RUSSIAN CHEMICAL REVIEWS
Uspekhi Khimii

April 1964

U.D.C. 547.234:615.7

MONOALKYLHYDRAZINES

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I. INTRODUCTION

Alkylhydrazines, being close analogues of aliphatic amines, have been known for a comparatively long time, but their study really began only recently, when these reactive substances were found to exhibit interesting features in their chemical and biochemical behaviour.

Alkylhydrazines, and especially aralkylhydrazines, are able to inhibit the enzyme monoamine oxidase. This has led to the discovery of effective nerve stimulants, which are widely used in modern psychiatry. Introduction of such compounds as phenylisopropylhydrazine into the animal or human organism increases the concentration of serotonin in nerve tissue[1-3]. An intensive search is therefore being undertaken in various laboratories in the world for new medicinal preparations containing an aralkylhydrazino--group, with the aim of synthesising analogues or antagonists of serotonin [4,5], as well as of likely antimetabolites of purine bases[6].

Recently, effective uterine stimulants have been discovered among the alkoxyaralkylhydrazines, resembling oxytocin in their action[7-9]. Alkylhydrazine derivatives have also found practical application in the synthesis of other drugs. Special mention must be made of systemic insecticides. Those based on alkylhydrazines are similar to the organophosphorus poisons in their effect, but are less toxic to warm-blooded animals.

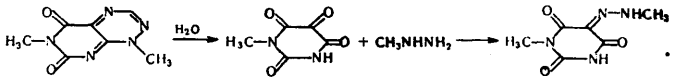
In spite of the large amount of work which has been done on the monoalkylhydrazines, the literature in this important field has not yet been surveyed. Existing review papers and monographs on the chemistry of hydrazine compounds[10-14] deal mainly with the chemistry of hydrazine hydrate and to some extent with phenylhydrazine, but contain only fragmentary information on alkylhydrazines.

In the present review the general term "monoalkylhydrazines" is used to cover monosubstituted hydrazine derivatives containing purely aliphatic and substituted aliphatic radicals, aralkyl and substituted aralkyl radicals, and also alicyclic and hydrogenated heterocyclic radicals. Arylhydrazines, *i.e.* compounds of the type of phenylhydrazine, which have been widely studied and have specific methods of preparation and properties, will not be dealt with here. Hydrazinium salts have been reviewed elsewhere[15].

II. METHODS OF PREPARATION

Alkylhydrazines are not found in Nature, but methylhydrazine has been isolated from the hydrolysis products of the antibiotic toxoflavine, which is produced by the

bacterium *Pseudomonas cocovenenans* [16,17]. The toxoflavine molecule is rapidly cleaved by mineral acids, with the formation first of *N*-methylalloxan and methylhydrazine, and then of "toxoflavine B", which is a methylhydrazone of *N*-methylalloxan:

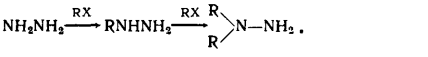


Methods of synthesising monoalkylhydrazines can be divided into two broad groups. The first comprises those in which hydrazine itself is the starting material. The second group can include methods in which the hydrazino--radical is synthesised from compounds containing no N–N bond.

1. Direct and Indirect Replacement of Hydrogen Atoms in Hydrazine

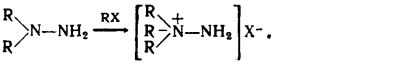
Alkylation of hydrazine. After the discovery by E. Fischer of the readily accessible phenylhydrazine, research workers concentrated their interest mainly on aromatic representatives of this class of compounds. In contrast, only complicated, inadequate methods of preparation were known for most of the alkylhydrazines.

Westphal [18,19] investigated the reaction of hydrazine with alkyl halides, but was mainly concerned, not with the monoalkylhydrazines, but with products of their further alkylation. In fact, alkylation of hydrazine first yields a monoalkylhydrazine, which readily undergoes further alkylation to form an unsymmetrical dialkylhydrazine [20,21]. Symmetrical dialkylhydrazines are not usually formed under these conditions.

