THE CHEMISTRY OF CARBOHYDRAZIDE AND THIOCARBOHYDRAZIDE

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Contents

I. Introduction

A. GENERAL AND HISTORICAL

Carbohydrazide and its thioanalog are surprisingly late arrivals on the chemical scene, considering their close relationship with urea, the compound most directly associated with the foundation of organic chemistry. The discovery of hydrazine was a prerequisite for that of carbohydrazide: although A. W. Hofmann had prepared *sym*-diphenylhydrazine in 1863, and E. Fischer began his classical researches on phenylhydrazine in 1875, the parent compound, hydrazine, was not known until 1887. T. Curtius (1857–1928), famous for the reaction that bears his name, is no less distinguished as the discoverer of hydrazine, hydrazoic acid, and related nitrogenous compounds, the systematic study of which formed one of the chief interests of his school at Heidelberg at the turn of the last century.

Having continued these investigations over a number of years, Curtius described in 1894[1] and more fully in 1895[2] the results of the hydrazinolysis of derivatives of carbonic acid. In the course of this work, carbohydrazide was obtained by the hydrazinolysis of diethyl carbonate, and was characterized by its conversion into suitable derivatives. Its interaction with ethyl orthoformate, though not correctly interpreted at the time, foreshadowed its applicability in heterocyclic synthesis. The same paper[2] also described the condensation of carbon disulfide with hydrazine to the hydrazine salt of dithiocarbazic acid (*i.e.*, $NH_2NHCSSH$, NH_2NH_2), but stopped short of the final hydrazinolysis stage. It was not until 1908 that R. Stollé,[3] formerly Curtius' assistant, and at that time associate professor at the same university, completed this series of reactions and so discovered thiocarbohydrazide.

Over the years, interest in the chemistry of carbohydrazide and thiocarbohydrazide, though first sporadic, has steadily increased; earlier major studies were undertaken by Wilson and his coworkers at Glasgow, and by Guha and his School at Dacca University, India. More recently, advances have been reported from numerous laboratories: they include the more notable contributions of Audrieth, who carefully reinvestigated and improved thiocarbohydrazide syntheses, of Sandström at Lund, and of Beyer and his coworkers at Rostock, whose main interests were the use of these nitrogenous compounds in heterocyclic synthesis.

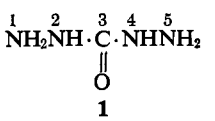
(1) T. Curtius and K. Heidenreich, *Chem. Ber.*, 27, 55 (1894).
(2) T. Curtius and K. Heidenreich, *J. Prakt. Chem.*, [2] **52**, 454 (1895).
(3) R. Stollé and P. E. Bowles, *Chem. Ber.*, 41, 1099 (1908).

In spite of this sustained interest, no systematic review of the chemistry of carbohydrazide and its thioanalog has so far appeared. Two brief summaries of the preparation and simple properties of these compounds formed part of wider surveys[4,5] of related nitrogenous compounds. A short discussion, erroneously reported[4] to deal with thiocarbohydrazides, is in fact concerned with dithiocarbazic acid derivatives.[6]

The present review attempts to provide, in the smallest possible space, a comprehensive and critical account of the chemistry of carbohydrazide and thiocarbohydrazide and all relevant derivatives, excepting only 1,5-dialkyl- (or aryl)-substituted compounds, which have been discussed elsewhere,[7,8] and "Dithizone" (1,2-dehydro-1,5-diphenylthiocarbohydrazide, PhN=NCSNHNHPh), which has been the subject of special treatises of analytical chemistry.[4b] The literature is covered, through *Chemical Abstracts*, to the end of 1966, and by the inclusion of an Appendix, to mid-1967. It is hoped that papers of significance that appeared during the subsequent 18 months have been located in the primary journals, and their content incorporated. The earlier literature concerning carbohydrazide and thiocarbohydrazide contains a good many erroneous structural assignments, particularly of cyclization products, which have been corrected by subsequent work. The preparation of this review has provided an opportunity of reducing some of this confusion by reporting the current state of knowledge, and of indicating some remaining doubtful formulations that are in obvious need of confirmation.

B. NOMENCLATURE AND STRUCTURE

The nomenclature of this class of compounds presents no difficulty. The term carbohydrazide, first suggested by Curtius,[2,3] has served satisfactorily as the generic name for all relevant compounds and is adopted in *Chemical Abstracts*. The conventional mode of numbering this structure (**1**, **2**) provides unambiguous names for all derivatives. Carbohydrazides and their thio analogs[9] are occasionally indexed as carbazides, or carbonohydrazides; according to Curtius[3] the former of these terms should be reserved for N_3CON_3.



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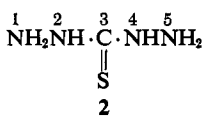
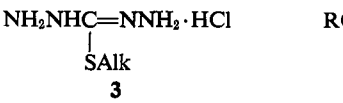


2

The names of S-substituted thiocarbohydrazides follow logically from those of comparable thioureas and thiosemicarbazides. Accordingly, compounds **3** are named S-alkylisothiocarbohydrazides (salts), and their derivatives **4** with aldehydes or ketones are S-alkylisothiocarbohydrazones. The usual mode of numbering is retained, so that **5** is named 1-carbamoyl-S-methylisothiocarbohydrazide.



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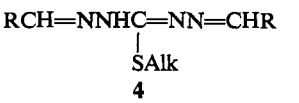

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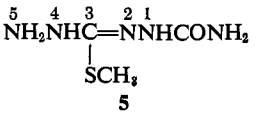
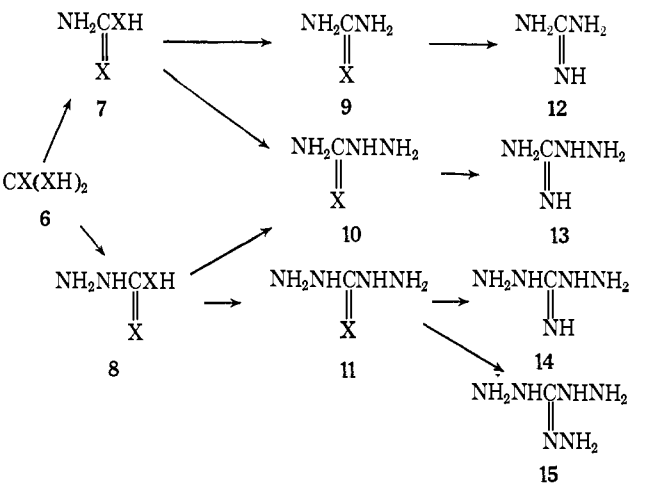


5

Carbohydrazide and thiocarbohydrazide are hydrazine derivatives of carbonic and thiocarbonic acids, **6** (X = O, S), respectively. The sequence in Scheme I illustrates the relationship between a number of relevant carbonic acid derivatives,[10,11] and emphasizes the degree of structural resemblance between the individual members, enabling possible syntheses to be envisaged and properties to be predicted. (Thio)carbohydrazide is seen to be the final member of the structural sequence (thio)urea (**9**), (thio)semicarbazide (**10**), and (thio)carbohydrazide (**11**), and to have, moreover, close links with (thio)carbamic (**7**) and (thio)carbazic acids (**8**), as well as with the aminoguanidines (**12–15**). Attention may be drawn in this connection to two recent comprehensive reviews by Willems of the use of carbon disulfide[12a] and, more particularly, of thiosemicarbazide[12b] in heterocyclic syntheses, which may be read with advantage in conjunction with the present summary.

Scheme I

Interrelation of Carbonic Acid Derivatives



II. Syntheses of Carbohydrazide and Thiocarbohydrazide

Syntheses of carbohydrazide and thiocarbohydrazide of preparative value are exclusively variations of one basic reaction, *viz.* the hydrazinolysis of carbonic and thiocarbonic acid derivatives. The individual variants of this general synthesis differ from one another in their applicability and relative merit and are discussed separately below.

(4) E. E. Reid, "Organic Chemistry of Bivalent Sulphur," Vol. V, Chemical Publishing Co. Inc., New York, N. Y., 1963: (a) p 206; (b) p 283.

(5) C. C. Clarke, "Hydrazine," Mathieson Chemical Corp., Baltimore, Md., 1953, p 75.

(6) J. Sandström, *Svensk Kem. Tidskr.*, 68, 131 (1956).

(7) R. G. Dubenko and P. S. Pelkis, *Zh. Obshch. Khim.*, 33, 290 (1963).

(8) E. P. Nesynov and P. S. Pelkis, *ibid.*, 34, 2672 (1964).

(9) In the following discussion the term "(thio)carbohydrazide" is meant to convey the meaning "carbohydrazide and thiocarbohydrazide" and is used to avoid frequent and cumbersome repetition.

(10) L. F. Audrieth, E. S. Scott, and P. S. Kippur, *J. Org. Chem.*, 19, 733 (1954).

(11) L. F. Audrieth and B. A. Ogg, "The Chemistry of Hydrazine," John Wiley and Sons, Inc., New York, N. Y., 1951, p 213.

(12) (a) J. F. Willems, *Fortschr. Chem. Forsch.*, 4, 554 (1963); (b) *ibid.*, 5, 147 (1965).

A. SYNTHESIS OF CARBOHYDRAZIDE

1. Hydrazinolysis of Carbonate Esters

One of the most practicable syntheses, first described by Curtius[1,2] and later by Kesting,[13,14] is the hydrazinolysis of diethyl carbonate.

$$(C_2H_5O)_2CO + 2N_2H_4\cdot H_2O \longrightarrow NH_2NHCONHNH_2 + 2C_2H_5OH + 2H_2O \quad (1)$$

Detailed directions, based on Kesting's procedure, have appeared in *Inorganic Syntheses*;[15] the volatile by-products are removed as they are formed, and the yields of carbohydrazide (60% crude, 49% pure) are raised (to *ca.* 80%) in a semicontinuous process[15,16] in which the mother liquor is recycled with fresh reagents.

The hydrazinolysis of diphenyl carbonate in aqueous media similarly affords carbohydrazide in satisfactory yields.[14,17] The use of this ester appears to be less advantageous, however, in that hydrazine phenate, the by-product of this particular example, is nonvolatile and must be removed in a separate operation.

2. Hydrazinolysis of Phosgene

Carbohydrazide is formed in high yield as the dihydrochloride by the interaction of phosgene and hydrazine hydrate in refluxing chlorobenzene.[18]

$$ClCOCl \xrightarrow{NH_2NH_2} NH_2NHCOCl \xrightarrow{NH_2NH_2} NH_2NHCONHNH_2$$
$$\mathbf{16} \qquad\qquad \mathbf{1}$$
$$\downarrow ClCOCl$$
$$ClCONHNHCOCl \xrightarrow{NH_2NH_2} NH_2NHCONHNHCONHNH_2$$
$$\mathbf{17} \qquad\qquad \mathbf{18}$$

In an alternative procedure,[19] hydrazine reacts with phosgene *in vacuo* producing carbohydrazide in moderate yield, together with hydrazine dihydrochloride and hydrazidocarbohydrazide (**18**). This hydrazinolysis is likely to proceed in two stages, involving the intermediate acid chloride **16**, which is either directly converted into carbohydrazide (**1**), or may react with phosgene to give the diacid dichloride **17**, and thence the observed hydrazidocarbohydrazide **18**.

The use of hydrazones in this reaction affords dicarbohydrazones directly (*cf.* section IV.F.1).[20] Ethyl carbazinate (NH_2NHCO_2Et) similarly yields 1,5-di(ethoxycarbonyl)carbohydrazide ($EtO_2CNHNHCONHNHCO_2Et$) as expected.[21]

3. Hydrazinolysis of Carbazic Acid[22,23]

Carbazic acid, obtainable by passing carbon dioxide into aqueous hydrazine, forms a salt with hydrazine which is converted quantitatively[23] into carbohydrazide at 140°. The reaction may be regarded as a hydrazinolysis involving the elimination of the elements of water.

$$NH_2NHCOOH\cdot NH_2NH_2 \longrightarrow NH_2NHCONHNH_2 + H_2O$$

4. Miscellaneous Reactions

a. Hydrazinolysis of Cyanuric Acid

A recent patent[24] claims the production of carbohydrazide by the hydrazinolysis of cyanuric acid. Thus, prolonged refluxing of the reactants, and partial evaporation and dilution with ethanol, is reported to afford pure carbohydrazide in 71% yield.

b. Hydrolysis of Tri(benzylideneamino)guanidine[25]

Treatment of tri(benzylideneamino)guanidine with boiling dilute hydrochloric acid yields carbohydrazide (isolated as the benzylidene derivative), among other products. The provisional report[25] does not appear to have been followed up by further work.

B. SYNTHESIS OF THIOCARBOHYDRAZIDE

In their efforts to provide a satisfactory synthesis of thiocarbohydrazide, Audrieth and his coworkers[10] undertook a thorough and critical reappraisal of the existing methods (reported up to 1954). In general, the published procedures[3,26–28] (eq 2–5) needed to be modified in order to produce satisfactory yields of pure material.

$$ClCSCl + 2NH_2NH_2 \longrightarrow NH_2NHCSNHNH_2 + 2HCl \quad (2)$$

$$CS_2 + 2NH_2NH_2 \longrightarrow [NH_2NHCSSH\cdot NH_2NH_2] \longrightarrow NH_2NHCSNHNH_2 + H_2S \quad (3)$$
$$\mathbf{19}$$

$$ROCSSR + 2NH_2NH_2 \longrightarrow NH_2NHCSNHNH_2 + ROH + RSH \quad (4)$$
$$\mathbf{20}$$

$$RSCSSR + 2NH_2NH_2 \longrightarrow NH_2NHCSNHNH_2 + 2RSH \quad (5)$$
$$\mathbf{21}$$

Effective methods of synthesizing thiocarbohydrazide now available include modifications of the above routes (eq 2–5) as well as additional novel methods.

1. Hydrazinolysis of Thiophosgene[3,26]

Like its oxygen analog, thiophosgene readily undergoes hydrazinolysis. Thiocarbohydrazide is thus formed both in ether[3] or in aqueous media[26] in satisfactory yield.

2. Hydrazinolysis of Carbon Disulfide

The reaction of hydrazine with carbon disulfide (eq 3) is no doubt the cheapest and most useful method for the preparation

(13) W. Kesting, *Chem. Ber.*, **57**, 1321 (1924).
(14) W. Borsche, W. Müller, and C. A. Bodenstein, *Ann.*, **475**, 120 (1929).
(15) E. B. Mohr, J. J. Brezinski, and L. F. Audrieth, *Inorg. Syn.*, **4**, 32 (1953).
(16) Brazaitis and Tarika, "Chemical Engineering Progress Reports," University of Illinois, 1949, quoted in ref 15.
(17) P. Cazeneuve and P. Moreau, *Compt. Rend.*, **129**, 1254 (1899).
(18) T. Lieser and G. Nischk, *Chem. Ber.*, **82**, 527 (1949).
(19) O. Glemser, H. Weber, and H. Duyster, *Z. Anorg. Allgem. Chem.*, **286**, 205 (1956).
(20) P. W. West and J. Warkentin, *J. Org. Chem.*, **33**, 2089 (1968).
(21) D. N. Majumdar and P. C. Guha, *J. Indian Chem. Soc.*, 10, 692 (1933).
(22) R. Stollé and K. Hofmann, *Chem. Ber.*, 37, 4523 (1904).
(23) F. Fichter and B. Becker, *ibid.*, 44, 3481 (1911).
(24) C. S. Argyle (to Whiffen and Sons Ltd.), U. S. Patent 3,258,485 (1966); *Chem. Abstr.*, **65**, 7067 (1966).
(25) R. Stollé, *Chem. Ber.*, **37**, 3548 (1904).
(26) W. Autenrieth and H. Hefner, *ibid.*, **58**, 2151 (1925).
(27) P. C. Guha and S. C. De, *J. Chem. Soc.*, **125**, 1215 (1924).
(28) N. Petri, *Z. Naturforsch.*, 16B, 769 (1961); see also S. M. Losanitch, *J. Chem. Soc.*, **121**, 2542 (1922).

of thiocarbohydrazide in quantity. The isolation and subsequent decomposition of the intermediate hydrazinium dithiocarbazinate **19**[3] may be dispensed with; direct interaction of carbon disulfide and a three-molar excess of aqueous hydrazine hydrate at the boiling point and periodic removal of thiocarbohydrazide gave approximately 60% yields of product.[9,29,30] In any large scale operation the excess of hydrazine could presumably be recovered, or recycled in a suitable continuous process (compare section II.A.1).

A modification of this method, in which the intermediate **19** is isolated and thermally decomposed, is claimed to afford thiocarbohydrazide in yields of the order of 70%.[28] However, the obviously dangerous nature of this procedure is a serious drawback: after thermolysis, rapid cooling is essential to minimize the risk of explosions.

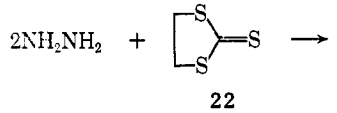
3. *Hydrazinolysis of Diethyl Xanthate*

The hydrazinolysis of diethyl xanthate (**20**; R = C_2H_5) is a possible route to thiocarbohydrazide (eq 4). An early procedure, employing ethanol as solvent,[27] has been found to be unsuitable,[9] but aqueous media at room temperature promote the production of thiocarbohydrazide in high yield.[9] At slightly higher temperatures (*ca.* 50°), 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole[31] is formed as a by-product, presumably by the further interaction of hydrazine and thiocarbohydrazide, a reaction that is known to form this heterocyclic product under these conditions.[3] The use of solvents may indeed be entirely dispensed with; thus, by merely warming the two reactants,[32] high yields of thiocarbohydrazide are claimed to be obtainable; the effluent gases, ethanol and ethanethiol, are ignited as they leave the reaction vessel.

4. *Hydrazinolysis of Dialkyl Trithiocarbonates*

Hydrazine and dialkyl trithiocarbonates (**21**; R = Alk) interact in ethanol with elimination of alkanethiol to give thiocarbohydrazide in good yield (eq 5).[33] The reaction is of course strictly analogous to the corresponding hydrazinolysis of diethyl xanthate (eq 4).

In an extension of this reaction, cyclic trithiocarbonates[34] are used as starting materials; thus, ethylene trithiocarbonate (**22**) affords, on treatment with 2 moles of hydrazine hydrate in boiling ethanol, pure thiocarbohydrazide in 71% yield.



$$2NH_2NH_2 + \text{(22)} \longrightarrow NH_2NHCSNHNH_2 + HSCH_2CH_2SH \quad (6)$$

5. *Hydrazinolysis of Methyl Dithiocarbazinate*

The hydrazinolysis of methyl dithiocarbazinate (**23**) in boiling ethanol (45 min for 0.2 *M* scale) produces thiocarbohydrazide in 65% yield.[10]

$$NH_2NH_2 + \underset{\textbf{23}}{NH_2NHCSSCH_3} \longrightarrow NH_2NHCSNHNH_2 + CH_3SH + H_2O \quad (7)$$

III. Physical Properties of Carbohydrazide and Thiocarbohydrazide

Carbohydrazide is a white crystalline solid melting with decomposition at 153–154°.[15] Its density is 1.616[35] (measured at −5°). It is very soluble in water, practically insoluble in the usual organic solvents,[1,15] and sparingly so in dimethylformamide and dimethyl sulfoxide.[36] The pH of a 1% aqueous solution is approximately 7.4.[15]

The dipole moment of carbohydrazide has been calculated to be 4.99 D,[37] special allowance being made to account for the modification of bond moments due to induction along polarizable bonds.[38] A polarographic study of carbohydrazide is available.[39]

Thiocarbohydrazide is a white, crystalline solid, melting with decomposition at 168°.[3,27,40] It may be recrystallized from water; its solubility in a number of solvents is shown in Table I.

Table I

Solubilities of Thiocarbohydrazide

Solvent	*Temp, °C*	*Solubility, g/100 g*
Water	0	0.18
Water	24.7	0.55
Ethanol	24.7	0.26
Chloroform	24.7	0.05
Carbon tetrachloride	24.7	0.03
Hydrazine hydrate	24.7	13.60

Thiocarbohydrazide is almost completely nonhygroscopic.[10] When the compound was stored during 7 days in desiccators containing saturated solutions of salts ($CaCl_2$, KSCN, NH_4Cl, $ZnSO_4$) producing known relative humidities (32–90%), the weight increases were negligible.

A half-cell potential discharge curve for thiocarbohydrazide in aqueous 1.44 *M* sodium hydroxide has been determined.[41]

The electrophoretic behavior of thiocarbohydrazide on paper wetted with buffer solutions containing silver nitrate has been examined.[42] Differences in mobility were recorded due to changes in pH and the silver ion concentration.

The ir spectrum of carbohydrazide is recorded in Sadtler's Standard Spectra Catalogue;[43] it has certain characteristics in common with that of thiocarbohydrazide[36] which includes the following major peaks (with suggested assignments in paren-

(29) L. F. Audrieth and P. S. Kippur (to University of Illinois Foundation), U. S. Patent 2,726,263 (1955); *Chem. Abstr.*, **50**, 10128 (1956).
(30) Olin Mathieson Chemical Corp., British Patent 754,756 (1956); *Chem. Abstr.*, **51**, 8782 (1957).
(31) E. Hoggarth, *J. Chem. Soc.*, 4817 (1952).
(32) H. Beyer, W. Lässig, and U. Schultz, *Chem. Ber.*, **87**, 1401 (1954).
(33) J. Sandström, *Arkiv Kemi*, **4**, 297 (1952).
(34) R. Mayer and K. Schäfer, *J. Prakt. Chem.*, **26**, 279 (1964).
(35) G. Beck, *Wien Chemiker-Ztg.*, **46**, 18 (1943); *Chem. Abstr.*, **39**, 4593 (1945).
(36) F. Kurzer and M. Wilkinson, unpublished work.
(37) B. S. S. Rao and S. Soundararajan, *Proc. Indian Acad. Sci.*, **50A**, 149 (1959).
(38) R. P. Smith, T. Ree, J. L. Magee, and H. Eyring, *J. Am. Chem. Soc.*, **73**, 2263 (1951).
(39) M. Fedoroňko, O. Manoušek, and P. Zuman, *Chem. Listy*, **49**, 1494 (1955); *Chem. Abstr.*, **50**, 79 (1956).
(40) R. Stollé and E. Gaertner, *J. Prakt. Chem.*, **132**, 209 (1931).
(41) R. Glicksman, *J. Electrochem. Soc.*, **110**, 353 (1963).
(42) S. Shuzuki and W. Takahashi, *Denki-Kagaku*, **33**, 13 (1965); *Chem. Abstr.*, **65**, 9783 (1966).
(43) Sadtler's Standard Spectra Catalogue, No. 5701, Sadtler Research Laboratories Inc., Philadelphia, Pa.

theses): 3280 s, 3200 s (NH); 1645 s (NH_2 deformation); 755 s (NH bending); 1530 s, 1285 s, 1140 s, 1015 s, and 935 s cm^{-1}.

The ir spectra of seven dicarbohydrazones [RCH=NNHCONHN=CHR; R = C_6H_{13} to $C_{11}H_{23}$] have been described and discussed[44] and their similarity with those of secondary amides noted. They show strong absorption, due to NH stretching, at 3260–3240 cm^{-1}, with a weaker overtone at 3100–3090 cm^{-1}. The "double-bond region" (1700–1500 cm^{-1}) contains four bands; of these, the strong peak at 1670–1660 cm^{-1} is attributed to C=O stretching vibration, that at 1560–1550 cm^{-1} to CNH vibration, and that at 1610–1600 cm^{-1} to C=N stretching vibration. A weak band in the 1635-cm^{-1} region may be due to a N–C–N stretching vibration.[44] Further peaks appear at 1240–1235 and 725 cm^{-1}, for which assignments were suggested.[44] The ir spectra of dicarbohydrazones derived from aromatic aldehydes and simple ketones resembled those described above, but were not fully specified.[44]

Information on the ir spectrum of 1,5-bis(methylcarbamoyl)carbohydrazide [$(MeNHCONHNH)_2CO$] is also on record.[45]

IV. Chemical Properties of Carbohydrazide and Thiocarbohydrazide

The chemical behavior of carbohydrazide and thiocarbohydrazide shows the obvious general similarities to be expected from their very close structural relationship. However, although many reactions are common to both compounds, certain properties are shown exclusively by one or the other, or have been investigated more fully for one particular analog. In general, the greater chemical versatility of the thiono group, compared with that of the keto group, is responsible for the more varied behavior of thiocarbohydrazide.

In the following pages, the chemical properties of the oxygen and sulfur analog are described side by side; it is hoped that in this way the large body of information can be dealt with most concisely and appropriate comparisons made most conveniently.

A. THERMOLYSIS

Both carbohydrazide and thiocarbohydrazide decompose at their melting point,[3,27,40] the latter with loss of ammonia and hydrogen sulfide.[27] The decomposition of thiocarbohydrazide sets in at temperatures considerably below its melting point (*e.g.*, 110°), with speeds that increase to a constant rate after 6 days, resulting in a 24.5% loss in weight after 14 days.[10]

B. ACIDIC AND BASIC PROPERTIES

Carbohydrazide is a diacid base forming a mono-[15] and dihydrochloride,[1,18] sulfate,[1] and oxalate.[15] Unlike the sulfate and oxalate, the hydrochlorides are highly water soluble.[15] The salts formed with nitric and phosphoric acids[15,46] have not been isolated in a crystalline form. Thiocarbohydrazide, incorporating both acidic and basic functions in its structure, is amphoteric, being soluble both in dilute bases and acids. However, quantitative measurements of the acidity and basicity have apparently not been made. The pH of a saturated solution of thiocarbohydrazide in carbon dioxide-free water is 6.95. This slight *acid* character may be ascribed, as in analogous examples, to the mobile hydrogen atom adjacent to the thiocarbonyl group permitting the formation of the acidic mercapto function in the iso form

$$NH_2NHC(=S)NHNH_2 \rightleftharpoons NH_2N{=}C(SH)NHNH_2$$

Thiocarbohydrazide also behaves as a diacid *base*, forming a dihydrochloride and a monosulfate, the composition of which was established by titration in aqueous solution.[10]

The preparation of thiocarbohydrazide salts requires carefully controlled conditions.[47] The sulfate is obtainable on a scale (1–2 g) in approximately 50% yields by dissolving thiocarbohydrazide in hot glacial acetic acid, supercooling the liquid, and then adding a solution of sulfuric acid in acetic acid. On a larger scale, longer heating is required to dissolve the thiocarbohydrazide; this results in its reaction with acetic acid, and cyclization to 4-amino-3-methyl-5-mercapto-1,2,4-triazole (see section IV.G.1), before the sulfuric acid has been added. However, the sulfate is obtainable in bulk in 95% yield when cold sulfuric acid is added to a suspension of thiocarbohydrazide in glacial acetic acid.[47]

C. HYDROLYTIC REACTIONS

Carbohydrazide is somewhat unstable in acid and alkaline solution.[1] Prolonged treatment with these reagents cleaves the molecule into carbon dioxide and hydrazine.

D. REDUCTION AND OXIDATION

1. Reduction

Carbohydrazide is catalytically hydrogenated over Raney nickel at low pressure to semicarbazide and ammonia[48] (eq 8). In contrast, other methods of reduction are ineffective in bringing about this reaction. Prolonged hydrogenation (24 hr)

$$NH_2NHC(=O)NHNH_2 + H_2 \longrightarrow NH_2NHC(=O)NH_2 + NH_3 \quad (8)$$

causes no further change, showing that semicarbazide is resistant to hydrogenation under these conditions. This difference in behavior toward hydrogenation of carbohydrazide and semicarbazide agrees with the order of their relative acidity.[48] Regarded as the addition of electrons, the reduction should proceed more readily in the case of the more acidic of the two compounds. A comparison of the acidities in liquid ammonia by the method of McEwen[49] showed carbohydrazide to be indeed a stronger acid than semicarbazide.

2. Oxidation

Carbohydrazide is oxidized by Fehling's solution in the cold.[1] Sodium hypochlorite causes oxidation in both neutral and alkaline media.[50] In neutral solution the reaction occurs vigorously and exothermically with evolution of carbon dioxide and nitrogen, probably according to eq 9. Its exact mecha-

(44) D. M. Wiles and T. Suprunchuck, *Can. J. Chem.*, **46**, 701 (1968).
(45) C. M. Kraebel, S. M. Davis, and M. J. Landon, *Spectrochim. Acta*, **23A**, 2541 (1967).
(46) Beck, Thesis, University of Illinois, 1948, quoted in ref 15.
(47) H. Beyer and C. F. Kröger, *Ann.*, **637**, 126 (1960).
(48) A. H. Corwin and J. D. Reinheimer, *J. Am. Chem. Soc.*, **73**, 11 4 (1951).
(49) W. K. McEwen, *ibid.*, **58**, 1124 (1936).
(50) F. Fehér and K. H. Linke, *J. Prakt. Chem.*, **32**, 190 (1966).

nism is not known, but the intermediate formation of an N-chlorocarbohydrazide is ruled out by the absence, in the uv spectrum, of absorption bands between 2000 and 3000 Å, characteristic of N–Cl compounds.[51]

$$NH_2NHCONHNH_2 + 4OCl^- \longrightarrow 2N_2 + CO_2 + 3H_2O + 4Cl^- \quad (9)$$

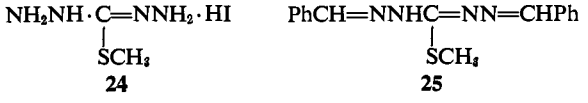
Oxidation by alkaline hypochlorite proceeds vigorously, apparently also according to eq 9, but slackens after the addition of half the calculated quantity of the oxidant, as shown by the slower evolution of gas. This has been ascribed to the intermediate formation of hydrazine (isolable as its salicaldehyde derivative), but the mode of its formation in this reaction is not clear.

Thiocarbohydrazide is also oxidized by sodium hypochlorite in neutral or alkaline medium. This oxidation, which occurs vigorously with evolution of gas[50] and the production of repulsive odors, has not been studied closely and its course remains obscure.

Thiocarbohydrazide is oxidized by ammoniacal silver nitrate in the cold, and by ferric chloride or iodine with evolution of nitrogen.[27]

E. S-ALKYLATION OF THIOCARBOHYDRAZIDE

Like analogous thioamido compounds such as thiourea or thiosemicarbazide, thiocarbohydrazide is S-alkylated readily by the usual methods. Thus, S-methylisothiocarbohydrazide is rapidly formed from thiocarbohydrazide and methyl iodide in ethanol in 80% yield and advantageously isolated as the highly crystalline hydriodide **24**.[52] The compound has been characterized by analysis of the hydriodide and picrate, and by its conversion into the dibenzaldehyde derivative **25**. In contrast, no O-alkylisocarbohydrazides appear to be on record so far (but see sections V.A.1 and VI.A.1).

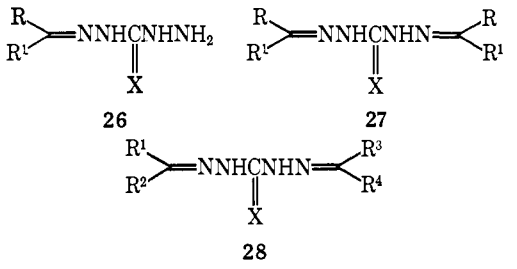


24 **25**

S-Alkylisothiocarbohydrazides are presumably stronger bases than the nonalkylated parent compound, but no quantitative information is available. Their reactions with hydrazine and with aliphatic carboxylic acids have been studied in some detail and are discussed in the appropriate sections below (IV.P and IV.G.3).

