THE CHEMISTRY OF AMIDRAZONES

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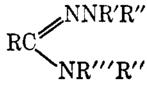
Contents

I. Scope of the Review

This review covers the monoacid bases characterized by the structural formula 1, where R, R′, R″, R‴, and R⁗ can be any of a wide variety of atomic or organic moieties. A particularly well-known example of this class of compounds is aminoguanidine (2). No previous comprehensive survey of amidrazones has been noted in the literature although a section is to be found in "Open Chain Nitrogen Compounds" by Smith[1] dealing with these compounds. A brief survey also serves as the introduction to the Ph.D. thesis of Newlands,[2] one of the coauthors of this review. Aminoguanidine (2), however, has been the subject of several reviews,[3-5] two of which are of recent origin, and hence its chemistry will not be discussed extensively in this review. Alkyl isosemicarbazides and isothiosemicarbazides (3) may be looked on as amidrazones and have a chemistry closely related to the title compounds of this review, and hence comparisons will be made where applicable. However, cyclic structures such as the 1,2,4-triazoles (4) or the 1,2,4-triazines (5) and their reduction products which contain amidrazone-type groupings within the ring structure will be omitted except in so far as these compounds can be synthesized from amidrazones or arise as by-products during amidrazone syntheses. Other cyclic structures containing amidrazone groupings partly within and partly *exo* to a heterocyclic ring system will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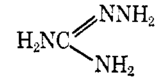
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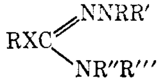
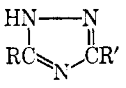

3, X = O or S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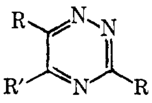
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(1) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin Inc., New York, N. Y., 1966, p 173.

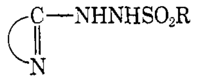
(2) L. R. Newlands, Ph.D. Thesis, The University of St. Andrews, 1955.

(3) E. Lieber and G. B. L. Smith, *Chem. Rev.*, 25, 213 (1939).

(4) F. Kurzer and L. E. A. Godfrey, *Chem. Ind.* (London), 1962, 1584.

(5) F. Kurzer and L. E. A. Godfrey, *Angew. Chem. Intern. Ed. Engl.*, 2, 459 (1963).

be introduced from time to time, but no completely exhaustive review of their chemistry will be made. A recent review[6] discusses compounds of this type—the sulfonyl hydrazones of cyclic amides (6) and their oxidation products.



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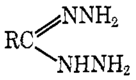
No attempt will be made in this article to list the individual amidrazones described in the literature, but rather our aim will be to give a broad general review of the syntheses, properties, and reactions of these compounds. It is hoped to include papers accessible to the authors up to the end of 1968 as there has been a recent revival of interest in this field (*cf.* sections VI.E,F). However, it is not claimed that the review is totally comprehensive as amidrazones are at times mentioned in papers only as intermediates in synthesis.

II. Nomenclature

The nomenclature applied to compounds of type **1** has over the years been somewhat confusing, and the reader of original literature is warned that from time to time the term "hydrazidine"[1,7] has been given to these compounds (**1**). Besides this, the name "hydrazidine" has been applied to compounds of type **7** which are also termed hydrazide-hydrazones or dihydroformazans. Other names which have been suggested for amidrazones (**1**) include "amide hydrazones" and "hydrazide imides."[1,8] These names cover, respectively, amidrazones of the types **8** and **9** ($R' \neq H$) which are incapable of tautomerism. Where tautomerism is possible ($\mathbf{8} \rightleftharpoons \mathbf{9}$; $R' = H$) the terms "amide hydrazone" and "hydrazide imide" cannot strictly be applied, and the term "amidrazone" is used.[8] In this review it is intended to adhere to the name amidrazone for all compounds of type **1** and furthermore to employ the nomenclature introduced by Rapoport and Bonner[9] as we consider it to be the least ambiguous. Alternative naming and numbering is described in ref 8. In this review an amidrazone is named after the acid theoretically obtained from it by hydrolysis.[9] Hence, $CH_3C(=NNH_2)NH_2$ is acetamidrazone. In addition, in compounds containing N substituents, the nitrogen atoms are numbered[9] as shown in formula **10** which is therefore named N^1-phenyl-N^1,N^3,N^3-trimethylpropionamidrazone. Compound **11** is thus a true diamidrazone (oxaldiamidrazone).



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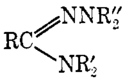

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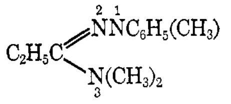

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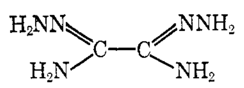

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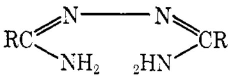
Related compounds having structure **12** were initially termed "dihydrazidines" but have more recently become known as "amide-azines."[8] Again difficulty arises with these compounds when their structures preclude tautomerism (*e.g.*, compound **13**, $R = C_6H_5$; $R' = CH_3$), and it may well be more convenient to look on compounds **12** and **13** as N,N'-diamidines. Formula **12** thus represents N_1,N_1'-dimethyl-N_2,N_2'-diphenyl-N_1,N_1'-diformamidine. Otherwise, these compounds might be described as 1,2-seco-4,5-dihydro-*sym*-tetrazines (**13**) or diazabutadienes (**12**).



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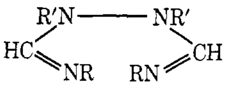

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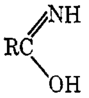
III. Introduction

The chemistry of the derivatives of the hypothetical imidic acids (**14**) has aroused the interest of chemists since the pioneering work of Pinner,[10] and reviews have appeared dealing with the esters (**15**, imidates),[11,12] amides (**16**, amidines),[13] and the amidoximes[14] (**17**), but the hydrazides (**1**, amidrazones) do not appear to have been reviewed comprehensively. The acid halides or imidoyl halides (**18**, X = halogen) are the subject of a recently published book.[15]



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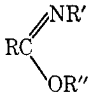

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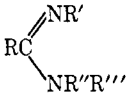

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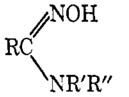

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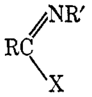

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A large number of possible structures exists for any given R group in formula **1**, depending on whether the symbols R'–R'''' represent either hydrogen or some other atom or group. The various classes of amidrazones are listed in Table I although it does not appear that compounds representative of them all have been synthesized. The compounds are arbitrarily ascribed to two classes: class I contains compounds capable of exhibiting tautomerism (although only one tautomer is drawn), and class II gives compounds whose structure precludes tautomerism. Extension of some synthetic methods in this review to types other than those described may well be feasible.

IV. Methods of Synthesis of Amidrazones

A. INTERACTION OF NITRILES WITH HYDRAZINES

1. Hydrazine

Nucleophilic attack of hydrazine on a nitrile can give to an amidrazone.[16]

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[6] S. Hünig, W. Brenninger, H. Geiger, G. Kaupp, W. Kniese, W. Lampe, H. Quast, R. D. Rauschenbach, and A. Schütz, *Angew. Chem. Intern. Ed. Engl.*, **7**, 335 (1968).

[7] I. T. Millar and H. D. Springall, "Sidgwick's Organic Chemistry of Nitrogen," 3rd ed, Clarendon Press, Oxford, 1966, p 529.

[8] "IUPAC, Nomenclature of Organic Chemistry," Section C, Butterworth & Co., Ltd., London, 1965, p 221.

[9] H. Rapoport and R. M. Bonner, *J. Amer. Chem. Soc.*, **72**, 2783 (1950).

(10) A. Pinner, "Die Imidoäther und ihre Derivate," Oppenheim, Berlin, 1892.

(11) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(12) W. Seelinger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nering, W. Thier, and H. Hellmann, *Angew. Chem. Intern. Ed. Engl.*, **5**, 875 (1966).

(13) R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).

(14) F. Eloy and L. Lenaers, *ibid.*, **62**, 155 (1962).

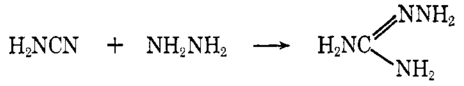
(15) H. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, N. Y., 1968.

(16) G. Pelizarri and A. Gaiter, *Gazz. Chim. Ital.*, **44**, 72 (1914).

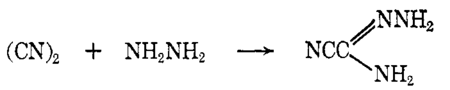
Table I[a]

Type	*Class I*	*Class II*
1. Unsubstituted	$RC(=NNH_2)NH_2$	
2. Monosubstituted	$RC(=NNH_2)NHR'$ $RC(=NNHR')NH_2$	$RC(=NH)NR'NH_2$
3. Disubstituted		
(a) Symmetrically	$RC(=NNHR')NHR''$	$RC(=NR')NR''NH_2$
(b) Unsymmetrically	$RC(=NNR'R'')NH_2$	$RC(=NH)NR'NHR''$ $RC(=NNH_2)NR'R''$
4. Trisubstituted	$RC(=NNR'R'')NHR'''$	$RC(=NR')NR''NHR'''$ $RC(=NH)NR'NR''R'''$ $RC(=NNHR')NR''R'''$
5. Tetrasubstituted		$RC(=NNR'R'')NR'''R''''$ $RC(=NR')NR''NR'''R''''$

[a] In the table R', R'', R''', and $R'''' \neq H$.


$$H_2NCN + NH_2NH_2 \longrightarrow H_2NC(=NNH_2)NH_2$$

One important aspect of this work has been the reaction of cyanogen with hydrazine, usually in aqueous media. The earlier work in this part of the field has been reviewed;[17] however, this aspect has again been the subject of renewed interest, and more recently the cyanoformamidrazone (**19**) has been isolated in good yield from the interaction of the reagents cyanogen and hydrazine (1:1) in dioxane–methanol at 5°.[18,19]


$$(CN)_2 + NH_2NH_2 \longrightarrow NCC(=NNH_2)NH_2$$

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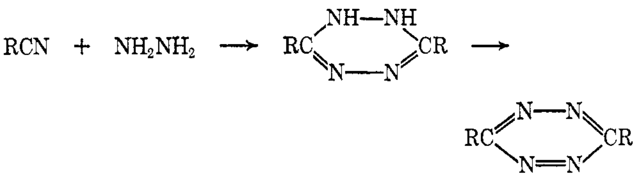
Perfluoroalkyl cyanides have also received some attention of late,[20–22] and this work has been extended to the synthesis of fluorinated polymers containing amidrazone groupings.[23] Similarly, polyacrylonitrile has been treated with hydrazine hydrate and polymeric amidrazone intermediates postulated in the reaction which ultimately yields triazoles.[24]

Pteridine amidrazones have also been prepared by this route from the corresponding nitriles.[25,26] However, it appears that the reaction depends on the nature of the nitrile; *e.g.*, 4-cyanopyridine failed to yield an amidrazone on treatment with hydrazine,[27] whereas the more reactive 2-cyanothiazole,[27] 2-cyanopyridine,[28,29] and 3-cyanoisoquinoline[30] have been converted into the corresponding amidrazones in this way.

Moreover, the reaction between nitriles and hydrazine is not so simple as the above would suggest and 2 moles of hydrazine can react with 1 mole of nitrile, especially at elevated temperatures, to give dihydrotetrazines and hence tetrazines (**20**) by oxidation.[31–33] A further complication



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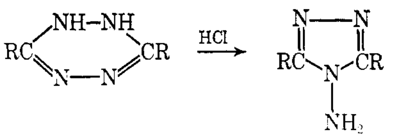
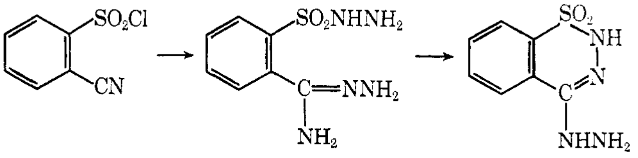
in this synthesis is the production of 4-amino-1,2,4-triazoles; thus Brown and Pilipovich[20,34] found that the perfluoroalkyl cyanides, $C_3F_7^-$ and above, gave the amidrazone as the predominant product whereas CF_3CN and C_2F_5CN produced the aminotriazole as the final product. It is of course a well-known phenomenon that dihydrotetrazines rearrange under various conditions, *e.g.*, very readily in hydrochloric acid solution, to give 4-amino-1,2,4-triazoles, and hence the appearance of these compounds in this reaction is not at all surprising.[33,35]



Finally, a novel cyclization reaction[36] based on *o*-cyanobenzenesulfonyl chloride is seen in the ring closure of the amidrazone **21** to the thiodiazine dioxide **22**.



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(17) T. K. Brotherton and J. W. Lynn, *Chem. Rev.*, **59**, 841 (1959).

(18) K. Matsuda and L. T. Morin, *J. Org. Chem.*, **26**, 3783 (1961).

(19) T. Morin and K. Matsuda (American Cyanamid Co.), U. S. Patent 3,033,893 (1962); *Chem. Abstr.*, **57**, 14948 (1962).

(20) H. C. Brown and D. Pilipovich, *J. Amer. Chem. Soc.*, **82**, 4700 (1960).

(21) D. C. Remy (E. I. du Pont de Nemours and Co.), U. S. Patent 3,115,498 (1963); *Chem. Abstr.*, **60**, 5512 (1964).

(22) E. K. Gladding and D. C. Remy (E. I. du Pont de Nemours and Co.), U. S. Patent, 3,102,889 (1963); *Chem. Abstr.*, **60**, 4155 (1964).

(23) D. C. Remy (E. I. du Pont de Nemours and Co.), U. S. Patent 3,061,590 (1962); *Chem. Abstr.*, **58**, 8057 (1963).

(24) S. Sönnerskog, *Acta Chem. Scand.*, **12**, 1241 (1958).

(25) E. C. Taylor and J. Weinstock, British Patent 951,653 (1964); *Chem. Abstr.*, **61**, 4378 (1964).

(26) J. Weinstock (Smith, Kline and French Laboratories), U. S. Patent, 3,111,520 (1963); *Chem. Abstr.*, **60**, 5523 (1964).

(27) D. D. Libman and R. Slack, *J. Chem. Soc.*, 2253 (1956).

(28) F. H. Case, *J. Org. Chem.*, **30**, 931 (1965).

(29) F. H. Case, *ibid.*, **31**, 2398 (1966).

(30) F. H. Case and L. Kennon, *J. Heterocycl. Chem.*, **4**, 483 (1967).

(31) E. Oliveri-Mandala, *Gazz. Chim. Ital.*, **54**, 774 (1924).

(32) J. Lifschitz and W. F. Donath, *Rec. Trav. Chim.*, **37**, 270 (1918).

(33) V. P. Wystrach, "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1967, p 105.

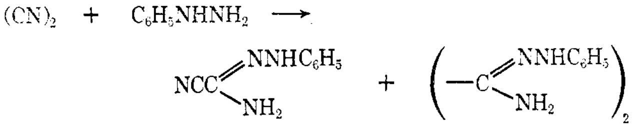
(34) H. C. Brown, U. S. Department of Commerce, Office Technical Service, Report A.D. 257,033, 1961.

(35) K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).

(36) E. Schrader, *J. Prakt. Chem.*, **96**, 180 (1917).

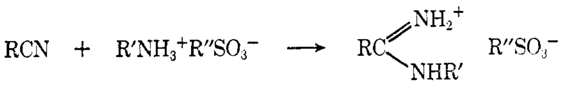
2. *Monosubstituted Hydrazines*

Fischer[37] showed that the reaction between phenylhydrazine and cyanogen can give rise to two products. The constitutions of these were established some years later by Bamberger and de Gruyter[38] *via* the action of phenylhydrazine on flaveanic and rubeanic acids, respectively (*cf.* section IV.G).



