The Diazotization of Heterocyclic Primary Amines

R. N. BUTLER

Department of Chemistry, University College, Galway, Ireland

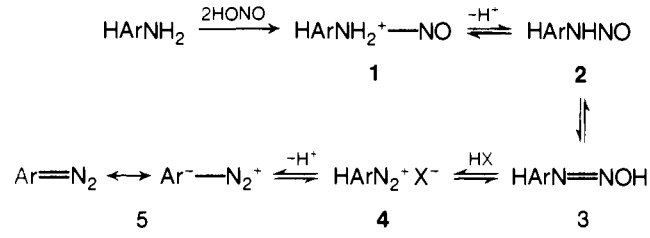
Received February 11, 1974 (Revised Manuscript Received April 23, 1974)

Contents

I. Introduction. Scope and Aims

This review is concerned with the nature of the products formed in the diazotization of heteroaromatic primary amines in which the amino group is bonded directly to the heteroaromatic ring. It is also concerned with the further reactions of the diazotization products insofar as these reactions are useful for structural elucidation. The paper does not cover diazonium salts or diazo compounds prepared by direct introduction of the diazonium group or synthesized in any manner other than by diazotization of amines. A large number of reviews and discussions have been published on diazo compounds and the diazotization process,[1-5] but the diazotization of heterocyclic primary amines has not been covered in detail previously. In general the diazotization reaction is now considered to involve the following equilibria at the relatively high acidities used in most heterocyclic synthetic work, the products being compounds **1–5.** The controversy surrounding the first step has been reviewed[5] and is not discussed herein since, except for the work of Kalatzis (below), little or no systematic kinetic studies on the mechanism of the reaction with heterocyclic amines have been carried out. Recent kinetic studies[6,7] of the diazotization of aniline, in aqueous solutions of acidity up to 6.5 *M* perchloric acid, have indicated a rate-determining first step which involves an initial attack of the nitrosating agent on the aromatic ring of the protonated amine followed by proton loss from the NH_3^+ group and migration of the nitrosating agent to the amino-nitrogen atom.

SCHEME I



The products **5** are diazo compounds which are generally more stable than the other species. Such diazo compounds arise when base is added to the diazonium solution or when the aromatic ring possesses a hydrogen atom acidic enough to be donated to the medium, as is sometimes the case with heterocyclic compounds. A previous review,[8] which dealt with one aspect of diazotization in the heterocyclic series, was specifically limited to diazo compounds such as **5.** In the present paper compounds of type **5** are considered to be of interest mainly insofar as they indicate the precursory presence of the diazonium form **4.** Recently the synthetic chemistry of various classes of organic diazo compounds has been reviewed,[9] and the reactivity of and the various types of reactions undergone by aromatic diazonium ions have been discussed.[10] Albert[11] has described the diazotization of six-membered heterocyclic amines in some detail, and the present discussion is concerned with recent developments and the comparisons with five-membered systems. Most books on general heterocyclic chemistry describe earlier work on the more simple heterocyclic amines, and these should be consulted along with ref 11. The present review is considered to be complementary to the existing literature, and references to earlier papers are included only in cases where these are required for important comparisons.

The nature of the products formed in the diazotization of many primary amines of the less common five-membered heterocycles is a subject marked by a certain degree of obscurity. Discussions of such systems are usually very limited or entirely absent from general books on heterocyclic chemistry. This seems to have arisen, in part, because workers were sometimes concerned not with the products of diazotization themselves but with the conversion of these products into other derivatives by reactions which were often carried out in situ. In practically all such cases a diazonium salt is assumed to be the diazotization product. Since the solution containing the products will, in most cases, contain a number of the species **1** to **4,** the term "product" itself may be ambiguous. Herein the product is taken to be the main com-

pound which may be unequivocally detected or isolated from the reaction, or, alternatively, the point at which the sequence of reactions in Scheme I stops under the particular conditions. A further difficulty arises in the present work since in very few cases have diazotizations of heterocyclic amines been carried out under identical conditions of acidity although in many cases conditions of "strong acidity" have been used. Despite these difficulties useful generalizations can now be made. It is hoped that the review will identify both the main ambiguities in the field and the progress made and thereby stimulate some further work.

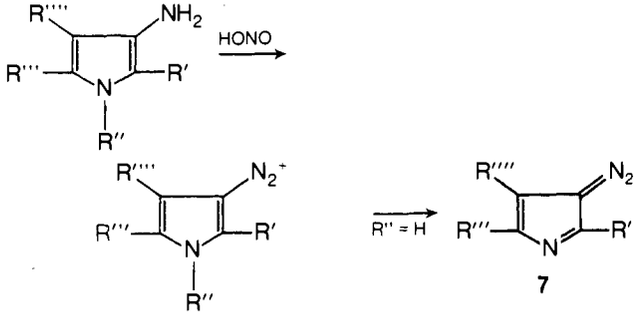
The literature is covered up to ca. January 1974. Compounds containing the linkage -N=NNH- are referred to as diazoamino compounds or triazenes. Substitution reactions involving displacement of a diazonium group by another atom or group are referred to in general as dediazoniation reactions.[12] For convenience heterocycles containing OH substituents are referred to as hydroxy derivatives in general, although the tautomeric ketone form is usually the dominant form in such compounds.

II. Five-Membered (π-Excessive) Ring Systems. Azoles

A. Pyrroles and Diazoles

1. Pyrroles

Substituted 3-aminopyrroles, when treated with sodium nitrite in acetic acid, readily yield 3-diazonium pyrroles, e.g., **6**, which may lose a proton to give 3-diazopyr-



6, R'' = H, R' = R''' = R'''' = Ph

8, R' = R'' = R''' = R'''' = Ph

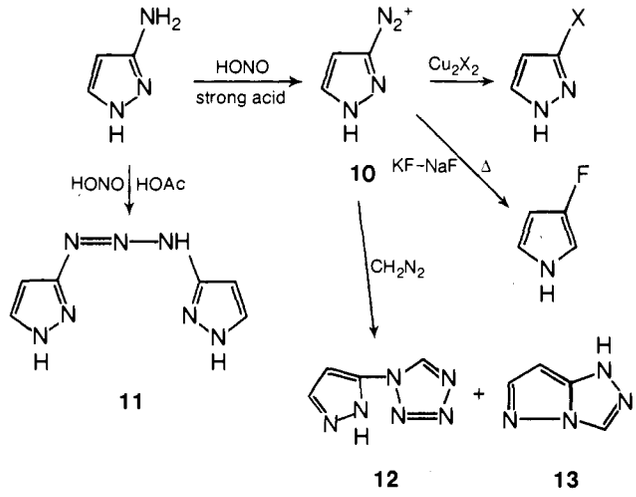
9, R' = R'' = R''' = Ph; R'''' = H

roles.[13] The diazonium salts **6** failed to couple with phenols in acidic media, but coupling occurred when the diazo compounds **7** were heated with β-naphthol in chloroform. The N-substituted pyrrole diazonium salts **8** and **9** were formed by diazotization of the corresponding amine in hydrochloric acid solution.[14-16] These diazonium compounds underwent normal dediazoniation reactions. There are conflicting and contradictory reports[14,16] of the coupling ability of compound **8**, the most recent account[14] being that it undergoes normal coupling. 2-Diazopyrroles have been prepared by direct introduction of the diazo group[17] and not by diazotization of amines, few of which are known. The 2-diazopyrroles are less stable than the 3-isomers. Tedder[8] has discussed the chemistry of a range of diazopyrroles including Bamberger's early work on 2-diazoindoles, and repetition here is undesirable. In general, the number of aminopyrroles which has been diazotized is small because of paucity of simple amine derivatives. In those cases which have been investigated, either in dilute or concentrated acid, the diazotization appears to proceed through to the final stages of Scheme I, the products being diazonium or diazo compounds.

2. Diazoles

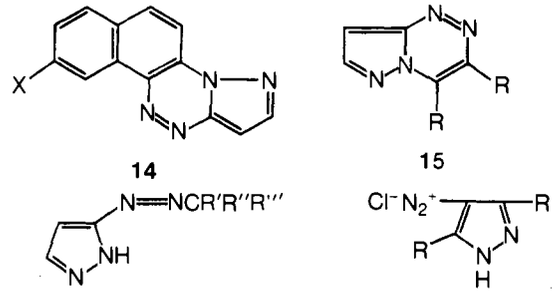
a. Pyrazoles

Diazotization of 3-amino-1*H*-pyrazoles in strong acids, e.g., concentrated hydrochloric or phosphoric acid, yielded pyrazole-3-diazonium salts **10**, while in acetic acid the product was the diazoaminopyrazole[18,19] **11**. The diazonium salts **10** underwent normal dediazoniation and coupling reactions.[20-22]

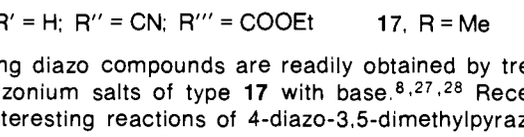


10 **11** **12** **13**

The Sandmeyer reaction yielded 3-halopyrazoles, and heating pyrazole-3-diazonium fluoroborates with alkali fluorides yielded 3-fluoropyrazoles.[20] When treated with diazomethane, the diazonium salts formed the tetrazolylpyrazole **12** along with pyrazolo[5,1-*c*]triazole[21,22] (**13**). Coupling of the diazonium salt **10** or the corresponding diazo compound (readily obtained by treating compound **10** with base[18]) with phenols yielded pyrazolotriazines **14** by an intramolecular condensation reaction which occurred also under the coupling conditions.[18,20] Pyrazole-3-diazonium chloride, when treated with β-keto acids or esters, gave products which spontaneously cyclized to the pyrazolo-as-triazines[23] **15**. Coupling with compounds such as ethyl cyanoacetate gave azo compounds of type **16** which also readily cyclized to pyrazolotriazines.[23] Diazotization of 4-aminopyrazoles in strong acids also yields diazonium salts.[24-28] Thus, for example, treatment of 4-amino-3,5-dimethylpyrazole with nitrous acid in hydrochloric acid yielded a stable crystalline diazonium chloride **17** which coupled with β-naphthol.[25,26] The corre-

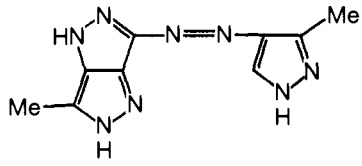


14 **15**



16, R' = H; R'' = CN; R''' = COOEt 17, R = Me

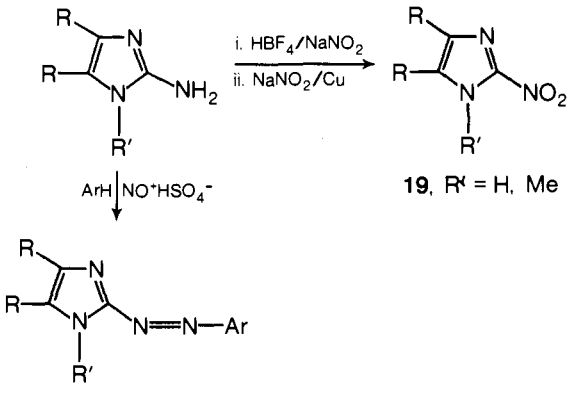
sponding diazo compounds are readily obtained by treating diazonium salts of type **17** with base.[8,27,28] Recently,[29] interesting reactions of 4-diazo-3,5-dimethylpyrazole have been reported. For example, heating this compound in benzene gave 4-phenyl-3,5-dimethylpyrazole as well as 3,5-dimethylpyrazole and biphenyl via a free radical reaction, while heating in *t*-BuOH gave the azo compound **18** as the main product.[29]



18

b. Imidazoles

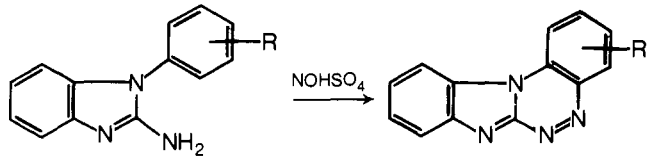
Aminoimidazoles are readily diazotized to diazonium salts which give normal coupling and dediazoniation reactions,[30] thereby providing synthetic routes to a number of important pharmaceuticals. In many cases the products of the diazotization have not been isolated but treated further in situ. Thus a range of mono-, di-, and trimethyl-2-nitroimidazoles **19**, including 2-nitroimidazole (Azomycin), has been prepared by treating the amine with sodium nitrite in fluoboric acid followed by sodium nitrite and powdered copper,[30,31] the so-called[32] nitro-Sandmeyer reaction. Treatment of a range of 1-substituted-2-amino-4,5-diphenylimidazoles with nitrosylsulfuric acid in the presence of aromatic hydrocarbons yielded the corresponding 2-arylazoimidazoles[33] **20**. Similarly



19, R′ = H, Me

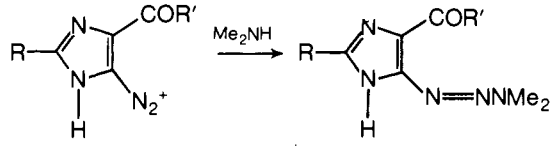
20, R′ = H, alkyl

1-*N*-phenyl-2-aminoimidazoles, when treated with nitrosylsulfuric acid in phosphoric acid, yielded imidazo[2,1-c]-1,2,4-triazines **21** by intramolecular coupling.[34]



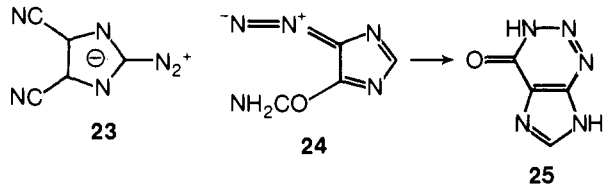
21

Irradiation of imidazole-2- and -4-diazonium tetrafluoroborates in tetrafluoroboric acid solution has yielded a number of 2- and 4-fluoroimidazole derivatives, the first fluoroimidazoles to be prepared.[35-37] These, in turn, have provided routes to fluorohistamine derivatives.[35-37] A range of 2-substituted-4-amino-5-acylimidazoles has been diazotized and coupled with dimethylamine to give the diazoamino compounds[38] **22**.