F. CONDENSATION WITH CARBONYL COMPOUNDS

Both hydrazine groups of (thio)carbohydrazide display normal reactivity toward carbonyl compounds and give rise to a large variety of crystalline mono- and dihydrazones. In general, the diaddition products (**27**) are formed so rapidly that the monoadducts (**26**) are only obtainable under specially controlled conditions.



26 **27**

28

1. Simple Mono- and Dicarbohydrazones

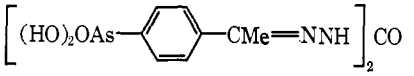
The preparation of 1,5-dicarbohydrazones (**27**, X = O) is straightforward[2,14,44,53–55] and need not be commented upon further. A list of monocarbohydrazones (**26**, X = O)[36,53,56–59] that have been described is given in Table II. Attempts to repeat the preparation of the monobenzophenone derivative under a variety of conditions were unsuccessful.[36]

Table II

Monocarbohydrazones

Carbonyl compound	*Ref*
Acetone	36
Acetophenone	53
Benzaldehyde	53
p-Nitrobenzaldehyde	36
p-Methoxybenzaldehyde	36
Benzil	53
Benzophenone	53
Diacetyl	53
5-Nitrofurfural	56–59

A number of 1,5-dicarbohydrazones (*e.g.*, **29**) have been prepared from arsenic-containing carbonyl compounds,[60] such as *p*-acetophenonearsonic acid.



29

A number of *unsymmetrical* 1,5-dicarbohydrazones (**28**, X = O) have been obtained using a monocarbohydrazone as starting material.[20,36,53] For example, 1-(5′-nitrofurfurylidene)carbohydrazide (**26**, R = H, R′ = 5-nitrofurfuryl) has been condensed with a large number of carbonyl compounds to give unsymmetrical dihydrazones **28**.[56,58,59]

1,5-Dibenzophenone carbohydrazone (**32**) is formed, together with other products (**31**, **34**), in the interaction at

(51) E. Colton, M. M. Jones, and L. F. Audrieth, *J. Am. Chem. Soc.*, 76, 2572 (1954).

(52) E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, 19, 1231 (1954).

(53) A. C. Brown, E. C. Pickering, and F. J. Wilson, *J. Chem. Soc.*, 107 (1927).

(54) A. M. Munro and F. J. Wilson, *ibid.*, 1257 (1928).

(55) J. Szmuszkovicz and M. E. Greig, *J. Med. Pharm. Chem.*, 4, 259 (1961).

(56) R. G. Haber, U. S. Patent 3,231,570 (1966); *Chem. Abstr.*, 64, 9685 (1966).

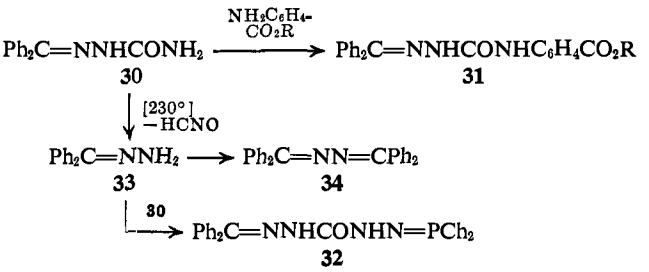
(57) P. Koschucharov and T. Harisanova, *Pharmazie*, 15, 492 (1960).

(58) R. G. Haber (to ABIC Chemical Laboratories Ltd.), Belgian Patent 618,951 (1962); *Chem. Abstr.*, 58, 11334 (1963).

(59) ABIC Chemical Laboratories Ltd., British Patent 959,130 (1964); *Chem. Abstr.*, 61, 9467 (1964).

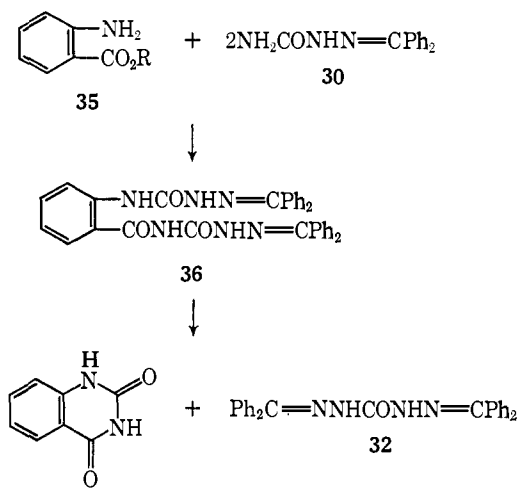
(60) A. Albert, German Patent 463,313 (1928); *Chem. Abstr.*, 22, 4128 (1928).

high temperatures of benzophenone semicarbazone (**30**) and arylamines.[61] The dicarbohydrazone **32** is in fact likely to arise



(**30** → **33** → **32**) from the thermolysis of the semicarbazone **30** itself; decompositions of this type are known.[62]

An alternative mechanism, outlined below, may be operative in the reaction involving *o*-amino compounds, the benzouracil **37** being one of the products of the reaction.



Dibenzophenonecarbohydrazone (**32**) has also been prepared[20] by a third route, based on a standard synthesis of the parent compound (see section II.A.2), by condensing the preformed monobenzophenone hydrazone with phosgene.

$$2Ph_2C{=}NNH_2 + COCl_2 \longrightarrow Ph_2C{=}NNHCONHN{=}CPh_2 + 2HCl$$

32

Reaction proceeds in pyridine at 0° in high yield. The use of an excess of phosgene is to be avoided, since it reacts further with the product **32** to yield water-soluble unidentified substances. The route is superior, in this instance, to the direct interaction of benzophenone and carbohydrazide and is no doubt widely applicable.[20]

2. *Simple Mono- and Dithiocarbohydrazones*

Thiocarbohydrazide reacts readily with two molar proportions of aldehydes and ketones to yield 1,5-bisthiocarbohydrazones (**27**, X = S).[20,27,63–67] These are usually highly crystalline and have been suggested[65] to be useful for characterizing aldehydes and ketones. In certain cases, however, there is a distinct difference in the reactivity of the first and second hydrazine groups of thiocarbohydrazide toward carbonyl compounds. The dihydrazones derived from acetone, acetophenone, and dibenzyl ketone are formed only after prolonged boiling using an excess of ketone.[64]

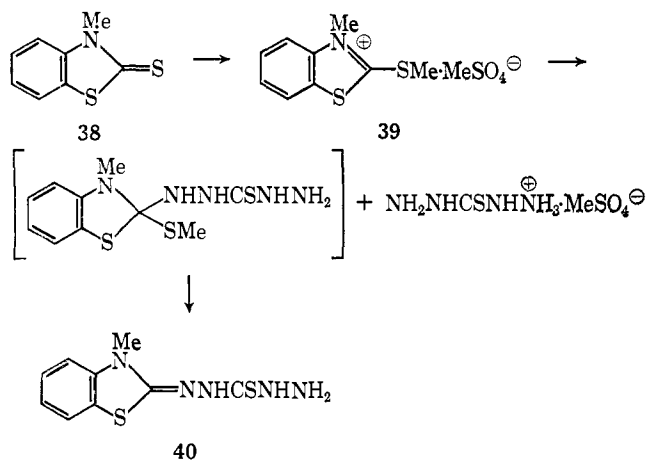
An effective method for the preparation of monothiocarbohydrazones (**26**, X = S), based on a previous report by Stollé,[40] has been developed by Sandström:[68] a 50% excess of the aldehyde or ketone in ethanol is added to a warm solution of thiocarbohydrazide in 1 *N* acetic acid; the product separates quickly on cooling. Table III shows the derivatives that have been prepared by this method.[40,68,69] Applied to the preparation of 1-isopropylidene-*carbo*hydrazide the procedure gave only the di-carbohydrazone.[36]

Table III

Monothiocarbohydrazones (26, X = S)

R	R_1	*Mp*, °C	*Ref*
Ph	H	193	40
Me	Me	195	68
Me	Ph	170	68
Cyclohexylidene		166	68
Ph	Ph	213	69

A novel route to a monothiocarbohydrazone is the treatment of the benzthiazolium salt **39** (obtained by quaternization of the benzthiazole **38**) with thiocarbohydrazide in aqueous solution at 80°.[70] Nucleophilic displacement of the methylthiol group (of **39**) yields 1-(3′-methylbenzthiazol-2′-ylidene)thiocarbohydrazide (**40**) as shown.

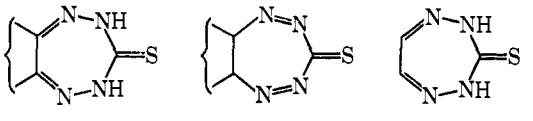


3. *Condensation with* ortho *Diketones*

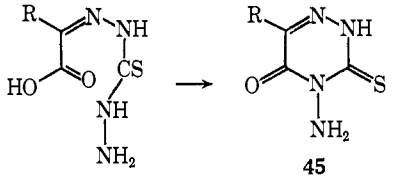
The condensation of (thio)carbohydrazide with cyclic *ortho* diketones was investigated in 1926–1928 by Guha[63] and De.[71] The reaction may be subdivided into two groups, initiated respectively by the primary formation of mono- or 1,5-

(61) F. J. Wilson and A. B. Crawford, *J. Chem. Soc.*, 127, 103 (1925).
(62) W. Borsche and C. Merkwitz, *Chem. Ber.*, 37, 3177 (1904).
(63) P. C. Guha and S. C. De, *J. Indian Chem. Soc.*, 2, 225 (1926).
(64) H. W. Stephen and F. J. Wilson, *J. Chem. Soc.*, 2531 (1926).
(65) N. P. Buu-Hoi, T. B. Loc, and N. D. Xuong, *Bull. Soc. Chim. France*, 694 (1955).
(66) W. Ried and G. Oertel, *Ann.*, **590**, 136 (1954).
(67) C. Runti, *Ann. Chim.* (Rome), **46**, 731 (1956).
(68) J. Sandström, *Acta Chem. Scand.*, 14, 1037 (1960).
(69) J. Sandström, *ibid.*, 14, 1939 (1960).
(70) R. Riemschneider, B. Böttcher, and S. Georgi, *Monatsh.*, **91**, 630 (1960).
(71) S. C. De, *J. Indian Chem. Soc.*, **5**, 373 (1928).

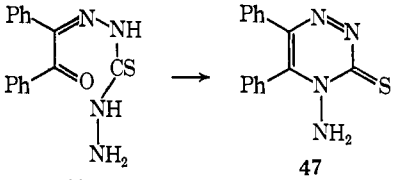
dihydrazones. Thus, thiocarbohydrazide reacts with 1 molar equiv of benzil, acenaphthaquinone, camphorquinone, or alloxan in acetic acid to give unspecified yields of products formulated as seven-membered rings **41**. Adequate evidence for the correctness of the suggested structures was not provided. The products were insoluble in base, suggesting the absence of a thioureido group (–NHCSNH–); structure **42** was therefore proposed as being in better agreement with this observation. The bisulfite compound of glyoxal similarly condenses with thiocarbohydrazide yielding the parent compound **43** of this series,[63,71] which is alkali soluble. Remembering the general tendency of thiocarbohydrazide to yield N-amino compounds in ring closures [*e.g.*, its condensation with α-ketocarboxylic acids to *as*-triazines **45** (*cf.* section



41 42 43



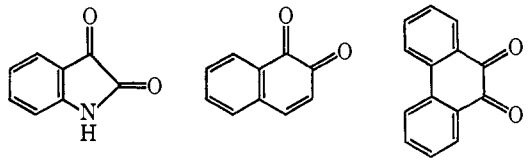
44 45



46 47

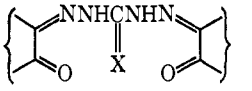
IV.H)], it would seem feasible that the present condensation with α-diketones proceeds in fact analogously, yielding the alkali-insoluble *as*-triazines (*e.g.*, **47**) by way of intermediates of type **46**.

In the second group of reactions, (thio)carbohydrazide condenses with an excess of the *ortho* diketones isatin (**48**), β-naphthaquinone (**49**), and phenanthraquinone (**50**) to produce dihydrazones.[63,71] Since these compounds are



48 49 50

insoluble in alkali, Guha and De[63] favored structure **52** over **51**, in accordance with the views of Liebermann,[72] who accounted for the insolubility in alkalis of azonaphthol dyes, *e.g.*, **53** by assigning to them the structure **54**. However, more recent spectroscopic studies[73–75] have shown that this insolubility is in fact due to strong hydrogen bonding (*e.g.*, **55**, **55a**). Furthermore, benzil monophenylhydrazone is found[76] to be extremely resistant to acetylation, even under very severe conditions. This observation again suggests the existence of a hydrogen-bonded structure of type **56**, and this is supported by the ir data.



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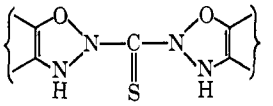
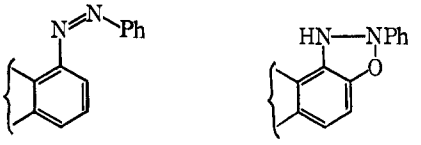
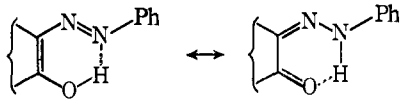


52

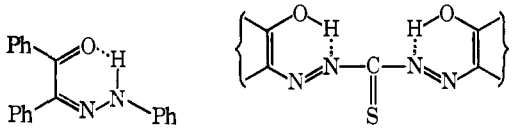
In the light of this evidence the dihydrazones **51** could well be rewritten as **57**, accounting for their insolubility in alkali by chelation of their hydroxyl group. Isatin (**48**) may behave exceptionally in this respect, since only its 3-carbonyl group reacts normally to form hydrazones, the other being an amide function.[77] Thus, isatin dihydrazone may be represented as **58**, with "reverse" hydrogen bonding.



53 54



55 55a



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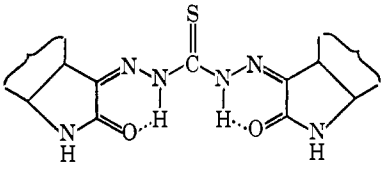


58

The condensation of (thio)carbohydrazide with phenanthraquinone has been extended to a number of bromo- and nitro-substituted phenanthraquinones.[71] (Table IV). In formulating

Table IV

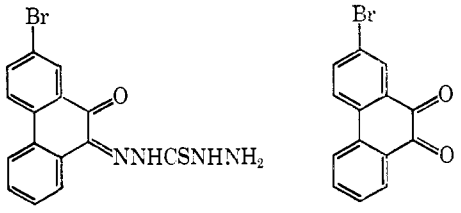
Phenanthraquinone Di(thio)carbohydrazones (61, X = O or S)

1	R_2 = Br	R_4 =	R_5 = R_7 = H	
2	R_2 = R_7 = Br		R_4 = R_5 = H	
3	R_2 = NO_2	R_4 =	R_5 = R_7 = H	
4	R_4 = NO_2	R_2 =	R_5 = R_7 = H	
5	R_4 = R_5 = Br		R_2 = R_7 = H	
6	R_4 = R_5 = NO_2		R_2 = R_7 = H	
7	R_2 = R_7 = NO_2		R_4 = R_5 = H	

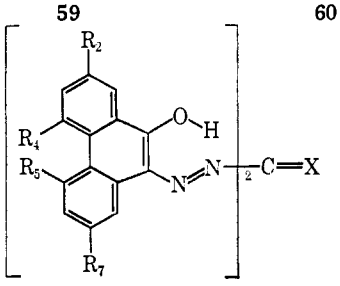
their products (as **61**), the authors disregarded the possible formation of isomeric products from unsymmetrically sub-

(72) C. Liebermann, *Chem. Ber.*, **16**, 2858 (1883).
(73) D. Hadži, *J. Chem. Soc.*, 2143 (1956).
(74) K. J. Morgan, *ibid.*, 2151 (1961).
(75) V. Bekárek, K. Rothschein, P. Vetesnik, and M. Večera, *Tetrahedron Letters*, 3711 (1968).
(76) H. El-Khadem, Z. M. El-Shafei, and M. M. Hashem, *J. Chem. Soc., C*, 949 (1968).
(77) E. H. Rodd, Ed., "The Chemistry of Carbon Compounds," Vol. IVA, Elsevier Publishing Co., New York, N. Y., 1957, p 106.

stituted diketones; the intermediate condensation product **59** may obviously react with *either* of the two carbonyl groups of a further molecule of diketone (*e.g.*, **60**), so that two possible structural isomers may clearly arise.



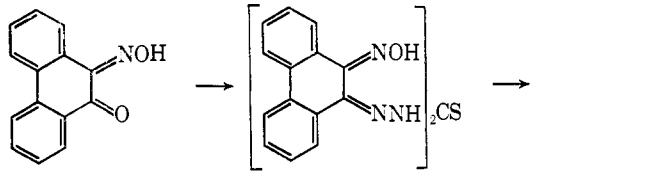
59 **60**



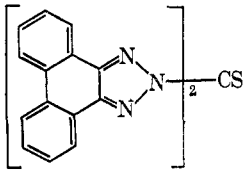
61

4. *Condensation with Monoximes of Cyclic ortho Diketones*

The condensation of (thio)carbohydrazide with monoximes of various cyclic *ortho* diketones is reported to yield bis(triazolyl) (thio)ketones[63] (*e.g.*, **64** from phenanthraquinone monoxime (**62**)), but structural proofs were not provided. In the case of isatin monoxime, the acyclic intermediate of type **63** was isolated and ring-closed with concentrated hydrochloric acid in a sealed tube. As in the corresponding experiments involving diketones (*cf.* section IV.F.3 above), a number of bromo- and nitrophenanthraquinone monoxime derivatives were also prepared.[71]



62 **63**



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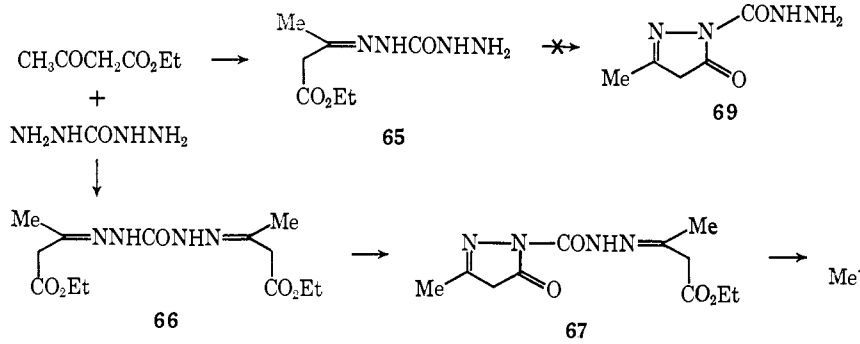


65 **66** **67** **68** **69**

5. *Condensation of Carbohydrazide with Acetylacetone and Ethyl Acetoacetate*

The action of acetylacetone on carbohydrazide in boiling ethanol results in unspecified yields of 3,5-dimethylpyrazole;[53] *i.e.*, the product also formed directly from hydrazine. No further details concerning the course of the reaction were given.

The reaction between carbohydrazide and ethyl acetoacetate yields, apart from the expected mono- and dihydrazones **65** and **66**, the cyclized products **67** and **68**. The structural assignments were based entirely on analytical results.[54]

Equimolar quantities of the reactants afforded the monohydrazone **65** exclusively. The use of 2 moles of ester gave a mixture of the dihydrazone **66** and *either* the monocylic product **67** *or* the dicyclic product **68**. The pyrazolylcarbohydrazide **69** was not obtained.

6. *Reactions of (Thio)carbohydrazones*

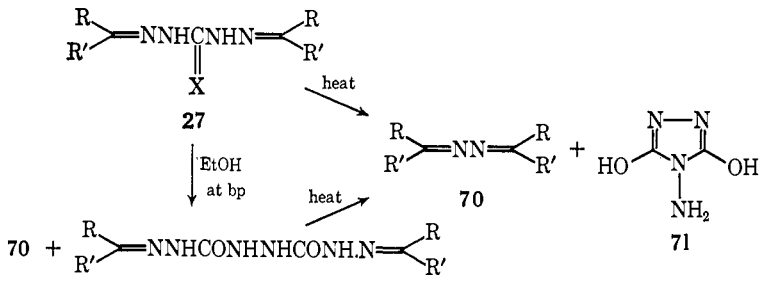
Mono(thio)carbohydrazones (**26**, X = O, S), retaining the essential structural features of (thio)carbohydrazide, resemble their parent compounds in their general chemical behavior. A number of strictly comparable reactions are therefore described in the appropriate sections dealing with (thio)carbohydrazide. A few reactions that show no such obvious resemblance (particularly those of the fully blocked di(thio)carbohydrazones (**27**, X = O, S)) are described more conveniently immediately below. The infrared spectra of certain dicarbohydrazones are dealt with in section III.

a. Thermal Decomposition

The thermolysis of di(thio)carbohydrazones appears to proceed in stages, depending on the conditions. Boiling ethanol has no effect on dithiocarbohydrazones[78] (**27**, X = S) but causes the oxygen analogs **27** (X = O) to disproportionate to azines **70** and hydrazidicarbohydrazones **72**.[53,54] Dicarbohydrazones **27** (X = O) decompose above their melting points,[53] yielding 4-aminourazole (**71**) and the corresponding azine **70**. The sulfur analogs undergo more extensive decomposition, azines **70** being the only products isolated.[78]

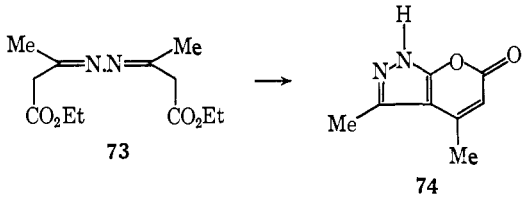
Hydrazidicarbohydrazones **72** (R = Ph, Me, H; R′ = H, Me, *t*-Bu) decompose above their melting points to the same products, **70** and **71**, as the dicarbohydrazones **27** (X = O), and are therefore regarded as intermediates in the thermolysis of the latter.[54] The parallel behavior of the unsubstituted parent hydrazidicarbohydrazide **72** (R = R′ = H), yielding 4-aminourazole (**71**) and the azine **70** (R = R′ = H), supports this view.

(78) H. W. Stephen and F. J. Wilson, *J. Chem. Soc.*, 1415 (1928).



27 72

The thermolysis of monocarbohydrazones closely resembles that of the dicarbohydrazones. Thus, 1-benzylidenecarbohydrazide (**26**, R = Ph; R′ = H; X = O) at its melting point yields 4-aminourazole (**71**) and benzylidene azine (**70**, R = Ph; R′ = H), and decomposes in refluxing toluene to hydrazidicarbohydrazide **72** and the azine **70**.[53] Monoethyl acetoacetate carbohydrazone follows the general reaction pattern, but yields in addition the pyrazolopyrone **74** as a decomposition product of the substituted azine **73**.[54] The thermolysis of thiocarbohydrazones **26** (X = S) has apparently not been studied.



73 74

b. Reduction and Oxidation

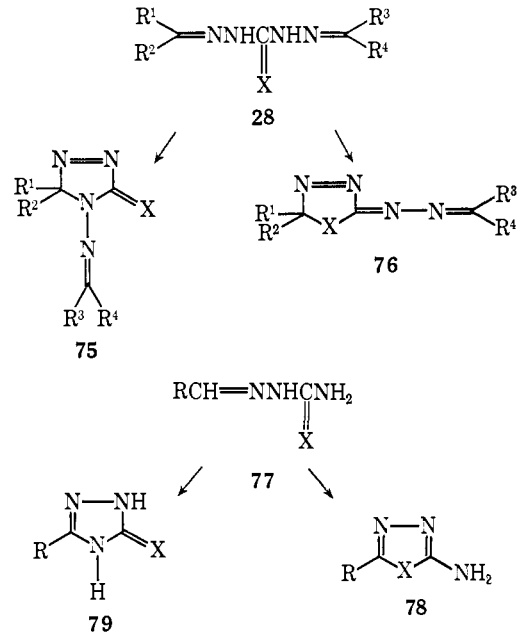
1,5-Diisopropylidenecarbohydrazide is catalytically hydrogenated over platinum to 1,5-diisopropylcarbohydrazide in moderate yield.[55]

$$[(CH_3)_2C{=}NNH]_2CO \xrightarrow{H_2} [(CH_3)_2CHNHNH]_2CO$$

Dicarbohydrazones (and their thio analogs) **28** (X = O, S; R = Alk or Ar) derived from ketones are oxidatively cyclized by lead tetraacetate in methylene chloride to 2-alkyl- (or -aryl-) idenehydrazono-5,5-dialkyl- (or -aryl-) Δ^3-1,3,4-oxa(thia)diazolines **76** (X = O, S; R = Alk or Ar) in moderate to good yields.[20,79] The alkyl compounds **76** are formed rapidly at 0°, but the aryl analogs are produced more slowly and in poorer yields, probably due to both steric and polar effects.[80] The influence of these effects is clearly apparent in the case of unsymmetrical carbohydrazones (*e.g.*, **28**; X = O; $R^1 = R^2$ = Me; $R^3 = R^4$ = Ph), where cyclization occurs selectively toward the alkylidene end of the molecule, yielding **76** (X = O; $R^1 = R^2$ = Me; $R^3 = R^4$ = Ph) exclusively. Catalytic reduction reconverted the heterocyclic products **76** (X = O) into the parent carbohydrazones in good yield, suggesting the absence of alkyl or aryl migrations during the cyclization process.

A provisional report[79] by the same authors had formulated the oxidation products of diketocarbohydrazones as 4-ketimino-Δ^1-1,2,4-triazolin-3-ones **75** (X = O). Since the oxidation of aldehyde thiosemicarbazones **77** (X = S) to 1,3,4-thiadiazoles **78** (X = S) is a well-documented reaction,[81-83] the analogous interpretation of the comparable mild oxidation of diketothiocarbohydrazones **28** (X = S) to thiadiazoles (*e.g.*, **76**, X = S) appears reasonable. A comparison of the spectra (ir, uv, nmr, and mass) of **76** (X = S) with those of the products of the mild oxidation of diketocarbohydrazones suggests that the latter are probably Δ^3-1,3,4-oxadiazolines **76** (X = O). Indeed, this cyclization is not without precedent, since benzylidenesemicarbazone (**77**, X = O; R = Ph) is ring-closed[84] by sodium hypoiodite to 2-amino-5-phenyl-1,3,4-oxadiazole (**78**, X = O; R = Ph), although, in general, oxidation of semicarbazones with ferric chloride, yields triazolin-3-ones **79** (X = O, R = Ph).[85]

Although the weight of the above evidence favors the oxa- (and thia-) diazoline structures **76** (X = O, S) over those of **75** (X = O, S), an unequivocal synthesis of either is clearly desirable.



28 75 76 77 78 79

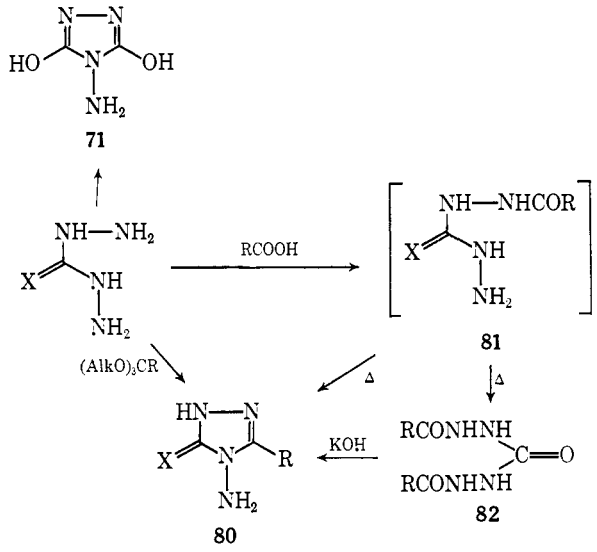
1,5-Dibenzylidenecarbohydrazide (**27**, X = O; R = Ph; R′ = H) is reported[50] to resist the action of sodium hypochlorite in acidic or basic media, but the monobenzylidene compound is decomposed with evolution of nitrogen and carbon dioxide.

(79) J. Warkentin and P. R. West, *Tetrahedron Letters*, 5815 (1966).
(80) M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc., C*, 735 (1967).
(81) R. Duschinsky and H. Gainer, *J. Am. Chem. Soc.*, 73, 4464 (1951).
(82) T. R. Vakula, V. R. Rao, and V. R. Srinivasan, *Current Sci.*, 35, 487 (1966).
(83) G. Young and W. Eyre, *J. Chem. Soc.*, 79, 54 (1901).
(84) G. Valenti and F. Maggio, *Ann. Chim.* (Rome), 42, 18 (1952).
(85) J. R. Bailey and A. T. McPherson, *J. Am. Chem. Soc.*, 39, 1322 (1917).

G. REACTION WITH ALIPHATIC CARBOXYLIC ACIDS AND THEIR ORTHO ESTERS (INCLUDING IMINO ETHERS)

1. (Thio)carbohydrazide

The product of the reaction of carbohydrazide with ethyl orthoformate, originally believed to be a tetrahydrotetrazine derivative,[2,86] was correctly formulated as 4-amino-1,2,4-triazol-5-one by Stollé[87] who also extended[8] this reaction to the synthesis of 4-amino-1,2,4-triazole-5-thione from thiocarbohydrazide. More extensive later studies[88,89] showed the general character of this reaction. Thus, (thio)carbohydrazide reacts with the ethyl esters of orthoformic, orthoacetic, and orthopropionic acids at their boiling points, with simultaneous cyclization, to give 4-amino-3-alkyl-1,2,4-triazole-5-(thi)ones (**80**, X = O, S; R = H, CH_3, C_2H_5) in moderate to good yields.

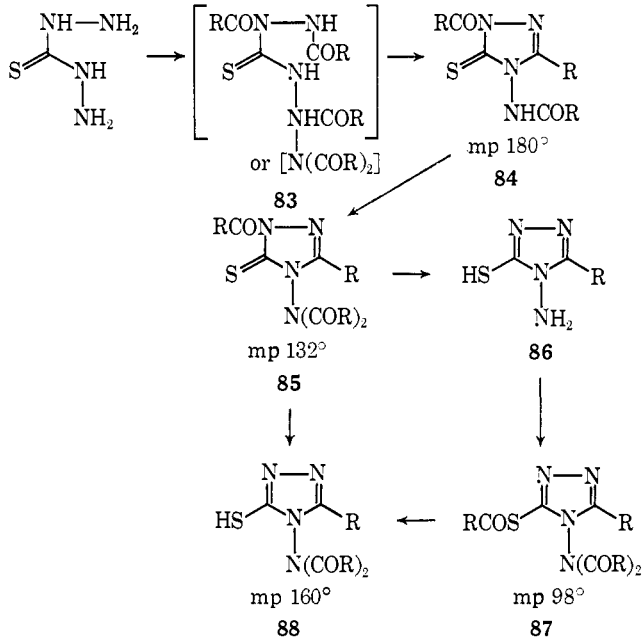


Carbohydrazide[89] and thiocarbohydrazide[88] differ markedly in their behavior toward aliphatic carboxylic acids. Thiocarbohydrazide reacts with hot 100% formic, acetic, or propionic acids during 15 min, affording good yields of the triazoles **80** (X = S; R = H, Me, Et) in one stage. A number of 3-substituted phenoxymethyltriazoles **80** (X = S, R = CH_2OPh, etc.) are similarly accessible from the appropriate substituted acetic acids.[90] Efforts to isolate the intermediate 1-acylthiocarbohydrazides **81** (X = S) by performing the reaction in dilute solution or by using carboxylic acid esters were unsuccessful.[88]

In contrast, carbohydrazide yields, under the same conditions, the open-chain 1,5-diacylcarbohydrazides **82** (R = H, Me, Et) in good yields[89] (see also acylcarbohydrazides, section VI.A.1). After more prolonged interaction (3 hr), acetic acid gives the triazole **80** (R = Me), but formic and propionic acids yield only the acyclic diacyl compound, their cyclization requiring longer reaction times (10 hr). However, during such prolonged heating, carbohydrazide is lost in a simultaneous side reaction, undergoing self-condensation to 4-aminourazole (**71**)[91] (see also section IV.O). The 4-aminotriazolones **80** (X = O) are obtained from the diacylcarbohydrazide **82** in good yield on being refluxed in 10% aqueous potassium hydroxide.