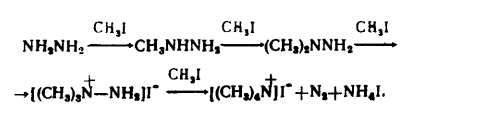


In the case of phenylhydrazine, on the other hand, symmetrical alkylation (*i.e.* formation of 1-alkyl-2-phenylhydrazines) also occurs, since the phenyl group makes alkylation of one of the nitrogen atoms more difficult.

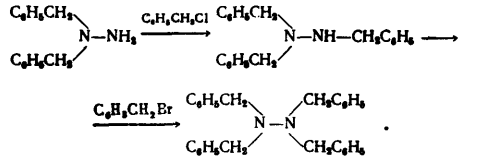
Unsymmetrical dialkylhydrazines, on further alkylation, add on the new alkyl radical to the already substituted nitrogen atom, yielding a quaternary hydrazinium salt:



Active alkylating agents (for example, alkyl iodides) give such quaternary salts directly and almost exclusively on reaction with hydrazine [22]. After formation of the hydrazinium salt, reaction ceases, the second amino-group remaining unsubstituted. This was first established by Harries and Haga [20] for the methylation of hydrazine with methyl iodide in the presence of an excess of caustic potash. Methylhydrazine, dimethylhydrazine, and, as final product of the reaction, trimethylhydrazinium iodide were isolated. An attempt at further methylation of this quaternary salt at 130° gave only tetramethylammonium iodide, so that the hydrazine molecule had been cleaved with rupture of the nitrogen–nitrogen bond:

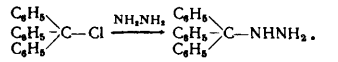


In isolated cases a trialkylhydrazine can be obtained by direct alkylation. Thus Franzen and Kraft [23,24] subjected hydrazine hydrate to prolonged treatment with benzyl chloride, and obtained tribenzylhydrazine, from which Wieland and Schamberg [25] subsequently prepared tetrabenzylhydrazine by the action of benzyl bromide:



This result is due primarily to steric hindrance, which prevents the attachment of a third benzyl radical to an already substituted nitrogen atom and hence the formation of a quaternary salt.

The effect of steric hindrance in raising the yield of monoalkylhydrazine is especially evident in the reaction of hydrazine with chlorotriphenylmethane [26,27]. In this case the yield of methyltriphenylhydrazine is 87%, and there is practically no further alkylation:



By exploiting similar favourable steric factors, Klages [28,29] synthesised triisopropylhydrazine, and from 1,2-dimethylhydrazine and isopropyl bromide obtained 1,2-diisopropyl--1,2-dimethylhydrazine. Elimination of halogen with formation of the hydrocarbon takes place as a side-reaction in the interaction of hydrazine with tertiary halides [27].

Thus direct alkylation of hydrazine usually yields monoalkylated and unsymmetrically dialkylated hydrazines, and as the last stage hydrazinium salts, which do not react with alkylating agents (or else break down with rupture of the N–N bond). In practice, alkylation of hydrazine with an equivalent quantity of an alkyl halide gives a mixture of these compounds, only a small proportion of the monoalkylhydrazines being obtained [18,23,24,28–30]. When hydrazine is treated with the higher 1-chloroalkanes (above C_8), practically no quaternary salt is formed, and with alkyl chlorides containing more than twelve carbon atoms the main reaction products are monoalkylated and unsymmetrically dialkylated hydrazines [18,19].

The above facts make clear why the view has become established in the literature that direct alkylation of hydrazine cannot serve for the preparation of monoalkylhydrazines [13,15,30,31]. Nevertheless, other results have been published for this reaction. Thus Gabriel [32] worked out a method for obtaining allylhydrazine from hydrazine hydrate and allyl chloride, the yield being 34%. Votoček and Lemiger [33] reported the synthesis of phenethylhydrazine in 41% yield from hydrazine hydrate and phenethyl chloride. Westphal [18] obtained hexyl-, octyl-, dodecyl-, and hexadecyl-hydrazine from hydrazine hydrate and the corresponding chlorides, the respective yields being 26, 26, 47, and 62%. The synthesis of butyl- and octyl-hydrazine as their sulphates, from hydrazine sulphate and the corresponding halides, has been reported in the patent literature [34]. It has been stated [1] that the aralkylation of hydrazine with secondary halides gives yields of 35–45%, but the reaction is complicated by elimination of hydrogen halide with formation of a carbon–carbon double bond.