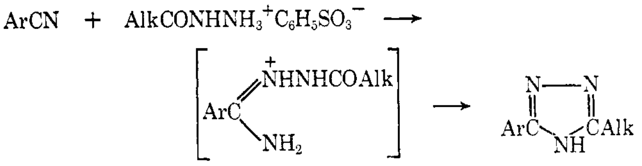
$$(\mathrm{CN})_2 + \mathrm{C_6H_5NHNH_2} \longrightarrow \mathrm{NCC}(\mathrm{=NNHC_6H_5})\mathrm{NH_2} + \left(-\mathrm{C}(\mathrm{=NNHC_6H_5})\mathrm{NH_2}\right)_2$$

Paralleling the amidine synthesis devised by Oxley and Short,[39] Potts and Liljegren[40,41] have postulated the formation



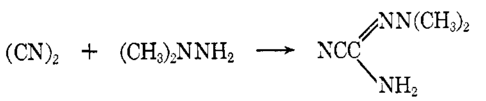
$$\mathrm{RCN} + \mathrm{R'NH_3^+R''SO_3^-} \longrightarrow \mathrm{RC}(\mathrm{=NH_2^+})\mathrm{NHR'}\ \ \mathrm{R''SO_3^-}$$

of N^1-acylamidrazonium salts as intermediates in the reaction of aryl cyanides with hydrazide benzenesulfonates of aliphatic acids. As the reaction requires fusion of the reactants, the final products are 1,2,4-triazoles rather than amidrazones; however, it might be possible to use monosubstituted hydrazines such as phenylhydrazine in place of the hydrazides in this reaction and hence isolate amidrazones as the final products. This does not appear to have been tried.



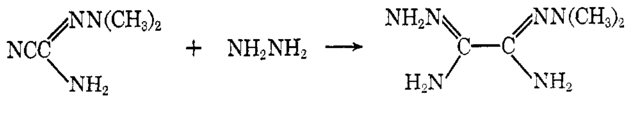
3. *Disubstituted Hydrazines*

Herbicides of the general formula $(\mathrm{CH_3})_2\mathrm{NNHC({=}NH)C({=}NH){-}NHN{=}CR'R''}$ have been synthesized in a two-step process from cyanogen.[42] This involves the reaction of the cyanogen with dimethylhydrazine in hexane at 5°



$$(\mathrm{CN})_2 + (\mathrm{CH_3})_2\mathrm{NNH_2} \longrightarrow \mathrm{NCC}(\mathrm{=NN(CH_3)_2})\mathrm{NH_2}$$

followed by treatment of the resultant cyanoformamidrazone at higher temperatures with hydrazine in isopropyl alcohol.



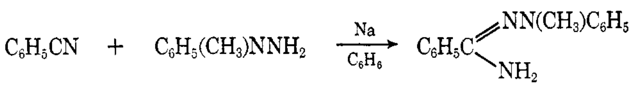
$$\mathrm{NCC}(\mathrm{=NN(CH_3)_2})\mathrm{NH_2} + \mathrm{NH_2NH_2} \longrightarrow \mathrm{NH_2N{=}C(NH_2){-}C(NH_2){=}NN(CH_3)_2}$$

Related compounds were prepared by substituting methyl- and phenylhydrazine for hydrazine in the second state.

Perfluoroalkyl cyanides have also been treated with dimethylhydrazine to give N^1,N^1-dimethylamidrazones.[20]

B. INTERACTION OF NITRILES WITH HYDRAZINES IN THE PRESENCE OF SODIUM

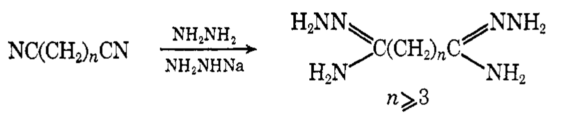
A modification of the foregoing process consists in the introduction of sodium into the reaction. Thus Engelhardt[43] condensed methylphenylhydrazine and benzonitrile in benzene in the presence of sodium and obtained N^1-methyl-N^1-phenylbenzamidrazone.



$$\mathrm{C_6H_5CN} + \mathrm{C_6H_5(CH_3)NNH_2} \xrightarrow[\mathrm{C_6H_6}]{\mathrm{Na}} \mathrm{C_6H_5C}(\mathrm{=NN(CH_3)C_6H_5})\mathrm{NH_2}$$

When phenylhydrazine was employed, the product was the expected N^1-phenylbenzamidrazone when equimolar quantities were employed, but a triphenyltriazole if 2 moles of nitrile to 1 mole of hydrazine was used.

More recently sodium hydrazide has been condensed in inert solvents with a series of aliphatic and aromatic nitriles and aliphatic dinitriles. The reaction appears to be fairly general and the yields excellent except for nitriles such as malononitrile which can readily form stable sodio derivatives.[44-46]



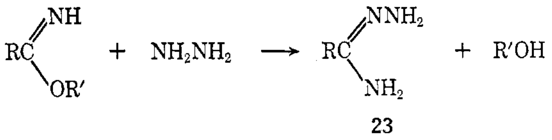
$$\mathrm{NC(CH_2)}_n\mathrm{CN} \xrightarrow[\mathrm{NH_2NHNa}]{\mathrm{NH_2NH_2}} (\mathrm{H_2NN{=}})(\mathrm{H_2N})\mathrm{C(CH_2)}_n\mathrm{C}(\mathrm{=NNH_2})\mathrm{NH_2} \quad n \geqslant 3$$

This modification permits less reactive nitriles to be converted into amidrazones as the conditions required, for the direct nitrile–hydrazine reaction would in these cases give rise, in the main, to secondary products.

C. FROM IMIDATES AND THEIR SALTS BY REACTION WITH HYDRAZINES

1. *Hydrazine Hydrate*

Pinner in the course of his classical work on imidates directed attention toward the products obtained from the interaction of aromatic and heterocyclic imidates with hydrazine.[10,47-49] The fundamental product, normally isolated in the form of its salt, he termed a "monosubstituted hydrazidine" or amidrazone (**23**). However, Pinner found that the amidrazones themselves formed the starting point for the preparation of



$$\mathrm{RC}(\mathrm{=NH})\mathrm{OR'} + \mathrm{NH_2NH_2} \longrightarrow \mathrm{RC}(\mathrm{=NNH_2})\mathrm{NH_2} + \mathrm{R'OH}$$

23

further compounds in the alkaline reaction mass. Thus, Pinner stated that the freshly formed amidrazone could react with excess imidate to form a "dihydrazidine" (**24**), which could then eliminate a molecule of ammonia to yield a triazole (**25**). Moreover he suggested that condensation be-

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(37) E. Fischer, *Ann.*, **190**, 67 (1877).

(38) E. Bamberger and P. de Gruyter, *Ber.*, **26**, 2385 (1893).

(39) P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946).

(40) K. T. Potts, *ibid.*, 3461 (1954).

(41) D. R. Liljegren and K. T. Potts, *ibid.*, 518 (1961).

(42) R. G. Haldeman, L. T. Morin, and K. Matsuda (American Cyanamid Co.), U. S. Patent 3,073,013 (1963); *Chem. Abstr.*, **58**, 11276 (1963).

(43) R. Engelhardt, *J. Prakt. Chem.*, [2] **54**, 143 (1896).

(44) T. Kauffmann, *Angew. Chem., Intern. Ed. Engl.*, **2**, 217 (1963).

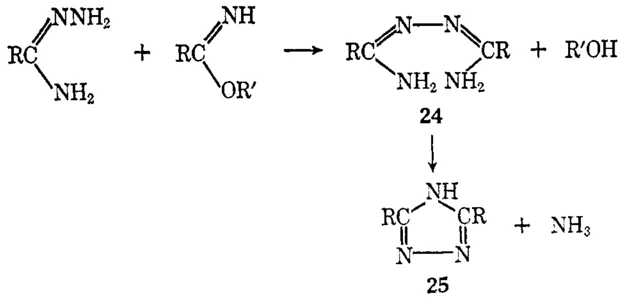
(45) T. Kauffmann, S. Spaude, and D. Wolf, *Chem. Ber.*, **97**, 3436 (1964).

(46) T. Kauffmann and L. Ban, *ibid.*, **99**, 2600 (1966).

(47) A. Pinner and N. Caro, *ibid.*, **28**, 465 (1895).

(48) A. Pinner, *Ann.*, **297**, 221 (1897).

(49) A. Pinner, *ibid.*, **298**, 1 (1897).



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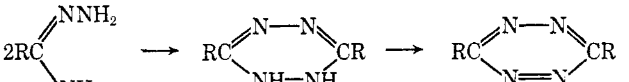
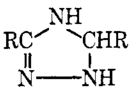
tween two molecules of amidrazone could give rise to a dihydrotetrazine (**26**) readily oxidizable by atmospheric oxygen to the corresponding tetrazine (**27**).



26 27

A dihydrotriazole (**28**) was also reported, but its mode of formation remains somewhat obscure.



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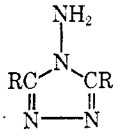

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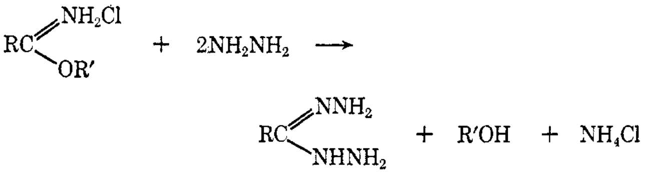
Oberhummer[50,51] parallelled the work of Pinner but concentrated on aliphatic imidates and found that the optimum conditions for the formation of amidrazones (**23**) required the interaction of hydrazine (1 mole) and imidate salt (1 mole) under anhydrous conditions at temperatures below 0°. When 2 moles of hydrazine to 1 mole of imidate salt was employed, a dihydroformazan (**30**) was isolated. At higher temperatures (40–50°) other secondary reaction products (**27** and **29**) appeared. It has been suggested more recently that, in at least one example, adjustment of pH can help to control the product ratio (compounds **23** and **24**).[27] This method has found application in the work of Lossen and Colman[52,53] and of Ainsworth,[54] but the amidrazones have not always been characterized, being merely used *in situ* for further synthesis. However several compounds, *e.g.*, **31**, tested for their antitubercular activity have been made by this route.[55]



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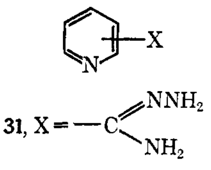
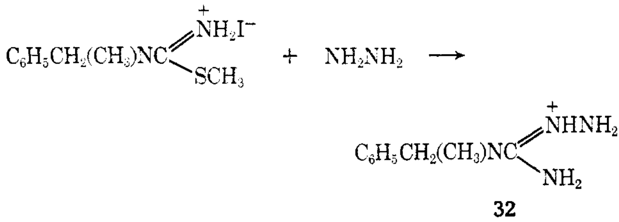


The use of thioimidates[56] has received less attention but an aminoguanidinium iodide (**32**) was obtained by warming hydrazine hydrate with the corresponding isothiourea,[57] and



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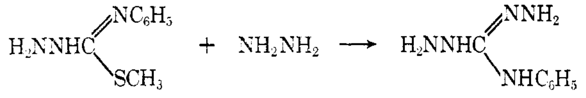
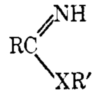
the diaminoguanidine (**33**) similarly was produced by interaction of hydrazine hydrate and the isothiosemicarbazide **34**.[58]

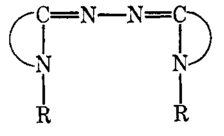


34 33

On the other hand, a dihydrotetrazine (**26**, R = 4-pyridyl) and a 4-amino-1,2,4-triazole (**29**, R = 4-pyridyl) resulted from the interaction of benzyl pyridine-4-thioimidate and hydrazine hydrate in alcohol.[27] In this connection it has been reported that the Pinner procedure can be modified to give good yields of *s*-tetrazines (**27**), *via* their dihydro derivatives (**26**), in place of amidrazones by working in anhydrous conditions and using methanolic triethylamine in place of aqueous base.[59,60] It does appear, however, that the nature of the grouping, R of the imidate or thioimidate (**35**), also plays at least some part in determining the form of the final product.[61] Other compounds prepared *via* thioimidates include some in which the amidrazone grouping is partly contained within a heterocyclic ring system[6,62,63] (**36**) and also polymeric amidrazones (**37**).[63]



35, X = O or S



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[50] W. Oberhummer, *Monatsh. Chem.*, **57**, 106 (1931).

[51] W. Oberhummer, *ibid.*, **63**, 285 (1933).

[52] W. Lossen and J. Colman, *Ann.*, **298**, 107 (1897).

[53] J. Colman, *Ber.*, **30**, 2010 (1897).

[54] C. Ainsworth, *J. Amer. Chem. Soc.*, **75**, 5728 (1953).

[55] J. Bertrand, C. Dobritz, and H. Beerens, *Bull. Soc. Pharm. Lille*, **1**, 39 (1956); *Chem. Abstr.*, **51**, 1168 (1957).

[56] G. W. Kirsten and G. B. L. Smith, *J. Amer. Chem. Soc.*, **58**, 800 (1936).

[57] W. G. Finnegan, R. A. Henry, and E. Lieber, *J. Org. Chem.*, **18**, 779 (1953).

[58] F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc., C*, 742 (1967).

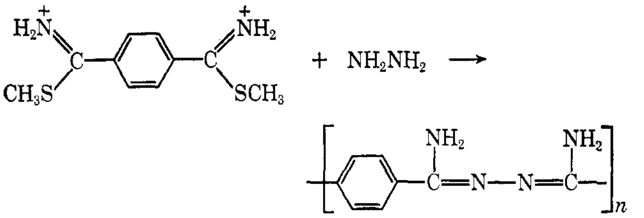
[59] R. H. Wiley, C. H. Jarboe, Jr., and F. N. Hayes, *J. Org. Chem.*, **22**, 835 (1957).

[60] F. R. Benson in ref 33, p 1.

[61] P. Westermann, *Chem. Ber.*, **97**, 523 (1964).

[62] S. Hünig, H. Balli, H. Conrad, and A. Schott, *Ann.*, **676**, 36 (1964).

[63] P. Mukaiyama and S. Ono, *Tetrahedron Lett.*, **32**, 3569 (1968).



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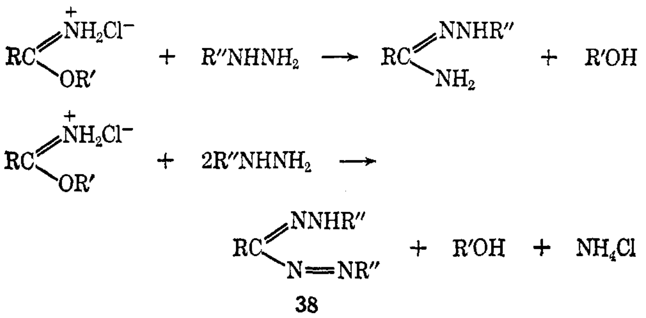
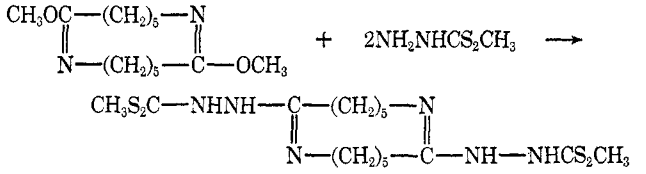
2. Monosubstituted Hydrazines

The use of monosubstituted hydrazines reduces the number of byproducts found in the above reaction, and imidate salts react smoothly in alcohol at room temperatures with monosubstituted hydrazines. The products are in the main N^1-substituted amidrazones but also some formazan (**38**) or, exceptionally, dihydroformazan. The amount of formazan is minimal when equimolar quantities of the reactants are used, but when two parts of hydrazine to one part of imidate are employed, formazans are obtained in good yield.[2,64-71]



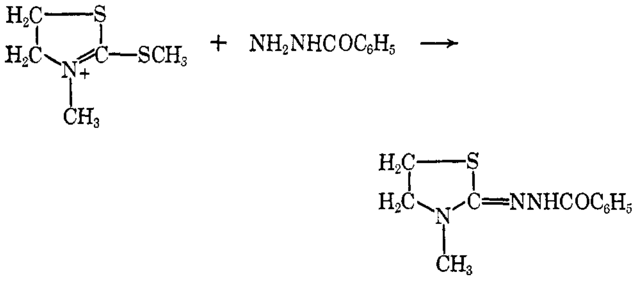
38

Diamidrazones (**39**) based on cyclic imidates have also been prepared by the following reaction sequence.[72]



39

Thioimidate salts have also been used successfully in the synthesis of some heterocyclic amidrazones,[73] diamidrazones,[73] and compounds in which the amidrazone grouping forms part of a heterocyclic ring system[74] (**40**).