In view of the ready cyclization of thiocarbohydrazide to 1,2,4-triazoles under the influence of aliphatic carboxylic acids, it is not surprising that the reported[27] formation of a "diacetylthiocarbohydrazide" (mp 180°) by treatment of thiocarbohydrazide with acetic anhydride has proved erroneous. The reaction yields in fact[88] a diacetyl, **84** (mp 180°), and triacetyl derivative, **85** (mp 132°), of the triazole **86**; the latter (**86**) is obtained by the acid hydrolysis of *either* derivative. However, acetylation of this parent triazole **86** yielded yet another triacetyl derivative **87** (mp 98°), which on brief heating in water gave a further diacetyl compound **88** (mp 160°).

These results are accounted for in terms of two separate acylation paths producing isomeric acetyl compounds. By postulating the primary acetylation of thiocarbohydrazide to occur at N(4), *i.e.*, adjacent to the thiono group, the triazole derivatives arising by this route would incorporate an acetyl group in the heteronucleus. If this interpretation is correct, the triacetyl derivative **85** should be convertible into the diacetyl derivative **88** by the mildest hydrolysis; N-acyl groups of triazoles and related heterocycles are known to be remarkably mobile.[92]

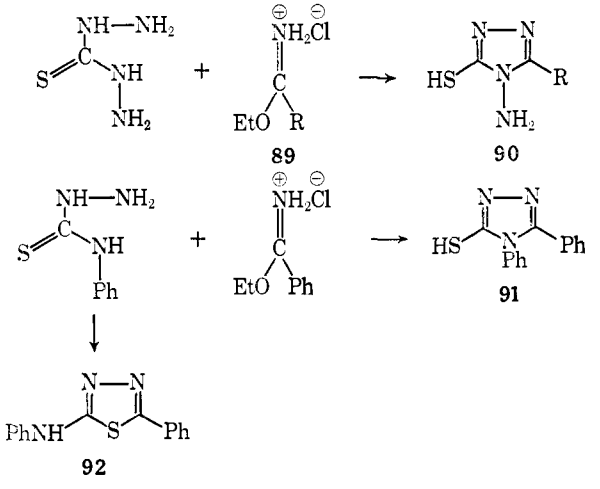


In the case of formic acid, the general cyclization outlined above takes place not only with the free acid, but with its amide also. Thus, formamide and thiocarbohydrazide condense with elimination of ammonia to give 4-amino-1,2,4-triazole-5-thione (**80**, X = S, R = H). Other amides, however, give only resinous products.[68,88]

(86) M. Busch, "Festschrift zum 80. Geburtstag des Prinzregenten Luitpold von Bayern," Band 4, Teil 2, Erlangen, 1901, p 165; *Chem. Zentr.*, I, 937 (1901).
(87) R. Stollé, *J. Prakt. Chem.*, 75, 416, 423 (1907).
(88) H. Beyer and C. F. Kröger, *Ann.*, 637, 135 (1960).
(89) C. F. Kröger, L. Hummel, M. Mutscher, and H. Beyer, *Chem. Ber.*, 98, 3025 (1965).
(90) M. Kuranari and H. Takeuchi (to Chugai Pharmaceutical Co. Ltd.), Japanese Patent 21,420 (1965); *Chem. Abstr.*, 64, 2097 (1966).
(91) L. F. Audrieth and E. B. Mohr, *Inorg. Syn.*, 4, 29 (1953).
(92) H. A. Staab, *Angew. Chem. Intern. Ed. Engl.*, 1, 355 (1962).

When carbohydrazide is treated with anhydrides of dicarboxylic acids (*e.g.*, oxalic, sebacic) at 180–230°, polymeric products are obtained.[93]

Reaction with Imino Ethers. The condensation of thiocarbohydrazide with imino ethers appears to have been reported in only one instance, in the patent literature.[94] Thus a boiling suspension of thiocarbohydrazide and heptadecylimino ethyl ether hydrochloride **89** (R = $C_{17}H_{35}$) rapidly deposits 4-amino-3-heptadecyl-5-mercapto-1,2,4-triazole (**90**, R = $C_{17}H_{35}$) (55%). Confirmation for the assigned structure would appear to be desirable, particularly in the light of the observation[95] that 4-phenylthiosemicarbazide yields, in this reaction, a thiadiazole **92** or a triazole **91** in acidic or basic media, respectively.



89 **90**

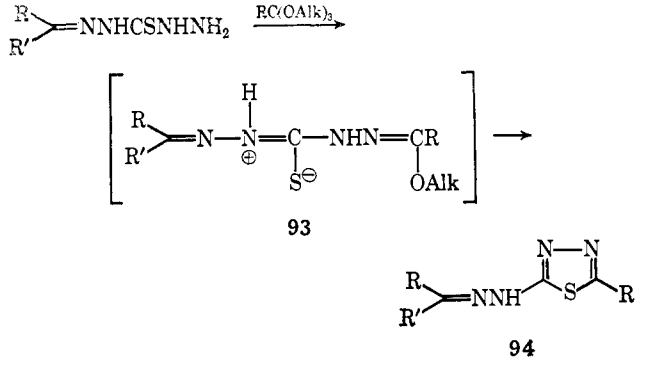
91

92

2. Thiocarbohydrazones

In contrast to thiocarbohydrazide, which gives rise to triazoles **80** (see preceding section), monthiocarbohydrazones react[68] with ortho esters to produce, by an alternative mode of ring closure, 2-substituted 1,3,4-thiadiazol-5-yl hydrazones (**94**), though in poor to moderate yields.

The participation of the sulfur atom in this cyclization may be favored by the resonance form **93** of the primarily formed adduct; in this structure, the sulfur is clearly more nucleophilic than the 2-nitrogen, thus favoring thiadiazole formation.[68] Support for the existence of conjugation of



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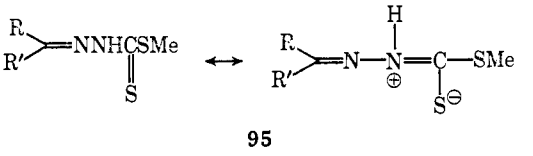
94

this type is provided by an analysis of the uv spectra[68] of the comparable S-alkylthiosemicarbazones **95**. Although the

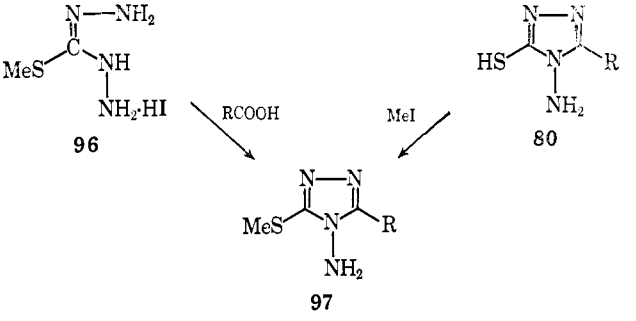


95

preferential formation of a thiadiazole **94** is explained by this interpretation, it does not account for the relatively poor yields. Since the reaction of 1-benzylidenethiocarbohydrazide and triethyl orthoformate does indeed produce 4-benzylideneamino-3-mercapto-1,2,4-triazole in 55% yield, it is likely that steric factors are of considerable significance.

3. S-Alkyl Isothiocarbohydrazides

The condensation of thiocarbohydrazide and carboxylic acids to 3-substituted 4-amino-5-mercapto-1,2,4-triazoles (**80**, X = S) is readily extended to the corresponding S-alkylthio analogs. Thus, S-methylisothiocarbohydrazide (hydriodide) reacts with formic or acetic acid to give fair yields of 3-alkyl- (or H) 4-amino-5-methylthio-1,2,4-triazoles (**97**, R = H, CH_3)[96] as their hydriodides, from which the free bases are liberated by treatment with lead acetate.



96 **80**

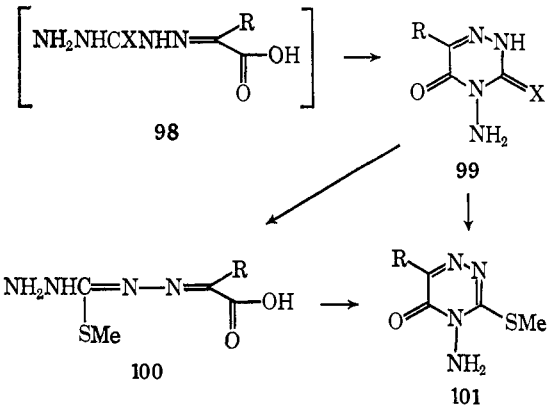
97

H. REACTION WITH α-KETOCARBOXYLIC ACIDS

The condensation of (thio)carbohydrazide with α-ketocarboxylic acids differs markedly from that of carboxylic acids in yielding 4-amino-1,2,4-triazines **99**[97,98] instead of 4-amino-1,2,4-triazoles **80** (*cf.* section IV.G.1). Thus, pyruvic acid and (thio)carbohydrazide react in aqueous solution to afford 4-amino-5-oxo-3-thioxo- (or oxo-) 6-methyl-2,3,4,5-tetrahydro-1,2,4-triazine (**99**, X = O, S; R = CH_3) in good yield. Similarly, benzoylformic acid produces the triazine **99** (X = S; R = Ph) in excellent yield. It is probable that the first stage of the reaction does not involve the carboxyl group (as is the case with carboxylic acids) but the keto group, resulting in the formation of the hydrazones **98** (X = O, S; R = CH_3, Ph). This type of hydrazone can be isolated as its S-methyl derivative **100** (R = Ph, Me), when the triazine **99** is treated with methyl iodide in *aqueous* alkali.[98] Methylation in sodium methoxide proceeds without ring opening to give the S-methyl-*as*-triazine **101** (R = CH_3, Ph), which is also obtainable from the acyclic S-methylthiol **100** (R = CH_3, Ph) by loss

(93) Phrix Arbeitsgemeinschaft, German Patent 740,829 (1943); *Chem. Abstr.*, **40**, 600 (1946).
(94) W. Lässig and E. Günther, German Patent 1,058,844 (1959); *Chem. Abstr.*, **55**, 26806 (1961).
(95) H. Weidinger and J. Kranz, *Chem. Ber.*, **96**, 1059, 1064 (1963).
(96) C. F. Kröger, E. Tenor, and H. Beyer, *Ann.*, **643**, 121 (1961).
(97) A. Dornow and H. Pietsch, *Chem. Ber.*, **100**, 2585 (1967).
(98) A. Dornow, H. Menzel, and P. Marx, *ibid.*, **97**, 2173 (1964).

of water, in boiling methanol. The facile ring opening of 1,2,4-triazines in aqueous base has previously been described.[99]

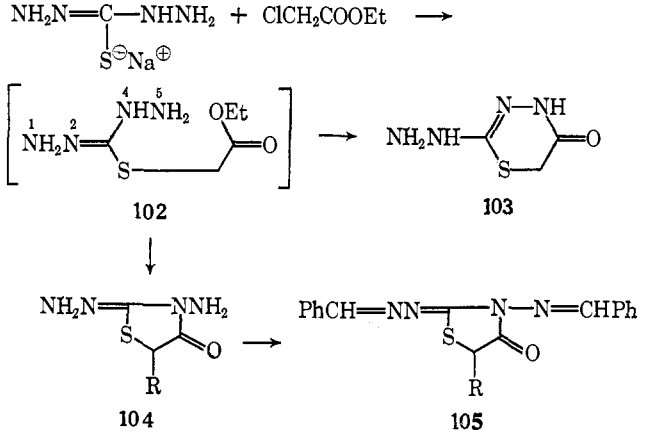


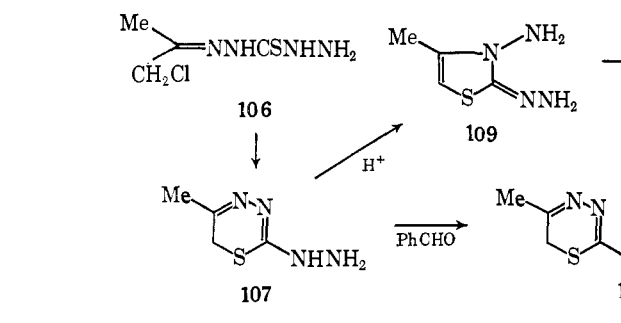
I. REACTION WITH α-HALO ESTERS, KETONES, AND β-KETO ESTERS

1. Thiocarbohydrazide

a. α-Halo Esters and α-Halo Ketones

The interaction of thiocarbohydrazide and α-halo carboxylic esters in alkaline media gives heterocyclic products that were formulated as thiadiazines **103** by Guha and De in 1924,[100] but as thiazolidine derivatives **104** (R = H, CH_3, C_2H_5, C_6H_5) by Stephen and Wilson in 1928.[78] *Either* structural type could arise from the common intermediate **102** by the participation of the N(5) or N(4) atom, respectively, in the ring closure. The observed formation of dibenzylidene derivatives **105** from all four representatives of the series **104** (R = H, CH_3, C_2H_5, C_6H_5) would favor the latter formulation.





(99) R. H. Hall, *J. Am. Chem. Soc.*, 80, 1145 (1958).
(100) P. C. Guha and S. C. De, *J. Indian Chem. Soc.*, 1, 141 (1924).

More recent work[82] concerning the condensation of thiocarbohydrazide and α-halo ketones in acidic media has provided clear evidence for the participation, in these reactions, of thiadiazines **107**, but these are easily converted into thiazolines. Thus, chloroacetone gives the primary monoadduct **106** which is cyclized in ethanol nearly quantitatively to the hydrazinothiadiazine **107**. This can give only a monobenzal derivative **108**, also obtainable by condensing chloroacetone with either mono- or dibenzal thiocarbohydrazide in ethanol (1 mole of benzaldehyde being split out in the latter reaction).

Treatment with benzaldehyde in acid solution rearranges the hydrazinothiadiazine **107** into benzaldehyde (3-benzalamino-4-methylthiazolin-2-one)azine (**111**). This reaction can also be performed in stages by first rearranging **108** to **110** in acid solution and preparing its dibenzylidene derivative **111** subsequently. A further demonstration of this facile rearrangement is given by the smooth conversion, by mineral acid, of the hydrazinothiadiazine **107** into 3-amino-2-hydrazino-4-methylthiazoline (**109**); this gives a dibenzal compound identical with **111**.

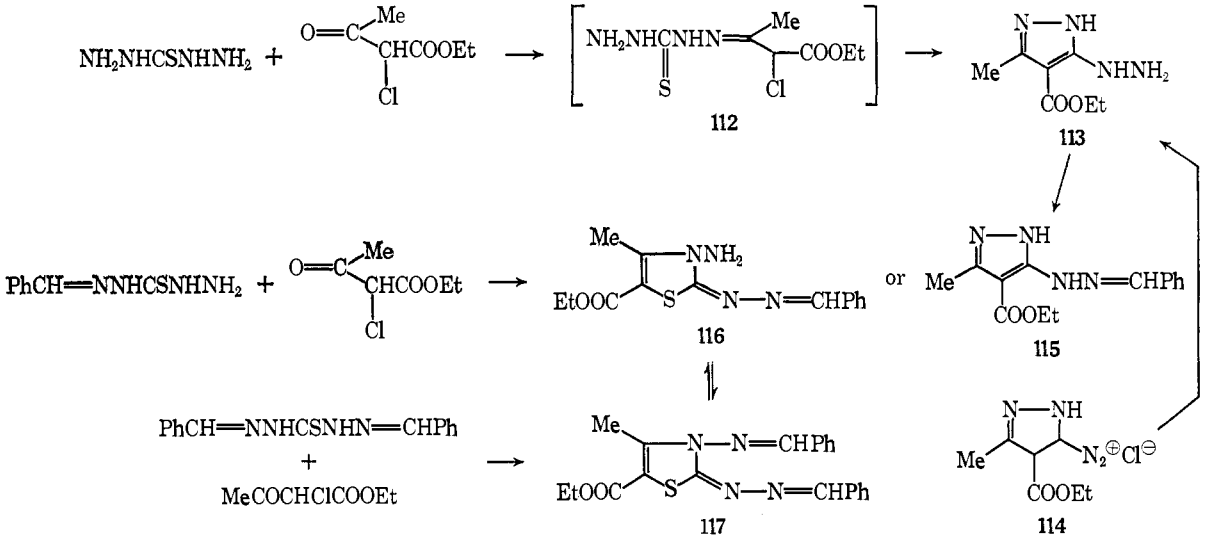
b. α-Chloro-β-keto Esters

The initial stage of the interaction of thiocarbohydrazide and α-chloro-β-keto esters appears to be formation of hydrazones **112** (compare preceding section a); this is followed by cyclization, with loss of sulfur, to 5-hydrazinopyrazoles **113**. By this sequence, ethyl α-chloroacetoacetate gives 3-methyl-4-ethoxycarbonyl-5-hydrazinopyrazole hydrochloride (**113**) in moderate yield.[101] The formulation of this product (as **113**) was confirmed by its alternative synthesis by reduction of the diazonium salt of 3-methyl-4-ethoxycarbonyl-5-aminopyrazole (**114**) with sodium sulfite.[102] Further, the use of 1-benzylidenethiocarbohydrazide in this reaction yields the benzylidene derivative **115** of the pyrazole **113**, which is also obtainable from the parent **113** and benzaldehyde. In acidic solution, however, 1-benzylidenethiocarbohydrazide gives rise to the thiazolon-2-azine **116** which is in turn convertible by benzaldehyde into the dibenzylidene derivative **117**, also directly obtainable from 1,5-dibenzylidenethiocarbohydrazide. The last two reactions resemble the condensation of chloroacetone and thiocarbohydrazide (see section a above), and the whole sequence generally parallels the behavior of thiosemicarbazide.[102]

2. 1,5-Bisthiocarbohydrazones

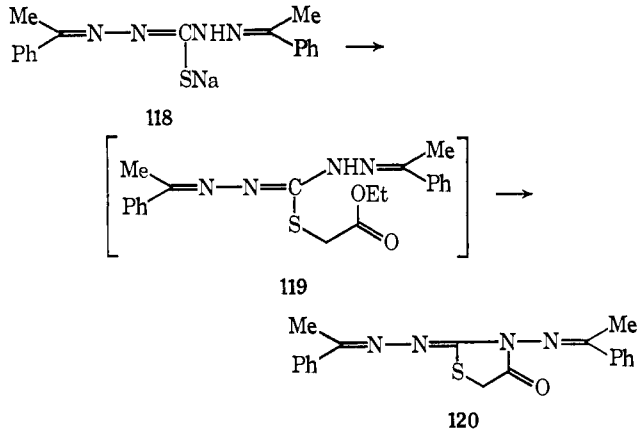
1,5-Bisthiocarbohydrazones, having both hydrazino groups blocked, are reported[64] to react at their free 3-thio position

(101) H. Beyer, G. Wolter, and H. Lemke, *Chem. Ber.*, 89, 2550 (1956).
(102) H. Beyer and G. Wolter, *ibid.*, 89, 1652 (1956).

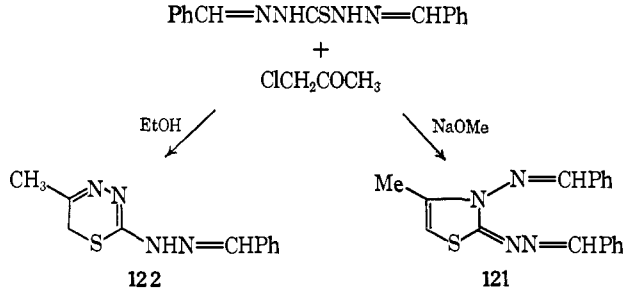


with ethyl chloroacetate to form thiazolidine derivatives **120**. The reaction is thus entirely analogous to that of thiocarbohydrazide itself (*cf.* section IV.I.1.a).

Diacetophenonethiocarbohydrazone (preferably in the form of its sodium salt **118**), for example, reacts with ethyl chloroacetate in ethanol to yield the diacetophenone derivative of 3-amino-2-hydrazinothiazolidin-4-one (**120**) in good yield (85%). The use of suitably substituted α-halo esters gave 5-substituted homologs (**120**, R = CH_3, C_2H_5, C_6H_5) as expected,[78] but the attempted hydrolysis of these acetophenone derivatives to the parent bases was unsuccessful.



The condensation of chloroacetone with dibenzylidenethiocarbohydrazide yields the thiazoline derivative **121** in basic media (sodium methoxide)[82] but the thiadiazine compound **122** in neutral solution[3,82] thus again resembling the behavior of thiocarbohydrazide (see section IV.I.1.a).



J. REACTION WITH CARBON DISULFIDE AND RELATED COMPOUNDS

Thiocarbohydrazide condenses readily with carbon disulfide, and sulfur-containing acids and esters derived therefrom. The reaction is generally initiated by the introduction of the CSS– function at one or both of the hydrazine groups, followed by cyclization processes, the nature of which depends on the structure of the compounds participating in the reaction.

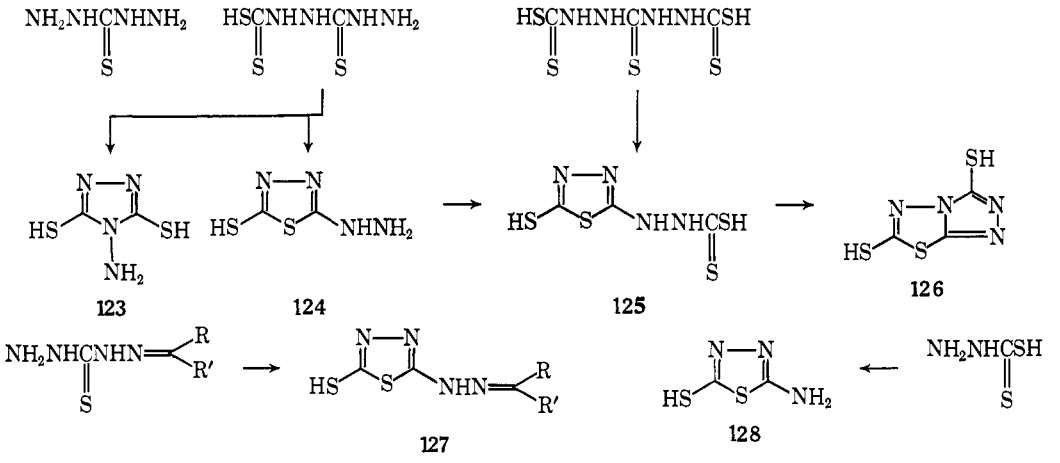
1. Carbon Disulfide

Thiocarbohydrazide reacts with 2 moles of carbon disulfide in boiling pyridine to yield 4-amino-3,5-dimercapto-1,2,4-triazole (**123**) (50%, as the pyridinium salt) and 2,4-dimercapto-*s*-triazolo[4,3-*b*]-1,3,4-thiadiazole (**126**) (40%).[103] The proposed course of the reaction is summarized in the reaction scheme. 2-Hydrazino-5-mercapto-1,3,4-thiadiazole (**124**), obtained by an independent synthesis, is found to react with carbon disulfide in pyridine to give the dicyclic end product **126**, but 4-amino-3,5-dimercapto-1,2,4-triazole (**123**) fails to do so; the former **124** is therefore likely to be concerned as an intermediate in the present reaction. However, attempts to isolate it after condensing equimolar quantities of thiocarbohydrazide and carbon disulfide failed, the usual products (**123** and **126**) being again obtained in diminished yields, together with recovered thiocarbohydrazide.

The reaction of thiocarbohydrazide with carbon disulfide thus differs from that of thiosemicarbazide which gives 2-amino-5-mercapto-1,3,4-thiadiazole (**128**) in high yield.[103]

Monothiocarbohydrazones, on the other hand, resemble the behavior of thiosemicarbazide in producing 5-mercapto-1,3,4-thiadiazole-5-hydrazones (**127**) in moderate to good yields.[103] Small quantities of 3,5-dimercapto-4-amino-1,2,4-triazole (**123**) are formed as by-product; a possible disproportionation mechanism accounting for its production has been proposed.[103]

(103) J. Sandström, *Acta Chem. Scand.*, 15, 1295 (1961).



2. *Xanthates (Alkyl Dithiocarbonates)*

The interaction of thiocarbohydrazide and potassium ethyl xanthate in closed vessels gives a product which was originally formulated as 3,6-dithioxotetrahydro-1,2,4,5-tetrazine (**129**) ("dithio-*p*-urazine") by Guha and De.[27] The same compound arose in the condensation of hydrazine hydrate and carbon disulfide,[100] and the monooxo analog **129** (X = O) was similarly accessible from carbohydrazide and potassium ethyl xanthate. In his treatise on tetrazines, Wiley[104] carefully related the methods and conditions used by Guha and De[27,100] to the older literature, and agreed with their formulation (*i.e.*, **129**). Spectral and degradative evidence has since demonstrated,[105] however, that the compound is in fact 4-amino-3,5-dimercapto-1,2,4-triazole (**130**). This conclusion was arrived at independently and almost simultaneously by three investigators.[103,106,107]

Thus, the infrared spectrum of the compound contains a band at 1610 cm^{-1} attributed to NH deformation of an amino group. This band is absent in corresponding triazoles which lack a 4-amino substituent. Furthermore, the compound **130** was convertible into the dimethylthio derivative **131** which was smoothly deaminated to the known[108,109] 3,5-di(methylthio)-1,2,4-triazole (**132**). Finally, the compound was identical with authentic 4-amino-3,5-dimercapto-1,2,4-triazole synthesized independently from dithiobiurea and hydrazine.[31,110] In the course of the preparation of Guha's triazole **130**, but employing a shorter time of heating,[106] a compound of molecular formula $C_3H_{10}N_8S_2$ was obtained. This was tentatively formulated as 1,1′-(thiocarbonyl)di(thiocarbohydrazide) (*i.e.*, $NH_2NHCSNHNHCSNHNHCSNHNH_2$), but definite proof supporting the correctness of this polythioamido chain is so far lacking.

Authentic "dithio-*p*-urazine" (**129**) is in fact accessible by a synthesis of recent date:[111] thiocarbohydrazide reacts with aqueous disodium di(carboxymethyl) trithiocarbonate (**133**) at room temperature to afford up to 45% yields of the desired product **129**.[111] Applied to 4-di(methylthio)methylene-1,2-diphenyl-3,5-pyrazolidinedione (**134**),[112] the reaction produces a compound of probable structure **135**, but the alternative triazole structure **136** is not wholly excluded.

A second alleged synthesis[113] of dithio-*p*-urazine (**129**), in which thiophosgene instead of potassium ethyl xanthate is condensed with thiocarbohydrazide, yields in fact Guha's compound, *i.e.*, 4-amino-3,5-dimercapto-1,2,4-triazole (**130**).

3. *Dialkyl Trithiocarbonates*

Thiocarbohydrazide reacts with dimethyl trithiocarbonate in alkaline solution to form 1-dithiomethoxycarbonylthiocarbohydrazide (**137**) as a crystalline solid in high yield.[69] The stability of this monoadduct is remarkable; in contrast, thiocarbohydrazide generally reacts with comparable reagents (*e.g.*, carbon disulfide, iso(thio)cyanate esters, and carbonyl compounds) rapidly at *both* terminal nitrogen atoms despite precautions to prevent it. When monoaddition does take place (*e.g.*, with ortho esters and imino ethers), it is usually attended by immediate cyclization *in situ*.

The monoadduct **137** is readily cyclized in ethanolic hydrochloric acid[69] to 2-mercapto-5-methylthio-1,3,4-thiadiazole (**138**) in high yield. Above its melting point, **137** evolves hydrogen sulfide and methanethiol, with formation of **138** (23%), together with the known 2-hydrazino-5-methylthio-1,3,4-thiadiazole (**140**) (55%) and 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (**139**) (10%).

The formation of the triazole **139** can be accounted for by a side reaction in which the adduct **137** condenses with liberated hydrazine (from **137**) to form the unstable acyclic intermediate **141**.

The behavior of monothiocarbohydrazones in this reaction is entirely analogous. Interaction with dialkyl trithiocarbonates in ethanolic sodium ethoxide at room temperature yields 1-dithioalkoxycarbonylthiocarbohydrazones **142** in good yield.[69]

They are also very readily cyclized by thermolysis or by hot ethanolic hydrochloric acid;[69] the products, obtained in good yield, are 2-alkylthio-1,3,4-thiadiazol-5-yl hydrazones (**143**) and 2-alkylthio-5-mercapto-1,3,4-thiadiazoles (**138**), respectively.

(104) P. F. Wiley in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1956, p 191.

(105) V. P. Wystrach in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley and Sons Inc., New York, N. Y., 1967, p 135.

(106) A. W. Lutz, *J. Org. Chem.*, 29, 1174 (1964).

(107) N. Petri, *Z. Naturforsch.*, **16B**, 767 (1961).

(108) F. Arndt and E. Milde, *Chem. Ber.*, **54**, 2089 (1921).

