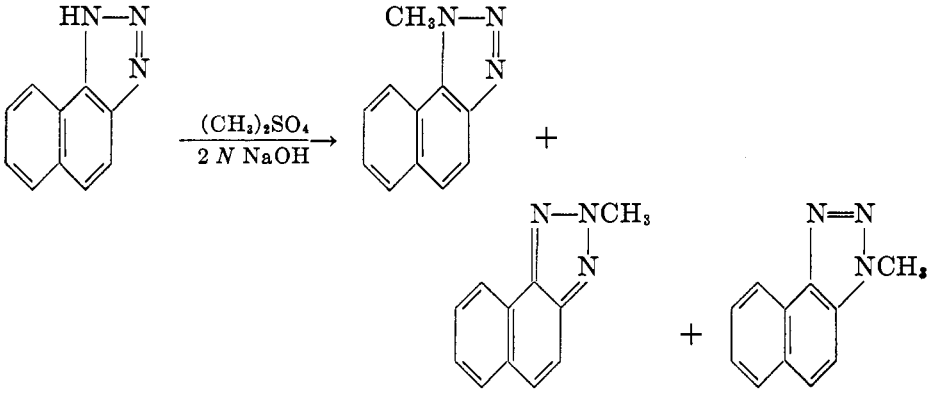


When substitution of benzotriazole is effected under more vigorous conditions, only 1-substituted derivatives result. Thus, 3-bromobenz[*de*]anthrone-7 on reaction with benzotriazole in boiling nitrobenzene substitutes only on the 1-position (211). The correctness of the structure given for this substance was demonstrated by preparing the same compound by means of a diazo reaction with the appropriate *o*-diamine of unequivocal constitution. Likewise, α-chloroanthraquinone forms solely 1-(α-anthraquinonyl)benzotriazole (209). Noelting and Abt

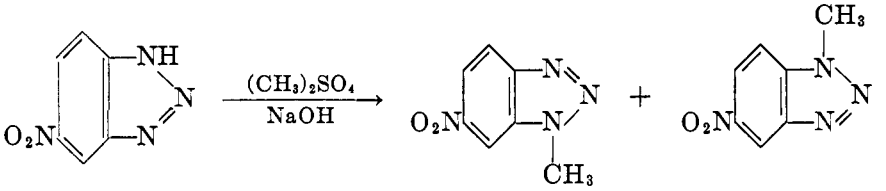
(171) obtained 1-ethyl-5-methylbenzotriazole by the action of ethyl iodide and sodium hydroxide on 5-methylbenzotriazole in a sealed tube.



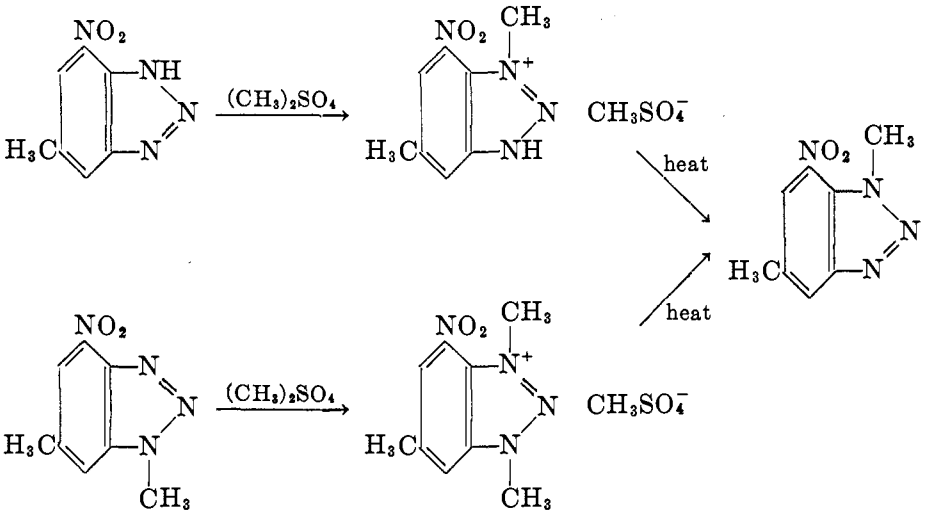
When naphtho[1.2]triazole is treated with dimethyl sulfate and dilute alkali all possible isomers are obtained (144). Naphtho[2.3]triazole, however, yields only the 1-methyl derivative (97).