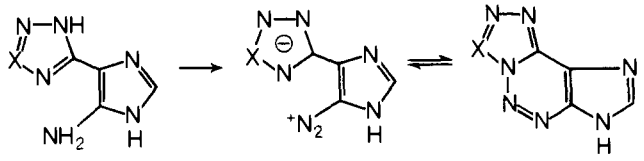
22, R = alkyl; R′ = OR

Diazotization of aminoimidazoles containing electron-withdrawing groups yields diazo compounds directly. Thus 2-amino-4,5-dicyanoimidazole, when treated with sodium nitrite in hydrochloric acid, gave the diazo compound **23** directly.[39] The diazo compound **24** was also obtained by diazotization of 5-aminoimidazole-4-carboxamide hydrochloride with sodium nitrite in 1 *M* hydrochloric acid solution.[40] The compound readily cyclized to the 2-azahypoxanthine **25** on storage in neutral, acidic, or



23 **24** **25**

basic aqueous solution,[40] and the cyclization was more rapid than photofluorodediazoniation, thus preventing the synthesis of 5-fluoroimidazole-4-carboxamide.[35] Diazotization of 5-amino-4-(tetrazol-5-yl or 1,2,4-triazol-5-yl)imidazoles **26** with sodium nitrite in hydrochloric acid gave the diazo compounds[41] **27**. These were in equilibrium with the imidazole-*v*-triazine ring systems **28**. The influence of substituent and solvent effects on this equilibrium has been discussed.[41]



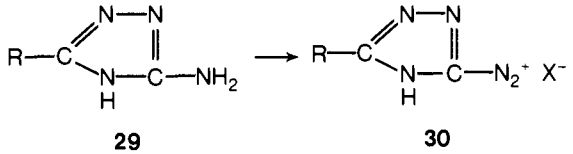
26, X = N, CH **27** **28**

Diazotization of the 8-amino group (imidazole ring) of purines occurs readily yielding diazopurines. These have been discussed in detail previously[8,11] and are not considered further here. In general it appears that the diazotization reaction of aminodiazoles proceeds to the final stages of the reaction. However, in view of the results quoted below, a closer examination of the reaction with ring N-alkylated diazoles under conditions of dilute acidity would seem to be desirable particularly since the diazoamino compounds formed under these conditions could also possibly arise from primary nitrosoamine intermediates.

B. Triazoles

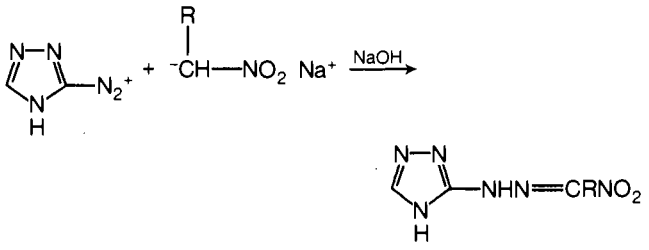
1. 1,2,4-Triazoles

A wide range of 3-substituted-5-amino-1,2,4-triazoles **29** has been diazotized, the products being diazonium salts[42-49] **30**. Thus a number of diazonium salts of type



29 **30**

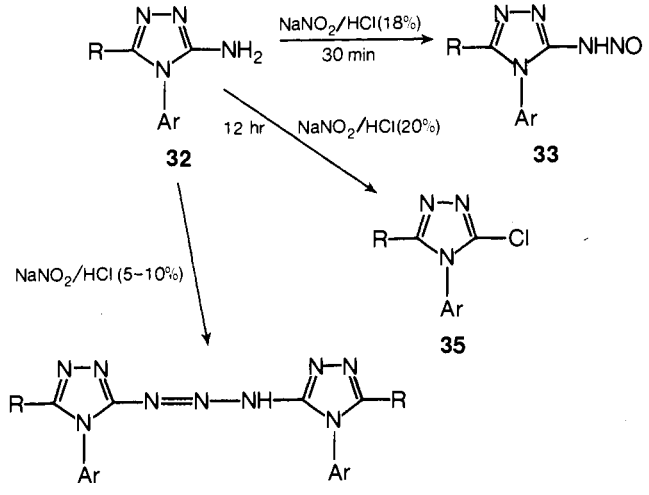
30 with R = aryl,[42,43] alkyl,[44,45] carboxy, and carbomethoxy[46,47] have been reported. The salts may be chlorides, tetrafluoroborates, perchlorates, or nitrates, and the ring N-H bond is reported to be highly acidic.[42] These diazonium salts are useful for further syntheses of triazole derivatives. Azido-[49] and hydroxydediazoniation[47,48] both occur readily and nitrodediazoniation with sodium nitrite gives the 3-nitrotriazole derivative.[46] The parent diazonium salts **30** (R = H) have also been prepared and coupled in high yields (78–82%) with *N*,*N*-dialkylanilines.[50] Treatment of the compounds **30** (R = H) with nitroalkane anions in NaOH solution yielded the hydrazones[51] **31**.



31

Diazotization of the 4-N-substituted aminotriazoles **32** with sodium nitrite in hydrochloric acid yielded the stable primary nitrosoamines[52] **33.** The reaction was particularly sensitive to the hydrochloric acid concentration, and best yields of the nitrosoamines were obtained with ca. 18% HCl although optimum conditions varied with the amine (Scheme II). In more dilute acid solution the diazoamino

SCHEME II



34

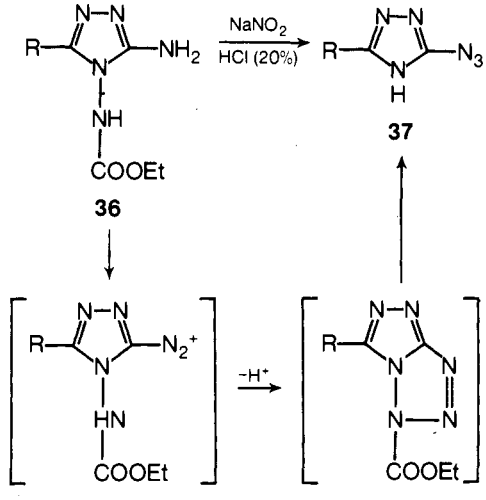
R = *n*-alkyl; Ar = *p*-XC_6H_4

compounds **34** were the products and, when the diazotization solution was stirred for longer periods with slightly more concentrated acid, the 3-chlorotriazoles **35** were formed. The nitrosoamines **33** gave positive Liebermann tests, and elemental and molecular weight analyses were consistent with a nitrosoamine or diazohydroxide structure. They were reduced to the corresponding hydrazones under mild conditions with zinc dust in acetic acid and gave azo-coupling reactions with *N,N*-dimethylaniline in acidic alcoholic solutions.[52] The diazotization of the 4-N-substituted triazoles **32** therefore contrasts with that of the N-unsubstituted cases by stopping at an earlier stage. This phenomenon is a feature of the diazotization of many amines of the higher azoles (below) and provides direct evidence for the intermediacy of primary nitrosoamines in the diazotization process.

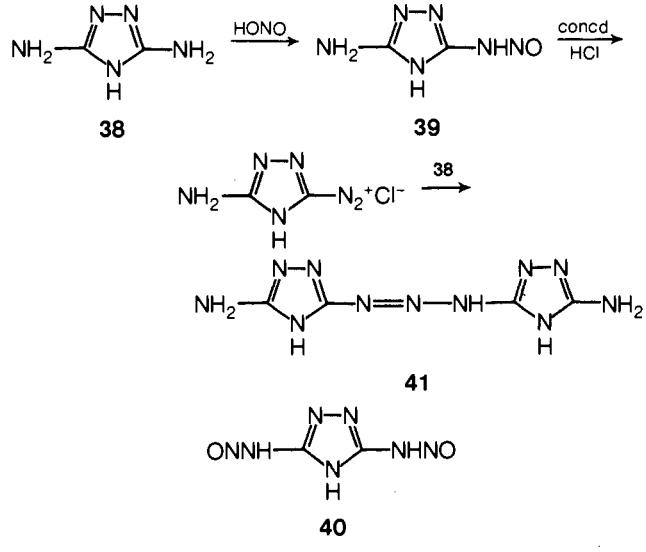
Primary nitrosoamines have not been isolated with 4-N-substituted-1,2,4-triazole systems where the 4-N substituent is itself reactive. Thus, when the 4-N-substituent is an amino group, N-deamination occurs along with normal diazotization of the C-amino group, and the products are the compounds **30** (R = H).[53,54] If the 4-*N*-amino group is protected by acylation, e.g., compounds **36,** diazotization yields the triazolyl azide **37** in an interesting reaction and no nitrosoamines have been detected.[55,56] A mechanism involving a triazolotetrazole intermediate (Scheme III) has been suggested.[55]

The primary nitrosoamines **39** and **40** have been reported from the diazotization of 3,5-diamino-1,2,4-triazole **38** with sodium nitrite in dilute acetic acid.[57] Concentrat-

SCHEME III



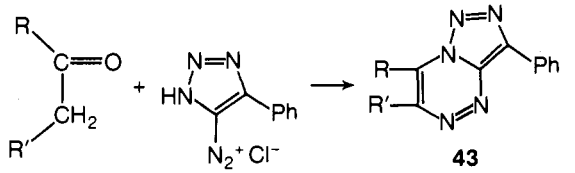
ed hydrochloric acid converts compound **39** to a diazonium chloride.[57,58] The material **39** has also been prepared in more recent times[59] when it was treated with hydrochloric acid and coupled with the parent amine **38** to give the diazoamino compound **41,** without particular reference to its structure. A modern structural confirmation on compounds **39** and **40** seems desirable. They are the



only such compounds containing a labile H atom on the heterocyclic ring, and they contrast with the other ring-unsubstituted 1,2,4-triazoles discussed above, although these compounds have not been diazotized in dilute acetic acid solution. For example, the evidence quoted[58] for structure **40** is a reduction to the dihydrazine with stannous chloride and concentrated hydrochloric acid and the cleavage of nitrous acid from the compound on warming with dilute hydrochloric acid. Such reactions are not conclusive proofs for the primary nitrosoamine structures.[59a] It is also of interest that the compounds **33** gave positive Liebermann nitroso reactions while the materials **39** and **40** did not. Also in cases where some other heterocyclic amines have been diazotized in aqueous acetic acid or very dilute mineral acids, diazoamino compounds were formed, e.g., compounds **11, 34** (also **48** below). These often separate as hydrates and are cleaved by concentrated hydrochloric acid to hydrazines and amines. Nitrous acid deamination of both N- and C-amino groups in 1,2,4-triazoles has also been used in triazole synthesis to prepare parent ring systems, particularly with fused triazolo heterocycles.[60]

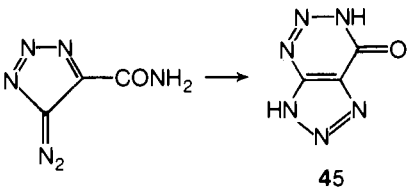
2. 1,2,3-Triazoles

In general, there have been few reports of diazotization of amino-1,2,3-triazoles.[8] The diazonium salt **42** of 4-phenyl-5-amino-1,2,3-triazole has been prepared and coupled with acetylacetone and similar carbonyl compounds in aqueous ethanol containing sodium acetate to give triazolotriazines of type[61] **43.** This useful reaction may involve the diazo form of compound **42.**



42 **43**

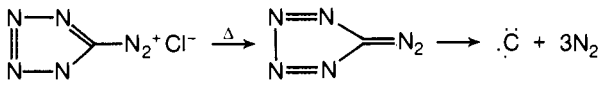
The diazo-1,2,3-triazole **44** was formed directly when 5-amino-1,2,4-triazole-4-carboxamide was treated with pentyl nitrite in aqueous acetic acid.[40] When the reaction was carried out, using sodium nitrite in aqueous acetic acid followed by adjustment of the solution to pH 9 with 1 *M* NaOH, the product was the 2,8-diazahypoxanthine **45,** resulting from cyclization of compound **44.**



44 **45**

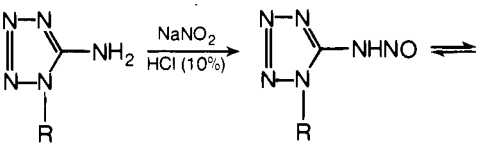
C. Tetrazoles

Diazotization of 5-aminotetrazole[62-64] with sodium nitrite in hydrochloric acid readily yields the diazonium salt **46** which is highly explosive.[65] Recently, Shevlin[63] has isolated compound **46** as a crystalline solid by treating 5-aminotetrazole with isoamyl nitrite in THF containing hydrochloric acid. Controlled thermal decomposition of compound **46** has been used to produce atomic carbon whose reactions with carbon monoxide and ethylene have been reported.[63,64] Hydrogenodediazoniation of compound **46** with hypophosphorous acid has been developed as an effective synthesis of tetrazole itself, particularly by carrying out the diazotization of the readily available 5-aminotetrazole in hypophosphorous acid.[66] Reduction of the salt **46** with $SnCl_2$ in HCl yields the corresponding hydrazine.[67] When the labile hydrogen atom

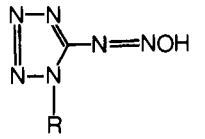


46

of the tetrazole ring is replaced by an alkyl or aryl substituent, diazotization of 1- or 2-substituted 5-aminotetrazoles with sodium nitrite in 10% hydrochloric acid parallels that of the ring-substituted 1,2,4-triazoles and the products are the stable primary nitrosoamines[68-70] **47.** These compounds are readily reduced to hydrazines by zinc dust in aqueous acetic acid,[69] a characteristically easy reaction also observed with secondary 5-nitrosoaminotetrazoles.[71] Heating the compounds **47** in aromatic hydrocarbons resulted in displacement of the nitrosoamine moiety in a Gomberg–Bachmann-type reaction which yielded the corresponding 5-aryltetrazoles,[69] probably by homolysis of the diazohydroxide form **47a.** Spectra of the nitrosoamines suggest that the main structural contributions come from the tautomeric forms[69] **47** and **47a.** Diazotization of 2-benzyl-5-aminotetrazole also yielded a primary nitrosoamine as a viscous oil. On the other hand, treatment of 2-methyl-5-aminotetrazole with amyl nitrite in aqueous acetic acid[72] or sodium nitrite in dilute nitric acid[73] yielded the diazoamino compound **48,** and the primary nitrosoamine was not encountered, although compound **48** could have been formed from it. A primary nitrosoamine has been reported[68] from the diazotization of 1-methyl-5-aminotetrazole, but recent attempts[69,70] to isolate this compound have been unsuccessful and only with larger ring substituents were the compounds **47** readily encountered.