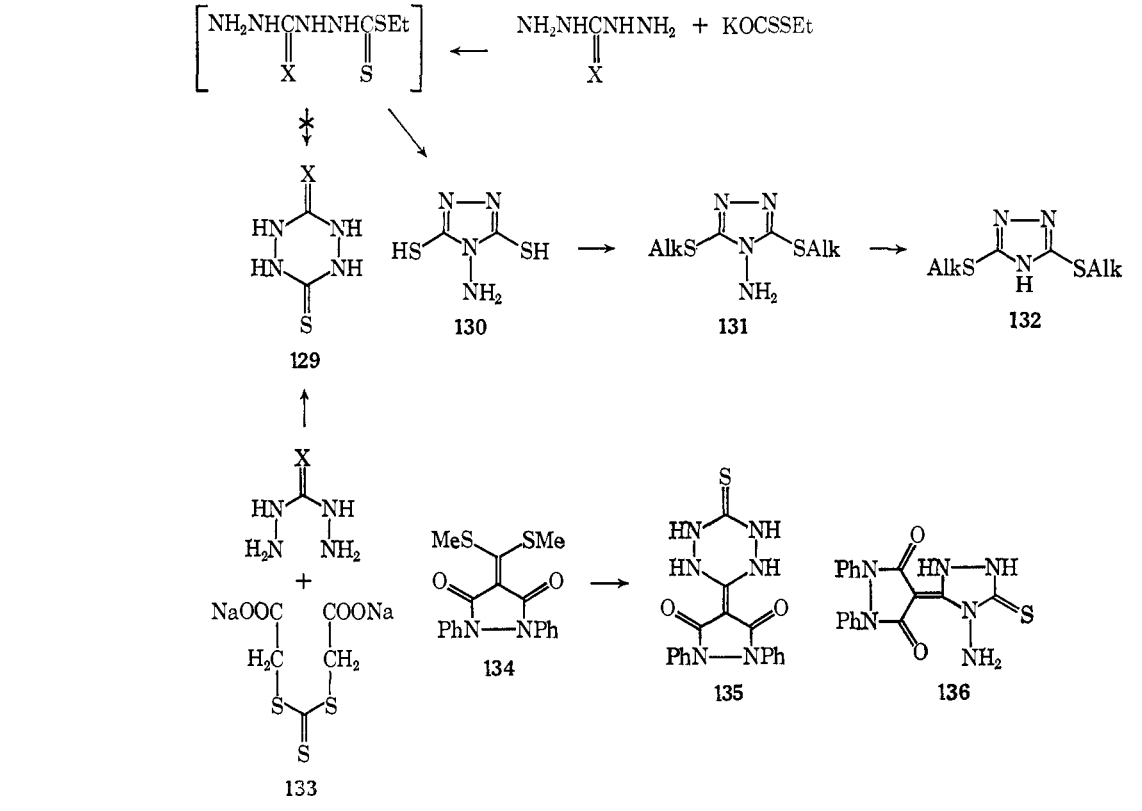
(109) L. Loewe and M. Türgen, *Rev. Fac. Sci. Univ. Istanbul*, **14A**, 227 (1949); *Chem. Abstr.*, **44**, 6415 (1950).

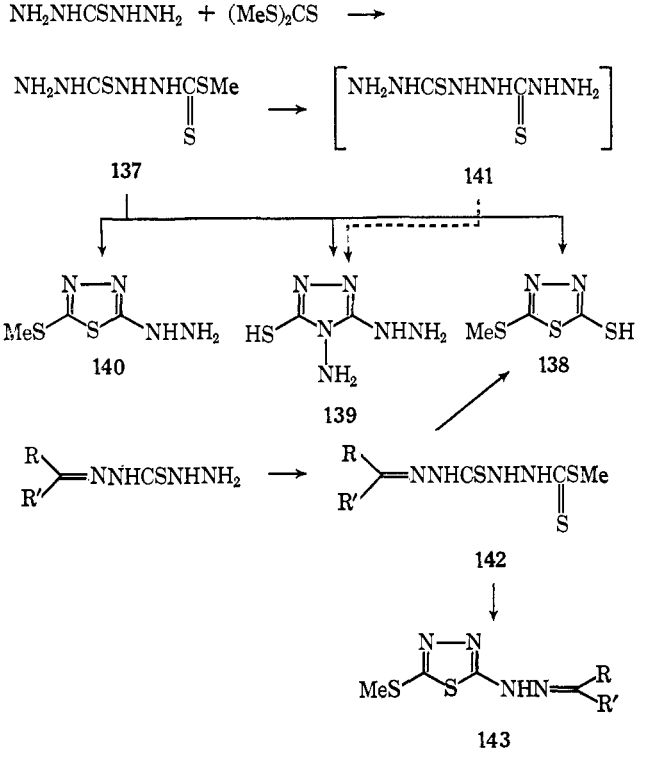
(110) F. Arndt and F. Bielich, *Chem. Ber.*, **56**, 809 (1923).

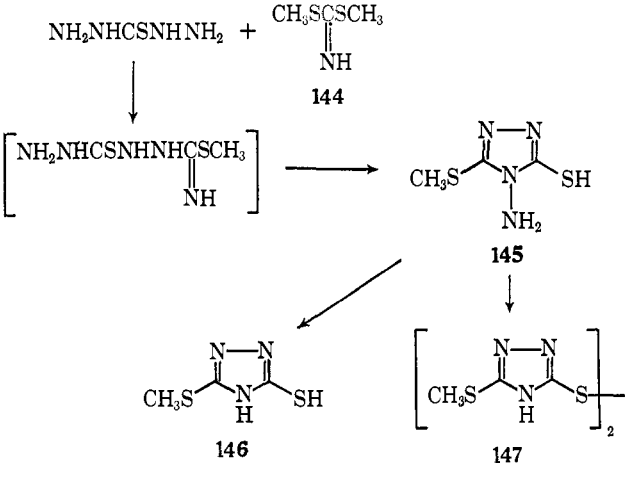
(111) J. Sandström, *Acta Chem. Scand.*, **15**, 1575 (1961).

(112) K. Swincicki, R. Gompper, and W. Toepfl (to Farbenfabriken Bayer A.G.), Belgian Patent 617,873 (1962); *Chem. Abstr.*, **59**, 636 (1963).

(113) T. Beckett and G. M, Dyson, *J. Chem. Soc.*, 1358 (1937).







4. *Dialkyl Dithioimidocarbonates*

Thiocarbohydrazide and dimethyl dithioimidocarbonate hydrochloride (**144**) react slowly in aqueous solution, 4-amino-3-methylthio-1,2,4-triazolin-5-thione (**145**) (60%) being gradually deposited.[106] Its structure is confirmed by its further S-methylation, by the formation of a benzylidene derivative, and by its deamination to the two known triazoles **146** and **147**.

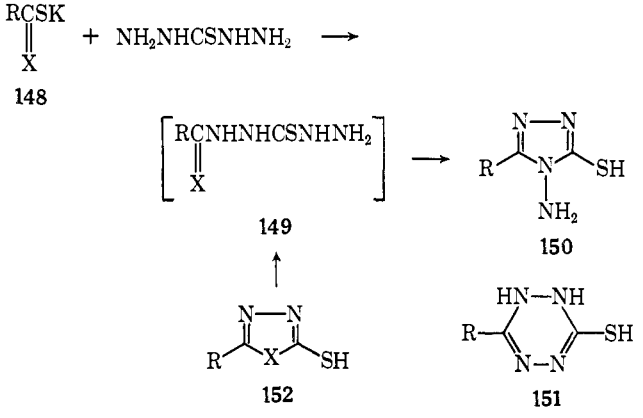
5. *Dithiocarboxylic Acids*

In contrast to carbon disulfide, as well as xanthates and trithiocarbonates, which react with thiocarbohydrazide by initially incorporating the CSS– grouping (*cf.* preceding sections IV.J.1–3), dithiocarboxylic acids and their esters generally introduce the thiono moiety (–CS–) only. Relatively little work has been done using the parent dithiocarboxylic acids, but the action of their esters has been investigated in more detail. Carboxymethyl dithiobenzoate, a well-known thiobenzoylating agent,[114,115] has been employed with more particular success in the present series (see section IV.J.6).

The interaction of thiocarbohydrazide and the potassium salt of dithioisonicotinic acid (**148**, X = S; R = 4′-pyridyl)

(114) F. Kurzer, *Chem. Ind.* (London), 1333 (1961).
(115) F. Kurzer and A. Lawson, *Org. Syn.*, 42, 100 (1962).

in boiling ethanol gives a product that has been formulated as 4-amino-3-mercapto-5-(4′-pyridyl)-1,2,4-triazole (**150**, R = 4′-pyridyl).[116,117] This structure, rather than the alternative tetrazine structure **151** (R = 4′-pyridyl), is likely to be the correct one, in view of the established analogous formation of 4-aminotriazoles from carboxylic acids (see section IV.G.1). The same aminotriazole **150** (R = 4′-pyridyl) was also obtained by treating 2-mercapto-5-(4′-pyridyl)-1,3,4-oxadiazole (**152**, R = 4′-pyridyl, X = O) with boiling hydrazine.[118] This interconversion proceeds undoubtedly by a transient ring opening (of a type that is well established[119,120]), through the open-chain intermediate **149** (X = O), which, on ring closure with loss of water, would give the observed triazole **150** (R = 4′-pyridyl).



6. *Carboxymethyl Dithiobenzoate*

Thiocarbohydrazide is smoothly monothiobenzoylated by alkaline carboxymethyl dithiobenzoate (**153**)[114,115] in high yield.[121] An excess of thiocarbohydrazide is used to prevent dithiobenzoylation. The resulting 1-(thiobenzoyl)thiocarbohydrazide (**154**) is a thermolabile solid which does not give identifiable derivatives with carbonyl compounds.[121] It is stable in alkaline media, even at high temperatures, but is ring-closed rapidly in ethanolic hydrochloric acid to a mixture of 2-hydrazino- **155** (31%) and 2-mercapto-5-phenyl-1,3,4-thiadiazole (**156**) (65%). Thermolysis yields the same cyclization products, in slightly different proportions, together with small quantities of 4-amino-3-mercapto-5-phenyl-1,2,4-triazole (**157**).

Unlike 1-(thiobenzoyl)thiocarbohydrazide (**154**), the 1-benzoyl analog **159** appears to be unstable in alkaline solution. The compound probably functions as the intermediate in the hydrazinolysis of 1-benzoyl-2-dithiomethoxycarbonylhydrazine (**158**) which yields 4-amino-5-mercapto-3-phenyl-1,2,4-triazole (**157**) as the main product.[122]

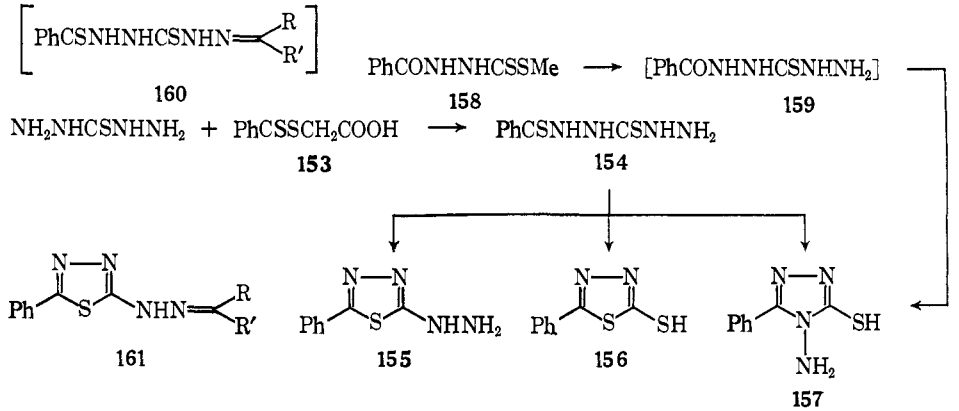
Monothiocarbohydrazones do not form readily isolable monoadducts **160** with carboxymethyl dithiobenzoate as does thiocarbohydrazide, but react in aqueous solution to yield noncrystalline, unidentifiable substances.[121] In boiling pyridine, however, a smooth addition–cyclization takes place with formation of good yields of 2-phenyl-1,3,4-thiadiazol-5-yl hydrazones **161**.[121]

K. REACTION WITH CYANIC AND THIOCYANIC ACIDS AND THEIR ISOESTERS

1. *Addition of Cyanic Acid*

a. Carbohydrazide

Carbohydrazide reacts with cyanic acid to give either 1-carbamoyl- **162** or 1,5-dicarbamoylcarbohydrazide **163** in high yield,[123,124] depending on the conditions. The former arises readily from equimolar quantities of carbohydrazide and potassium cyanate in glacial acetic acid. The use of 2 moles of potassium cyanate produces 1,5-dicarbamoylcarbohydrazide in poor yield,[123] probably because the action is terminated by the separation of the insoluble monoadduct **162**. The 1,5-diadduct **163** is accessible in good yield from the hydrochloride of the monoadduct **162** by the addition of an equimolar quantity of potassium cyanate.[124] 1-Carbamoylcarbohydrazide (**162**) is cyclized by 12 *M* hydrochloric acid to 4-amino-1,2,4-triazolidine-3,5-dione (**164**).[91] Both carbamoyl compounds **162** and **163** are white crystalline solids soluble in dilute mineral acids but only sparingly soluble in water and the usual organic solvents.[124]



(116) H. B. König, W. Siefken, and H. A. Offe, *Chem. Ber.*, 87, 825 (1954).

(117) H. B. König and H. A. Offe (to Farbenfabriken Bayer A.G.), German Patent 953,802 (1956); *Chem. Abstr.*, 53, 4309 (1959).

(118) H. B. König and H. A. Offe (to Farbenfabriken Bayer A. G.), German Patent 953,801 (1956); *Chem. Abstr.*, 53, 4309 (1959).

(119) W. R. Sherman and A. von Esch, *J. Org. Chem.*, 27, 3472 (1962); U. S. Patent 3,058,988 (1962) (to Abbot Laboratories); *Chem. Abstr.*, 58, 9030 (1963).

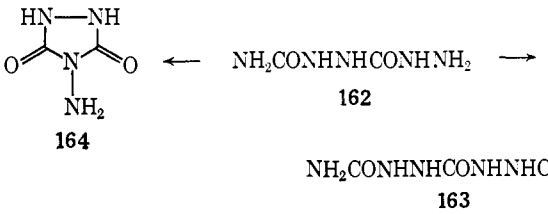
(120) A. Stempel, J. Zelauskas, and J. A. Aeschlimann, *J. Org. Chem.*, 20, 412 (1955).

(121) J. Sandström, *Acta Chem. Scand.*, 17, 1595 (1963).

(122) M. Kanaoka, *J. Pharm. Soc. Japan.* 76, 1133 (1956); *Chem. Abstr.*, 51, 3579 (1957).

(123) G. Pellizzari and F. Roncagliolo, *Gazz. Chim. Ital.*, 37 I, 434 (1907).

(124) L. F. Audrieth and E. B. Mohr, *Inorg. Syn.*, 4, 36 (1953).



164 ← $NH_2CONHNHCONHNH_2$ (162) → $NH_2CONHNHCONHNHCONH_2$ (163)

b. Thiocarbohydrazide

Although an early report by Guha[100] claiming the preparation of 1-carbamoylthiocarbohydrazide (**165**) from thiocarbohydrazide and potassium cyanate could not be confirmed by later work,[125] the method does in fact yield this compound under carefully controlled conditions.[125] Potassium cyanate in acetic acid (eq 10) or nitrourea (eq 11) may serve as source of cyanic acid. The assigned structure of the product is supported by its conversion into a number of derivatives, and by an additional efficient synthetic route, *viz.* the hydrazinolysis of 1-dithiomethoxycarbonylsemicarbazide (**166**) in ethanol (eq 12).

$$NH_2NHCSNHNH_2 + KOCN + HAc \longrightarrow NH_2NHCSNHNHCONH_2 + KAc \quad (10)$$

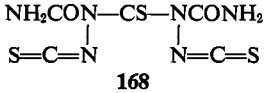
$$NH_2NHCSNHNH_2 + NH_2CONHNO_2 \longrightarrow NH_2NHCSNHNHCONH_2 + H_2O + N_2O \quad (11)$$

$$\underset{\mathbf{166}}{CH_3SCSNHNHCONH_2} + NH_2NH_2 \longrightarrow \underset{\mathbf{165}}{NH_2NHCSNHNHCONH_2} + CH_3SH \quad (12)$$

Of the alternative reactions (eq 10 and 11), the method employing nitrourea as reagent is probably the more attractive procedure because no contaminating ions remain in the reaction mixture to complicate the isolation of the rather soluble product. The hydrazinolysis (eq 12), employing an excess of anhydrous hydrazine, is an efficient method of preparing pure **165** in 70% yield.

The addition of 2 moles of cyanic acid to thiocarbohydrazide gives a crude product that is probably impure 1,5-dicarbamoylthiocarbohydrazide (**167**); repeated crystallization converts it slowly into the monoadduct **165**. The authentic diaddition product **167** is available by the addition of ethereal thiophosgene to an excess of aqueous semicarbazide, the product separating slowly as a white solid (eq 13).[113] The use of semicarbazide hydrochloride in this reaction, however, leads to the formation of another product, to which the structure **168** has been assigned, without further proof.

$$2NH_2CONHNH_2 + CSCl_2 \longrightarrow \underset{\mathbf{167}}{NH_2CONHNHCSNHNHCONH_2} \quad (13)$$



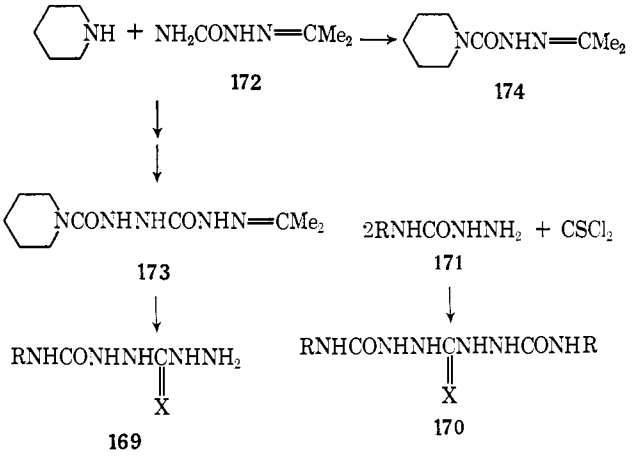
168

1-Carbamoylthiocarbohydrazide (**165**) is claimed[100] to be cyclized in hot concentrated hydrochloric acid to 4-amino-3-hydroxy-1,2,4-triazoline-5-thione, but a later attempt to repeat the experiment was unsuccessful.[125]

2. *Addition of Isocyanate Esters*

Both carbohydrazide and thiocarbohydrazide react with phenyl isocyanate rapidly at both hydrazino groups to form 1,5-diphenylcarbamoyl(thio)carbohydrazide (**170**, X = O, S).[36,100] The reaction is performed in dilute hydrochloric acid[100] or, preferably, in aqueous ethanol or dimethylformamide,[36] when the sparingly soluble product is rapidly precipitated from the hot reaction mixture in high yield. Monoaddition of isocyanate (despite the use of equimolar quantities of reactants) to form 1-phenylcarbamoyl(thio)carbohydrazide (**169**, X = O, S; R = Ph) does not appear to be feasible. In this respect the behavior of isocyanate esters differs sharply from that of cyanic acid (see preceding section).

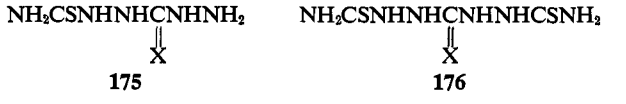
Products of both the mono- and diaddition type (**169** and **170**) are, however, accessible from suitable substituted semicarbazides: 4-phenylsemicarbazide (**171**, R = Ph), for example, reacts with thiophosgene yielding **170** (R = Ph; X = S). 1-Piperidinoformylcarbohydrazide (**169**, R = C_5H_9; X = O), a representative of the monoaddition series, is obtained[126] by the interaction of acetone semicarbazone **172** and piperidine in boiling toluene, followed by hydrolysis of the resulting substituted carbohydrazone **173**; the reaction proceeds with evolution of ammonia, and terminates under strictly anhydrous conditions with the formation of acetone piperidinoformylhydrazone **174**. 1-Piperidinoformylcarbohydrazide **169** (R = C_5H_9; X = O) reacts readily with acetone, benzaldehyde, and acetophenone to form the corresponding hydrazones (*e.g.*, **173**).[126]



3. *Addition of Thiocyanic Acid*

a. Carbohydrazide

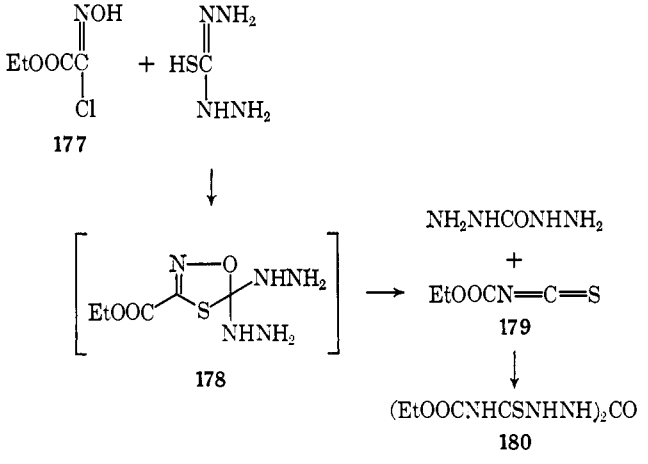
The reaction of thiocyanic acid and carbohydrazide, which should afford mono- or dithiocarbamoyl carbohydrazide (**175**, **176**; X = O) has apparently not been examined. The corresponding thiocarbohydrazide derivatives (**175**, **176**; X = S), on the other hand, have received considerable attention. These will be described and discussed in the following section.



(125) E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, 19, 742 (1954).

(126) J. M. Stratton and F. J. Wilson, *J. Chem. Soc.*, 1154 (1931).

It is appropriate at this point to describe the preparation of a derivative of the unknown parent diadduct **176** (X = O)[127] by a novel route using ethyl chlorooximinoformate (**177**). It reacts with thiocarbohydrazide in aqueous solution forming 1,5-di(ethoxycarbonylthiocarbamoyl)carbohydrazide (**180**) in 24% yield. The reaction may proceed by way of the intermediate 1,2,4-oxathiazole (**178**); this decomposes spontaneously into ethoxycarbonyl isothiocyanate (**179**) and carbohydrazide, which recombine to yield **180**. This type of decomposition of 1,2,4-oxathiazoles has in fact been previously reported in detail.[128,129]



177 178 179 180

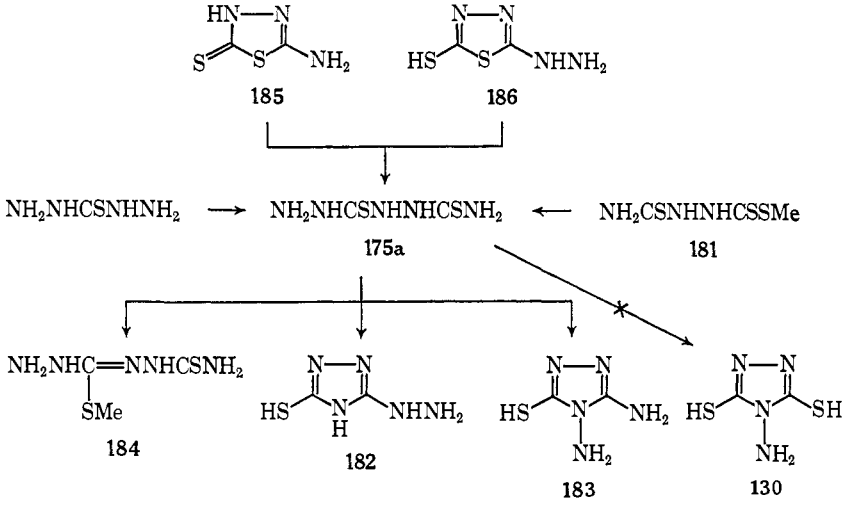
b. Thiocarbohydrazide

The preparation of 1-thiocarbamoylthiocarbohydrazide (**175**, X = S) ("mp 218°") from 2 moles of potassium thiocyanate and 1 mole of thiocarbohydrazide in boiling water, originally claimed by Guha and De,[100] could not be repeated by later investigators,[106,125] but the reaction did afford this product (mp 203–204°) under modified conditions. Equimolar quantities of the reactants in boiling water containing 1 equiv of concentrated hydrochloric acid gave moderate, though erratic yields of **175a**. Diaddition of thiocyanic acid was not observed, but the reaction was complicated by the tendency of both thiocarbohydrazide and the product to cyclize under the prevailing reaction conditions. Of these cyclization products, 3-hydrazino-5-mercapto-1,2,4-triazole (**182**) could be identified,[81] the other being probably 3,4-diamino-5-mercapto-1,2,4-triazole (**183**).[81] The formation of these products, both of which could arise from **175a** by loss of hydrogen sulfide, accounts for the difficulties encountered in the purification of **175a** and for the low yield.

A more effective route to 1-thiocarbamoylthiocarbohydrazide (**175a**) is the hydrazinolysis of 1-dithiomethoxycarbonyl-3-thiosemicarbazide (**181**), which proceeds smoothly and in good yield in ethanol when anhydrous hydrazine is employed. In aqueous media cyclic products are obtained.

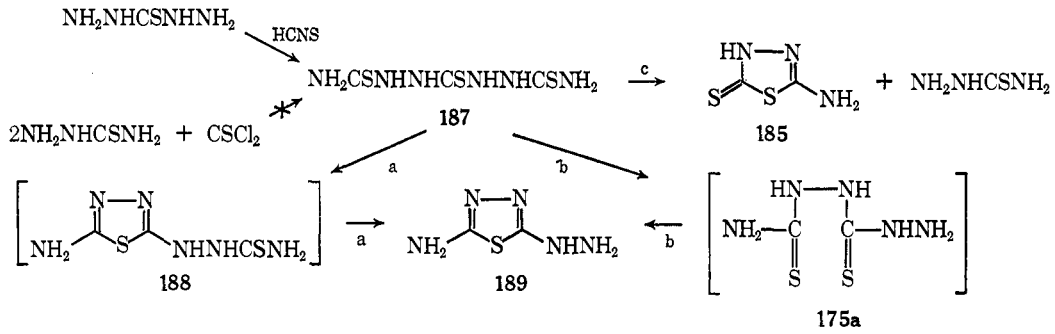
1-Thiocarbamoylthiocarbohydrazide (**175a**), mp 204–205°, crystallizes from water as needles, but is insoluble in most organic solvents. It resists air oxidation when dry, after having been crystallized from a weakly acid solution, but alkaline solutions turn deep red on exposure to air. It reacts readily with carbonyl compounds and may be mono-S-methylated to 1-thiocarbamoyl-S-methylisothiocarbohydrazide (**184**) by the standard method. Evidence that the methyl group is situated on the sulfur atom adjacent to the free hydrazine group is provided by cyclization of **184** to the triazole **182** by alkali, with loss of methanethiol.

Guha and De's[100] alleged 1-thiocarbamoylthiocarbohydrazide (mp 218°) had been reported to be cyclizable to 4-amino-3,5-dimercapto-1,2,4-triazole by concentrated hydrochloric acid. This result was not observed when the authentic reactant **175a** was used;[47,106] the products were in fact 2-amino-Δ^2-1,3,4-thiadiazoline-5-thione (**185**) (in its low-melting form),[130] 2-hydrazino-5-mercapto-1,3,4-thiadiazole (**186**) (as its hydrochloride), and hydrazine dihydrochloride (arising in the former cyclization).[47] 1,5-Di(thiocarbamoyl)thiocarbohydrazide (**187**) is accessible directly from its constituents under carefully controlled conditions. Although the use of potassium thiocyanate in conjunction with thiocarbohydrazide was not successful (see above), the diadduct was obtained in moderate yield by the addition of thiocarbohydrazide sulfate to a threefold excess of ammonium thiocyanate in boiling water.[47] Small amounts of the monoadduct **175a** can be isolated as the benzaldehyde derivative, suggesting its intermediate formation in this reaction. An attempt to synthesize



185 186 175a 181 184 182 183 130

(127) A. Dornow and K. Fischer, *Chem. Ber.*, 99, 72 (1966).
(128) R. Huisgen, W. Mack, and E. Anneser, *Angew. Chem.*, 73, 656 (1961).
(129) R. Huisgen, *ibid.*, 75, 604 (1963).
(130) L. L. Bambas in "The Chemistry of Heterocyclic Compounds," Vol. 4, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1952, p 149 ff.



1,5-di(thiocarbamoyl)thiocarbohydrazide (**187**) from thiophosgene and thiosemicarbazide (*i.e.*, the method that yields the corresponding 1,5-di(carbamoyl) analog without difficulty;[113] see above) was not successful.[47]

Both the mono- and diadduct (**175a** and **187**) have the same melting point and show no depression in melting point on admixture. They have identical crystalline form and resemble one another closely in their solubilities [insoluble in the common organic solvents; diadduct somewhat less soluble in water (0.9 g/100 ml)].[47]

Hot concentrated hydrochloric acid cyclized 1,5-di(thiocarbamoyl)thiocarbohydrazide (**187**) to a mixture of compounds that were separated by fractional dissolution in cold water and selective precipitation with hydrochloric acid.[47] The identified products were 2-amino-5-hydrazino-1,3,4-thiadiazole dihydrochloride (**189**), together with approximately equivalent quantities of thiosemicarbazide hydrochloride and 2-amino-5-thioxo-Δ^2-1,3,4-thiadiazoline (**185**) (low-melting form).[130] The formation of the latter two is readily accounted for by the reaction path c. The thiadiazole **189** arises obviously from **187** by loss of both hydrogen sulfide and the elements of thiocyanic acid, suggesting the possible reaction paths a or b. Path b involves 1-thiocarbamoylthiocarbohydrazide (**175a**) as intermediate, which is known (see above) to undergo cyclization in concentrated hydrochloric acid to give products *not* including **189**. The present cyclization is therefore concluded to proceed by route a.[47]

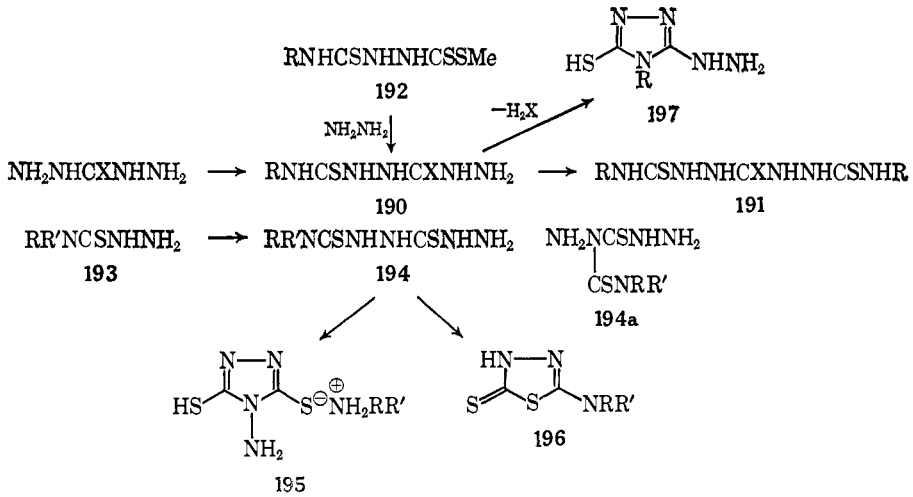
tures such as **187** tends to produce 1,3,4-thiadiazoles in acid and 1,2,4-triazoles in alkaline media.

4. Addition of Isothiocyanate Esters

(Thio)carbohydrazides condense rapidly[27,36,65,133] in high yield with a variety of aryl isothiocyanates in dimethylformamide or alcohol to give the sparingly soluble 1,5-di(arylthiocarbamoyl)(thio)carbohydrazides **191** (X = O, S; R = Ar). Monoadducts **190** cannot, apparently, be isolated; both hydrazino groups react so rapidly that even the use of only 1 mole of isothiocyanate[36] yields the diadducts **191**.

