ALKYL AND ARYL AZIDES[1]

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I. INTRODUCTION

The azido group has attracted attention since the discovery of phenyl azide (192) in 1864 and of hydrogen azide (79) in 1890. The literature contains reviews (70, 351) of the chemistry of organic azides; however, a thorough survey of the available information on alkyl and aryl azides has not previously been reported. The present discussion has been limited to these two groups because of their similarities. Certain other groups have been dealt with previously, e.g., acyl azides (358) and those α-azidoalkylidenimines which undergo cyclic isomerization to tetrazoles (31). Also excluded from this review are the thioacyl azides, the sulfonyl azides, amine salts of hydrogen azide, and complexes of metal azides and amines.

Older nomenclature which has been used to describe the azido group, such as "triazo" and "diazoimide," is not used here. In general, the terms "azido" and "triazo" are used synonymously in the literature. An exception is the name "triazoacetic acid," introduced by Curtius and Lang (98) to describe a trimer of diazoacetic acid in which an azido group is not present. Whenever possible, common or trivial names for compounds have been indicated. All numbering systems and the more complex nomenclature are those used by *Chemical Abstracts.*

II. METHODS FOR INTRODUCING THE AZIDO GROUP INTO ORGANIC MOLECULES

A. DIRECT INTRODUCTION

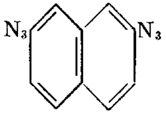
1. Displacement of other groups

Since Curtius obtained benzyl azide from benzyl iodide and silver azide (86), not only halo but also sulfate (129, 367), nitro, phenylazo (273), hydroxyl (258), nitrate (154, 155), iodoxy (399), and alkoxy (ethylene oxide type) (270) groups have been found to enter into displacement reactions with metallic or hydrogen azides. Methyl and ethyl azides have been prepared from sodium azide and the corresponding sulfates, while higher aliphatic azides have been conveniently obtained from the organic halides and sodium azide. The use of "activated" sodium azide and sealed tubes is generally not necessary. Substitution of halogen by the azido group proceeds without inversion of configuration in allylic halides of the type $CH_2{=}CHCHRX$; however, for saturated alkyl derivatives substitution is connected with inversion, with the assumption that substitution of the azido group for halogen proceeds by the same mechanism as the substitution of one halogen for another (253).

Other aliphatic azides (table 1) which may be obtained by the action of sodium azide upon the corresponding halides include azido carbonyl compounds, azido nitro compounds, azido halides, azido amines, azido nitriles, azido ethers, and azidohydrins. Two examples have been reported in which the formation of the azidohydrin involved exchange of positions of the functional groups. From methyl α-bromo-β-hydroxypropionate, α-hydroxy-β-azidopropionic ester was obtained.

TABLE 1

Methods for the preparation of organic azides

NAME	FORMULA	METHOD*	YIELD	REFERENCES
	Azido hydrocarbons			
			per cent	
Allyl azide	$CH_2{=}CHCH_2N_3$	A	30	(150)
3-Azido-1-heptene	$CH_2{=}CHCHN_3(CH_2)_3CH_3$	A	78	(253)
4-Azidononane	$CH_3(CH_2)_2CHN_3(CH_2)_4CH_3$	A	78	(249)
2-Azidopropane	$(CH_3)_2CHN_3$	B		(336)
p-Azidotoluene	$CH_3C_6H_4N_3$	E		(265)
11-Azido-1-undecyne	$CH\equiv C(CH_2)_8CH_2N_3$	A	80	(306)
Benzyl azide	$C_6H_5CH_2N_3$	H		(82)
1,4-Diazidobenzene	$N_3C_6H_4N_3$	C		(201, 354)
4,4′-Diazidobiphenyl	$N_3C_6H_4C_6H_4N_3$	F		(64)
1,2-Diazidoethane	$N_3CH_2CH_2N_3$	A	32	(153)
2,7-Diazidonaphthalene		G		(280)
Dodecyl azide	$CH_3(CH_2)_{10}CH_2N_3$	A	80	(216)
Ethyl azide	$CH_3CH_2N_3$	A	80	(367)
n-Hexyl azide	$CH_3(CH_2)_4CH_2N_3$	A	50	(216)
Methyl azide	CH_3N_3	A	80	(302)
		G		(129)
α-Naphthyl azide	$C_{10}H_7N_3$	G	71	(147)
β-Naphthyl azide	$C_{10}H_7N_3$	E	50	(147)
Phenyl azide	$C_6H_5N_3$	H	65	(104, 262)
		D	Quantitative	(80)
Triphenylmethylazide	$(C_6H_5)_3CN_3$	H	Quantitative	(341, 405)

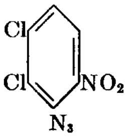
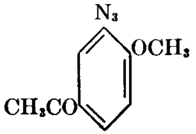
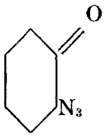
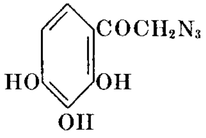
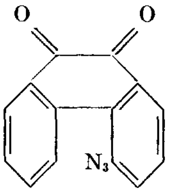
		Azido halides		
p-Bromophenyl azide	$BrC_6H_4N_3$	C, J		(194, 104)
p-Chlorophenyl azide	$ClC_6H_4N_3$	C, J		(194, 141)
β-Azidoethyl bromide	$N_3CH_2CH_2Br$	PBr_3 and $N_3CH_2CH_2OH$	34	(163)
o, *m*, and *p*-Iodophenyl azide	$IC_6H_4N_3$	G		(168)
5,6-Dichloro-2-nitrophenyl azide		H		(287)
Pentabromophenyl azide	$C_6Br_5N_3$	C		(210)
		Azido alcohols, azido phenols, and azido ethers		
2-Azidoethanol	$N_3CH_2CH_2OH$	A	86	(152)
o-Azidophenol	$N_3C_6H_4OH$	E	52	(147)
m-Azidophenol	$N_3C_6H_4OH$	E		(147)
p-Azidophenol	$N_3C_6H_4OH$	E	38	(147)
2-Azido-2-phenylethanol	$C_6H_5CHN_3CH_2OH$	A	63	(270)
5-Acetyl-2-methoxyphenyl azide		C	75	(45)
Azidoacetone	$N_3CH_2COCH_3$	A	83	(148)
p-Azidobenzaldehyde	$N_3C_6H_4CHO$	G	48	(145, 156)
3-Azido-2-butanone	$CH_3COCHN_3CH_3$	A	Quantitative	(149)

TABLE 1—*Continued*

NAME	FORMULA	METHOD*	YIELD	REFERENCES
	Azido alcohols, azido phenols, and azido ethers—*Continued*			
			per cent	
α-Azidocyclohexanone		A		(148)
ω-Azidogallacetophenone		A	50	(30)
4-Azidophenanthrenequinone		C		(57, 60)
	Azido acids and esters			
m-Azidobenzoic acid	$N_3C_6H_4COOH$	C	72	(16, 28)
o-, *m*-, and *p*-Azidocinnamic acid	$N_3C_6H_4CH{=}CHCOOH$	G		(326)
α-Azidoisobutyric acid	$(CH_3)_2CN_3COOH$	A	77	(158)
α-Azidoisovaleric acid	$(CH_3)_2CHCHN_3COOH$	H	70	(108)
N-Cyanomethyl-α-azidoacetamide	$N_3CH_2CONHCH_2CN$	A	65	(172)
Ethyl α-azidoacetate	$N_3CH_2COOC_2H_5$	A	90	(148)

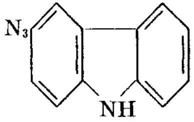
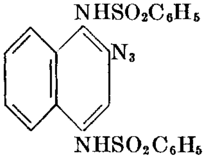
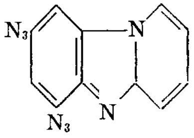
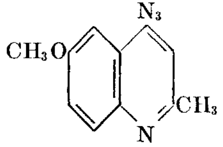
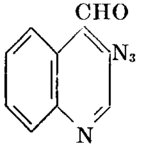
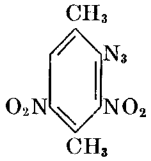
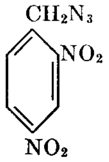
Ethyl γ-azidobutyrate	$N_3(CH_2)_3COOC_2H_5$	A	75	(94)
Ethyl α-azidohydrocinnamate	$C_6H_5CH_2CHN_3COOC_2H_5$	H	50	(107, 110)
Ethyl α-azidopropionate	$CH_3CHN_3COOC_2H_5$	A	Quantitative	(149)
Ethyl α,α-diazidoacetate	$(N_3)_2CHCOOC_2H_5$	A	15	(153)
Ethyl α-azidoaceto-α-methylacetate	$CH_3COCN_3(CH_3)COOC_2H_5$	A	34	(162)
Ethyl α-azido-α-methylmalonate	$CH_3CN_3(COOC_2H_5)_2$	A	12	(160)
Ethyl α-azido-α-phenylacetate	$C_6H_5CHN_3COOC_2H_5$	A	84	(52)
		H		(110)
Azido amines and derivatives				
8-Azidocarbazole		G	Quantitative	(281)
β-Azidoethylamine	$N_3CH_2CH_2NH_2$	A	40	(165)
γ-Azidopropylamine	$N_3CH_2CH_2CH_2NH_2$	A	90	(169)
2-Azido-1,4-naphthalenedibenzenesulfonamide		B	94	(1)
4,6-Diazidopyrido-(1,2-1′,2′)benzimidazole		G		(283)

TABLE 1—*Continued*

NAME	FORMULA	METHOD*	YIELD	REFERENCES
Azido amines and derivatives—*Continued*				
4-Azido-6-methoxy-2-methylquinoline		H	*per cent* 70	(234)
3-Azidoquinoline-4-aldehyde		Nitrous acid and 3-aminolepidine	Quantitative	(295a)
Azido nitro compounds				
2-Azido-1,4-dimethyl-3,5-dinitrobenzene		C	88	(183)
2,4-Dinitrobenzyl azide		G		(416)

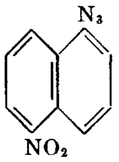
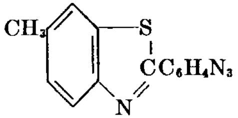
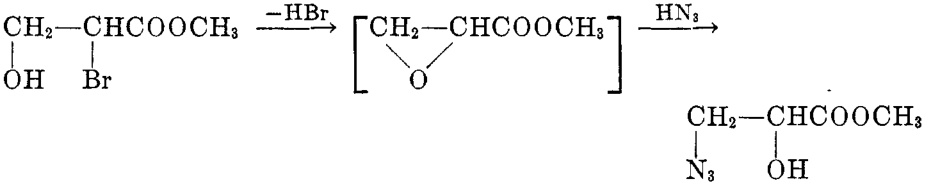
2,4-Dinitrophenyl azide	$(O_2N)_2C_6H_3N_3$	C		(419)
		H		(322)
2-Azido-3,5-dinitrotoluene	$(O_2N)_2(N_3)C_6H_2CH_3$	C		(422)
1-Azido-5-nitronaphthalene		E, G		(147, 388)
o-Nitrophenyl azide	$O_2NC_6H_4N_3$	E	31	(217)
m-Nitrophenyl azide	$O_2NC_6H_4N_3$	E	71	(217)
p-Nitrophenyl azide	$O_2NC_6H_4N_3$	D	Quantitative	(80)
		E	44	(217)
		H	27	(263)
		J		(104)
		Miscellaneous		
Azidoacetonitrile	N_3CH_2CN	A	64	(172)
p-Azidoazobenzene	$N_3C_6H_4N{=}NC_6H_5$	C		(197, 392, 393, 421)
m-Azidobenzenesulfonic acid	$N_3C_6H_4SO_3H$	D, H		(259)
p-Azidobenzenesulfonamide	$N_3C_6H_4SO_2NH_2$	F		(64)
ω-Azidocapronitrile	$N_3(CH_2)_5CN$	A	90	(202)
o-, *m*-, and *p*-Azidoiodoxybenzene	$N_3C_6H_4IO_2$	A		(168)
Azidomethyl isocyanate	N_3CH_2NCO	A		(161)
Dipentene nitrosoazide	$C_{10}H_{15}({=}NOH)N_3$	A	80	(155)
p-Azidophenylarsonic acid	$N_3C_6H_4AsO_3H_2$	G	89	(222, 223)
2-(*p*-Azidophenyl)-6-methylbenzthiazole		G		(284)

TABLE 1—*Concluded*

NAME	FORMULA	METHOD*	YIELD	REFERENCES
Miscellaneous—*Continued*				
			per cent	
4,4′-Diazidodiphenyl sulfide	$(N_3C_6H_4)_2S$	F		(64)
4,4′-Diazidodiphenyl sulfone	$(N_3C_6H_4)_2SO_2$	D	70	(29)
α-Azido-α-(3,4-dimethoxyphenyl)acetamide	$H_2NCOCHN_3C_6H_3(OCH_3)_2$	A	77	(206)

* A: Displacement of halo, sulfate, nitrate, and alkoxy (ethylene oxide type) groups.
B: Addition of hydrogen azide to an olefin (may be followed by rearrangement).
C: Diazo compound and ammonia.
D: Diazo compound and (a) hydrazine.
E: Diazo compound and (a) hydroxylamine.
F: Diazo compound and sulfonamides.
G: Diazo compound and hydrazoic acid.
H: Monosubstituted hydrazines and nitrous acid.
I: Oxidation of monoaryl hydrazines.
J: Molecular rearrangement.

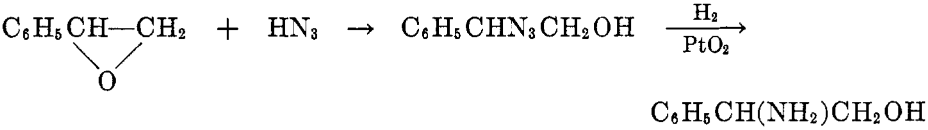
Levene and Schormiller have suggested the formation of an intermediate ethylene oxide ring and subsequent ring-opening by hydrazoic acid (256).



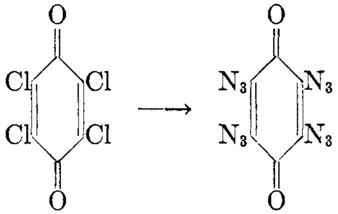
A few years earlier a similar exchange had been demonstrated in the formation of β-azido-α-hydroxyhydrocinnamic acid from α-chloro-β-hydroxyhydrocinnamic acid. The correct structure was established by Oesterlin by identification of the

$$C_6H_5CHOHCHClCOOH \rightarrow C_6H_5CHN_3CHOHCOOH$$

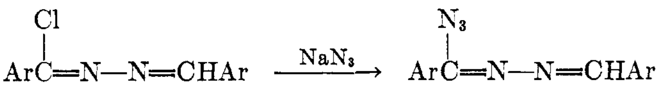
reduction product as phenylisoserine, $C_6H_5CH(NH_2)CHOHCOOH$ (166, 167, 297). In agreement with these observations styrene oxide and hydrazoic acid were found to bring about the formation of β-azido-β-phenylethanol, as shown by hydrogenolysis to β-amino-β-phenylethanol (270).



Displacement of halogen in vinyl halides in general fails to occur. Vinyl azide was prepared by the dehydrohalogenation of 1-azido-2-iodoethane (163, 165). If, however, the halogen is also attached to a carbon atom adjacent to a carbonyl group, displacement may occur. Through stepwise replacements 2,3,5,6-tetraazidobenzoquinone was obtained from the corresponding tetrachloride (184, 365). Halo (321, 340), nitro, and phenylazo (54, 273) groups in positions activated by nitro groups have been displaced by the azido group.



