Syntheses of Heterocyclic Compounds from Aminoguanidine

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Due to its unique structure, aminoguanidine is capable of reacting as a derivative of hydrazine, guanidine or formamidine. Addition and condensation reactions yield products which can be cyclized to heterocyclic compounds. Frequently, heterocyclics are directly accessible from aminoguanidine in one stage.

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Introduction

Ever since the discovery of the parent compound in 1892 by *Thiele* [1], the chemistry of aminoguanidine and related compounds has been a fruitful field of research and has yielded interesting results from both the theoretical and practical points of view. The particular usefulness of aminoguanidine for the synthesis of heterocyclics had become obvious very early as a result of the fundamental investigations of *Thiele* and his collaborators.

A comprehensive survey by *Lieber* and *Smith* [2] provides an excellent summary of aminoguanidine chemistry up to 1938. Since then, the field has expanded rapidly. Much progress has been recorded in the synthesis of aminoguanidine and its derivatives, both by consolidation of the existing methods and by the discovery of new reactions. This aspect of the subject has been reviewed by us recently [3].

Even more significant and extensive research projects applied aminoguanidine derivatives for synthetizing heterocyclics. The presence in the aminoguanidine structure of a chain of three nitrogen and one carbon atoms makes this compound a versatile starting material for a wide variety of cyclizations. The present survey attempts to review the advances in the use of aminoguanidine in heterocyclic chemistry during the past twenty-five years. The material is dealt with in the order of increasing ring complexity of the resulting heterocyclic systems.

A. Pyrazoles

I. Synthesis of Pyrazole Derivatives

Condensation of aminoguanidine *(1)* with β-diketones, such as acetylacetone *(2)*, is a well established synthesis of 3,5-dialkyl-1-guanylpyrazoles *(3)* [4]. By this general

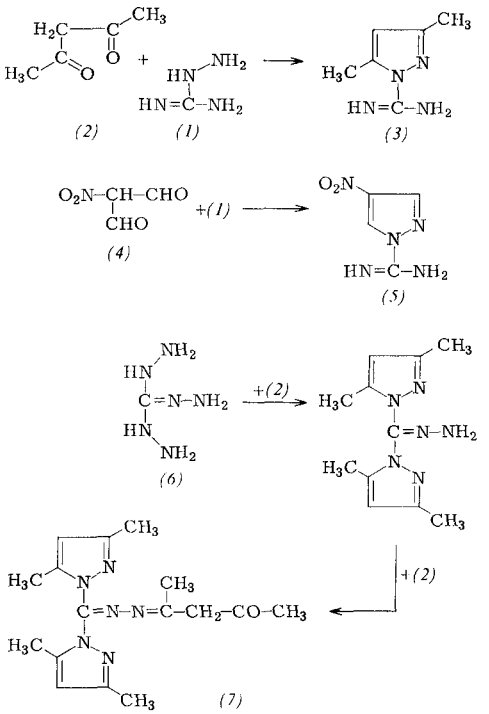
[1] *J. Thiele*, Liebigs Ann. Chem. *270*, 1 (1892).

[2] *E. Lieber* and *G. B. L. Smith*, Chem. Reviews *25*, 213 (1939).

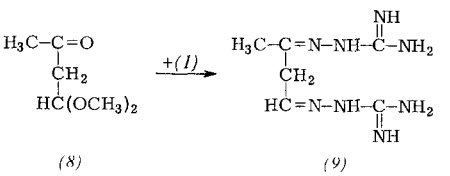
[3] *F. Kurzer* and *L. E. A. Godfrey*, Chem. and Ind. *1962*, 1584.

[4] *J. Thiele* and *E. Dralle*, Liebigs Ann. Chem. *302*, 275 (1898).

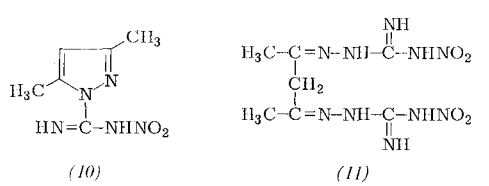
method, nitromalondialdehyde *(4)* yields 1-guanyl-4-nitropyrazole *(5)* [5], and 3 moles of acetylacetone *(2)* react similarly with 1,2,3-triaminoguanidine *(6)* to yield 1,1-bis-(3,5-dimethylpyrazol-1-yl)-4-methyl-2,3-diaza-1,3-heptadien-6-one *(7)* as main product [6]. The corresponding reaction of diaminoguanidine has apparently not yet been studied.



In contrast to the general ready formation of pyrazoles from acetylacetone and aminoguanidine, *Burness* [7] found that 4,4-dimethoxy-2-butanone *(8)* reacts with one or two moles of aminoguanidine sulfate *(1)* to give merely butane-1,3-dione bis(guanylhydrazone) *(9)*, which could not be cyclized to a pyrazole by any of the usual methods.



3,5-Dimethyl-1-nitroguanylpyrazole *(10)* has recently been obtained similarly from 3-nitro-1-aminoguanidine [8, 9]. A certain amount of osazone *(11)* is also formed. In general, the relative proportions of hydrazone and pyrazole formed in the reaction between acylhydrazides and β-diketones depend on the electrophilic nature of the acyl group of the hydrazide involved [9, 10].



II. The Chemistry of 1-Guanylpyrazoles

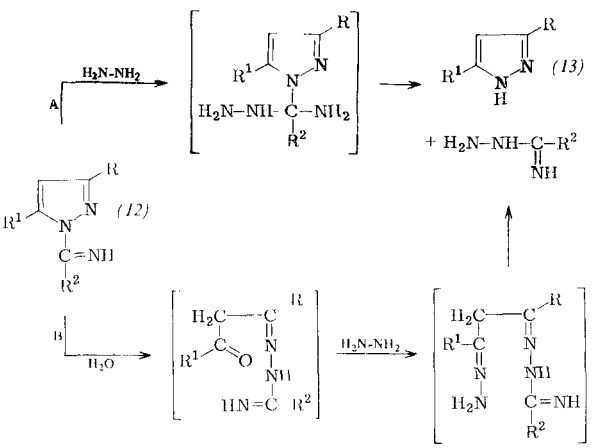
1-Guanylpyrazoles and 1-nitroguanylpyrazoles may be formally regarded as cyclic aminoguanidines, and are therefore briefly discussed.

3,5-Dimethyl-1-guanylpyrazole is sufficiently stable to withstand boiling acetic anhydride in acetic acid, or treatment for two hours with fuming nitric acid at 50 °C [11]. However, it is cleaved remarkably easily by hydrazines, amines, or azides.

1. *Hydrazinolysis*

The action of hydrazine hydrate on 3,5-dimethyl-1-guanylpyrazole *(12)* yields aminoguanidine and 3,5-dimethylpyrazole *(13)* [11, 12]. Use of an excess of hydrazine hydrate produces triaminoguanidine *(6)* [11, 12].

The reaction may proceed either by addition of the hydrazine molecule onto the 1-substituent and its subsequent detachment (A) or by initial hydrolytic ring-opening, followed by displacement of the ketonic oxygen by hydrazine and ring-closure (B). With hydrazine itself, the products from either



scheme would be identical, but an unsymmetrically substituted hydrazine such as phenylhydrazine would give rise to different products. Since 1-anilinoguanidine is in fact obtained together with 3,5-dimethylpyrazole, it appears that the reaction follows the first route (A).

3,5-Dimethyl-1-nitroguanylpyrazole is cleaved similarly by hydrazine [10] or phenylhydrazine [9] into 3,5-dimethylpyrazole and nitroaminoguanidine or 3-phenyl-1-nitroaminoguanidine, respectively. The reaction has been extended to many other hydrazines, including quinol-2-ylhydrazine, benzthiazol-2-ylhydrazine, and benzhydrazide [12].

[5] *F. L. Scott* and *J. Reilly*, Chem. and Ind. *1952*, 907.

[6] *F. L. Scott*, *M. Cashman*, and *J. Reilly*, J. Amer. chem. Soc. *75*, 1510 (1953).

[7] *D. M. Burness*, J. org. Chemistry *21*, 97 (1956).

[8] *R. A. Henry* and *G. B. L. Smith*, J. Amer. chem. Soc. *74*, 278 (1952).

[9] *F. L. Scott*, *M.T. Kennedy*, and *J. Reilly*, J. Amer. chem. Soc. *75*, 1294 (1953).

[10] *F. L. Scott*, *M.T. Kennedy*, and *J. Reilly*, Nature (London) *169*, 72 (1952).

[11] *F. L. Scott*, *C. M. B. Murphy*, and *J. Reilly*, Nature (London) *167*, 1037 (1951).

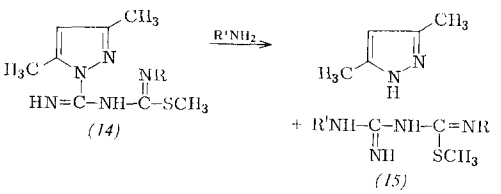
[12] *F. L. Scott*, *D. G. O'Donovan*, and *J. Reilly*, J. Amer. chem. Soc. *75*, 4053 (1953).

2. *Aminolysis*

The action of amines on 1-guanyl- or 1-nitroguanyl-3,5-dimethylpyrazole yields substituted guanidines together with 3,5-dimethylpyrazole [9, 10].

This reaction has been applied to heterocyclic bases, and to 1-guanylpyrazoles containing substituted guanyl groups. In many cases, the reaction proceeds as with the simple 1-guanyl compounds, but it is sometimes complicated by the formation of by-products. Thus, for example, on treating 1-benzoylguanyl-3,5-dimethylpyrazole with morpholine, a mixture of 1-(benzoylguanyl)morpholine and 1-[*N*-benzoyl-*N'*-(morpholino-1-yl)guanyl]morpholine is obtained [13].

The ease with which scission of the guanyl group occurs is strikingly illustrated by the observation that *S*-methylamidinothioureas *(15)* are obtainable on treatment of *S*-methylthioureides of type *(14)* with amines. At higher temperatures, however, further aminolysis yields trisubstituted biguanides [13].

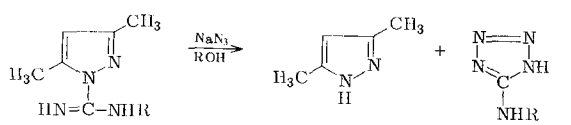


(14) *(15)*

Deguanylation of guanylpyrazoles is also brought about by other nucleophilic reagents such as sodium acetate [13]. Ethanolysis, although comparatively slow, is rapid enough for its progress to be followed spectrometrically [14].

3. *Azidolysis*

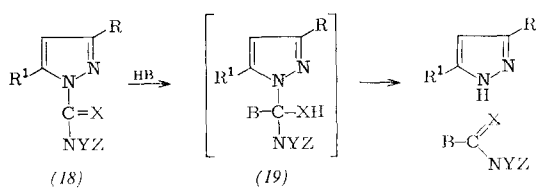
Deguanylation of 1-guanyl-3,5-dimethylpyrazole by boiling alcoholic sodium azide [13] gives 5-aminotetrazole *(16)* as the product other than 3,5-dimethylpyrazole. The corresponding 1-nitroguanyl derivative similarly affords 5-nitraminotetrazole *(17)* [13].



(16), R = H
(17), R = NO_2

4. *Mechanism of Deguanylation*

Preliminary studies suggested that deguanylation of guanylpyrazoles *(18)* proceeds by a mechanism involving slow formation of an adduct *(19)* followed by rapid elimination of part of the molecule [12]. The readiness with which the initial condensation occurs thus presumably depends upon the ease with which the substituted hydrazine or amine anion is attached to the carbonium ion; the more electrophilic the latter, the more readily should reaction take place [12].

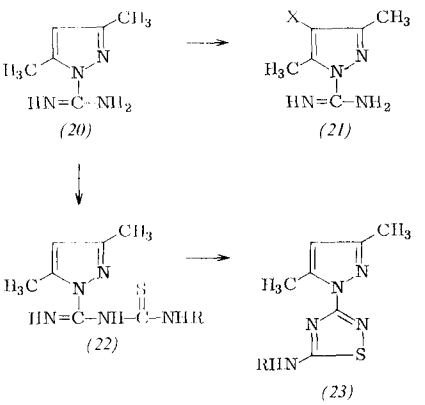


(18) *(19)*

From the results of a large number of pyrazole deacylations [10, 12, 13] it was indeed concluded that the mechanism was of the $B_{Ac}2$-type [14], analogous to that operating in many ester hydrolyses [15]. Support for this mechanism is provided by the effect of various substituents on the rate of ethanolysis of 1-guanylpyrazoles; it is probably the operative mode of deguanylation with amines and hydrazines [15]. In the deacylation of 3,5-dimethyl-1-(*N*,*N*-diphenyl-carbamyl)pyrazole *(19)*, R = R' = CH_3, X O, Y = Z = C_6H_5, this $B_{Ac}2$ mechanism would appear to be the only possible one [16].

5. *Halogenation*

Chlorine and bromine rapidly halogenate 3,5-dimethyl-1-guanylpyrazole *(20)* to 4-chloro- or 4-bromo-3,5-dimethyl-1-guanylpyrazole *(21)* [11, 17]. Iodine reacts more slowly and, under the necessarily more drastic conditions required, deguanylation occurs with formation of 3,5-dimethyl-4-iodopyrazole.



(20) *(21)* *(22)* *(23)*

Condensation of 3,5-dimethyl 1-guanylpyrazole *(20)* (as the free base only) and aryl isocyanates or isothiocyanates gives the corresponding 1-thiocarbamyl derivatives *(22)* [17]. On reaction with halogens, these gave labile products that were difficult to isolate [17]. The final stable products proved to be oxidation products, which were correctly formulated [18] as pyrazolyl-1,2,4-thiadiazoles *(23)*, having previously been erroneously regarded as disulfides [17].

3,5-Dimethyl-1-nitroguanylpyrazole reacts analogously with bromine or chlorine to give 4-bromo or 4-chloro derivatives [9]. Under strongly alkaline conditions, partial deguanylation was responsible for the formation of some 4-halogeno-3,5-dimethylpyrazole [9]. Iodine and sodium acetate also gave a deguanylated product, but the 4-iodo derivative was obtained by treating the nitroguanylpyrazole with iodine monochloride in acetic acid [9].