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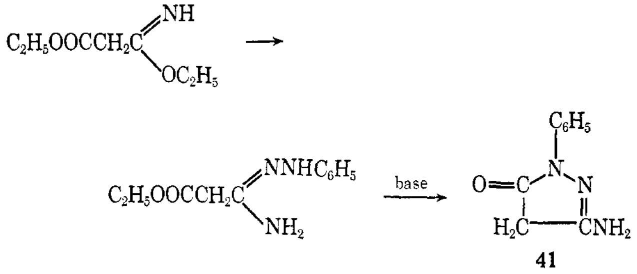
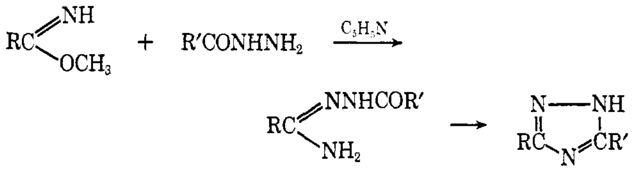
Another condensation of this type is the reaction of ethyl carbethoxyacetimidate with substituted hydrazines which gives rise to 5-pyrazolones (**41**) *via* amidrazone intermediates.[75]

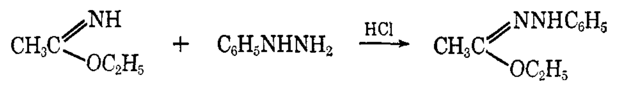


41

Acyl derivatives of hydrazines[76-78] and ethyl hydrazylformate[79] have also been used to prepare N^1-substituted amidrazones. The N^1-acylamidrazones usually cyclize readily under mild alkaline conditions and provide a means of synthesis of 1,2,4-triazoles.



The position is more complex than the above would suggest in that a further product, the hydrazonate ester (**42**), can be formed.[80] Hydrazonate esters, however, are more readily prepared by the action of ortho esters on hydrazines,[81-84]



42

but this latter reaction can also give rise to formazans.[85,86] Weidinger and Kranz[87] claim to have shown that when an imidate salt is treated with an acid hydrazide, it is possible to isolate an intermediate hydrazonate ester (**43**) which, however, cyclizes readily to the 1,3,4-oxadiazole (**44**) (com-

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(64) A. Pinner, *Ber.*, **17**, 182 (1884).

(65) A. Pinner, *ibid.*, **17**, 2002 (1884).

(66) H. Voswinckel, *ibid.*, **36**, 2483 (1903).

(67) D. Jerchel and H. Fischer, *Ann.*, **574**, 85 (1951).

(68) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 3319 (1954).

(69) N. Kunimine and K. Itano, *J. Pharm. Soc. Jap.*, **74**, 726 (1954); *Chem. Abstr.*, **49**, 11,627 (1955).

(70) F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.*, 2853 (1956).

(71) A. W. Nineham, *Chem. Rev.*, **55**, 355 (1955).

(72) J. Körösi and P. Berencsi, *Chem. Ber.*, **101**, 1979 (1968).

(73) J. Jaeken and R. L. Jansseune (Gevaert Photo-Producten, N.V.), U. S. Patent 3,245,788 (1966); *Chem. Abstr.*, **65**, 844 (1966).

(74) S. Hünig and F. Müller, *Ann.*, **651**, 89 (1962).

(75) A. Weissberger, H. D. Porter, and W. A. Gregory, *J. Amer. Chem. Soc.*, **66**, 1851 (1944).

(76) I. Ya. Postovskiy and N. N. Vereshchagina, *Zh. Obshch. Khim.*, **29**, 2139 (1959); *Chem. Abstr.*, **54**, 9898 (1960).

(77) E. J. Browne and J. B. Polya, *J. Chem. Soc.*, 5149 (1962).

(78) P. Westerman, H. Paul, and G. Hilgetag, *Chem. Ber.*, **97**, 528 (1964).

(79) M. Pesson, S. Dupin, and M. Antoine, *Compt. Rend.*, **253**, 285 (1961).

(80) E. Schmidt, *Ber.*, **47**, 2545 (1914).

(81) C. Ainsworth, *J. Amer. Chem. Soc.*, **77**, 1148 (1955).

(82) C. Ainsworth, *ibid.*, **78**, 1973 (1956).

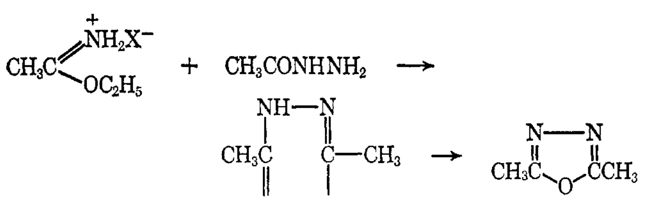
(83) M. E. C. Biffin and D. J. Brown, *Tetrahedron Lett.*, **21**, 2503 (1968).

(84) H. Neunhoeffer and H. Henning, *Chem. Ber.*, **101**, 3947 (1968).

(85) L. Claisen, *Ann.*, **287**, 360 (1895).

(86) D. A. V. Peters, Ph.D. Thesis, University of St. Andrews, 1963.

(87) W. Weidinger and J. Kranz, *Chem. Ber.*, **96**, 1049 (1963).


43 44

pare this reference to the work of Brown and Polya discussed earlier in this section[77]).

The whole picture is, therefore, complex, and it is possible that several factors such as pH and the nature of the acylhydrazine play a role in determining the reaction path. This is certainly true of the related reaction of imidates with thiosemicarbazide which at pH's above 7 gives 1,2,4-triazoles but yields 1,3,4-thiadiazoles at pH's lower than 7. The report of this work records no isolation of any intermediate so it is not known whether the triazole[88] (or the corresponding hydroxy compound prepared from semicarbazide)[89] is formed *via* an amidrazone intermediate. Similar syntheses of oxa- and thiadiazoles are discussed by Browne and Polya.[90]

In passing, it is of interest to note that the action of phenylhydrazine on imidates under reductive conditions (3% sodium amalgam in dilute mineral acid) gives rise to aldehyde phenylhydrazones.[91]

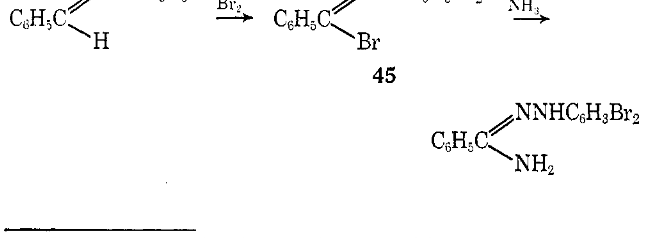
3. *Disubstituted Hydrazines*

Newlands[2] has obtained a series of N^1-disubstituted amidrazones by the interaction of ethyl mandelimidate hydrochloride and unsymmetrical diphenyl- or methylphenylhydrazine in alcohol at room temperatures.


R = $C_6H_5CH(OH)$

D. FROM HYDRAZONOYL HALIDES BY AMINOLYSIS

Halogenation with bromine of benzaldehyde phenylhydrazones occurs both in the ω position and in the N-phenyl group (**45**). The ω-bromine is very reactive and reacts with concentrated aqueous ammonia solutions to give amidrazones.[92-96]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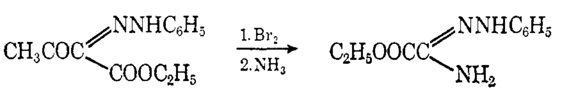
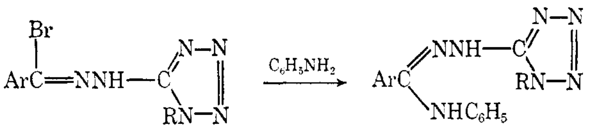
A somewhat similar reaction sequence permitted Bowack and Lapworth[97] to prepare N^1-phenylcarbethoxyformamidrazone from hydrazonoacetoacetic ester.

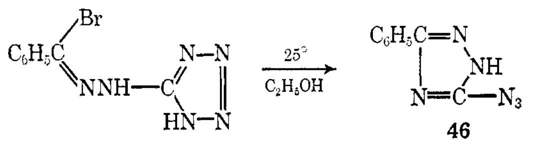


The use of amines has extended the scope of the synthesis and has permitted the synthesis of N^1,N^3-disubstituted amidrazones.[98,99]



The corresponding hydrazonoyl chlorides have also been prepared and used in this reaction to yield amidrazones.[47,100-103]

An interesting cyclization process based on this reaction is reported by Scott and Holland[103] who synthesized the triazole **46**. The reaction does not always give the desired products, however, for Bacchetti[104] found that the hydrazonoyl halide **47** reacted with ammonia to give the amidrazone **48** along with 2-ethoxy-5-phenyl-1,3,4-oxadiazole but gave only products of the form $C_6H_5CONHNHCONHAr$ on reaction with arylamines.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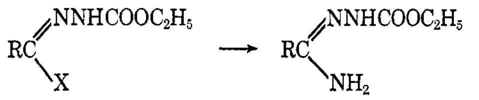
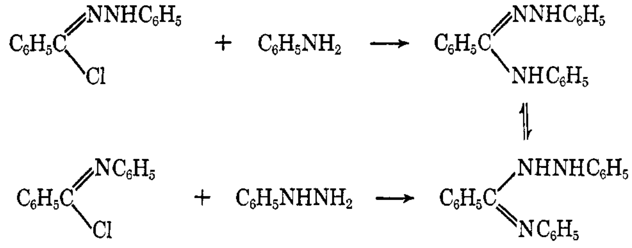

47 48

R = C_6H_5

An older application of this reaction is found in the attempt by von Pechmann[105] to obtain two different amidrazones, now known to be tautomeric, using the hydrazonoyl and imidoyl halides as starting points and reacting them with amine and hydrazine, respectively.



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(88) H. Weidinger and J. Kranz, *Chem. Ber.*, **96**, 1059 (1963).

(89) H. Weidinger and J. Kranz, *ibid.*, **96**, 1064 (1963).

(90) E. J. Browne and J. B. Polya, *J. Heterocycl. Chem.*, **3**, 523 (1966).

(91) F. Henle, *Ber.*, **38**, 1362 (1905).

(92) F. D. Chattaway and A. J. Walker, *J. Chem. Soc.*, **127**, 975 (1925).

(93) F. D. Chattaway and A. J. Walker, *ibid.*, **127**, 1687 (1925).

(94) F. D. Chattaway and G. D. Parkes, *ibid.*, 113 (1926).

(95) F. D. Chattaway and A. B. Adamson, *ibid.*, 2787 (1931).

(96) D. B. Sharp and C. S. Hamilton, *J. Amer. Chem. Soc.*, **68**, 588 (1946).

(97) D. A. Bowack and A. Lapworth, *J. Chem. Soc.*, **87**, 1854 (1905).

(98) R. W. Butler and F. L. Scott, *ibid.*, *C*, 239 (1967).

(99) R. W. Butler and F. L. Scott, *ibid.*, *C*, 1711 (1968).

(100) C. Bülow and P. Neber, *Ber.*, **46**, 2370 (1913).

(101) C. Bülow and R. Huss, *ibid.*, **50**, 1478 (1917).

(102) R. Fusco and S. Rossi, *Rend. Ist. Lombardo Sci., Pt. I*, **91**, 186 (1957); *Chem. Abstr.*, **52**, 11866 (1958).

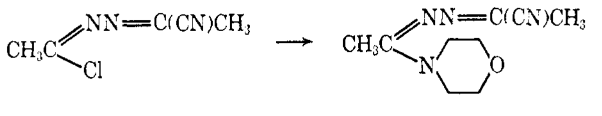
(103) F. L. Scott and M. Holland, *Proc. Chem. Soc.*, 106 (1962).

(104) T. Bacchetti, *Gazz. Chim. Ital.*, **91**, 866 (1961).

(105) H. von Pechmann, *Ber.*, **28**, 2373 (1895).

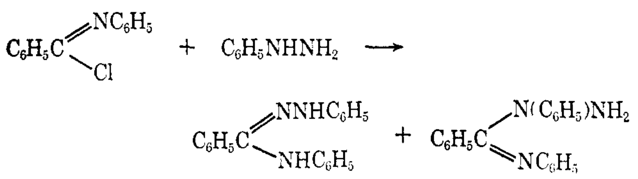
von Pechmann did in fact isolate two products, but not the tautomers that he had hoped for; *cf.* next section.

N^3,N^3-Disubstituted amidrazones have also been prepared.[106]

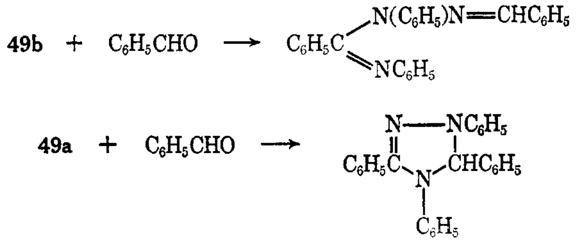


E. FROM IMIDOYL HALIDES WITH HYDRAZINES OR ACID HYDRAZIDES

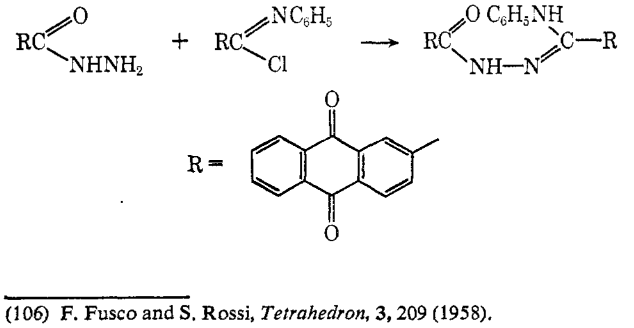
This process, closely related to that discussed in the foregoing section, consists in the action of an imidoyl halide[15] and a substituted hydrazine. As mentioned above, this reaction can give rise to two products if suitably chosen monosubstituted hydrazines are used.[105] These products are the N^1,N^3- and the N^2,N^3-disubstituted amidrazones (**49a** and **49b**, respectively). These two compounds were characterized first by Wheeler and Johnson[107] and later by Busch, Ruppenthal, and Schneider[108,109] who found that compound **49b** reacted with benzaldehyde to give a Schiff base, whereas compound **49a** reacted with the same substance to form a dihydrotriazole.