Replacement of halogen activated by the azomethine linkage may be accompanied by ring-closure to the isomeric tetrazole; occasionally the intermediate azide may be isolated (375, 376). The azomethine linkage in nitrogen hetero-

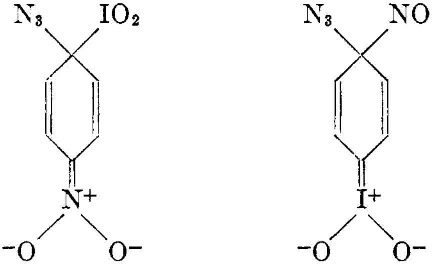


$$\mathrm{Ar}\overset{\overset{\mathrm{Cl}}{|}}{\mathrm{C}}{=}\mathrm{N}{-}\mathrm{N}{=}\mathrm{CHAr} \xrightarrow{\mathrm{NaN_3}} \mathrm{Ar}\overset{\overset{\mathrm{N_3}}{|}}{\mathrm{C}}{=}\mathrm{N}{-}\mathrm{N}{=}\mathrm{CHAr}$$

AR = o-$CH_3OC_6H_4$.

cycles also gives rise to an active halogen which may be replaced. The reaction of α-bromopyridine with hydrazoic acid affords good yields of pyridotetrazole (see table 3) (62).

In an interesting study of the displacement reaction the iodoxy group, but not the nitro group, in *p*-nitroiodoxybenzene was replaced by the azido group (398, 399). In an explanation for this observation it was pointed out that the transition state with the lower energy does not involve a carbon–iodine double bond (49).

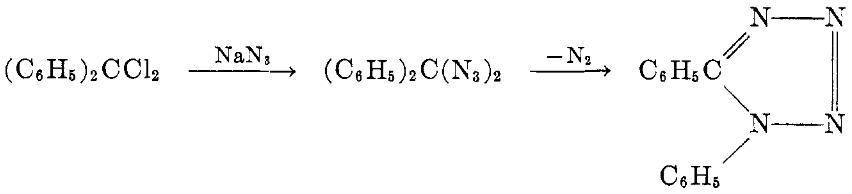


Replacement of the hydroxyl group by the azido group in the presence of strong acid may have generality; however, only one azide prepared by this method has so far been resistant to the acid-catalyzed decomposition of the azido group. Triphenylmethyl azide was obtained from triphenylcarbinol and sodium azide in the presence of perchloric acid or sulfuric acid (13, 258).

$$(C_6H_5)_3COH + NaN_3 \xrightarrow[\text{or } HClO_4]{H_2SO_4} (C_6H_5)_3CN_3$$

Triphenylmethyl azide

Displacement of more than one halogen attached to a carbon atom has also been observed. Schroeter in 1909 found that dichlorodiphenylmethane and silver azide brought about the formation of diazidodiphenylmethane, which underwent the loss of nitrogen, rearrangement, and ring-closure to form a



tetrazole (189, 342). In a similar manner 5-azido-1-phenyltetrazole was formed from the reaction between $C_6H_5N{=}CCl_2$ and sodium azide (312). A stable diazido compound from dichloromalonic ester was reported, whereas diazidoacetic ester slowly decomposed (160).

Compounds with more than two azido groups attached to the same carbon atom, as well as compounds in which the azido group is attached to an acetylenic carbon, have not been reported.

2. *Addition of hydrazoic acid to olefins*

The formation of alkyl azides by the acid-catalyzed addition of hydrazoic acid to an isolated carbon–carbon double bond was recently reported (336), whereas previous attempts had met with failure (304). Conjugation with a carbonyl group, a nitro group, or an azomethine linkage allowed addition to occur more readily. Oliveri-Mandala was the first to recognize this reaction in the formation of 2,5-dihydroxyphenyl azide from benzoquinone and hydrazoic acid (133, 298, 303). A similar addition to quinonimines was more recently observed (1).

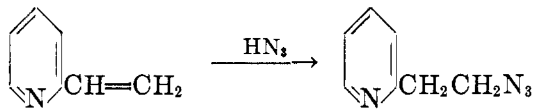
The reaction is fairly general for α,β-unsaturated carbonyl compounds; however, a phenyl group in the 4-position did not allow a reaction to occur. The addition of hydrogen azide to nitrostyrene, on the other hand, was highly exothermic (50). β-(α-Pyridyl)ethyl azide resulted from the combination of hydrazoic acid and α-vinylpyridine in the presence (404) or absence (50) of concentrated sulfuric acid.

$$\mathrm{CH_2{=}CHCHO} \xrightarrow{\mathrm{HN_3}} \mathrm{N_3CH_2CH_2CHO}$$

$$\mathrm{C_6H_5CH{=}CHCHO} \xrightarrow{\mathrm{HN_3}} \text{no reaction}$$

$$\mathrm{C_6H_5CH{=}CHNO_2} \xrightarrow[0^\circ\mathrm{C.}]{\mathrm{HN_3}} \mathrm{C_6H_5CHN_3CH_2NO_2}$$

Nitrostyrene



α-Vinylpyridine β-(α-Pyridyl)ethyl azide

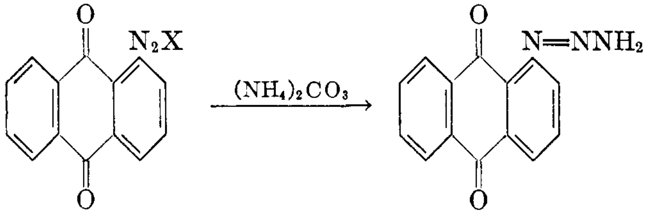
Vinyl azides have not been prepared by the addition of hydrogen azide to an acetylenic linkage. Instead, addition of the azido group brings about the formation of triazoles (page 43). That vinyl azide is not an intermediate in the synthesis of triazole from acetylene and hydrazoic acid was indicated by heating an ethanolic solution of vinyl azide at 100°C. for 12 hr. The azide was recovered, and no triazole was detected (163). The reaction conditions were not, however, strictly comparable, since traces of hydrochloric acid were also present in the synthesis of triazole (123).

B. STEPWISE INTRODUCTION OF THE THREE AZIDO NITROGEN ATOMS

1. *Diazo compounds and ammonia*

Investigations on his recently discovered aromatic diazonium compounds led Peter Griess in 1864 to the preparation of phenyl azide through the action of ammonia upon benzenediazonium perbromide (192, 193, 194, 195). During the following quarter of a century the azido group received little attention in the laboratory. It was just prior to the discovery of hydrogen azide that the preparations and properties of organic azides were beginning to attract the interest of several research groups. Variations on Griess's original method were reported. It was found that hydrazine, hydroxylamine, sulfonamides, chloramine, and hydrazoic acid also reacted with both aromatic and aliphatic diazonium groups to bring about the formation of the azido group.

Griess's original synthesis for phenyl azide is general for nearly all diazonium perhalides, even the tetrachloroiodides, ArN_2ICl_4, and the plumbichlorides, ArN_2PbCl_6 (73). Reaction failures have been reported for the perbromides of diazotized *o*-aminobenzaldehyde (21), α-aminopyridine (52), and 5-dimethylamino-2-hydroxy-3-nitroaniline (272). Certain discrepancies in melting point and volatility with steam are recorded for 2,4,5-tribromophenyl azide as prepared by the action of ammonia upon the corresponding diazonium perbromide (355), with that prepared by the action of hydroxylamine upon the corresponding diazonium chloride (147). The diazonium perbromides were obtained from either the diazonium bromide or the corresponding hydrazine (198, 277, 293, 354). With his observation that chloramine also condensed with aromatic diazonium salts to form azides, Forster suggested that the initial reaction is the halogenation of ammonia by the perhalide (143). It appears more likely, however, that an intermediate triazene is involved. In the absence of halogen, diazotized 1-aminoanthraquinone reacted with ammonia to form the corresponding triazene (400). The facile oxidation of aryltriazenes to aryl azides by hypochlorite solution has been reported (118). Griess observed that the substitution of primary and secondary amines for ammonia led to the formation of substituted triazenes (192).



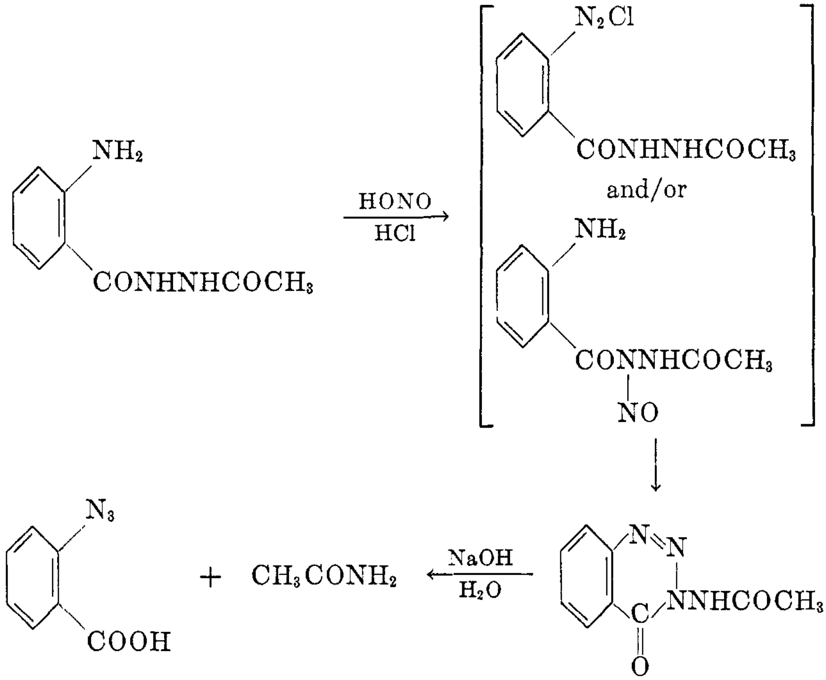
$$C_6H_5N_2X\cdot X_2 \xrightarrow{RNH_2} C_6H_5N{=}NNHR$$

2. *Diazo compounds and hydrazine*

The condensation between benzenediazonium chloride and hydrazine, with the resulting formation of phenyl azide, was initially observed by Emil Fischer (138) and later studied in more detail by Curtius (80) and by Wohl (409). An unstable intermediate condensation product was found to undergo decomposition by two different paths, one of which gave the predominant products, phenyl azide and ammonia, in better than 90 per cent yield. The alternate decomposition led to aniline and hydrogen azide in 10 per cent yield.

$$\begin{array}{ccc} C_6H_5N{=}NNHNH_2 & \rightleftharpoons & C_6H_5NHN{=}NNH_2 \\ \downarrow & & \downarrow \\ C_6H_5N_3 + NH_3 & & C_6H_5NH_2 + HN_3 \end{array}$$

In the use of substituted hydrazines or hydrazides, a molecule of an amine or amide was produced along with the azide. Thus, phenyl azide and aniline were formed by mixing phenylhydrazine and benzenediazonium chloride (138) or benzenediazonium perbromide (296). In a similar manner, phenyl azide was obtained from hippuryl hydrazide or benzoyl hydrazide and benzenediazonium bisulfate (80). In these cases hippurylamide and benzamide, respectively, were also formed. Diazotization of the amino group or nitrosation of the hydrazide of anthranilic acid apparently was followed by ring-closure and then reopening upon hydrolysis to *o*-azidobenzoic acid (215). Aryl azides were also prepared from the corresponding diazonium salt and benzene-ψ-semicarbazinocamphor (141). Diazotized aminosulfonic acids with phenylhydrazine afforded good yields of the corresponding azidosulfonic acids (200). As would be expected, four different products were obtained from a substituted benzenediazonium salt and phenylhydrazine or from a substituted phenylhydrazine and benzenediazonium chloride (196). Reduction of aryldiazonium salts under conditions which allowed the intermediate formation of the arylhydrazine also resulted in the formation of the corresponding azides (78, 190, 390).



$$\left.\begin{array}{c} m\text{-}HOOCC_6H_4N_2Cl + C_6H_5N_2H_3 \\ \text{or} \\ m\text{-}HOOCC_6H_4N_2H_3 + C_6H_5N_2Cl \end{array}\right] \longrightarrow \begin{array}{r} m\text{-}HOOCC_6H_4N_3 + m\text{-}HOOCC_6H_4NH_2 \\ + C_6H_5N_3 + C_6H_5NH_2 \end{array}$$

In a somewhat similar situation it was suggested that reduction of 1,3-diphenyltriazene by zinc in sulfuric acid involved initial hydrolysis to benzenediazonium sulfate and aniline sulfate. Reduction of the diazonium salt, followed by condensation between the correspnoding hydrazine and unreduced diazonium salt, then accounted for the formation of phenyl azide (170).

The use of hydrazones has also been reported. From *p*-nitrobenzenediazonium chloride and the benzoylhydrazone of pyruvic acid, *p*-nitrophenyl azide and benzamide were obtained (311). Release of pyruvic acid from its benzoylhydrazone by the action of benzenediazonium chloride (311) also indicated a tetrazene (I) as a probable intermediate. A similar tetrazene (II) structure may describe the product $C_{12}H_{12}N_4$, m.p. 71°C., obtained from phenylhydrazine

$$\underset{\text{I}}{C_6H_5N{=}NNHNHCOC_6H_5} \qquad \underset{\text{II}}{C_6H_5N{=}NNHNHC_6H_5}$$

acetate and benzenediazonium acetate in acetic acid (407).

Condensation between hydrazine and aliphatic diazo compounds may lead to the formation of an azide; e.g., the hydrazide of azidoacetic acid was obtained from either diazoacetamide or diazoacetic ester (88). In the presence of hydrazine, secondary amides of α-diazo acids, however, yielded derivatives of 5-triazolone-1-acetic acid instead of the azide (page 46) (102a).

$$N_2{=}CHCOR \xrightarrow{N_2H_4} N_3CH_2CON_2H_3 + RH$$

R = NH_2, OC_2H_5.

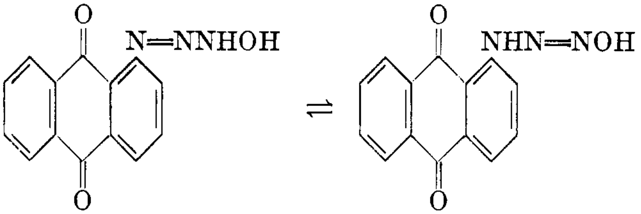
3. Diazo compounds and hydroxylamine

Emil Fischer observed that the reaction of hydroxylamine with benzenediazonium salts led to the formation of phenyl azide (138). Later Mai discovered that phenyl azide was produced by the action of benzaldoxime upon benzenediazonium chloride (265). Further experiments (63) showed that intermediate condensation products involving one or two molecules of the oxime were involved and that these intermediates from hydroxylamine or the oximes could be broken up to give either amines and nitrous oxide or azides and water (267).

That the condensation reaction may involve a nitrogen–hydrogen bond in hydroxylamine was illustrated by the formation of *p*-nitrophenyl azide from the corresponding diazonium acetate and O-benzylhydroxylamine (27). Curiously

$$p\text{-}O_2NC_6H_4N_2OCOCH_3 + C_6H_5CH_2ONH_2 \longrightarrow p\text{-}O_2NC_6H_4N_3 + C_6H_5CH_2OH + N_2O$$

enough, *p*-nitroaniline was not also reported as a product. It would appear that the intermediate which underwent decomposition with the formation of an azide had a triazene structure. These observations are in agreement with the isolation of a stable condensation product from diazotized 1-aminoanthraquinone and hydroxylamine (186, 400) from which only 1-azidoanthraquinone was reported as a product (186).