III. Synthesis of Pyrazolones

Beyer and *Badicke* [19] showed that ethyl α-chloroacetoacetate is converted by amino- and nitroaminoguanidines into the correspondingly substituted hydrazone

[13] *F. L. Scott*, Chem. and Ind. *1956*, 547.

[14] *C. K. Ingold:* Structure and Mechanism in Organic Chemistry. Bell, London 1953, p. 752 *et seq.*

[15] *F. L. Scott*, Chimia *11*, 163 (1957).

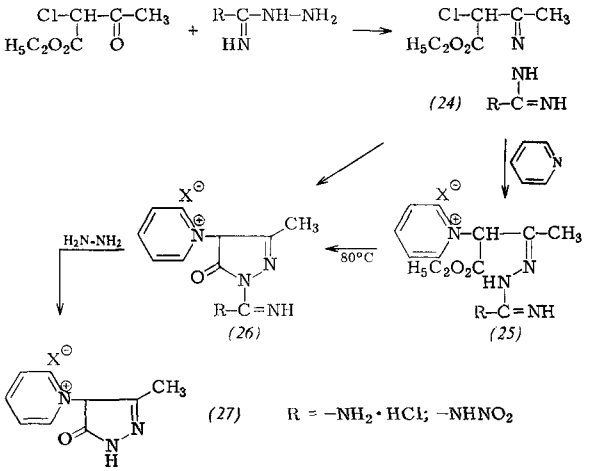
[16] *F. L. Scott, A. Ahearne*, and *J. Reilly*, J. org. Chemistry *22*, 1688 (1957).

[17] *F. L. Scott* and *J. Reilly*, J. Amer. chem. Soc. *74*, 4562 (1952).

[18] *F. L. Scott*, Chem. and Ind. *1958*, 463.

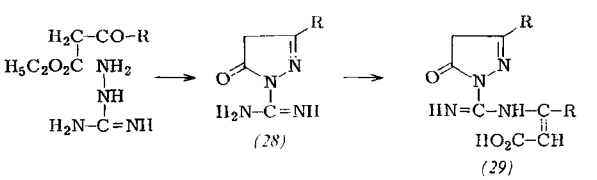
[19] *H. Beyer* and *G. Badicke*, Chem. Ber. *93*, 826 (1960).

hydrochlorides *(24)*. Further treatment of *(24)* with bases *(e.g.* pyridine, piperidine, or aniline) replaces the α-chlorine atom to yield ethyl α- pyridinioacetoacetate guanylhydrazone chloride *(25)*. Boiling ethanolic pyridine eliminates a molecule of alcohol either from the hydrazone *(24)* or from *(25)* to afford 1-guanyl-3-methyl-4-pyridiniopyrazol-5-one chloride *(26)*, an enol-betaine hydrochloride [19].



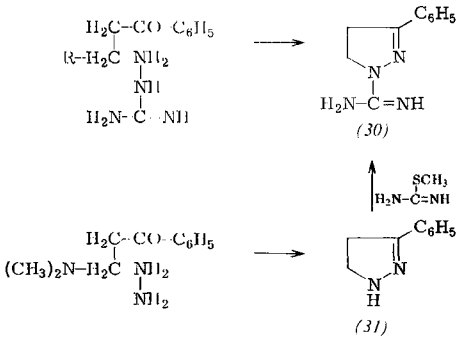
The formal resemblance of 1-guanylpyrazolones and 1-guanylpyrazoles (see above) is reflected in their analogous hydrazinolysis and aminolysis. Thus, treatment of 1-guanyl-3-methyl-4-pyridiniopyrazol-5-one chloride *(26)* with an excess of hydrazine hydrate yields 3-methyl-4-pyridinio-5-pyrazolone halide *(27)* and aminoguanidine. The production and hydrazinolysis of the corresponding 1-nitroguanyl compounds occurs in parallel fashion [19].

Like other hydrazine derivatives, aminoguanidine reacts with unsubstituted β-oxo-esters to form pyrazolones directly. *Vystrcil* and *Prokes* [20] prepared a number of these compounds and studied their infrared spectra [21]. 1-Guanyl-3-methyl-5-pyrazolone *(28)*, the simplest member of the series, first prepared by *De* [22], was obtained from aminoguanidine nitrate and ethyl acetoacetate. With an excess of the ester, the heterocyclic compound *(28)* continued to react to form *(29)*. Analogous compounds resulted from other esters such as benzoylacetic ester [20, 21].



IV. Synthesis of Pyrazolines

Condensation of aminoguanidine with a number of Mannich bases derived from acetophenone (or their oximes) [5, 23] yields 1-guanyl-3-phenyl-Δ²-pyrazoline *(30)*. Since the substituted amino moiety is lost from each Mannich base, the same pyrazoline *(30)* is obtained from different bases.



Since the possible formulation of the product as isomeric phenyl vinyl ketone guanylhydrazone had to be considered, and could not be excluded on the basis of ultraviolet and infrared spectra, an attempt was made to synthetize the pyrazoline *(30)* by an unambiguous route [23]: Authentic 3-phenyl-Δ²-pyrazoline *(31)* was converted with *S*-methylisothiouronium nitrate into a compound identical with the pyrazoline obtained from the Mannich bases. A possibility of ring-opening exists, but appears unlikely; however, reaction at the *N*(2)-nitrogen atom might also occur [23].

When treated with aminoguanidine, phenyl vinyl ketone also furnished a small yield of 1-guanyl-3-phenyl-Δ²-pyrazoline *(30)* [23].

B. 1,2,4-Triazoles

Aminoguanidine and its derivatives have been widely used in the synthesis of 3-amino-1,2,4-triazoles [2, 24]. Suitable intermediates are produced from aminoguanidine by acylation, or interaction with isothiocyanates, cyanates, or carbodiimides, or by direct synthesis by application of general methods.

I. Cyclization of Acylaminoguanidines

1. *Acylation of Aminoguanidine with Aliphatic Acids*

The classical synthesis of amino-1,2,4-triazoles introduced by *Thiele* [1, 25] involves acylation of aminoguanidine at the hydrazino moiety and cyclization of the resulting intermediate with alkali to the 3-amino-5-substituted-1,2,4-triazole.

The parent compound of the series, 3-amino-1,2,4-triazole, was first prepared by this method by *Thiele* and *Manchot* [26] using formic or oxalic acids, and has attracted much attention in recent years as a plant growth regulator [24, 27]; two satisfactory laboratory preparations based on *Thiele*'s synthesis have been

[20] *A. Vystrcil* and *R. Prokes*, Chem. Listy *46*, 670 (1952); Chem. Abstr. *48*, 165 (1954).

[21] *A. Vystrcil* and *R. Prokes*, Chem. Listy *47*, 160 (1953); Chem. Abstr. *48*, 3349 (1954).

[22] *S. C. De* and *P. C. Rakshit*, J. Indian chem. Soc. *13*, 509 (1936).

[23] *F. L. Scott* and *M.T. Scott*, Chimia *12*, 148 (1958).

[24] *K.T. Potts*, Chem. Reviews *61*, 87 (1961).

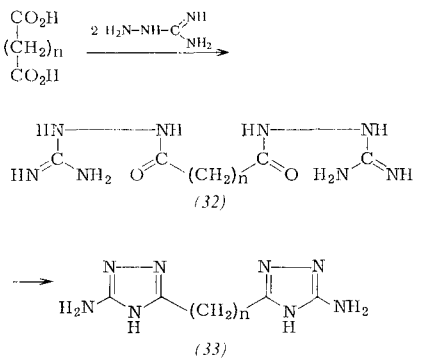
[25] *J. Thiele* and *K. Heidenreich*, Ber. dtsch. chem. Ges. *26*, 2598 (1893).

[26] *J. Thiele* and *W. Manchot*, Liebigs Ann. Chem. *303*, 33 (1898).

[27] *C. J. Grundmann* and *A. Kreutzberger*, U.S.-Pat. 2763661; Chem. Abstr. *51*, 3669 (1957).

described in detail [28, 29]. A recent patent [30] describing a preparation of this type suggests that the presence of an entraining agent to remove the water formed may be beneficial. Other triazoles prepared directly from aliphatic acids and aminoguanidine include 5-ethyl-, 5-propyl-, 5-isopropyl-, and 5-hexyl-3-amino-1,2,4-triazoles [31].

Dibasic aliphatic acids yield diguanidyl-dicarboxamides *(32)* in this condensation; they are advantageously isolated as mineral acid salts. Cyclization to the corresponding 'linked' triazole *(33)* is carried out in the normal manner by heating with aqueous potassium carbonate [32]. The diaminoditriazoles *(33)* can be diazotized and are said to give excellent dyes when coupled with ß-naphthol.

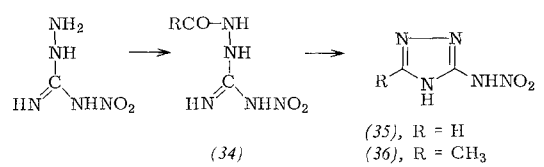


(32)

(33)

2. *Acylation of Nitroaminoguanidine*

Nitroaminoguanidine reacts with organic acids as does aminoguanidine; the intermediate acyl derivative *(34)* is cyclized to 3-substituted 5-nitroamino-1,2,4-triazoles by alkali. Thus, reaction with formic or acetic acid yields 3-nitramino- *(35)* or 3-methyl-5-nitramino-1,2,4-triazole *(36)*, respectively [33].



(34)

(35), R = H
(36), R = CH_3

The pyrazoline *(30)* resists bromination and aminolysis. This inactivity is striking contrast to the reactivity of the corresponding pyrazoles and pyrazolones, and may be ascribed to inability of the partly reduced ring to form a stable anion [23]. 3,5-Dinitramino-1,2,4-triazole has been obtained by *Henry, Skolnik*, and *Smith* [34] by diazotizing 1,6-dinitro-2-aminoguanylbiguanidine: the unstable intermediate tetrazole decomposed to yield the nitraminotriazole among other products.

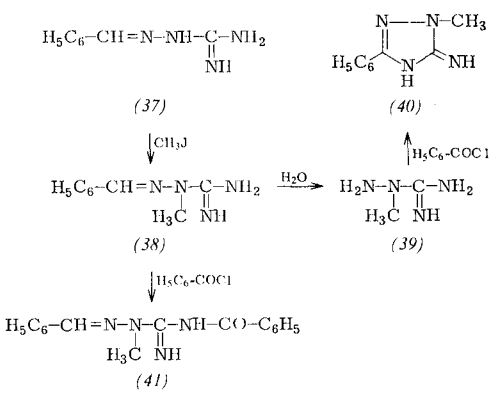
Nitraminotriazoles are fairly strong acids [35, 36] capable of forming salts [33, 34] and are convertible by reduction into the corresponding 3-hydrazino derivatives [34, 37]. 3-Hydrazino-1,2,4-triazole has been used for the preparation of a compound containing two triazole rings linked in the 1,3-positions [31]: thus 3,5-dimethyl-1-(1,2,4-triazol-3-yl)-1,2,4-triazole was obtained in 9 % yield by heating the hydrazino-triazole with diacetamide in acetic acid.

3. *Acylation of Aminoguanidine by Aromatic Acids and their Derivatives*

Unlike their aliphatic counterparts, aromatic acids react only reluctantly with aminoguanidine. Thus the action of benzoic acid afforded only very poor yields of 3-amino-5-phenyl-1,2,4-triazole [31], and salicyclic acid failed to react [31]. On the other hand, good yields of triazoles were obtained from pyridine-2- or 3-carboxylic acids [31].

Considerable attention has therefore been given to aroylation of aminoguanidine with aromatic acid chlorides. *Benack* [38] claimed that 3-amino-5-phenyl-1,2,4-triazole was formed on heating aminoguanidine bicarbonate with benzoyl chloride. It appears more advantageous, however, to isolate the aroyl aminoguanidine, and to perform the cyclization separately [39]. Benzamidoguanidine is obtainable from benzoyl chloride and aminoguanidine in pyridine [39], or in benzene [40]; nicotinamido- and isonicotinamido-guanidine are also successfully prepared from the acid chlorides in pyridine [40, 41] and cyclized to triazoles by heating at 250 °C [40].

A disubstituted aminotriazole, *viz.* 5-amino-1-methyl-3-phenyl-1,2,4-triazole, is obtainable by this general method [31] as follows:



(37) *(40)* *(38)* *(39)* *(41)*

[28] *G. Sjostedt* and *L. Gringas*, Org. Syntheses, Coll. Vol. 3, Wiley, New York 1955, p. 95.

[29] *C. F. H. Allen* and *A. Bell*, Org. Syntheses *26*, 11 (1946).

[30] *M. Niese* and *D. Delfs*, U.S.-Pat. 2875209; Chem. Abstr. *53*, 17151 (1959).

[31] *M. R. Atkinson, A. Komzak, E. A. Parkes*, and *J. B. Polya*, J. chem. Soc. (London) *1954*, 4508.

[32] *N. R. Shreve* and *R. K. Charlesworth*, U.S.-Pat. 2744116; Chem. Abstr. *51*, 489 (1957).

[33] *R. A. Henry*, J. Amer. chem. Soc. *72*, 5343 (1950).

[34] *R. A. Henry, S. Skolnik*, and *G. B. L. Smith*, J. Amer. chem. Soc. *75*, 955 (1953).

[35] *J. E. DeVries* and *E. S. C. Gantz*, J. Amer. chem. Soc. *76*, 1008 (1954).

[36] *J. H. Boyer*, in *R. C. Elderfield:* Heterocyclic Compounds, Wiley, New York 1961, Vol. 7, p. 457.

[37] *E. Lieber, S. Schiff, R. A. Henry*, and *W. G. Finnegan*, J. org. Chemistry *18*, 218 (1953).

[38] *Benack*, Ph. D. Thesis, Universität München, 1896, p. 19; see Beilstein's Handbook, Vol. 26, 1st Suppl., p. 45.

[39] *E. Hoggarth*, J. chem. Soc. (London) *1950*, 612.