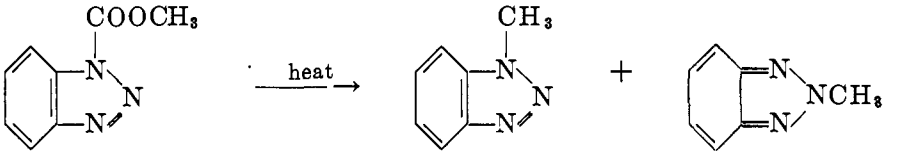
No 2-substituted compounds are formed when nitrobenzotriazoles are methylated with dimethyl sulfate and dilute alkali. Both possible 1-isomers are produced. Thus, both 1-methyl-6-nitro- and 1-methyl-5-nitro-benzotriazoles are obtained from 5-nitrobenzotriazole, the former in larger amount (32).



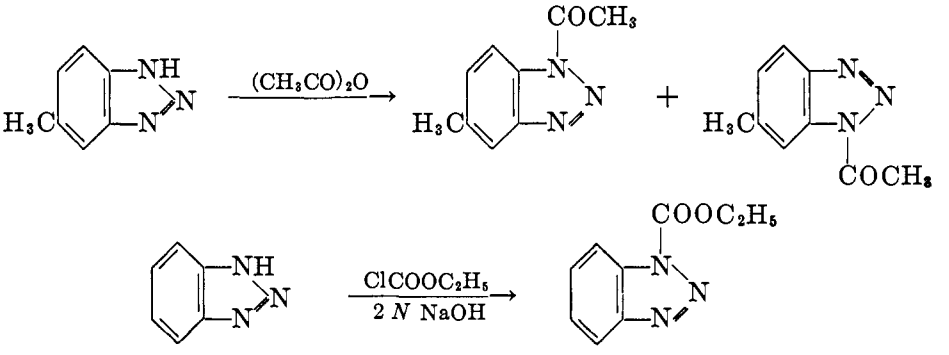
If 5-methyl-7-nitrobenzotriazole is heated alone with dimethyl sulfate a benzotriazolium methosulfate is formed; when this is thermally decomposed the sole compound formed is 1,5-dimethyl-7-nitrobenzotriazole (32). This is consistent with the fact that the isomer of this product, 1,6-dimethyl-4-nitrobenzotriazole, also yields the same substance by the action of dimethyl sulfate. Evidently, the elimination from the triazolium salt of a hydrogen or a methyl group attached to a triazole nitrogen meta to the nitro group is more easily accomplished than with such a group on an ortho nitrogen.



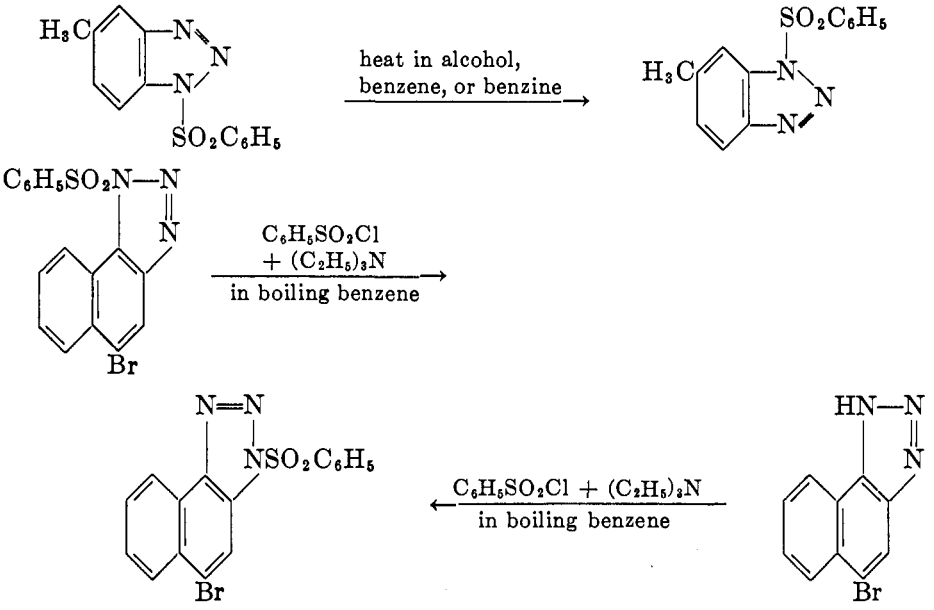
Although not an alkylation reaction in the strict sense of the term, the formation of the methyl- or ethyl-benzotriazoles by decomposition of 1-carbalkoxybenzotriazoles is of interest in the present discussion. When, for example, the methyl ester of benzotriazole-1-carboxylic acid is heated, carbon dioxide is eliminated, and 60 per cent of 1-methyl- and 35 per cent of 2-methyl-benzotriazole are formed (143).