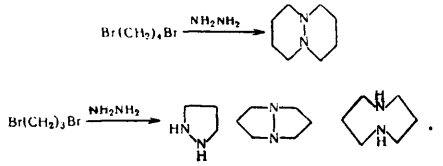
Polyalkylation is considerably diminished[35] by slow addition of the alkyl halide to a tenfold excess of hydrazine hydrate with vigorous stirring of the reaction mixture. However, complete removal of the resulting monoalkylhydrazine from the reaction mixture is sometimes achieved only by continuous and prolonged extraction in a suitable apparatus. It is probable that here the usual partition of alkylhydrazine between solvent and hydrazine hydrate is accompanied by equilibrium between a salt of the alkylhydrazine and the hydrazine itself, which prevents rapid extraction of the alkylhydrazine. In some cases a considerably smaller excess of hydrazine can be used. Thus isopropylhydrazine has been obtained in 68% yield by the reaction of isopropyl bromide with a fourfold excess of hydrazine hydrate. This can probably be explained by steric hindrance, which prevents the formation of diisopropylhydrazine. It is true that here, owing to the lower reactivity of the halide, the reaction mixture must be heated. In several cases (with butyl- and nonyl-hydrazine) the use of alcohol as solvent cannot be avoided, since otherwise only a dialkylhydrazine is obtained[36]. Kost and Sagitullin proposed this method for the synthesis of alkylhydrazines[36-38] and aralkylhydrazines[8,39,40].

Biel and his coworkers[1,41] have recently made similar observations on the possibility of the direct synthesis of alkylhydrazines (see also Refs. 42 and 43).

Dreyfus[44,45] patented the preparation of dihydrazines from hydrazine hydrate and dihalides in which the halogen atoms were attached to two different methylene groups:

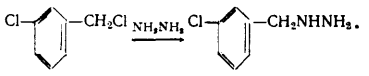
$$Cl(CH_2)_6Cl \xrightarrow{NH_2NH_2} NH_2NH(CH_2)_6NHNH_2.$$

It was shown later that reaction of hydrazine with such dihalides may also yield heterocyclic compounds. Thus 1,4-dibromobutane and hydrazine hydrate gave decahydro-9,10-diazanaphthalene[46], while from 1,3-dibromopropane were obtained pyrazolidine, trimethylenepyrazolidine, and 1,5-diazacyclooctane[47]:



Formation of this last compound can be explained by the reducing action of diimide HN : NH.

If a halogen atom is attached to an aromatic nucleus, it usually remains unaffected. Thus reaction of hydrazine with *m*-chlorobenzyl chloride produces *m*-chlorobenzylhydrazine[48]:



Monoalkylhydrazines can be synthesised without complication from hydrazine and halogen derivatives containing a hydroxy-group or a substituted amino-group, for example a diethylamino-group[41,49,50]:

$$(C_2H_5)_2NCH_2CH_2Br \xrightarrow{NH_2NH_2} (C_2H_5)_2NCH_2CH_2NHNH_2.$$

However, reaction of 4-chlorobutanol with hydrazine in the presence of alkali at 95–100° gave only tetrahydrofuran, whereas in the absence of alkali at 30° 4-hydrazinobutanol is formed[51].

α-Halogenated acids react with hydrazine to form α-hydrazino-acids, which are hydrazine analogues of α-amino-acids[52-54]. The use of ion-exchange resins for their isolation has been developed[55]:

$$R{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}COOH \xrightarrow{NH_2NH_2} R{-}\underset{\displaystyle NHNH_2}{\underset{|}{CH}}{-}COOH.$$

Chloroacetic acid and hydrazine give mainly hydrazinediacetic acid[56-58], which serves as an intermediate in the synthesis of azocarboxylic ester:

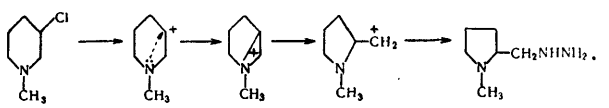
$$ClCH_2COOH \xrightarrow{NH_2NH_2} \underset{\displaystyle HN{-}CH_2COOH}{\underset{|}{HN}}{-}CH_2COOH.$$

The reaction of hydrazine with halogenated derivatives of this type is complicated by secondary processes. Thus treatment of α-bromoacetoacetic[59] and benzoylbromoacetic[60] ester, bromo-diketones[61,62], β-halogeno-α-nitro-derivatives of aliphatic acids[62], and chloronitromethane[63] with hydrazine hydrate results in replacement of the halogen by hydrogen.