[40] *R. Giuliano* and *G. Leonardi*, Il Farmaco (Pavia), Ed. Sci. *9*, 529 (1954).

[41] *H. L. Yale, K. A. Losee, F. M. Perry*, and *J. Bernstein*, J. Amer. chem. Soc. *76*, 2208 (1954).

Benzylideneaminoguanidine *(37)* is methylated with methyl iodide, and the intermediate *(38)* hydrolysed to 1-amino-1-methylguanidine *(39)* which, on treatment with benzoyl chloride, yields the cyclized product *(40)* as a benzoyl derivative in one step. Direct reaction of benzoyl chloride with *(38)* does not result in cyclization, but only gives 1-benzylidineamino-3-benzoyl-1-methylguanidine *(41)*.

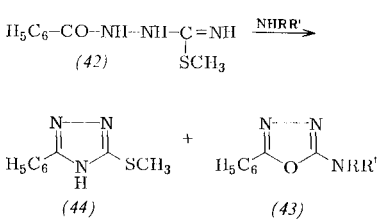
Since direct syntheses of acylamidoguanidines from aromatic acids or acid chlorides often give erratic results, indirect syntheses of the amides have been devised (see below).

4. *Reduction of Nitroguanidines in the Presence of Acids*

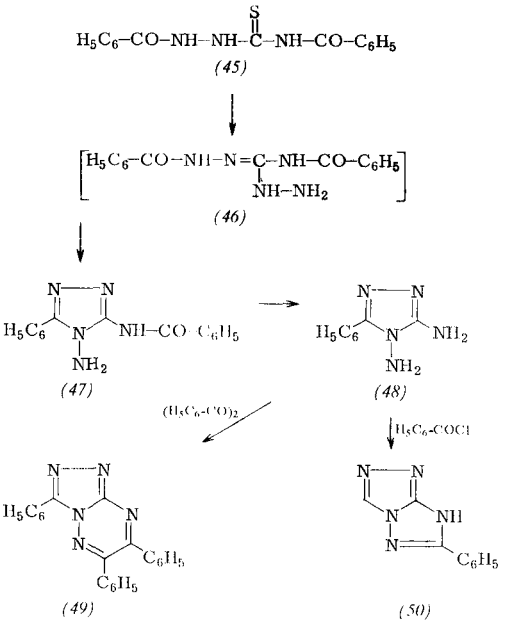
Reductions of nitroguanidine carried out in acetic acid produce 3-amino-5-methyl-1,2,4-triazole as a by-product [37, 42]. Nitroaminoguanidine similarly affords 3,4-diamino-5-methyl-1,2,4-triazole [37, 42] as a by-product, the structure of which is confirmed by diazotization in the presence of hypophosphorous acid, when removal of both amino groups yields the known compound 3-methyl-1,2,4-triazole [37] in 63 % yield. The initial diazotization product can be coupled with β-naphthol to afford the azo dye, 1-(3-methyl-1,2,4-triazol-5-yl)azo-2-naphthol, which is also obtainable by diazotization and coupling of 3-amino-5-methyl-1,2,4-triazole [37].

5. *Aminolysis of Acyl-S-alkylisothiosemicarbazides*

The action of ammonia or amines on 1-benzoyl-*S*-methylisothiosemicarbazide *(42)* does not yield the expected benzamidoguanidines [39] but affords a mixture of 2-amino-5-phenyl-1,3,4-oxadiazole *(43)* and 5-methylthio-3-phenyl-1,2,4- triazole *(44)* directly. The oxadiazoles probably arise from an intermediate aminoguanidine derivative by loss of a molecule of ammonia instead of water [39].

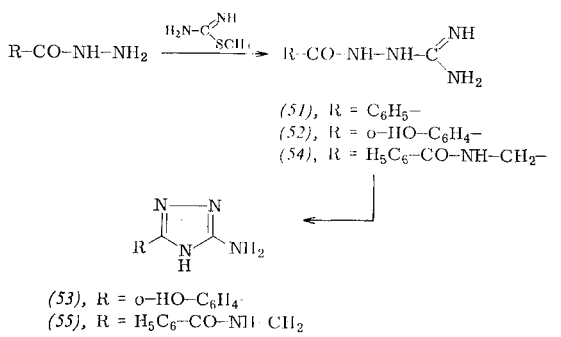


The interaction of 1,4-dibenzoylthiosemicarbazide *(45)* with hydrazine hydrate [43] proceeds with loss of hydrogen sulfide to yield a product formulated as 3,4-diamino-5-phenyl-1,2,4-triazole *(48)*, possibly arising via the hypothetical dibenzoyldiaminoguanidine *(46)*. Support for the structure *(48)* is provided by the formation of an *N,N'*-bis(benzylidene) derivative with benzaldehyde, and by its reaction with benzil to give a compound believed to be triphenyl-1,2,4,7,9-pentaazaindene *(49)* [43]. On treatment with benzoyl chloride, *(48)* gives a monobenzoyl derivative. Excess of the reagent yields a product with a composition which corresponds to a dibenzoyl derivative less one molecule of water. Mild hydrolysis produced a compound *(50)* believed to contain two fused rings [43].



6. *Synthesis of Acylaminoguanidines from Acylhydrazines*

The action of *S*-alkylisothiourea on acylhydrazines has proved a good general method for the synthesis of acylaminoguanidines and thence of 1,2,4-triazoles. Thus, 1-benzamidoguanidine *(51)* is easily obtained from benzhydrazide and *S*-methylisothiouronium sulfate in the presence of alkali [39]. 1-Salicylamidoguanidine *(52)* is prepared similarly and is readily cyclized to 3-amino-5-(*o*-hydroxyphenyl)-1,2,4-triazole *(53)* [31].



Biemann and *Bretschneider* [44] have described a number of further applications of this synthesis: Benzamidoacetyl hydrazide presumably affords the appropriate intermediate *(54)*, which cyclizes spontaneously with loss of water to 3-amino-5-benzamidomethyl-1,2,4-triazole *(55)*; final debenzoylation in acid medium slowly yields 5-aminomethyl-1,2,4-triazole. In a similar manner, both the 3-amino-5-(2-benzamidoethyl)- and 3-amino-5-(1-acetylamino-2-phenylethyl)-1,2,4-triazoles were prepared and were deacylated to the diamines [44].

1-Isonicotinamidoguanidine, prepared from isonicotinoylhydrazin, had a m.p. of 276 277 °C [44], but no reference was made to that previously reported (m.p. 177 °C) by *Giuliano* and *Leonardi* [40]. Pyrolysis at 200 °C cyclized 1-isonicotinamidoguanidine to 3-amino-5-(pyrid-3-yl)-1,2,4-triazole, which had the same m.p. (277 °C) as that previously reported (273–274 °C) [40]. The possibility of the supposed intermediate being a hydrate of the triazole was rejected on the grounds that the ultraviolet spectra of the two compounds were different.

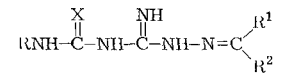
[42] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly*, J. appl. Chem. *2*, 184 (1952).

[43] *E. Hoggarth*, J. chem. Soc. *1950*, 614.

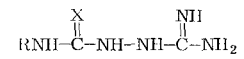
[44] *K. Biemann* and *H. Bretschneider*, Monatsh. Chem. *89*, 603 (1958).

II. Cyclization of Aminoguanyl(thio)ureas and Guanylthiosemicarbazides

Interaction of aminoguanidine with isocyanates or isothiocyanates gives rise either to substituted *N*-(1-aminoguanyl)-ureas or -thioureas *(56)* or to 4-substituted 1-guanyl(thio)semicarbazides *(57)*, in the presence or absence, respectively, of a blocking group on the hydrazine residue. Both series of products are readily cyclized to 1,2,4-triazoles.

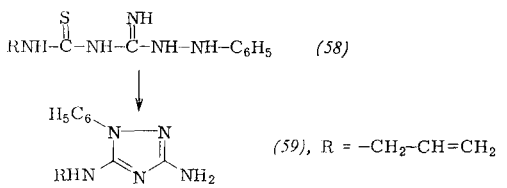


(56), X = O, S



(57), X = O, S

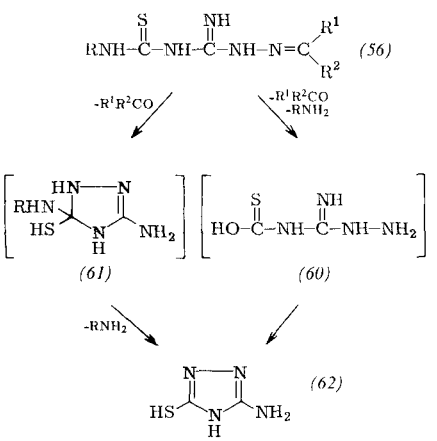
Addition of allyl or phenyl isothiocyanate onto 1-anilinoguanidine yields the expected *N*-(1-anilinoguanyl)thiourea derivative *(58)* [45]; the allyl homologue has been cyclized by alkali to give 5-allylamino-3-amino-1-phenyl-1,2,4-triazole *(59)* [45].



(58)

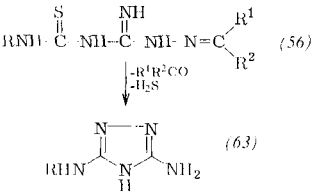
(59), R = $-CH_2-CH=CH_2$

1-Substituted 3-(1-aminoguanyl)thioureas, which have been obtained only in the form of hydrazones *(56)* [46], are cyclized by mineral acids to 3-amino-5-mercapto-1,2,4-triazole *(62)* in excellent yields. A mechanism for this general reaction involving the hypothetical 1-aminoguanylthiocarbamic acid *(60)* has been considered [46], but an addition-elimination mechanism involving an intermediate of type *(61)* may be more likely.



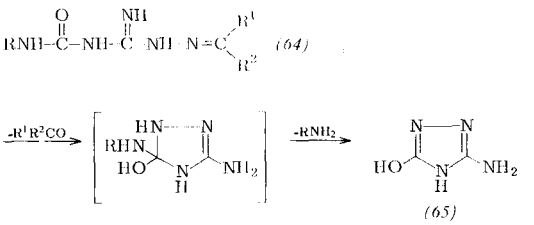
(56), *(61)*, *(60)*, *(62)*

The action of weak acids, or of alkalis, results in an alternative ring closure of *(56)*, involving loss of hydrogen sulfide to give 3,5-diamino-1,2,4-triazoles *(63)* [46].



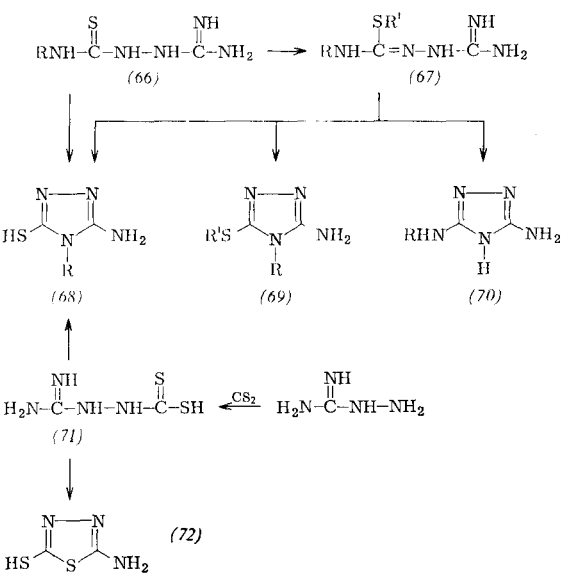
(56), *(63)*

The hydrazones in the corresponding urea series *(64)* are also cyclized by strong acids, albeit more slowly than the sulfur analogues, to form 3-amino-5-hydroxy 1,2,4-triazole *(65)* [46].



(64), *(65)*

The action of phenyl isothiocyanate on aminoguanidine hydrogen carbonate in ethanol was originally shown [45] to result directly, with loss of ammonia, in 3-amino-5-mercapto-4-phenyl-1,2,4-triazole *(68)*, R = C_6H_5. 4-Substituted 1-guanylthiosemicarbazides *(66)* are obviously concerned as intermediates in this reaction and were isolated as salts by *Fry* and *Lambie* [47], when



(66), *(67)*, *(68)*, *(69)*, *(70)*, *(71)*, *(72)*

aminoguanidine hydrochloride or nitrate were employed. They are rapidly converted into 4-substituted 3-amino-5-mercapto-1,2,4-triazoles *(68)* by alkalis [48] or, more slowly, in acid media, so that both products *(66)* and *(68)* are obtained side by side on prolonged interaction of aminoguanidine salts and isothiocyanates, particularly aromatic isothiocyanates [49]. Use of dimethylformamide as solvent and isolation of

[45] *P. Fantl* and *H. Silbermann*, Liebigs Ann. Chem. *467*, 274 (1928).

[46] *L. E. A. Godfrey* and *F. Kurzer*, J. chem. Soc. (London) *1960*, 3437.

[47] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 741280; Chem. Abstr. *50*, 16842 (1956).

[48] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 741228; Chem. Abstr. *50*, 9913 (1956).

[49] *L. E. A. Godfrey* and *F. Kurzer*, J. chem. Soc. (London) *1961*, 5137.

the products as crystalline toluene-*p*-sulfonates greatly facilitate production of the 4-substituted thiosemicarbazides *(66)* [49].

Benzylation of *(66)*, R = C_6H_5, yields the corresponding *S*-benzyl ether *(67)* which, like the parent compound *(66)*, also undergoes cyclization readily [49]. Boiling alkali removes the benzylthio residue as a whole and affords 3-amino-5-anilino-1,2,4-triazole *(70)* in excellent yield. Boiling aniline acts on *S*-benzyl-1-guanyl-4-phenylisothiosemicarbazide *(67)*, R = C_6H_5, R′ = $C_6H_5CH_2$ in two distinct ways. The free base *(67)* yields approximately equal quantities of 3-amino-5-benzylthio-4-phenyl- *(69)* and 3-amino-5-anilino-1,2,4-triazole *(70)*; the toluene -*p*-sulfonate of *(67)*, on the other hand, gives 3-amino-4-phenyl-5-mercapto-1,2,4-triazole *(68)* almost quantitatively; in the latter case, the *S*-alkyl derivative is simply dealkylated, and the resulting parent compound *(66)* subsequently cyclizes in the usual way [49].