Acylation of *v*-triazoles occurs only on the 1(or 3)-nitrogen atom; the known 2-acyl derivatives have been obtained by indirect means. Treatment of 5-methylbenzotriazole with either acetyl chloride or acetic anhydride leads to a mixture of the two possible 1-acetyl derivatives (163, 227). In like manner benzotriazole interacts with chloroformic ester to yield the ethyl ester of benzotriazole-1-carboxylic acid (143).



Benzenesulfonyl derivatives of fused-ring *v*-triazoles undergo an intramolecular rearrangement on heating as well as by treatment with acetic anhydride or benzenesulfonyl chloride. The 1-benzenesulfonyl-5-methylbenzotriazole, for example, is converted to the isomeric 1-benzenesulfonyl-6-methylbenzotriazole (164). Similarly, 1-benzenesulfonyl-5-bromonaphtho[1.2]triazole is transformed to the 3-isomer; the same substance is produced by direct reaction of 5-bromonaphtho[1.2]triazole and benzenesulfonyl chloride (161).



VI. Uses

The number of actual uses to date of *v*-triazoles are few. Claims are made for various 2-arylnaphtho[1.2]triazoles and 2-arylbenzotriazoles as intermediates for the preparation of dyes (29, 127, 197). Thus 2-(3′-hydroxynaphthyl-2′)-4-hydroxynaphtho[1.2]triazole is coupled with diazo compounds either in substance or on the fiber (126). The dyes formed are stated to have a good affinity for vegetable fibers. Quite a number of 5-α-acetylacetamido-2-arylbenzotriazoles have been prepared for use as coupling agents (132, 196). The azo compounds derived therefrom are claimed to be useful for coloring lacquers or varnishes or as pigments (126).

Because of their ability to absorb ultraviolet light, 1-methyl-6-dimethylaminobenzotriazole (159) and 2-*p*-nitrophenylbenzo[*h*]triazole[*f*]quinoline (128) are claimed, respectively, as a sunburn preventative and for inclusion in cellophane films.

Benzotriazole finds some use as an antifogging agent in photography (153). Phenazinotriazole has also been suggested for this purpose (200).

The pharmacological properties of several *v*-triazole derivatives have been investigated. Elbs and coworkers (84) prepared 2-substituted benzotriazole de-

rivatives of phenacetin, salicylic acid, and aspirin as possible analgesics. Whereas these compounds are more persistent in their action than their prototypes, their excretion in the urine takes longer and all exhibit toxic effects if administered for longer than 8 to 10 days. Similarly, the dimethyl-, diethyl-, and diisobutylamides of 5-methyl-1-phenyl-*v*-triazole-4-carboxylic acid as well as the ethyl ester of 5-amino-1-phenyl-*v*-triazole-4-carboxylic acid were tested for antipyretic activity in rats (53). None of this group offered any promise over aminopyrine as an antipyretic or analgesic drug.

The sodium salt of ethyl 5-hydroxy-1-sulfanilyl-*v*-triazole-4-carboxylate was found to be approximately as effective a bacteriostatic agent as sulfapyridine toward *E. coli* as well as toward pneumococci, meningococci, and gonococci *in vitro*, but was inferior to sulfathiazole (83). Roblin and his associates prepared several triazolopyrimidines which were structural analogs of various purines (192). All of these triazolopyrimidines were found to have some growth-inhibiting action on *E. coli* and *S. aureus;* this effect was reversed by closely related purines. The guanine analog, 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine, when used in combination with sulfanilamide, exerted a synergistic bacteriostatic effect toward *S. aureus*.

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VII. References

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