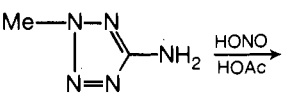


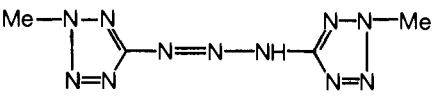
47



R = benzyl, *p*-XC_6H_4

47a

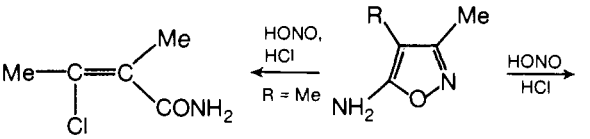




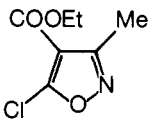
48

D. Oxygen Azoles

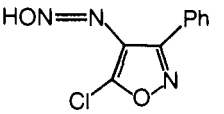
Treatment of the 5-aminoisoxazole **49** with nitrous acid in a large excess of hydrochloric acid yielded the corresponding 5-chloro derivatives[74] **50** probably via a diazonium salt. When the 4-ethoxycarbonyl substituent was replaced by a methyl group, degradation of the ring occurred under the same conditions, yielding compound[75] **51.** Wieland[76] in 1903 reported that diazotization of



51 R = −COOEt **49**



50



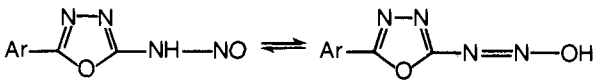
52, R = H

53, R = Me

3-phenyl-4-aminoisoxazole gave an unstable diazo compound which may have structure **52.** Diazotization of 5-methyl-4-amino-3-phenylisoxazole with sodium nitrite in dilute sulfuric acid has also been reported.[77] The product, which may have been a form of compound **53,** was

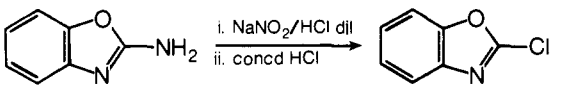
not investigated but treated in situ with concentrated hydrochloric acid to give the corresponding 4-chloro derivative or heated directly to give the 4-hydroxy derivative.[77]

Diazotization of 2-aryl-5-amino-1,3,4-oxadiazoles with sodium nitrite in 10% hydrochloric acid gave the stable primary nitrosoamines[69,70,78] **54.** These compounds give positive Liebermann nitroso tests and undergo the ready reduction to hydrazines and the homolytic displacement of the nitrosoamino group already mentioned for the tetrazoles **47** above.[69] Infrared spectra suggest the presence of both forms **54** and **54a.**



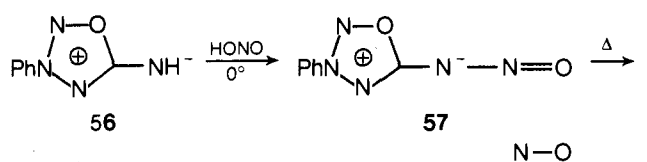
54 **54a**

Diazotization of 2-aminobenzoxazole **55** with sodium nitrite in dilute hydrochloric acid has been reported[79] but the products were not isolated. The solution instead was treated with concentrated hydrochloric acid and yielded 2-chlorobenzoxazole,[79] as would be expected whether the initial product of the diazotization in dilute acid was a diazonium salt or a primary nitrosoamine.

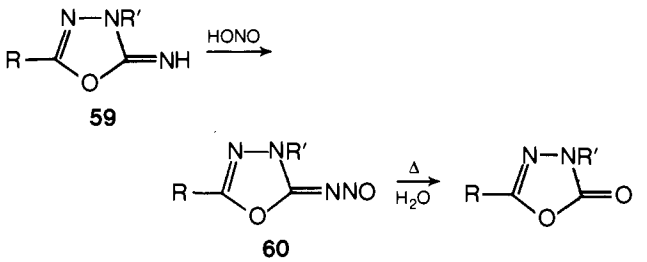


55

Recently, an interesting reaction of the mesoionic oxatriazolio amide **56** with nitrous acid has been reported.[80-82] The product was the unstable *N*-nitroso compound **57,** which lost nitrogen on warming to room temperature yielding the oxide **58.** Treatment of the 2-imino-1,3,4-oxadiazoles **59** with nitrous acid also resulted in nitrozation of the exocyclic imino-nitrogen atom yielding the nitrosimines[83] **60.** These hydrolyzed to triazolones when heated in water.[83]



56 **57** **58**

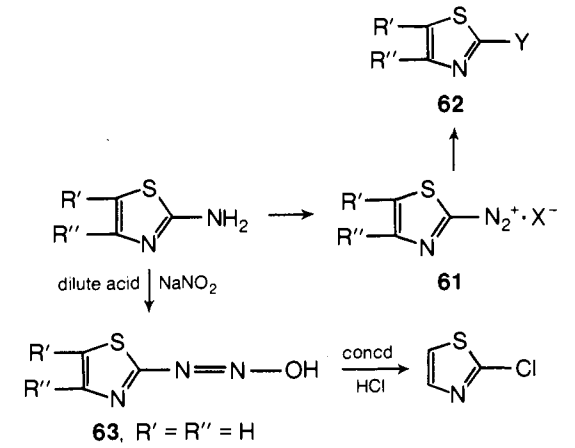


59 **60**

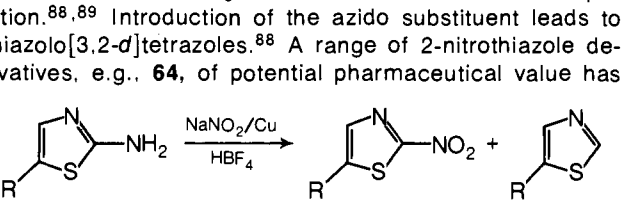
E. Sulfur Azoles

1. *Thiazoles and Isothiazoles*

2-Aminothiazoles and 2-aminobenzothiazoles are readily diazotized to diazonium salts, e.g., **61** with sodium nitrite in strong oxyacids such as phosphoric acid,[84] sulfuric acid,[85] or nitric acid.[85] In concentrated hydrochloric acid the diazonium salts react rapidly and 2-chlorothiazoles are formed.[85,86] The diazonium salts couple normally with aromatic hydrocarbons and phenols.[84] Normal dediazoniation reactions, e.g., **61** → **62** are also observed.[87] A wide range of dediazoniations with thiazole-2-diazonium tetrafluoroborates **61** (X^- = BF_4^-; R′, R″ = alkyl, aryl) has been achieved, and substituents such as Cl, Br, I, F, and N_3 have been introduced at the 2 position.[88,89] Introduction of the azido substituent leads to thiazolo[3,2-*d*]tetrazoles.[88] A range of 2-nitrothiazole derivatives, e.g., **64,** of potential pharmaceutical value has been prepared by diazotization of 2-aminothiazole derivatives with nitrous acid in the presence of copper by the nitro-Sandmeyer reaction.[90-93] In some cases hydrogenodediazoniation occurs as well as the nitrodediazoniation, yielding deaminated products,[90] e.g., **65.** Diazotization of **2**-aminothiazole in dilute acid solution gave an unstable orange red solid thought to be the diazohydroxide[85,94] **63.** This solid, when treated with concentrated hydrochloric acid, gave 2-chlorothiazole. Aprotic diazotization of 2-aminothiazoles with isoamyl nitrite in aromatic hydrocarbons has been used to[95,96] obtain thiazol-2-yl radicals by thermolysis of diazoates such as **63** (OH replaced by *O*-alkyl) in a reaction similar to that observed with the compounds **47** and **54.** Attempts to obtain thiazolynes by treating 2-aminothiazoles with isoamyl nitrite in ethylene chloride were unsuccessful.[97]



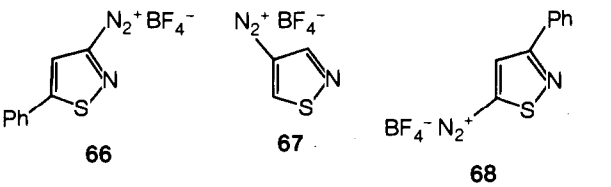
62 **61** **63**, R′ = R″ = H



64 **65**

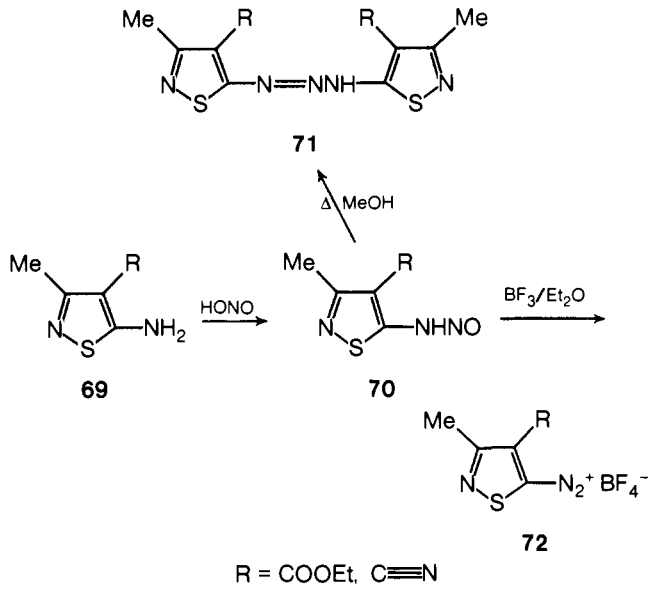
R = 1,2,4-oxadiazol-3-yl

The diazonium salts **66–68** have been isolated from the diazotization of 3-, 4-, and 5-aminoisothiazoles with nitrosyl tetrafluoroborate in a 1:1 mixture of acetic and propionic acids.[98] These diazonium salts undergo coupling and dediazoniation reactions.[99-101] Isothiazolediazonium salts may also be generated in solution for further reaction by treating the amine with sodium nitrite and concentrated acids.[98]



66 **67** **68**

When the 5-aminoisothiazoles **69** were treated with sodium nitrite in dilute sulfuric acid, 80% phosphoric acid, or formic acid, the stable primary nitrosoamines **70** were obtained.[98] These compounds, when heated in methanol,

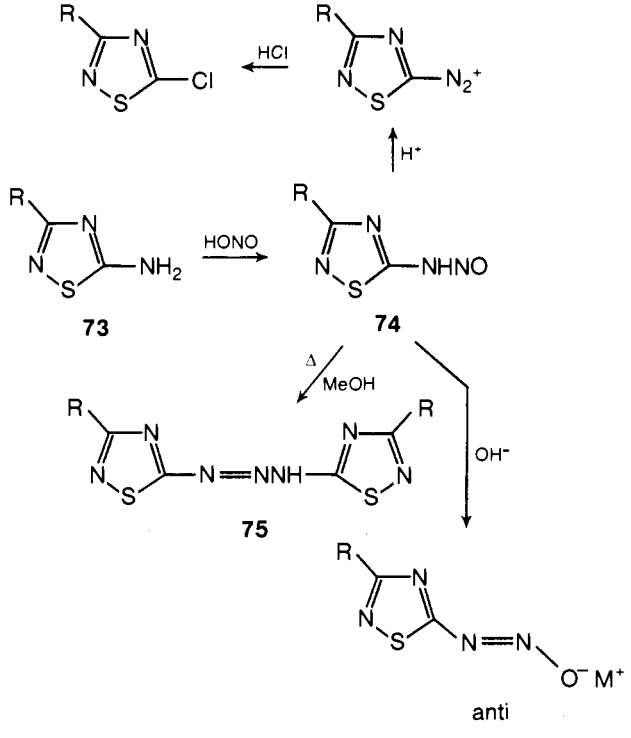


R = COOEt, C≡N

gave the diazoamino compounds **71.** Treatment of the nitrosoamines **70** with boron trifluoride etherate gave the diazonium fluoroborates **72.** The nitrosoamines **70** are of particular interest since they are among the few such compounds which do not have the nitrosoamine moiety bonded directly to a C=N unit (cf. section II.F).

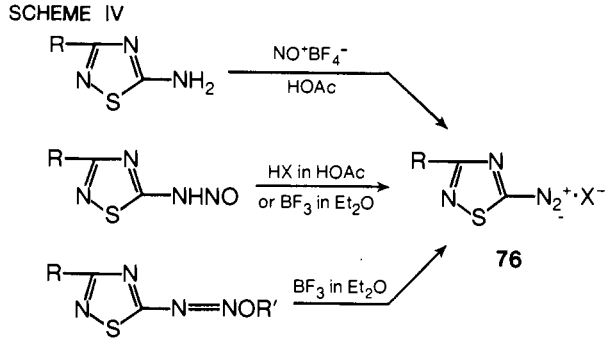
2. *Thiadiazoles*

Diazotization of 5-amino-1,2,4-thiadiazoles **73** with sodium nitrite in 2 *N* sulfuric acid yielded the stable primary nitrosoamines[102] **74.** Infrared and ultraviolet spectra were consistent with the primary nitrosoamine structure of the compounds, and alkali solutions of the compounds showed properties characteristic of an anti (iso) diazoate form.[102] Electron-withdrawing substituents stabilized the nitrosoamines, and a dilute acid medium for the diazotization gave enhanced yields of the compounds. The yield of the nitrosoamine, in fact, varied almost inversely with the acidity of the medium.[102] In acidic solution the nitrosoamines were in equilibrium with the diazonium form,

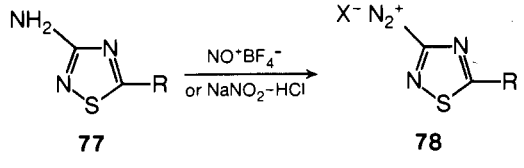


and coupling with β-naphthol and both chloro- and hydroxydediazoniations were possible.[102] When heated in methanol, two molecules of nitrosoamine combined to form the triazenes[103] **75.** The 1,2,4-thiadiazole-5-diazonium salts **76** have been obtained by a number of routes as shown[104] (Scheme IV). These compounds undergo

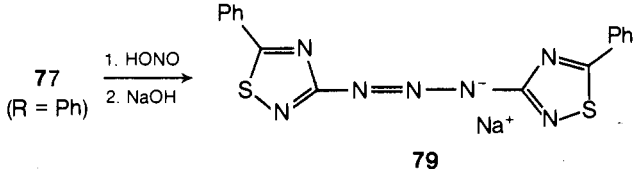
SCHEME IV



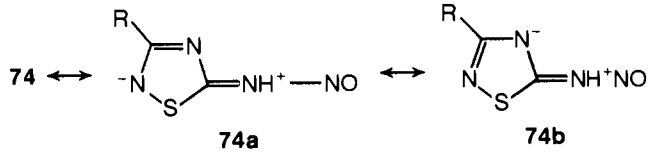
dediazoniation and coupling reactions[84] thereby providing routes to a wide range of 5-substituted thiadiazole derivatives.[104] Diazotization of 3-amino-1,2,4-thiadiazoles **77** also gave diazonium salts **78** but with these compounds primary nitrosoamines have not been encountered.[104-107] The compounds **78** were unstable[107] but useful dediazo-



niations have been achieved.[104-107] For example, heating the diazonium fluoroborate gives the corresponding 3-fluorothiadiazole.[104] Sandmeyer-type reactions were best carried out in situ with the reagents present during the diazotization.[106] Interestingly, when the compound **77** (R = Ph) was treated with nitrous acid followed by an excess of sodium hydroxide, the expected sodium diazoate was not encountered.[107] Instead the product proved to be the triazene salt[107] **79.** The failure to detect or isolate

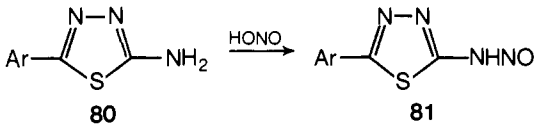


primary nitrosoamines from the 3-amino-1,2,4-thiadiazoles suggests a particular instability for these nitrosoamines which is not easily explained although amino groups between two sp^2 nitrogens are known to be exceptionally unreactive. Goerdeler[102] has pointed to the loss of the resonance form comparable to **74a** of the 5-nitrosoamino compounds **74** as a possible explanation for the failure to detect 1,2,4-thiadiazole-3-nitrosoamines.