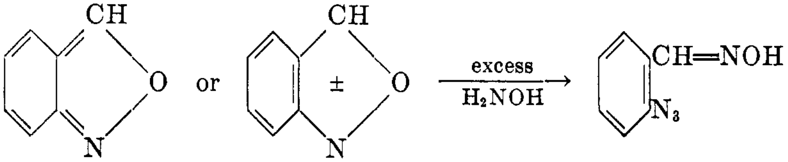


An interesting synthesis of *p*-anilinophenyl azide from *p*-anilinonitrosobenzene and hydroxylamine involved initial diazotization of the nitroso group (12). In the

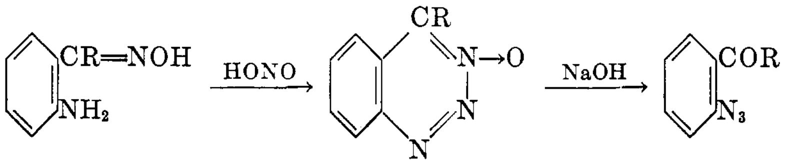
$$p\text{-}C_6H_5NHC_6H_4NO \xrightarrow{H_2NOH} p\text{-}C_6H_5NHC_6H_4N_2OH \xrightarrow{H_2NOH} p\text{-}C_6H_5NHC_6H_4N_3$$

p-Anilinophenyl azide

transformation of phenylhydroxylamine to phenyl azide by the action of hydroxylamine (17), the probable intermediate formation of a diazonium compound may have resulted from the oxidation of phenylhydroxylamine to nitrosobenzene, followed by diazotization. It is more difficult, however, to understand the transformation of anthranil into *o*-azidobenzaldoxime by the action of hydroxylamine (24); however, a diazonium intermediate is not inconceivable.

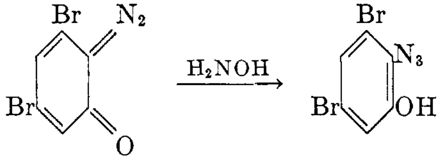


A related situation consists in the transformation of *o*-aminobenzaldoxime and derivatives into the corresponding azido carbonyl compounds by diazotization followed by a base-catalyzed rearrangement (22, 271, 380). Careful hydrolysis of the cyclic intermediate allowed the isolation of a hydroxytriazene, which upon long standing underwent dehydration to the azide. Nitrosation of 3-aminolepidine brought about the formation of 3-azidoquinoline-4-aldehyde in quantitative yield. An explanation of this transformation assumed the initial formation of the corresponding diazotized *o*-aminoaldoxime, which then underwent the expected cyclization and rearrangement (295a).



R = H, CH_3, C_6H_5.

That aliphatic diazo compounds will react with hydroxylamine has not been established; however, this possible synthesis for aliphatic azides is suggested by the preparation of 4,6-dibromo-2-hydroxyphenyl azide from the anhydride of diazotized 4,6-dibromo-2-hydroxyaniline and hydroxylamine (305).



4,6-Dibromo-
2-hydroxyphenyl azide

4. Diazo compounds and sulfonamides; sulfonyl azides and Grignard reagents

Methyl-, benzyl- and *p*-toluenesulfonamides have entered into condensation with aromatic diazonium salts (64, 132, 229, 356). Decomposition of the intermediate triazene led to the formation of the corresponding sulfinic acid and an aromatic azide. Combinations of ammonia or chloramine-T with diazonium salts have also been used.

A related reaction involves alkaline decomposition of a substituted triazene obtained from the addition of an aryl Grignard reagent to an aromatic sulfonyl azide. The overall process allows conversion of an aromatic halide into the corresponding azide in good yield (364).

5. Diazo compounds and hydrazoic acid

Direct replacement of the diazonium group by the azido group, first accomplished by Noelting and Michel (295), may be used in all cases in which the corresponding primary amine may be diazotized (279, 326). Upon addition, with stirring, of an aqueous solution of sodium azide to an aqueous acid solution of the diazotized amine, there is separation of the azide as an oil or solid accompanied by a mild evolution of nitrogen. The yields are often quantitative (see table 1).

Although it is not customary to isolate an intermediate diazonium azide, it is of interest that these compounds have been obtained (208, 278). *p*-Nitrobenzenediazonium azide was similarly prepared and found to decompose at 116°C. Morgan and Webster claimed that a *syn*-diazonium azide decomposes into nitrogen and the aryl azide, whereas the corresponding *anti*-modification upon

$$p\text{-}RC_6H_4N_2OH \xrightarrow{N_3COOC_2H_5} p\text{-}RC_6H_4N_2N_3$$

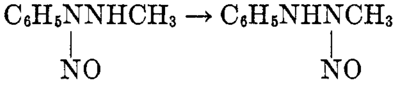
$R = NO_2, C_6H_5CO.$

formation from the aqueous solution of the diazonium chloride immediately decomposes into aniline, nitrogen, and nitrous oxide (284).

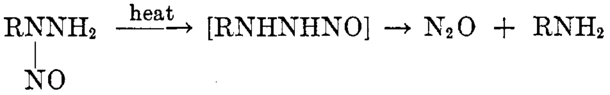
Apparently the only investigation of the action of hydrazoic acid upon aliphatic diazo compounds involved the preparation of methyl azide from diazomethane and this reagent (302).

6. Monosubstituted hydrazines and nitrous acid

Nitroso compounds are obtained from nitrous acid and either aryl- or alkylhydrazines. Upon treatment with acids or alkalis, dehydration with the formation of azides occurs (75, 82, 84, 97, 100, 102, 139, 140, 234, 259, 408). The reaction, discovered by E. Fischer, may involve migration of the nitroso group to the terminal nitrogen. A similar rearrangement was demonstrated for the isomerization of *N*′-methyl-*N*-nitroso-*N*-phenylhydrazine (11) and was suggested to account for the formation of a primary amine and nitrous oxide upon pyrolysis of nitroso derivatives of hydrazines (11, 108, 386) (page 15). Nitrosyl chloride has been substituted for nitrous acid; in this case the azide was obtained directly (391).

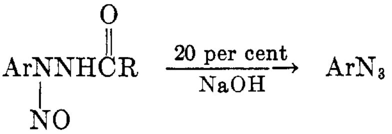


$$C_6H_5\underset{\displaystyle NO}{N}NHCH_3 \rightarrow C_6H_5NH\underset{\displaystyle NO}{N}CH_3$$



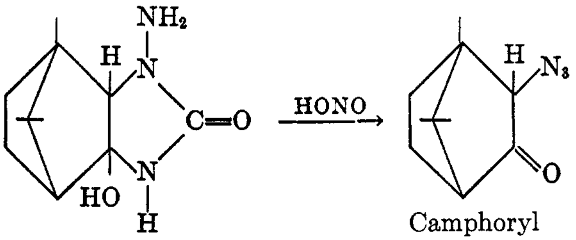
$$R\underset{\displaystyle NO}{N}NH_2 \xrightarrow{\text{heat}} [RNHNHNO] \rightarrow N_2O + RNH_2$$

This method has been used to prepare the enantiomorphs of ethyl α-azido-α-phenylacetate from the corresponding optically active forms of the nitroso derivative of ethyl α-hydrazino-α-phenylacetate (106, 109). A modification of the method consisted in treating the nitroso derivative of an aryl hydrazide with dilute alkali (263, 319). A similar reaction was reported for certain alkylated semicarbazides. Forster and Fierz thus obtained camphoryl azide from camphoryl ψ-semicarbazide (146).



$$Ar\underset{\displaystyle NO}{N}NH\overset{\displaystyle O}{\overset{\|}{C}}R \xrightarrow[\text{NaOH}]{\text{20 per cent}} ArN_3$$

R = H, CH_3, but not C_6H_5.



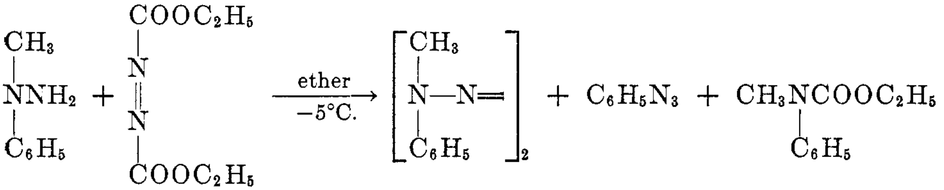
Camphoryl azide

Little work has been done on the reaction between organic nitrites and hydrazines. Stolle reported that diazonium salts were obtained from phenylhydrazine and ethyl nitrite in the presence of sodium ethoxide, whereas benzyl-hydrazine under similar conditions was transformed into dibenzylhydrazine along with the formation of sodium azide (369).

7. *Oxidation of arylhydrazines*

Aryl azides have also been obtained by the gentle oxidation of monoarylhydrazines (138); e.g., phenyl azide resulted from the oxidation of phenylhydrazine by mercuric oxide or iodine in potassium hydroxide. The use of hydrogen peroxide has also been reported (415). It was suggested that symmetrical tetrazenes, ArNHN=NNHAr, were the initial products which decomposed into the azide and amine (351).

Demethylation and dehydrogenation of *N*-methyl-*N*-phenylhydrazine by ethyl azoformate resulted in a mixture of ethyl *N*-methyl-*N*-phenylcarbamate, 1,4-dimethyl-1,4-diphenyltetrazene, and phenyl azide (112).



$$\begin{array}{c} CH_3 \\ | \\ NNH_2 \\ | \\ C_6H_5 \end{array} + \begin{array}{c} COOC_2H_5 \\ | \\ N \\ \| \\ N \\ | \\ COOC_2H_5 \end{array} \xrightarrow[-5^\circ C.]{ether} \left[\begin{array}{l} CH_3 \\ | \\ N{-}N{=} \\ | \\ C_6H_5 \end{array}\right]_2 + C_6H_5N_3 + \begin{array}{c} CH_3NCOOC_2H_5 \\ | \\ C_6H_5 \end{array}$$

Phenyl azide Ethyl *N*-methyl-*N*-phenylcarbamate

C. REARRANGEMENTS (CARBON TO NITROGEN)

Rearrangements of unstable intermediates which have been postulated for a number of the syntheses already discussed have involved migration of groups from one nitrogen to another. Migration from carbon to nitrogen may also occur.

Aryl semicarbazides were oxidized by hypochlorite to azo compounds, which upon further action by hypochlorite underwent the Hofmann reaction. The expected product, an aryltriazene, was immediately oxidized to an aryl azide (104, 105). Azides were not obtained from benzyl and benzoyl semicarbazides by similar treatment.

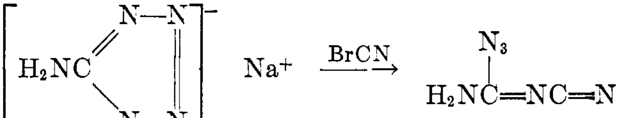
$$ArNHNHCONH_2 \xrightarrow{NaOCl} ArN{=}NCONH_2 \xrightarrow{NaOCl} ArN{=}NNH_2 \xrightarrow{NaOCl} ArN_3$$

Transformation of aryl diazohydroxamic acids in the presence of sodium hydroxide into aryl azides was reported by Ponzio (318). Presumably the oxidizing agent in this case was atmospheric oxygen.

$$ArN{=}NCONHOH \xrightarrow{NaOH} ArN_3$$

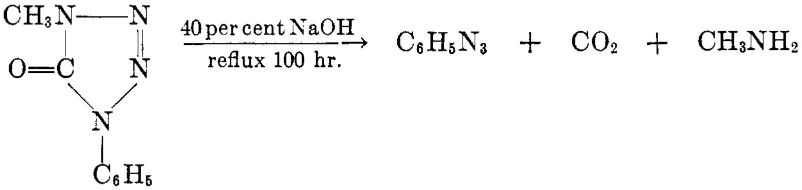
D. AZIDES FROM TETRAZOLES AND DIHYDROTETRAZOLES

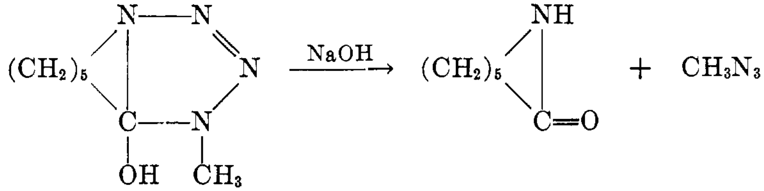
The opening of a tetrazole ring to form an azide was first reported by Hart (211). By the action of cyanogen bromide upon the sodium salt of 5-amino-tetrazole he obtained *N*-cyanoazidoformamidine, presumably *via* the intermediate, 5-amino-1-cyanotetrazole.



N-Cyanoazidoformamidine

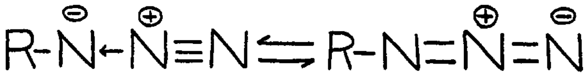
Basic cleavage of 4,5-dihydro-5-keto-4-methyl-1-phenyltetrazole was observed to bring about the formation of phenyl azide and methylamine (377). It is of interest to note that the alternate cleavage leading to methyl azide and aniline apparently failed to occur. Information given by K. Schmidt in a footnote of the above report (377) described the formation of methyl azide by the action of sodium hydroxide on the pseudo-base obtained from the methiodide of cardiazole.



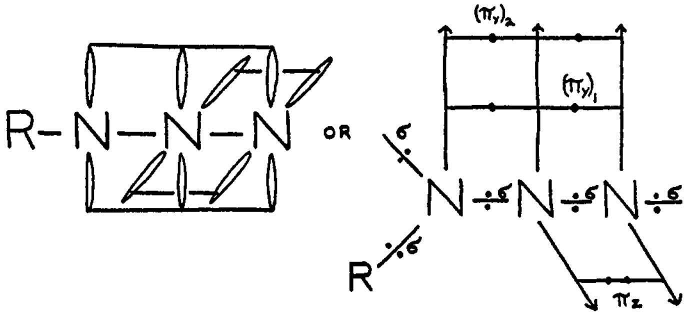


III. STRUCTURE AND PHYSICAL PROPERTIES OF AZIDES

A linear structure for the azido group which is in agreement with its known chemical and physical properties was finally established by electron diffraction data on methyl azide (67) and by x-ray analysis of cyanuryl azide (55, 220, 232, 233, 382). Earlier work by Carothers demonstrated the isosteric relationship between phenyl azide and phenyl isocyanate (72). Interpretation of parachor values and dipole moment studies (34, 35, 188, 261, 334, 379, 381) also indicated a resonance-hybrid linear structure as suggested by Brockway and Pauling (67, 310). Recently phenyl azide containing terminal N^{15} was prepared from phenylhydrazine and nitrous acid containing N^{15}. A study of the reduction products of 1,3-diphenyltriazene obtained from the azide and phenylmagnesium bromide was in agreement with the linear structure (76). A revision of the classical representation of the resonance hybrid describes the overlapping of p atomic orbitals of all three nitrogen atoms which gives rise to π-type molecular orbitals.



$$R-\overset{\ominus}{N}\leftarrow\overset{\oplus}{N}\equiv N \rightleftharpoons R-N=\overset{\oplus}{N}=\overset{\ominus}{N}$$



(46)

Calculations according to the method of molecular orbitals indicated that in covalent azides, e.g., methyl azide, the nitrogen atoms have charges of −0.37, 0.52, and −0.15, respectively (46). Bond distances between the nitrogen atoms calculated by the electron diffraction method (67, 310) are 1.24 Å. and 1.10 Å., respectively, and are in close agreement with 1.25 and 1.12 Å., which are the values obtained by the molecular orbital method (46), and with 1.22 and 1.10 Å., which were obtained from considerations of dipole moment data (334). Interpretations of electron diffraction studies on methyl azide (67, 310) suggested a C—N—N bond angle of 120°, in agreement with interpretation of absorption spectra (44). From heats of combustion for phenyl azide and ethyl azidoacetate the heat of formation of the azido group is known to be 205–208 kg.-cal. (332). The approximate heat of formation calculated for the linear resonance hybrid is about 20 kg.-cal. smaller. This difference may represent the stability gained from resonance or delocalization of π-electrons. From force–area and potential–area measurements on monolayers of α-azidopalmitic acid it was concluded that in water solution the azido group assumes the structure represented by $R—N\leftarrow N_2$ (9).