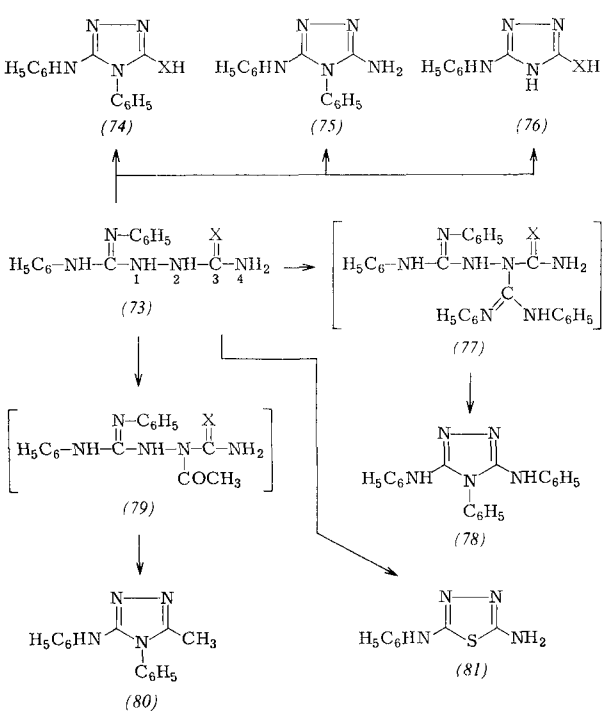
A closely related triazole synthesis involves production of guanidinodithiocarbamic acids *(71)* from aminoguanidine bicarbonate and carbon disulfide in acetic acid [51] and their cyclization in basic media [52]; a mixture of 3-amino-5-mercapto-1,2,4-triazole *(68)*, R = H and 2-amino-5-mercapto-1,3,4-thiadiazole *(72)* is obtained, the former predominating when higher temperatures and stronger alkalis are employed. Substituted aminoguanidines yield the appropriate homologues of *(68)* in this reaction.

Addition of diphenylcarbodiimide onto thiosemicarbazide yields 1-(*N*,*N*′-diphenylguanyl)thiosemicarbazide *(73)*, X = S [54], which may be formally regarded as an aminoguanidine derivative. In common with suitably substituted thiosemicarbazides in general [50], *(73)* undergoes cyclization readily, being converted into the appropriate 1,3,4-thiadiazole *(81)* in acidic, and into 1,2,4-triazoles, *(74)* and *(75)*, in alkaline media. Pyrolysis of *(73)*, results in loss of aniline and exclusive formation of 3-anilino-5-mercapto-1,2,4-triazole *(76)*, X = S [54].

1-(*N*,*N*′-Diphenylguanyl)semicarbazide *(73)*, X = O, is converted pyrolytically, or by alkaline hydrolysis, with loss of ammonia, into 3-anilino-5-hydroxy-4-phenyl-1,2,4-triazole *(74)*, X = O. Successive treatment of *(73)*, X = O, with acetic anhydride and alkali yields 3-anilino-5-methyl-4-phenyl-1,2,4-triazole *(80)*, presumably by the route *(73)* → *(79)* → *(80)* [54].

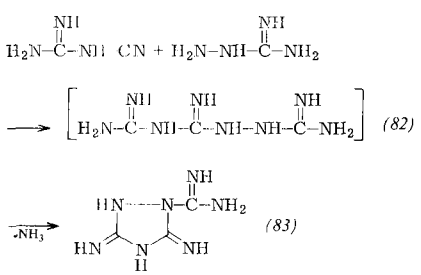
Further action of diphenylcarbodiimide on either 1-(*N*,*N*′-diphenylguanyl)thiosemicarbazide *(73)*, X = S, or 1-(*N*,*N*′-diphenylguanyl)-semicarbazide *(73)*, X = O, affords good yields of 3,5-dianilino-4-phenyl-1,2,4-triazole *(78)*, probably by way of the intermediate *(77)*, X = S or O [54].

Interaction of diphenylcarbodiimide and 4-phenylthiosemicarbazide does not result in simple addition: the monoadduct apparently cyclizes immediately with elimination of hydrogen sulfide or aniline to yield a mixture of 3,5-dianilino-4-phenyl-1,2,4-triazole *(78)* and (mainly) 3-anilino-5-mercapto-4-phenyl-1,2,4-triazole *(74)* X = S [54].



III. Synthesis of Triazoles from Biguanidines

Addition of dicyandiamide onto aminoguanidine yields 3,5-diimino-1-guanyl-1,2,4-triazolidine *(83)*, presumably by spontaneous cyclization, with loss of ammonia, of the intermediate 1-guanylbiguanidine *(82)* [53].



Interaction of excess aminoguanidine and diphenylcarbodiimide in dimethylformamide produces 1,2-diphenylbiguanidine *(84)* and 1-guanyl-4-phenyl-3,5-diphenylimino-1,2,4-triazolidine *(86)* in approximately equal proportions [54]. These compounds probably arise by successive addition of two moles of carbodiimide, one to each of the nitrogen atoms of the hydrazino group in aminoguanidine, followed by elimination of aniline [*(84)* → *(85)* → *(86)*]. The triazolidine *(86)* is in fact prepared more advantageously by the action of a second mole of carbodiimide on 1,2-diphenylbiguanidine *(84)*. The 4-imino-group in the biguanidine *(84)* thus acts as a particularly active centre, competing

[50] *W. R. Sherman*, in *R. C. Elderfield:* Heterocyclic Compounds. Wiley, New York 1961, Vol. 7, p. 587 *et seq.*

[51] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 737567; Chem. Abstr. *50*, 13086 (1956).

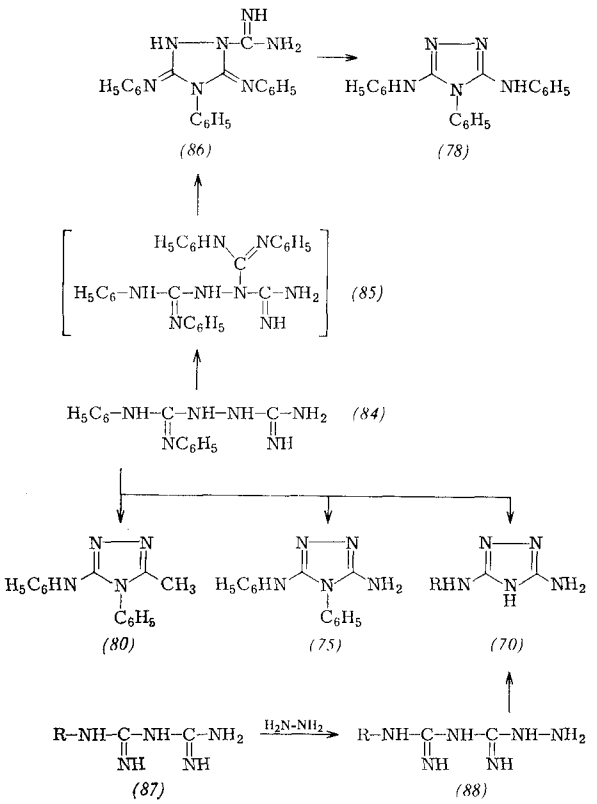
[52] *D. J. Fry* and *A. J. Lambie*, Brit. Pat. 737568; Chem. Abstr. *50*, 13097 (1956).

[53] *J. K. Simons*, U.S.-Pat. 2456090; Chem. Abstr. *43*, 3843 (1949).

[54] *L. E. A. Godfrey* and *F. Kurzer*, J. chem. Soc. (London) *1962*, 3561.

strongly for the available carbodiimide, since *(84)* and *(86)* are formed side by side, even when an excess of aminoguanidine is employed [54].

1-Guanyl-4-phenyl-3,5-diphenylimino-1,2,4-triazolidine *(86)* is converted rapidly and almost quantitatively into 3,5-dianilino-4-phenyl-1,2,4-triazole *(78)* by hydrolysis. As expected, this triazole is also the direct product of the interaction of aminoguanidine and diphenylcarbodiimide in the molar proportion 1:2 [54].



1,2-Diphenylbiguanidine *(84)* is a diacidic base, which is stable towards acids and alkalis, but is pyrolysed at 160 °C, with loss of either ammonia or aniline, to give 3-amino-5-anilino-4-phenyl-1,2,4-triazole *(75)* and 3-amino-5-anilino-1,2,4-triazole *(70)* side by side. Acetylation of *(84)* and subsequent treatment with alkali yields 3-anilino-5-methyl-4-phenyl-1,2,4-triazole *(80)* probably by way of the intermediate acetyl derivative *(79)*, X = NH, followed by the well established dehydrative cyclization (see Sections B I, 1–3) with simultaneous removal of the guanyl side-chain at *N*-1 [54].

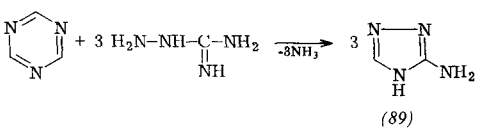
IV. Synthesis of Triazoles from Biguanides

Substituted amino- or diaminoguanidines are likely intermediates in the synthesis of certain 3-amino- or 3-hydrazino-1,2,4-triazoles from biguanides. Thus, the formation of 3-amino-5-(*p*-hydroxyanilino)-1,2,4-triazole *(70)*, by the action of hydrazine on *p*-hydroxyphenylbiguanide *(87)* probably proceeds via the guanylaminoguanidine *(88)* (R = *p*-HO–H_4C_6 in each case) [55]. Other reactions of this type entail additions of hydrazine or acylated hydrazines onto dicyandiamide to produce 3,5-diamino-1,2,4-triazole [56], or 1-acyl-3,5-diamino-1,2,4-triazoles [53], respectively. Semicarbazide, thiosemicarbazide, and hydrazides react analogously.

Another group of reactions that may possibly involve transitory formation of aminoguanidines is the hydrazinolysis of esters of *N,N*-dimethyldithiocarbamic acids to give thiols and 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole [57].

V. Synthesis of Triazoles from s-Triazine

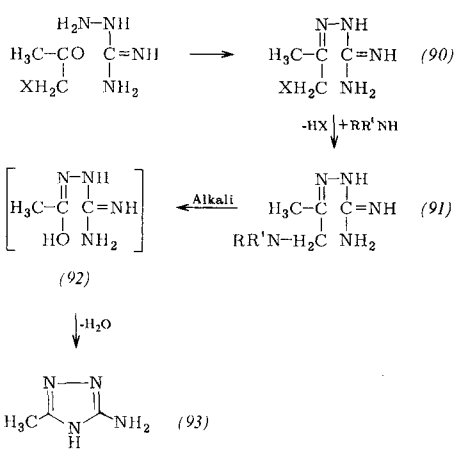
An interesting conversion of *s*-triazine into the more stable triazoles was discovered by *Grundmann* and *Kreutzberger* [27, 58], who found that *s*-triazine reacts readily with semicarbazide, thiosemicarbazide, or aminoguanidine to give 3-substituted 1,2,4-triazoles. Thus, the action of freshly liberated aminoguanidine base on *s*-triazine gave a 47 % yield of 3-amino-1,2,4-triazole *(89)*.



(89)

VI. Other Syntheses of Triazoles

A novel synthesis of 3-amino-5-methyl-1,2,4-triazole *(93)*, reported by *Beyer* and *Pyl* [59], makes use of guanyl- and nitroguanylhydrazones of ω-halogeno-ketones *(90)*. These react with many organic nitrogen bases to form derivatives *(91)* that are stable and may be isolated as salts. The salts are cleaved by alkali into methanol, the appropriate base, and acylaminoguanidine *(92)*, which then cyclizes with loss of water to the triazole *(93)*.



C. Thiadiazoles

The condensation of aminoguanidine with certain compounds containing sulfur gives rise to structures that are suitable intermediates for the production of 1,3,4-thiadiazoles.

[55] *G.F. D'Alelio*, U.S.-Pat. 2406591; Chem. Abstr. *41*, 488 (1947).

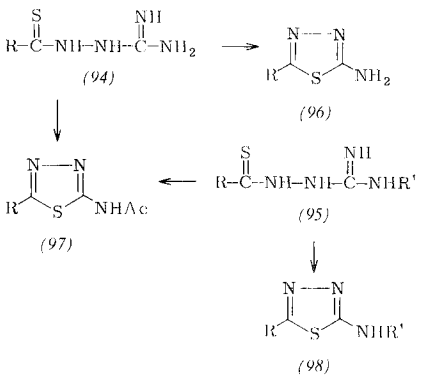
[56] *D.W. Kaiser, G. A. Peters*, and *V. P. Wystrach*, J. org. Chemistry *18*, 1610 (1953).

[57] *M. Kulka*, Canad. J. Chem. *34*, 1093 (1956).

[58] *C. J. Grundmann* and *A. Kreutzberger*, J. Amer. chem. Soc. *79*, 2839 (1957).

[59] *H. Beyer* and *T. Pyl*, Chem. Ber. *89*, 2556 (1956).

Thiobenzoylation with thiobenzoylthioacetic acid [62] of aminoguanidine [60, 61] or 1-amino-3-arylguanidines [61] yields *N*-(thiobenzamido)guanidine *(94)* or its 3-aryl analogues *(95)* which are readily cyclized to 1,3,4-thiadiazoles in acid media (compare the dehydrative cyclization of corresponding acylaminoguanidines to 1,2,4-triazoles in alkalis; cf. Sections B. I. 1–3). Phosphoric acid or acetic anhydride convert the parent compound *(94)*, with loss of ammonia, into 2-amino-5-phenyl-1,3,4-thiadiazole *(96)* or its acetyl derivative *(97)*, respectively [61]. Aryl analogues *(95)* afford the expected 2-arylamino-5-phenyl-1,3,4-thiadiazoles *(98)* on treatment with mineral acid, but lose arylamine to form 2-acetamido-5-phenyl-1,3,4-thiadiazole *(97)* under the influence of acetic anhydride [61].