49a 49b



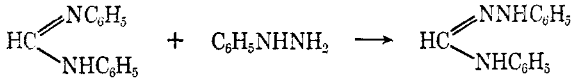
A more recent application of this synthesis has been in the production of triazoles and amidrazones of the anthraquinone series using acid hydrazides. The amidrazone is really an intermediate in this synthesis but is, in some instances, stable enough to be isolated.[110]



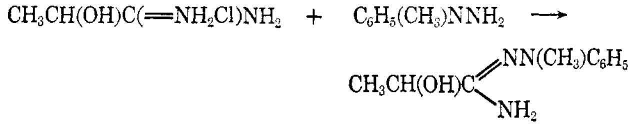
Triazolones involving amidrazone intermediates have also been synthesized from imidoyl chlorides and alkyl hydrazinocarboxylates.[111]

F. REACTION OF OTHER IMIDIC ACID DERIVATIVES WITH HYDRAZINES

N,N′-Disubstituted amidines react with phenylhydrazine at temperatures around 100° to give N^1,N^3-disubstituted amidrazones.[112,113]

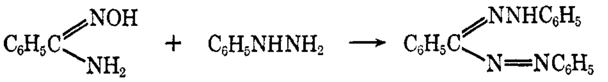


In our own hands it was found that lactamidinium chloride on heating with methylphenylhydrazine in alcohol gave the corresponding amidrazone (**50**) but that atrolactamidinium chloride failed to yield an amidrazone on similar treatment with phenylhydrazine.[114]



50

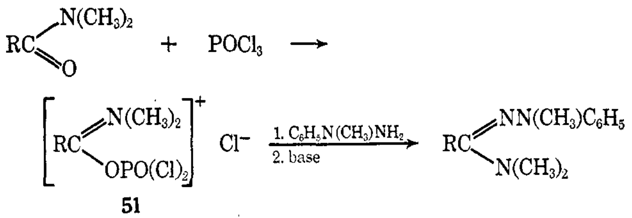
In the only reaction observed between an amidoxime and phenylhydrazine, excess phenylhydrazine was used and hence the product was a triphenylformazan.[115]



G. FROM AMIDES AND THIOAMIDES

1. Amides

Amides have also provided a feasible starting point in the synthesis of amidrazones, either directly or *via* the imidoyl halide (*cf.* section IV.E). A typical example of a direct synthesis is the condensation of an N,N-disubstituted amide with a substituted hydrazine in the presence of phosphorus oxychloride.[9,73,116,117]



51

The intermediate, **51**, has been obtained crystalline from benzene solution but need not be isolated.[118] When phenyl-

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(106) F. Fusco and S. Rossi, *Tetrahedron*, **3**, 209 (1958).

(107) H. L. Wheeler and T. B. Johnson, *Amer. Chem. J.*, **31**, 577 (1904).

(108) M. Busch and R. Ruppenthal, *Ber.*, **43**, 3001 (1910).

(109) M. Busch and C. Schneider, *J. Prakt. Chem.*, **89**, 310 (1914).

(110) E. Klingsberg (American Cyanamid Co.), U. S. Patent 2,884,424 (1959); *Chem. Abstr.*, **54**, 2763 (1960).

(111) K. H. Hauptmann and K. Zeile (Boehringer Sohn), German Patent 1,126,882 (1962); *Chem. Abstr.*, **57**, 2229 (1962).

(112) O. Zwinger and R. Walther, *J. Prakt. Chem.*, **57**, 223 (1898).

(113) R. Walther and A. Grossmann, *ibid.*, **78**, 489 (1908).

(114) D. G. Neilson, private communication.

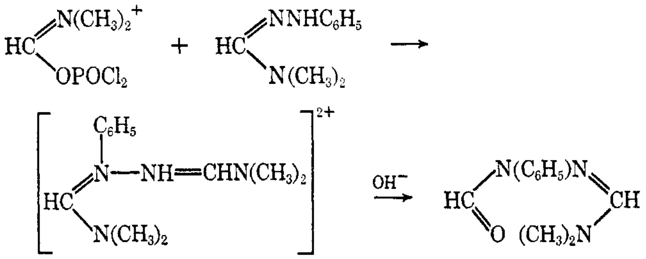
(115) E. Bamberger, *Ber.*, **27**, 160 (1894).

(116) H. Bredereck, R. Gompper, H. G. Shuh, and G. Theilig, *Angew. Chem.*, **71**, 753 (1959).

(117) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).

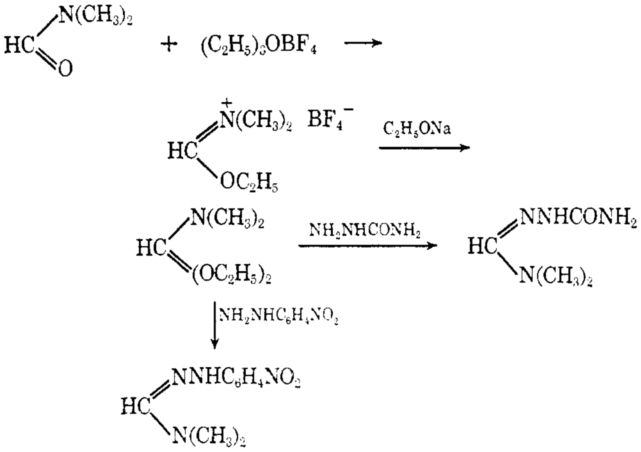
(118) H. Bredereck, R. Gompper, H. G. V. Schuh, and G. Theilig, "Newer Methods of Preparative Organic Chemistry," W. Foerst, Ed., translated by H. Birnbaum, Academic Press, New York, N. Y., 1964, p 241.

hydrazine is used, however, the amidrazone can condense with a further molecule of phosphorus oxychloride adduct as follows, giving the N^1-formyl product **52**.[117,118]

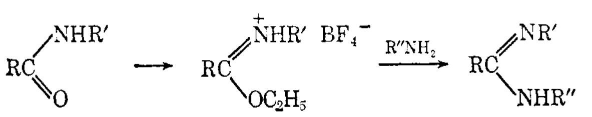


52

An alternative route for converting N,N-dimethylformamide into an amidrazone consists in treating the amide with boron trifluoride etherate, basifying, and then finally treating the resultant acetal with a hydrazine.[119]

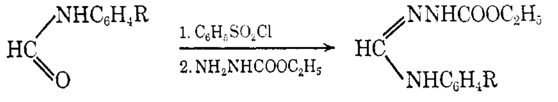


In this connection a recent amidine synthesis based on the boron trifluoride etherate–amide reaction may well open up a new route to N^1,N^3-disubstituted and N^1,N^1,N^3-trisubstituted amidrazones,[120] by the substitution of hydrazines



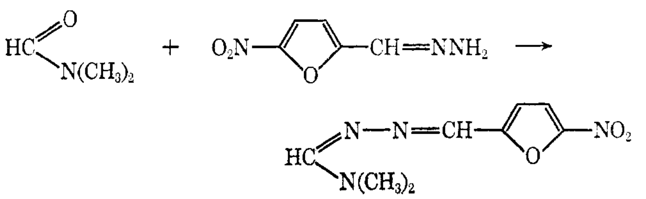
for amines.

Benzenesulfonyl chloride has also been used as the condensing reagent in the interaction of the N-substituted formamides with ethyl hydrazinoformate



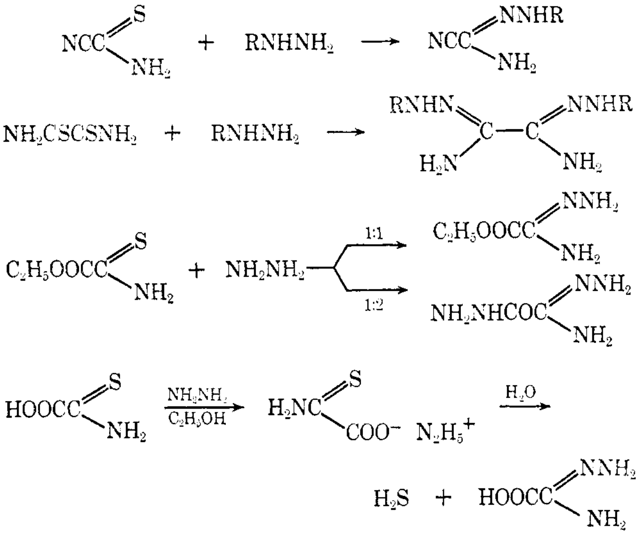
and Hoyle[121] has used a similar procedure to obtain N^1-furfurylidene-N^3,N^3- disubstituted amidrazones.

The reaction of $(CH_3CO)_2NH$ with methylphenylhydrazine is reported to give mainly the acylated hydrazine but also small quantities of N^1-methyl-N^1-phenylacetamidrazone.[122]



2. Thioamides

Thioamides react with hydrazines to give amidrazones among other products. Various oxalic acid derivatives have been prepared in this way using $NCCSNH_2$,[38] $H_2NCSCSNH_2$,[38,123] $C_2H_5OOCCSNH_2$,[124] and $HOOCCSNH_2$[125] as starting materials.



Several unsubstituted amidrazones have been prepared from heterocyclic acid thioamides such as isonicotinic[126] and picolinic acid thioamides,[127] but it is reported that prolonged interaction gives rise to thiadiazoles.[127]

A series of N^3-substituted amidrazones has been prepared by the action of hydrazine hydrate on arylthiocarboxanilides (**53**, Ar = C_6H_5, 2-pyridyl, p-$(CH_3)_2NC_6H_4$) but again if higher temperatures and prolonged reaction times were employed, secondary reaction products appeared, *e.g.*, dihydrotetrazines.[128–133] The use of phenylhydrazine led simi-

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(119) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961).

(120) L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.*, **33**, 1679 (1968).

(121) W. Hoyle, *J. Chem. Soc., C*, 690 (1967).

(122) K. Brunner, W. Seeger, and S. Dettrich, *Monatsh. Chem.*, **45**, 69 (1924).

(123) G. Dedichen, *Avhandl. Norske. Videnskaps-Akad. Oslo. I. Mat-Naturv. Kl.*, (5) 42 (1936); *Chem. Abstr.*, **31**, 4985 (1937).

(124) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **38**, 1560 (1955).

(125) R. Rätz and H. Schroeder, *J. Org. Chem.*, **23**, 1931 (1958).

(126) T. P. Sycheva, T. Kh. Trupp, I. V. Lebedeva, and M. N. Shchukina, *Zh. Obshch. Khim.*, **32**, 3669 (1962); *Chem. Abstr.*, **58**, 12528 (1962).

(127) W. J. Van Der Burg, *Rec. Trav. Chim.*, **74**, 257 (1955).

(128) A. Spassov and E. Golovinsky, *Compt. Rend. Acad. Bulgare Sci.*, **14**, 163 (1961); *Chem. Abstr.*, **55**, 27300 (1961).

(129) A. Spassov and E. Golovinsky, *Zh. Obshch. Khim.*, **32**, 3394 (1962); *Chem. Abstr.*, **58**, 11324 (1963).

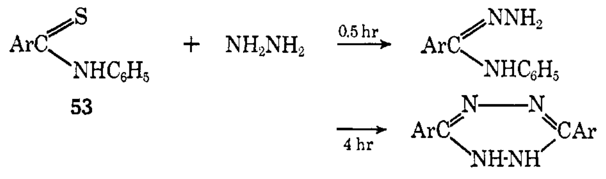
(130) A. Spassov, E. Golovinsky, and G. Russev, *Chem. Ber.*, **96**, 2996 (1963).

(131) A. Spassov, E. Golovinsky, and G. Demirov, *ibid.*, **98**, 932 (1965).

(132) A. Spassov, E. Golovinsky, and G. Demirov, *ibid.*, **99**, 3734 (1966).

(133) A. Spassov, E. Golovinsky, and G. Russev, *ibid.*, **99**, 3728 (1966).

larly to N^1,N^3-diarylamidrazones[129] from compounds of the type **53**.

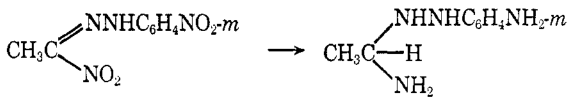


53

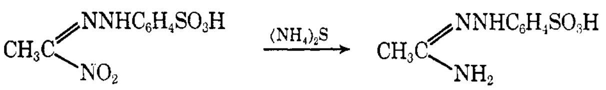
Amidrazones are also postulated as intermediates in the reaction of N-substituted thioamides with ethyl hydrazinocarbonate although the reaction conditions precluded their isolation and 1,2,4-triazoles were formed instead.[134]

H. FROM NITRAZONES BY REDUCTION

Hallmann[135] obtained a tin double salt of the reduced N^1-(*m*-aminophenyl)acetamidrazone by reduction with tin and hydrochloric acid of the N-*m*-nitrophenylacetnitrazone. He failed, however, to isolate any amidrazone.

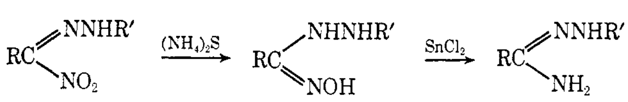


Later, Kappeler,[136] prepared the N^1-substituted amidrazone **54** from the corresponding acetnitrazone and ammonium sulfide.



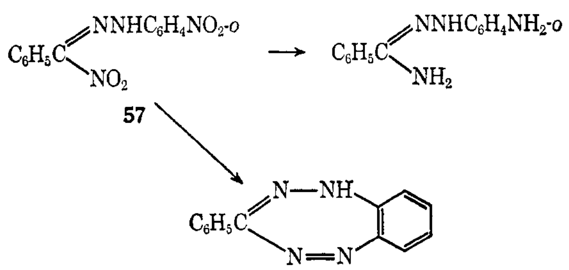
54

This reaction appears to proceed *via* the hydroximinohydrazide **55** which, in some instances, may be isolated. Indeed it may be sufficiently stable to require the use of more powerful reducing agents, *e.g.*, stannous chloride in the final reduction step to the amidrazone.[137,138]



55

Alcoholic ammonia has also been used to "reduce" nitrazones to amidrazones[139,140] as has hydrogen over 5% palladium on barium sulfate[67,141] or over Raney nickel.[142] Zinc in alkali gave the cyclic formazan **56** directly from the nitrazone **57** although Raney nickel in methanol gave the desired amidrazone.[142]

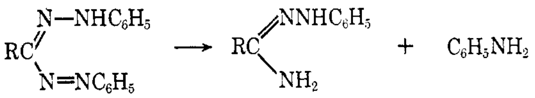


57

56

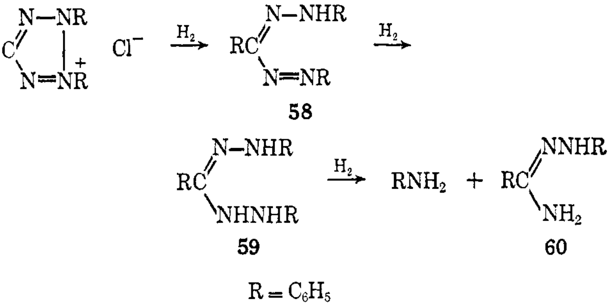
I. REDUCTION OF FORMAZANS AND TETRAZOLIUM SALTS

The initial studies on the reduction of formazans to amidrazones centered around the use of cold alcoholic solutions of ammonium sulfide. Amines were produced as byproducts and the yields were not always encouraging.[143–146]



Sugar formazans, *e.g.*, derived from D-galactose, are reduced by mercaptals to amidrazones although the use of hydrogen sulfide gave the phenylhydrazides of the corresponding thioaldonic acids. Sugar amidrazones are, however, somewhat unstable.[147]

More recently the stepwise hydrogenation of tetrazolium salts and formazans has been studied.[67,148,149] The successful methods of reduction are (a) hydrogenation using 5% palladium on barium sulfate, (b) Raney nickel in methanol, and (c) the use of sodium dithionite. The reduction process follows the scheme



The dihydroformazan **59** is only stable in solution and on exposure to air is oxidized back to the formazan **58**.

Lithium aluminum hydride is without effect on triphenylformazan (**58**, R = C_6H_5) in ether–tetrahydrofuran at room temperature but cleaves it on boiling for several hours, giving the corresponding amidrazone[150] (**60**).

Phenylhydrazine at 50–100° has also found use as a reducing agent.[151]

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(134) M. Pesson, S. Dupin, and M. Antoine, *Compt. Rend.*, **253**, 992 (1961).

(135) F. Hallmann, *Ber.*, **9**, 389 (1876).

(136) C. Kappeler, *ibid.*, **12**, 2285 (1879).

(137) E. Bamberger and J. Frei, *ibid.*, **35**, 1084 (1902).

(138) H. Voswinckel, *ibid.*, **35**, 3271 (1902).

(139) G. Ponzio, *Gazz. Chim. Ital.*, **40**, 77 (1910).

(140) G. Ponzio, *ibid.*, **40**, 312 (1910).

(141) D. Jerchel, German Patent, 884,368 (1953); *Chem. Abstr.*, **52**, 11919 (1958).

(142) D. Jerchel and W. Elder, *Chem. Ber.*, **88**, 1284 (1955).

(143) E. Bamberger and J. Lorenzen, *ibid.*, **25**, 3539 (1892).