An approximate comparison of the cross-sections of the methyl group, the bromine atom, and the azido group on the basis of the known parachors of compounds containing these groups indicates that the azido group is about 25 per cent larger than the methyl group and 9 per cent larger than the bromine atom (9). In other studies close similarities between the physical properties of organic azides and the corresponding organic bromides were revealed in their boiling points (350), their molecular refractivities (68, 314), their refractive dispersion values (314), their molecular coefficients of magnetic rotation (313), and the acid strengths of α-substituted acetic and propionic acids (148, 149, 207, 314) (table 2).

Other optical properties of azides which have been observed include rotatory dispersion and non-anisotropic absorption in the ultraviolet region at 2900 Å. (240, 251, 347). Raman lines for several alkyl azides have been tabulated; two characteristic frequencies for the azido group are (*s*) 1177–1343 cm.$^{-1}$ and (*as*) 2080–2169 cm.$^{-1}$ (246, 348). These are also characteristic strong absorption bands for the azido group; however, the latter is of far more value for characterization purposes and has been ascribed to the stretching vibration of the $-N \equiv N$ bond (352). A strong absorption band at 1.0 μ has been observed for methyl azide (44).

The difference between the absorption coefficients of *N*,*N*-dimethyl-α-azidopropionamide for dextro- and levo-circularly polarized light of 2900 Å. is around 2–3 per cent and the energy absorbed brings about decomposition with the evolution of nitrogen. A hexane solution of the racemic amide upon decomposition to the extent of 40 per cent by dextro- and levo-circularly polarized light gave corresponding rotations of 0.78° and $-1.04°$. Although the products were not isolated and identified, the results demonstrated the possibility of asymmetric decomposition by means of dextro- and levo-circularly polarized light. It was determined that one molecule of azide was decomposed per quantum of light absorbed (240, 241).

TABLE 2

Dissociation constants (26°C.) for substituted acetic and propionic acids

ACID	$K_a \times 10^3$	ACID	$K_a \times 10^3$
CH_3COOH	0.018	CH_3CH_2COOH	0.014
CH_2ICOOH	0.75	$CH_3CHICOOH$	0.62
CH_2N_3COOH	0.93	CH_3CHN_3COOH	0.9
$CH_2BrCOOH$	1.38	$CH_3CHBrCOOH$	1.1
$CH_2ClCOOH$	1.55	$CH_3CHClCOOH$	1.5

The configurational relationship of *l*-iodo- and *d*-azidopropionic acids (151) was established by demonstrating that the partial rotation of the carboxyl group in both cases is dextrorotatory and that the partial rotations of the iodine atom and of the azido group are both levorotatory (239). *d*-Azidopropionic acid is also correlated with *l*-alanine (250) and *l*-lactic acid. Attempts to correlate configurations in the series $CH_3CHR(CH_2)_nN_3$ by a comparison of rotatory phenomena were partially successful only for $n > 0$ (252).

The molecular structure of those heterocyclic azides which bear formal resemblance to the azidoalkylidenimines by possessing the structural unit $N_3-\overset{|}{C}=N-$ is of interest. In linear systems irreversible isomerization to a tetrazole occurs (259, 275). Eight examples in which the azomethine linkage is a portion of a five-membered heterocycle are known to exist as azides. Whereas there is no known example in which the isomerization to a tetrazole involves the azomethine link of a five-membered heterocycle, the analogous six-membered heterocyclic monoazides exist only as the isomeric tetrazoles (table 3). Curiously enough, six-membered heterocyclic diazides of this type may exist with one free azido group and one tetrazole system. The three azidoazomethine units in cyanuryl azide have no tendency for tetrazole formation nor has either of the two such units in 6-amino-2,4-diazido-*sym*-triazine.

TABLE 3

Heterocyclic azides which have the azidoazomethine group

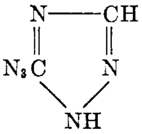
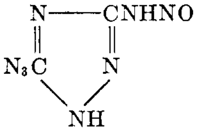
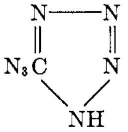
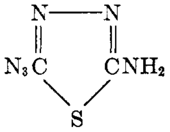
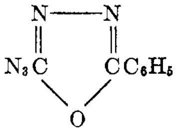
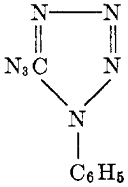
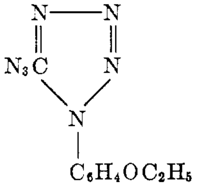
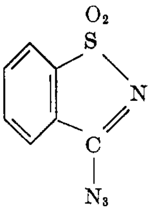
NAME	FORMULA	REFERENCES
5-Azido-1,2,4-triazole		(266)
5-Azido-3-nitrosoamino-1,2,4-triazole		(370)
Azidotetrazole		(182, 218, 257, 387)
5-Amino-2-azido-1,3,4-thiazole		(372)
2-Azido-5-phenyl-1,3,4-oxadiazole		(372)
5-Azido-1-phenyltetrazole		(312, 371)
5-Azido-1-*p*-phenetyltetrazole		(371)
3-Azido-1,1-dioxo-4,5-benzthiazole-1,2		(341)

TABLE 3—*Continued*

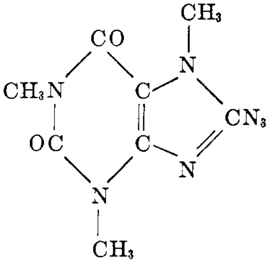
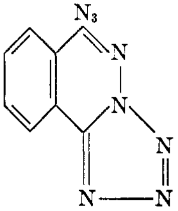
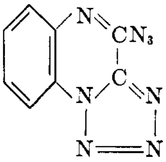
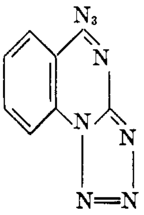
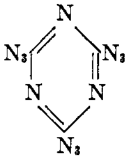
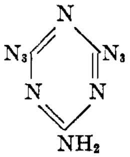
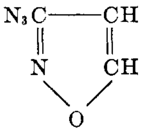
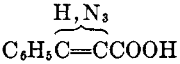
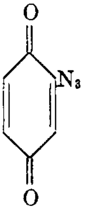
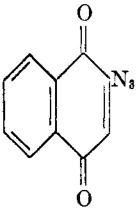
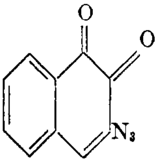
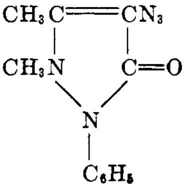
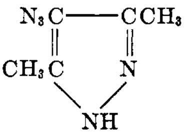
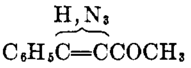
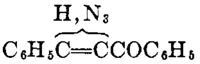
NAME	FORMULA	REFERENCES
8-Azidocaffeine		(77)
5-Azidotetrazole[*a*]phthalazine		(378)
4-Azidotetrazolo[*a*]quinoxaline		(373, 374)
5-Azidotetrazolo[*a*]quinazoline		(374)
Cyanuryl azide		(137, 308)
6-Amino-2,4-diazido-*sym*-triazine		(211)
3-Azidoisoxazole		(323)

TABLE 4

Compounds containing the azidoölefinic group

NAME	FORMULA	REFERENCES
Vinyl azide	$CH_2{=}CHN_3$	(163, 165)
α(or β)-Azidocinnamic acid	 $C_6H_5\overbrace{C{=}C}^{H,N_3}COOH$	(326)
Azido-*p*-quinone (and derivatives)		(184, 236)
2-Azido-1,4-naphthoquinone (and derivatives)		(184)
3-Azido-1,2-naphthoquinone		(184)
Azidoantipyrine		(159)
4-Azido-3,5-dimethylpyrazole		(282)
α(or β)-Azidobenzalacetone	 $C_6H_5\overbrace{C{=}C}^{H,N_3}COCH_3$	(177, 243)
α(or β)-Azidobenzalacetophenone	 $C_6H_5\overbrace{C{=}C}^{H,N_3}COC_6H_5$	(245)

The structurally somewhat related vinyl azide unit, $N_3—\overset{|}{C}{=}\overset{|}{C}—$, in contrast with earlier speculations (299, 300), has little, if any, tendency to undergo cyclization to form the isomeric triazole (table 4).

IV. Chemical Properties of the Azido Group

A. DISPLACEMENT REACTIONS OF THE AZIDO GROUP

Displacement of the azido group by groups other than hydroxyl and amino has not been reported.

1. Acid hydrolysis

Curtius observed that hydrazoic acid was obtained by the action of dilute sulfuric acid upon aliphatic azides such as azidoacetic acid (149) or benzyl azide (79, 86). The recent isolation of trace amounts of acetanilide from a mixture of methyl azide, acetophenone, and concentrated sulfuric acid (66, 359) has indicated that initial hydrolysis of the azide to hydrazoic acid was involved. Resistance to acid hydrolysis, a characteristic property of most azides, favors the acid-catalyzed decomposition reaction. On the other hand, displacement of the azido group may be favored by the presence of another functional group attached to the carbon atom holding the azido group. Hydrolysis of one or both groups of *gem*-diazides proceeded easily in neutral solution. From dimeric cyanogen azide in boiling water, the replacement of both azido groups resulted in the formation of cyanamide and carbon dioxide (211). Complete hydrolysis of certain benzal diazides afforded the corresponding substituted benzaldehydes (260). The acid-catalyzed transformation of certain *gem*-diazides into amides may involve formation of hydrazoic acid by hydrolysis (189, 359).

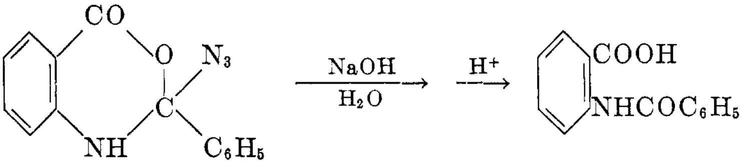
$$N{\equiv}CN{=}C(N_3)_2 \xrightarrow{HOH} N{\equiv}CNH_2 + CO_2 + HN_3$$

$$ArCH(N_3)_2 \xrightarrow{HOH} ArCHO + HN_3$$

Azidomethylurethan and azidomethylurea were hydrolyzed to hydrazoic acid in boiling water (85, 165). By treating azidomethylurea with silver nitrate solution a precipitate of silver azide was obtained (85).

2. Basic hydrolysis

With the exception of α-azido carbonyl compounds and *o*-azido aromatic aldehydes and ketones, the decomposition of azides is not base-catalyzed; consequently the more rigorous conditions necessary for hydrolysis may be attained in this case. Even strong alkali at elevated temperatures, however, fails to attack a great number of azides. The presence of activating groups in the organic molecule is definitely helpful. In addition to decomposition of the azido group, attack by hydroxide ion upon α-azido carbonyl compounds always results in small amounts of displacement (154). The azido group in ethyl α-azidosuccinate was more easily removed by base, in which case the elimination of hydrogen azide resulted in the formation of ethyl fumarate (95). Transformation of 2-azido-4-keto-2-phenyl-3,1,4-benzoxazine into benzoylanthranilic acid involved


Benzoylanthranilic acid

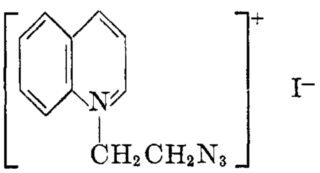
basic hydrolysis of the azide (214). Partial hydrolysis together with decarboxylation of diazidomalonic ester led to the formation of α-azidoglycolic acid (160). It is appropriate to note that products from the addition of hydrazoic acid to aldehydes and ketones (301) have a similar azidohydrin structure, although cyclic structures have also been suggested (285, 357).

$$(N_3)_2C(COOC_2H_5)_2 \xrightarrow[H_2O]{OH^-} N_3CHOHCOOH$$

Diazidomalonic ester α-Azidoglycolic acid

Lack of reactivity of aliphatic azides towards basic reagents is illustrated by 1-azido-2-iodoethane in dehydrohalogenation by potassium hydroxide and the formation of its corresponding quaternary quinoline iodide (165).

$$N_3CH_2CH_2I + KOH \rightarrow CH_2{=}CHN_3 + KI + HOH$$

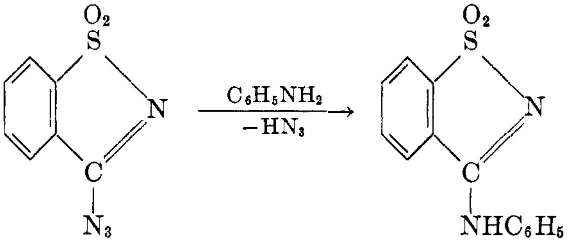


Even β-azido aldehydes, ketones, acids, nitro compounds, and nitriles withstood mild treatment with alkali (50, 93); however, removal of the elements of hydrogen azide under more strenuous basic conditions was observed (50). A suggested qualitative test for the azido group consists of basic hydrolysis, followed by neutralization and treatment with ferric chloride. The deep burgundy-red color of ferric azide may be detected in such dilution as 1 part per 100,000 (14, 211). Failure of many organic azides to give this very sensitive test again indicates their resistance to hydrolysis.

More success has been realized with the basic hydrolysis of activated aromatic azides (69, 287, 289, 292). Potassium hydroxide readily converted *o*-nitrophenyl azide and the *p*-isomer, but not the *m*-isomer, into the corresponding phenol (147). Small amounts of sodium azide were detected from the reaction between sodium hydroxide and 2,4,6-tribromophenyl azide (293). Displacement is also favored through activation by the azomethine linkage. Azidotetrazole, for example, was readily transformed by alkali into hydroxytetrazole (387). In the case of *o*-azidobenzonitrile, however, hydrolysis of the cyano group and not displacement of the azido group occurred (156).

When metallic alkoxides were employed, replacement led to the formation of the corresponding ether. Again, activating groups were required. From 2,4-dinitronaphthyl azide and sodium ethoxide the expected 2,4-dinitroethoxynaphthalene was obtained (289). Triazole formation was a competing reaction (page 45).

Sufficient activation allows the azide to act as an alkylating agent towards amines and hydrazines (10). Picryl-*m*-toluidine was obtained from picryl azide and *m*-toluidine. In a similar manner aniline was alkylated by picryl azide (236) and by 3-azido-α,β-benzisothiazole-1,1-dioxide (341).



A rather curious formation of intense blue salts occurred upon the combination of sodium or potassium hydroxide with certain aryl azides which contain a hydroxyl group in the para position (147, 156, 298). The azides were recovered upon acidification with dilute mineral acid.

B. DECOMPOSITION OF THE AZIDO GROUP

1. *Acid-catalyzed reactions*

(a) Alkyl azides

The exploratory work of Curtius and his students (83, 86, 87, 92) in the early part of the century provided a large portion of the information now available on the acid-catalyzed decomposition of azides. Curtius pictured four different reactions proceeding simultaneously and leading to amines, Schiff bases, and

$$(1)\quad RCH_2N_3 \rightarrow RCH{=}NH + CH_2{=}NR + N_2$$

$$(2)\quad RCH_2N_3 \xrightarrow{H_3O^+} RCH_2NH_2 + N_2$$

$$(3)\quad RCH_2N_3 \rightarrow RCH{:} + HN_3$$

$$RCH{:} + RCH_2N{:} \rightarrow RCH{=}NCH_2R$$

$$(4)\quad RCH_2N_3 \xrightarrow{HOH} RCH_2OH + HN_3$$

alcohols, all of which were obtained or detected from benzyl azide and ring-substituted derivatives. Hydrolysis of the products from the action of fuming sulfuric acid upon ethyl azide afforded a mixture of formaldehyde, acetaldehyde, ammonia, and methylamine, in agreement with path 1 (349).