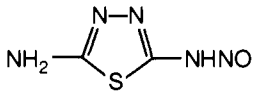


Diazotization of the amino-1,3,4-thiadiazoles **80** with sodium nitrite in dilute hydrochloric acid readily gave the stable primary nitrosoamines[69,108] **81.** These compounds underwent the reduction and homolytic replacement reactions[69] already discussed for compounds **47** and **54.** When the aminothiadiazoles **80** and **73** were treated with

sodium nitrite in phosphoric acid solution, diazonium salts were the products. These exhibited a high coupling reactivity which surpassed even that of diazotized 2,4-dinitroaniline.[84] The nitrosoamine **82** has been reported

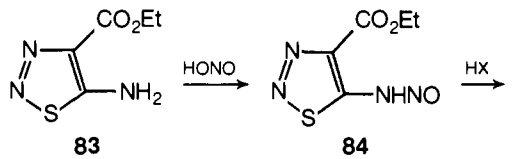


80 **81**

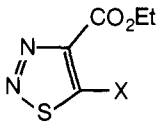


82

from the diazotization of the corresponding diamino compound with sodium nitrite in 12% acetic acid.[78] The compound did not give a Liebermann nitroso test, and the comments made above in regard to compounds **39** and **40** are also applicable. Diazotization of the 5-amino-1,2,3-thiadiazole **83** in 2 *N* sulfuric acid also yielded a stable primary nitrosoamine[109] **84.** In acidic solution this compound gave dediazoniation reactions with such groups as OH, Cl, and Br and it also exhibited diazo coupling with β-naphthol.[109] The compound **84** is also of interest since the nitrosoamino group is not bonded directly to a C=N moiety.

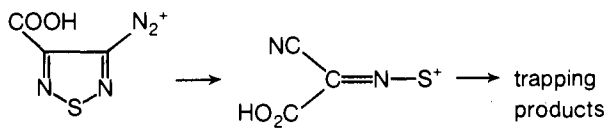


83 **84**



X = OH, Cl, Br

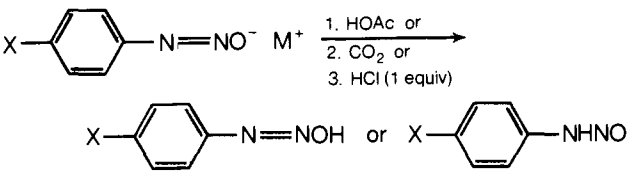
In a recent attempt to generate 1,2,5-thiadiazolyne by diazotization of 3-amino-1,2,5-thiadiazole-4-carboxylic acid, a fragmentation of the intermediate diazonium salt **85** was observed,[110] and the thiadiazolyne was not encountered. Decomposition of 5-amino-1,2,3,4-thiatriazole also occurred when it was treated with nitrous acid in an attempted diazotization.[84]



85

F. Nitrosation vs. Diazotization. Stability of Primary Nitrosoamines

The special stability of the primary nitrosoamines and their significance in the diazotization process is considered here. In general, while primary nitrosoamines have been considered to be unstable intermediates in the diazotization of carbocyclic aromatic amines, attempts to isolate and characterize pure samples of such compounds from normal diazotization reactions have not been successful because of their inherent instability.[111-115] These attempts, in general, involved careful acidification of basic solutions of para-substituted benzenediazoates where the para substituent was electron withdrawing. Thus, for example, a white solid obtained, by acidification of potassium *p*-benzoylphenyldiazoate, was assigned the primary nitrosoamine structure[111] **86** from a comparison of its spectroscopic properties with those of secondary nitrosoamines. Similar solids which may be compounds **87** and **88** have also been isolat-

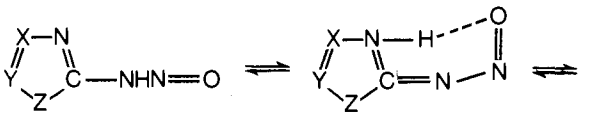


86, X = PhCO (ref **111**)
87, X = NO_2 (ref 112-115)
88, X = Cl

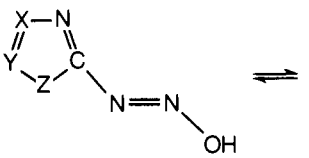
ed[113-115] by careful acidification of the corresponding alkali diazoates with acetic acid, carbon dioxide bubbling, or **1** mol of hydrochloric acid, but definite structural assignments could not be made because of the instability and impurity of the compounds.[112] Primary nitrosoamines of substituted anilines have, however, been obtained by treating the amine with NOCl at −78° in an anhydrous medium under an atmosphere of nitrogen.[116] These had ultraviolet spectra similar to those of the corresponding secondary alkylnitrosoamines.[116] In view of the difficulties associated with the instability of the carbocyclic primary nitrosoamines, the stable heterocyclic primary nitrosoamines, which are isolated directly from the diazotization reaction, afford striking evidence for the intermediacy of such species in the diazotization process.

In theory the heterocyclic primary nitrosoamines could exist in any of the tautomeric forms **89-93** (Scheme V).

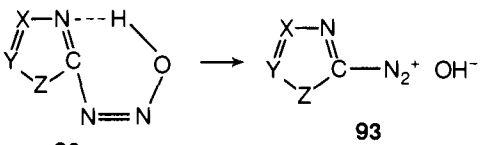
SCHEME V



89 **90**



91 anti

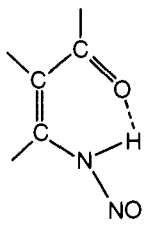


92 syn **93**

The imino form **90** has been ruled out by all of the workers who have isolated primary nitrosoamines to date, and spectroscopic evidence for contributions from forms **89** and a diazohydroxide form has been obtained in recent work. Thus the nitrosoamines generally show a nitroso stretching absorption at ca. 1500-1560 cm^{-1} and an OH bonding band similar to that in oximes at ca. 1435 cm^{-1}. Diazonium absorptions at ca. 2220 cm^{-1} are entirely absent. Exocyclic imino absorptions for the particular heterocycle are also absent as judged by comparisons with model imino compounds.[69,102] Ultraviolet spectra of the nitrosoamines are generally almost identical with those of corresponding secondary alkylnitrosoamines and are quite different from the ultraviolet spectra of model secondary nitrosoimines.[69,102] Such data, therefore, rule out

the possibility of contributions from a form such as **90**. Ultraviolet spectra of tetrazolyl nitrosoamines **47** in sodium hydroxide solution showed absorptions at λ_{max} 273–276 nm which compare with the anti benzenediazoate absorptions at ca. 270–280 nm. The homolytic Gomberg–Bachmann-type reactions exhibited by the nitrosoamines[69] also suggest the presence of a diazohydroxide form. No detailed study appears to have been made on the possibility of syn–anti isomerism in solution, and such isomeric forms have not been encountered. An investigation of this nature might prove fruitful since the nitrosoamines are stable and can be purified. On the other hand, with the carbocyclic compounds, where these intermediates cannot be isolated in pure form, extensive and controversial[112,117-122] studies on the equilibria of the syn and anti isomers which exist in solution at various pH's have been carried out. However, it seems to be generally accepted now that both syn and anti forms of diazoates and diazohydroxides do exist in solution and that the diazonium form arises from the syn diazohydroxide.[10,112,122,123]

Among the various types of heterocyclic amines from which primary nitrosoamines have been isolated, three common structural features which appear to favor the formation of the nitrosoamines are recognizable. (i) Electron-withdrawing substituents and electron-withdrawing rings tend to stabilize the nitrosoamines probably by resonance as in forms **74** ↔ **74a** ↔ **74b**. This stability is also probably reflected in the general observation that primary nitrosoamines are more ubiquitous among the higher azoles. (ii) The presence of labile ring protons appears to militate against the nitrosoamines and to favor the diazonium forms. This is clearly evident with the 1,2,4-triazoles and tetrazoles, and indeed the only primary nitrosoamines encountered with a labile proton in the ring were the compounds **39** and **40**. (iii) With the exception of the compounds **70** and **84** all of the primary nitrosoamines isolated have the nitrosoamino moiety bonded directly to a >C=N unit. The compounds 70 and **84** each have the nitrosoamino group bonded to a >C=C< unit, but the α-carbon atom in each case carries a substituent capable of hydrogen bonding with the N–H of the nitrosoamino group, e.g., **94**, and, as suggested by Goer-



94

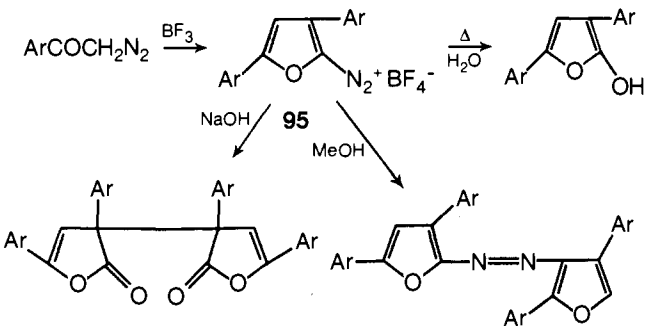
deler and Gnad, (cf. ref 109, footnote **16**), such hydrogen bonding may stabilize the nitrosoamine. The conditions of the diazotization may also favor either nitrosoamine or diazonium formation and, in general, the acidity of the medium appears to be critical. Nitrosoamines are favored under dilute acid conditions, and diazonium formation is favored under strong acid conditions. It is relevant to mention, at this point, that the three structural features (above), which appear to favor primary nitrosoamine formation with the five-membered ring systems, are also present in most six-membered heterocyclic amines; e.g., 2-aminopyridine has a deactivated ring, no labile hydrogen atoms, and the amino group bonded to a C=N unit. Yet stable primary nitrosoamines of the six-membered heterocyclic systems have not been isolated or even directly detected and, if nitrosoamines are involved during diazotization of these systems, they must be highly unstable.

In the absence of definite kinetic data on the equilibria involved in the heterocyclic diazotization solutions, it is not possible yet to fully rationalize the above observations. However, it is tentatively suggested here that the isolation of the primary nitrosoamines must imply a stopping of the sequence of equilibria **89** → **93** at some point prior to the formation of the diazonium form. If the isomerism already established for the carbocyclic amines also applies in the heterocyclic case, then a likely stopping point in the sequence is a stabilization of the syn diazohydroxide form **92** by an intramolecular hydrogen bond as shown. Labile protons undergoing annular tautomerism should disrupt this stabilization, thereby allowing diazonium formation to occur. Strong acid, by protonating not only the nitrosoamino moiety but also the cyclic >C=N– lone pair, should prevent this stabilization and therefore favor diazonium formation. The amino derivatives of the six-membered nitrogen heterocycles are considerably stronger bases than those of the higher azoles,[124] and imidazole alone among the azoles compares with them in basicity.[124] Hence, even in dilute acidic solution the cyclic >C=N– lone pair of the six-membered heterocyclic ring may be considerably more protonated than that of the five-membered ring, and stabilization as in form **92** may thus be prohibited for these compounds. Kalatzis[125] has investigated the kinetics of diazotization of 4-aminopyridine in 0.0025–5.0 *M* perchloric acid and found that the reaction proceeds by a single mechanism over the entire range of acidity. The reaction, which showed a rate dependence on the ionic strength of the medium, was acid catalyzed and first order in amine and nitrous acid. The rate was comparable with the rates of nitrosation of *N*-methylaniline[6] and diazotization of aniline,[7] and the results were interpreted in terms of a reaction between the ring-protonated amine and nitrous acidium ion leading to a primary nitrosoamine and subsequently to a diazonium salt. Kalatzis[125] suggested that the nitrosation of the amino moiety was facilitated by the formation of an initial complex between the nitrous acidium ion and the electrons of the aromatic ring. These conclusions are in agreement with the synthetic work on the five-membered amines, and the data also suggest that ring protonation may account for the failure to isolate stable primary nitrosoamines with six-membered systems with basicities similar to that of 4-aminopyridine. The question as to whether the primary nitrosoamines of the five-membered systems are protonated in the relatively dilute acidic solutions from which they are obtained has not been investigated. Indeed, at the present time, possibly the most obscure area in the diazotization of the five-membered heterocyclic amines is the early part of the reaction. The early steps in aqueous diazotization of carbocyclic amines have been categorized into three types: (i) uncatalyzed, (ii) hydrogen-ion catalyzed, and (iii) anion catalyzed.[126] Until such an analysis is possible for the full heterocyclic series, the general synthetic patterns recognized herein will not be fully rationalized. Hence the above suggestion must be viewed in this light and in the further realization that amine protonation effects in the heterocyclic series may be considerably more complex than in the carbocyclic series. For example, while diazotization of amino derivatives of the higher five-membered azoles may lead to diazonium salts in concentrated acid and to primary nitrosoamines in relatively dilute acids, in some cases the reaction in very dilute acid leads to triazene derivatives directly, e.g., compounds **11**, **34**, and **48**.

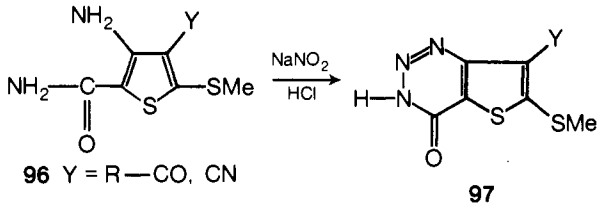
III. Five-Membered Ring Systems. Miscellaneous and Non-Azoles

Little work has been carried out on diazotizations of five-membered heterocyclic amines with ring systems other than those described above, mainly because of paucity of suitable stable amines. In the furan series, 2-methyl- and 2,5-dimethyl-3-aminofuran have been treated with sodium nitrite in 10% sulfuric acid solution.[127] Transient blue-green colors were observed after each addition of sodium nitrite, and the diazotization product coupled normally with β-naphthol but not with dimethylaniline.[127] Normal dediazoniation reactions could not be carried out. However, the coupling reaction with β-naphthol may suggest that a diazonium group was indeed present at the furan 3 position. Preparation of a furan with a diazonium group at the 2 position, compound **95**, has also been achieved but not from the parent amine.[128] This diazonium compound underwent normal hydrolysis and also gave the interesting reactions outlined in Scheme VI.