4-Substituted 1-guanylthiosemicarbazides *(94)*, R = ArNH, obtained from aryl isothiocyanates and aminoguanidine, are cyclized similarly by phosphoric acid at 120–130 °C to give 2-amino-5-arylamino-1,3,4-thiadiazoles *(96)*, R = ArNH, in satisfactory yields [49]. Boiling acetic anhydride affords the corresponding diacetyl derivatives [49].

The cyclization of the structurally related compound guanidinodithiocarbamic acid *(71)* [51, 52] has already been discussed (cf. Section B. II).

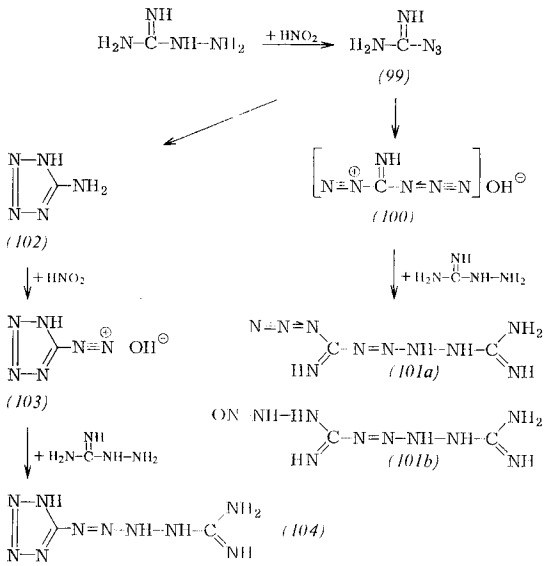
D. Tetrazoles

I. Reaction between Nitrous Acid and Aminoguanidine

Thiele [1] was the first to investigate the action of nitrous acid on aminoguanidine, and his interesting observations have prompted many other studies of these reactions. Their variable course and the instability of some of the products make this work difficult, and certain questions remain controversial. *Lieber* and *Smith* [2] have dealt with these reactions at length, and other briefer discussions have appeared in recent years [63–65]. The course of the reaction depends greatly on the acidity of the solution.

1. *Reaction in Neutral or Weakly Acidic Solution*

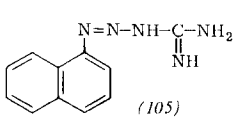
Hofmann and *Roth* [66] showed that neutral cold aqueous aminoguanidine nitrate reacts slowly with excess sodium nitrite over a period of days to produce an open-chain compound formulated as *(101a)* or *(101b)*, presumably by a sequence such as that shown. *Hofmann* and co-workers [67, 68] favoured the β-nitrosohydrazino structure *(101b)*; although *Lieber* and *Smith* [2] regard the evidence as conclusive, there still appears to be some room for speculation.



A different product *(104)* is obtained if guanyl azide *(99)*, formed as primary intermediate, cyclizes to 5-aminotetrazole *(102)*. This amine then reacts with a further molecule of nitrous acid to form a diazo-compound *(103)*, which couples with unreacted aminoguanidine to give guanyltetrazyltetrazene *(104)*. The two compounds *(101)* and *(104)* have been re-examined by *Hofsommer* and *Pestemer* [64], who attempted to confirm the assigned structures by an examination of the ultraviolet spectra of intermediate stages of known structure, but the results obtained were not entirely conclusive.

2. *Dyes from Diazotized Aminoguanidine*

Hofmann, *Hock*, and *Roth* [67] found that neutral solutions containing 'diazotized' aminoguanidine couple slowly with suitable intermediates, such as β-naphthol, to form colored compounds. *Shreve*, *Carter*, and *Willis* [65] reinvestigated this reaction, performing the coupling at 80–85 °C. They proposed structure *(105)* for the product obtained from β-naphthol and claimed this to be the first example of a dye derived from an aliphatic diazo compound. Reduction gave 1-amino-2-naphthol, but aminoguanidine or its decomposition products could not be isolated.



[60] *K. A. Jensen* and *J. F. Miquel*, Acta chem. scand. *6*, 189 (1952).

[61] *F. Kurzer*, J. chem. Soc. (London) *1961*, 1617.

[62] *F. Kurzer*, Chem. and Ind. *1961*, 1333.

[63] *J. Reilly*, *J. P. Teegan*, and *M. F. Carey*, Sci. Proc. Roy. Dublin Soc. *24*, 349 (1948).

[64] *R. Hofsommer* and *M. Pestemer*, Z. Elektrochem. *53*, 383 (1949).

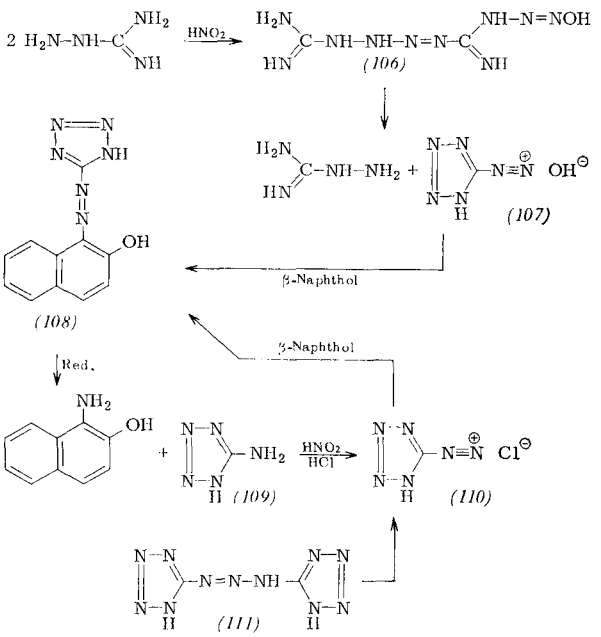
[65] *R. N. Shreve*, *R. P. Carter*, and *J. M. Willis*, Ind. Engng. Chem. *36*, 426 (1944).

[66] *K. A. Hofmann* and *R. Roth*, Ber. dtsch. chem. Ges. *43*, 682 (1910).

[67] *K. A. Hofmann*, *H. Hock*, and *R. Roth*, Ber. dtsch. chem. Ges. *43*, 1087 (1910).

[68] *K. A. Hofmann*, *H. Hock*, and *H. Kirmreuther*, Liebigs Ann. Chem. *380*, 131 (1911).

The reason for this became apparent when *Reilly* et al. [63] showed that the dye formed during the coupling process was actually a derivative of 5-diazotetrazole of structure *(108)*. The guanylnitrosoaminoguanyltetrazene



(106) initially formed splits into two fragments, one of which cyclizes to the tetrazole *(107)* and couples with the β-naphthol. 5-Aminotetrazole *(109)* can in fact be isolated as one of the reduction products of the dye *(108)* [63].

The structure of the dye *(108)* was confirmed by synthesis from diazotized 5-aminotetrazole *(110)* and suitable naphthols. The same dye also resulted from 1,3-ditetrazolyltriazene *(111)* and β-naphthol [67], at 80 °C, *(111)* being first split at the –NH–N=N link to form 5-aminotetrazole and tetrazolyldiazonium chloride.

3. *Reaction in Strongly Acid Solution: Guanyl Azide*

Thiele [1] was again the first to treat aminoguanidine with nitrous acid in strongly acid solution; the product was later [69] identified as guanyl azide nitrate. The corresponding sulfate has recently been prepared [64]. Nitroguanyl azide, obtained analogously from nitroaminoguanidine and nitrous acid [70–72], undergoes the same types of reaction as guanyl azide.

4. *Reactions of Guanyl Azides*

a) Conversion of Guanyl Azide into Guanidine or Aminoguanidine Derivatives

Treatment of guanyl azide with hydrazine hydrate displaces the azide radicle to give a good yield of aminoguanidine [73], together with small quantities of 5-aminotetrazole, which is formed as by-product by cyclization. The use of excess hydrazine hydrate produces mixtures of di- and triaminoguanidines, and this reaction has been suggested as a preparative method for these compounds [73]. Nitroguanyl azide similarly yields nitroaminoguanidine [72].

Guanyl azide nitrate and nitroguanyl azide are converted by aniline into phenylguanidine (70 %) [74] and 1-phenyl-3-nitroguanidine (75 %) [74], respectively. By a comparable azide displacement, phenylhydrazine yields 1-anilino-3-nitroguanidine from nitroguanyl azide [74].

Azide displacement appears to be the preferential mode of reaction when the basicity of the base is low, and its nucleophilic activity towards carbonyl carbon [74] is high. Aniline and phenylhydrazine fulfil both these conditions, but hydrazine hydrate causes a certain amount of tetrazole formation because of its higher basicity.

Reduction of nitroguanyl azide with hydrogen sulfide gives nitroguanidine in 90 % yield [71]. When attempts were made [72] to obtain the monoazide of diaminoguanidine by gently reducing nitroguanyl azide with sodium bisulfite, nitroguanidine was the actual product (58 %).

b) Cyclization of Guanyl Azide to Tetrazoles

The most valuable reaction of guanyl azide in heterocyclic synthesis is its ready cyclization by weak bases to 5-aminotetrazole [1]. The product is slightly acidic and can be separated either as a free acid or as the salt of an organic or inorganic base. Nitrous acid reacts with substituted aminoguanidines in acid conditions to give substituted guanyl azides, which are readily cyclized by weak bases to mono- or di-substituted tetrazoles [70, 71, 74–76]. Substituted guanyl azides, unlike their parent compound, may cyclize in two ways: With most alkyl- or aryl-guanyl azides, reaction proceeds almost exclusively by route (A), and yields of up to 95 % 1-alkyl- or 1-aryl-5-aminotetrazoles *(113)* [75] are obtained. A certain amount of 5-alkyl- or 5-arylaminotetrazole *(114)* is usually formed as a by-product [75]. The presence of an electronegative substituent (*e.g.* a nitro-group) promotes cyclization by the second route (B), and 5-nitraminotetrazole *(114)*, R = NO_2, becomes the main product [70, 71, 74].

The relative proportions of 5-alkylaminotetrazole *(114)* and 1-alkyl-5-aminotetrazole *(113)* resulting from cyclization of guanyl azides vary according to the conditions, because isomerization may take place simultaneously [75, 77]. This occurs readily at 180–200 °C and reaches an equilibrium in homogeneous systems (*e.g.* in solution in glycerol), the position of the equilibrium depending mainly on the electronegativity of the substituent [77]. Equilibrium is not necessarily attained above the melting point of the tetrazole: if the isomerized product melts at a higher temperature, the equi-

[69] *A. Hantzsch* and *A. Vogt*, Liebigs Ann. Chem. *314*, 339 (1900).

[70] *T. E. O'Connor, G. Fleming*, and *J. Reilly*, J. Soc. chem. Indust. *68*, 309 (1949).

[71] *E. Lieber, E. Sherman, R. A. Henry*, and *J. Cohen*, J. Amer. chem. Soc. *73*, 2327 (1951).

[72] *F. L. Scott, D. G. O'Donovan*, and *J. Reilly*, J. appl. Chem. *2*, 368 (1952).

[73] *T. E. O'Connor, K. Horgan*, and *J. Reilly*, J. appl. Chem. *1*, 91 (1951).

[74] *F. L. Scott, F. C. Britten*, and *J. Reilly*, J. org. Chemistry *21*, 1519 (1956).

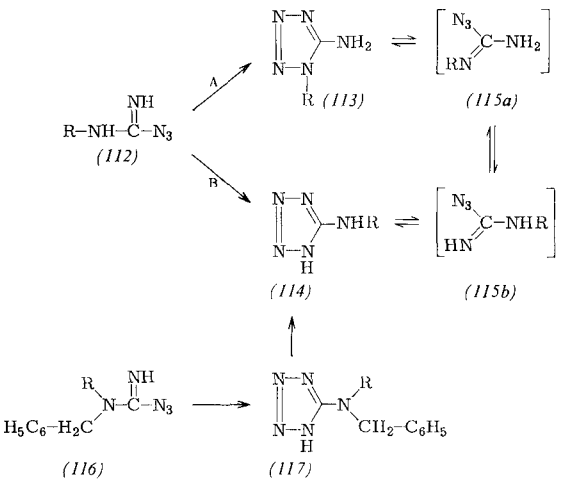
[75] *W. G. Finnegan, R. A. Henry*, and *E. Lieber*, J. org. Chemistry *18*, 779 (1953).

[76] *L. H. Schwartzman* and *B. B. Corson*, J. Amer. chem. Soc. *76*, 781 (1954).

[77] *R. A. Henry, W. G. Finnegan*, and *E. Lieber*, J. Amer. chem. Soc. *76*, 88 (1954).

librium is continually displaced by solidification. The isomerization probably involves initial ring-opening to form the substituted guanyl azide *(115)*, which exists in two isomeric forms, followed by recyclization in two ways [77] as shown. The relative proportion of the isomers *(113)* and *(114)* in a mixture can be determined by titrating the acidic 5-alkyl- or 5-arylaminotetrazoles *(114)* [77].

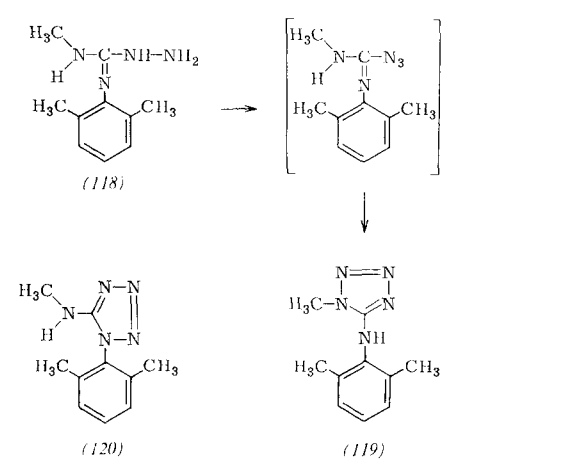
Although only small amounts of 5-aryl- or 5-alkylaminotetrazoles *(114)* are normally formed, they are easily isolated by precipitation as copper salts [75]. Decomposition with hydrogen sulfide yields the free amines [75], many of which are as strongly acidic as acetic acid [77].