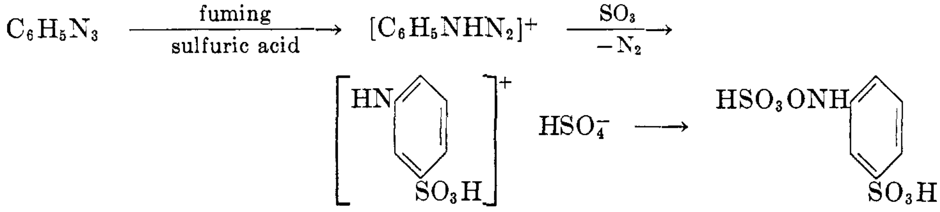
Additional support for these interpretations came from the work of Forster and his pupils. One of the first successful methods for the determination of elementary nitrogen in organic azides involved acid decomposition to liberate molecular nitrogen, followed by a Kjeldahl nitrogen determination on the residue. In a large number of samples analyzed, the ratio of nitrogen found as ammonia to molecular nitrogen liberated varied from 1:1.83 to 1:2.02 (330, 360). Apparently decomposition by path 1 is predominant in the preparation of several nitro derivatives of benzaldehyde from the corresponding nitro derivatives of benzyl azide and dilute sulfuric acid (416).

The reaction between α-azido carbonyl compounds and concentrated sulfuric acid is often violent. In contrast, triphenylmethyl azide (13) and 3-azido-1,3,3-triphenyl-1-propyne (244) were not decomposed by cold sulfuric acid. Both alkyl and aryl azides may be decomposed by Lewis acids (44, 160).

(b) Aryl azides

The acid-catalyzed decomposition of aromatic azides was first observed by Griess (192). An explanation of the reaction with halogen acids (199, 219, 401) accounts for the transformation of the azido group into an amino group and introduction of halogen into the unoccupied ortho and para positions of the aromatic nucleus (363). It was observed that the reaction rate increased with increasing acid strength of the medium and was retarded by base-weakening substituents on the azide. The substitution of two nitro groups in *o*-azidobiphenyl was found sufficient to fortify the molecule against hydrogen bromide, even when one nitro group and the azido group were on different rings.

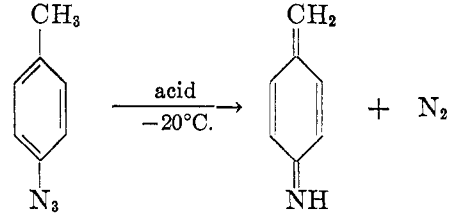
Decomposition of phenyl azide in fuming sulfuric acid involved substitution in the meta position and the formation of *m*-sulfophenylhydroxylamine-*O*-sulfonic acid (349).



$$C_6H_5N_3 \xrightarrow[\text{sulfuric acid}]{\text{fuming}} [C_6H_5NHN_2]^+ \xrightarrow[-N_2]{SO_3}$$

Other strong acids, such as sulfuric acid, perchloric acid, and boron trifluoride, may also release nitrogen from aryl azides; however, the reactions are usually more complicated. A violent explosion resulted from a mixture of phenyl azide and aluminum chloride; however, the same reactants in carbon disulfide brought about liberation of nitrogen and the formation of phenyl isothiocyanate. Azobenzene resulted from the reaction of similar mixtures in chloroform, while the reaction in benzene brought about the formation of aniline and diphenylamine and the reaction in acetyl chloride afforded *p*-chloroacetanilide (47, 48). From aryl azides and sulfuric acid Friedlander and Zeitlein obtained aminophenols in which the hydroxyl group became substituted para to the amino group (181).

To illustrate the complexity of the reaction with sulfuric acid (17, 18), six different compounds consisting of amines and aminophenols plus unidentified amorphous acids and bases were obtained from the decomposition of *p*-tolyl azide by aqueous acid (19, 20). By carrying out the reaction at −20°C. it was possible to isolate a low-molecular-weight polymer of the monovalent nitrogen intermediate from *p*-tolyl azide, which Bamberger considered to have a quinonoid monomeric structure (18). Similar results were found with *o*-tolyl azide. Those aryl azides with electron-withdrawing groups in positions ortho and/or para to the azido group are more resistant to acid decomposition (222).



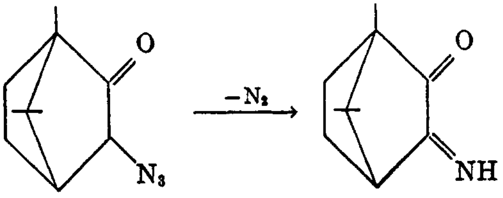
p-Tolyl azide

By blocking the position ortho and/or para to the azido group, introduction of the hydroxyl group into the organic molecule may not occur (363). Dilute sulfuric acid transformed 3-azidophenanthrenequinone into 3-aminophenanthrenequinone (59).

2. Base-catalyzed reactions

(a) Alkyl azides

With the exception of α-azido carbonyl compounds, the azido group in alkyl azides resists base-catalyzed decomposition. There are numerous reports of the decomposition of α-azido ketones, aldehydes, and esters. In several cases an intermediate α-iminocarbonyl compound was isolated, e.g., α-iminocamphor (146). The formation of hydrogen cyanide and isonitriles was noted in several instances (153, 160, 163, 304). The imines are easily hydrolyzed to the corresponding dicarbonyl compounds. A necessary structural feature requires the carbon atom holding the azido group to be primary or secondary. In those cases in which the α-carbon was tertiary, the compound resisted decomposition by base until cleavage of carbon–carbon bonds also occurred (154). More recent observations have supported the earlier work (52). These results indicated that the initial



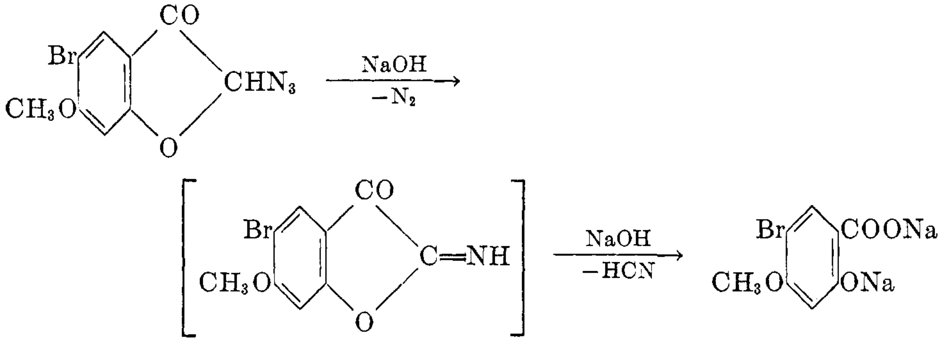
α-Iminocamphor

attack by the base is upon a proton; the carbanion thus formed loses nitrogen. Reaction with a molecule of water then accounts for the formation of the imine.

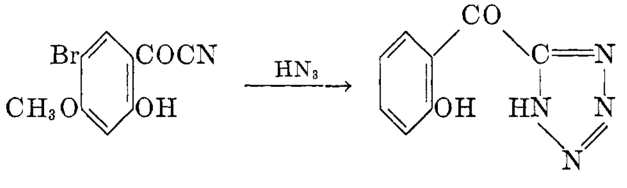
$$\mathrm{RCOCHRN_3} \underset{\mathrm{HOH}}{\overset{\mathrm{OH^-}}{\rightleftharpoons}} \mathrm{RCO\overset{\ominus}{C}RN_3} \xrightarrow{-\mathrm{N_2}}$$

$$\mathrm{RCOCR{=}\overset{\ominus}{N}} \xrightarrow{\mathrm{HOH}} \mathrm{RCOCR{=}NH} + \mathrm{OH^-}$$

The transformation of 2-azido-5-bromo-2,3-dihydro-6-methoxy-3-coumaranone by sodium hydroxide into the sodium salt of 5-bromo-4-methoxysalicylic acid probably involved an imine intermediate (185). Treating the azide with sodium acetate in ethanol resulted in the formation of the corresponding ethyl ester with the elimination of nitrogen and hydrogen cyanide, while sodium azide in acetic acid brought about formation of the tetrazole, presumably by the action of hydrogen azide upon the nitrile.



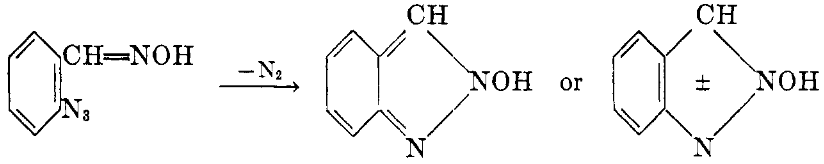
Sodium 5-bromo-4-methoxysalicylate



(b) Aryl azides

In agreement with the behavior of aliphatic azides, aryl azides in general resist decomposition by base. In refluxing aqueous sodium hydroxide *o*-azidobenzaldehyde (21) underwent oxidation–reduction to anthranilic acid with the liberation of nitrogen. Anthranil was considered to be an intermediate (22) and was obtained by heating the azide with water at 110°C. or alone at 120°C. (23). Similar acid-catalyzed (271) and pyrolytic (page 36) transformations of *o*-azidoacetophenone and *o*-azidobenzophenone into the corresponding 3-methyl- and

3-phenylanthranils have been discussed. In hot 2 *N* sodium hydroxide, *o*-azidobenzoic acid was transformed into *o,o'*-dicarboxyazoxybenzene (26). A more complicated reaction occurred upon refluxing *o*-azidobenzaldoxime with aqueous sodium hydroxide. Identified products were *o*-aminobenzaldoxime, *o*-azidobenzamide, 2-hydroxyindazole (compare anthranil formation above), and possibly *o*-azidobenzoic acid (25). The hydroxyindazole was reduced to indazole by tin and hydrochloric acid. The alkaline isomerization of *o*-azidobenzaldoxime into *o*-azidobenzamide was established by an unequivocal synthesis of the amide.



The identity of the product having the formula $C_{12}H_{12}N_2$ and melting at 151°C., which was obtained by decomposing phenyl azide in aniline at 150°C., has not been established (411).

3. *Pyrolysis*

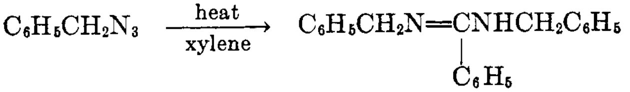
(a) Alkyl azides

Methyl and ethyl azides are quite stable at room temperature but are apt to detonate upon rapid heating. Both undergo homogeneous and unimolecular pyrolysis at measurable rates in the gas phase at temperatures between 200° and 250°C. Ramsperger (324) found that methyl azide decomposed into hydrogen azide and ethylene. Formation of the same products from ethyl azide was accompanied by the loss of nitrogen and products resulting from the rearrangement of CH_3CH_2N: (247). The critical explosion pressure for ethyl azide varies from 105.2 mm. at 258.5°C. to 3.1 mm. at 320.2°C. Admixture with helium appreciably raised the critical pressure, while carbon dioxide had no effect (71, 170a, 210a, 329, 329a).

$$CH_3N_3 \rightarrow CH_2\colon + HN_3$$

$$2CH_2\colon \rightarrow CH_2{=}CH_2$$

Pyrolysis of carbon–nitrogen as well as nitrogen–nitrogen bonds upon heating benzyl azide in xylene and recombination of groups resulted in the formation of *N,N'*-dibenzylbenzamidine (92). An original claim that pyrolysis of benzyl

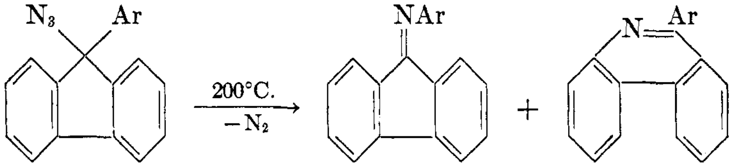


$$C_6H_5CH_2N_3 \xrightarrow[\text{xylene}]{\text{heat}} C_6H_5CH_2N{=}\underset{\displaystyle C_6H_5}{\underset{|}{C}}NHCH_2C_6H_5$$

N,N'-Dibenzylbenzamidine

azide in malonic ester involved abstraction of hydrogen with the formation of benzylaminomalonic ester was later retracted in favor of complex products which presumably resulted from combinations of $C_6H_5CH_2$: and $C_6H_5CH_2N$: (92, 101). On the other hand, benzyl azide with barbituric acid at 165°C. for 3 hr. underwent the loss of nitrogen and apparently abstracted hydrogen to bring about the formation of benzylaminobarbituric acid (96).

Triarylmethyl azides were found to undergo pyrolysis with the migration of an aryl group to nitrogen (171, 320, 345). The reaction has been applied to the synthesis of substituted phenanthridines from 9-aryl-9-azidofluorene (315).



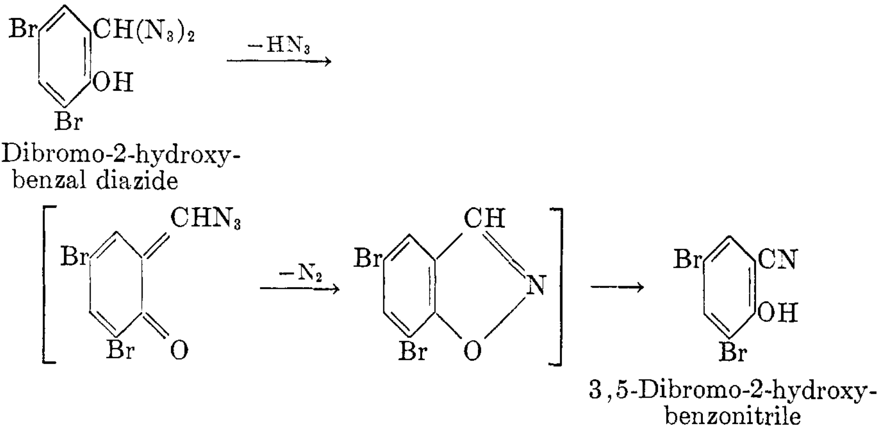
Certain α-azido carbonyl compounds have long been known to be unstable substances. α-Azidoacetaldehyde could not be purified (152), while α-azidoacetone has been reported to decompose upon storage in the refrigerator (366). A strong odor of benzaldehyde and a negative test for an azido group by testing for decomposition in sulfuric acid was characteristic of the material resulting from the storage of desyl azide for several months at room temperature (52).

Most pure α-azido carbonyl compounds, however, may be stored indefinitely in the refrigerator. Phenacyl azide was purified by recrystallization and finally by careful distillation (b.p. 140°C./1 mm.). Pyrolysis of pure α-azido carbonyl compounds occurs at a moderate rate in the neighborhood of 200°C., and at a lower temperature if impure. Pyrolysis of phenacyl azide and structurally related α-azido ketones apparently involved dimerization of an intermediate α-imino ketone, with dehydration to an imidazole. Pyrolysis of α-azidoacetone and α-azidopinacolone also occurred at this temperature but did not lead to imidazoles (52). Combinations of H, CH_3, and C_6H_5 as substituents in the α-position of phenacyl azide afforded a study of the rearrangement step. Without exception, migration from carbon to nitrogen followed the pattern $H > C_6H_5 > CH_3$ (52).