A 1-(alkylthiocarbamoyl)thiocarbohydrazide **190** (X = S; R = *i*-Bu) has recently been described[134] but was prepared by a different route. Treatment of 4-isobutyl-1-dithiomethoxycarbonyl-3-thiosemicarbazide (**192**, R = *i*-Bu) with hydrazine hydrate in boiling ethanol gave 1-(isobutylthiocarbamoyl)-thiocarbohydrazide (**190**, R = *i*-Bu) in moderate yield, together with 4-isobutyl-3-hydrazino-5-mercapto-1,2,4-triazole (**197**, R = *i*-Bu). This reaction had previously been wrongly interpreted.[133] In contrast, the 4-phenyl analog[134,135] **192** (R = Ph) yields on hydrazinolysis only cyclized products, one of which is **197** (R = Ph). Clearly, the aromatic intermediate **190** (R = Ph) is unstable under the prevailing conditions, whereas the alkyl derivative is not. The stability of a larger number of the monoadducts **190** would clearly need to be examined to allow a valid generalization to be made.

A third route to (alkyl thiocarbamoyl)thiocarbohydrazides

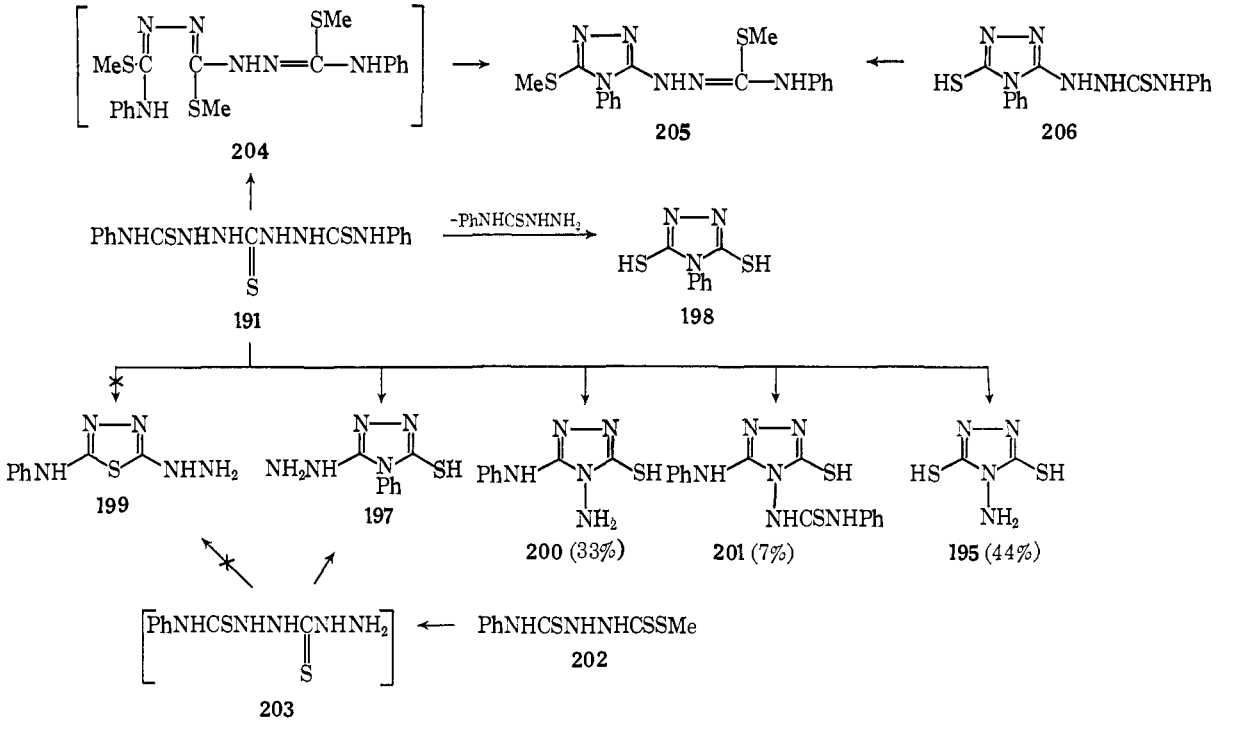


Attention may be drawn to the exclusive formation of thiadiazoles in this reaction. This is in accord with the rules formulated by Arndt[108,131,132] that ring closure of thioamido struc-

194 (R = R′ = CH_3, C_2H_5, or C_3H_7) is the thermolysis of 4,4-dialkylthiosemicarbazides (**193**).[136] The diethyl and di-

(131) F. Arndt and F. Bielich, *Chem. Ber.*, **56**, 2276 (1923).
(132) F. Arndt, E. Milde, and F. Tschenscher, *ibid.*, **55**, 349 (1922).
(133) R. S. McElhinney, *J. Chem. Soc., C*, 1256 (1956).
(134) F. Kurzer and M. Wilkinson, *ibid.*, 2108 (1968).
(135) A. Dornow and H. Paucksch, *Chem. Ber.*, **99**, 81 (1966).
(136) C. Larsen and E. Binderup, *Acta Chem. Scand.*, 21, 1984 (1967).

propyl homologs **193** (R = R′ = C_2H_5, C_3H_7) are converted at 110° (0.2 mm) into compounds formulated as **194** (R = R′ = C_2H_5, C_3H_7), but the alternative structure **194a** has not been conclusively rejected. The dimethyl compound, on thermolysis at 165°, gave the dimethylamine salt of 4-amino-3,5-dimercapto-1,2,4-triazole (**195**) and 2-dimethylamino-1,3,4-thiadiazolin-5-thione (**196**), probably by way of the intermediate **194** (R = R′ = CH_3).



(Alkylthiocarbamoyl)thiocarbohydrazides (**190**) are converted into the corresponding hydrazones by aldehydes and ketones as expected.[137] Though monoalkylthiocarbamoylcarbohydrazides (**190**, X = O; R = Alk) have not been described, there is no reason to believe that they could not be synthesized by the established general procedures.

Cyclization of 1,5-Di(arylthiocarbamoyl)(thio)carbohydrazides. The cyclization of 1,5-di(arylthiocarbamoyl)carbohydrazides (**191**, X = O) has so far not been examined, but that of a thio analog has been studied in detail under various conditions.[135,138] Thus, 1,5-di(phenylthiocarbamoyl)thiocarbohydrazide (**191**, X = S) is cyclized almost quantitatively by boiling 2 *N* sodium hydroxide to 3,5-dimercapto-4-phenyl-1,2,4-triazole (**198**) with presumed loss of 4-phenyl-3-thiosemicarbazide.[135]

Cyclization also occurs rapidly in boiling pyridine;[135] this reaction proceeds less uniformly, giving the three 1,2,4-triazoles **200**, **201**, **195** (the last a pyridinium salt), as well as the supposed 1,3,4-thiadiazole **199**. The products were separated almost quantitatively from one another, and, except for **199**, were identified satisfactorily.[135] The alleged 2-anilino-5-hydrazino-1,3,4-thiadiazole (**199**), which was also prepared[135] by the hydrazinolysis of 1-dithiomethoxycarbonyl-4-phenyl-3-thiosemicarbazide (**202** → **203** → "**199**") has since been identified[134] as 3-hydrazino-5-mercapto-4-phenyl-1,2,4-triazole (**197**). During later attempts[134] to repeat the pyridine cyclization, this product could not in fact be obtained at all. The original report[135] had not specified the conditions of the cyclization precisely; according to Arndt's[108,131,132] generalization, supported by much subsequent evidence, the formation of a 1,3,4-thiadiazole under *basic* conditions in the above reaction must be regarded as most unlikely.

Yet another cyclization of 1,5-di(phenylthiocarbamoyl)thiocarbohydrazide (**191**, X = S) occurs almost quantitatively, with simultaneous S-methylation, under the influence of methyl iodide–methanolic potassium hydroxide (24 hr at room temperature).[138] The structure of the product, 1-(3-methylthiol-4-phenyl-1,2,4-triazol-5-yl)-4-phenyl-3-methylisothiosemicarbazide (**205**), was verified by its chemical reactions,[138–140] and by its identity with material obtained from 3-hydrazino-5-mercapto-4-phenyl-1,2,4-triazole (**206**) by treatment with phenyl isothiocyanate and subsequent di-S-methylation.[134]

L. REACTION WITH CARBODIIMIDES

Like other heterocumulenes[142] diarylcarbodiimides react additively[141] with (thio)carbohydrazides. Under the prevailing conditions, the primary adducts usually undergo immediate further cyclization reactions.

Thus, thiocarbohydrazide reacts with 2 moles of diarylcarbodiimide in dimethylformamide or dimethyl sulfoxide to yield 5-arylamino-4-(N,N′-diaryl)guanidino-3-mercapto-1,2,4-triazoles (**210**) as principal products (45–55%). Carried out in methanol, the reaction also yields appreciable quantities of 4-aryl-3-arylamino-5-mercapto- (**214**) and 4-aryl-3,5-diarylamino-1,2,4-triazoles (**215**), with corresponding lowering of yields of **210**. The structure of the new class of triazoles **210** was established by the alternative synthesis of their 5-alkyl-

(137) V. E. Bogachev (to Organisation of the State Committee for Defence, USSR), USSR Patent 174,635 (1965); *Chem. Abstr.*, **64**, 8047 (1966).

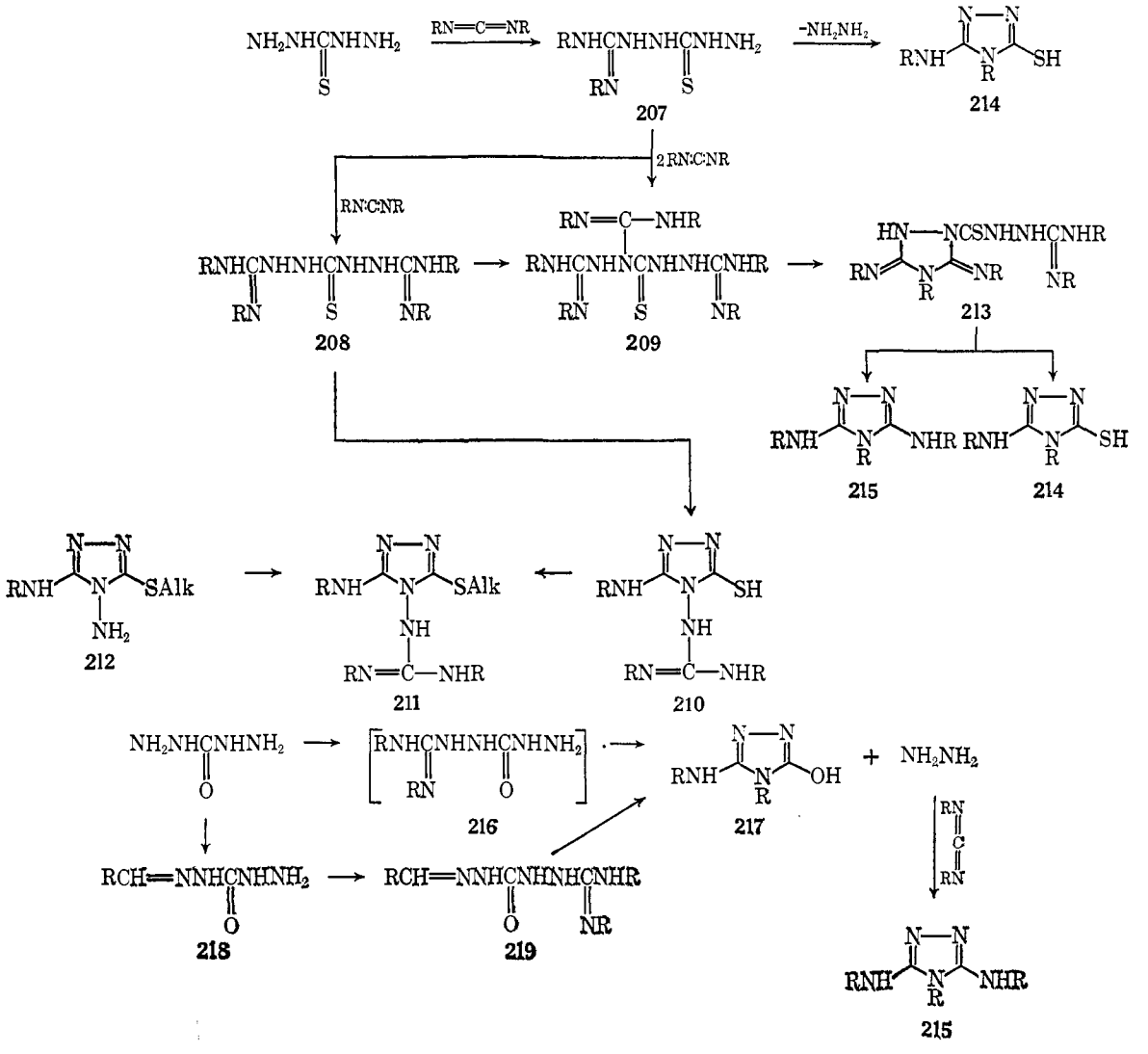
(138) A. Dornow and H. Paucksch, *Chem. Ber.*, **99**, 85 (1966).

(139) E. Hoggarth, *J. Chem. Soc.*, 614 (1950).

(140) H. Gehlen and G. Röbisch, *Ann.*, 660, 148 (1962).

(141) F. Kurzer and M. Wilkinson, *J. Chem. Soc., C*, 2099 (1968).

(142) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967.



thiol derivatives **211** from authentic 5-alkylthio-4-amino-3-arylamino-1,2,4-triazoles (**212**) and diarylcarbodiimides.[141]

The formation of the main products **210** is accounted for by the cyclization, with loss of arylamine, of the intermediate symmetrical diadduct **208**. The production of the triadduct **209** and its subsequent cyclization to **213**, followed by prototropic fission and ring closure of the severed side chain, accounts for the production of the by-products **214** and **215**. The latter might also arise directly by cyclization of the primary monoadducts **207**, the eliminated hydrazine reacting with excess of carbodiimide to produce **215**.[143] These and other possible mechanisms have been discussed, and the analogous behavior of thiocarbohydrazide and diaminoguanidine[144] in this series of reactions emphasized.[141]

Carbohydrazide yields, in this reaction,[145] 4-substituted 3-anilino-5-hydroxy-1,2,4-triazoles (**217**). The 4-aryl-3,5-diarylamino-1,2,4-triazoles (**215**) that are formed as by-product may again arise by interaction of eliminated hydrazine and excess of carbodiimide.[143] Monocarbohydrazones derived from aromatic aldehydes and carbodiimides form stable adducts **219** that may be isolated in satisfactory yield; they are cyclized by boiling mineral acid, and more effectively upon thermolysis, to the hydroxy-1,2,4-triazoles **217**.

M. ACTION OF NITROUS ACID

Depending on conditions, the reaction of carbohydrazide with nitrous acid yields either carbonyl azide (**220**) or hydrazidocarbamoyl azide (**221**).[1,2,18,146,147]

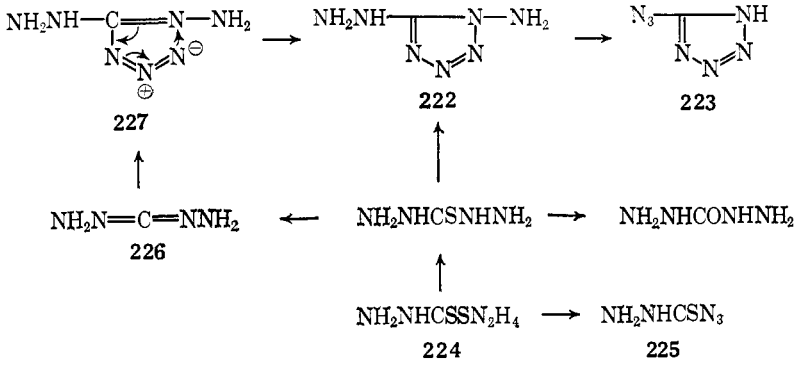
N_3CON_3 **220** $N_3CONHNHCON_3$ **221**

The use of a two-phase system (water–benzene) during the diazotization gives a mixture containing the diazide **221** in the benzene layer,[18] from which it may be isolated in 20% yield. Addition of the calculated amount of hydrochloric acid to a mixture of carbohydrazide and sodium nitrite in the absence of a solvent affords carbonyl azide (**220**). This highly explosive compound, which decomposes violently even under ice-water,[18] was identified by its conversion into *sym*-diphenylurea by aniline.

N. ACTION OF HYDRAZOIC ACID

Thiocarbohydrazide, on treatment with lead oxide and sodium azide in boiling ethanol in an atmosphere of carbon dioxide,

(143) M. Busch and Th. Ulmer, *Chem. Ber.*, **35**, 1721 (1902).
(144) F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc.*, 3912 (1965); *C*, 742 (1967).
(145) F. Kurzer and M. Wilkinson, *ibid.*, in press.
(146) T. Curtius and K. Heidenreich, *Chem. Ber.*, 27, 2684 (1894).
(147) E. Lieber, R. L. Minnis, Jr., and C. N. R. Rao, *Chem. Rev.*, **65**, 377 (1965).

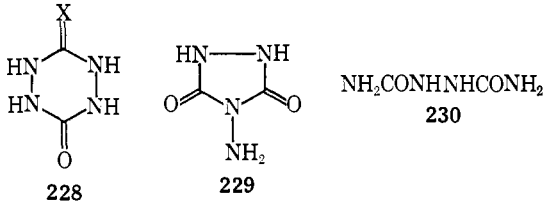


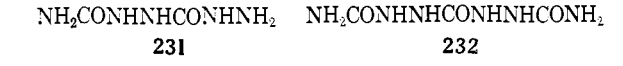
yields 1-amino-5-hydrazinotetrazole (**222**).[40] Di(benzylidene)-thiocarbohydrazide affords the corresponding dibenzylidene derivative, which is convertible into **222** by hydrolysis. The tetrazole **222** was also obtained (together with thiocarbohydrazide, carbohydrazide, and thiocarbazic acid azide (**225**)) when hydrazine dithiocarbazate (**224**) was treated with lead oxide and sodium azide. The tetrazole **222** reacts with nitrous acid to yield the very explosive azide **223**. The production of the tetrazole **222** probably involves the intermediate formation of the carbodiimide structure **226** by desulfurization of thiocarbohydrazide by lead oxide,[148] a general reaction that is well documented.[149] Subsequent addition of hydrazoic acid to the carbodiimide **226** would yield the imidyl azide **227**, which would then cyclize spontaneously to the tetrazole **222**. The cyclization of azides of this type **227** is a well-known general route to 1,5-disubstituted tetrazoles.[150a,151]

O. REACTION WITH UREA

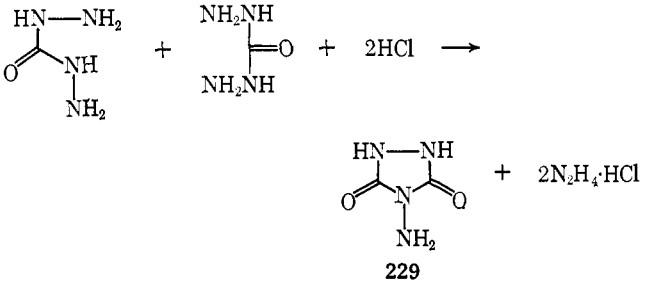
The interaction of carbohydrazide and thiocarbohydrazide with urea at elevated temperatures was first examined by Guha and De[27] who formulated the resulting products as "*p*-urazine" (**228**, X = O) and "thio-*p*-urazine" (**228**, X = S), respectively. The latter arose also in the interaction of carbohydrazide and potassium ethyl xanthate in closed vessels (*cf.* section IV.J.2). In a discussion of this work, Wiley[104,105] came to the conclusion that Guha and De's alleged "*p*-urazine" was formulated more satisfactorily as 4-amino-1,2,4-triazolidine-3,5-dione (**229**). [It is noteworthy that the same author agrees, in another review,[104] with the "dithio-*p*-urazine" structure **129** (X = S) assigned to a compound very similarly obtained (*cf.* section IV.J.2).]

The triazolidine structure **229** has recently been confirmed by a detailed reinvestigation[106] of this group of reactions which showed that the published methods allegedly yielding "*p*-urazine" (not all of which use carbohydrazide as starting material) produce in fact the known 4-amino-1,2,4-triazolidine-3,5-dione (**229**) or biurea (**230**). Thus, the fusion of urea with either carbohydrazide[27,100] or thiocarbohydrazide[27] gives biurea (**230**).[106] Yet another careful examination[152] of this reaction again failed to yield "*p*-urazine," but produced no less than three open-chain compounds, *viz.* biurea (**230**), 1-carbamoylcarbohydrazide (**231**), and 1,5-dicarbamoylcarbohydrazide (**232**) (*cf.* Tabl V).[128,153]





Self-Condensation of Carbohydrazide. Carbohydrazide undergoes self-condensation, with loss of hydrazine, yielding 4-aminourazole (**229**) in 73% yield on treatment with 12 *M* hydrochloric acid at 220° during 4 hr.[91]



P. REACTION WITH HYDRAZINE

It is expedient to deal first with the hydrazinolysis of S-alkylisothiocarbohydrazides; this reaction takes a more straightforward course than that of the parent thiocarbohydrazide itself.

The well-known synthesis of guanidine and its mono-**233** and diamino derivatives **234** by the aminolysis[154] and hydrazinolysis[155,156] of S-alkylisothioureas and S-alkylisothiosemicarbazides, may be applied to the production of triaminoguanidine (**235**)[52] as expected.

Thus, hydrazinolysis of S-methylisothiocarbohydrazide proceeds smoothly and rapidly in ethanol to give **235** in good yield. The method has been successfully extended to N-substituted S-methylisothiocarbohydrazide,[52] so that the corresponding substituted triaminoguanidines have become avail-

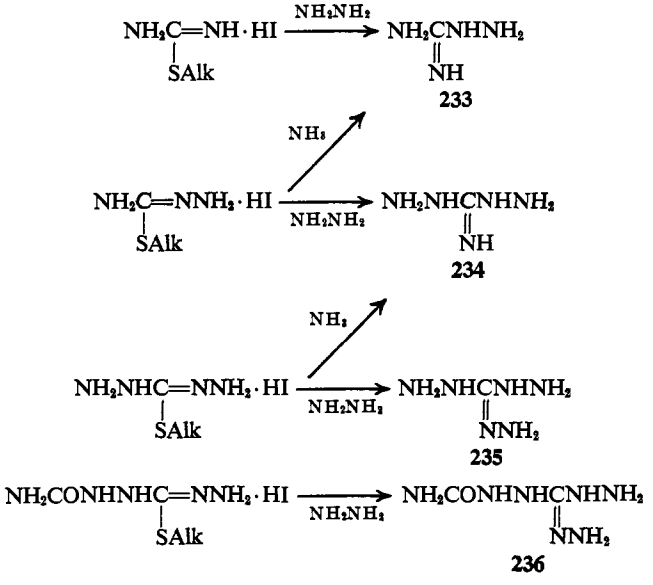
(148) R. Stollé, *Chem. Ber.*, **55**, 1289 (1922).
(149) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, 67, 108 (1967).
(150) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966: (a) p 243; (b) p 127.
(151) P. A. S. Smith, *J. Am. Chem. Soc.*, **76**, 436 (1954).
(152) F. Eloy and C. Moussebois, *Bull. Soc. Chim. Belges*, **68**, 433 (1959).
(153) P. F. Wiley, *J. Am. Chem. Soc.*, 76, 5176 (1954).
(154) S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 2492 (1951).
(155) G. B. L. Smith and E. Anzelmi, *J. Am. Chem. Soc.*, 57, 2730 (1935).
(156) G. I. Keim, R. A. Henry, and G. B. L. Smith, *ibid.*, 72, 4944 (1950).

Table V

Interaction of Urea and Carbohydrazide[152]

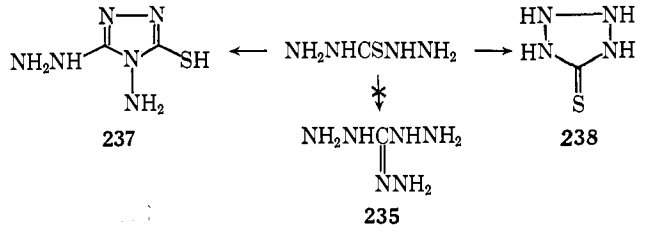
Carbohydrazide, mole	*Urea, moles*	*Temp, °C*	*Time, hr*	*Product*	*Ref to alternative syn*	*Ref*
1	4	120	4	**232**	Carbohydrazide + 2HOCN	123
1	1	120	4	**231**	Carbohydrazide + 1HOCN	123
1	1	200	4	**230**	Semicarbazide + NaOBr	153

able. Thus 1-carbamoylthiocarbohydrazide[125] gave, on successive S-methylation and hydrazinolysis, 1,2-diamino-3-ureidoguanidine hydriodide (**236**).[125] Efforts to synthesize this product directly from triaminoguanidine and cyanic acid, however, were not successful.[52]



In contrast to the ease with which S-alkylisothiocarbohydrazides lose alkanethiol by displacement with hydrazine, thiocarbohydrazide does not eliminate hydrogen sulfide to any appreciable extent,[52] and loss of water from carbohydrazide under the same conditions does not occur at all. The hydrazinolysis of thiocarbohydrazide is further complicated in that both the reactant and product are unstable in the alkaline medium: thiocarbohydrazide is cyclized, with loss of hydrogen sulfide, to 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (**237**).[3]

By performing the hydrazinolysis in an effectively acidic medium[52] (hydrazine monohydrochloride and thiocarbohydrazide in aqueous solution), cyclization is prevented and any triaminoguanidine formed stabilized, but yields of only 3% of triaminoguanidine, together with large quantities of recovered thiocarbohydrazide, are obtained on prolonged boiling. The interaction of equimolar proportions of the hydrochlorides of hydrazine and thiocarbohydrazide at 170–180° is reported to give very poor yields of tetrazolidine-5-thione (**238**) but no structural proof is on record.[100]



V. Alkyl and Aryl Homologs of (Thio)carbohydrazide

The following sections deal systematically with aliphatic and aromatic homologs of (thio)carbohydrazide, in order of increasing structural complexity. 1,5-Diaryl- (and alkyl-) carbohydrazides and their thio analogs, however, are excluded from the present review, having been adequately treated elsewhere.[7,8,157–159] In particular, the 1,2-dehydro derivative of 1,5-diphenylthiocarbohydrazide (*i.e.*, PhN=NCSNHNHPh), generally known as "1,5-diphenylthiocarbazone" or "dithizone," is a most important complexing reagent and is widely used in analytical practice for the detection of minute quantities of metals. A comprehensive review dealing exclusively with this compound forms part of Reid's "Organic Chemistry of Bivalent Sulphur."[4b]

A. 1-ARYL(THIO)CARBOHYDRAZIDES

1. Synthesis

a. Hydrazinolysis of (Thio)carbazic Esters

1-Aryl(thio)carbohydrazides (**240**) are produced conveniently by the hydrazinolysis of alkyl aryl(thio)carbazates **239** (X = O, S; R = Me, Et). In the preparation of the oxygen compounds **240** (X = O), the ethyl esters **239** (X = O; R = C_2H_5) are heated in ethanolic hydrazine to 120–125° in closed vessels[160,161] or preferably in refluxing hydrazine hydrate.[170] Although small quantities of starting material are recovered, the yields are usually good (Table VI). The hydrazinolysis of alkyl thiocarbazates proceeds in refluxing methanol[170] and ethanol[162] in satisfactory yields.

Table VI

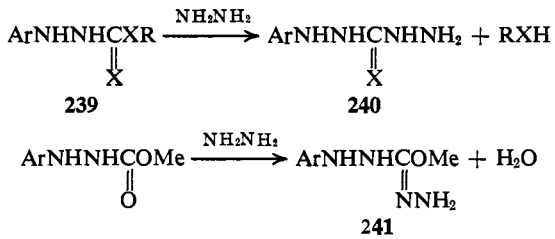
Preparation of 1-Arylcarbohydrazides 240

Ar	*Mp, °C*	*Yield, %*
Ph	151[a]	60
o-$CH_3C_6H_4$	153	43
p-$CH_3C_6H_4$	149	100

[a] Correct mp 131°.[170]

(157) M. Freund and F. Kuh, *Chem. Ber.*, 23, 2821 (1890).
(158) S. Skinner and S. Ruhemann, *J. Chem. Soc.*, 53, 550 (1888).
(159) M. Mistry and P. C. Guha, *J. Indian Chem. Soc.*, 7, 793 (1930).
(160) P. C. Guha and M. A. Hye, *ibid.*, 7, 933 (1930).
(161) M. M. J. Sutherland and F. J. Wilson, *J. Chem. Soc.*, 125, 2145 (1924).
(162) P. C. Guha and S. K. Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 149 (1928).

The hydrazinolysis of methyl arylcarbazates[163,164] in sealed tubes gives anomalous results; unlike the ethyl esters, they do not lose the elements of alcohol, but are attacked at their carbonyl functions to yield 1-aryl-3-O-methylcarbohydrazides (**241**). These compounds, if correctly formulated, appear to be the first known examples of O-alkylcarbohydrazides; the same authors[163] also report the preparation of certain O-aryl derivatives (see section VI.A.1).



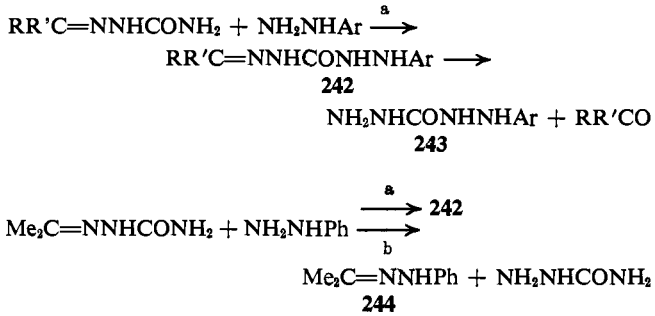
239 **240**

241

b. Hydrazinolysis of Semicarbazones

1-Substituted carbohydrazides (in the form of their carbohydrazones **242**) are also accessible by the hydrazinolysis, using arylhydrazines, of semicarbazones.[161] Equimolar quantities of the reactants are refluxed in toluene until ammonia ceases to be evolved. The resulting carbohydrazones **242** are hydrolyzed to 1-arylcarbohydrazides (**243**) by dilute hydrochloric acid. More concentrated acid cleaves the products into ketone, hydrazine, phenylhydrazine, and carbon dioxide.

Depending on the nature of the semicarbazone used, the reaction may take another course (path b), yielding merely semicarbazide and the appropriate phenylhydrazone **244**.[161] In an examination of this effect,[165] the behavior of 7 aldehydes and 14 ketones was examined: all the aldehyde hydrazones, except that from *n*-heptaldehyde (which gave 8% yields of **242**), reacted according to path b.