Unequivocal proof of the structure of *(114)* is provided by synthesis from 1-alkyl-1-benzylaminoguanidine [75]. Ring closure of 1-alkyl-1-benzylguanyl azide *(116)* can occur in only one direction yielding 5-alkyl-5-benzyl-aminotetrazole *(117)*. Removal of the blocking benzyl group by catalytic hydrogenation [75] gives the desired tetrazole *(114)*.

Percival and *Herbst* [78] prepared a series of 1-alkyl-5-alkylaminotetrazoles with identical substituents by the general method. 1-Amino-2,3-dialkylguanidine was treated with nitrous acid and the resultant azide cyclized to the tetrazoles. This method failed, however, with 1-amino-2-benzyl-3-di-(β-cyanoethyl)guanidine[79].

The ready isomerization of substituted 5-aminotetrazoles and the two alternative modes of ring closure sometimes complicate the formulation of products. Thus, after carrying out a Schmidt reaction on 2,6-dimethylacetophenone, *Schwartzmann* and *Corson* [76] obtained a tetrazole which they formulated as 1-methyl-5-(2,6-dimethylanilino)tetrazole *(119)*, and then attempted to synthetize it by the supposedly unequivocal route *(118)* → *(119)*.

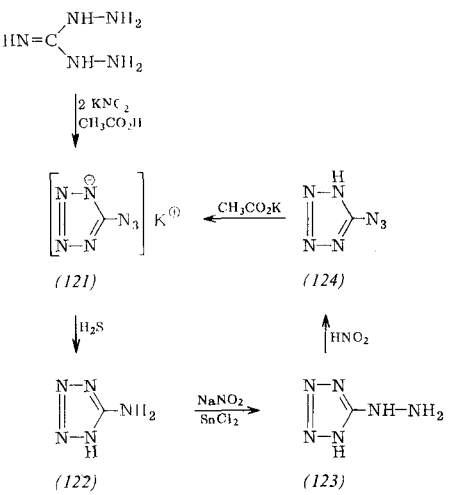


However, *Finnegan*, *Henry*, and *Olsen* [80] pointed out that comparable reactions usually yielded the isomeric 1-aryl-5-alkylaminotetrazoles [75]. Owing to steric hindrance, it was difficult to fix the structure by chemical means but infrared spectra indicated that *Schwartzmann* and *Corson*'s compound was in fact 5-methylamino-1-(2,6-dimethylphenyl)tetrazole *(120)* [80].

c) Cyclization of Guanyl Azide Derivatives Containing Electronegative Substituents

α) Reaction of 1,3-Diaminoguanidine with Nitrous Acid

In the reaction between 1,3-diaminoguanidine and nitrous acid in buffered or weakly acid solution, initial diazotization is followed by a more rapid cyclization than that which occurs with aminoguanidine [81]. The use of two moles of alkali nitrite yields the alkali salt of tetrazolyl azide *(121)* as the sole product [81].



Potassium tetrazolyl azide crystallizes as lustrous white platelets which are highly sensitive to pressure, friction, or heat; less than 0.01 g sometimes give rise to violent explosions, particularly if the product is contaminated with acetic acid. The free azide *(124)* prepared from 5-hydrazinotetrazole *(123)* is less sensitive to shock than the salts. The properties of this azide do not correspond with those reported by *Thiele* [1], but the structure he assigned to it was confirmed by infrared spectra and by reduction with hydrogen sulfide to the known compound 5-aminotetrazole *(122)*.

The use of only one equivalent of nitrous acid gave merely a diminished yield of *(121)* together with unchanged diaminoguanidine [81].

β) Nitroguanyl Azide

In its reaction with nitrous acid, 3-nitro-1-aminoguanidine behaves like 1,3-diaminoguanidine [70, 71]. In mineral acid solution, nitroguanyl azide *(125)* is produced [70, 71] as colorless platelets, m.p. 56 °C. In

[78] *D. F. Percival* and *R. M. Herbst*, J. org. Chemistry *22*, 925 (1957).

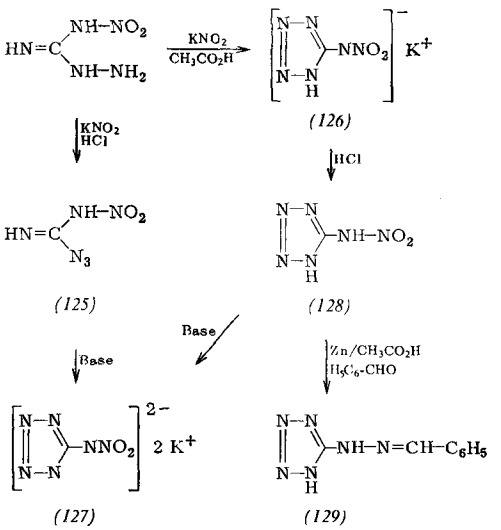
[79] *D. W. Renn* and *R. M. Herbst*, J. org. Chemistry *24*, 473 (1959).

[80] *W. G. Finnegan*, *R. A. Henry*, and *A. L. Olsen*, J. Amer. chem. Soc. *77*, 4420 (1955).

[81] *E. Lieber* and *D. R. Levering*, J. Amer. chem. Soc. *73*, 1313 (1951).

neutral or acetic acid solution, the alkali salt of 5-nitroaminotetrazole *(126)* is formed with alkali nitrite.

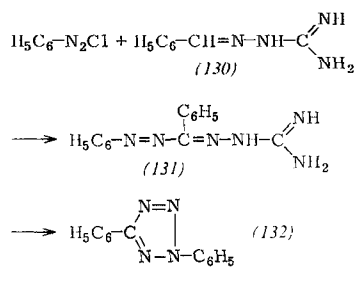
Nitroguanyl azide is cyclized almost quantitatively by dilute alkalis, including ammonium hydroxide [70–72] and organic bases [82], to di-salts of 5-nitroaminotetrazole *(127)*. Free 5-nitroaminotetrazole *(128)* is liberated from its salts by acids and is very sensitive to both mechanical and thermal shock and may explode violently [70, 71].

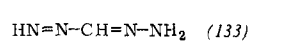


The structure of 5-nitroaminotetrazole was confirmed by reducing it with zinc and acetic acid to 5-hydrazinotetrazole, which was isolated as its benzylidene derivative *(129)*. The ultraviolet spectra of 5-nitroaminotetrazole and some of its salts have been described and a zwitterion structure has been proposed [83].

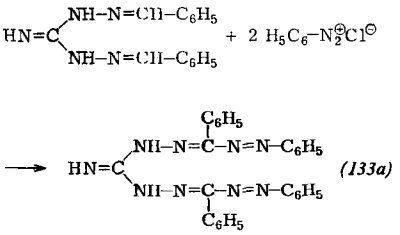
II. Synthesis of Tetrazoles from Aminoguanidine via Formazans

Towards the end of the nineteenth century, *Wedekind* [84] prepared so-called "guanazyl" compounds*(131)* by condensing aryldiazonium salts with the tertiary hydrogen in aldehyde guanylhydrazones *(130)*, usually in alkaline medium. These compounds were readily oxidized to 2,5-diaryltetrazoles *(132)*. The chemistry of formazans *(133)* has recently been reviewed by *Nineham* [85].





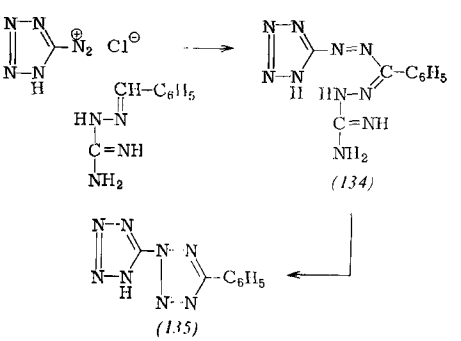
The coupling reaction has been extended to hydrazones derived from diaminoguanidine [86, 87]. Both their tertiary hydrogen atoms react with aryldiazonium salts in the expected manner to yield bis-(3,5-diarylformazan-1-yl)formimine *(133a)* [86, 87].



Ring-substituted aryldiazonium compounds were also applicable, but with regard to heterocyclic diazonium salts, only that derived from 4-aminoantipyrine underwent condensation.

Mild oxidation of the bisformazanylformimines *(133a)* did not yield the expected bis-(5-aryl-2-tetrazolyl)formimines, because oxidation was accompanied by fission, and only single-ring disubstituted tetrazoles, *e.g.* *(132)*, were obtained [86–88]. Concentrated nitric acid oxidizes and nitrates *(133a)* simultaneously yielding 2,5-di(nitrophenyl)-tetrazole as the main product [88].

An interesting attempt was made to prepare a system containing two tetrazole rings by oxidation of the formazan *(134)* obtained from tetrazole-5-diazonium chloride and 1-benzylideneaminoguanidine [89]. Concentrated nitric acid was unsuitable because it caused complete destruction, bromine gave tetrazines, but aqueous permanganate gave the desired product *(135)* in 70 % yield [89].



A logical extension of this work was the attempt to prepare formazans from derivatives of triaminoguanidine [87], the tris-benzylidene derivative *(136)* of which was coupled with a number of diazonium salts. The diazotates of *p*-nitroaniline, β-naphthylamine, and 4-chloro-2-toluidine coupled in the expected manner to form iminourea derivatives, *e.g.* *(137)*, but phenyldiazonium chloride behaved anomalously, introducing

[82] *E. Lieber, C. C. Herrick,* and *E. Sherman,* J. Amer. chem. Soc. *74,* 2684 (1952).

[83] *E. Lieber, E. Sherman* and *S. H. Patinkin,* J. Amer. chem. Soc. *73,* 2329 (1951).

[84] *E. Wedekind,* Ber. dtsch. chem. Ges. *30,* 444 (1897).

[85] *A. W. Nineham,* Chem. Reviews *55,* 355 (1955).

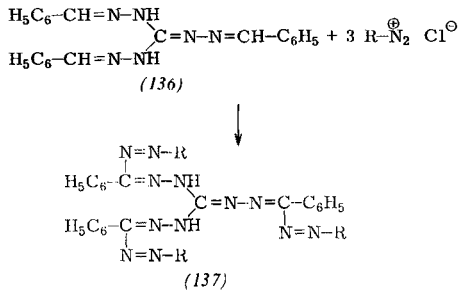
[86] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* J. chem. Soc. (London) *1951,* 3508.

[87] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* Chem. and Ind. *1952,* 782.

[88] *F. L. Scott, D. A. O'Sullivan,* and *J. Reilly,* J. Amer. chem. Soc. *75,* 5309 (1953).

[89] *V. A. Grakauskas, A. J. Tomasewski,* and *J. P. Horwitz,* J. Amer. chem. Soc. *80,* 3155 (1958).

only a phenoxy group [87]. All heterocyclic diazonium salts, excepting tetrazole-5-diazonium salts [87], failed to react.



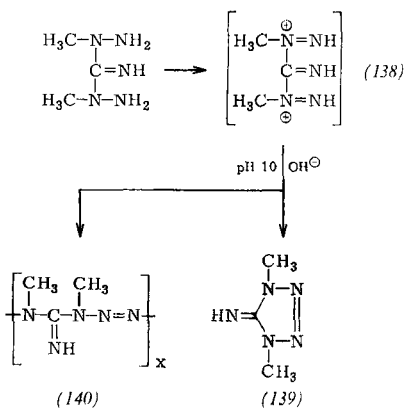
(136)

(137)

In the above coupling reactions, the diazonium compound may attack the aminoguanidine derivative at three centres, *viz.* the =CH-group, the –NH-group, or even in the aromatic ring. A number of problems are posed by this reaction [85], and *Scott* [88] has suggested that formazan formation is more likely when the carbon atom of the =CH-group is the centre of highest electron density. *Busch* et al. [90] postulated initial coupling of the diazonium ion at the nitrogen atom, followed by rearrangement of the tetrazene to a formazan.

III. Other Syntheses of Tetrazoles

A novel synthesis of tetrazoles from aminoguanidine derivatives has been developed by *McBride*, *Finnegan*, and *Henry* [91]. 1,2-Dimethyl-1,2-diaminoguanidine, prepared from 2,3-dimethylisothiosemicarbazide and methylhydrazine, was oxidized to a diazonium-like intermediate *(138)* with potassium bromate or iodate in 6 N hydrochloric acid. Subsequent basification (to pH 10) either cyclized the intermediate to 1,4-dimethyl-5-iminotetrazole *(139)* or converted it by intermolecular coupling into a water-soluble polytetrazene *(140)*.



(138)

(140) *(139)*

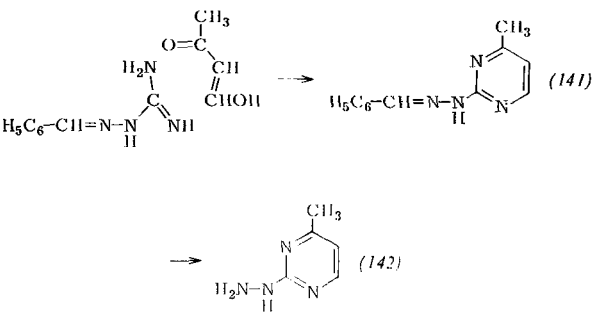
The tetrazole *(139)* was isolated by further reaction with phenyl isothiocyanate and separation of the resultant 1-(1,4-dimethyltetrazolyl)-3-phenylthiourea [91]. The polytetrazene *(140)* could not be isolated, and its formation was only adduced from spectroscopic evidence.

[90] *M. Busch* and *H. Pfeiffer*, Ber. dtsch. chem. Ges. *59*, 1162 (1926); *M. Busch* and *R. Schmidt*, J. prakt. Chem. *131*, 182 (1931).

[91] *W. R. McBride*, *W. G. Finnegan*, and *R. A. Henry*, J. org. Chemistry *22*, 152 (1957).