An amino group in the ortho position of phenacyl azide allowed an intramolecular ring-closure with subsequent dimerization to indigo, accompanied by the elimination of ammonia. Curiously enough, pyrolysis of *o*-hydroxyphenacyl azide brought about the formation of the corresponding imidazole (52).

Introduction of more than one azido group into the molecule increases its instability. In the determination of the weight of a sample of 1,3-diazidopropene a violent explosion occurred which prompted the cancellation of further investigations on the compound (169). On the other hand, azido quinones up to tetra-azido-*p*-benzoquinone have been reported (184).

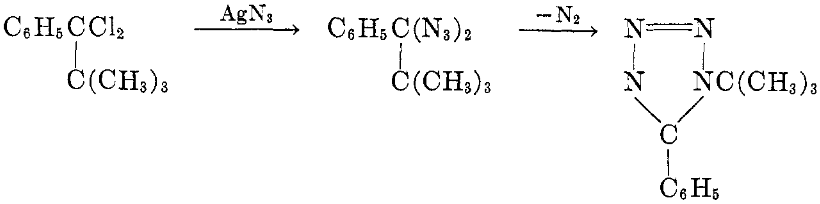
Controlled pyrolysis of *gem*-diazides has successfully been applied to certain substituted derivatives of benzal diazide. From 3,5-dibromo-2-hydroxybenzal diazide there was obtained 3,5-dibromo-2-hydroxybenzonitrile (260).



3,5-Dibromo-2-hydroxybenzal diazide

3,5-Dibromo-2-hydroxybenzonitrile

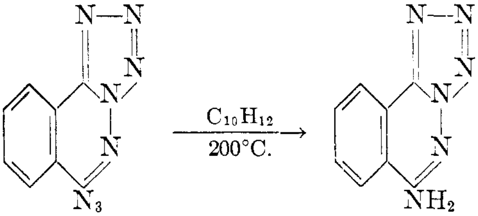
gem-Diazidodiarylmethanes and diazidoarylalkylmethanes upon pyrolysis were transformed into tetrazoles (342, 343, 344).



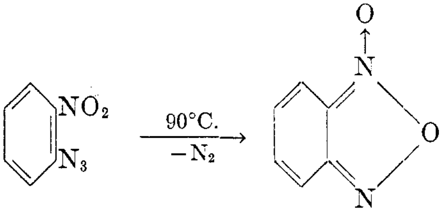
(b) Aryl azides

The stability of the azido group is somewhat enhanced by an attached aromatic nucleus; however, the presence of functional groups in the ortho position often leads to greater instability. Pyrolysis usually occurs with a moderate evolution of nitrogen; however, rapid heating may produce an explosion (262). Nitrogen was liberated at temperatures as low as 85°C. for *o*-nitrophenyl azide (294, 423). On the other hand, the Schiff base formed from 2-formylanthraquinone and 2-amino-1-azidoanthraquinone in boiling nitrobenzene was reported to melt at 331–333°C. with no reported decomposition (242). Most of the aromatic azides undergo decomposition at 150–200°C.

Rearrangement of the univalent nitrogen derivative resulting from the loss of nitrogen is apparently not possible. The end products have been identified as azo compounds, amines, or fused heterocyclic ring compounds. Bertho has reported that phenyl azide in either benzene or xylene at 160°C. is transformed into azobenzene by coupling of the monovalent nitrogen intermediate and into aniline by hydrogen abstraction (36). An azo compound was reported as a decomposition product from azidoantipyrine (159). The coupling reaction, however, does not appear to be as general as hydrogen abstraction, presumably from solvent molecules. In addition to the formation of aniline from phenyl azide in an aromatic hydrocarbon at 160°C., the formation of α-naphthylamine from α-naphthyl azide in trichlorobenzene at 180°C. has been reported (360). When possible, intramolecular hydrogen abstraction occurs and results in the formation of five-membered rings. The reaction has been applied to the synthesis of carbazoles from derivatives of *o*-azidobiphenyl (362), carboline from β-(*o*-azidophenyl)pyridine, and thienoindole from α-(*o*-azidophenyl)thiophene (360). That the ring-closure reaction was preferred was shown by carrying out the pyrolysis of *o*-azidobiphenyl in such hydrogen-providing solvents as benzyl mercaptan, diethyl malonate, aniline, and decalin. In each case carbazole was the only product detected. The reduction of an aryl azide to the corresponding amine by heating in tetralin has been reported (378).

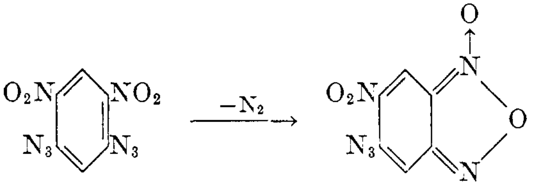


Compounds containing fused-ring systems have been obtained from the pyrolysis of other ortho-substituted aryl azides. *o*-Nitrophenyl azide (361) at 85–90°C. underwent loss of nitrogen with the formation of benzofuroxan (294, 418, 423).



o-Nitrophenyl azide Benzofuroxan

In most cases in which nitro and azido groups are on adjacent carbon atoms of an aromatic ring this reaction has been observed. Pyrolysis of 1,5-diazido-2,4-dinitrobenzene readily liberated one molecule of nitrogen with the formation of

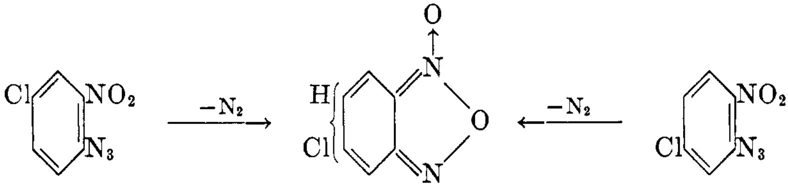


1,5-Diazido-
2,4-dinitrobenzene

6(or 5)-azido-5(or 6)-nitrobenzofuroxan; however, since the molecule resisted further pyrolysis until complete decomposition occurred, a second furoxan ring was presumably incapable of formation (225). Structural representation of the product from the pyrolysis of 1,3,5-triazido-2,4,6-trinitrobenzene may involve six nitroso groups, as suggested by Turek (394), but that structure which involves three furoxan rings should also be considered.

The acid-catalyzed decomposition of *o*-nitrophenyl azide did not yield a furoxan but instead brought about the formation of 4-amino-3-nitrophenol (226). In a similar manner, *p*-amino-*o*-nitrophenol and *o*-amino-*p*-nitrophenol were obtained from *m*-nitrophenyl azide (227). When the positions ortho and para to the azido group are blocked, acid decomposition may lead to the formation of the corresponding furoxan (289).

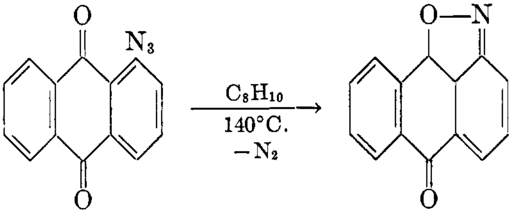
It is of particular interest to note that unsymmetrical derivatives of benzofuroxan fail to exist in the two isomeric forms required by the generally accepted *o*-quinonoid structure. From either 4-chloro-2-nitrophenyl azide or 5-chloro-2-nitrophenyl azide the same 5(or 6)-chlorobenzofuroxan was obtained. Similarly, 5(or 6)-methylbenzofuroxan and naphtho-1,2-furoxan fail to exist in isomeric forms (144, 191).



4-Chloro-2-nitrophenyl azide

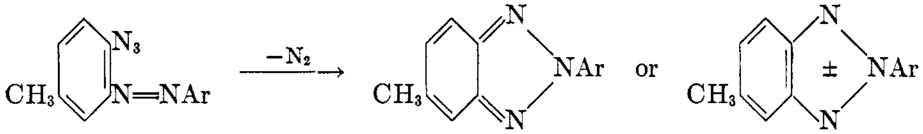
Pyrolysis of both 1-azido-8-nitronaphthalene (147) and *o*-azido-*o*′-nitrobiphenyl (363) led to unidentified products.

Anthranils were obtained from the pyrolysis of aryl azides which had carbonyl groups in the ortho position. The reaction has also been carried out in basic solution (page 31). The anthranil from 1-azidoanthraquinone was obtained in boiling xylene, whereas pyrolysis of the azide by itself yielded the azo compound, which was obtained in the two geometric forms (186). From 1,4- and 1,5-diazidoanthraquinone two molecules of nitrogen were eliminated with the formation of two anthranil rings (337); however, 1,8-diazidoanthraquinone afforded the corresponding azidoanthranil, which is more stable than the typical α-azidoanthraquinone (56, 61). The β-azidoanthraquinones (61, 337) are more resistant to pyrolysis.



1-Azidoanthraquinone

Pyrolysis of *o*-azido aromatic azo compounds results in the formation of the corresponding substituted 2-arylbenztriazoles (420, 421).



In an interesting attempt to obtain an iodine analog of benzofuroxan, decomposition of *o*-azidoiodoxybenzene led to unidentified products (168). The failure is reminiscent of the reaction between *p*-iodoxynitrobenzene and sodium azide, in which case the exclusive replacement of the iodoxy group was attributed to the difficulty of forming a carbon–iodine double bond (page 10).

4. Photolysis

Most organic azides are sensitive to light. Experiments on the controlled decomposition of the azido group by exposure to ultraviolet light have been few in number. In the photolysis of α-azidopropionamide (page 22) apparently no effort was made to identify the decomposition products. Recently, photolysis by ultraviolet light of a series of *o*-azidobiphenyls brought about good yields of the corresponding carbazoles (362).

5. By thioketones

The formation of Schiff bases has been reported from various combinations of aryl azides and thioketones. Heating a mixture of phenyl azide and thiobenzophenone, for example, brought about the formation of benzophenone anil. A

$$\begin{array}{cccccc} (C_6H_5)_2CS & + & C_6H_5N_3 & \xrightarrow[-N_2]{110^\circ C.} & (C_6H_5)_2C{=}NC_6H_5 \\ \text{Thiobenzophenone} & & \text{Phenyl azide} & -S & \text{Benzophenone anil} \end{array}$$

similar reaction with benzophenone failed to occur (338). (Compare the acid-catalyzed decomposition of phenyl azide in the presence of carbon disulfide, page 29.)

C. ADDITION REACTIONS

1. Hydrogen

(a) Chemical methods

In addition to the transformation of aryl azides into amines by acid-catalyzed decomposition of the azido group, the reactions which involve hydrogen abstraction from organic solvents and the base-catalyzed decomposition of *o*-azidobenzaldehydes, there are some other chemical methods for effecting the reduction of azides to amines. In all cases it has been found that the azido group is extremely easy to reduce; in most cases nearly quantitative yields of the corresponding primary amines are obtained.

In the first chemical reduction of an organic azide (157), benzyl azide reacted exothermally with zinc and acetic acid to liberate nitrogen and bring about the formation of benzylamine. Other metal combinations which have been used for this purpose include tin and hydrochloric acid (30), zinc and sulfuric acid (81, 157), aluminum amalgam in moist ether (151) (or ammonium hydroxide), and sodium in alcohol (81, 304). Sodium sulfide (166), ammonium sulfide (148, 326), stannous chloride (148), titanous chloride (327), sodium arsenite (203, 204, 205), sodium dithionite (1, 190), lithium aluminum hydride (51), 1,4-naphthohydroquinone (136), hydrazine (89), hydrogen bromide with phenol (363), and hydrogen iodide (363) have also successfully been used.

Reduction of α-azido carbonyl compounds resulted in the formation of pyrazines by the condensation of the intermediate α-amino carbonyl compound (154). Lithium aluminum hydride, however, transformed α-azido carbonyl compounds into the corresponding amino alcohols in good yields (51).

Several optically active azides have been reduced by chemical means to optically active amines. Based on the assumption that there is no configurational change in the molecule during the reduction, correlations between the two optical series have been recognized (249, 250, 252, 253).

That initial attack involves the terminal nitrogen of the azido group is indicated by the formation of phenyltriazene from phenyl azide with stannous chloride in hydrochloric acid at −20°C. (118, 128). Warming the triazene, or contact with practically any reagent, brought about decomposition into aniline and nitrogen. Picryl azide was reduced by titanous chloride to 2,4,6-triaminophenyltriazene (327). In addition to nitrogen, ammonia and hydrazine have been reported as by-products from the reduction of organic azides (304, 351).

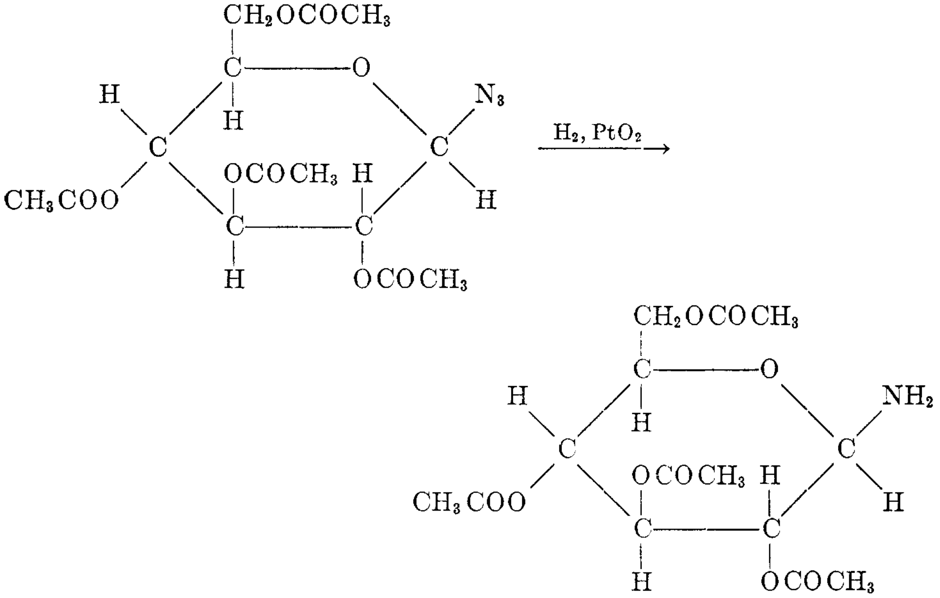
(b) Catalytic

Investigations on the catalytic reduction of azides to primary amines were first started in 1913 (406). Since that time the use of only two catalysts, palladium and platinum oxide (248, 254, 255), has been reported. Mild reaction conditions and good yields of products are again characteristic features.

Bertho has developed two interesting applications of the reaction,—one for the synthesis of peptides and the other for amino sugar molecules. α-Azido acid chlorides were readily obtained and condensed with an amino acid. The resulting azide was reduced, using a palladium catalyst, to an amino acid, and the process was repeated (42, 172).

$$\begin{tikzcd} \mathrm{RCHN_3COCl} + \mathrm{R'CHNH_2COOH} \arrow[r] & \mathrm{RCHN_3CONHCHR'COOH} \arrow[d, "\mathrm{H_2}"', "\mathrm{palladium}"] \\ & \mathrm{RCHNH_2CONHCHR'COOH} \end{tikzcd}$$

A convenient synthesis for amino sugars, e.g., β-aminotetraacetylglucose, consisted in the reduction of the corresponding azide, using hydrogen over platinum oxide (38, 41, 42, 43). The somewhat lower yields were in the range of 40–60 per cent.



β-Aminotetraacetylglucose

The reduction of certain azides, using platinum oxide catalyst in the presence of ethyl chloroformate and potassium carbonate, allowed isolation of the corresponding urethan (175).