α-Halogeno-ketones form with hydrazine a mixture of various compounds, including pyrazines[64].

Sometimes the reaction of hydrazine with halogenated derivatives is accompanied by rearrangement. Thus treatment of 3-chloro-1-methylpiperidine with hydrazine results in contraction of the piperidine ring, with formation of 2-hydrazinomethyl-1-methylpyrrolidine[41]. The structure of this compound has been proved by reduction to the corresponding amine, which has been prepared in a different way, and also by synthesis of a compound known to be 3-hydrazino-1-methylpiperidine.

It is probable that an initially formed carbonium cation is stabilised by the lone pair of electrons from the nitrogen atom, after which cleavage of the three-membered ring leads to a Dem'yanov rearrangement:



In several cases esters of mineral acids are used instead of alkyl halides for the alkylation of hydrazine. A 32% yield of ethylhydrazine has been reported from the action of diethyl sulphate on an alkaline alcoholic solution of hydrazine[65], and propylhydrazine has been obtained by the interaction of hydrazine hydrate and potassium propyl sulphate[66,67]. The reaction of hydrazine with nitric esters[68,69] is considerably more complicated. Primary aliphatic (ethyl, butyl, isopentyl) nitrates, with a sufficiently high concentration of hydrazine, undergo mainly reduction with the formation of gaseous nitrogen, nitrous oxide, ammonia, the nitrite and nitrate ions, and also alkylated hydrazines, alcohol, and traces of aldehyde. In the case of benzyl nitrate, it has proved possible to isolate benzylhydrazine (as the nitrate) and di-, tri-, and tetra-benzylhydrazines, together with benzaldehyde dibenzylhydrazone. This reaction is unsuitable for the preparation of monoalkylhydrazines.

Finally, hydrazine can add on to an activated double bond. Thus it adds on to β-nitrostyrene and to styrene itself to form the corresponding phenethylhydrazines[70,71]:

$$C_6H_5{-}CH{=}CH_2 \xrightarrow{NH_2NH_2} C_6H_5CH_2CH_2NHNH_2.$$

Nitriles of unsaturated aliphatic acids (acrylic, crotonic, cinnamic), as well as their esters and amides, are able to add on a molecule of hydrazine to form monosubstituted hydrazines[72-78]. For example, the reaction of hydrazine with acrylonitrile (cyanoethylation) gives β-hydrazinopropionitrile in yields up to 90%:[74]

$$CH_2{=}CHCN \xrightarrow{NH_2NH_2} NH_2NH{-}CH_2CH_2CN.$$

With excess of acrylonitrile a second molecule of the latter adds on both at the NH and at the NH_2 group[79]. In the presence of sodium ethoxide, cyanoethylation is accompanied by cyclisation giving 3-aminopyrazoline as a secondary product[78].

Dimethyl fumarate, however, does not add on hydrazine on heating, but is converted into the dihydrazide of fumaric acid[80]. A non-conjugated double bond in unsaturated acids is reduced in good yield on being heated with hydrazine hydrate[81-85]. The action of hydrazine on fluoroalkenes has been studied[85].

Hydrazine adds on smoothly to ethylene oxide and its homologues, the oxide ring undergoing cleavage with the formation of 2-hydrazinoethanols[32,51,86-92]:

$$\underset{\diagdown O \diagup}{CH_2{-}CH_2} \xrightarrow{NH_2NH_2} HOCH_2CH_2NHNH_2.$$

Thus hydrazinoethanols have been used for the synthesis of several hydrazides[93] and semicarbazones[51] in the search for antibacterial agents. With acetylenic oxides hydrazine forms *N*-aminopyrroles[90]. The interaction of hydrazine with epoxypropionic esters has been described[94].