E. Pyrimidines

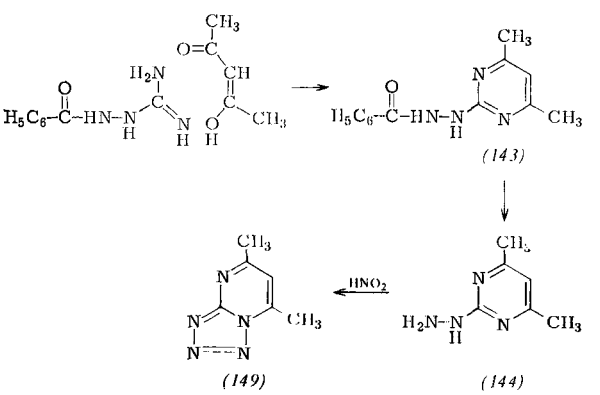
Thiele [92] realized that because it contains a formamidino group, aminoguanidine could be utilized in pyrimidine synthesis provided the hydrazino group be suitably blocked. The obvious method of protecting this group, *viz.* by hydrazone formation [5], was utilized by *Shiho* and *Kanai* [93], who condensed benzylideneaminoguanidine with formylacetone to give 2-benzylidenehydrazino-4-methylpyrimidine *(141)*. This was hydrolysed, albeit in poor yield, to the free hydrazine *(142)* by dilute hydrochloric acid at 80 °C in 5 hours. The structure of *(142)* was confirmed by its preparation from 2-chloro-4-methylpyrimidine and hydrazine hydrate.



(141)

(142)

Alternatively, the hydrazino group in aminoguanidine may be blocked by acylation. Thus, condensation of benzamidoguanidine with acetylacetone [96] yields the benzoyl derivative *(143)* of 2-hydrazino-4,6-dimethylpyrimidine, which can be converted into the free hydrazine *(144)* by hydrolysis.



(143)

(149) *(144)*

A second product, m.p. 165 °C, was isolated from the mother liquors and was formulated [96] as 2-phenyl-5,7-dimethyltriazolo[2,3-*a*]pyrimidine *(145)*; this was thought to have arisen by the alternative condensation *via (146)*. The same compound *(145)* was obtained by refluxing acetylacetone and 3-amino-5-phenyl-1,2,4-triazole *(147)* in ethanol containing pyridine [96]. This synthesis does not, as the authors believed,

[92] *J. Thiele* and *R. Biehan*, Liebigs Ann. Chem. *302*, 299 (1898).

[93] *D. Shiho* and *T. Kanai*, J. chem. Soc. Japan, Pure Chem. Sect. *73*, 862 (1952); Chem. Abstr. *48*, 2070 (1954).

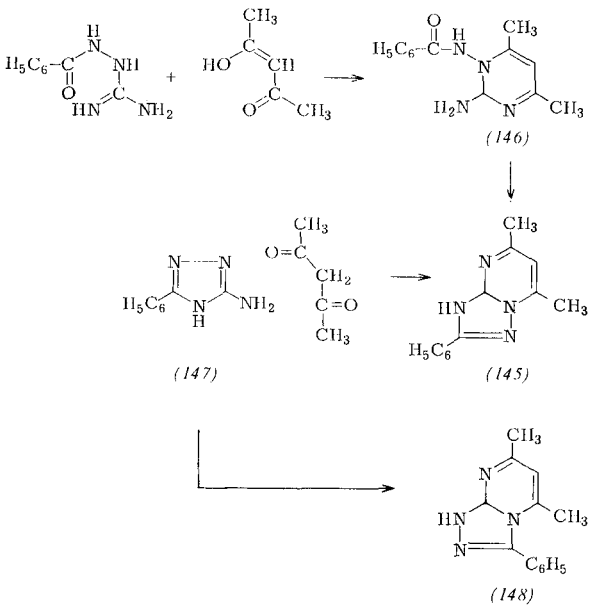
[94] *D. Shiho* and *N. Takahayashi*, J. pharm. Soc. Japan *75*, 773 (1955); Chem. Abstr. *50*, 4976 (1956).

[95] *A. Vystrcil* and *J. Vidlicka*, Chem. Listy *45*, 407 (1951); Chem. Abstr. *46*, 7567 (1954).

[96] *R. Giuliano* and *G. Leonardi*, Il Farmaco (Pavia), Ed. Sci. *11*, 389 (1956).

constitute a structural proof, because there is an equally possible condensation to *(148)*. This second formulation does in fact appear more likely since *(148)* could then be formed simply by the dehydrative cyclization of *(143)*.

Treatment of *(144)* with nitrous acid in dilute acetic acid solution gave the interesting dicyclic compound 5,7-dimethyltetrazolo[2,3-*a*]pyrimidine *(149)*.



An aminoguanidine derivative of pyrimidine was prepared by *Shiho* and *Takahayashi* [94], who converted 2-amino-4-chloro-6-methylpyrimidine by treatment with hydrazine hydrate into the 4-hydrazino-derivative, which on condensation with cyanamide gave 1-(2-amino-6-methylpyrimidin-4-yl)aminoguanidine. Another pyrimidine incorporating the aminoguanidine skeleton was prepared by treating 2-ethylthio-6-methoxy-4-methylpyrimidine with hydrazine hydrate [95].

F. 1,2,4-Triazines

Aminoguanidine, incorporating a chain of one carbon and three nitrogen atoms, is a suitable starting material in the synthesis of 3-amino-1,2,4-triazines, many of which have been obtained by condensing aminoguanidine with bifunctional carbonyl compounds. The use of *o*-quinones in this reaction has proved particularly useful for the preparation of compounds containing a triazine ring fused onto another aromatic system.

I. Synthesis of 1,2,4-Triazines from Aminoguanidine

1. *With Halogenated Carbonyl Compounds*

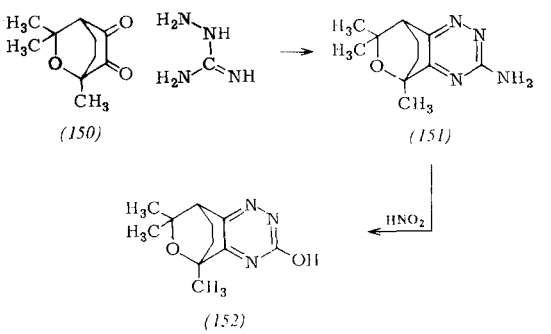
In general, it has not proved possible to obtain 3-amino-1,2,4-triazines by the action of halogenated carbonyl compounds on aminoguanidine. *Thiele* and *Dralle* [4] were the first to show that chloral and aminoguanidine did not give the desired six-membered ring, but merely the unstable guanylhydrazone of chloral, which was converted hydrolytically into the guanylhydrazone of glyoxylic acid. Similarly, monochloroacetaldehyde gave glyoxal diguanylhydrazone [4]. Recently [59], attempted cyclizations of guanyl- and nitroguanylhydrazones of α-halogenoacetophenones again gave either triazoles or eight-membered ring compounds instead of the required triazines.

2. *With Dicarbonyl Compounds*

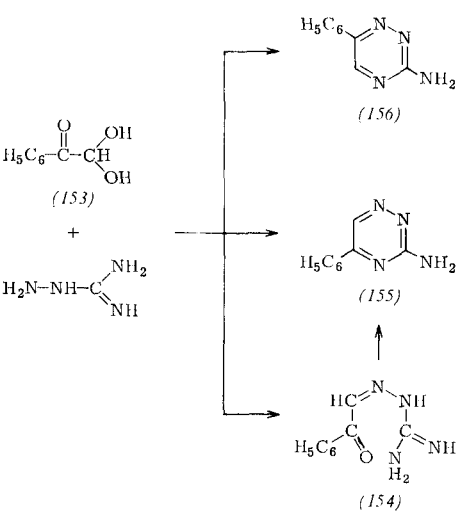
Thiele and *Dralle* [4] were also unsuccessful in their attempts to prepare aminotriazines from aminoguanidine and aliphatic dicarbonyl compounds (*e.g.* glyoxal or diacetyl): osazone-like compounds incorporating two molecules of aminoguanidine and one of the carbonyl compound were isolated.

However, a recent patent [97] describes the synthesis of a large number of triazines from aminoguanidine and aliphatic dicarbonyl compounds including acids such as pyruvic, glyoxylic, or oxalic acids. In a typical example, cyclohexenedione in ethanol is added to aqueous aminoguanidine, with simultaneous addition of a solution of sodium hydroxide to maintain the pH at about 8. The resulting 3-amino-5,6,7,8-tetrahydro-1,2,4-benzotriazine separates out on chilling.

Erickson [98] has described an elegant method of preparing aminotriazines by addition of aliphatic dicarbonyl compounds onto aqueous suspensions of aminoguanidine bicarbonate. Since the latter is only slightly soluble, the solution contains a very low concentration of aminoguanidine and cyclization proceeds faster than osazone formation.



The bicyclic ketone dioxocineole *(150)* reacts with aminoguanidine to yield a monoguanylhydrazone, which is cyclized to an aminotriazole by alkali [99]. Because of steric hindrance around the carbonyl group adjacent to the methyl group, the hydrazino group probably attacks at the alternative carbonyl group. If so, the cyclized product is to be formulated as *(151)*.



[97] Brit. Pat. 755036, Merck & Co. Inc.; Chem. Abstr. *51*, 8151 (1957).

[98] *J. G. Erickson*, J. Amer. chem. Soc. *74*, 4706 (1952); U.S.-Pat. 2653933; Chem. Abstr. *48*, 12815 (1954).

[99] *G. Cusmano*, Anales real. acad. farm. *9*, 307 (1943); Chem. Abstr. *43*, 7926 (1949).

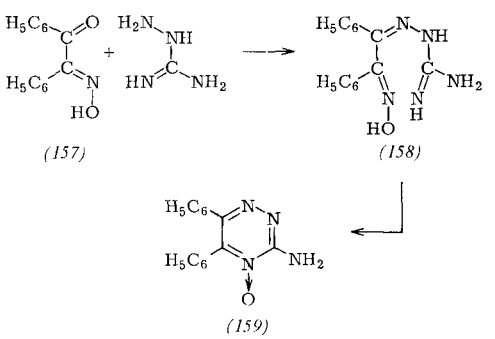
Nitrous acid converts this amine into the corresponding hydroxy compound *(152)*, which is also obtainable from dioxocineole and semicarbazide [99].

Depending on the conditions used, reaction between aminoguanidine and phenylglyoxal hydrate *(153)* yields three different products [100]. In acid media, an intermediate, presumably the monoguanylhydrazone *(154)* is isolated, which can be dehydrated pyrolytically to 3-amino-5-phenyl-1,2,4 triazine *(155)*. This amine, which also results in lower yield on addition of 30 % sodium hydroxide to a suspension of aminoguanidine bicarbonate in boiling phenylglyoxal hydrate, is converted by nitrous acid or boiling potassium hydroxide solution into 3-hydroxy-5-phenyl-1,2,4-triazine.

A second product, thought to be 3-amino-6-phenyl-1,2,4-triazine *(156)* was obtained in 30 % yield on mixing aqueous solutions of aminoguanidine hydrochloride and phenylglyoxal followed by slow basification with excess aqueous potassium hydroxide solution.

Addition of aqueous aminoguanidine hydrochloride to a strongly alkaline solution of *(153)* affords a third product, which is formulated as the imino form of 3-amino-6-phenyl-1,2,4-triazine *(156)* [100]. However, the existence of a separate stable imino-form would appear unlikely, particularly as the two compounds form distinct hydrochlorides and acetyl derivatives.

Reaction between benzil and aminoguanidine gives 3-amino-5,6-diphenyl-1,2,4-triazine [92]. Benzil monoxime *(157)* forms a guanylhydrazone *(158)* [5], the nitrate of which is cyclized in acetic acid to 3-amino-5,6-diphenyl-1,2,4-triazine-*N*-4-oxide *(159)*.

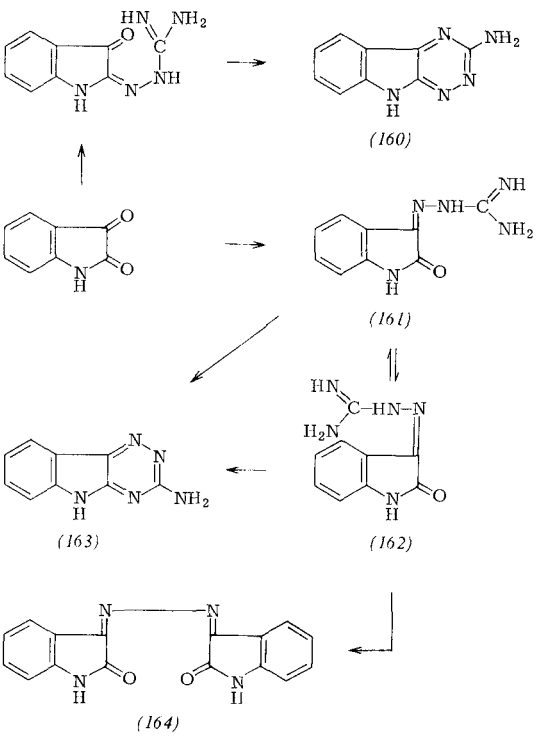


(157) *(158)* *(159)*

Since either carbonyl group of a dicarbonyl compound may undergo the initial condensation with the hydrazino group of aminoguanidine, it is often difficult to assign structures to the resulting triazines.

De [101] condensed isatin with aminoguanidine and formulated the product obtained as *(160)*; he then assigned structures analogous to *(160)* to a series of dyestuffs prepared from substituted indoles [102]. *Rajagopalan* [103] repeated the condensation of isatin in acetic acid. His product, which differed in melting point from that of *De*, had the correct nitrogen content, but the yield was 122 % when calculated from his figures.

This anomaly was cleared up by *King* and *Wright* [104]; on the basis of other evidence for the greater reactivity of the β-carbonyl group in isatin, they suggested that β-guanylhydrazones would be formed preferentially in the initial condensation. By *Rajagopalan*'s procedure, they obtained a base which was shown to be isatin *syn*-β-guanylhydrazone *(161)*. As this material was difficult to crystallize, it was converted into its hydrochloride. Basification of this hydrochloride at 80 °C gave a second crystalline isomeric base, which formed a nitrate and hydrochloride distinct from those of the original base; it was regarded as isatin *anti*-β-guanylhydrazone *(162)*. Boiling 16 % hydrochloric acid reconverted the *anti*-hydrochloride into the *syn*-form. Comparison with relevant compounds suggested that *Rajagopalan* had actually prepared the crude *syn*-β-guanylhydrazone of isatin and not the tricyclic compound claimed [104].