(144) E. Bamberger and P. de Gruyter, *ibid.*, **26**, 2783 (1893).

(145) E. Bamberger and F. Kuhlemann, *ibid.*, **26**, 2978 (1893).

(146) E. Bamberger, R. Padova, and E. Ormerod, *Ann.*, **446**, 260 (1925).

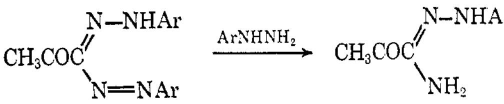
(147) E. Móczár and L. Mester, *Bull. Soc. Chim. Fr.*, 186 (1962).

(148) D. Jerchel and R. Kuhn, *Ann.*, **568**, 185 (1950).

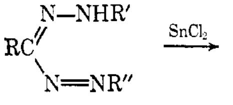
(149) D. Jerchel and W. Wotichy, *ibid.*, **605**, 191 (1957).

(150) W. Reid and F. Müller, *Chem. Ber.*, **85**, 470 (1952).

(151) M. Regitz and B. Eistert, *ibid.*, **96**, 3121 (1963).



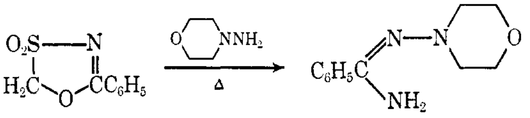
The use of more powerful reducing agents, *e.g.*, stannous chloride, leads to degradation of the formazan to its parent acid and amines and does not give an amidrazone.[152,153]



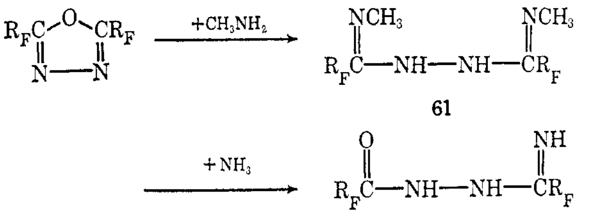
$$RCOOH + R'NH_2 + R''NH_2 + 2NH_3$$

J. FROM HETEROCYCLIC SYSTEMS

In addition to the tetrazolium salts mentioned in section IV.I, various heterocyclic systems have been used to prepare amidrazones through interaction with hydrazines, although the heterocyclic precursors themselves are not always easily formed. Thus the reaction of 1,3,4-oxathiazoline 3-dioxide in dioxane solution with hydrazine gives good yields of amidrazones.[154]



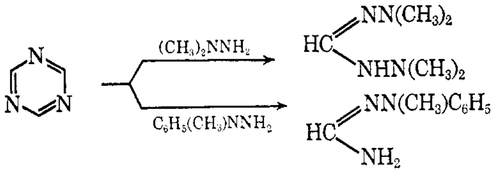
2,5-Bis(perfluoroalkyl)-1,3,4-oxadiazoles readily undergo nucleophilic attack at a ring carbon atom to give products[155] of the type **61** but react with ammonia to give compounds of formula **62**.



61

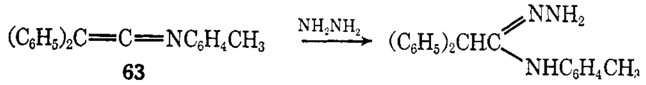
62

s-Triazine reacts with hydrazine and substituted hydrazines to give triazoles, dihydroformazans, or amidrazones depending on the hydrazine used. This work is reviewed by Grundmann[156] in an article dealing with the synthetic uses of *s*-triazine.



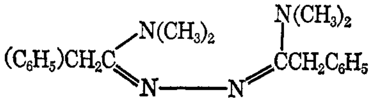
K. FROM KETIMINES, ACETYLENES, AND CARBODIIMIDES

Addition of hydrazine to a ketimine of type **63** has produced N^3-substituted amidrazones.[157]



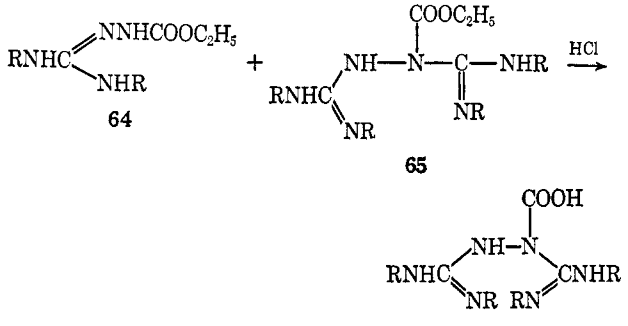
Addition of hydrazine across the unsaturated center of alkynylamines in acetonitrile solution under acidic conditions gives dihydrazidines.[158] It would appear from the reaction of these compounds with hydroxylamine and amines, that it might be possible to extend this synthesis by the use of phenylhydrazine, thereby obtaining amidrazones. A Russian patent describes similar compounds from dimethylhydrazine and perfluoroolefins.[159]

$$2C_6H_5C{\equiv}CN(CH_3)_2 + NH_2NH_2 \longrightarrow$$



Carbodiimides add hydrazine or its derivatives to form amidrazones. The reaction involves the addition of one or two molecules of the imide to give compounds **64** and **65**, respectively.[160] This latter compound (**65**) gives the hydrolysis product (**66**) on treatment with acid.[160] Much of the work in this field has been surveyed by Kurzer and Douraghi-Zadeh[161] in a recent review on carbodiimides. Similarly the addition of aminoguanidine, thiosemicarbazide, and semicarbazide to carbodiimides also yields compounds which can be looked on as highly substituted amidrazones but which we believe lie outside the scope of this review.

$$RN{=}C{=}NR + NH_2NHCOOC_2H_5 \longrightarrow$$



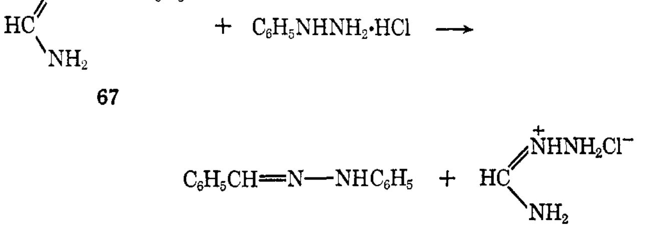
64

65

66

L. MISCELLANEOUS PREPARATIONS

Formamidrazone hydrochloride[84] has been prepared by the following reaction sequence, the initial amidrazone (**67**) arising through condensation of benzaldehyde hydrazone, ethyl orthoformate, and ammonia.



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(152) I. Hauser, D. Jerchel, and R. Kuhn, *Chem. Ber.*, **84**, 651 (1951).

(153) M. Ragno and S. Bruno, *Gazz. Chim. Ital.*, **77**, 12 (1947).

(154) K. Dickoré, *Ann.*, **671**, 135 (1964).

(155) H. C. Brown and M. T. Cheng, *J. Org. Chem.*, **27**, 3240 (1962).

(156) C. Grundmann, *Angew. Chem. Intern. Ed. Engl.*, **2**, 309 (1963).

(157) C. L. Stevens, R. C. Freeman, and K. Noll, *J. Org. Chem.*, **30**, 3718 (1965).

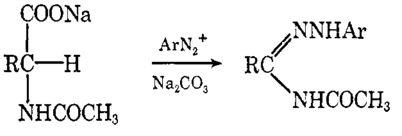
(158) H. G. Viehe, R. Fuks, and M. Reinstein, *Angew. Chem. Intern. Ed. Engl.*, **3**, 581 (1964).

(159) A. V. Fokin, Yu. N. Studnev, and N. A. Proshin, USSR Patent 172,822 (1965); *Chem. Abstr.*, **64**, 591 (1966).

(160) F. Kurzer and D. R. Hanks, *J. Chem. Soc., C*, 1375 (1968).

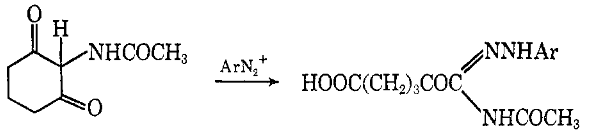
(161) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).

Diazonium salts couple with derivatives of acylaminomalonic acid to give N^3-acyl amidrazones suitable as intermediates in the preparation of triazoles.[162,163]



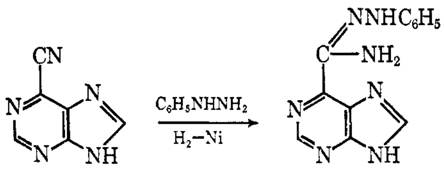
R = CN or C_2H_5OOC

Various 2-amino-1,3-diones including 2-acylamino-cyclohexa-1,3-dione (**68**) have been used in similar condensation reactions.[161]



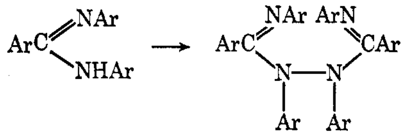
68

Attempts[164] to reduce 6-cyanopurine to the corresponding aldehyde with hydrazine or phenylhydrazine and hydrogen over Raney nickel resulted in the formation of the corresponding purine 6-carboxamidrazone (**69**).



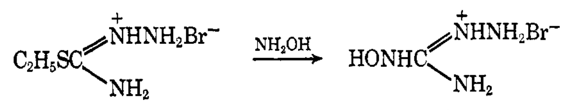
69

Oxidation of N,N′-diarylamidines in acid permanganate solution[165] gives rise to compounds of type **70**.



70

An interesting extension of the thioimidate reaction lies in the synthesis of N-amino-N′-hydroxyguanidinium bromide (**71**) from hydroxylamine and S-ethyl isothiosemicarbazide hydrobromide and in the application of this reaction to amidrazone systems contained in heterocyclic rings.[166]



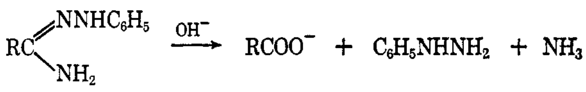
71

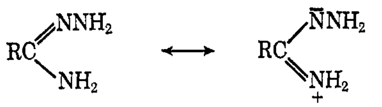
In addition amidrazones have from time to time been quoted as intermediates in other reactions but have not been isolated or characterized.[167]

V. Properties of Amidrazones

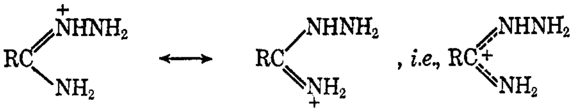
A. GENERAL PROPERTIES

Amidrazones are, in general, monoacid bases which form salts with inorganic acids, the hydrochlorides being most commonly described in the literature, although carbonates, nitrates, picrates, benzoates, sulfates, and chloroplatinates have all been reported.[43,48,49,64,65,128] In the free state, amidrazones tend to be either liquids or low-melting solids, and unsubstituted amidrazones show strong reducing properties akin to hydrazine itself.[9,127] Indeed the unsubstituted amidrazones are almost unknown in the free state, the perfluoroalkyl compounds being almost unique in having been successfully characterized.[34] Thus amidrazones in general tend to be unstable in alkaline solution undergoing hydrolysis[2] but are much more stable in acid;[168,169] *e.g.*, heating N^1-phenylcyanoformamidrazone at 100° for a few hours in concentrated hydrochloric acid solution caused only slight decomposition to the amidrazone group.[169] The enhanced stability of the ion over that of the free base can be seen in the light of resonance theory which has been applied to the closely related amidines.[170] The free amidrazones can be looked on as mesomeric, but the charge separation in structure **72b** suggests that it does not contribute greatly to the resonance hybrid (**72a** ↔ **72b**). In the case of the cation, however, spreading of the charge (**73a** ↔ **73b**) leads to enhanced stability.





72a 72b



73a 73b

However, little quantitative work appears in the literature on the measurement of the base strengths of amidrazones,[20] but K_b for compounds of type **74** lies between 9.34×10^{-11} (**74**, $R = CF_3$) and 6.6×10^{-11} (**74**, $R = C_5F_{11}$), whereas compound **75** ($R_F = C_3F_7$) has $K_b = 1.74 \times 10^{-11}$.

$R_FC(NH_2){=}NN(CH_3)_2$ **74** $R_FC(NH_2){=}NNH_2$ **75**

B. TAUTOMERISM

In section III we arbitrarily divided amidrazones into two classes: those able to exhibit tautomerism between N^2 and N^3 and those unable to exhibit this phenomenon. Although amidines of the type **76** have been reported to have been isolated in two distinct forms (**76a** and **b**), presumably due

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(162) H. Hellmann and W. Schwiersch, *Chem. Ber.*, **94,** 1868 (1961).

(163) H. Hellmann and W. Elser, *ibid.*, **95,** 1955 (1962).

(164) A. Giner-Sorolla, I. Zimmerman, and A. Bendich, *J. Amer. Chem. Soc.*, **81,** 2515 (1959).

(165) S. P. Joshi, A. P. Khanolkar, and T. S. Wheeler, *J. Chem. Soc.*, 793 (1936).

(166) A. Dornow and H. Pietsch, *Chem. Ber.*, **100,** 2585 (1967).

(167) H. Stetter, R. Engl, and H. Rauhut, *ibid.*, **92,** 1184 (1959).

(168) G. Ponzio, *Gazz. Chim. Ital.*, 40 (I) 433 (1910).

(169) E. Fischer, *Ann.*, **190,** 139 (1877).

(170) M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Clarendon Press, Oxford, England, 1949, p 95.

to the presence of the sulfonyl groups,[171] no substantiated

$C_6H_5C(=NSO_2R)NH_2$ **76a** $\quad$ $C_6H_5(=NH)NHSO_2R$ **76b**

claim for the isolation of any two tautomers of an amidrazone is known, the earlier claims of von Pechmann[105] having been proved false (*cf.* section IV.E).

C. SPECTRAL PROPERTIES

Brown and Pilipovich[20] quote infrared characteristics for perfluoroalkylamidrazones. Their unsubstituted amidrazones showed three medium-strong bands in the 3500–3100-cm^{-1} region due to NH_2 and NH stretch. Two other strong bands in the 1700–1600-cm^{-1} region were assigned to C=N stretch (1690 cm^{-1}) and NH_2 deformation (1655 cm^{-1}). A weak band due to NH deformation was also noticed around 1590 cm^{-1}. The N^1,N^1-dialkyl compounds also gave two bands in the region 3550–3380 cm^{-1} as well as the 1670- and 1655-cm^{-1} bands. N^3-Arylamidrazones of the type $ArC(=NNH_2)NHAr$ have also been found to exhibit bands at 3427 and 3330 cm^{-1}, indicating interaction between the NH_2 and NH vibrations.[129]

Optical rotatory dispersion measurements on the compounds **77** (R = H or CH_3O, X = Cl) gave plain curves down

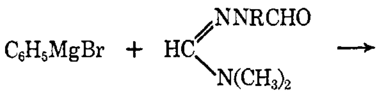
$o\text{-}RC_6H_4CH(OH)C(NH_2)=NHNHC_6H_5^+X^-$
77

to 285 mμ at which point light absorption proved too great for further examination.[172] However, the (+)-amidrazone (−)-mandelate (**77**, R = CH_3O; X = $C_6H_5CH(OH)COO$) exhibited a Cotton effect curve of high amplitude (+4260 peak, 283 mμ; −7390 trough, 263 mμ) due probably to the presence of the various aromatic chromophores.[172] (The authors[173] prepared the optically active amidrazone **77** (R = H) and its hydrochloride by interaction of phenylhydrazine with ethyl (−)-mandelimidate hydrochloride. N^1-Phenyl-2-methoxymandelamidrazone has been resolved by means of the mandelic acids.)