242 **243**

244

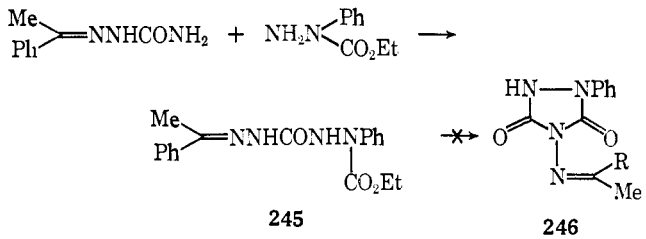
Table VII

Preparation of 1-Phenylcarbohydrazones (242, Ar = Ph)

R	*R'*	% *yield*	*R*	*R'*	% *yield*
Me	Me	5	Me	Ph	95
Me	Et	0	Me	$PhCH_2$	13
Me	*n*-Pr	0	Me	$PhCH_2CH_2$	8
Et	Et	2	$PhCH_2$	$PhCH_2$	90
Me	*t*-Bu	60	Ph	Ph	95
n-Pr	*n*-Pr	13	Cyclohexanone		12
i-Pr	*i*-Pr	90	1-Methylcyclohexan-2-one		10

Reactions involving the ketonic semicarbazones generally proceeded by *both* pathways. The yields of the desired 1-phenylcarbohydrazones **242** (Ar = Ph) obtained from various ketone semicarbazones are given in Table VII. The observations suggest that the size of the groups R and R' may be of significance: when both substituents are sufficiently bulky, the formation of the phenylhydrazone **244** is inhibited and the reaction proceeds by pathway a. Further results concerning different hydrazines appear to support this conclusion. Thus, while acetone semicarbazone and phenylhydrazine give only 10% of the substituted carbohydrazone **242** (R = R' = Me; Ar = Ph), the use of 1-methyl-1-phenylhydrazine results in 52% yields of the methyl homolog **242**, and 1,1-diphenylhydrazine affords the appropriate carbohydrazone in 80% yield.

A further interesting structural variant **245** of arylcarbohydrazides was obtained[165] by this general reaction from acetophenone semicarbazone and 1-ethoxycarbonyl-1-phenylhydrazine. Attempts to ring-close this product to the triazole **246** failed, however, extensive decomposition taking place.



245 **246**

Efforts to apply the present reaction to the hydrazinolysis of thiosemicarbazones as a route to 1-arylthiocarbohydrazides have so far not met with success.[166]

2, *Chemical Properties*

1-Aryl(thio)carbohydrazides are white crystalline solids, soluble in water, ethanol, and mineral acids. In common with their parent compound (see section IV.B), aromatic thiocarbohydrazides display amphoteric character: they form both hydrochlorides (*e.g.*, 1-phenylthiocarbohydrazide hydrochloride, mp 181°) and are soluble in alkalis, from which they are precipitated by acids.[160,162]

The (thio)carbonylhydrazide moiety of 1-aryl(thio)carbohydrazides retains the properties typical of this functional group. 1-Substituted (thio)carbohydrazides therefore resemble their parent compounds, and a number of parallel reactions may be usefully contrasted and compared with one another.

a, Condensation with Carbonyl Compounds

i. Aldehydes and Ketones. 1-Aryl(thio)carbohydrazides react at their free hydrazino group with a wide variety of aldehydes and ketones forming the expected 1-aryl(thio)carbohydrazones in high yield.[160,162] The condensation of phenylthiocarbohydrazide and *o*-chlorobenzaldehyde[162] does not yield the substituted carbohydrazone **247**, however, but proceeds with cyclization to a product that has been formulated as **248**. The structure of this product, which would arise by a ring closure recalling a standard synthesis of benzthiazoles,[167] needs final confirmation.

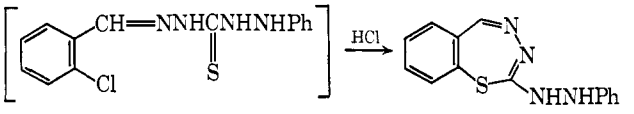
(163) E. P. Nesynov and P. S. Pelkis, *Dopovidi Akad. Nauk Ukr. RSR*, 8, 1080 (1962); *Chem. Abstr.*, **58**, 10,117 (1963); *Zh. Org. Khim.*, **4**, 837 (1968).

(164) P. S. Pelkis and E. P. Nesynov, USSR Patent 165,748 (1964); *Chem. Abstr.*, 62, 10384 (1965).

(165) W. Baird and F. J. Wilson, *J. Chem. Soc.*, 2367 (1926).

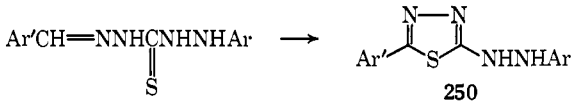
(166) W. Baird and F. J. Wilson, *ibid.*, 2114 (1927).

(167) J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, New York, N. Y., 1957, pp 484, 512.



247 248

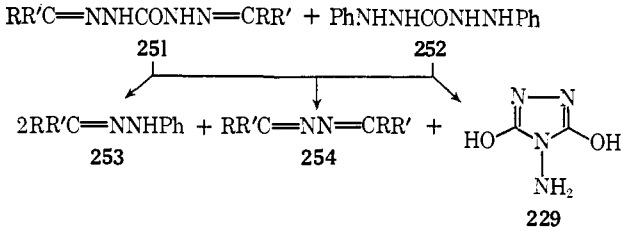
The arylthiocarbohydrazones **249** undergo oxidative cyclization with ferric chloride solution,[162] affording 2-aryl-5-phenylhydrazino-1,3,4-thiadiazoles (**250**) in undisclosed yields.



249 250

On thermolysis, 1-phenylcarbohydrazones are reported[165,166] to yield 4-aminourazole (**229**), together with the phenylhydrazone **253** of the parent carbonyl compound, and a small amount of the substituted ketazine **254**, probably by the scheme outlined below.

The ketazine **254** may arise from the intermediate carbohydrazone **251** which is known[53] to yield **229** and **254** under these conditions. The soundness of the overall reaction scheme is supported by the observation that diacetone carbohydrazone (**251**, R = R′ = CH_3) and diphenylcarbohydrazide (**252**) yield, on being heated together, the same three products **253**, **254**, and **229**. Further, the reaction of acetone 1,1-diphenylcarbohydrazone was observed to conform to the general scheme.



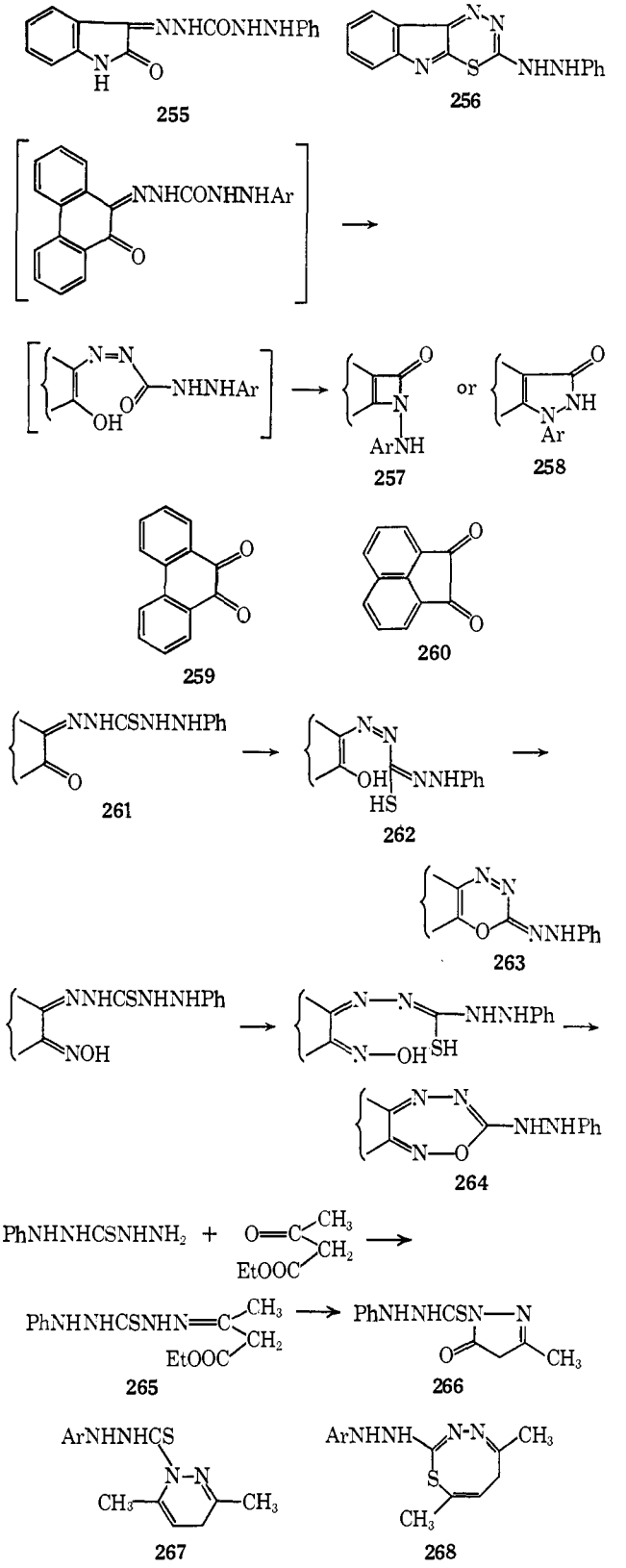
251 252 253 254 229

ii. Condensation with ortho Diketones. The condensation of phenyl(thio)carbohydrazide and aromatic diketones (as well as β-ketonic esters and their α-halogenated derivatives; see subsequent two sections) was examined in 1928–1930 by Guha and his coworkers.[160,162] The reactions generally proceed by the initial formation of (thio)carbohydrazones, followed by cyclization to various heterocyclic systems. It is unfortunate that no adequate proofs were produced supporting the formulation of the variety of products that were described.

Phenylcarbohydrazide reacts with isatin in hot acetic acid to form[160] the monohydrazone **255**, but phenylthiocarbohydrazide affords the substituted thiadiazine **256**.[162]

Arylcarbohydrazides also condense with phenanthraquinone in hot acetic acid,[160] with simultaneous cyclization involving loss of nitrogen and the elements of water. Of the two formulations (**257**, **258**) considered for the products, **258** was discounted because of their alkali insolubility, but confirmation of **257** would clearly be desirable.

The reaction of 1-phenylthiocarbohydrazide (and its *m*-tolyl homolog) with *ortho* diketones such as phenanthraquinone (**259**) and acenaphthaquinone (**260**) also proceeds with cyclization, but yields oxadiazine derivatives **263** by loss of hydrogen sulfide.[162] In the same reaction, phenanthraquinone monoxime yields an "oxaheptatriazine" (**264**) by an analogous mechanism.

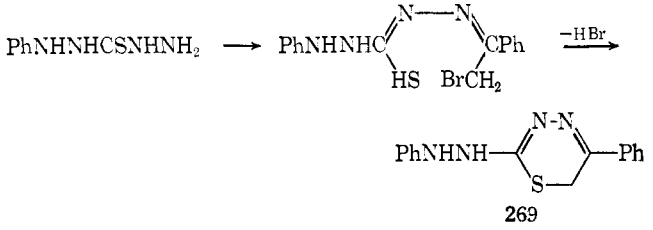


255 256 257 258 259 260 261 262 263 264 265 266 267 268

iii. Reaction of β-Ketonic Esters and 1,4-Diketones. 1-Phenylthiocarbohydrazide and acetoacetic ester yield initially a thiocarbohydrazone **265** which may be isolated or cyclized *in situ* by sodium ethoxide to the pyrazolone **266**.[162]

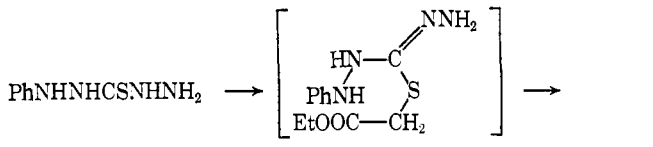
The analogous condensation with acetonylacetone does not proceed to form the expected compound **267** but rather the thiaoctadiazine **268**. Its formulation requires confirmation.

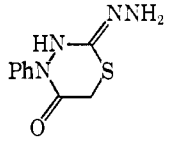
iv. Action of Halogenated Ketones and Esters. 1-Phenylthiocarbohydrazide is reported[162] to condense with bromoacetophenone at room temperature in acetic acid to form the thiadiazine **269** by the route shown, resembling the corresponding reaction of the parent thiocarbohydrazide (see section IV.I.1.a).



269

Monochloroacetic ester,[162] rather surprisingly, gave a product still retaining a free hydrazino function, as shown by its readiness to form a benzaldehyde derivative. The reaction was therefore thought to proceed as outlined in the reaction scheme below, giving **270**. Once again, not only is proof supporting these formulations lacking, but the authors' case is weakened by inconsistencies in their interpretation of the behavior of phenylthiocarbohydrazones (*e.g.*, PhNHNHCSNHN=CHPh) in these two reactions. The products of these reactions, differing from one another in physical properties and being obviously distinct, were written as **271** and **272**, which are of course seen to be identical structures.





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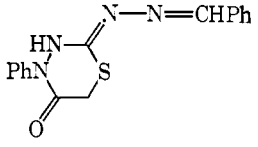

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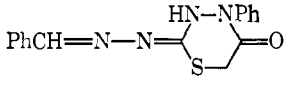
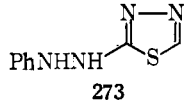


272

b. Reaction with Carboxylic Acids and Their Derivatives

Information concerning the interaction of 1-phenylthiocarbohydrazide and 100% formic acid is not satisfactory.[21,168] Two successive reports from the same laboratory formulate the product as 2-phenylhydrazino-1,3,4-thiadiazole (**273**)[168] or as the acyclic adduct **274**, a different analysis being given in support in each case.



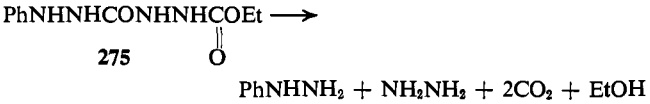
273

PhNHNHCSNHNHCHO

274

Treatment of phenylthiocarbohydrazide with acetic anhydride at room temperature yields a monoacetyl derivative.[168] Ring closure was not observed, even on heating.

1-Phenylcarbohydrazide reacts rapidly with ethyl chloroformate in aqueous solution to form the 5-ethoxycarbonyl derivative **275**.[160] This is degraded by hot concentrated hydrochloric acid; cyclization is not observed.

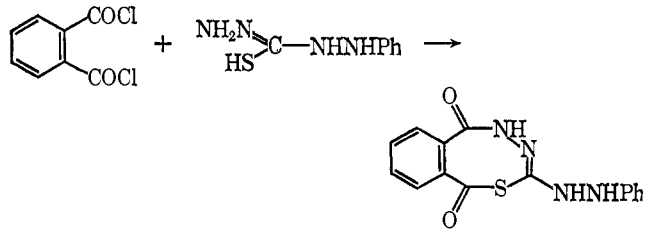


275

$$PhNHNH_2 + NH_2NH_2 + 2CO_2 + EtOH$$

Reaction with Acid Chlorides (see also section VI). The action of acetyl chloride, benzoyl chloride, and phosgene in various solvents on 1-phenylthiocarbohydrazide has in all cases resulted merely in the conversion of the reactant into its hydrochloride, no other product being obtained.[168] This surprising result may possibly have been due to hydrolysis of the acid chlorides to hydrochloric acid by wet solvents or atmospheric moisture before they could exert their acylating action.

Reaction with phthaloyl chloride in benzene is reported[168] to yield the so-called "octathiadiazine" (**276**) in high yield. Malonyl chloride analogously forms a "heptathiadiazine" (**277**).



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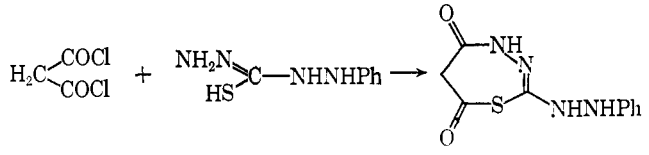

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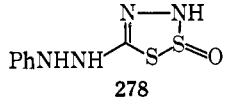
Thionyl chloride cyclizes the substituted thiocarbohydrazide to the dithiodiazole **278**. Phosgene, though failing to react with 1-phenylthiocarbohydrazide, reacts with and cyclizes the benzaldehyde derivative readily to a substituted thiadiazolone **279**.[168] This difference in behavior is stated to be due to the lower basicity of the hydrazone, which consequently does not form a hydrochloride as does the parent hydrazide.[168]



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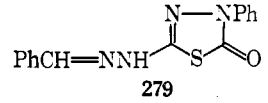


279

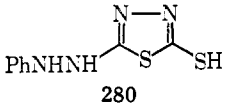
In none of the above instances (**276–279**) was adequate evidence produced in support of the assigned structures, which must therefore be regarded with reserve.

c. Reaction with Carbon Disulfide

The reaction of 1-phenyl(thio)carbohydrazide and carbon disulfide in ethanolic potassium hydroxide closely resembles that of their parent bases (see section IV.J.1).[160,168] The cyclic product from phenylthiocarbohydrazide, formulated[168] as 2-mercapto-5-phenylhydrazino-1,3,4-thiadiazole (**280**), should,

(168) P. C. Guha and S. K. Roy-Choudhury, *J. Indian Chem. Soc.*, 5, 163 (1928).

in the light of later corrections concerning the parent compounds, almost certainly be reformulated as 4-anilino-3,5-dimercapto-1,2,4-triazole (**281**).



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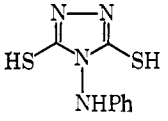

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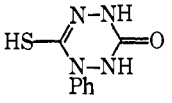

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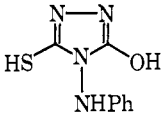


283

Arylcarbohydrazides, in their reaction with carbon disulfide at room temperature, first yield potassium dithiocarboxylates, ArNHNHCONHNHCSSK, that may be isolated. The cyclic product, formed with evolution of hydrogen sulfide at reflux temperature, has been formulated[160] as "1-N-phenylmonothiourazine" (**282**). For the reasons mentioned above, it should very probably be reformulated as 4-anilino-3-hydroxy-5-mercapto-1,2,4-triazole (**283**).

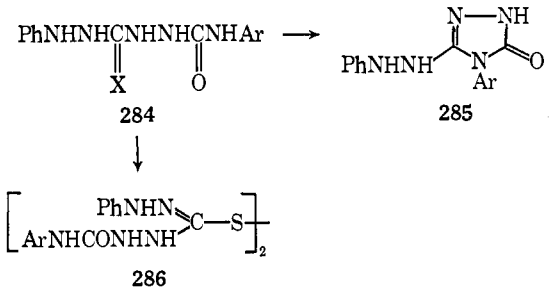
d. Reaction with Cyanic Acid and Isocyanate Esters

1-Phenylcarbohydrazide hydrochloride reacts additively with aqueous potassium cyanate[160] to form 1-carbamoyl-5-phenylcarbohydrazide, identical with the product obtained from 1-phenylcarbohydrazide and urea (see section IV.O).

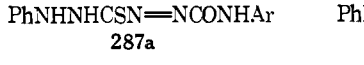
1-Phenyl(thio)carbohydrazides react in an equally straightforward manner[160,168] with aryl isocyanates to yield the sparingly soluble 1-arylcarbamoyl-5-phenyl(thio)carbohydrazides (**284**, X = O, S).

The oxygen and sulfur analogs differ markedly from one another in their tendency toward cyclization. 1-Phenyl-5-phenylcarbamoylcarbohydrazide (**284**) (X = O; Ar = Ph) is recovered unchanged after being boiled with concentrated hydrochloric acid.[160] On the other hand, the sulfur analogs **284** (X = S) are ring-closed[168] by boiling aqueous 20% potassium hydroxide to triazoline-3-ones **285**, though in small yield.

$PhNHNHCXNHNH_2 + ArNCO \longrightarrow$



284 **285** **286**



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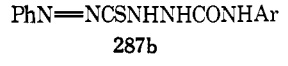


287b

The action of ferric chloride on 1-aryl-5-arylcarbamoylthiocarbohydrazides (**284**, X = S), resulting in dehydrogenation, was thought to give the disulfide **286**. However, the product is described as a red crystalline solid, insoluble in alkali; it may therefore be in fact an azo compound such as **287a** or **b**; oxidation of 1,5-disubstituted thiocarbohydrazides to this type of red azo compound is well known.[169]

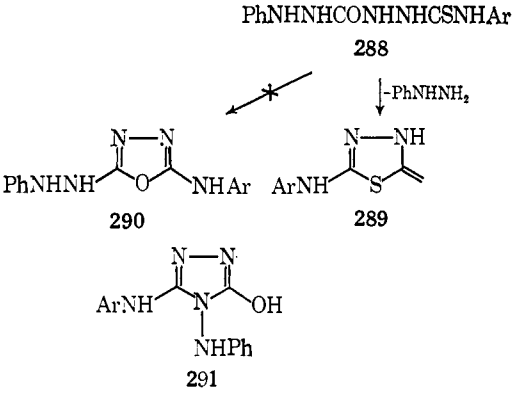
e. Reaction with Isothiocyanate Esters

i. 1-Arylcarbohydrazides. 1-Phenyl- and 1-*o*-tolylcarbohydrazides react readily with a variety of isothiocyanates in ethanol to yield the expected 1-phenyl- (or *o*-tolyl-) 5-substituted thiocarbamoylcarbohydrazides (**288**).[160] These sparingly soluble compounds are crystallizable from large volumes of ethanol, and are all soluble in alkali and reprecipitated by acid. They are ring-closed by acid or alkali or oxidatively by ferric chloride.

1-Phenyl-5-phenylthiocarbamoylcarbohydrazide (**288**, Ar = Ph) is converted by boiling concentrated hydrochloric acid or by ferric chloride solution at 100° into 2-anilino-1,3,4-thiadiazolin-5-one (**289**). Phenylhydrazine, which is eliminated during this process, was isolated as the benzaldehyde derivative.

On being boiled with 20% potassium hydroxide, **288** (Ar = Ph) gave a product formulated as the substituted 1,3,4-oxadiazole **290**. In general, cyclizations in alkali tend to yield triazoles;[108,131,132] the product has in fact since been shown[170] to be the triazole **291** (see section V.A.2.f).

$PhNHNHCONHNH_2 + ArNCS \longrightarrow$

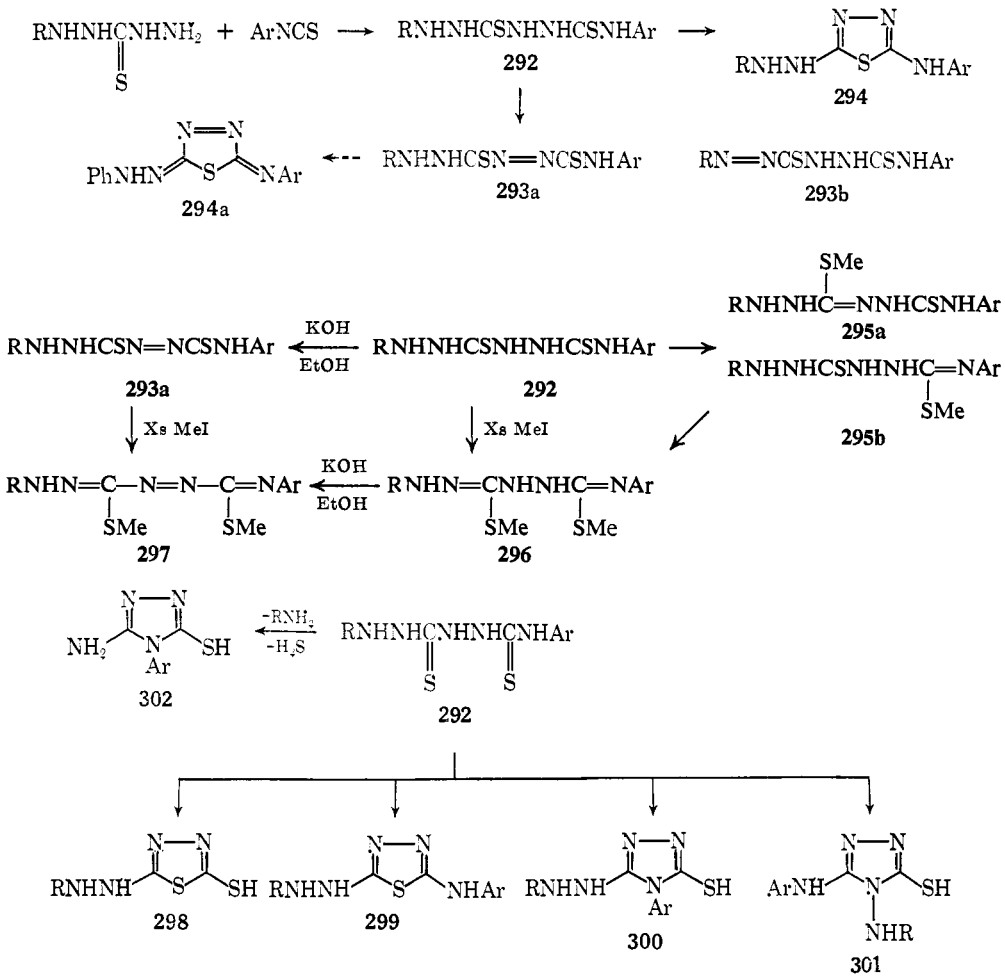


288 **290** **289** **291**

ii. 1-Arylthiocarbohydrazides. Among the adducts dealt with in this and the preceding sections, those derived from substituted thiocarbohydrazides and isothiocyanates (*i.e.*, **292**) containing *two* thiocarbonyl groups undergo the most numerous and varied chemical transformations.

1-Phenylthiocarbohydrazide[168,169] (and its 1-*p*-tolyl homolog[171]) react with a variety of aromatic isothiocyanates in ethanol to afford good yields of 1-arylthiocarbamoyl-5-phenylthiocarbohydrazides (**292**).[168–170] They resemble structurally the 1,5-diphenylthiocarbohydrazides and like them[7] undergo oxidation in ethanolic potassium hydroxide relatively easily to form orange-red azo compounds **293a** or **b** in good yield. Of the two possible structures of these products, **293a** was favored[169] on the grounds that **292** (Ar = Ph) is cyclized in *aqueous* alkali to 2-anilino-5-phenylhydrazino-1,3,4-thiadiazole (**294**). The validity of this argument is obviously questionable, since both **293a** and **293b**, if concerned as inter-

(169) R. G. Dubenko and P. S. Pelkis, *Zh. Obshch. Khim.*, **33**, 2298 (1963); *J. Gen. Chem.*, **33**, 2237 (1963).
(170) F. Kurzer and M. Wilkinson, *J. Chem. Soc., C*, in press.
(171) R. G. Dubenko, I. M. Bazavova, and P. S. Pelkis, *Ukr. Khim. Zh.*, **33**, 638 (1967); *Chem. Abstr.*, **67**, 90736 (1967).



mediates in this oxidation, would yield **294a**, a compound distinct from **294**.

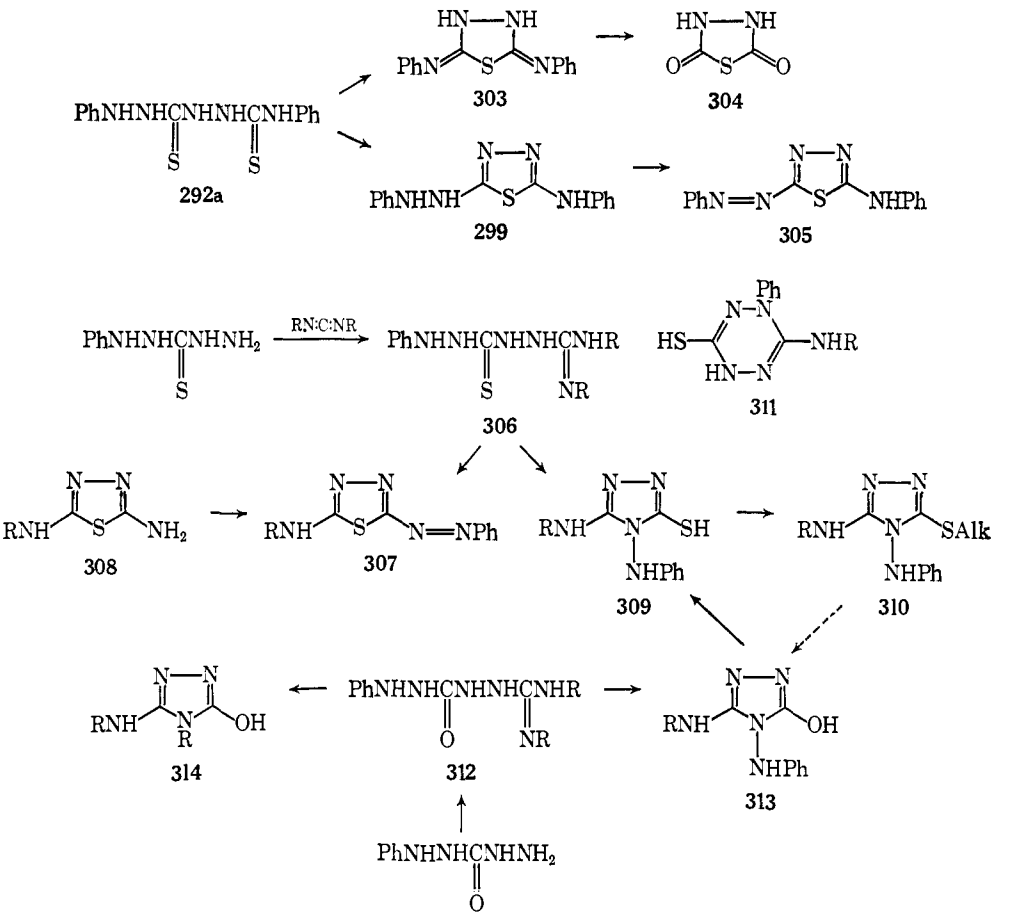
Depending on conditions, the adducts **292** may be mono- (**295a,b**) or di-S-methylated (**296**) by dimethyl sulfate or methyl iodide in alkaline medium.[172] Similarly, the azo compounds **293a** or **b** readily form di-S-methyl derivatives **297** which are also easily obtained from **296** by oxidation.

The cyclization of the adducts **292** by 20% *aqueous* potassium hydroxide has been examined repeatedly.[168,170–172] While it is agreed that the reaction yields two main products, one alkali-insoluble, and the other alkali-soluble, their formulation is not completely settled. Guha and Roy-Choudhury[168] originally reported the isolation of two 1,3,4-thiadiazoles **299** (Ar = Ph; alkali-insoluble; mp 199°) and **298** (Ar = Ph; alkali-soluble, mp 259°), arising from **292** by loss of hydrogen sulfide or arylamine, respectively. In contrast, Dubenko and Pelkis[172] observed that *both* products arise by loss of hydrogen sulfide; the alkali-insoluble product was represented, in agreement with Guha, *et al.*,[168] as **299**, while the alkali-soluble isomer was formulated, without further evidence, as **300**; the melting point of neither compound (**299**, **300**; Ar = Ph) was recorded, but other pairs of isomers (**299**, **300**) were characterized. In another repetition of this reaction,[170] the alkali-soluble product, though agreeing in melting point with the literature value,[168] proved to be in fact the known 3-amino-5-mercapto-4-phenyl-1,3,4-triazole (**302**); its formation clearly presupposes the cleaving of the arylhydrazino group of **292** or **300**. According to its composition and melting point, the alkali-insoluble product appeared to be again identical with Guha's[168] 2-anilino-5-hydrazino-1,3,4-thiadiazole **299** (Ar = Ph). However, this formulation still requires final confirmation, since cyclization of **292** under strongly *alkaline* conditions to an amino-1,3,4-thiadiazole (rather than a mercapto-1,2,4-triazole) is in conflict with Arndt's rule.[108,131,132] Of the two possible structures (**300**, **301**; discounting tetrazine formation) that might thus be considered, **301** is excluded by the nonidentity of the alkali-insoluble product with authentic 3,4-dianilino-5-mercapto-1,2,4-triazole,[170] but structure **300** cannot be entirely rejected. An unambiguous degradation of the product in question, or an unequivocal synthesis of **299** or **300**, would clearly be desirable in this connection. In a recent report, the Russian workers[171] have reaffirmed the production of **299** and **300**; on steam distillation of the reaction mixture, however, 3-amino-5-mercapto-4-phenyl-1,2,4-triazole (**302**, Ar = Ph) was obtained in good yield, together with arylamine.