Alkylation of hydrazine derivatives. Because of the above difficulties in the direct alkylation of hydrazine, workers long ago searched for various indirect methods, including processes involving temporary protection of the amino-group.

A typical example of such alkylation is the method proposed by Thiele in 1910[30] for preparing methylhydrazine†. It is based on the conversion of benzylidene azine into a hydrazinium salt by reaction with dimethyl sulphate, the quaternary salt being decomposed by water into one mole of methylhydrazine and two moles of the aldehyde. The methylhydrazine is isolated as the sulphate, the yield of which is 51–54%:[12,30,95,96]

$$C_6H_5CH{=}NN{=}CHC_6H_5 \xrightarrow{(CH_3O)_2SO_2} [C_6H_5CH{=}\overset{+}{N}(CH_3){=}CHC_6H_5]CH_3SO_4^- \xrightarrow{H_2O}$$

$$\longrightarrow CH_3NHNH_2 + 2C_6H_5CHO + CH_3OSO_3H.$$

This convenient method is of extremely limited application, since reaction does not take place with diethyl sulphate, and this applies especially to the higher dialkyl sulphates. Ethylhydrazine can be obtained in low yield by alkylating benzylidene azine with ethyl iodide. This is mentioned by Thiele[30] without any indication of the experimental details. Azines of aliphatic aldehydes[97] and ketones[98], on treatment with alkyl halides, undergo intramolecular cyclisation with the formation of 1-alkylpyrazolines.

† In the opinion of Weygand[95], only one preparative method exists in the chemistry of the alkylhydrazines, and this is Thiele's preparation of methylhydrazine.

As azines are derivatives of carbonyl compounds, they are able, like aldehydes and ketones, to add on organomagnesium compounds. Addition of one molecule of phenylmagnesium bromide to ethylidene azine followed by treatment with water gives a 30% yield of a hydrazone, hydrolysis of which produces α-methylbenzylhydrazine[99]:

$$CH_3CH{=}N{-}N{=}CHCH_3 \xrightarrow[H_2O]{C_6H_5MgBr} C_6H_5{-}CH(CH_3){-}NH{-}N{=}CHCH_3 \xrightarrow{NaOH}$$

$$\longrightarrow C_6H_5CH(CH_3){-}NHNH_2.$$

Similarly, α-methylphenethylhydrazine was obtained from benzylmagnesium chloride[100,101], and from isopropylidene azine and with methylmagnesium bromide the product was t-butylhydrazine[102].

The reaction of benzylidene azine with organomagnesium compounds is more complicated, the products including hydrocarbons as well as aralkylhydrazones, which can be explained by partial breakdown at an azo-link, caused by migration of the double bond to the N:N position[103]:

$$C_6H_5CH{=}N{-}N{=}CHC_6H_5 \xrightarrow[H_2O]{RMgX} C_6H_5{-}\underset{\displaystyle R}{\underset{|}{CH}}{-}NH{-}N{=}CHC_6H_5 \longrightarrow$$

$$\longrightarrow \left[C_6H_5{-}\underset{\displaystyle R}{\underset{|}{CH}}{-}N{=}N{-}CH_2C_6H_5\right] \longrightarrow C_6H_5{-}\overset{\displaystyle H}{\overset{|}{\underset{\displaystyle R}{\underset{|}{C}}}}\cdot + N_2 + \cdot CH_2C_6H_5.$$

Grandberg and Kost[104] worked out a synthesis of benzylhydrazine by the benzylation of the sodium derivative of the enol form of acetone acetylhydrazone. Hydrolysis of the reaction product with hydrochloric acid gave a 76% yield of benzylhydrazine:

$$NH_2NH_2 \xrightarrow{CH_3COOC_2H_5} CH_3{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NHNH_2 \xrightarrow{(CH_3)_2CO} CH_3{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}NHN{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_3 \xrightarrow{NaOH}$$

$$\rightarrow CH_3{-}\underset{\displaystyle ONa}{\underset{|}{C}}{=}N{-}N{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_3 \xrightarrow{C_6H_5CH_2Cl} CH_3{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}N(CH_2C_6H_5){-}N{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_3 \xrightarrow[H_2O]{HCl} C_6H_5CH_2NHNH_2.$$