VI. Reactions of Amidrazones

A. REACTION WITH GRIGNARD REAGENTS

The formyl group of N^1-formylformamidrazones (**78**) is split off on treatment of these compounds with phenylmagnesium bromide, benzaldehyde and a little benzhydrol being obtained. N^3,N^3-Dimethyl-N^1-phenylformamidrazone was


$C_6H_5MgBr + HC(=NNRCHO)N(CH_3)_2 \longrightarrow$
78

$C_6H_5CHO \longrightarrow C_6H_5CH(OH)C_6H_5$

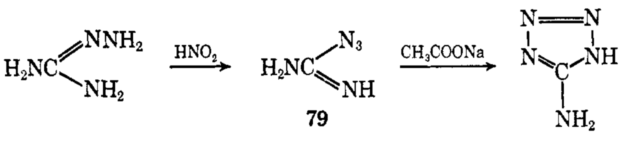
found to give only a trace of benzaldehyde on treatment with the Grignard reagent.[117]

Likewise, Newlands[2] failed to find any reaction between N^1-phenylmandelamidrazone or its hydrochloride and ethylmagnesium iodide or between the amidrazone base and phenylmagnesium bromide in refluxing toluene. (Reid[174] similarly showed that mandelamidine was resistant to Grignard reagent attack.) These negative results may be of importance in that the Grignard reagent could be made to react with other functional groups on the molecule as in, *e.g.*, benzoylformamidrazone, leaving the amidrazone grouping unchanged.

B. ACTION OF NITROUS ACID ON AMIDRAZONES

1. *Unsubstituted Amidrazones*

Nitrous acid reacts with amidrazones to form tetrazoles. Wieland[175] mentions this in his monograph "Die Hydrazine" and the reaction is discussed more fully in two reviews of tetrazole chemistry by Benson.[60,176] The use of aminoguanidine in tetrazole synthesis has also been reviewed.[5] It is now accepted[60] that the reaction involves the formation of an imide azide (**79**) which subsequently rearranges to the tetrazole (**80**). Acetamidrazone decomposes under the normal conditions of diazotization in acid media to acetic acid, hydrazoic acid, and ammonium chloride but is successfully converted into 5-methyltetrazole by the action of ethyl nitrite in ethanol.[50,51] Other 5-alkyl-[45] as well as 5-aryl-[177,178] and 5-heterocyclo-substituted tetrazoles[47,127] among others[179] have all been successfully synthesized through the medium of nitrous acid.

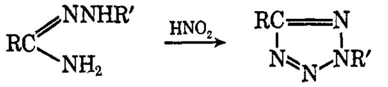


79
80

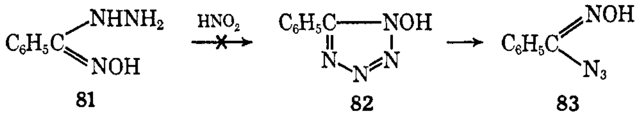
Bis(tetrazoles) have also been reported.[46]

2. *Monosubstituted Amidrazones*

Although N^1-substituted amidrazones cannot form imide-azides, they nevertheless form 2,5-disubstituted tetrazoles on treatment with nitrous acid.[94]



The claim by Wieland,[180] however, that N^3-hydroxybenzamidrazone (**81**) reacted with nitrous acid to give the 1-hydroxytetrazole **82** has not stood up to modern spectral investigation which showed the presence in the product of azide bands both in the infrared and ultraviolet regions.[181] *Structure* **83** *is now ascribed to the product of this reaction.*



81 82 83

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(171) S. J. Angyal and W. K. Warburton, *Aust. J. Sci. Res., Ser. A*, **4**, 93 (1951).

(172) D. G. Neilson, "Some Newer Physical Methods in Structural Chemistry," R. Bonnett and J. G. Davis, Ed., United Trade Press, London, 1967, p 186.

(173) J. M. Heatlie, D. G. Neilson, L. R. Newlands, and R. Roger, private communication.

(174) S. G. Reid, Ph.D. Thesis, University of St. Andrews, 1948.

(175) H. Weiland, "Die Hydrazine," Enke, Stuttgart, 1913, p 194.

(176) F. R. Benson, *Chem. Rev.*, **41**, 1 (1947).

(177) A. Pinner, *Ber.*, **27**, 984 (1894).

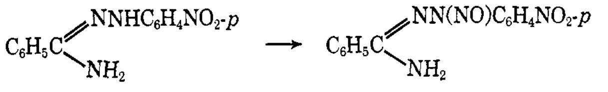
(178) A. Pinner, *ibid.*, **30**, 1871 (1897).

(179) T. Kuraishi and R. N. Castle, *J. Heterocycl. Chem.*, **1**, 42 (1964).

(180) H. Wieland, *Ber.*, **42**, 4199 (1909).

(181) F. Eloy, *J. Org. Chem.*, **26**, 952 (1961).

Two further exceptions to tetrazole formation have been noticed in the literature. Thus Ponzio[182] found that N^1-nitrophenylamidrazones reacted with nitrous acid to produce nitroso compounds, *e.g.*, compound **84**, and Newlands[2] found that N^1-phenylmandelamidrazone reacted to give mandelic acid phenylhydrazide (**85**).



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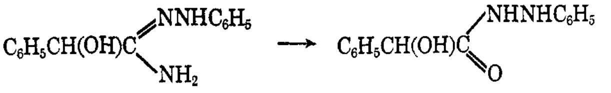
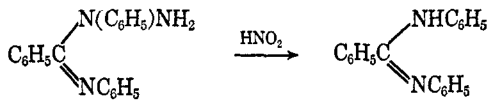


85

3. Disubstituted Amidrazones

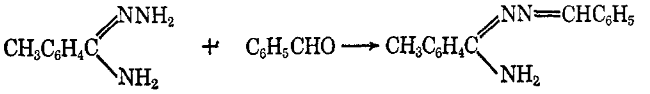
N^2,N^3-Diphenylbenzamidrazone is converted into N,N'-diphenylbenzamidine by the action of nitrous acid.[108]



C. CONDENSATION OF AMIDRAZONES WITH ALDEHYDES OR KETONES

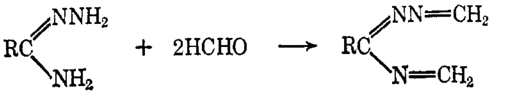
1. Unsubstituted Amidrazones

Pinner[47,177] found that if a weakly acidic solution of an amidrazone was warmed with an aldehyde, a Schiff base was formed. Thus *p*-toluamidrazone gave compound **86** on treatment with benzaldehyde. Aminoguanidine reacts similarly with aldehydes.[183]



86

When formaldehyde is used, reaction occurs at both N^1 and N^3 (**87**).[49]



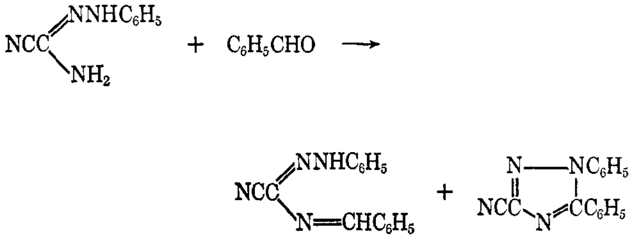
87

A process has also been described for obtaining thermally stable polymers containing amidrazone groupings in the chain by condensing hexafluoroglutaramidrazone and isophthalaldehyde.[28] Other perfluoro compounds, useful as heat transfer media, have been obtained by the condensation of benzaldehyde and heptafluorobutyramidrazone.[21]

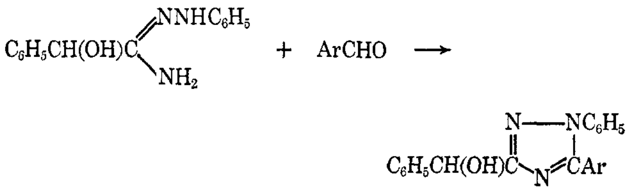
The reaction of amidrazones with dicarbonyl compounds is discussed in the section dealing with triazine formation (section VI.F).

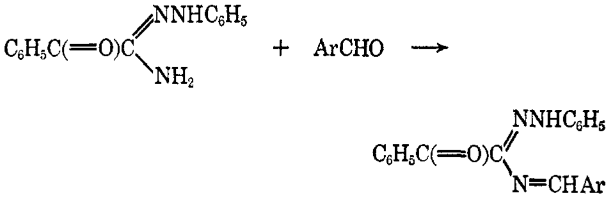
2. N-Substituted Amidrazones

Bladin[184,185] obtained two products from the action of excess benzaldehyde with an alcoholic solution of N^1-phenylcyanoformamidrazone, namely a Schiff base (**88**) and a triazole (**89**). Later he showed that the Schiff base was readily oxidized to the triazole, *e.g.*, by ferric chloride. Newlands[2] also found that N^1-arylmandelamidrazones condensed with a series of aldehydes (aromatic or heterocyclic) to give 1,2,4-triazoles directly. The corresponding benzoylformamidrazone, however, gave a stable Schiff base (**90**) which required ferric chloride to convert it into the triazole. Newlands[2] suggests that the isolation of the Schiff bases **88** and **90** can be accounted for by the enhanced stability arising through conjugation of the NC or C_6H_5CO groups with the amidrazone grouping.



88 89



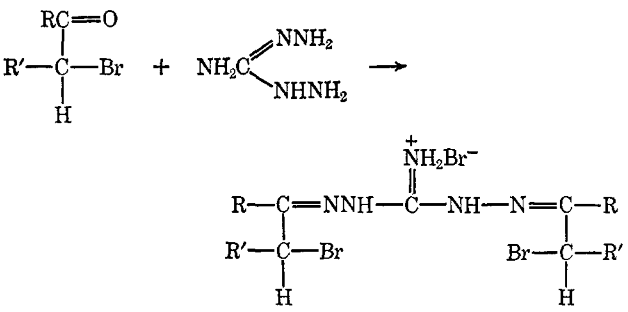


90

However, it should be noted that Baccar and Mathis[186] claim, on spectroscopic evidence, that the reaction of aldehydes with N^1-phenylbenzamidrazone gives rise to 1,2,4-triazolines rather than Schiff bases.

N^3-Substituted arylamidrazones also react with aryl aldehydes to give Schiff bases, readily oxidizable by, *e.g.*, yellow mercury oxide, to the corresponding 1,2,4-4H-triazoles.[128-130] Triazole formation is more fully discussed in section VI.E.

α-Halo ketones react with N,N'-diaminoguandiine or oxalamidrazone to give, for example, compound **91**.[187]



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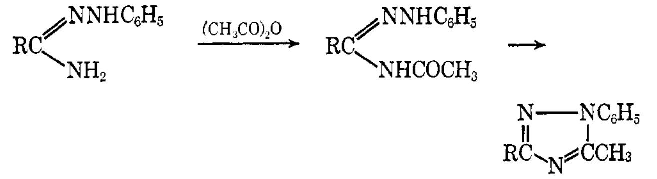
(182) G. Ponzio and C. Gastaldi, *Gazz. Chim. Ital.*, **41**, 793 (1911).
(183) J. Thiele and R. Bihan, *Ann.*, **302**, 299 (1898).
(184) J. A. Bladin, *Ber.*, **22**, 796 (1889).
(185) J. A. Bladin, *ibid.*, **25**, 183 (1892).
(186) B. Baccar and F. Mathis, *Compt. Rend.*, **258**, 6470 (1964).
(187) T. Pyl, L. Seidl, and H. Beyer, *Chem. Ber.*, **101**, 29 (1968).

D. PREPARATION OF ACYL AND SULFONYL DERIVATIVES OF AMIDRAZONES

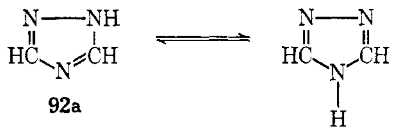
Acyl derivatives of amidrazones may be made either by direct synthesis or by acylation of unsubstituted or monosubstituted amidrazones. In either case, triazoles may be formed by subsequent loss of water. Syntheses leading to N^1- or N^3-acylamidrazones are to be found in the relevant sections on synthesis and in particular references.[76,77,110,151,155,163]

The use of alkyl- or arylsulfonylhydrazines has led similarly to N^1-sulfonylamidrazones through interaction of these compounds with suitable precursors.[36,78] However, carboxylic acid chlorides[148,177] and anhydrides[140,144,148,188–192] have been used in acylation procedures to a very large extent although at times the acyl derivatives have been synthesized merely as precursors for triazole[193] or other heterocyclic systems.[194]



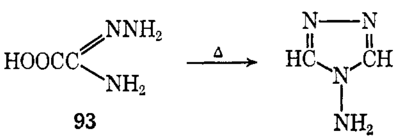
E. SYNTHESIS OF 1,2,4-TRIAZOLES FROM AMIDRAZONES

1,2,4-Triazoles (**92a** ⇌ **92b**) may be looked on as cyclic amidrazones, the properties of which are modified by the ring structure. Indeed amidrazones and, in particular, their acyl derivatives have been convenient starting points for the synthesis of 1,2,4-triazoles, and much of the earlier work is discussed in reviews by Potts[85] and by Boyer.[195] The application of amidrazones to the synthesis of triazoles has constituted the greatest single study of amidrazone chemistry, and in this review we will attempt to show how the title compounds can be used to give triazoles with varying substitution patterns.



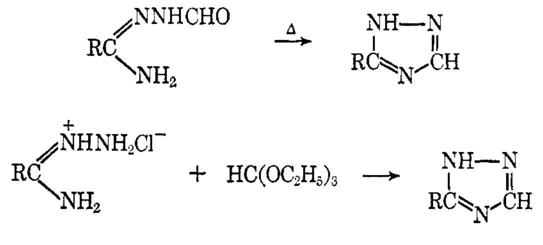
92a **92b**

Monosubstituted triazoles have been synthesized in the following ways: 4-amino-1,2,4-4H-triazole arises by the action of heat on the amidrazone **93** (or by similar treatment of the related dihydroformazan).[125]



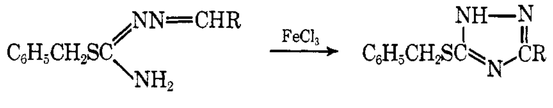
93

3-Nitroamino-1,2,4-1H-triazole has been formed similarly from N^1-formyl-N^3-nitroaminoformamidrazone.[196] Recently, a series of 3-alkyl-1,2,4-1H-triazoles has also been prepared by the cyclization of other N^1-formylamidrazones or by the reaction of the amidrazone salt with triethyl orthoformate.[197]



Amidrazones are also postulated as intermediates in the reaction of *s*-triazine with hydrazine salts whereby 1-substituted triazoles are obtained.[156,198]

Disubstitution patterns can arise in the following ways. 3,5-Disubstituted 1,2,4-1H-triazoles have been prepared by oxidation of the condensation products (**94**) of aldehydes with amidrazones (see also section VI.C).[195,199] Similarly, 3,5-disubstituted triazoles (**96**) form spontaneously or under mild conditions of heating from N^1-acylamidrazones (**95**)[76,77,193–195,200] (see section VI.D for further references). However, certain exceptions have been noted in this reaction[77] (*e.g.* **95**, R = H, CH_3, and $CH_3CH{=}CH$). Amidrazone intermediates have also been postulated in the Pellizzari reaction[85] leading to 3,5-disubstituted triazoles and in the reaction of nitriles with acylhydrazine sulfonates (**97**).[40,41] However, the experimental conditions of these reactions tend to preclude the isolation of any amidrazone and lead directly to the cyclized products.



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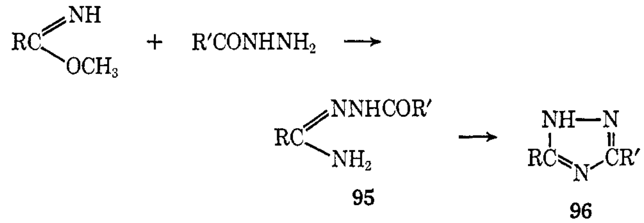
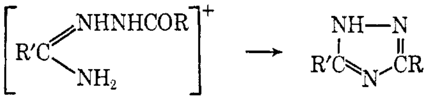


95 **96**

$$R'CN + RCONHNH_3^+C_6H_5SO_3^- \longrightarrow$$

97



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(188) J. A. Bladin, *Ber.*, **18**, 1544 (1885).

(189) J. A. Bladin, *ibid.*, **25**, 174 (1892).

(190) E. Bamberger and H. Witter, *ibid.*, **26**, 2786 (1893).