The cyclization of the adduct **292a** by hot concentrated hydrochloric acid[168] is reported to proceed with separation of sulfur and formation of the diketothiadiazolidine **304**, possibly by the route shown.

The action of hot aqueous ferric chloride on the adduct **292a** yields the deep-orange phenylazo-1,3,4-thiadiazole (**305**)[168] possibly by the sequence **292a** → **299** → **305**. The supposed intermediate **299** which is one of the products of the aqueous alkaline cyclization of **292a** (see above) was not

(172) R. G. Dubenko and P. S. Pelkis, *Zh. Obschch. Khim.*, 33, 2682 (1963); *J. Gen. Chem.*, 33, 2612 (1963).



isolated; its separate oxidation by hydrogen peroxide to the same final product **305** has been claimed[168] but not confirmed[170] (see section f, immediately below).

f. Reaction with Carbodiimides

The general study of the reaction between (thio)carbohydrazides and carbodiimides (see section IV.L) has been extended[170] to 1-phenyl(thio)carbohydrazides with the object of blocking *one* of the positions to which carbodiimide is rapidly added; the interaction of *equimolar* quantities of the reactants could therefore be profitably examined.

1-Phenylthiocarbohydrazide and diarylcarbodiimides reacted additively under restrained conditions to give stable 1:1 adducts **306** in good yield. These adducts were cyclized by *alcoholic* potassium hydroxide to the deep-orange 2-arylamino-5-phenylazo-1,3,4-thiadiazoles (**307**), the structure of which was confirmed by their unequivocal synthesis from 2-arylamino-5-amino-1,3,4-thiadiazole (**308**, R = Ph) and nitrosobenzene, by the Mills reaction, using the procedure of Ueno.[173] The production of a 1,3,4-thiadiazole (rather than a 1,2,4-triazole) from **306** under strongly alkaline conditions is, in the present instance, not in conflict with Arndt's rule[108,131,132] (see also section IV.K.3.b); it is believed that dehydrogenation of the phenylhydrazino group (of **306**, to PhN=N) precedes ring closure, thereby precluding the formation of a 1,2,4-triazole by loss of arylamine.[170]

Aqueous potassium hydroxide, on the other hand, converted the adducts **306** into 4-anilino-3-arylamino-5-mercapto-1,2,4-triazoles (**309**), which were convertible into S-alkylthiol derivatives **310** as expected. Their alternative formulation as the isomeric tetrazines **311** was excluded on the basis of ir spectroscopic evidence.[170]

1-Phenylcarbohydrazide underwent an analogous series of reactions. Its adducts **312** gave, under the influence of aqueous alkali, excellent yields of 4-anilino-3-arylamino-5-hydroxy-1,2,4-triazoles (**313**). One member of this series (**313**, R = Ph) was converted by phosphorus pentasulfide in pyridine[174] into the corresponding mercapto analog **309**. The reverse conversion occurred when the alkylthiol compound **310** (R = Ph, Alk = Me) was treated with alkaline hydrogen peroxide; although the product **313** (R = Ph) could not be isolated, its presence was demonstrated by thin layer chromatography. The structural analogy of the substituted mercapto- (**309**) and hydroxy-1,2,4-triazoles (**313**) was thus confirmed.[170]

Thermolysis of the adduct **312** (R = Ph) proceeded with loss of arylamine (from the amidino function) and arylhydrazine, with production of the substituted 3-hydroxy-1,2,4-triazoles **313** and **314** side by side. The tolyl analog **312** (R = *p*-$CH_3C_6H_4$) gave the 4-*p*-tolyltriazole **314** (R = *p*-$CH_3C_6H_4$) exclusively in high yield.[170]

The formal analogy of the behavior of (thio)carbohydrazide and its 1-phenyl derivatives in this series of reactions is clearly apparent, the principal products being, in each case, 4-(substituted)amino-1,2,4-triazoles. While the parent (thio)carbohydrazide, reacting with 2 moles of carbodiimides, yields 4-(N,N'-diaryl)guanidino-1,2,4-triazoles (**210**), the 1-phenyl-(thio)carbohydrazides, reacting with only 1 mole of carbodiimide, give, by the same ring closure, the corresponding 4-anilino-1,2,4-triazoles (**309**, **313**).[170]

(173) K. Ueno, *J. Am. Chem. Soc.*, 74, 4508 (1952).

(174) E. Klingsberg and D. Papa, *ibid.*, 73, 4988 (1951).

g. Reaction with Nitrous Acid

Unlike its parent compound (see section IV.M), 1-phenylcarbohydrazide reacts with nitrous acid at 0° to yield not the expected azide **315** but the hydroxysemicarbazide **317** with evolution of nitrogen,[160] possibly *via* the intermediate azo compound **316**. The compound is claimed to be the first known 4-hydroxysemicarbazide, but its formulation requires further substantiation.

$$\underset{\mathbf{315}}{PhNHNHCON_3} \leftarrow\times\rightarrow PhNHNHCONHNH_2 \longrightarrow$$

$$[PhNHNHCONHN{=}NOH] \longrightarrow \underset{\mathbf{317}}{PhNHNHCONHOH} + N_2$$

$$\mathbf{316}$$

h. Reaction with Urea

A mixture of dry urea and 1-phenylcarbohydrazide in molecular proportions reacts at 135° with evolution of ammonia and formation of 1-carbamoyl-5-phenylcarbohydrazide[160] ($NH_2CONHNHCONHNHPh$). The reaction thus corresponds entirely to that of the parent carbohydrazide[152] (see section IV.O).

B. 2-SUBSTITUTED (THIO)CARBOHYDRAZIDES

1. Synthesis

The only members of this structural type so far described are 2-alkylthiocarbohydrazides: they have been obtained by the application of one of the general syntheses, *viz.* the hydrazinolysis of suitably substituted dithiocarbazates.

Thus, 2-methylthiocarbohydrazide (**319**) has been prepared by the action of hydrazine on methyl 2-methyldithiocarbazate (**318**),[175] which is in turn accessible by treatment of methyl hydrazine with either carbon disulfide and methyl iodide, or with dimethyl trithiocarbonate.[176] The method appears to be a general one, provided the alkyl groups of the desired products are small.[150b] Bulky (including aryl) groups would direct the entering dithiocarboxy moiety into the free amino group of the substituted hydrazine, with formation of the alternative structure RNHNHCSSR′.

$$MeNHNH_2 \xrightarrow[\text{or } CS(SMe)_2]{CS_2,\ MeI} \underset{\mathbf{318}}{NH_2NMeCSSMe} \longrightarrow \underset{\mathbf{319}}{NH_2NMeCSNHNH_2}$$

$$MeNHN{=}CHPh \xrightarrow[CS(SMe)_2]{} PhCH{=}NNMeCSSMe \longrightarrow \underset{\mathbf{320}}{}$$

$$PhCH{=}NNMeCSNHNH_2 \longrightarrow \underset{\mathbf{321}}{} \mathbf{319}$$

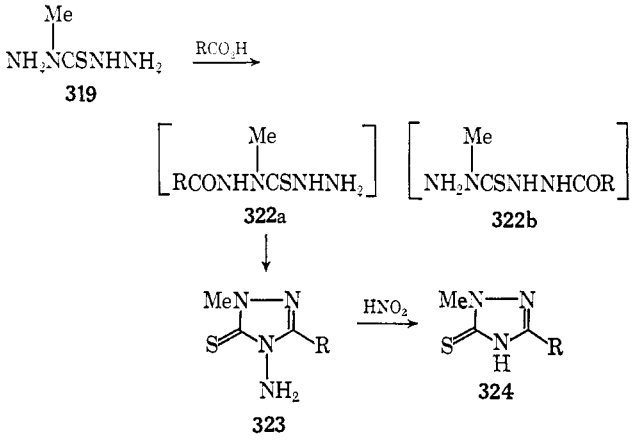
An even more effective variety of this synthesis is the use of alkylhydrazones, which restricts the introduction of the dithiocarboxy group to the desired position.[177] Benzylidene methylhydrazine, for example, reacts with dimethyl trithiocarbonate[176] to yield methyl 2-methyl-3-benzylidenedithiocarbazate (**320**); successive hydrazinolysis and hydrolysis affords the required 2-methylthiocarbohydrazide (**321** → **319**). This method could clearly be extended to a variety of 2-substituted thiocarbohydrazides by a suitable choice of starting materials, and there is every reason to suppose that it is equally applicable to the analogous carbohydrazides.

(175) G. Schleitzer, Dissertation, University of Greifswald, Institute for Inorganic Chemistry, 1956.
(176) J. Sandström, *Arkiv Kemi*, **9**, 255 (1956).
(177) J. Sandström, *Acta Chem. Scand.*, **18**, 871 (1964).

2. Chemical Reactions

a. Condensation with Carboxylic Acids

The condensation of 2-methylthiocarbohydrazide (**319**) with aliphatic carboxylic acids[96] closely resembles that of the parent thiocarbohydrazide[88] (see section IV.G.1). Thus, its treatment with boiling formic, acetic, or propionic acids results in good yields of 3-alkyl-4-amino-1-methyl-5-thiono-1,2,4-triazolines (**323**, R = H, Me, Et), which may be characterized as benzylidene and diacetyl derivatives. Deamination, by means of nitrous acid, converts them into 1-methyl-3-alkyl-5-thiono-1,2,4-triazolines (**324**, R = H, Me, Et), one of which (**324**, R = Me) has been independently synthesized by another route.[178] This clearly establishes the site of primary attack of the acyl group at the substituted hydrazine end of 2-methylthiocarbohydrazide, since the alternative intermediate **322b** cannot yield the triazole **323**.

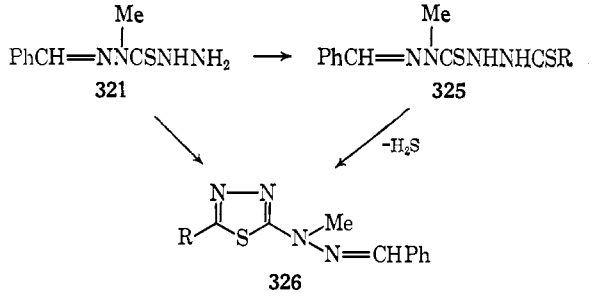


b. Other Cyclization Reactions

The 1-benzylidene derivative of 2-methylthiocarbohydrazide (**321**) is cyclized to variously substituted 1,3,4-thiadiazoles, due to the reactivity of its free hydrazino function toward suitable reagents.[177]

Brief refluxing with triethyl orthoformate affords 1-benzylidene-2-methyl-(1,3,4-thiadiazol-2-yl)hydrazone (**326**, R = H) in 60% yield. The action of dimethyl trithiocarbonate in sodium ethoxide produces the open-chain 1-benzylidene-2-methyl-5-dithiomethoxycarbonylthiocarbohydrazide (**325**, R = SMe) in 95% yield, which is cyclized on thermolysis at 150° to the thiadiazole **326** (R = SMe) in 72% yield.

Thiobenzoylation of **321** by carboxymethyl dithiobenzoate[114,115] in ethanol–alkali rapidly precipitates 2-phenyl-1,3,4-thiadiazol-5-yl-(1′-benzylidene-2′-methyl)hydrazone (**326**, R = Ph) (64%), by way of the intermediate **325** (R = Ph), and loss of hydrogen sulfide.

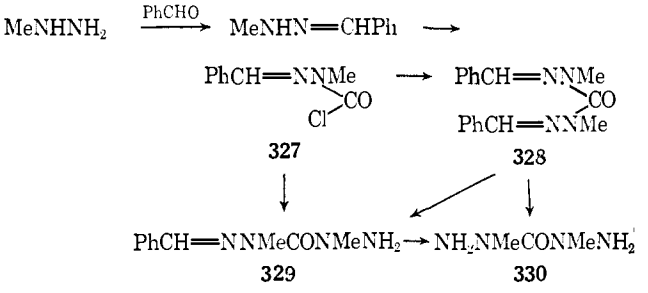


(178) G. Losse, W. Hessler, and A. Barth, *Chem. Ber.*, **91**, 150 (1958).

C. 2,4-DISUBSTITUTED (THIO)CARBOHYDRAZIDES

2,4-Dimethylcarbohydrazide (**330**) has recently been synthesized from methylhydrazine and phosgene[179] by the sequence of reactions in Scheme II.

Scheme II



Treatment of benzaldehyde methylhydrazone with phosgene yielded, depending on conditions (*i.e.*, temperature and relative molar proportions), either 1,5-dibenzylidene-2,4-dimethylcarbohydrazide (**328**) (89%) or 2-benzylidene-1-methylchloroformohydrazide (**327**). Either **327** or **328** is convertible into 2,4-dimethylcarbohydrazide (**330**); the dibenzylidene compound **328** yields the required end-product **330** *either* by hydrolysis with 25% hydrochloric acid *via* the monobenzylidene compound **329**, *or* directly by transhydrazinolysis using 2,4-dinitrophenylhydrazine. Alternatively, the chloroformohydrazide **327** is treated with methylhydrazine and the oily product hydrolyzed to give **330** in 23% yield. Clearly, the method would seem to be more generally applicable and could no doubt be extended to the thio analogs.

D. 1,1,4-TRISUBSTITUTED (THIO)CARBOHYDRAZIDES

1. Synthesis

1,1,4-Trimethylthiocarbohydrazide (**334**) has recently been synthesized in varying yields by the hydrazinolysis of three compounds, **331**–**333**,[180] using methylhydrazine. Thus, hydrazinolysis of N,N-dimethylthiocarbazoylimidazole (**331**) at room temperature produces **334**, mp 150°, in 56% yield. The method is based on the analogous synthesis of thiosemicarbazides from **331** and amines.[181] The interaction of methylhydrazine and carboxymethyl N,N-dimethyldithiocarbazate (**332**) in aqueous solution also gives **334**; the moderate yield (38%) may be considerably improved by the recovery of material from the mother liquors. This method is also an extension of an established synthesis of thiosemicarbazides.[182,183] The best method, however, appears to be the reaction of methylhydrazine and 1-dithiomethoxycarbonyl-2,2-dimethylhydrazine (**333**) which affords **334** in 86% yield.

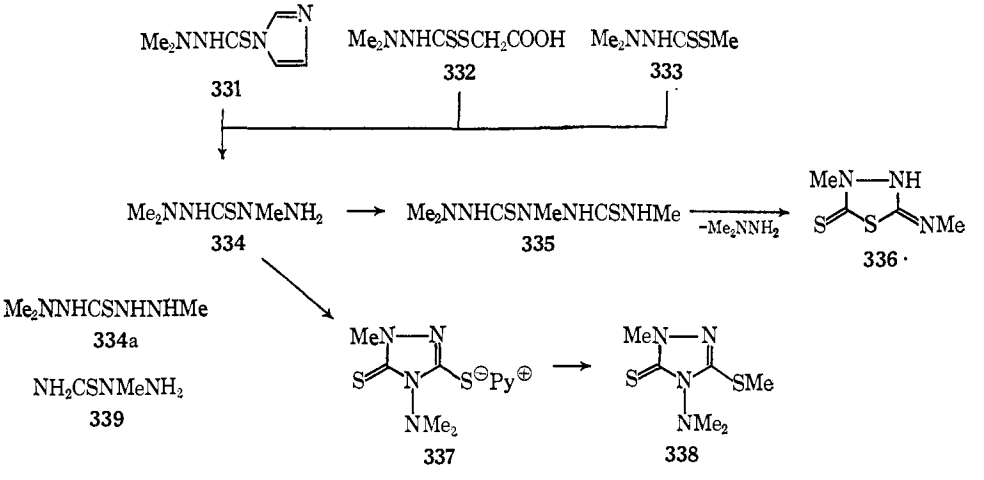
The structure of **334** is supported by its infrared spectrum. The presence of a band at 1650 cm^{-1}, characteristic for NH_2, ruled out the alternative possible structure **334a**. Moreover, the analogous synthesis[184] of 2-alkylthiosemicarbazides (**339**) would also seem to preclude structure **334a**.

2. Chemical Properties

As expected, the free amino group of 1,1,4-trimethylthiocarbohydrazide (**334**) readily participates in addition and cyclization reactions with reagents such as isothiocyanates and carbon disulfide. Unlike the parent thiocarbohydrazide, however, it does not react with dialkyl trithiocarbonates (see section IV.J.3); in its reaction with thiophosgene, only complex intractable reaction mixtures have so far been obtained.[180]

1,1,4-Trimethyl-5-methylthiocarbamoylthiocarbohydrazide (**335**),[180] the adduct of **334** with methyl isothiocyanate, is cyclized by boiling concentrated hydrochloric acid, with loss of dimethylhydrazine, to give low yields (15%) of 2-methylimino-4-methyl-1,3,4-thiadiazolidine-5-thione (**336**). This formulation, though not rigorously proved, is supported by ir and nmr evidence.[180]

The interaction of **334** with carbon disulfide in boiling pyridine produces the pyridinium salt of 4-dimethylamino-1-methyl-3-mercapto-1,2,4-triazoline-5-thione (**337**) almost quantitatively. Further treatment with methyl iodide yields the S-methyl derivative **338** which was identical with authentic[180] material.



(179) L. Raphaelian, H. Hooks, and G. Ottmann, *Angew. Chem. Intern. Ed. Engl.*, 6, 363 (1967); U. S. Patent 3,304,327 (1967); *Chem. Abstr.*, 66, 75821 (1967).

(180) U. Anthoni, C. Larsen, and P. H. Nielson, *Acta Chem. Scand.*, 22, 309 (1968).

(181) U. Anthoni, C. Larsen, and P. H. Nielson, *ibid.*, 21, 1201 (1967).

(182) K. A. Jensen, *J. Prakt. Chem.*, **159**, 189 (1941).

(183) F. C. Brown, C. K. Bradsher, B. F. Moser, and S. Forrester, *J. Org. Chem.*, 24, 1056 (1959).

(184) K. A. Jensen, U. Anthoni, B. Kägi, C. Larson, and C. T. Pedersen, *Acta Chem. Scand.*, 22, 1 (1968).

VI. Acylcarbohydrazides

A. 1-ACYLCARBOHYDRAZIDES

1. Synthesis

It does not appear to be possible to synthesize 1-acylcarbohydrazides (**340**) directly from acid chlorides and carbohydrazide. In this reaction, both terminal amino groups are rapidly attacked and 1,5-diacyl compounds **341** are invariably formed.[119,185]

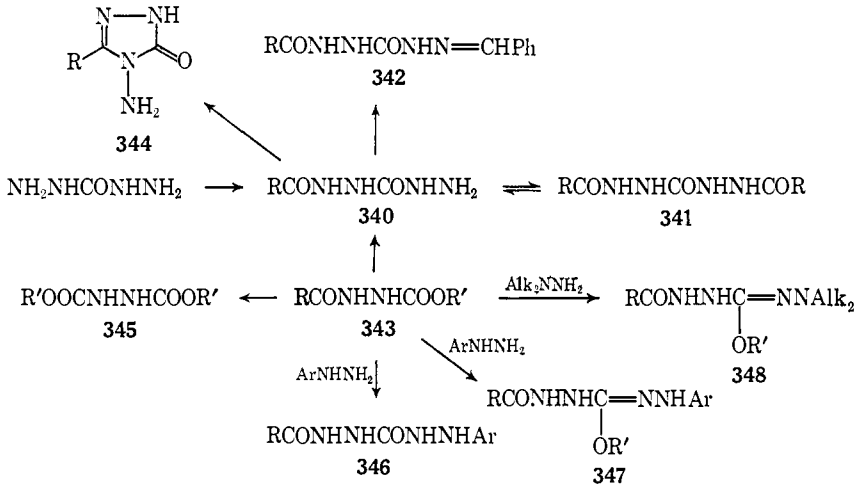
1-Acylcarbohydrazides are obtainable in moderate yield (isolated as benzylidene derivatives **342**) by the mild acid hydrolysis[89] of the 1,5-disubstituted compounds **341**.

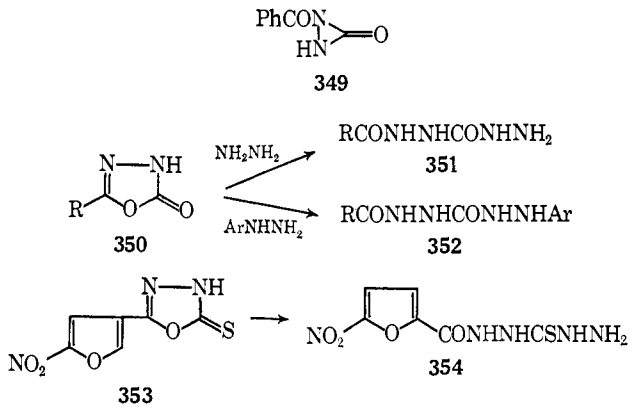
A successful route to 1-acylcarbohydrazides (**340**) is the hydrazinolysis of 1-acylcarbazic acid aryl esters (**343**).[163,186] Thus, *p*-nitrophenyl 1-acylcarbazates (**343**, R′ = *p*-$NO_2C_6H_4$) react with hydrazine at 100° to produce 1-acylcarbohydrazides (**340**) in poor to moderate yields. The structure of the products was verified in one case (**340**, R = Ph) by its conversion into the known[185] 1,5-dibenzoylcarbohydrazide, by the action of benzoyl chloride.

The method is applicable to the production of aromatic analogs, *i.e.*, 1-acyl-5-arylcarbohydrazides (**346**), by employing the appropriate *p*-nitrophenyl esters **343** (R′ = *p*-NO_2-C_6H_4) in conjunction with *aromatic* hydrazines.[163] If, however, the aryl group R′ of the ester **343** lacks the electron-withdrawing substituent, the reaction proceeds differently, resulting merely in the condensation of the hydrazine with the carbonyl moiety of the ester group, and consequent formation of **347**.[187,188] The same type of condensation occurs also with dialkylhydrazines at elevated temperatures, and results in the production of **348**.[163,189]

Different results are obtained when alkyl esters **343** (R′ = alkyl) are subjected to hydrazinolysis. When **343** (R = Me, R′ = Et) is heated with 100% hydrazine hydrate, both its ethoxy and its acetyl groups are replaced, with formation of carbohydrazide. A comparable loss of acyl groups under these conditions has been observed for 1-acylsemicarbazides.[190] In contrast, the use of dilute (10%) hydrazine hydrate leaves the acetyl group intact; however, the primary product **340** undergoes cyclization *in situ* to 4-amino-3-methyl-1,2,4-triazolin-5-one (**344**, R = Me). Again, the action of 10% hydrazine hydrate on **343** (R = Et) affects the acyl group, while the ester group remains intact. The resulting intermediate carbazic acid ethyl ester disproportionates to form hydrazine-N,N′-dicarboxylic acid diethyl ester (**345**, R′ = Et).[163,186]

A second efficient synthesis of 1-acylcarbohydrazides takes advantage of the facile ring opening of 1,3,4-oxadiazol-2-ones with hydrazine. The use of amines in this ring cleavage is an established[120] route to 1-acylsemicarbazides. The earliest example of this synthesis, described by Diels,[191–193] was the conversion of the supposed diaziridine **349** ("benzoylhydrazicarbonyl") into 1-benzoylcarbohydrazide (**351**, R = Ph). The compound erroneously described as **349** was correctly identified by Stollé[194] as 5-phenyl-1,3,4-oxadiazolin-2-one (**350**, R = Ph). More recent reports have described[120,195] the preparation of 1-isonicotinoylcarbohydrazide (**351**, R = 4-pyridyl) by this route in high yield; the method appears to be generally applicable to the production of aroylcarbohydrazides and has, by the use of aromatic hydrazines, been





(185) R. Stollé and K. Krauch, *Chem. Ber.*, 47, 724 (1914).
(186) P. S. Pelkis and E. P. Nesynov, USSR Patent 170,523 (1965); *Chem. Abstr.*, 63, 9823 (1965).
(187) E. P. Nesynov and P. S. Pelkis, USSR Patent 179,775 (1966); *Chem. Abstr.*, 65, 7102 (1966).
(188) E. P. Nesynov and P. S. Pelkis, USSR Patent 179,777 (1966); *Chem. Abstr.*, 65, 10544 (1966).
(189) E. P. Nesynov and P. S. Pelkis, USSR Patent 179,776 (1966); *Chem. Abstr.*, 65, 7102 (1966).
(190) H. Gehlen and W. Schade, *Naturwissenschaften*, 46, 667 (1959).
(191) O. Diels and H. Okada, *Chem. Ber.*, 45, 2437 (1912).
(192) O. Diels and A. Wagner, *ibid.*, 45, 874 (1912).
(193) O. Diels and H. Okada, *ibid.*, 46, 1870 (1913).
(194) R. Stollé and K. O. Leverkus, *ibid.*, 46, 4076 (1913).
(195) J. A. Aeschlimann (to Hoffmann-La Roche Inc.), U. S. Patent 2,665,279 (1954); *Chem. Abstr.*, 49, 2521 (1955).

extended to the production of 1-acyl-5-arylcarbohydrazides (**352**).

1-Acyl-5-arylthiocarbohydrazides have been prepared analogously by the ring cleavage of 1,3,4-oxadiazoline-2-thiones with arylhydrazines in ethanol.[119] Thus, 5-(5′-nitro-2′-furyl)-1,3,4-oxadiazoline-2-thione (**353**) reacts with phenyl- and *p*-nitrophenylhydrazine to give 1-aryl-5-(5′-nitro-2′-furoyl)-3-thiocarbohydrazides (**354**, Ar = Ph, *p*-$NO_2C_6H_4$) in moderate yields.

2. Reactions

1-Acylcarbohydrazides, retaining the free hydrazino function, react normally with aldehydes and ketones in dioxane, in presence of catalytic quantities of acetic acid, to form 1-acyl-5-arylidene- (or alkylidene-) carbohydrazides[196] in variable yields. Their hydrazino group also reacts with aryl isothiocyanates as expected to give 1-acyl-5-(arylthiocarbamoyl)carbohydrazide in moderate yield.[197]

B. 1,5-DIACYLCARBOHYDRAZIDES

1. Synthesis

a. Direct Acylation

Carbohydrazide reacts readily with acyl chlorides at both its terminal amino groups to yield 1,5-diacylcarbohydrazides (**355**).[119,185,198] 5-Nitro-2-furoyl chloride, for example, converts carbohydrazide in dioxane into 1,5-di(5′-nitro-2′-furoyl)carbohydrazide in good yield.[119]

RCONHNHCONHNHCOR (**355**) RCONHNHCONHNHCOR′ (**356**)

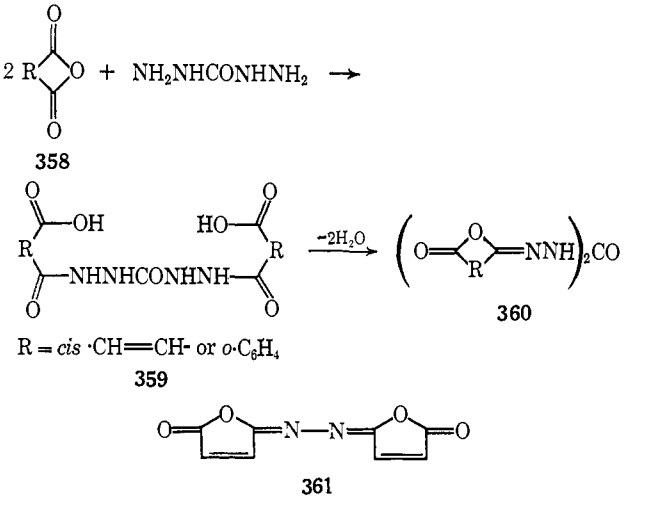
RCON=NCONHNHCOR′ (**357**)

Both symmetrical and unsymmetrical (**356**) 1,5-diacylcarbohydrazides may be prepared in moderate yield by further acylation of 1-acylcarbohydrazides.[163,198,199]

In a variant of this synthesis, boiling carboxylic acids are successfully used as reagents;[89] thus, formic, acetic, and propionic acids produce the diacyl derivatives **355** (R = H, Me, Et) in good yield.

Since 1,5-diacylcarbohydrazides tend to undergo oxidation, though less readily than their thio analogs, yielding azo compounds of type **357**, they need to be protected from atmospheric oxygen and are crystallized advantageously in an atmosphere of nitrogen.[199]

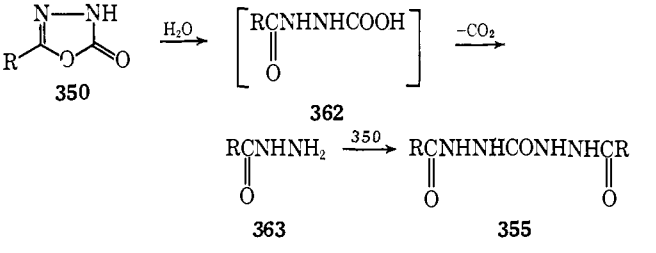
The interaction of carbohydrazide and maleic and phthalic anhydrides[200] has given results of interest. Reaction in glacial acetic acid at room temperature produces almost quantitative yields of the diacyl derivatives **359**. Further treatment of these products with a dehydrating agent such as trifluoroacetic anhydride affords the diisoimides **360** in excellent yield. Their formulation was based on infrared, ultraviolet, and nmr spectra and received additional support from their formal analogy with N,N′-diisomaleimide (**361**) of established structure.[201]



b. Ring Cleavage of 1,3,4-Oxadiazolin-2-ones

Like 1-monoacylcarbohydrazides, the 1,5-diacyl derivatives are formed by the ring opening of 1,3,4-oxadiazolin-2-ones.[119]

The reaction, which proceeds in varying yield in boiling water, is initiated by the hydrolytic cleavage of the oxadiazolone **350** to the unstable acylcarbazic acid **362**. This is immediately decarboxylated to the hydrazide **363**, which in turn ring-opens the remaining oxadiazolone to give the 1,5-diacylcarbohydrazide **355**. The participation of the acylcarbazic acid **362** in the mechanism was demonstrated by performing the ring cleavage using ethanol, when **362** was isolated as the ethyl ester.[119]



2. Chemical Properties

Acid hydrolysis converts 1,5-diacylcarbohydrazides successively into 1-acylcarbohydrazide and the parent base.[89] Under mild conditions the intermediate 1-acyl compounds may be isolated as their benzal derivatives. The action of warm aqueous alkali[89] cyclizes 1,5-diacylcarbohydrazides to 4-amino-3-alkyl(H)-1,2,4-triazol-5-ones.

In this context, the condensation of hydrazine and carbon monoxide under high pressure (50–150° at 500–3000 atm)[202–204] is of interest. It produces, under increasingly severe conditions, either semicarbazide, 4-amino-1,2,4-triazolin-3-one, or 4-amino-1,2,4-triazole, and has accordingly been represented to proceed by the reaction path a. In view of

(196) E. P. Nesynov, M. M. Besprozvannaya, and P. S. Pelkis, *Zh. Organ. Khim.*, 2, 25 (1966); *Soviet J. Org. Chem.*, 2, 21 (1966).