2. Metallic and hydrogen cyanides

Quantitative addition of hydrogen cyanide to the terminal nitrogen of the azido group has been known since 1904 (414). Acid hydrolysis of the addition product with phenyl azide afforded benzenediazonium chloride and urea, whereas dilute base apparently promoted isomerization with hydrolysis to aniline. Substitution of sodium or potassium cyanide for hydrogen cyanide brought about the

$$C_6H_5N_3 + HCN \rightarrow C_6H_5N{=}NNHCN$$

$$C_6H_5N{=}NNHCN \xrightarrow[H_2O]{HCl} C_6H_5N_2Cl + CO(NH_2)_2$$

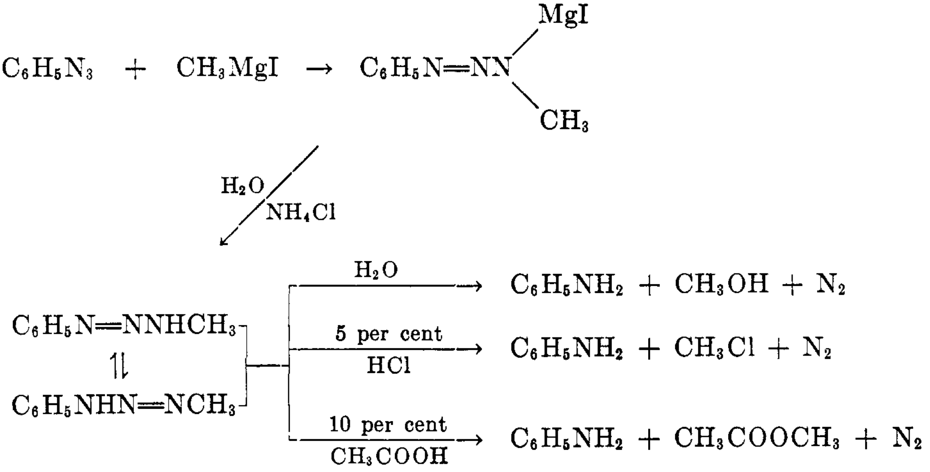
$$C_6H_5N{=}NNHCN \rightleftharpoons C_6H_5NHN{=}NCN \xrightarrow{10\%\ KOH} C_6H_5NH_2$$

formation of the corresponding salt of 3-cyanophenyltriazene (412). A recent application of the addition of sodium cyanide to a large variety of substituted phenyl azides provided a series of cyanotriazenes, some of which were found to have good antibacterial effect against pneumococcus, staphylococcus, and hemolytic streptococcus (64, 65).

A greater facility for potassium cyanide to react with the azido group than with the aldehyde carbonyl group was illustrated in the formation of the salt of 3-cyano(4-formylphenyl)triazene rather than the benzoin from *p*-azidobenzaldehyde (156).

3. Grignard reagents

Grignard reagents also react by addition with the azido group. Presumably the initial product involves attack at the terminal nitrogen; however, tautomerism of the hydrolyzed addition product has been recognized (115, 116, 117, 122, 317). An interesting property of 3-methyl-1-phenyltriazene is



$$C_6H_5N_3 + CH_3MgI \rightarrow C_6H_5N{=}NN(MgI)CH_3 \xrightarrow{H_2O,\ NH_4Cl} C_6H_5N{=}NNHCH_3 \rightleftharpoons C_6H_5NHN{=}NCH_3$$

$$\xrightarrow{H_2O} C_6H_5NH_2 + CH_3OH + N_2$$

$$\xrightarrow[HCl]{5\text{ per cent}} C_6H_5NH_2 + CH_3Cl + N_2$$

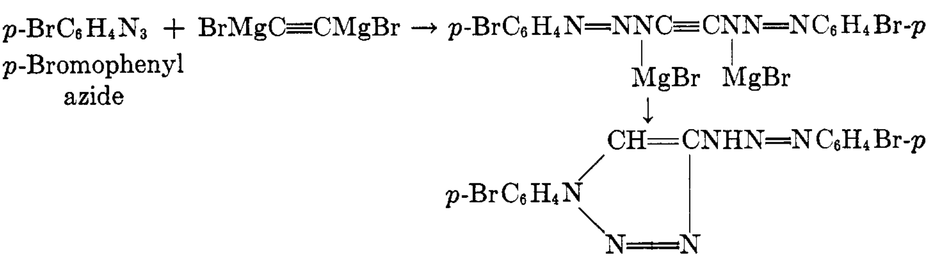
$$\xrightarrow[CH_3COOH]{10\text{ per cent}} C_6H_5NH_2 + CH_3COOCH_3 + N_2$$

$$C_6H_5N_3 + CH_2{=}CHCH_2MgBr \xrightarrow{HOH} C_6H_5N{=}NNHCH_2CH{=}CH_2$$

that as a methylating agent it rivals diazomethane. In addition to phenyl azide and a variety of ring-substituted derivatives, methyl azide has participated in an addition reaction with Grignard reagents. 1,3-Dimethyltriazene, isolated and purified as its copper salt, was an explosive liquid, b.p. 92°C. (117).

Bistriazenes were obtained from combinations of aryl azides and ethynyldimagnesium bromide or from aryl diazides and reagents such as ethyl or phenylmagnesium bromide. The competitive reaction, cyclization to a triazole (page 43), may predominate (230, 231).

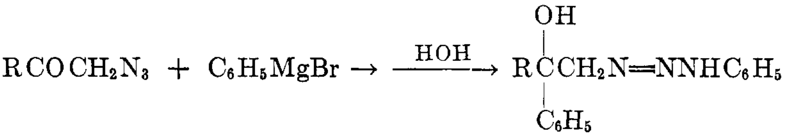
$$C_6H_5N_3 + BrMgC{\equiv}CMgBr \rightarrow C_6H_5N{=}NNHC{\equiv}CNHN{=}NC_6H_5$$



p-$BrC_6H_4N_3$ + $BrMgC{\equiv}CMgBr \rightarrow$ p-$BrC_6H_4N{=}NN(MgBr)C{\equiv}CN(MgBr)N{=}NC_6H_4Br$-$p$

p-Bromophenyl azide

Phenylmagnesium bromide added to the carbonyl as well as to the azido groups in azidoacetone and phenacyl azide (317).

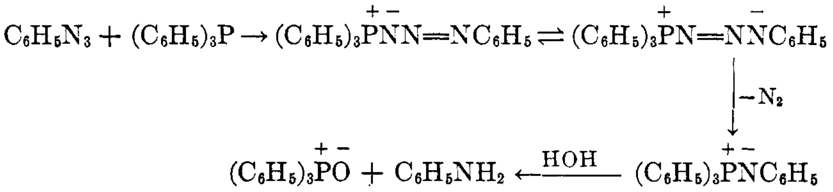


$$RCOCH_2N_3 + C_6H_5MgBr \rightarrow \xrightarrow{HOH} R\overset{\overset{OH}{|}}{\underset{\underset{C_6H_5}{|}}{C}}CH_2N{=}NNHC_6H_5$$

R = CH_3, C_6H_5.

4. Tertiary phosphines

A complex which contains one molecule of each was formed upon mixing an alkyl or aryl azide with a tertiary phosphine in an inert solvent. Upon isolation it readily lost nitrogen with the formation of a phosphinimine, which in turn was hydrolyzed to a phosphine oxide and an amine (56, 269, 367, 368).



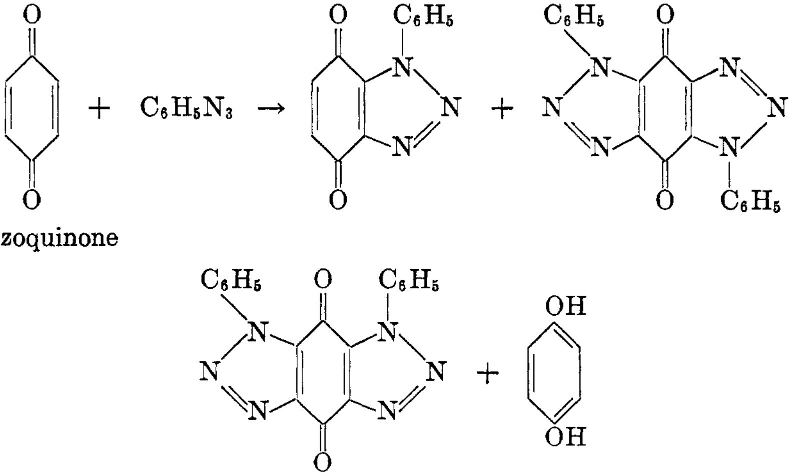
$$C_6H_5N_3 + (C_6H_5)_3P \rightarrow (C_6H_5)_3\overset{+}{P}\overset{-}{N}N{=}NC_6H_5 \rightleftharpoons (C_6H_5)_3\overset{+}{P}N{=}N\overset{-}{N}C_6H_5$$

$$\Big\downarrow{-N_2}$$

$$(C_6H_5)_3\overset{+}{P}\overset{-}{O} + C_6H_5NH_2 \xleftarrow{HOH} (C_6H_5)_3\overset{+}{P}\overset{-}{N}C_6H_5$$

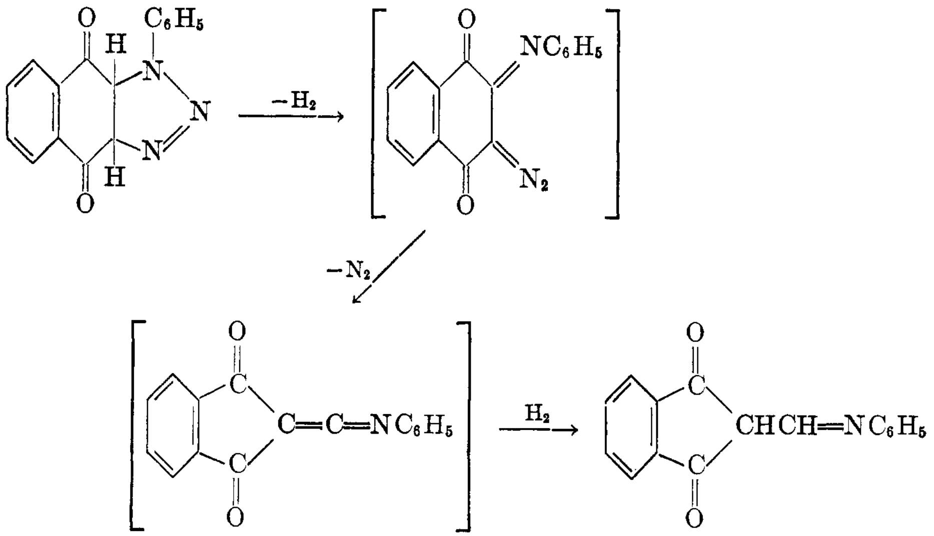
5. Olefins

Addition of the azido group to an olefinic linkage was introduced by Wolff and Grau (411, 412). They obtained the mono- and two bis-adducts with phenyl azide and *p*-benzoquinone. Dehydrogenation of the adducts accounted for the formation of hydroquinone. Similar mono-adducts were obtained from α-naphthoquinone and from methyl-*p*-benzoquinone (74, 413). β-Naphthoquinone failed to react with organic azides (135). Unexplained ring-contraction products are reminiscent of the light-catalyzed transformation of benzene diazo oxides into derivatives of cyclopentadienecarboxylic acid and the pyrolysis of

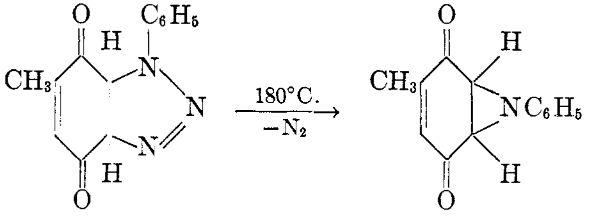


p-Benzoquinone

the addition product from α-naphthoquinone and diphenyldiazomethane into 4-hydroxy-1-phenyl-2,3-benzofluorenone (15). Their formation may involve ring-opening with the formation of a diazo compound, followed by a rearrangement similar to the Wolff rearrangement of α-diazo ketones.



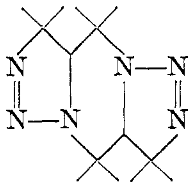
That the adducts undergo the loss of nitrogen with the formation of a three-membered ring has been demonstrated (74, 91). The introduction of a nitro group in the para position of the N-phenyl substituent renders the triazole



so unstable that it decomposes at once (71a).

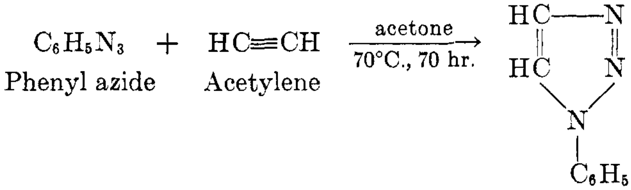
A great variety of olefins have undergone this addition reaction with azides but somewhat less readily than the similar reaction with aliphatic diazo compounds. Conditions which promote the addition are not fully understood; however, addition to a double bond in conjugation with an aromatic system occurs sluggishly, whereas addition to a double bond in a cyclic system in which there is considerable ring strain occurs readily (2, 3, 4, 5, 6, 7, 8, 103, 309). Addition products were obtained from phenyl azide with styrene and with fumaric ester but only at higher temperatures (411). Stilbene and cinnamic ester failed to react. The addition of phenyl azide to olefinic linkages in strained cyclic compounds has been used to detect and characterize the olefins. Examples of addition of an organic azide to an aromatic system have not been reported.

The interesting dimerization of allyl azide probably does not involve the formation of a four-membered ring, as originally suggested (150), but more likely involves addition of azido and olefinic groups with the formation of a fused three-ring heterocyclic system.

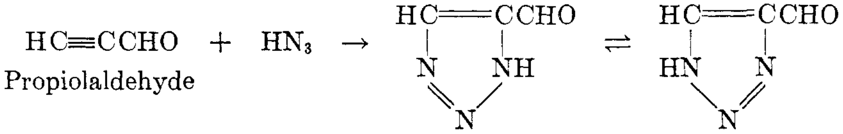


6. *Acetylenes*

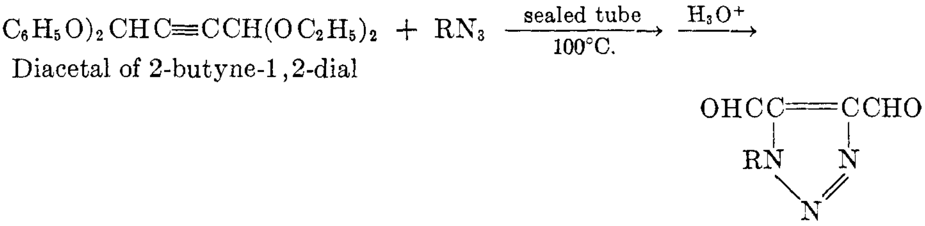
An unidentified adduct from phenyl azide and methyl acetylenedicarboxylate was first observed in 1893 (275, 276). A few years later Dimroth and Fester recognized that 1-phenyltriazole was produced by the sluggish addition of phenyl azide to acetylene (123). The reaction has not been extensively investigated but appears to be quite general (32). Esters of azidoacetic acid readily added to methyl acetylenedicarboxylate; however, poor yields of the corresponding product with methyl azidoformate were obtained (96). Phenyl azide usually adds to an acetylene so that nitrogen attached to the phenyl group is also bound to the acetylenic carbon which bears a hydrogen substituent (286). Hydrogen azide also reacts with the acetylenic linkage to form triazoles. Propiolaldehyde and hydrogen azide afforded the expected adduct (221).