SCHEME VI



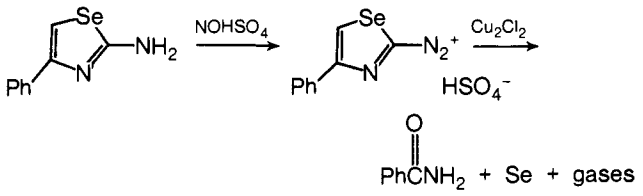
2-Aminothiophene has been successfully diazotized in the form of a double salt $(C_4H_3S\text{-}NH_2\cdot HCl)_2\text{-}SnCl_4$, in 10% hydrochloric acid solution with sodium nitrite.[129,130] The product was a diazonium salt which gave a wide range of coupling reactions leading to a number of azo dyes in the thiophene series.[130] Recently, the diazotization of the 3-aminothiophene-2-carboxamides **96** in concentrated hydrochloric acid has been reported to yield the thieno-1,2,3-triazines[131] **97**. This reaction parallels those observed with compounds **24** and **44** above. A similar reaction was observed with the 4-carboxamide derivatives, and with 2,4-dicarboxamide derivatives cyclization of the diazo group to the 2 position was preferred.[131]



96 Y = R—CO, CN

97

Diazotization of the hydrochlorides of 2-aminoselenazole and 2-amino-5-phenylselenazole with nitrosylsulfuric acid in a 1:1 mixture of concentrated sulfuric and phosphoric acids has been attempted.[132] Treatment of the diazonium solutions with Cu_2Cl_2 yielded only decomposition products, and free selenazoles could not be obtained.[132] The diazonium solutions gave purple colors when treated with β-naphthol at pH 3–4.



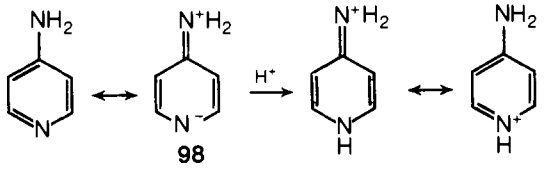
IV. Six-Membered (π-Deficient) Ring Systems

A. Pyridines and Compounds with One Heteroatom

1. Aminopyridines

The diazotization reactions of the six-membered heterocyclic amines differ from those of the five-membered systems in that the same variety of products is not encountered and primary nitrosoamines have not been isolated or directly detected. With the six-membered systems the products are generally diazonium salts or their dediazoniation products. 3-Aminopyridines are readily diazotized and coupled and behave like normal aromatic amines.[11,133] Pyridine-3-diazonium fluoroborate was isolated when the amine was diazotized in 40% fluoboric acid.[134] The 2-diazonium isomer could not be isolated and 4-isomer was isolated but once from many attempts.[134] The Schiemann reaction with the diazotization products of 2-, 3-, and 4-aminopyridines in 40% fluoboric acid yielded 2-fluoropyridine (34%) and 3-fluoropyridine (50%), but the unstable 4-fluoro derivative was not isolated.[134] However, 4-fluoropyridine has been successfully prepared recently in 22% yield by treating 4-aminopyridine with sodium nitrite in fluoboric acid.[135] The compound was stable at 5–10° in a sealed ampoule and was isolated by vacuum distillation from the neutralized diazotization solution.[135] An impure sample of the compound was also obtained in earlier work[136] by treating 4-aminopyridine with sodium nitrite in hydrogen fluoride. Pyridine-2- and -3-diazonium fluorosilicates, $(C_5H_5N\text{—}N_2)_2SiF_6$, have also been prepared by treating the amine fluorosilicate with ethyl nitrite in anhydrous acetic acid.[137] Higher yields of 2-fluoropyridine were obtained from diazonium fluorosilicates than from the Schiemann reaction, but lower yields were encountered with the 3-fluoro isomer.[137] Diazotization of aminopyridines in anhydrous HF followed by heating in an autoclave also gave fluoropyridines but in lower yields than from diazonium fluoroborates or fluorosilicates.[137]

In general, 2- and 4-aminopyridines tend to be resistant to diazotization in dilute mineral acids or form the corresponding hydroxy or halogeno derivatives when a reaction occurs.[138] Recently, however, it has been demonstrated that these compounds diazotize normally in aqueous hydrochloric, sulfuric, and perchloric acid solutions giving diazonium salts which were directly detected from ultraviolet spectra measured immediately after diazotization.[139] The diazonium salts couple with β-naphthol and hydrolyze rapidly to the corresponding hydroxy compounds in dilute acidic solutions.[139] When the diazonium solutions were rapidly brought to pH 10–11, stable alkali diazoates were formed. In view of this work it seems likely that similar heterocyclic amines, which tend to resist diazotization, may well behave normally if the correct conditions are employed. The unreactivity of compounds such as 2- and 4-aminopyridines towards diazotization may be understood in terms of contributions from reso-

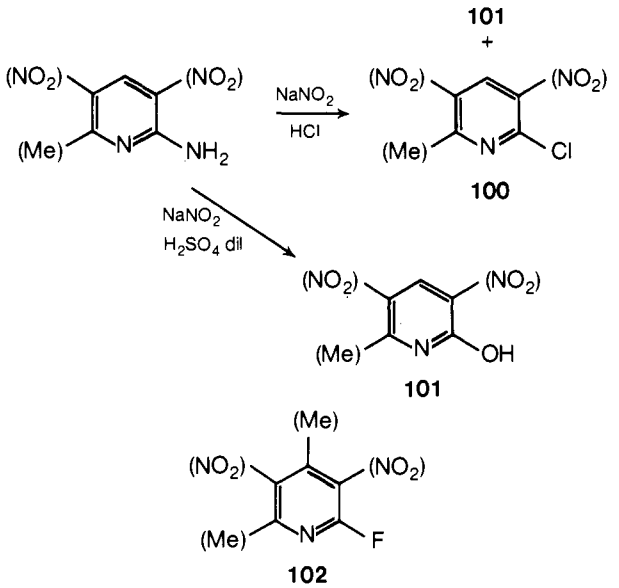


98 **99**

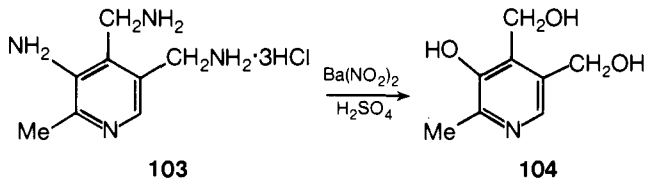
nance forms such as **98** and from the amidine-type nature of these compounds.[11] If, as is likely, the protonated form **99** enters the diazotization reaction, lesser reactivity still may be expected. Recent studies[125] of the mechanism of diazotization of 4-aminopyridine have been discussed in section II.F.

2. *Substituted Aminopyridines*

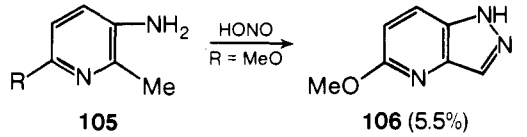
Dediazoniation reactions carried out in situ have been widely used in the synthesis of various pyridine derivatives. 2-Fluoro-3-methylpyridine has been obtained in low yield by diazotization of the 2-amino derivative in anhydrous hydrogen fluoride.[140] Series of the 2-chloro derivatives **100** and the 2-hydroxy derivatives **101** have also been obtained from diazotization of the corresponding 2-aminopyridines.[141] The 2-fluoro derivatives **102** were formed in 52–85% yields by diazotization of the 2-amino derivatives in 65% hydrogen fluoride.[142]



Diazotization of 3-amino-4,5-bis(aminomethyl)-2-methylpyridine trihydrochloride **103** with barium nitrite in aqueous sulfuric acid gave a high yield of high-purity pyridoxin **104** (vitamin B_6).[143] Attempts to prepare pyrazolopyrimi-



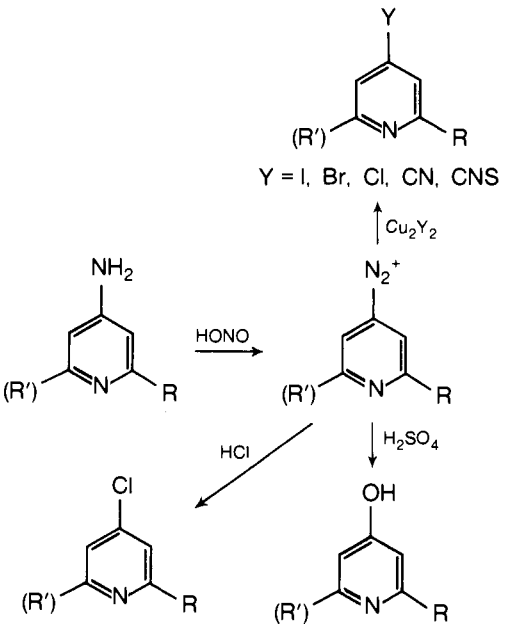
dines by diazotization of 2-methyl-3-aminopyridines **105** gave the corresponding 3-hydroxy derivatives.[144] When the substituent R was a methoxy group, a low yield of the pyrazolopyrimidine **106** was obtained.[144] Similar activa-



tion and internal attack of methyl groups by o-diazonium substituents has been observed in a number of cases with other six-membered heterocyclic systems (sections IV.A.3 and IV.B), and the reaction has been well documented with the carbocyclic analogs.[145]

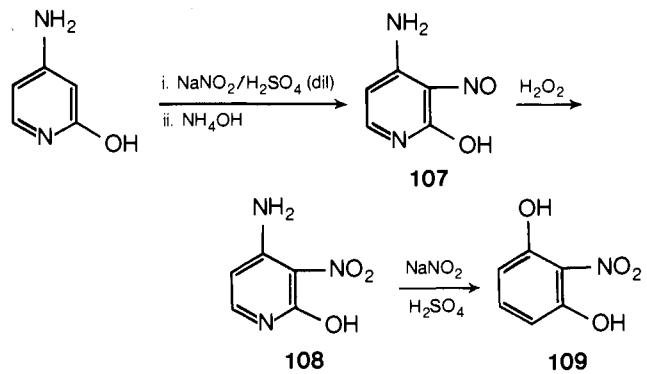
Talik[146-150] has used dediazoniation reactions to introduce a wide range of substituents at the 4 position of the

SCHEME VII

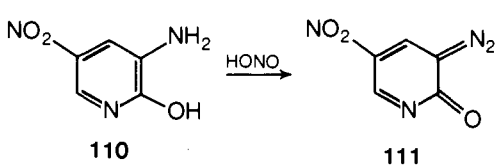


pyridine ring (Scheme VII). It is of interest that these reactions were also successful with 4-amino-2-methoxypyridine[147] since diazotization of 4-amino-2-hydroxypyridine with sodium nitrite in dilute sulfuric acid followed by neutralization with ammonia gave 4-amino-2-hydroxy-3-nitrosopyridine (**107**), presumably by preferential electrophilic attack at the more active 3 position.[151]

Preferential nitrosation of sites more active than the primary amino nitrogen has also been observed with other π-deficient heterocyclic amines[11] (section IV.B). The compound **107** was readily oxidized to the 3-nitro derivative **108** which gave hydroxydediazoniation yielding compound **109** when diazotized in aqueous sulfuric

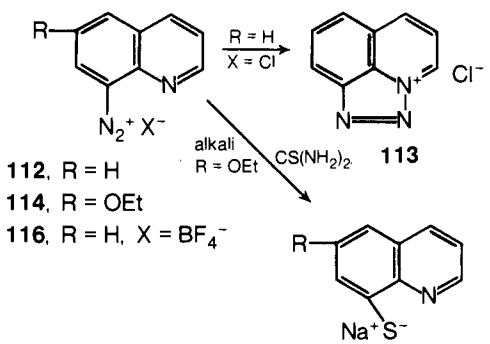


acid.[151] Diazotization of 3-amino-2-hydroxy-5-nitropyridine (**110**) gave the azo compound[152] **111**. This showed a carbonyl band in the infrared and did not possess the pyridine ring vibrations at 1138 and 897 cm^{-1}, thereby suggesting a major contribution from the quinonoid structure.[152] The comparison between the behavior of compound **110** and that of its isomer **108** again illustrates the greater stability of the pyridine-3-diazonium ion.

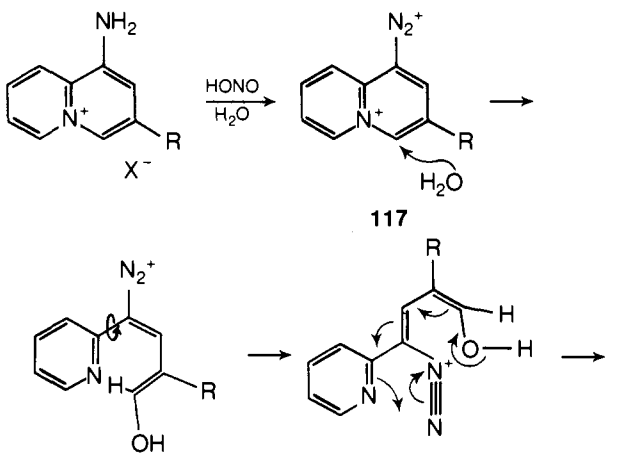


3. Quinolines and Other Systems

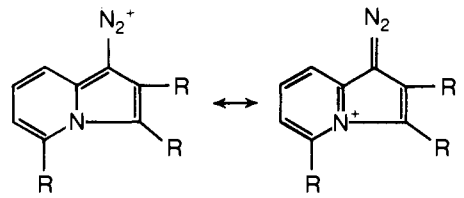
Amino groups at any of the positions 2 to 8 of the quinoline ring system are readily diazotized and undergo dediazoniation reactions.[153] The quinoline diazonium salts are more stable than the corresponding pyridine derivatives. Thus fluoroquinolines with the fluorine at the 2, 3, 4, 5, 6, 7, and 8 positions have been obtained from the corresponding diazonium fluoroborates.[153] Quinoline-3-diazonium fluoroborate was isolated and found to be more stable than the pyridine analog.[153] Quinoline-4-diazonium salts have also been isolated by diazotizing 4-aminoquinolines with sodium nitrite in concentrated sulfuric acid followed by addition of diethyl ether.[154] These, when treated with copper(I) salts, gave normal dediazoniation reactions. Quinoline-2-diazonium fluorosilicate has also been isolated and used to prepare 2-fluoroquiniline.[137] Diazotization of 8-aminoquinolines gave diazonium salts **112** which undergo internal coupling as in[11] **113.** The