(197) E. P. Nesynov, M. M. Besprozvannaya, and P. S. Pelkis, *Zh. Organ. Khim.*, 2, 484 (1966); *Soviet J. Org. Chem.*, 2, 486 (1966).

(198) P. S. Pelkis and E. P. Nesynov, USSR Patent 170,524 (1965); *Chem. Abstr.*, 63, 9823 (1965).

(199) E. P. Nesynov and P. S. Pelkis, *Zh. Organ. Khim.*, 2, 459 (1966); *Soviet J. Org. Chem.*, 2, 460 (1966).

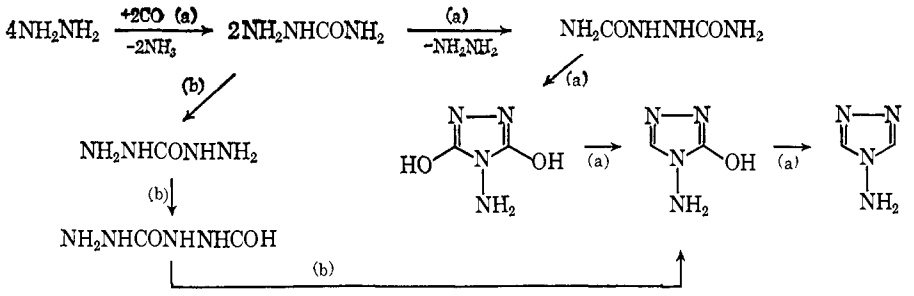
(200) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.*, 31, 1317 (1966).

(201) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, 31, 1311 (1966).

(202) G. D. Buckley and N. H. Ray, *J. Chem. Soc.*, 1156 (1949).

(203) G. D. Buckley and N. H. Ray, British Patent 649,445 (1951); *Chem. Abstr.*, 45, 8560 (1951).

(204) H. J. Sampson Jr., U. S. Patents 2,589,289 and 2,589,290 (1952); *Chem. Abstr.*, 46, 11234 (1952).



the demonstrated ready cyclization of acylcarbohydrazides to triazolones, the alternative reaction sequence (b) would appear to merit consideration.

1,5-Dibenzoylcarbohydrazide (**355**, R = Ph) is oxidized by sodium hypochlorite or hypochlorous acid in aqueous ethanol at −70° to a complex mixture of products[205] which include benzoic acid, carbon dioxide, ethyl benzoate, 2-phenyl-1,3,4-oxadiazol-5-one, N,N′-dibenzoylhydrazine, and 1-benzoyl-2-ethoxycarbonylhydrazine. The reaction mixture first turns a dark red color which slowly fades. The red color is attributed to the initial formation of "di(benzoylimino)urea" (PhCON=NCON=NCOPh) which is then slowly decomposed by nucleophilic attack of ethanol and water. An elaborate reaction scheme was put forward[205] to account for the formation of the individual products; since this would appear to require further substantiation, it is not given here in full.

VII. Analytical

A. QUANTITATIVE ESTIMATION OF (THIO)CARBOHYDRAZIDE

Methods of determining (thio)carbohydrazide so far described are based on suitable quantitative oxidation reactions.

1. Iodic Acid

Carbohydrazide reacts quantitatively with potassium iodate in acid solution,[156,206–208] each hydrazino group consuming 1 mole of iodate, with the liberation of nitrogen, according to the following stoichiometric equation.

$$N_2H_5^{\oplus} + IO_3^{\ominus} + H_3O^{\oplus} + Cl^{\ominus} \longrightarrow N_2 + ICl + 4H_2O$$

In practice, the determination is carried out gasometrically[156,208] or potentiometrically.[206,207] In the former method the nitrogen evolved is simply measured in a gas buret or, more accurately, in a Warburg apparatus.[209] The potentiometric titration may be based on *either* of two equivalence points, *viz.* the reduction of iodate to iodine monochloride ($IO_3^{\ominus} \rightarrow ICl$), or the liberation of iodine.

2. Bromine

(Thio)carbohydrazide can also be determined by coulometric bromination,[210] according to the overall equation

$$-CXNHNH_2 + 4Br + H_2O \longrightarrow -CXOH + N_2 + 4HBr$$

Thus, 2 moles of bromine are consumed per hydrazino group. Analysis of carefully purified samples of carbohydrazide from a variety of sources consistently indicated only 90% purity; the use of nmr and mass spectrometry, and exhaustive drying, eventually showed that carbohydrazide crystallizes as a hemihydrate.

Thiocarbohydrazide consumes a total of 6 moles of bromine indicating that both hydrazino, as well as the sulfur groups are involved in the reaction.

B. APPLICATIONS OF (THIO)CARBOHYDRAZIDE IN ANALYTICAL CHEMISTRY

Thiocarbohydrazide is useful in analytical chemistry for the identification and estimation of both organic and inorganic compounds.[65,211–213]

Thiocarbohydrazide precipitates aldehydes and ketones quantitatively, giving derivatives having sharp melting points, which are suitable for identification purposes and in gravimetric procedures. Their thermal stability has been investigated using a thermobalance and their optimum drying temperatures have thus been found.[211]

With certain ions, including U^{VI}, Mo^{IV}, Ni^{2+}, Bi^{3+}, and Cu^{2+}, (thio)carbohydrazide forms characteristic precipitates, for which thermogravimetric curves have been constructed.[65,212] The gravimetric determination of molybdenum in the presence of tungsten and uranium is based on these observations.[65,212] Insoluble calcium and barium salts of thiocarbohydrazide have also been described.[27]

Numerous color tests of a variety of anions and cations, using (thio)carbohydrazide as the reagent, are based on the complexing power of the latter. Thus, carbohydrazide (R) forms complexes (MR_q)[214] with metal ions such as Cu^{2+}, Ni^{2+}, Co^{2+}, and Ru^{2+} in acidic solutions, evidently by chelation involving two nitrogen atoms. Stability constants were determined for values of q = 1–3 as well as formation constants for the species RH_2^{2+} and RH^{+}.

The ease with which (thio)carbohydrazide forms characteristically colored complexes with certain metal ions has been used to identify the constituent elements in polished sections of minerals.[215] In a simple contact-print method, gelatin-soaked paper, impregnated with a reagent capable of freeing the metal ions from the mineral, is pressed on the surface of

(205) H. Minato, R. Hisada, and M. Tanaka, *Bull. Soc. Chem. Japan*, 39, 2512 (1966).
(206) W. R. McBride, R. A. Henry, and S. Skolnik, *Anal. Chem.*, 23, 890 (1951).
(207) W. R. McBride, R. A. Henry, and S. Skolnik, *ibid.*, 25, 1042 (1953).
(208) H. McKennis Jr. and A. S. Yard, U. S. Department of Commerce, Office of Technical Services, P.B. Report, 143,914, (1957); *Chem. Abstr.*, 55, 17375 (1961).
(209) H. Guérin, "Traité de Manipulation et d'Analyse des Gaz," Masson et Cie, Paris, 1952.
(210) A. F. Krivis, E. S. Gazda, G. R. Supp, and P. S. Kippur, *Anal. Chem.*, 35. 1955 (1963).
(211) C. Duval and N. D. Xuong, *Mikrochim. Acta*, 747 (1956).
(212) C. Duval and T. B. Loc, *ibid.*, 458 (1956).
(213) C. Duval and T. B. Loc, *Compt. Rend.*, 240, 1097 (1955).
(214) E. Campi, G. Ostacoli, A. Vanni, and E. Casorati, *Ric. Sci., Rend., Sez. A*, 6, 341 (1964); *Chem. Abstr.*, 62, 15490 (1965); B. Steiger, *Mikrochem.*, 16, 193 (1934).
(215) D. Williams and F. M. Nakhla, *Bull. Inst. Mining Met.*, 533, 257 (1951); *Chem. Abstr.*, 45, 6956 (1951).

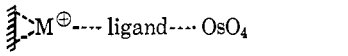
the polished section. The released metal ions are trapped in the gelatin and are detected with specific reagents such as (thio)-carbohydrazide. The colored image indicates the distribution of the elements in the polished surface.

The complex formation of cupric ions and monoacid hydrazides occurs with release of protons,[216,217] but that involving cadmium ions proceeds without release of protons.[218] In the case of carbohydrazide (*i.e.*, a diacid hydrazide), complexing with Cd ion occurs *via* a neutral species.[219] Polarographic studies of the complexing were carried out to determine stability and other constants for complexes formed successively in solution. It is postulated that the complexes form six-membered ring structures involving both hydrazine functions.

C. HISTOCHEMICAL USES

Thiocarbohydrazide is useful as an osmiophilic reagent for demonstrating the presence of aldehyde-containing macromolecules, originating from iodic acid oxidation of tissue, and of lipid-containing membranes in osmium tetroxide-fixed tissue.[220,221] Carbohydrazide is of limited use, but thiocarbohydrazide is a suitable reagent, superior to thiosemicarbazide, for demonstrating the presence of a wide variety of oxidized macromolecules.

Osmium black, which is widely used for cytological staining in light and electron microscopy, is selectively deposited at the tissue-binding sites of other metal ions. By bridging osmium tetroxide to these ions by bidentate ligands such as thiocarbohydrazide, the technique is considerably improved.[222]



Osmium, for example, is bridged through thiocarbohydrazide to uranium onto acrolein-fixed antigen sections localized by uranium-labeled antibodies.[223] The contrast normally afforded in the absence of this ligand is thereby greatly enhanced.

VIII. Biological Properties

A. BIOCHEMICAL

Carbohydrazide acts as a denaturing agent for bovine serum albumin[224] and for DNA.[225] The effect is attributed to stabilization of the denatured DNA relative to native DNA by a decrease in the ion-solvating power and an increase in the hydrophobic character of the solvent. No such correlation was observed for bovine serum albumin when a variety of substituted carbohydrazides and ureas were used.

Thiocarbohydrazide causes the irreversible inhibition of purified recrystallized catalase preparations (ox liver) in the presence of hydrogen peroxide.[226]

B. PHARMACOLOGICAL AND RELATED PROPERTIES

The degradation of serotonin by ceruloplasmin is severely inhibited by thiocarbohydrazide[227] *in vitro*, but no correlation between inhibition and the presence of –SH or –$NHNH_2$– groupings could be established.

Studies have been carried out *in vitro* concerning the hypotensive and reserpine-antagonizing effects of thiocarbohydrazide to enzyme and metal catalysis of biogenic amines.[228]

Carbohydrazide, in the form of its cobalt complex, produces hypertension without toxicity, and a simultaneous acute pyridoxine deficiency in dogs (administered intramuscularly in doses of 0.2–2 mg/kg of body weight).[229]

1. Convulsant Activity

Unsubstituted hydrazides such as (thio)carbohydrazides are carbonyl-trapping agents, diamine oxidase inhibitors, and inhibitors of enzyme systems and produce convulsions after a latent period of 1 hr.[230–232] Repeated maximal seizures occur for 4–5 hr. When topically applied to the cerebral cortex, they produce fast high-voltage spiking activity as recorded by the electroencephalogram. The B_6 group of vitamins act as antidotes to hydrazide seizures.

Injected (together with L-tryptophan) in dogs, thiocarbohydrazide causes an increase in xanthurenic acid excretion.[233] This xanthurenuria-inducing potency in dogs is roughly correlated with the potency in producing seizures in mice.[231,232]

The convulsant activity of thiocarbohydrazide at a single unit level has been assayed using the giant neurons of *Aplysia californica* under carefully controlled conditions.[234]

2. Anticarcinogenic Properties

Carbohydrazide is reported to show no activity against Myeloid mouse leukemia C1498.[235]

A comparative study has been made on the effects of thiocarbohydrazide and chemically modified DNA on reticulosarcoma ST4 and leukemia L1210 in mice. The survival times that were achieved using the thiocarbohydrazide compared favorably and sometimes exceeded those due to DNA.[236]

(216) A. Albert, *Experientia*, 9, 370 (1953).
(217) S. Fallab and H. Erlenmeyer, *Helv. Chim. Acta*, 36, 6 (1953).
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(219) A. F. Krivis, G. R. Supp, and R. L. Doerr, *ibid.*, 38, 936 (1966).
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(222) J. S. Hanker, C. Deb, H. L. Wasserkrug, and A. Seligman, *Science*, 152, 1631 (1966).
(223) L. A. Sternberger, J. S. Hanker, E. J. Donati, J. P. Petrali, and A. M. Seligman, *J. Histochem. Cytochem.*, 14, 711 (1966).
(224) J. A. Gordon and W. P. Jencks, *Biochemistry*, 2, 47 (1963).
(225) L. Levine, J. A. Gordon, and W. P. Jencks, *ibid.*, 2, 168 (1963).
(226) E. Margoliash, A. Novogrodsky, and A. Schejter, *Biochem. J.*, 74, 339 (1960).
(227) C. J. D. Zarafonetis and J. P. Kalas, *Proc. Soc. Exptl. Biol. Med.*, 105, 560 (1960); *Chem. Abstr.*, 55, 9657 (1961).
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(230) C. C. Pfeiffer, K. F. Killam, E. H. Jenney, and W. H. Marshall, *Epilepsia*, 3, 121 (1954); *Chem. Abstr.*, 49, 8507 (1955).
(231) E. H. Jenney and C. C. Pfeiffer, *J. Pharmacol. Exptl. Therap.*, 122, 110 (1958); *Chem. Abstr.*, 52, 6602 (1958).
(232) E. W. Maynert and H. K. Kaji, *J. Pharmacol. Exptl. Therap.*, 137, 114 (1962); *Chem. Abstr.*, 57, 11813 (1962).
(233) H. L. Williams and R. G. Wiegand, *J. Pharmacol. Exptl. Therap.*, 128, 344 (1960); *Chem. Abstr.*, 54, 11267 (1960).
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(235) B. L. Freedlander and A. Furst, *Proc. Soc. Exptl. Biol. Med.*, 81, 638 (1952).
(236) P. T. B. Loc, *Compt. Rend. Soc. Biol.*, 160, 36 (1966).

3. Antibacterial Properties

Thiocarbohydrazide is active *in vitro* against tubercle bacilli (strain $H_{37}RV$) in concentration 10^{-5}; against *Micrococcus pyogenes* var. *aureus* (strain Londres) (1 mg/ml, corresponding to 1.02 μg/ml of penicillin) and against *Escherichia coli* (1 mg/ml, corresponding to 1.2 μg/ml of chloramphenicol).[65] However, its tuberculostatic activity is not applicable *in vivo*. Activity is also exhibited, *in vitro*, against *Mycobacterium tuberculosis* (BCG strain).[237]

4. Miscellaneous Biological Properties

Carbohydrazide, when administered to rhesus monkeys (250 mg/(kg day) for 6 days) was only partially effective against *Schistosoma mansoni*.[238]

Inoculation of (thio)carbohydrazide on the chlorio-allantoic membrane of 14-day old chick embryos led to extensive tissue fragility in 48–72 hr.[239] (Thio)carbohydrazide is termed lathyrogenic. Attempts to demonstrate competitive antagonism between vitamin B_6 and these lathyrogens were unsuccessful.

Thiocarbohydrazide and carbohydrazide exhibit a toxicity toward the house-fly comparable to that of DDT.[240]

5. Fungicidal Properties

The fungicidal properties of a number of hydrazine derivatives, including (thio)carbohydrazides, were tested against *Helminthosporium salivum* and species of *Pythium* in agar cultures.[241] Thiocarbohydrazide and its 1-phenyl derivative inhibited growth at concentrations above 500 ppm. Activity appears to be enhanced by the presence in the molecular structure of thiocarbonyl and free hydrazine groups.

IX. Industrial and Other Uses

(Thio)carbohydrazide has found a variety of industrial uses, most of which are covered by the patent literature.

A. FORMATION OF POLYMERS

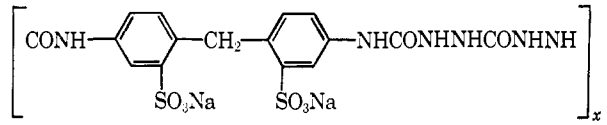
Carbohydrazide condenses with a large number of aromatic diisocyanates, hydroxyisocyanates, or polyester–isocyanate mixtures to form polyurethan elastomers, fibers, and plastic sheets.[242–250] Similar polymers are obtained from carbohydrazide and carboxylic,[251] dicarboxylic,[252] and α,β-unsaturated carboxylic acids.[253] These may be spinnable or can be used as coatings.

A synthetic high polymer has been prepared from pyromellitic anhydride and carbohydrazide in dimethylformamide at low temperatures. Subsequent heating of this product to 180° yields poly(pyromellitimide)urea.[254]

Carbohydrazide acts as a curing agent for epoxide-type resins.[255] Mixed with epoxide polymers, it gives resins stable at 40°F, which, after being cured at *ca.* 300°, have excellent salt-spray resistance.

Shaped articles of polyurethan elastomer are color stabilized by incorporation of 0.5–5% by weight of (thio)carbohydrazide.[256]

Polymeric carbohydrazides **364**, prepared from phenylcarbamic acid esters, are used as pharmaceuticals.[257]



364

B. PHOTOGRAPHY

Material suitable for the formation of black image tones in the silver halide diffusion process contains, besides the usual toners, carbohydrazide in amounts of 1–10 g/kg of emulsion.[258,259]

Color developers which produce dye images of the azomethine or azine classes are stabilized by the addition of 0.1–20 g/l. of carbohydrazide.[260]

Two-component photosensitive diazo reproduction materials developed by heat normally require for development liquids or gaseous ammonia. These two methods can be dispensed with by using a photosensitive diazonium compound and carbohydrazide, which acts as a thermosensitive base-releasing agent.[261]

C. MISCELLANEOUS USES

Carbohydrazide has been found useful as an antioxidant for carotene.[262] Its use, in small concentrations (0.05–1.0% by

(237) R. Donovick, F. Pansy, G. Stryker, and J. Bernstein, *J. Bacteriol.*, 59, 667 (1950).

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(243) H. Oertel and H. Rinke (to Farbenfabriken Bayer A.G.), Belgian Patent 621,379 (1962); *Chem. Abstr.*, **59**, 5347 (1963).

(244) W. Thoma, H. Rinke, and H. Oertel, German Patent 1,150,517 (1963); *Chem. Abstr.*, **59**, 8946 (1963).

(245) Farbenfabriken Bayer A.G., Netherlands Appl., 6,410,335 (1965); *Chem. Abstr.*, **63**, 13519 (1965).

(246) Farbenfabriken Bayer A.G., Netherlands Appl., 6,412,962 (1965); *Chem. Abstr.*, **63**, 13528 (1965).

(247) E. I. DuPont de Nemours and Co., Netherlands Appl., 6,508,384 (1965); *Chem. Abstr.*, **64**, 16051 (1966).

(248) H. Oertel, H. Rinke, F. K. Rosendahl, and H. Kleiner, Belgian Patent 648,812 (1964); *Chem. Abstr.*, **64**, 19903 (1966).

(249) Farbenfabriken Bayer A.G., Netherlands Appl., 6,510,890 (1966); *Chem. Abstr.*, **65**, 5639 (1966).

(250) Farbenfabriken Bayer A.G., Netherlands Appl., 6,515,899 (1966); *Chem. Abstr.*, **65**, 17179 (1966).

(251) W. R. Grace and Co., British Patent 1,019,847 (1966): *Chem. Abstr.*, **64**, 11396 (1966).

(252) Phrix Arbeitsgemeinschaft, Belgian Patent 443,954 (1942); *Chem. Abstr.*, **39**, 646 (1945).

(253) Y. Inaba, K. Kimoto, Y. Miyake, and S. Hamatani, Japanese Patent 10,046 (1957); *Chem. Abstr.*, **53**, 8652 (1959).

(254) T. Unishi and T. Tsujimura, *Kogyo Kagaku Zasshi*, **68**, 2275 (1965); *Chem. Abstr.*, **64**, 12811 (1966).

(255) H. H. Levine, U. S. Patent 3,014,009 (1959); *Chem. Abstr.*, **56**, 8932 (1962).

(256) R. J. Thurmaier, U. S. Patent 3,149,998 (1964); *Chem. Abstr.*, **62**, 734 (1965).

(257) W. Thoma, Belgian Patent 660,945 (1965); *Chem. Abstr.*, **64**, 2025 (1966).

(258) Gevaert Photo-Production N.V., German Patent 1,023,969 (1958); *Chem. Abstr.*, **54**, 15038 (1960).

(259) Gevaert Photo-Production N.V., Belgian Patent 542,151 (1956); *Chem. Abstr.*, **54**, 19244 (1960).

(260) J. W. Britain (to General Aniline and Film Corp.), U. S. Patent 2,772,973 (1956); *Chem. Abstr.*, **51**, 4188 (1957).

(261) J. Kosar, U. S. Patent 3,157,503 (1964); *Chem. Abstr.*, **62**, 2404 (1965).

(262) E. M. Bickoff, A. L. Livingston, J. Guggolz, and C. R. Thompson, *J. Am. Oil Chemists' Soc.*, **29**, 445 (1952); *Chem. Abstr.*, **47**, 829 (1953).

weight) in soap compositions containing phenolic bactericides, stabilizes the product against discoloration and rancidity.[263]

Thiocarbohydrazide is used as an additive to prevent the excessive loss of cellulose during the alkaline work-up of wood pulp.[264]

A projectile propellant has been developed which consists of carbohydrazide (34–64 parts), nitric acid (22–55), and water (75–16).[265]

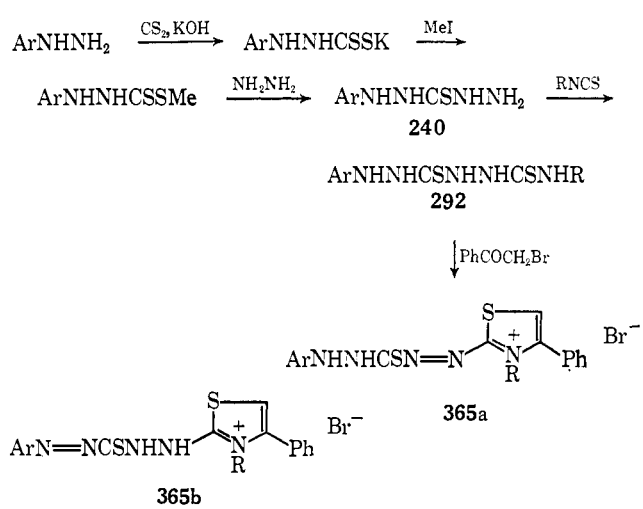
A process has been developed for the preparation of a level copper coating of high brightness by means of acid electrolytes.[266] The copper bath contains 1-phenylthiocarbohydrazide as a polishing and leveling agent.

X. Appendix

After the completion of this review, a few additional papers on carbohydrazide and thiocarbohydrazide derivatives have come to our notice, partly through the latest indexes of *Chemical Abstracts* and partly from our continued survey of the primary journals. Rather than breaking entirely fresh ground, these contributions have mostly served to supplement and consolidate previous work, which is already fully discussed in the main body of the review. Cross references are provided to correlate the new material reported in this Appendix with the appropriate main sections of the review.

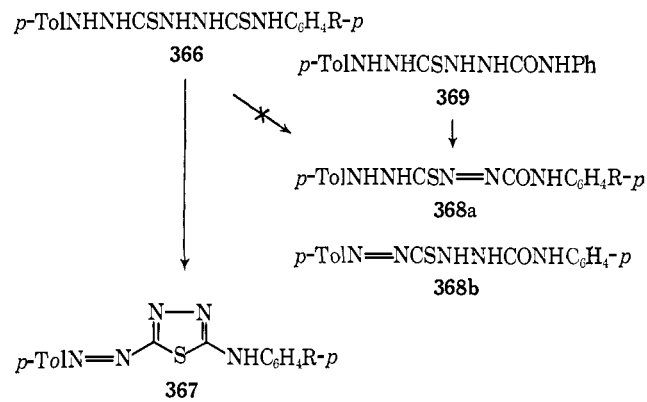
A. 1-ARYL-5-ARYLTHIOCARBAMOYL-THIOCARBOHYDRAZIDES (Section V.A.2.e)

1-Aryl-5-arylthiocarbamoylthiocarbohydrazides **292** have been the subject of continued investigations, which have given several results of interest.[267,268] Further examples of these compounds have been prepared by the conventional multistate synthesis (*via* **240**); their condensation with bromoacetophenone in alcohol has yielded thiazolium salts of type **365**. This reaction is an example of a well-known thiazole



synthesis,[269] but proceeds with simultaneous dehydrogenation to the corresponding azo compounds. In the light of the earlier discussion concerning closely related reactions (*cf.* section V.A.2.e,f), the structure **365a** proposed for these heterocyclics by the authors[267,268] may need to be revised in favor of the isomeric azo structure **365b** which contains the unsaturated azo linkage in conjugation with the terminal aryl group. The ultraviolet absorption spectra of certain of the intermediates (**240** and **292**) as well as the products **365** have been specified.[267]

The same workers[270] have also reexamined the oxidative cyclization of the 1-aryl-5-arylthiocarbamoylthiocarbohydrazides **366** (see section V.A.2.e). This reaction, previously shown[168] to afford very poor yields of deep-orange 2-arylamino-5-arylazo-1,3,4-thiadiazoles (**367**) under the influence of ferric chloride, has apparently now been performed[270] efficiently in near-quantitative yields by the use of various oxidizing agents, including bromine in chloroform or acetic acid, hydrogen peroxide in acetone, or aqueous ferric chloride.[271] The possible[272] alternative oxidation of the substituted thiocarbohydrazides **366**, by simultaneous dehydrogenation and replacement of sulfur by oxygen, to the open-chain products **368** did not occur. For comparison purposes, an example of this structural type (**368**, R = H) was separately synthesized by the mild oxidation, using hydrogen peroxide, of 1-phenylcarbamoyl-5-*p*-tolylthiocarbohydrazide (**369**, itself obtained from *p*-tolylcarbohydrazide and phenyl isocyanate). Ultraviolet and infrared spectra of some of the products were recorded.[270] Once again, the possible reformulation of the yellow product as **368b** (instead of **368a**), containing the N=N double bond in conjugation with the aromatic ring, should be considered.



B. 1-ACYL-2-SUBSTITUTED CARBOHYDRAZIDES (Sections VI.A.1, VI.B.1.b)

The ring-cleavage of oxadiazolin-5-ones by hydrazine is a useful synthetic route to acylated carbohydrazides (see sections VI.A.1 and VI.B.1.b). Gehlen[273] has extended this general method to the preparation of 1-aroyl-2-alkylcarbohydrazides (**371a**), by treatment of 2-alkyl-4-aryl-1,3,4-oxa-

(263) R. C. Harshman and V. C. Fusco, U. S. Patent 2,963,438 (1960); *Chem. Abstr.*, **55**, 5997 (1961).

(264) D. W. Clayton and L. M. Marraccini, *Svensk Papperstid.*, **69**, 311 (1966); *Chem. Abstr.*, **65**, 9160 (1966).

(265) D. W. Ryker, U. S. Patent 2,970,899 (1961); *Chem. Abstr.*, **55**, 10892 (1961).

(266) Riedel and Co., British Patent 985,316 (1965); *Chem. Abstr.*, **63**, 1558 (1965).

(267) R. G. Dubenko, I. M. Bazavova, and P. S. Pelkis, *Zh. Org. Khim.*, 4, 1057 (1968); *Chem. Abstr.*, **69**, 43841 (1968): structure **365** given therein lacks a double bond.

(268) R. G. Dubenko, I. M. Bazavova, and P. S. Pelkis, USSR Patent 206,581 (1967); *Chem. Abstr.*, **69**, 52123 (1968).

(269) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 484, 496.

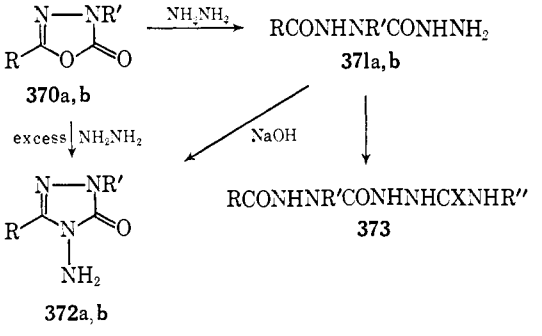
(270) R. G. Dubenko, I. M, Bazavova, and P. S. Pelkis, *Ukr. Khim. Zh.*, 10, 1038 (1968).

(271) We thank Miss J. Y. Comben for the translation of this paper from the Russian.

(272) (a) R. N. Hurd and G. De la Mater, *Chem. Rev.*, **61**, 66 (1961); (b) E. Papadopoulos, *J. Org. Chem.*, 31, 3060 (1966).

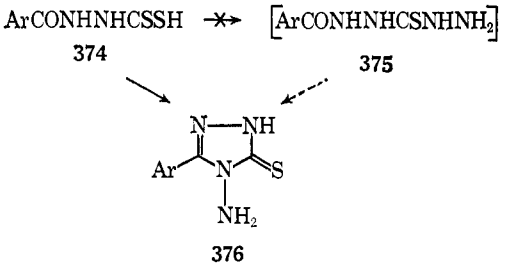
(273) H. Gehlen and P. Demin, *Z. Chem.*, **8**, 221 (1968).

diazolin-5-ones (**370a**) with equimolar proportions of hydrazine hydrate. The course of this reaction is influenced by the hydrazine concentration, and by the nature of the substituents (R, R′ in **370**). Thus, the use of an excess of hydrazine hydrate results merely in the formation of hydrazides ($RCONHNH_2$). Again, hydrazinolysis of **370** having the substituents R, R′ reversed (*i.e.*, **370b**) proceeds with transient ring opening and formation of 3-alkyl-4-amino-1-aryl-1,2,4-triazolin-5-ones (**372b**), presumably by way of the nonisolable 1-acyl-2-arylcarbohydrazides (**371b**); this interpretation is supported by the fact that the stable "reversed" 1-aroyl-2-alkylcarbohydrazides (**371a**) are readily cyclized by alkali to the corresponding 1-alkyl-4-amino-3-aryl-1,2,4-triazolin-5-ones (**372a**). The 1-acyl-2-substituted carbohydrazides **371a** thus obtained, having a free hydrazine function, yield the usual crystalline ketonic derivatives, and react normally with iso(thio)cyanate esters, forming acyclic adducts (**373**).[273]



a, R = Ar; R′ = Alk **b**, R = Alk; R′ = Ar

The alleged preparation of a series of 1-acylthiocarbohydrazides (**375**) by the hydrazinolysis of 1-aroyl-2-dithiocarboxyhydrazines (**374**) claimed by Varma[274] has not been confirmed.[275] This reaction had previously been observed[276,277] to occur with simultaneous cyclization, yielding 3-substituted 4-amino-1,2,4-triazolin-5-thiones (**376**), and a careful repetition of Varma's experiments has shown that the same heterocyclic products are in fact obtained[275] using his procedure.



C. ANALYTICAL METHODS (Section VII.A)

An accurate potentiometric method has recently been developed[278] for the determination of carbohydrazide and its derivatives. A sample of the compound (0.01–0.05 mmole), dissolved in dilute hydrochloric acid containing potassium bromide (0.1 g), is titrated potentiometrically with sodium nitrite solution, using a platinum electrode. The maximum error is given as 1%.

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