1-Phenyltriazole

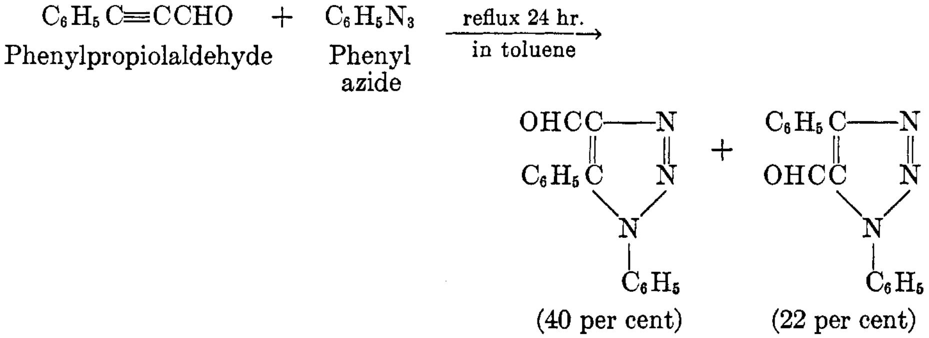


An interesting series of triazoles resulted from the addition of phenyl, benzyl, *n*-hexyl, and *n*-dodecyl azides to the diacetal of 2-butyne-1,2-dial. Hydrolysis of

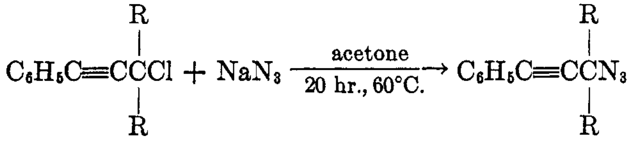


$R = C_6H_5, C_6H_5CH_2, CH_3(CH_2)_5, CH_3(CH_2)_{11}$.

the acetal groups gave the 1-substituted 4,5-triazoledialdehydes (216). Recently, both expected products from the addition of phenyl azide to an unsymmetrical acetylene, e.g., phenylpropiolaldehyde or the acetal of propiolaldehyde, have been observed (346).



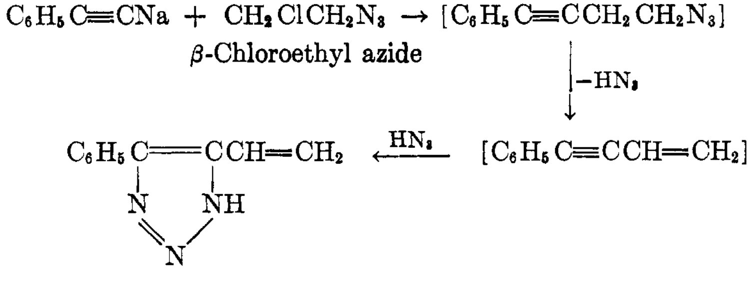
There are a few examples of compounds which contain both the acetylenic and the azido groups. Both 3-azido-1,3,3-triphenylpropyne and 3-azido-3,3-dimethyl-1-phenylpropyne were prepared from the corresponding chlorides and sodium azide (244). Dimerization was not reported.



$$C_6H_5C{\equiv}C\overset{R}{\underset{R}{C}}Cl + NaN_3 \xrightarrow[20\text{ hr., }60^\circ\text{C.}]{\text{acetone}} C_6H_5C{\equiv}C\overset{R}{\underset{R}{C}}N_3$$

R = C_6H_5, CH_3.

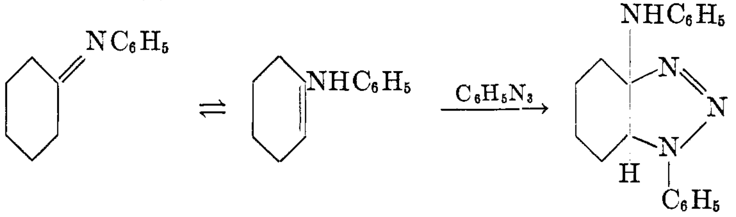
The sodium salt of phenylacetylene with β-chloroethyl azide in ether reacted to form 4-phenyl-5-vinyltriazole (established by oxidation and decarboxylation to the known 4-phenyltriazole and bromination to 5-(1,2-dibromoethyl)-4-phenyltriazole. Apparently loss of hydrogen azide from the coupled product, followed by addition to the acetylenic linkage, was involved (178, 180).



7. *Nitriles*

A patent claim (228) that certain ω-azido nitriles underwent intramolecular condensation between the azido and nitrile groups with the resulting formation of tetrazoles is not in agreement with very similar work of the same date in which metrazole could not be prepared from ε-azidohexanenitrile (202).

In all cases except the one cited above it has been observed that addition of organic azides to the nitrile linkage fails to occur. Phenyl azide, for example, did not react by addition with hydrogen cyanide or with cyanogen (123), while the addition to the olefinic linkage in β-aminocrotononitrile afforded the synthesis of 4-cyano-5-methyl-1-phenyltriazole (274) (page 40). Both azidoacetonitrile and azidoacetylaminoacetonitrile have been reported as monomers with no tendency to dimerize (172). The trimerization of cyanogen azide (11) to cyanuryl azide did not involve the azido group. In contrast, tetrazoyl azide was obtained from a cyanogen halide and hydrazoic acid (182). Anils of cyclic ketones underwent addition with phenyl azide; however, isomerization of an α,β-unsaturated amine was involved (6).

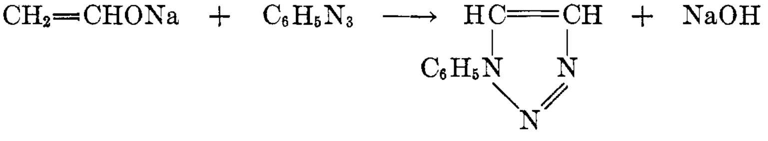


8. *Addition reactions in the presence of base*

(a) Sodium alkoxides

When phenyl azide was heated with sodium ethoxide in ethyl alcohol under ordinary pressure, phenyltriazole and aniline were formed, together with sodium hydroxide and nitrogen. It would appear that oxidation of sodium ethoxide to the sodium derivative of vinyl alcohol allowed the concurrent reduction of phenyl azide to aniline. Combination of phenyl azide with the olefin gave rise to the formation of phenyltriazole and sodium hydroxide (37, 39, 40). Phenyltriazoles with alkyl groups substituted in the 4-position were obtained from higher primary alcohols, while the use of secondary alkoxides allowed only the reduction to aniline. An unidentified by-product (m.p. 282°C., molecular weight 122–129) occurred from combinations of phenyl azide and any sodium alkoxide.

$$\mathrm{CH_3CH_2ONa + C_6H_5N_3 \longrightarrow CH_2{=}CHONa + C_6H_5NH_2 + N_2}$$

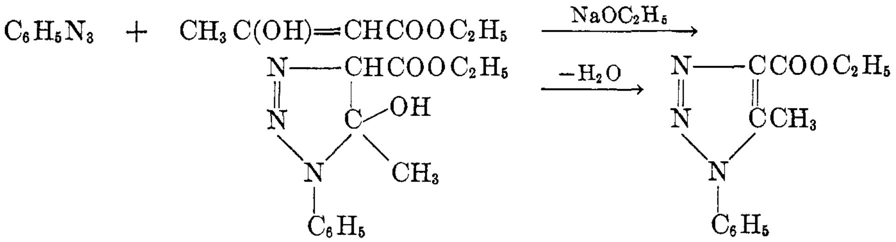


$$\mathrm{CH_2{=}CHONa + C_6H_5N_3 \longrightarrow \begin{array}{ccc} HC & = & CH \\ | & & | \\ C_6H_5N & & N \\ & \diagdown\!\!N\!\!/\!\!/ & \end{array} + NaOH}$$

Phenyltriazole

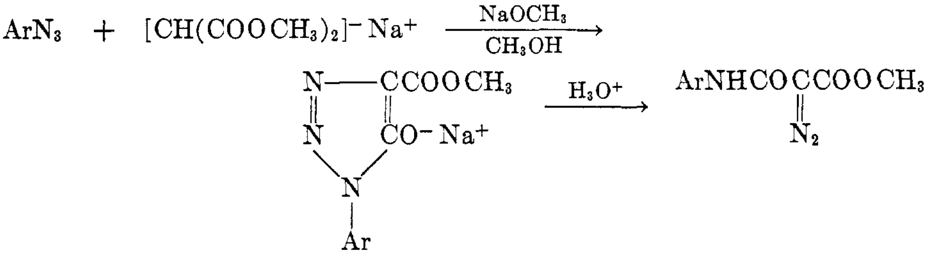
(b) Compounds containing active methylene groups

In the presence of sodium ethoxide, phenyl azide and acetoacetic ester combined with formation of the ester of 4-carboxy-5-methyl-1-phenyltriazole (structure established by its degradation to phenyltriazole). It is convenient to represent the reaction by addition of the azide group to the enol form of acetoacetic



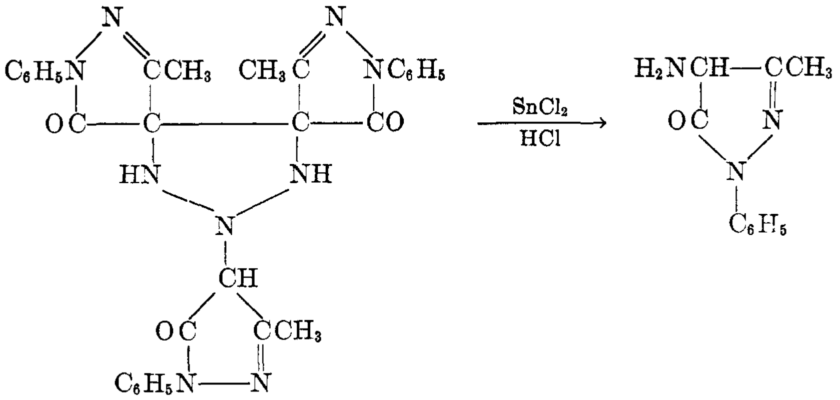
Ethyl ester of 4-carboxy-5-methyl-1-phenyltriazole

ester (114). Similar reactions with phenyl azide and other aryl azides (32, 187, 235) were observed with acetophenone, dypnone, dibenzoylmethane, phenylacetonitrile, cyanoacetic ester, malonic ester, and other compounds which contain enolizable methylene groups (113, 119, 120, 121, 124, 125, 127, 131, 235). The triazole which was obtained from malonic ester and an aryl or alkyl azide underwent a tautomeric change into an amide upon acidification (119, 289) (page 15).



p-Azidodiphenylamine with acetoacetic ester gave the expected triazole, but 2,6-diazidoanthraquinone failed to react with acetoacetic ester in the presence of sodium ethoxide (12, 56). In addition to the expected triazole, an appreciable amount of 3,5-dicarbomethoxy-4-hydroxypyrazole was obtained from phenyl azide and methylmalonic ester (120).

A high-molecular-weight (536–575) red solid, m.p. 184°C., obtained from the combination of aryl azides with 3-methyl-1-phenyl-5-pyrazolone in the presence of sodium ethoxide was assigned the following structure:



Reduction by stannous chloride gave 4-amino-3-methyl-1-phenyl-5-pyrazolone (213, 402).

(c) Hydrazones

Phenylhydrazones of aldehydes with phenyl azide in the presence of sodium ethoxide gave linear addition compounds consisting of one molecule of the azide and one of the hydrazone (126). From the phenylhydrazone of benzaldehyde and phenyl azide in the presence of sodium ethoxide, aniline and 1,3-diphenyltetrazole were obtained (75, 126).

$$RCH{=}NNHC_6H_5 + C_6H_5N_3 \xrightarrow[C_2H_5OH]{NaOC_2H_5} C_6H_5NHN{=}NCR{=}NNHC_6H_5$$

$R = CH_3$, COOH.

D. REACTIONS WHICH MAY OCCUR WITHOUT INVOLVING THE AZIDO GROUP

Ethylene azidohydrin was decomposed by sodium without a solvent but gave sodium β-azidoethoxide in ether. Treatment of the sodium salt with alkyl iodides in ether brought about the formation of the corresponding azido ethers (237).

Oximes, hydrazones, and semicarbazones of azido carbonyl compounds may be prepared by usual procedures (148, 149, 160). Quinoxalines have resulted from condensations between 2-, 3-, and 4-monoazidophenanthrenequinones and 4,5-diazidophenanthrenequinone with *o*-phenylenediamine (57, 58, 59).

Azido acids may be transformed into acyl chlorides or anhydrides by thionyl chloride (148, 149, 173, 176). A convenient preparation of certain esters (174) and amides (212) consists in the treatment of azido acyl halides with the appropriate alcohol or amine. Azido acyl hydrazides have been prepared from hydrazine and the corresponding azido esters (85, 88, 93, 94, 95). Basic hydrolysis of azido esters, amides, nitriles, and anhydrides yielded the corresponding azido acids (85, 94, 288). Azido phenols have been esterified with *p*-toluenesulfonyl chloride (147). Condensation of a silver salt of an azido acid with an azido aryl halide afforded a convenient preparation for azido acid anhydrides (172).

A variety of aromatic mono- and diazides have been nitrated (134, 147, 419). Picryl azide has been obtained from the nitration of phenyl azide (268). The nitration of *p*-azidophenol by nitrous acid brought about the formation of 4-azido-2-nitrophenol (147). In addition to the expected nitration product, a by-product, $C_7H_7O_5N_3$, which appeared to be a substituted β-phenylhydroxylamine, was obtained from 4-azido-3-nitrotoluene and nitric acid (130).

It has been claimed that sodium dithionate transforms diazonium chlorides into the corresponding azides (190, 390). The generality of this reaction must be questioned however, since this reagent has been found useful for the reduction of both nitro (59) and azido (1, 136) groups to amino groups. Iodosophenyl azide has been reduced to iodophenyl azide by sodium thiosulfate (168). When tetraazidobenzoquinone in acetone was mixed with aqueous potassium iodide and acidified with dilute hydrochloric acid it yielded tetraazidohydroquinone (365).

Resistance to decomposition and hydrolysis by strong base and stability in the presence of oxidizing agents have been demonstrated by the permanganate oxidation of allyl azide to azidoacetic acid (179).

V. Uses for Alkyl and Aryl Azides

A. *Analytical reagents*

The use of phenyl azide as a reagent for the detection of an isolated double bond has been discussed. In a recently reported colorimetric determination of aldrin, phenyl azide added to an olefinic linkage to form a dihydrotriazole. An unidentified colored compound was then produced by reaction of the triazole with a dinitrobenzenediazonium salt (103).

Characteristic color tests with thirty-six phenols have been described for 3-azido-2,4-dimethylpyrazole (282).

B. *Pharmaceuticals*

Phenyl azide has been investigated as an antipyretic (296) and as a growth inhibitor (389). A number of azidoaryl sulfones and sulfonamides have recently been found to possess considerable chemotherapeutic activity (29, 331). When the organic azide does not yield the azide ion under biological conditions, the bacteriostatic activity can be greater than that of sodium azide (403). Preliminary investigations on the azido group as an odoriphore have been reported (45, 148, 333).

C. *Explosives*

A few organic azides have received attention as explosives (14, 267, 316, 384, 410). These include β-azidoethyl alcohol and its nitrate ester (33, 397), cyanuryl azide (307, 415a), picryl azide, 1,3,5-triazido-2,4,6-trinitrobenzene (394, 395, 396, 415a), certain derivatives of tetrazoyl azide (291, 328), tetraazidobenzoquinone (365), and 6-azido-2,4-dinitrophenol (270a).

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