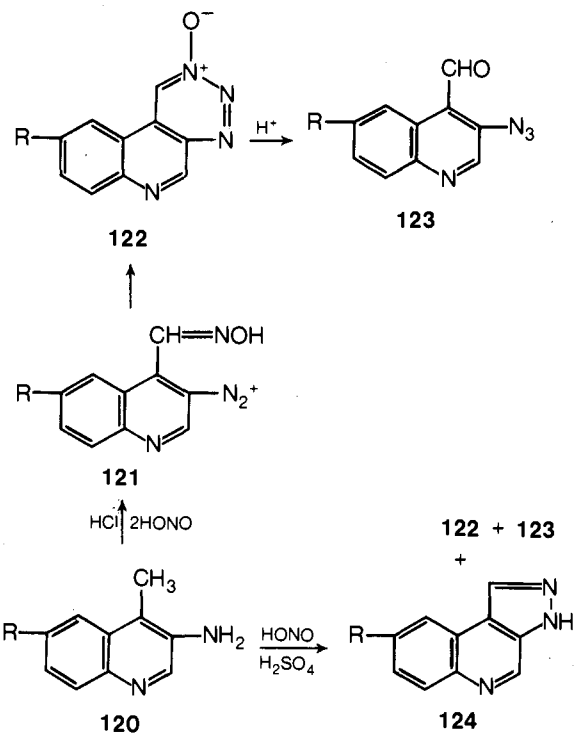
compound **114** has recently[155] been prepared and treated with thiourea and alkali in an interesting reaction which gave the thio derivative **115.** Photolysis of the stable diazonium fluoroborate **116** gave a 19% yield of 8-fluoroquinoline.[156] Diazotization of 3-aminoisoquinoline with sodium nitrite in dilute mineral acids gave 3-hydroxyisoquinoline.[157,158] When the reaction was carried out in dilute acetic acid with isoamyl nitrite, 3-hydroxyisoquinoline acetate was formed[157] and, when concentrated hydrochloric or hydrobromic acid was used, 3-chloro- and 3-bromoisoquinolines were formed along with the hydroxy de-



rivatives.[158] Recently, an interesting rearrangement of the quinolizinium diazonium salts **117** to the 1,2,3-triazolo[1,5-*a*]pyridines **118** has been reported.[159-161] The reaction is considered to involve a nucleophilic attack by water on the 4 position of the unstable dication **117** which results in cleavage of the six-membered ring. Subsequent internal coupling of the diazonium group (similar to **113**) and loss of a proton give the fused triazole ring.[159] The stable indolizine-1-diazonium salts **119** have been prepared by direct nitrosation of the parent compounds and not from the corresponding amines.[162]



Activation of a methyl group by the diazonium substituent has been observed in the diazotization of the 3-amino-4-methylquinolines[163] **120.** The reaction in hydrochloric acid consumed 2 mol of nitrous acid and gave as products the quinolino-*v*-triazine derivatives **122** and the 3-azidoquinoline-4-carboxaldehydes **123.** The species **121,**

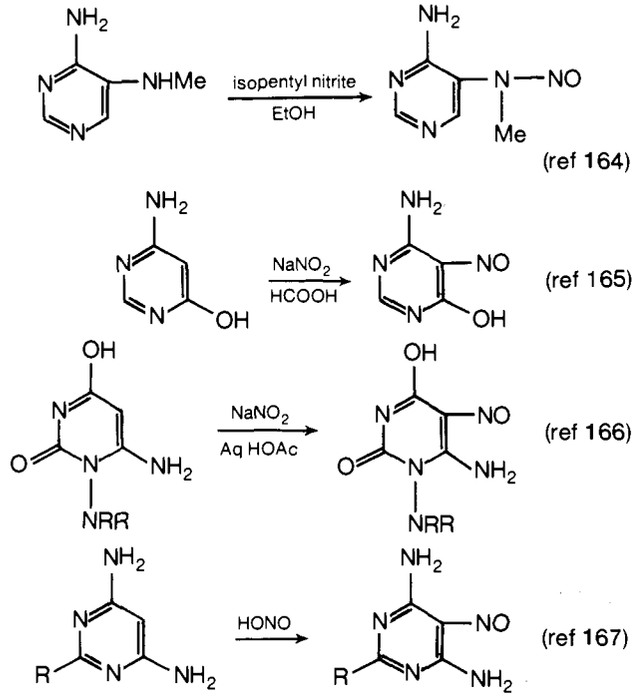


arising from attack of nitrous acid on the 4-methyl group of the diazonium intermediate, is considered to be a precursor to compound[163] **122** (cf. Scheme IX). When the reaction was carried out in sulfuric acid, a further product **124** was obtained by internal diazonium attack on the activated methyl group.[163]

B. Diazines and Compounds with More than One Heteroatom

Most of the recent work on this group of compounds has been concerned with diazotization of aminopyrimidine derivatives of potential pharmaceutical value, and some interesting fused ring systems have been prepared. No primary nitrosoamines have been detected and the

SCHEME VIII

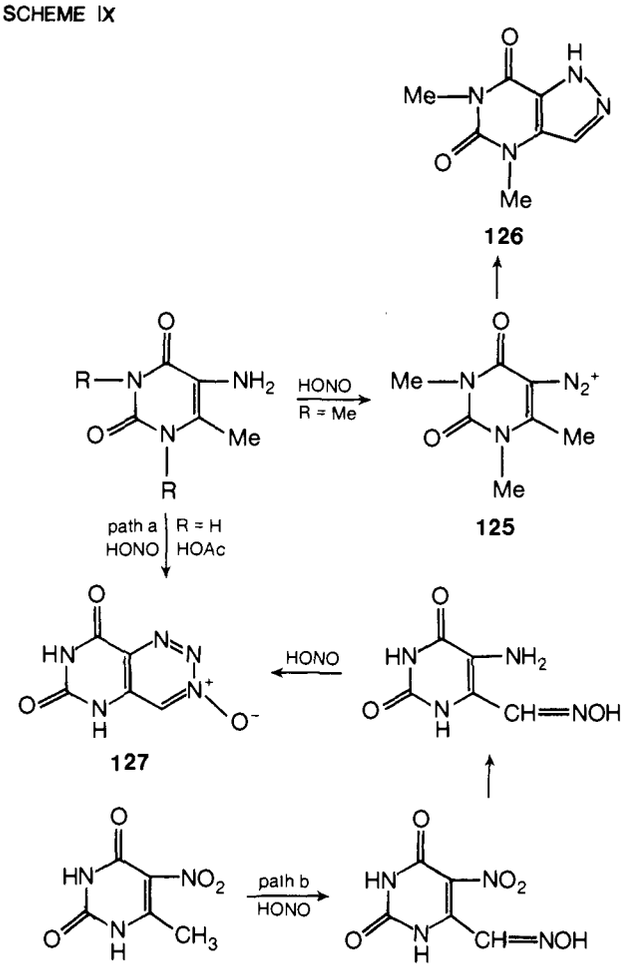


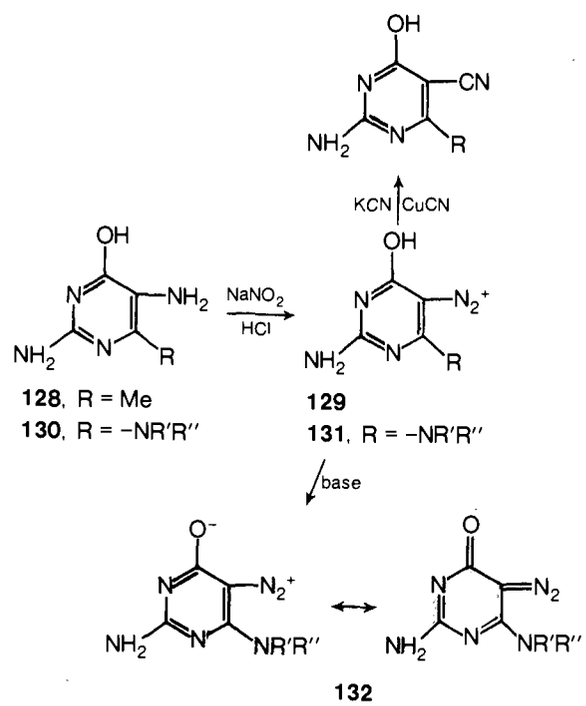
diazotization products are diazonium salts or compounds derived from them. A pattern of reactivity of amino groups toward diazotization, which parallels that of aminopyridines, is evident. Thus 4-aminopyrimidine derivatives, where the amino group is both α and γ to a potential (or actual) sp^2 nitrogen atom, resist diazotization, and the products from the reaction with nitrous acid are generally 5-nitroso derivatives or compounds nitrosated on more active side chain sites[164-167] (Scheme VIII). Although 5-aminopyrimidine itself has been reported not to give a diazonium salt,[168] derivatives of 5-aminopyrimidine are readily diazotized.[169] For example, diazotization of 1,3,6-trimethyl-5-aminouracil gave the corresponding diazonium salt **125** which was cyclized to the pyrazolopyrimidine **126** with strong base.[170] Also 5-aminouridine, when treated with sodium nitrite in acetic acid solution, gave 5-diazouridine.[171]

Treatment of 5-amino-6-methyluracil with excess nitrous acid in acetic acid gave the pyrimido-*v*-triazine[170,172,173] **127** (path a, Scheme IX) in a reaction similar to that of compound **120.** The compound **127** has also been prepared by a different route (path b, Scheme IX) which lends support for the intermediacy of oxime derivatives arising from attack by nitrous acid on the activated 6-methyl substituent of an intermediate diazonium salt.[173]

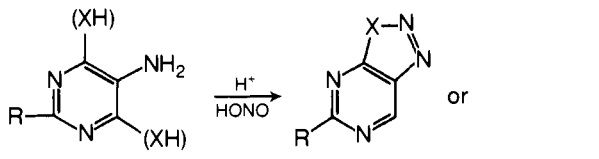
It has been reported recently that solutions obtained by diazotization of 2- and 4-aminopyrimidine in dilute sulfuric acid gave greenish-brown colors with alkaline β-naphthol, but the nature of the products was not elaborated on.[139] The relative reactivities of amino groups at the 2 and 5 positions of the pyrimidine ring are illustrated by the diazotization of compounds **128** and **130.** Diazotization of the diamine **128** gave the diazonium salt **129** which underwent dediazoniation reactions.[174] The compounds **130** were also readily diazotized with isoamyl nitrite in methanolic hydrochloric acid to the diazonium salts **131**, which gave the diazo compounds **132** on treatment with base.[175]

SCHEME IX



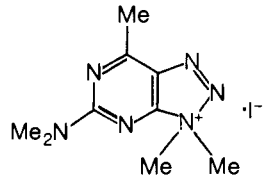


Diazotization of 5-aminopyrimidines containing active substituents in the 4 and 6 positions, e.g., **133**, have led to a range of fused pyrimidine ring systems, e.g., **134** and **135**, including 1,2,3-oxadiazolo-, 1,2,3-thiadiazolo-, and 1,2,3-triazolopyrimidines.[164,172,176,177] The 2-substituent R in these compounds may be NH_2, NHR, NR_2, S-R,[172,176,177] or OH or SH groups.[164] The ring closure of the diazonium group also occurs in alkaline solution when alkyl groups are present in the 4 and 6 positions.[164,172,176] This reaction, which gives pyrazolopyrimidines, was facilitated to the extent that base was not



133, X = O, S, NH, CH_2 134 or 135

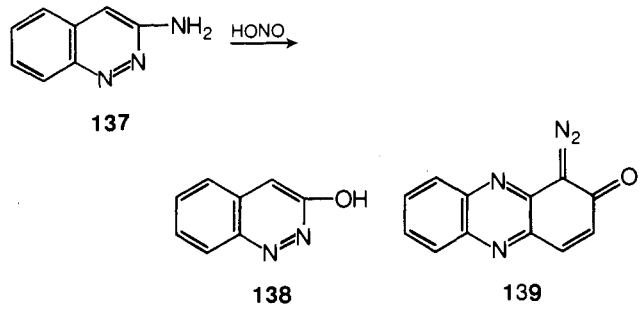
necessary by the presence of Me_2N- substituents on the pyrimidine ring, probably due to their stabilizing influence on the diazonium group.[176] This effect compares with the influence of the MeO group on the similar reaction of compound **105.** In one case the intermediate **136** was



136

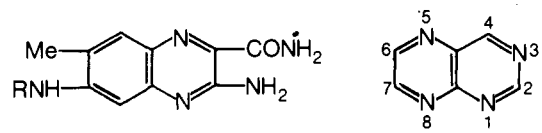
isolated.[176] It seems that internal diazonium attack on adjacent alkyl substituents may be enhanced not only by addition of base to ionize the alkyl group but also by the presence of substituents which increase the lifetime of the diazonium intermediate.

Diazotization of 3-aminocinnoline (**137**) with nitrous acid in dilute mineral acids gave 3-hydroxycinnoline[158] (**138**). In concentrated acids, mixtures of 3-hydroxy- and 3-chloro- or 3-bromocinnolines were obtained.[158] The first diazophenazine, **139.** has been reported from the



137 138 139

diazotization of 1-amino-2-ethoxyphenazine with nitrous acid.[178] The influence of the 1-diazonium substituent rendered the 2-ethoxy group labile to hydrolysis giving compound **139**, and the 2-ethoxyphenazine-1-diazonium salt could not be isolated from the aqueous diazotization mixture.[178] Attempted diazotization of aminopyrazine by normal procedures using dilute aqueous media was unsuccessful.[179] However, diazotization using nitrosylsulfuric acid in concentrated sulfuric acid readily gave hydroxypyrazine, and this procedure was also successful for converting 2-amino-3-carboxypyrazine to 2-hydroxy-3-carboxypyrazine.[179] Attempts to apply the Sandmeyer reaction to diazotized aminopyrazine were unsuccessful since hydroxydediazoniation was more rapid than the attempted halogenodediazoniation.[179] The general unreactivity of an amino group in a pyrazine ring to normal diazotization is also shown in compound **140** where diazotization occurred at the carbocyclic amino group.[180] When this group was protected as in compound **141**, failure to react with nitrous acid was observed.[180] In the pteridine system **142** amino groups at the 4 position were found to be unreactive to nitrous acid, whereas the 2-amino derivatives reacted readily and gave the corresponding hydroxy derivatives.[181,182] In general, it appears that the reactivity of an amino group in the pyrimidine ring of the pteridine system is highly sensitive to substituent effects and, for example, 2,4-diaminopteridines failed to react with nitrous acid.[181,182]



140, R = H
141, R = Ac
142

In concluding, it should be pointed out that, although further information on the diazotization of amino groups bonded directly to higher six-membered heteroaromatic systems does not appear to be readily available, it is not claimed here that some further information does not indeed exist. In a number of the papers already discussed above, we have found that the diazotization work was not the main topic of the paper but often appeared as a minor point in the discussion or in the experimental section and it was not mentioned in either the title, abstract, index entry, or keyword index. There may be a few other such papers, particularly in the nonwestern literature, and this possibility represents a limitation to the coverage of this review.

V. Addendum

This addendum necessarily contains only a brief mention of papers published between January and December 1974.

Five-Membered Ring Systems. Azoles. The increased acidity of the azole ring N-H moiety caused by the presence of a diazonium substituent and the general acid -base equilibrium between diazonium and diazo forms have recently been investigated for the full series of parent azoles.[183] New stable primary nitrosoamine derivatives of N-substituted benzimidazole[184] and benzothiazole[185] systems have been isolated. The isolation of these compounds is in agreement with the trends noted already, and the benzimidazole derivatives represent the first primary nitrosoamines involving the imidazole ring. In each case the nitrosoamines were obtained by acidification of the corresponding alkali diazotate solutions.