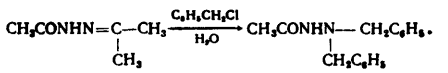
A year later Ronco and Erlenmeyer[105-107] used an analogous reaction to prepare 1-alkyl-1-acylhydrazones. They used biacetyl as carbonyl component, and carried out the hydrolysis under very mild conditions, which enabled the acyl group to be preserved. Better results were achieved by boiling the biacetyl 1-acyl-1-alkylhydrazone in aqueous alcohol with semicarbazide, which combined with the biacetyl that was eliminated:

$$RCONHNH_2 \xrightarrow{CH_3COCOCH_3} RCONHN{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}O \xrightarrow{R'Br}$$

$$\longrightarrow RCO{-}\underset{\displaystyle R'}{\underset{|}{N}}{-}N{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}O \xrightarrow{H_2O} RCO{-}\underset{\displaystyle R'}{\underset{|}{N}}{-}NH_2.$$

A detailed study of the reaction of benzylhydrazine with acylhydrazones has shown[108] that the latter, when in the form of the sodium derivatives of the enols in anhydrous medium, take up the benzyl radical at the nitrogen atom linked to the acyl group, whereas under severe conditions a second benzyl radical adds on to the other nitrogen atom.

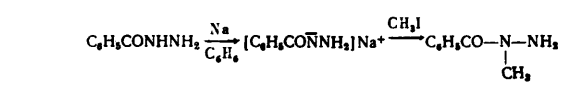
In aqueous media a ketone molecule is readily split off, and the resulting hydrazide is now benzylated at the amino-group instead of the carbamoyl group:



The yield of the 2,2-dibenzylhydrazide depends on the strength of the base used to combine with the hydrogen chloride liberated in the reaction. In the presence of pyridine a 14% yield of 1,1-dibenzyl-2-acetohydrazide is obtained, but with triethylamine the yield is increased to 50%. When, however, acetohydrazide is treated with benzyl chloride in aqueous sodium carbonate solution, the main product of the reaction is tetrabenzylhydrazine: *i.e.* under these conditions the acetyl group is eliminated as well.

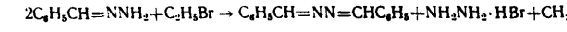
The simplest alkyl halides do not react at their boiling points with the sodium enolate of acetone acetylhydrazone, and when reaction is carried out in an autoclave at 150°, monoalkylhydrazines are not formed, but mainly symmetrical dialkylhydrazines [36,109].

Alkylation of hydrazides themselves is less suitable for the preparation of monoalkylhydrazines, since alkylation takes place at the non-acylated nitrogen atom, both amino-hydrogen atoms being replaced [110-113]. A monoalkylhydrazide can be obtained and isolated only by the action of the alkyl halide on the sodium derivative of the hydrazide (formed by the action of metallic sodium in benzene) [114]:



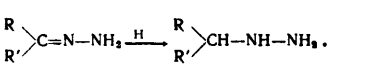
In the same way, cyanoethylation of hydrazides takes place at the NH_2 group, but in the presence of alkaline agents also at the NH group [78].

Attempts to alkylate non-acylated hydrazones with alkyl halides (which should give alkylhydrazines after hydrolysis of the alkylation products) give azines. For example, treatment of benzaldehyde hydrazone with ethyl bromide yields benzylidene azine [115]:

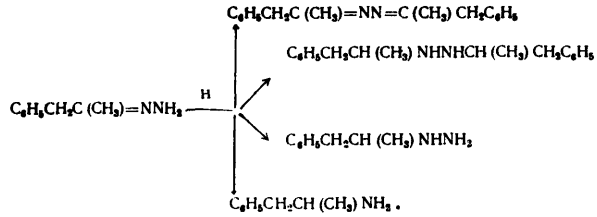


Sometimes, however, such alkylation can be carried out, for example in the case of acetone hydrazone [116].