(160) *(161)* *(163)* *(162)* *(164)*

Evidence supporting the assigned configurations was obtained from the observation that the hydrochloride of the *syn*-form was readily cyclized to a triazine *(163)* by boiling for several hours with dilute ammonium hydroxide, whereas the *anti*-form required heating to 250 °C under reduced pressure before undergoing cyclization. A parallel series of guanylhydrazones of *N*-methylisatin was cyclized in a similar manner, yielding the 5-methyl derivative of the tricyclic compound [104].

Acetylation of the *anti*-β-guanylhydrazones gave a mono- and diacetyl derivatives. The latter underwent an interesting transformation on boiling with 16 % hydrochloric acid, being converted into di-isatin azine *(164)* and not into the *syn*-form [104].

3. *With Quinones*

Thiele and *Dralle* [4] condensed α-nitroso-β-naphthol *(165)* with aminoguanidine nitrate and obtained α-oximo-β-naphthylideneaminoguanidine nitrate *(166)*, which cyclized in hot

[100] *J. B. Ekely, R. E. Carlson*, and *A. R. Ronzio*, Rec. Trav. chim. Pays-Bas *59*, 496 (1940).

[101] *S. C. De*, J. Indian chem. Soc. *4*, 183 (1927).

[102] *S. C. De* and *P. C. Dutta*, Ber. dtsch. chem. Ges. *64*, 2604 (1931).

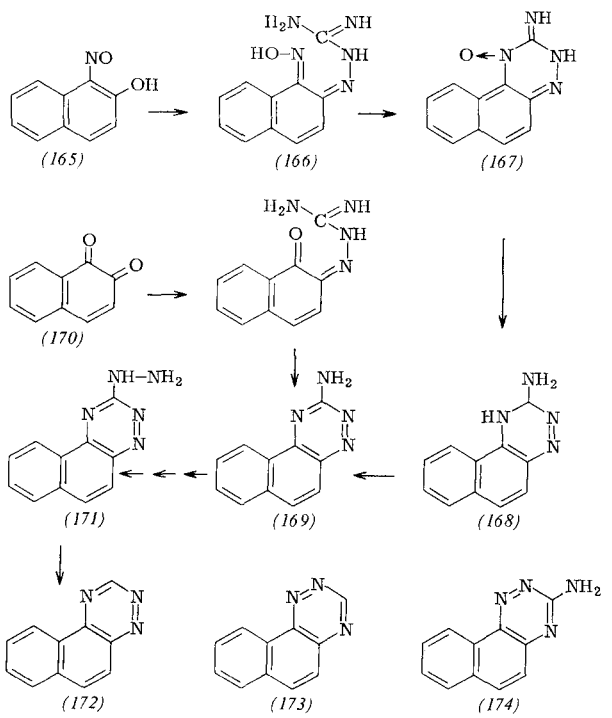
[103] *S. Rajagopalan*, Proc. Indian Acad. Sci. *18A*, 100 (1943).

[104] *H. King* and *J. Wright*, J. Chem. Soc. (London) *1948*, 2314.

aqueous solution to an iminotriazine-*N*-oxide of probable structure *(167)*. Reduction of this compound gave an intermediate *(168)*, which was converted by gentle oxidation into an aminotriazine, m.p. 200–201 °C. This product, which was probably 2-aminonaphtho[1,2]-*as*-triazine *(169)*, was almost certainly obtained by *De* [101] on condensing aminoguanidine with β-naphthoquinone *(170)* in the presence of acetic acid, although he reported the m.p. as 240 °C.

Two groups of workers have recently reexamined these reactions. *Scott* and *Reilly* [105] confirmed the structure assigned to the iminotriazine-*N*-oxide *(167)* by *Thiele* and *Dralle* and demonstrated its amphoteric nature by preparing both metal salts and the salts of organic acids including the picrate. On treating *(167)* with phenyl isocyanate, a urea derivative was obtained. The results of the reduction of the iminotriazine-*N*-oxide *(167)*, and the oxidation of the resulting intermediate *(168)* were confirmed; the final product was again an aminotriazine *(169)*, m.p. 201 °C. Condensation of the 1-*O*-methyloxime of 1,2-naphthoquinone with aminoguanidine gave the *O*-methyl derivative of *(166)*, which was stable towards boiling water.

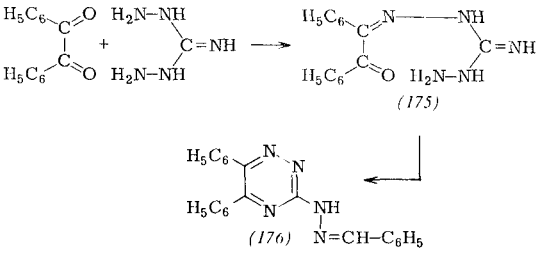
Fusco and *Bianchetti* [106] attempted to account for the difference in the melting points reported for *(169)* by *De* and by *Thiele* and *Dralle*. The two unsubstituted naphthotriazines *(172)* and *(173)* had been prepared previously [106];



when *De*'s aminotriazine was degraded *via* the hydrazine *(171)*, the parent compound *(172)* was obtained. *De*'s compound must therefore be *(169)*. As *De* might possibly have obtained a mixture of the two isomeric aminotriazines *(169)* and *(174)*, the latter was synthetized separately. A mixture of the two isomers melted at 180–190 °C, however; it therefore appears that the melting point reported by *De* is either an error or a misprint.

II. Synthesis of 1,2,4-Triazines from Diaminoguanidine

On condensing benzil with diaminoguanidine nitrate, *Lieber* and *Strojny* [107] did not obtain the expected seven-membered heterocyclic compound; instead, benzil mono(aminoguanyl)hydrazone *(175)* was the main product (85 %), and was still obtained when diaminoguanidine was employed in twofold excess.



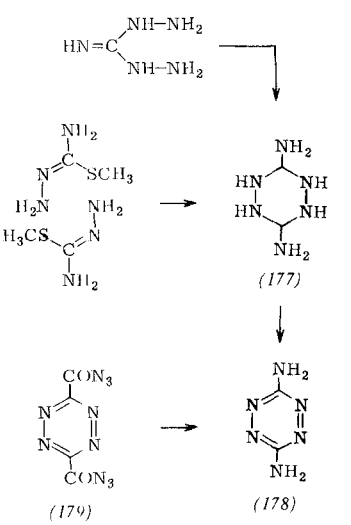
Further reaction of *(175)* with benzaldehyde afforded 3-benzylidenehydrazino-5,6-diphenyl-1,2,4-triazine *(176)* in 19 % yield [107].

G. Tetrazines

Aminoguanidine has so far not been used extensively for the synthesis of tetrazines, but such compounds have been isolated on several occasions from reactions involving aminoguanidine or designed to produce aminoguanidine derivatives.

In 1913, *Ponzio* and *Gastaldi* [108] isolated a violet solid by treating aminoguanidine with aqueous potassium hydroxide. They formulated this compound, on rather inadequate evidence, as 3,6-diamino-1,2,4,5-tetrazine. This work was later discussed by *Lieber* and *Smith* [2].

More recently, *Scott* and *Reilly* [5] found that, on treatment with various organic bases, *S*-methylisothiosemicarbazide yields a dark-red compound, m.p. 360 °C, which was formulated as 3,6-diamino-1,2,4,5-tetrazine *(178)*. The initial reaction product is presumably the dihydrotetrazine *(177)*, which is oxidized in air to the tetrazine. This compound *(178)* was not identical with *Ponzio* and *Gastaldi*'s product. Confirmation of the structure *(178)* assigned by *Scott* and *Reilly* was provided by *Lieber* and co-workers [109], who synthetized *(178)* unequivocally from authentic 3,6-dicarboxy-1,2-di-



[105] *F. L. Scott* and *J. Reilly*, Nature (London) *169*, 584 (1952).

[106] *R. Fusco* and *G. Bianchetti*, Gazz. chim. ital. *87*, 438, 446 (1957).

[107] *E. Lieber* and *E. J. Strojny*, J. org. Chemistry *17*, 518 (1952).

[108] *G. Ponzio* and *C. Gastaldi*, Gazz. chim. ital., *43*, II, 129 (1913); ibid. *44*, I, 257, 277 (1914); ibid., *45*, I, 181 (1915).

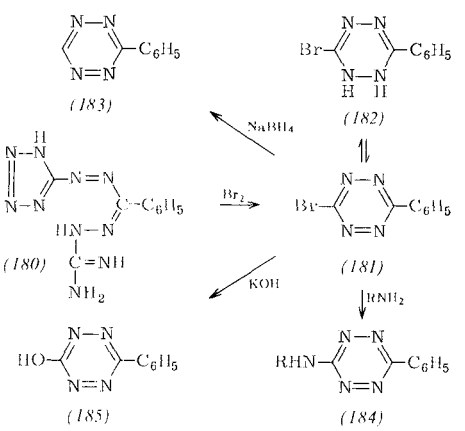
[109] *C. H. Lin*, *E. Lieber*, and *J. P. Horwitz*, J. Amer. chem. Soc. *76*, 427 (1954).

hydro-1,2,4,5-tetrazine, *via* the 3,6-dicarbonyl azide *(179)*, in 11 % overall yield. Suitable treatment of diaminoguanidine with nitrous acid gave an intermediate which was oxidized to the same diaminotetrazine *(178)* [109].

Diaminotetrazine is easily reduced and the reduced material readily reoxidized to the parent compound, a behaviour that is characteristic of tetrazines [109]. The aromatic nature of the tetrazine ring was illustrated by the ease of diazotization of both amino groups; the resulting bis-diazonium salt was coupled with β-naphthol to form a dye [109].

A 1,4-disubstituted 3,6-diaminotetrazine was obtained by *Scott* [110] by the action of bases on *S*-methyl-(or ethyl)-1-phenylisothiosemicarbazide.

Grakauskas, *Tomasewski*, and *Horwitz* [89] isolated a dark-red solid of composition $C_8H_5N_4Br$ by oxidizing 1-guanyl-3-phenyl-5-(tetrazol-5-yl)formazan *(180)* with bromine in glacial acetic acid solution at 40–60 °C. This compound was easily reduced with zinc dust to a pale yellow solid $C_8H_7N_4Br$ (*i.e.* containing two more atoms of hydrogen), which is reoxidized by bromine to the original product. More vigorous reduction of the red compound $C_8H_5N_4Br$ with sodium borohydride, followed by gentle oxidation with sodium nitrite gave the known compound 3-phenyl-1,2,4,5-tetrazine *(183)*. These results suggest that the red material was 3-bromo-6-phenyl-1,2,4,5-tetrazine *(181)*.

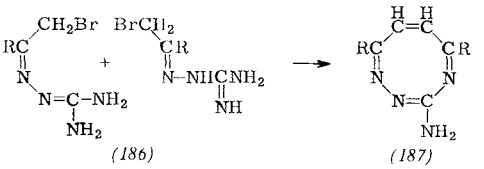


(183) *(182)* *(180)* *(181)* *(185)* *(184)*

The bromine atom in *(181)* proved to be readily displaceable by a number of reagents. Treatment with potassium hydroxide gave 3-hydroxy-6-phenyl-1,2,4,5-tetrazine *(185)*, whilst reaction with a number of amines gave a series of *N*-substituted 3-amino compounds *(184)* [89].

H. Eight-Membered Heterocyclics

Beyer and *Pyl* [111] found that ω-bromoacetophenone reacts with aminoguanidine in alcoholic hydrobromic acid to form the hydrobromide of ω-bromoacetophenone guanylhydrazone, m.p. 198 °C *(186)*. Under the influence of weak bases, *e.g.* sodium acetate or ammonia, two molecules of the hydrazone condensed at

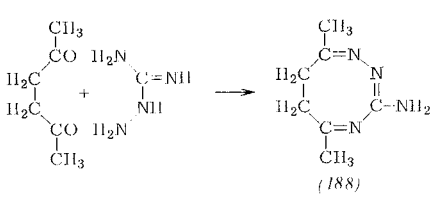


(186) *(187)*

room temperature, with loss of two molecules of hydrogen bromide and one of aminoguanidine, to form 3-amino-5,8-diphenyl-1,2,4-triazacyclooctatetraene *(187)* as orange brown prisms, m.p. 208 °C (decomp.), in 37–44 % yield. Similar heterocyclic compounds were prepared from *p*-chloro-, *p*-bromo-, and *m*-nitro-ω-bromoacetophenone [111].

Since dibenzoylethylene had been prepared by treating ω-bromoacetophenone with alcoholic potassium hydroxide [112], it appeared that the initial stage of the reaction might entail formation of dibenzoylethylene diguanylhydrazone, which then cyclized by elimination of one molecule of aminoguanidine. However, the diguanylhydrazone of either *cis*- or *trans*-dibenzoylethylene failed to cyclize under the conditions of the reaction, and a different mechanism must therefore be operative.

The carbon-carbon double bond in *(187)* adds on a molecule of bromine and then loses hydrogen bromide to form a monobromo derivative of *(187)*. The 3-amino group exhibits normal properties as was shown by the formation of salts (*e.g.* hydrochloride, hydrobromide) and acyl derivatives (*e.g.* acetyl and benzoyl). Treatment with phenyl isothiocyanate formed the appropriate phenylthiourea. An imino form of *(187)* also appears to exist; a crystalline nitroso compound which is soluble in both acids and alkalis was obtained by reaction with isoamyl nitrite. When *(187)* was oxidized with hydrogen peroxide or potassium permanganate, two molecules linked together to form 3,3′-azo-bis-1,2,4-triaza-5,8-diphenylcyclooctatetraene [111].



(188)

A precedent for this type of large-ring formation is the synthesis of 1,2,4-triaza-3-amino-5,8-dimethyl-2,4,8-cyclooctatriene *(188)* by reaction of aminoguanidine with diacetylethane [4].

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[110] *F. L. Scott*, Chem. and Ind. *1954*, 158.

[111] *H. Beyer* and *T. Pyl*, Angew. Chem. *68*, 374 (1956); Liebigs Ann. Chem. *605*, 50 (1957).

[112] *B. M. Bogoslowski*, Zh. Obsh. Khim. *14*, 993 (1944).