New synthetic uses for 4-diazo-3,5-dimethylpyrazole as an oxidizing agent[186] and in coupling reactions with compounds containing active methylene groups[187,188] have been developed. Coupling reactions of 1,2,4-triazole-3-diazonium and tetrazole-5-diazonium salts with phenols and other aromatic systems have been described.[189] Treatment of indazole-3-diazonium salts with active methylene compounds and cyclization reactions of the coupling products have also been reported.[187,190]

In the imidazole series new coupling reactions of 5-diazoimidazole-4-carboxamide with hydrazines[191] and mercapto compounds[192] have been carried out. The synthesis and cyclization, in aqueous ammonia solution, of 5-diazoimidazole-4-thiocarboxamide have also been reported.[193] A range of new 4,5-dicyanoimidazole derivatives has been obtained from reactions involving 2-diazo-4,5-dicyano-2*H*-imidazole.[194]

Six-Membered Rings. In the pyridine series a kinetic study of the diazotization of 2-aminopyridine in 0.0025-5.0 *M* perchloric acid has been reported.[195] The results indicate that the reaction takes place by one mechanism only over the entire range of acidity, and it

was suggested that this involved the protonated amine and nitrous acidium ion with a rate-determining formation of a primary nitrosoamine.[195] An interesting study of the pH dependence of the decomposition of pyridine-2- and -4-diazotates has been published recently.[196] Intermediates in the decomposition of pyridine-2-diazotate could not be trapped, but in the case of pyridine-4-diazotate a build-up of diazonium ion in the solution was detected and between pH 4 and 6 it was postulated that an unprotonated diazohydroxide form was the predominant species present. Syn-anti isomerism was not detected with the pyridine-4-diazotate, and it was suggested that the compounds were in the anti form under all conditions for acidities in the range pH >1. On the synthetic level 2,6-difluoropyridine has been prepared by diazotization of 2,6-diaminopyridine in HF,[197] and 3-aminopyridine-2-carboxamide has been diazotized and cyclized.[198] Pyridyl radicals have been obtained from so-called pseudo-Gomberg reactions involving amino pyridine derivatives and alkyl nitrites.[199]

Quinoline-3-diazonium tetrafluoroborate has been found useful for modifying lysil residues of some proteins.[200] Diazotization of diaminotriazaphenothiazine systems has also been briefly commented on in connection with the first synthesis of this ring system.[201] A recent review[202] on the chemistry of aminopyridazines comments on the lack of information on the diazotization of such systems and covers the earlier literature as well as the more recent work reviewed herein.[202]

VI. References and Notes

(1) D. A. Lewis, "Index of Reviews in Organic Chemistry," The Chemical Society, London, 1971, pp 69, 70, 83, and Supplement 1972, lists 62 reviews of diazo chemistry including 19 reviews on diazonium compounds.
(2) B. A. Porai-Koshits, *Russ. Chem. Rev.*, **39**, 283 (1970).
(3) H. Zollinger, *Chimia*, **22**, 9 (1968).
(4) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," I. T. Millar and H. D. Springall, Oxford University Press, Oxford, 1966, pp 533–565.
(5) J. H. Ridd, *Quart. Rev. Chem. Soc.*, 15, 418 (1961).
(6) E. Kalatzis and J. H. Ridd, *J. Chem. Soc. B*, 529 (1966).
(7) E. C. R. de Fabrizio, E. Kalatzis, and J. H. Ridd, *J. Chem. Soc. B*, 533 (1966).
(8) J. M. Tedder, *Adv. Heterocyclic Chem.*, **8**, 1 (1967).
(9) M. Regitz, *Synthesis*, 351 (1972).
(10) H. Zollinger, *Acc. Chem. Res.*, **6**, 335 (1973).
(11) A. Albert, "Heterocyclic Chemistry," Athlone Press, London, 1968, pp 80–85.
(12) J. F. Bunnett, *J. Chem. Soc.*, 4717 (1954). For example, substitution of a fluorine or hydroxy group for a diazonium group is called fluorodediazoniation or hydroxydediazoniation respectively, etc. This terminology is the most efficient way of describing such reactions and has been used previously and commented on by Zollinger; cf. ref 10 and also P. Burry and H. Zollinger, *Helv. Chim. Acta*, **56**, 2204 (1973).
(13) J. M. Tedder and B. Webster, *J. Chem. Soc.*, 3270 (1960).
(14) A. Mineo, *Corr. Farm.*, **21**, 318 (1966); *Chem. Abstr.*, **67**, 43617g (1967).
(15) S. Giambrone and J. Fabra, *Ann. Chim. (Rome)*, **50**, 237 (1960); *Chem. Abstr.*, **54**, 22563d (1960).
(16) T. Ajello and S. Giambrone, *Ric. Sci.*, **24**, 49 (1954); *Chem. Abstr.*, **49**, 3129c (1955).
(17) J. M. Tedder and B. Webster, *J. Chem. Soc.*, 1638 (1962).
(18) H. Reimlinger, A. van Overstraeten, and H. G. Viehe, *Chem. Ber.*, **94**, 1036 (1961).
(19) D. G. Farnum and P. Yates, *Chem. Ind. (London)*, 659 (1960).
(20) H. Reimlinger and A. van Overstraeten, *Chem. Ber.*, **99**, 3350 (1966).
(21) H. Reimlinger and R. Merenyi, *Chem. Ber.*, **103**, 3284 (1970).
(22) H. Reimlinger, G. S. D. King, and M. A. Peiren, *Chem. Ber.*, **103**, 2821 (1970).
(23) M. W. Partridge and M. F. G. Stevens, *J. Chem. Soc. C*, 1127 (1966).
(24) A. Michaelis and H. Bressel, *Justus Liebigs Ann. Chem.*, 407, 286 (1915).
(25) G. T. Morgan and J. Reilly, *J. Chem. Soc.*, **103**, 808 (1913).
(26) G. T. Morgan and J. Reilly, *J. Chem. Soc.*, 439 (1914).
(27) D. G. Farnum and P. Yates, *J. Am. Chem. Soc.*, **84**, 1399 (1962); see also ref 19.
(28) H. P. Patel and J. M. Tedder, *J. Chem. Soc.*, 4589 (1963).
(29) G. Fukata, Y. Kawazoe and T. Taguchi, *Tetrahedron Lett.*, 1199 (1973).
(30) G. C. Lancini and E. Lazzari, *Experientia*, **21**, 83 (1965).
(31) G. C. Lancini and E. Lazzari, British Patent, 1114154; *Chem. Abstr.*, **75**, 140848 (1971).
(32) Houben-Weyl, "Methoden der Organischen Chemie," Vol. X/1, 4th ed., G. Thieme, Stuttgart, 1971, p 836.
(33) A. M. Simonov and Yu. P. Andreichikov, *Zh. Org. Khim.*, **5**, 779 (1969); *Chem. Abstr.*, 71, 22071s (1969).
(34) S. N. Kolodyazhnaya, A. M. Simonov, N. N. Zheltikova, and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 714 (1973); *Chem. Abstr.*, **79**, 53266d (1973).
(35) K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 4619 (1973).
(36) K. L. Kirk and L. A. Cohen, *J. Am. Chem. Soc.*, **93**, 3060 (1971).
(37) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, 38, 3647 (1973).
(38) J. Heyes and N. Ward, German Offen. 2247065 (1973); *Chem. Abstr.*, **79**, 5342d (1973).
(39) W. A. Sheppard and O. W. Webster, *J. Am. Chem. Soc.*, **95**, 2695 (1973).
(40) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.*, **26**, 2396 (1961); see also V. I. Ofitserov, Z. V. Pushkareva, V. S. Mokrushin, and K. V. Aglitskaya, *Khim. Geterotsikl. Soedin.*, 1292 (1973); *Chem. Abstr.*, **79**, 146463f (1973); M. Masui and H. Iwata, Japanese Patent, 7324392 (1973); *Chem. Abstr.*, **79**, 115585t (1973).
(41) C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **32**, 2241 (1967).
(42) A. N. Frolov, M. S. Pevnser, I. N. Shokhor, A. G. Gal'kovskaya, and L. I. Bagal, *Khim. Geterotsikl. Soedin.*, 705 (1970); *Chem. Abstr.*, **73**, 45420k (1970).
(43) R. N. Butler, T. M. Lambe, and F. L. Scott, *Chem. Ind. (London)*, 628 (1970).
(44) G. T. Morgan and J. Reilly, *J. Chem. Soc.*, 109, 155 (1916).
(45) J. Reilly and D. Madden, *J. Chem. Soc.*, 815 (1929).
(46) A. N. Frolov, M. S. Pevzner, and L. I. Bagal, *Zh. Org. Khim.*, 7, 1519 (1971); *Chem. Abstr.*, **75**, 129025q (1971).
(47) G. Cipens, *Metody Poluch. Khim. Reakt. Prep.*, 14, 119 (1966); *Chem. Abstr.*, 67, 64307w (1967).
(48) G. Cipens, R. Balkalders, and V. Grinsteins, *Khim. Geterotsikl. Soedin.*, 110 (1966); *Chem. Abstr.*, **65**, 705a (1966).
(49) F. L. Scott, D. A. Cronin, and J. K. O'Halloran, *J. Chem. Soc. C*, 2769 (1971); see also ref 69.
(50) A. Spiliadis, D. Bretcanu, C. Eftimescu, and R. T. Schip, Romanian Patent. 50786 (1968); *Chem. Abstr.*, **70**, 4114h (1969).
(51) A. K. Pan'kov, M. S. Pevsner, and L. I. Bagal, *Khim. Geterosikl. Soedin.*, 713 (1972); *Chem. Abstr.*, 77, 126523l (1972).
(52) H. Gehlen and J. Dost, *Justus Liebigs Ann. Chem.*, **655**, 144 (1963).
(53) E. Lieber, S. Schilf, R. A. Henry, and W. G. Finnegan, *J. Org. Chem.*, **18**, 218 (1953).
(54) H. Gehlen and H. Elchlepp, *Justus Liebigs Ann. Chem.*, **594**, 14 (1955).
(55) H. Gehlen and K.-H. Uteg, *Z. Chem.*, **9**, 338 (1969).
(56) H. Gehlen and K.-H. Uteg, *Z. Chem.*, **8**, 60 (1968).
(57) R. Stolle and K. Krauch, *J. Prakt. Chem.*, [2] **88**, 311 (1913).
(58) R. Stolle and W. Dietrich, *J. Prakt. Chem.*, **139**, 193 (1934).
(59) M. Hauser, *J. Org. Chem.*, **29**, 3449 (1964).
(59a) Very recently we have isolated a product which appears to be the compound which has been assigned structure 40 (R. N. Butler and T. M. McEvoy, unpublished work). Our attempts at purification have not been successful to date (no purification procedures were reported in ref 53). Our preliminary data on the crude product include a strong infrared absorption band at 2220 cm^{-1} and suggest that structure 40 should be viewed with particular caution.
(60) K. T. Potts and C. A. Hirsch, *Chem. Ind. (London)*, 2168 (1966).
(61) H. Mackie and G. Tennant, *Tetrahedron Lett.*, 4719 (1972).
(62) J. Thiele, *Justus Liebigs Ann. Chem.*, **270**, 54 (1892).
(63) P. B. Shevlin, *J. Am. Chem. Soc.*, **94**, 1379 (1972).
(64) S. Kammula and P. B. Shevlin, *J. Am. Chem. Soc.*, **95**, 4441 (1973).
(65) Although harmless explosions have been ascribed to this compound (rel 8), the writer has experienced one serious case, in which a colleague was injured, while preparing a 40-g quantity of this material. The critical factor appeared to be an overcooling of the diazonium solution which caused crystals of the salt to separate as a suspension. The safest conditions were at ca. 2–5° and using excess of solvent. As long as the salt was kept in solution, no difficulties were encountered. Drained but unrinsed vessels, which had held the diazonium solutions, gave, when dry, a continuous series of sporadic minor crackling-type detonations, sometimes for days and particularly when exposed to sunlight.
(66) R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, **76**, 290 (1954).
(67) F. L. Scott, W. N. Morrish, and J. Reilly, *J. Org. Chem.*, **22**, 692 (1957).
(68) R. Stolle, *J. Prakt. Chem.*, 134, 282 (1932).
(69) R. N. Butler, T. M. Lambe, J. C. Tobin, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 1*, 1357 (1973).
(70) J. C. Tobin, R. N. Butler, and F. L. Scott, *Chem. Commun.*, 112 (1970).
(71) R. N. Butler and F. L. Scott, *J. Org. Chem.*, **31**, 3182 (1966).
(72) R. N. Butler and F. L. Scott, *J. Org. Chem.*, **32**, 1224 (1967).
(73) K. Hattori, E. Lieber, and J. P. Horwitz, *J. Am. Chem. Soc.*, **78**, 411 (1956).
(74) N. Saito, T. Kurihara, S. Yasuda, and M. Akagi, *Yakugaku Zasshi*, **90**, 32, (1970); *Chem. Abstr.*, **72**, 90353f (1970).
(75) N. Saito, T. Kurihara, S. Yasuda, and M. Akagi, *Yakugaku Zasshi*, **90**, 20 (1970); *Chem. Abstr.*, **72**, 90352e (1970).