(191) E. Bamberger and H. Witter, *J. Prakt. Chem.*, **65**, 142 (1902).

(192) H. Beyer and E. Kreutzberger-Reese, *Chem. Ber.*, **84**, 478 (1951).

(193) E. Hoggarth, *J. Chem. Soc.*, 612 (1950).

(194) E. Hoggarth, *ibid.*, 1918 (1949).

(195) J. H. Boyer, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1961, p 384.

(196) R. A. Henry, J. E. De Vries, and R. H. Boschan, *J. Amer. Chem. Soc.*, **77**, 5693 (1955).

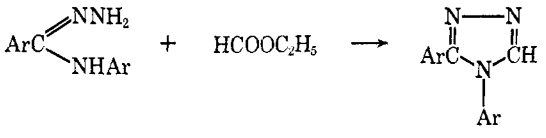
(197) H. Paul, G. Hilgetag, and G. Jähnchen, *Chem. Ber.*, **101**, 2033 (1968).

(198) C. Grundmann and R. Rätz, *J. Org. Chem.*, **21**, 1037 (1956).

(199) R. Duschinsky and H. Gainer, *J. Amer. Chem. Soc.*, **73**, 4464 (1951).

(200) E. J. Browne and J. B. Polya, *J. Chem. Soc.*, 824 (1968).

1,3-Disubstituted triazoles are formed by the cyclization of N^1-substituted amidrazones in the presence of formic acid,[68,201] higher acids giving 1,3,5-substitution patterns.[202] Similarly, 3,4-diaryl-1,2,4-4H-triazoles (**98**) arise from the condensation of N^3-arylamidrazones with ethyl formate.[132]



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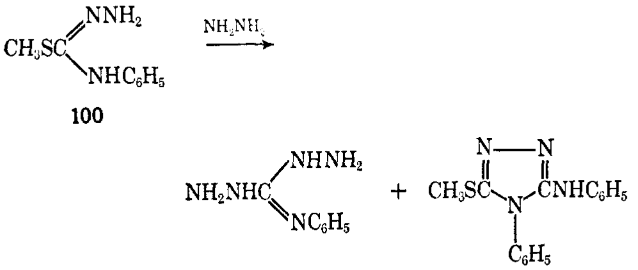
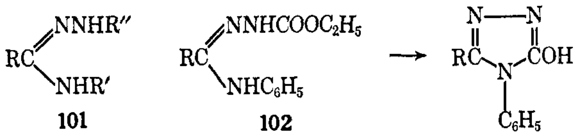
The details of syntheses of various trisubstituted triazoles *via* the use of amidrazones can also be found in the literature. Thus the triazole **99** is reported as a byproduct in the hydrazinolysis of the amidrazone **100**,[58] and earlier work describes a related hydrazinolysis reaction.[203]



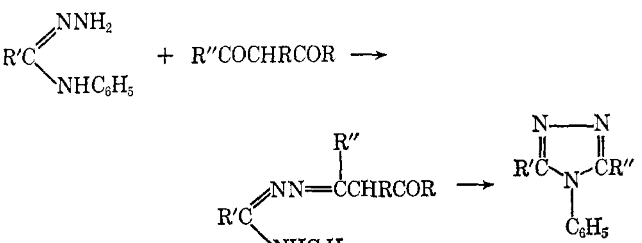
100

99

Amidrazones of the type **101** (R'' = CONH$_2$, COOC$_2$H$_5$, or COR''') have also formed feasible pathways to 3,4,5-trisubstituted 1,2,4-4H-triazoles,[109,110,160,204] (*e.g.*, **102** → **103**). Related compounds (**104**) have been synthesized by the action of N^3-substituted amidrazones with β-keto esters or β-diketones.[138] Other 3,4,5-trisubstituted triazoles (**105**) are reported to arise from the fusion of imidate salts with semicarbazide or thiosemicarbazide.[88,89] This reaction goes presumably *via* an intermediate of the type **106**, but this was not always isolated. Compounds similar to the intermediate (**106**) have been cyclized in alkaline media.[205,206]



101 **102** **103**



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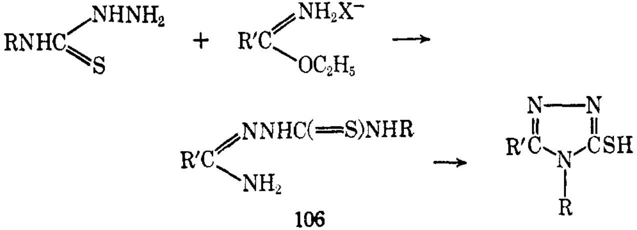
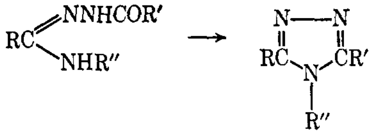
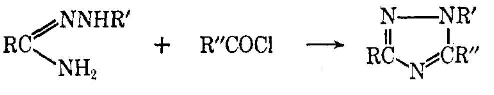


106 **105**

While cyclization of N^1-acyl-N^3-substituted amidrazones gives 3,4,5-trisubstituted triazoles[207]



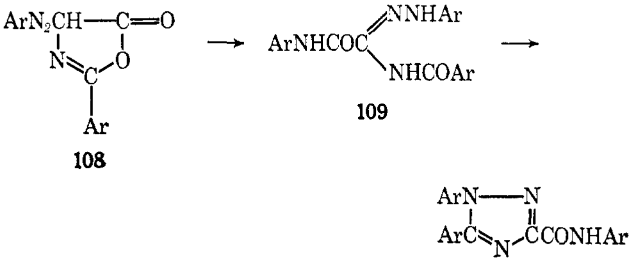
1,3,5-trisubstituted triazoles (**107**) arise readily through acylation of N^1-substituted amidrazones.[68,148,151,167]



107

As well as the more conventional acylating agents, phosgene[96] and ethyl chloroformate[68] have been used.

Arylazoaryloxazolinones (**108**) ring open under basic conditions to give amidrazones (**109**) which cyclize readily to 1,3,5-trisubstituted triazoles, and this reaction has been used to form triazole-3-aldehydes.[208,209]



108 **109**

The syntheses of other 1,3,5-trisubstituted 1,2,4-1H-triazoles[27,43] and of 3,4,5-trisubstituted 1,2,4-4H-triazoles[51] have been discussed earlier in this review; see sections IV.A,C and VI.C. In addition, the preparation of a large number of di- and trisubstituted triazoles from aminoguanidine and its derivatives is discussed by Kurzer and Godfrey[5] in a review of heterocyclic syntheses starting from aminoguanidine. More recent work is reported in later references.[160,210,211]

α,ω-Bis(1,2,3-triazolyl-3)alkanes have been prepared *via* the following reaction sequence[212]

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(201) M. R. Atkinson and J. B. Polya, *J. Amer. Chem. Soc.*, **75**, 1471 (1953).

(202) M. R. Atkinson, A. A. Komaz, E. A. Parkes, and J. B. Polya, *J. Chem. Soc.*, 4508 (1954).

(203) E. Hoggarth, *ibid.*, 1579 (1950).

(204) F. Kurzer and D. R. Hanks, *ibid.*, *C*, 746 (1967).

(205) D. J. Fry and A. J. Lambie (Ilford Ltd.), British Patent, 741,228 (1955); *Chem. Abstr.*, **50**, 9913 (1956).

(206) D. J. Fry and A. J. Lambie (Ilford Ltd.), British Patent, 736,568 (1955); *Chem. Abstr.*, **50**, 13097 (1956).

(207) R. Kraft, H. Paul, and G. Hilgetag, *Chem. Ber.*, **101**, 2028 (1968).

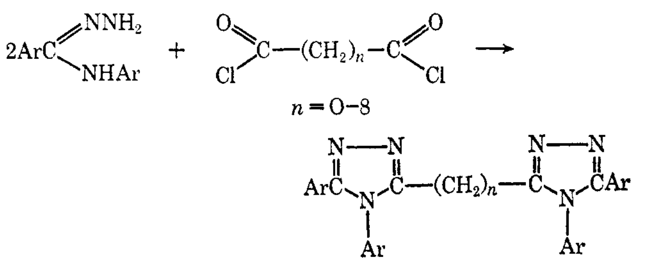
(208) E. J. Browne and J. B. Polya, *Chem. Ind.* (London), 1086 (1960).

(209) E. J. Browne and J. B. Polya, *J. Chem. Soc.*, 575 (1962).

(210) W. Ried and J. Valentin, *Chem. Ber.*, **101**, 2106 (1968).

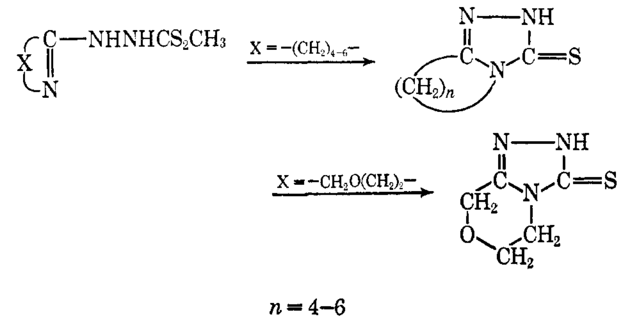
(211) W. Ried and J. Valentin, *ibid.*, **101**, 2117 (1968).

(212) A. Spassov and G. Demirov, *ibid.*, **101**, 4238 (1968).



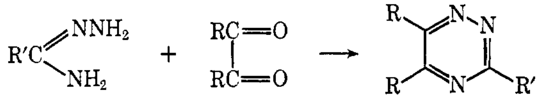
and 1,4-bis-triazolylbenzenes similarly, by the reaction of amidrazones with terephthalimidates.[213]

Fused heterocyclic systems based on triazoles have also been reported.[214]



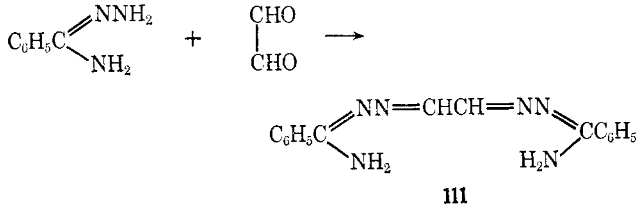
F. SYNTHESIS OF 1,2,4-TRIAZINES FROM AMIDRAZONES

The 1,2,4-triazine system is a further example of a heterocyclic system embracing the amidrazone grouping albeit modified by the aromatic nature of the ring. It would be reasonable to suppose that N-unsubstituted amidrazones would condense readily with dicarbonyl compounds to yield 1,2,4-triazines (**110**),[215,216] but there is also a tendency for this reaction to



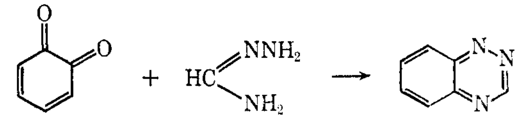
110

give acyclic products (**111**). For example, Matsuda and Morin[18] found that cyanoformamidrazone reacted with



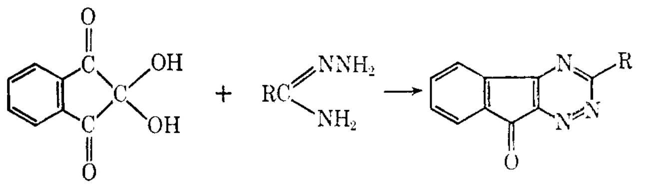
111

benzil or diacetyl to give triazines (**110**, R′ = CN; R = CH_3, or C_6H_5) but that it failed to cyclize with glyoxal. Dedichen,[123] on the other hand, reported the successful synthesis of 3,3-bis(1,2,4-triazinyl)s from glyoxal (among other diketones) and oxaldiamidrazone. Early workers[125] failed to prepare cyclic products from the action of glyoxal with carbethoxyformamidrazone (**112**) or with aminoguanidine,[217] but later workers using aminoguanidine bicarbonate[218] and carbethoxyformamidrazone[219] successfully prepared the desired 1,2,4-triazines. Subsequent decarboxylation of the latter triazine ester (**110**, R′ = $COOC_2H_5$; R = H) gave rise to the parent member of this class, 1,2,4-triazine (**110**, R = R′ = H). More recently, 1,2,4-triazine has been obtained by the direct condensation of glyoxal and formamidrazone.[84] This latter method has been extended to give 1,2,4-benzotriazines from *o*-benzoquinone[84]

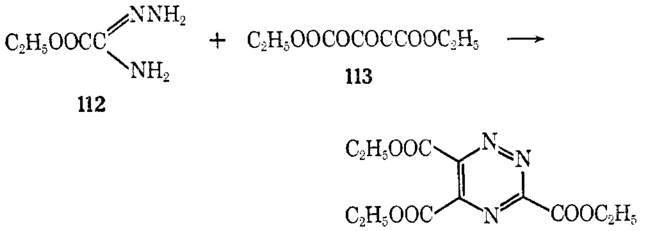


and other fused heterocyclic systems by the use of, *e.g.*, phenanthraquinone.[216]

Triketones, or their hydrates, have also been successfully condensed with amidrazones to give 1,2,4-triazines.[220]



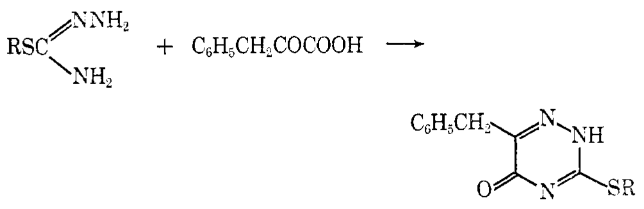
Keto acids and esters have also found use,[124,125] and syntheses of this type include that of 3,5,6-tricarbethoxy-1,2,4-triazine prepared by the condensation of the amidrazone **112** with the diketo diester **113**.



112

113

Similarly, amidrazones based on alkyl isothiosemicarbazide structures have been used in the synthesis of 6-azauracil[221] and 5-oxo-1,2,4-triazines (**114**).[222] The use of aminoguanidine



114

in the synthesis of 1,2,4-triazines has been reviewed.[5,223] However, more recent applications include the synthesis of 3-amino-5-hydroxy-1,2,4-triazines from α-keto acids and aminoguanidine.[224] Also, there is the formation of triazines by

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[213] W. Ried and P. Schomann, *Ann.*, 714, 122 (1968).

[214] J. Körösi and P. Berencsi, *Chem. Ber.*, 101, 1979 (1968).

[215] A. Pinner, *Ann.*, 297, 242 (1897).

[216] H. Paul, S. Chatterjee, and G. Hilgetag, *Chem. Ber.*, 101, 3696 (1968).

[217] J. Thiele and E. Dralk, *Ann.*, 302, 275 (1898).

[218] J. G. Erickson, *J. Amer. Chem. Soc.*, 74, 4706 (1952).

[219] W. W. Paudler and J. M. Barton, *J. Org. Chem.*, 31, 1720 (1966).

[220] W. Ried and P. Schomann, *Ann.*, 714, 128 (1968).

[221] P. K. Chang and T. L. V. Ulbricht, *J. Amer. Chem. Soc.*, 80, 976 (1958).

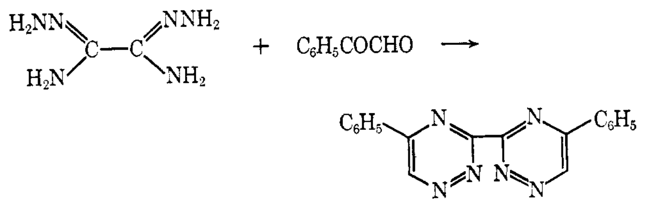
[222] E. Cattelain, *Bull. Soc. Chim. Fr.*, 11, 256 (1944).

[223] J. P. Horwitz, ref 195, p 720.

[224] T. Ueda and M. Furukawa, *Chem. Pharm. Bull. Tokyo*, 12, 100 (1964); *Chem. Abstr.*, 60, 9278 (1964).