Reduction of hydrazine derivatives. Many hydrazine derivatives containing a carbon–nitrogen double bond, which on reduction are converted into alkylhydrazines, have been tried. Thus hydrazones are reduced directly to monoalkylhydrazines:

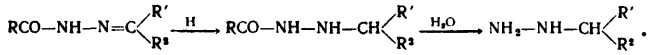


The reducing agents used have been sodium in alcohol [117,118], sodium amalgam [53,119-122], and lithium tetrahydroaluminate [123-125]. Catalytic hydrogenation has also been employed [126-129]. The N–N bond is sensitive to hydrogenation, and therefore the choice of reaction conditions is especially important in this last case for the successful preparation of alkylhydrazines. For example, hydrogenation of the hydrazone of benzyl methyl ketone can yield, depending on the conditions, four substances — the azine of this ketone, 1,2-bis-α-methylphenethylhydrazine, α-methylphenethylhydrazine, or α-methylphenethylamine [1]:



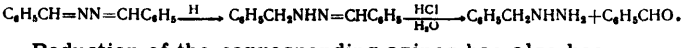
Platinum oxide or platinum on a carrier is usually employed as catalyst. Raney nickel is inconvenient, since it ruptures the N–N bond [130]. It must again be emphasised that the hydrogenation of hydrazones can yield alkylhydrazines only with a very delicate choice of conditions. Usually the N–N bond is broken with the formation of primary (and to some extent secondary) amines.

It is therefore preferable to reduce acylhydrazones instead of hydrazones themselves, since the N–N bond is rather more stable in the former. The resulting acyl derivatives can then be hydrolysed to the free monoalkylhydrazines:



The method of reduction most often used is hydrogenation of the acylhydrazones over a platinum catalyst (platinum oxide or platinum on a carrier) [2,126,131-145]. Raney nickel can also be used [116]. In several cases lithium tetrahydroaluminate has been employed [116,146,147]. It is true that in this case, depending on the nature of the initial acylhydrazone and the reaction conditions, reduction may go further, the corresponding 1,2-dialkylhydrazine being formed by reduction of the carbonyl group [147,148]. Nevertheless, predominant formation of 2-alkylhydrazides can be achieved, since the carbonyl group is more difficult to reduce [149,150].

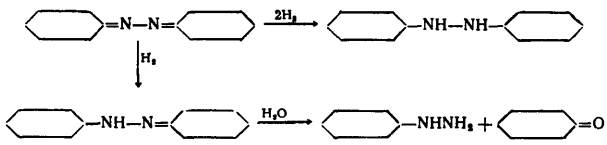
Aldazines and ketazines can be used as starting materials for the preparation of monoalkylhydrazines by reduction [30,117,151-156], although the C : N double bond in azines is fairly inert towards reduction [157,158]. Thus in 1900 Curtius [159] showed that, when benzylidene azine and its homologues are reduced in alkaline media (with sodium amalgam), one molecule of hydrogen is added, followed by a second molecule. In acid media (zinc dust in a mixture of acetic and hydrochloric acids), however, the N–N bond is broken with formation of mono- and di-benzylamines. Monoalkylhydrazines are obtained by hydrolysis of the products of the first stage in the reduction (with sodium amalgam), *i.e.* by hydrolysis of alkylhydrazones, an alkylhydrazine and a carbonyl compound being formed. In this way Wohl [160] and Curtius [159,161] synthesised benzylhydrazine from benzylidene azine:



Reduction of the corresponding azines has also been used to obtain nuclear-substituted benzylhydrazines, for example the 4-methyl, 2,4-dimethyl, and 2,4,5-trimethyl derivatives [159,162].

This process can be extended in only a limited degree to the purely aliphatic series, since aliphatic azines are considerably more resistant to reduction, as is confirmed by the work of Thiele [30], who was unable to reduce the azine of acetone electrolytically, although under these conditions benzylidene azine is reduced to 1,2-dibenzylhydrazine. On

the other hand, Kizhner[117] reduced cyclohexylidene azine with sodium in alcohol, and converted it into a mixture of cyclohexylhydrazine and 1,2-dicyclohexylhydrazine (he assumed that he had obtained the unsymmetrical derivative, the structure of his product being proved later[163]):

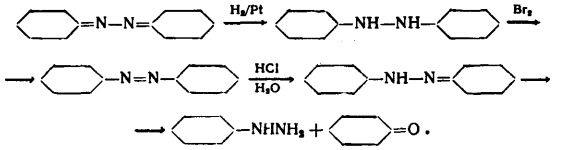


The azine of 3-methylcyclohexanone reacts similarly[164].