(76) H. Wieland, *Justus Liebigs Ann. Chem.*, **328**, 197 (1903).
(77) A. Quilico, R. Fusco, and V. Rosnati, *Gazz. Chim. Ital.*, **76**, 87 (1946); *Chem. Abstr.*, **41**, 383f (1947).
(78) R. Stolle and K. Fehrenbach, *J. Prakt. Chem.*, **122**, 289 (1929).
(79) R. D. Desai, R. F. Hunter, and A. R. K. Khalidi, *J. Chem. Soc.*, 1186 (1934).
(80) K. Masuda, T. Kamiya, and K. Kashiwa, *Chem. Pharm. Bull.*, **19**, 559 (1971).
(81) C. Christophersen and S. Treppendahl, *Acta Chem. Scand.*, **26**, 858 (1972).
(82) C. Christophersen and S. Treppendahl, *Acta Chem. Scand.*, **25**, 625 (1971).
(83) H. Gehlen and P. Demin, *Z. Chem.*, **8**, 221 (1968).
(84) J. Goerdeler and H. Haubrich, *Chem. Ber.*, **93**, 397 (1960).
(85) G. T. Morgan and G. V. Morrow, *J. Chem. Soc.*, **107**, 1294 (1915).
(86) R. F. Hunter and J. W. T. Jones, *J. Chem. Soc.*, 2190 (1930).
(87) L. I. Denisova and K. E. Lotukova, *Tr. Vses. Inst. Gel'mintol.*, **15**, 97 (1969); *Chem. Abstr.*, **75**, 35866n (1971).
(88) C. Gruenert and K. Wiechert, *Z. Chem.*, **10**, 396 (1970); *Chem. Abstr.*, **74**, 13043u (1971).
(89) C. Gruenert, H. Schellong, and K. Wiechert, *Z. Chem.*, **10**, 116 (1970); *Chem. Abstr.*, **72**, 132594t (1970).
(90) A. D. Borthwick, M. W. Foxton, B. V. Gray, G. I. Gregory, P. W. Seale, and W. K. Warburton, *J. Chem. Soc., Perkin Trans 1*, 2769 (1973).
(91) R. A. Parent, *J. Org. Chem.*, **27**, 2282 (1962).
(92) B. Prijs, J. Ostertag, and H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 1200, 2100 (1947).
(93) G. Asato, G. Berkelhammer, and E. L. Moon, *J. Med. Chem.*, **12**, 374 (1969).
(94) A. Hantzsch, *Justus Liebigs Ann. Chem.*, **249**, 1 (1888).
(95) G. Vernin, H. J. M. Dou, and J. Metzger, *J. Chem. Soc., Perkin Trans. 2*, 1093 (1973).
(96) J. I. G. Cadogan,D. A. Roy, and S. M. Smith, *J. Chem. Soc. C*, 1249 (1966).
(97) Y. Tamura, T. Miyamoto, and M. Ikeda, *Chem. Ind. (London)*, 1439 (1971).
(98) J. Goerdeler and M. Roegler, *Chem. Ber.*, **103**, 112 (1970).
(99) F. Hübenett, F. H. Flock, W. Hansel, and H. Hofmann, *Angew. Chem., Int. Ed. Engl.*, **2**, 714 (1963).
(100) J. Goerdeler and H. W. Pohland, *Angew. Chem.*, **72**, 77 (1960).
(101) J. Goerdeler and U. Keuser, *Chem. Ber.*, **97**, 3106 (1964).
(102) J. Goerdeler and K. Deselaers, *Chem. Ber.*, **91**, 1025 (1958).
(103) J. Goerdeler, K. Deselaers, and A. Ginsberg, *Chem. Ber.*, **93**, 963 (1960).
(104) A. Ginsberg and J. Goerdeler, *Chem. Ber.*, **94**, 2043 (1961).
(105) J. Goerdeler and A. Fincke, *Chem. Ber.*, **89**, 1033 (1956).
(106) F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 3234 (1960).
(107) J. Goerdeler and P. Mertens, *Chem. Ber.*, **103**, 1805 (1970).
(108) M. Freund and C. Meinecke, *Chem. Ber.*, **29**, 2511 (1896).
(109) J. Goerdeler and G. Gnad, *Chem. Ber.*, **99**, 1618 (1966).
(110) C. W. Bird and C. K. Wong, *Tetrahedron Lett.*, 2143 (1971).
(111) B. A. Porai-Koshits, V. I. Zaionts, and Ts. A. Eiges, *Zh. Org. Khim.*, **3**, 1262 (1967); *Chem. Abstr.*, **67**, 99769a (1967).
(112) E. S Lewis and M. P. Hanson, *J. Am. Chem. Soc.*, **89**, 6268 (1967).
(113) A. Hantzsch and W. Pohl, *Ber. Deut. Chem. Ges.*, **35**, 2964 (1902).
(114) A. Hantzsch and J. Lifschitz, *Ber. Deut. Chem. Ges.*, **45**, 3011 (1912).
(115) B. A. Porai-Koshits and B. V. Passet, *Zh. Obsch. Khim.*, **30**, 286 (1960).
(116) E. Mueller and H. Haiss, *Chem. Ber.*, **96**, 570 (1963).
(117) R. J. W. Le Fevre, R. Roper, and I. H. Reece, *J. Chem. Soc.*, 4104 (1959).
(118) B. A. Porai-Koshits, *Zh. Org. Khim.*, **2**, 1125 (1966); *Chem. Abstr.*, **65**, 16887c (1966).
(119) B. A. Porai-Koshits and V. V. Shadburov, *Zh. Org. Khim.*, **2**, 510 (1966); *Chem. Abstr.*, **65**, 8733c (1966).
(120) E. S. Lewis and H. Suhr, *Chem. Ber.*, **91**, 2350 (1958).
(121) E. Muller, W. Hoppe, H. Hagenmaier, H. Hais, R. Huber, W. Rundel, and H. Suhr, *Chem. Ber.*, **96**, 1712 (1963).
(122) Reference 4, pp 546 and 553–564.
(123) S. Radu, *Stud. Cercet. Chim.*, **20**, 1287 (1972); *Chem. Abstr.*, **78**, 109975h (1973).
(124) *Cf.* ref 11, Tables 13.3, 13.4, and 13.5, pp 438–442.
(125) E. Kalatzis, *J. Chem. Soc. B*, 277 (1967).
(126) E. D. Hughes, C. K.Ingold, and J. H. Ridd, *J. Chem. Soc.*, 88 (1958).
(127) H. B. Stevenson and J. R. Johnson, *J. Am. Chem. Soc.*, **59**, 2525 (1937).
(128) W. Reid and W. Bodenstedt, *Justus Liebigs Ann. Chim.*, **667**, 96 (1963).
(129) N. I. Putokhin and V. I. Yakovlev, *Dokl. Akad. Nauk SSSR*, **98**, 89 (1954); *Chem. Abstr.*, **49**, 12431 (1955).
(130) N. I. Putokhin and V. I. Yakovlev, *Sb. Nauchn. Tr. Kuibyshev. Ind. Inst.*, 175 (1953); *Chem. Abstr.*, **50**, 9741h 1956).
(131) L. Henriksen and H. Autrup, *Acta Chem. Scand.*, **26**, 3342 (1972).
(132) J. Metzger and P. Bailly, *Bull. Soc. Chim. Fr.*, 1249 (1955).
(133) R. G. D. Moore and R. J. Cox, British Patent, 870,027 (1961); *Chem. Abstr.*, **55**, 23134c (1961).
(134) A. Roe and J. F. Hawkins, *J. Am. Chem. Soc.*, **69**, 2443 (1947).
(135) P. B. Desai, *J. Chem. Soc. Perkin Trans 1*, 1865 (1973).
(136) J. P. Wibaut and W. J. Holmes-Kamminga, *Bull. Soc. Chem. Fr.*, 424 (1958).
(137) R. D. Beatty and W. K. R. Musgrave, *J. Chem. Soc.*, 875 (1952).
(138) E. Koenigs and H. Greiner, *Ber. Deut. Chem. Ges.*, **64**, 1049 (1931).
(139) E. Kalatzis, *J. Chem. Soc. B*, 273 (1967).
(140) R. F. Ferm and C. A. Vander Werf, *J. Am. Chem. Soc.*, **72**, 4809 (1950).
(141) E. D. Parker and W. Shive, *J. Am. Chem. Soc.*, **69**, 63 (1947).
(142) T. Talik and Z. Talik, *Rocz. Chem.*, 47, 441 (1973); *Chem. Abstr.*, **79**, 18534t (1973).
(143) F. B. Dorf, A. P. Bentz, and J. E. Gordon, U.S. Patent, 2788348 (1957); *Chem. Abstr.*, **51**, 14832e (1957).
(144) H. E. Foster and J. Hurst, *J. Chem. Soc., Perkin Trans. 1*, 2901 (1973).
(145) C. Ruchardt and V. Hassman, *Synthesis*, 375 (1972), and references therein.
(146) T. Talik and E. Plazek, *Rocz. Chem.*, **33**, 387 (1959); *Chem. Abstr.*, **53**, 18954d (1959).
(147) T. Talik and E. Plazek, *Rocz. Chem.*, **33**, 1343 (1959); *Chem. Abstr.*, **54**, 13123e (1960).
(148) T. Talik and E. Plazek, *Rocz. Chem.*, **29**, 1019 (1955); *Chem. Abstr.*, **50**, 12045f (1956).
(149) T. Talik, *Rocz. Chem.*, **31**, 569 (1957); *Chem. Abstr.*, **52**, 5407b (1958).
(150) T. Talik and E. Plazek, *Rocz. Chem.*, **35**, 463 (1961); *Chem. Abstr.*, **55**, 25943 (1961).
(151) T. Talik and Z. Talik, *Rocz. Chem.*, **37**, 75 (1963); *Chem. Abstr.*, **59**, 8698b (1963).
(152) B. Glowiak, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, **10**, 9 (1962); *Chem. Abstr.*, **58**, 501e (1965).
(153) A. Roe and J. F. Hawkins, *J. Am. Chem. Soc.*, 71, 1785 (1949).
(154) S. Fatutta, M. Mauro, and C. Pasin, *Ric. Sic., Rend., Sez. A*, **8**, 736 (1965); *Chem. Abstr.*, **64**, 19550d (1966).
(155) P. I. Brusilovskii, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 746, (1971); *Chem. Abstr.*, **76**, 153541w (1972).
(156) R. C. Peterson, A. Di Maggio, A. L. Hebert, T. J. Haley, J. P. Mykytka, and I. M. Sarkar, *J. Org. Chem.*, **36**, 631 (1971).
(157) J. H. Boyer and L. T. Wolford, *J. Org. Chem.*, 21, 1297 (1956).
(158) H. E. Baumgarten, W. F. Murdock, and J. E. Dicks, *J. Org. Chem.*, **26**, 803 (1961).
(159) L. S. Davies and G. Jones, *Tetrahedron Lett.*, 1549 (1969).
(160) A. R. Collicut and G. Jones, *J. Chem. Soc.*, 4101 (1960).
(161) T. L. Hough and G. Jones, *J. Chem. Soc. C*, 1088 (1968).
(162) J. M. Tedder, K. H. Todd, and W. K. Gibson, *J. Chem. Soc. C*, 1279 (1969).
(163) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 1915 (1953).
(164) A. Albert, *J. Chem. Soc. B*, 427 (1966).
(165) Kyowa Fermentation Co., Ltd., French Patent 1415149 (1965); *Chem. Abstr.*, **64**, 5116b (1966).
(166) E. Carstens and H. G. Kazmirowski, East German Patent 23487 (1962); *Chem. Abstr.*, **58**, 9103h (1963).
(167) E. C. Taylor and C. W. Jefford, *J. Am. Chem. Soc.*, **84**, 3744 (1962).
(168) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1218 (1951).
(169) K. Yanai, *J. Pharm. Soc. Jpn.*, **62**, 315 (1942); *Chem. Abstr.*, **45**, 5150i (1951).
(170) V. Papesch and R. M. Dobson, *J. Org. Chem.*, **30**, 199 (1965).
(171) J. P. Paolini, R. K. Robins, and C. C. Cheng, *Biochem. Biophys. Acta*, **72**, 114 (1963); *Chem. Abstr.*, **59**, 12900g (1963).
(172) F. L. Rose, *J. Chem. Soc.*, 3448 (1952).
(173) J. C. Davis, H. H. Ballard, and J. W. Jones, *J. Heterocycl. Chem.*, 7, 405 (1970).
(174) S. H. Chang, J. S. Kim, and T. S. Huh, *Daerhan Hwahak Hwoejee*, **13**, 177 (1969); *Chem. Abstr.*, **71**, 112880j (1969).
(175) R. Huigi and W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **759**, 76 (1972).
(176) F. L. Rose, *J. Chem. Soc.*, 4116 (1954).
(177) J. H. Boothe and C. W. Waller, U.S. Patent, 2534897 (1950); *Chem. Abstr.*, **45**, 4747c (1951).
(178) E. S. Olson and J. La Monte Cooper, *J. Heterocycl. Chem.*, 7, 693 (1970).
(179) A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, **68**, 400 (1946).
(180) T. S. Osdene and G. H. Timmis, *J. Chem. Soc.*, 2027 (1955).
(181) E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, 71, 2539 (1949).
(182) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).
(183) J. Villarrassa, E. Melendez and J. Elguero, *Tetrahedron Lett.*, 1609 (1974).
(184) A. M. Simonov, S. N. Kalodyazhnaya, and L. N. Podladchikova, *Khim. Geterotsikl. Soedin.*, 689 (1974); *Chem. Abstr.*, **81**, 77841e (1974).
(185) V. V. Shaburov, O. V. Vasil'eva, and A. V. El'tsov, *Khim. Geterotsikl. Soedin.*, 367 (1974); *Chem. Abstr.*, **81**, 25595h (1974).
(186) G. Fukata, Y. Kawazoe, and T. Taguchi, *Yakugaku Zasshi*, **94**, 31 (1974); *Chem. Abstr.*, **80**, 108435m (1974).
(187) R. Allmann, T. Debaerdemaeker, W. Grahn, and C. Reichardt, *Chem. Ber.*, **107**, 1555 (1974).
(188) G. Fukata, Y. Kawazoe, and T. Tanezo, *Yakugaku Zasshi*, **94**, 23 (1974); *Chem. Abstr.*, **80**, 108437p (1974).
(189) I. L. Shegal, K. V. Stanovkina, N. G. Kovalenko, and L. M. Shegal, *Khim. Geterotsikl. Soedin*, 422 (1974); *Chem. Abstr.*, **81**, 25609r (1974).
(190) D. Fortuna, B. Stanovnik, and M. Tisler, *J. Org. Chem.*, **39**, 1833 (1974).
(191) Y. F. Shealy and C. A. O'Dell, *J. Heterocycl. Chem.*, **10**, 839

(1974). For biological effects of these compounds, see *J. Med. Chem.*, **9**, 34, 733 (1966); *J. Pharm. Sci.*, **56**, 147 (1967); **60**, 554 (1971).
(192) M. Masui and H. Iwata, Japanese Patent 7324392 (1973); *Chem. Abstr.*, **79**, 115585t (1973); H. Iwata, I. Yamamoto, and E. Goda, Japanese Patent 7448664 (1974); *Chem. Abstr.*, **82**, 16841d (1975).
(193) V. I. Ofitserov, Z. V. Pushkareva, V. S. Mokrushin, and K. V. Aglitskaya, *Khim. Geterotsikl. Soedin.*, 1292 (1973); *Chem. Abstr.*, **79**, 146463f (1973).
(194) O. W. Webster, German Offen. 2317453 (1973); *Chem. Abstr.*, **80**, 14926v (1974).
(195) E. Kalatzis and C. Mastrokalos, *J. Chem. Soc., Perkin Trans. 2*, 498 (1974).
(196) C. A. Bunton, M. J. Minch, and B. B. Wolfe, *J. Am. Chem. Soc.*, **96**, 3267 (1974); for a similar study with 9-alkylpurine-6-diazotates, see C. A. Bunton and B. B. Wolfe, *J. Am. Chem. Soc.*, **96**, 7747 (1974).
(197) M. M. Boudakian and S. J. Chiras, U.S. Patent 3798228 (1974); *Chem. Abstr.*, **80**, 14026m (1974).
(198) K. Rufenacht, German Offen., 2314071 (1973); *Chem. Abstr.*, **80**, 3558a (1974).
(199) G. Fillipi, M. M. G. Vernin, H. J. M. Dou, and J. Metzger, *Bull. Soc. Chim. Fr.*, 1075 (1974).
(200) M. Kanazawa and S.-I. Ishii, *Biochim. Biophys. Acta*, **342**, 155 (1974).
(201) C. O. Okafor, *J. Org. Chem.*, **38**, 4386 (1974); see also *Int. J. Sulfur. Chem., Part B*, **6**, 345 (1971).
(202) T. Nakagome, *Heterocycl. Compd.*, **28**, 463 (1974); see also K. Dury, *Angew. Chem. Int. Ed. Engl.*, **4**, 292 (1965).