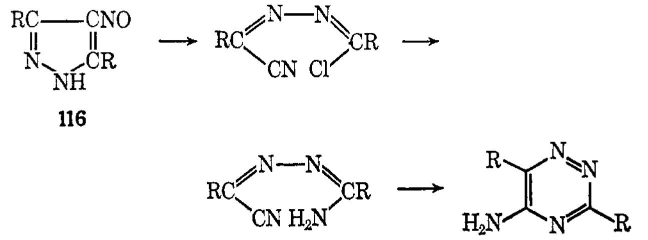
the action of alkali on the products of condensation of diaminoguanidine with α-halo ketones.[187]

3,3′-Bis(2,4-triazinyl)s (**115**) have been reported from the interaction of oxaldiamidrazone and dialdehydes[128] or α-keto aldehydes.[225] Other complex heterocyclic systems involving 1,2,4-triazines have been prepared from benzil and pyridyl[28,29] (*e.g.*, **110**, R = R′ = 2-pyridyl) among other diketo compounds.[225]



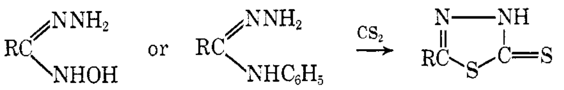
115

3,5-Disubstituted 4-nitrosopyrazoles (**116**) react with phosphorus pentachloride to give hydrazonoyl halides which, on subsequent treatment with ammonia and alkali, cyclize to 5-amino-1,2,4-triazines.[106] Two isomeric products arise if the 3 and 5 substituents of the pyrazoles are different.[106]

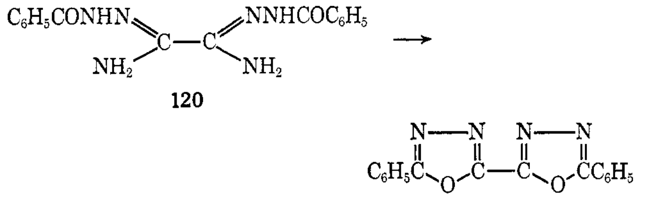


G. MISCELLANEOUS HETEROCYCLIC SYSTEMS PREPARED FROM AMIDRAZONES

A few, miscellaneous, heterocyclic systems have been obtained from amidrazones in specific, isolated syntheses. These include the reaction of carbon disulfide[226] with either **117** or **118** to give the 2-thioxothiadiazole **119** and the cyclization of the oxalamidrazone[87] **120** at 100° in dichloroacetic acid to give the bisoxadiazolyl **121**.

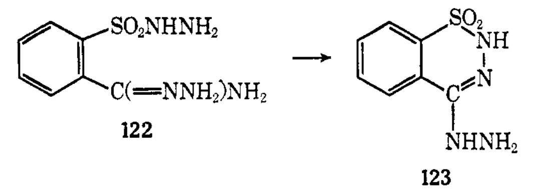


117 118 119



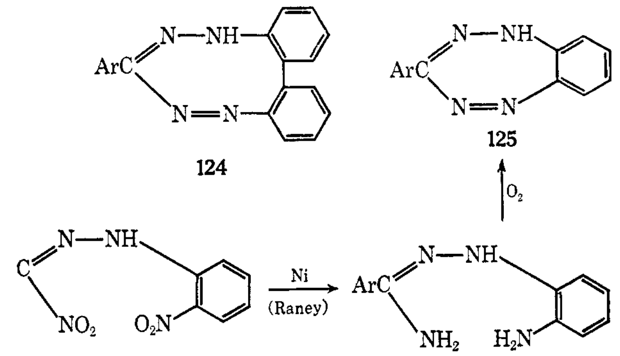
121

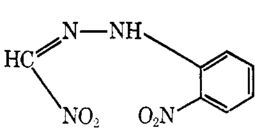
The amidrazone **122** also cyclizes readily to give a 1,2,3-thiodiazine dioxide (**123**).[86]



122 123

Cyclic formazans (**124** and **125**) have been obtained by the reduction of amidrazones[142] having an N¹-2-nitrophenyl substituent, but the closely related compounds **126** and **127** cyclize to 1,2,4-benzotriazines.[142,227]





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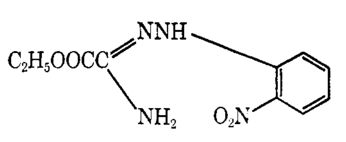
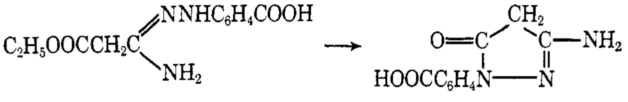


127

A 5-pyrazolone[69] is reported as the predominant product resulting from the cyclization of the carbethoxyacetamidrazone (**128**) in alkali at 60°.

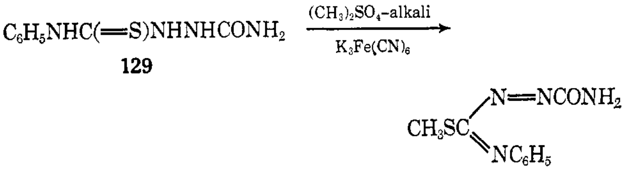


128

1,2,4,5-Tetrazines are not normally synthesized from amidrazones but can occur as by-products in the synthesis of these compounds[33] (*cf.* section IV) as they have similar methods of preparation. The Pinner synthesis involving the reaction of hydrazine with an imidate salt has been modified to give good yields of tetrazines in place of amidrazones.[59]

H. OXIDATION OF AMIDRAZONES

A dehydroamidrazone (**130**) results from the oxidation of the thiosemicarbazide[228] **129**, and an azo compound of related structure is reported to arise from the oxidation



130

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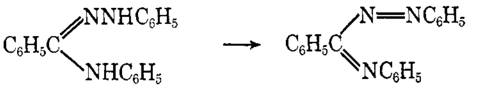
(225) B. M. Culbertson and G. R. Parr, *J. Heterocycl. Chem.*, **4**, 422 (1967).

(226) A. Dornow and K. Fischer, *Chem. Ber.*, **99**, 72 (1966).

(227) R. Fusco and S. Rossi, *Gazz. Chim. Ital.*, **86**, 484 (1956).

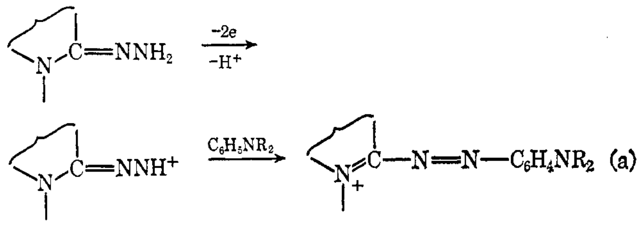
(228) F. Arndt and B. Eistert, *Ber.*, **60**, 2598 (1927).

of N^1,N^3-diphenylbenzamidrazone with mercuric oxide in alochol.[108]

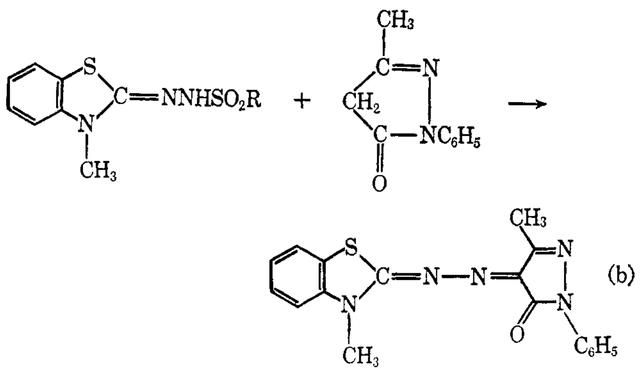


$$C_6H_5C(=NNHC_6H_5)NHC_6H_5 \longrightarrow C_6H_5C(N{=}NC_6H_5){=}NC_6H_5$$

Aromatic amines, phenols, and reactive methylene compounds undergo oxidative coupling with amidrazones. The main studies on these reactions have centered on sulfonylhydrazones of cyclic amidrazones and are illustrated by the following examples.



(a)

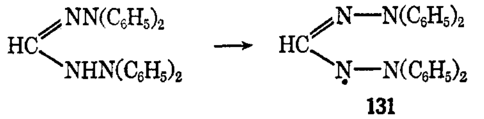


(b)

This work has been reviewed very recently by Hünig and his collaborators[6] and hence will not be dealt with further here.

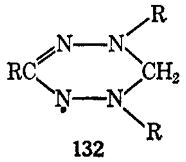
An example of oxidative hydrolysis occurs in the conversion of perfluorobutyramidrazone into perfluorobutyric acid in the presence of peroxide, the amidrazone being stable to normal hydrolysis procedures.[20]

N^3-Aminoamidrazones (dihydroformazans) are readily oxidized to blue-green free radicals (**131**) related to the verdazyl free radicals.[229–231] They are somewhat less stable than these cyclic compounds (**132**).



$$HC(=NN(C_6H_5)_2)NHN(C_6H_5)_2 \longrightarrow HC(=N{-}N(C_6H_5)_2)\dot{N}{-}N(C_6H_5)_2$$

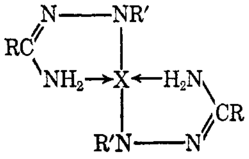
131



132

I. METAL COMPLEXES

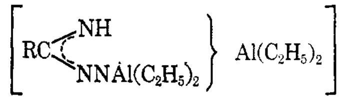
Amidrazones exhibit a tendency to form complexes with the ions of transition metals.[148] These deeply colored complexes which often have sharp melting points have been used to characterize amidrazones and are formulated as



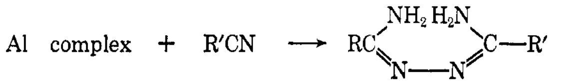
Dedichen[123] has in fact proposed the use of oxalamidrazone as a reagent for the detection of nickel as it is claimed that the presence of one part of nickel in three million can be demonstrated.

Tridentate ligands have also been prepared and used in complex formation. These ligands coordinate with metals to give complex salts[232,233] whose cations can be deprotonated in alkali giving colored, neutral complexes.

When two molar equivalents of triethylaluminum reacts with an amidrazone in benzene, a tetrameric bis(diethylalumino)amidrazone is formed;[234] these compounds are soluble in benzene and add to nitriles to give 1,4-disubstituted diazabuta-1,3-diene-1,4-diamines.



$$\left[RC(=NH)NNAl(C_2H_5)_2\ \ Al(C_2H_5)_2\right]_4$$



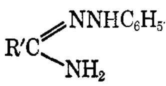
$$\text{Al complex} + R'CN \longrightarrow RC(NH_2){=}N{-}N{=}C(NH_2){-}R'$$

J. INDUSTRIAL AND MEDICINAL APPLICATIONS OF AMIDRAZONES

1. *Industrial*

A process has been described for obtaining thermally stable polymers containing amidrazones and/or 1,2,4-triazoles from, *e.g.*, isophthalaldehyde and hexafluoroglutaramidrazone.[23] A further patent describes the use of amidrazones, *e.g.*, from heptafluorobutyronitrile and hydrazine, as intermediates in the synthesis of 2-perfluoroalkyl-5-aryl-1,3,4-triazoles which are useful as heat-transfer media.[21,22]

Amidrazones have also been applied in combating fungal and bacterial infections on plants. They appear to work both by external action and by internal or systemic action. The most useful compounds of this type are represented by formula **133** where R′ contains not more than five carbon atoms.[235]



$$R'C(=NNHC_6H_5)NH_2$$

133

Other amidrazones of the types **134** and **135** have been applied as nematocides, herbicides, and rodenticides.[19,42,236]

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(229) R. Kuhn, F. A. Neugebauer, and H. Trischmann, *Angew. Chem. Intern. Ed. Engl.*, 3, 232 (1964).

(230) R. Kuhn and G. Fischer-Schwarz, *Monatsh. Chem.*, **97**, 517 (1966).

(231) O. Westphal, *Angew. Chem. Intern. Ed. Engl.*, 7, 489 (1968).

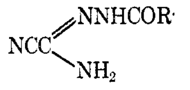
(232) J. F. Geldard and F. Lions, *Inorg. Chem.*, **2**, 270 (1963).

(233) F. Lions and K. V. Martin, *J. Amer. Chem. Soc.*, **80**, 3858 (1958).

(234) T. Kauffmann, L. Bán, and D. Kuhlmann, *Angew. Chem. Intern. Ed. Engl.*, **6**, 256 (1967).

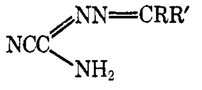
(235) J. T. Hackmann (Shell Development Co.), U. S. Patent 2,758,050 (1956); *Chem. Abstr.*, **50**, 17306 (1956).

(236) L. T. Morin and K. Matsuda (American Cyanamid Co.), U. S. Patent 3,038,928 (1962); *Chem. Abstr.*, **57**, 12329 (1962).



$NCC(=NNHCOR)NH_2$

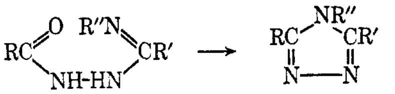
134



$NCC(=NN{=}CRR')NH_2$

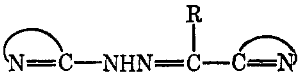
135

Amidrazones and triazoles of the anthraquinone series have been described and used in the production of vat dyes; these include compounds of the types **136** and **137** in which R, R′, and R″ are all aromatic radicals of which at least one is an anthraquinone residue.[110,237]



136 137

More recently amidrazones have found use in photographic processing including masking procedures in color correction processes.[78] Supports coated with silver salt, amidrazones, and a color former are reported to give intense dye images on development.[238] In addition compounds of the type **138** containing amidrazones partly within the heterocyclic ring have been tested as photocopying materials.[239]



138

Aminoguanidine is an important precursor for many useful compounds,[5] among them the plant growth regulator, 3-amino-1,2,4-triazole.[240]

2. *Medicinal*

Amidrazones derived from nicotinic and isonicotinic acids, among others, have been tested for their pharmacological activity.[55,126,241] Pyridine-4-carboxamidrazone is reported to be about half as effective as Isoniazid in its tuberculostatic properties but only about one-half to one-third as toxic. Moreover, the isonicotinamidrazone–rifamycin-O reaction product has been found to be very active against gram positive microorganisms.[242,243]

Pteridine amidrazones or their aldehyde or ketone condensation products have been the subject of several patents as these compounds have diuretic and natiuretic properties.[25,26]

VII. Conclusion

From the foregoing review of amidrazones and closely related compounds, it will be seen that the main emphasis has lain in synthetic work, both in the preparation of the title compounds and in their use as intermediates for further synthesis. There remains, however, large areas of the chemistry of these compounds, particularly regarding their physical properties, which are as yet unexplored and could well repay the attention of some interested research group. It may be that the recent upsurge of interest in these compounds as it appears in the patent literature will stimulate research in this direction.

Acknowledgment. The authors wish to record their thanks to Dr. K. M. Watson of this department for helpful discussions on the review and to Mrs. D. G. Neilson for her help in checking the references.

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(237) A. W. Joyce (American Cyanamid Co.), U. S. Patent 2,967,867 (1961); *Chem. Abstr.*, **55**, 8873 (1961).

(238) Gevaert-Agfa N.V. Netherlands Application 6,509,590 (1960); *Chem. Abstr.*, **64**, 18776 (1966).

(239) Gevaert-Agfa N.V. Netherlands Application 6,605,083 (1966); *Chem. Abstr.*, **66**, 90161 (1967).

(240) C. J. Grundmann and A. Kreutzberger, U. S. Patent, 2,763,661 (1956); *Chem. Abstr.*, **51**, 3669 (1957).

(241) D. Libermann, N. Rist, and F. Grundbach, *Bull. Soc. Chim. Biol.*, **38**, 321 (1946).

(242) P. Sensi, M. T. Timbal, and A. M. Greco, *Antibiot. Chemotherapy*, **12**, 488 (1962); *Chem. Abstr.*, **58**, 1304 (1963).

(243) A. M. Greco, R. Ballotta, and P. Sensi, *Farmaco* (Pavia), *Ed. Sci.*, **16**, 755 (1961); *Chem. Abstr.*, **57**, 12474 (1962).