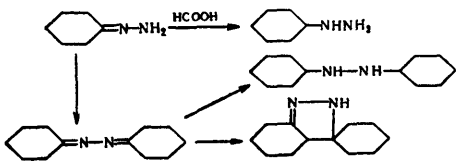
Taipale published a series of papers[152,165-169] on the hydrogenation of azines over platinum. In this case reaction takes place at normal temperatures with a slight excess pressure of hydrogen. If necessary, the process can be stopped after only one double bond has been hydrogenated, when alkylhydrazones of the corresponding aldehydes or ketones are obtained, hydrolysis of which can give alkylhydrazines, as shown above for benzylidene azine. However, this method was not adapted for preparative purposes.

Reduction of azines with lithium tetrahydroaluminate gave predominantly symmetrical dialkylhydrazines[155,170,171].

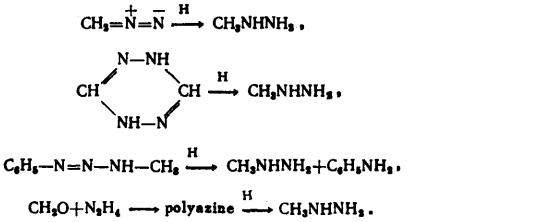
1,2-Dialkylhydrazines can be converted into monoalkylhydrazines by oxidation to the corresponding azo-compounds followed by hydrolysis with dilute mineral acid, which involves preliminary isomerisation to an alkylhydrazone. Harkins and Lochte[163] used this method to synthesise cyclohexylhydrazine from dicyclohexylhydrazine (obtained by catalytic hydrogenation of the azine of cyclohexanone over colloidal platinum):



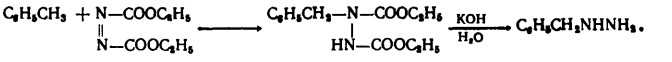
Cyclohexylhydrazine has been obtained in 31% yield also by the reduction of cyclohexanone hydrazone with anhydrous formic acid; 3,4-tetramethylene-5,5-pentamethylenepyrazoline and dicyclohexylhydrazine are also obtained, with the intermediate formation of cyclohexylidene azine[172]:



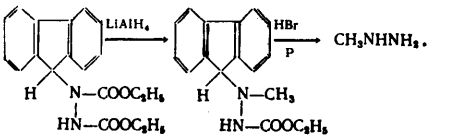
Finally, isolated reductions have been reported for the preparation of methylhydrazine — the reduction of diazomethane with sodium amalgam[173], of dihydrotetrazine with zinc and acetic acid[174], and of methylphenyltriazen[175] and the polymeric azine of formaldehyde with sodium amalgam[176]:



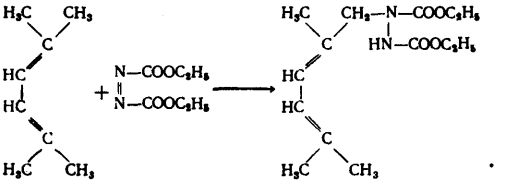
Syntheses with azocarboxylic ester. Azocarboxylic ester adds on various aromatic hydrocarbons containing alkyl radicals to form diethyl 1-aralkylhydrazine-1,2-dicarboxylates[150]. When the adducts are heated with methanolic caustic potash, aralkylhydrazines are obtained in yields up to 56% (based on the adduct, which in turn is formed in yields of 3–43% depending on the experimental conditions):



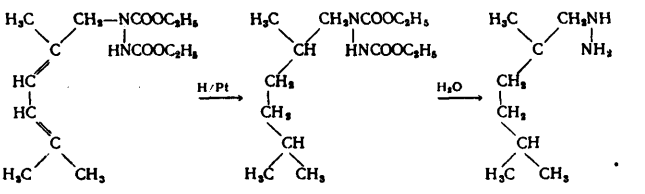
It is noteworthy that, on reduction with lithium tetrahydroaluminate, adducts of azocarboxylic ester and aromatic hydrocarbons are converted into ethyl 2-aralkyl-2-methylhydrazine-1-carboxylates, which on being heated with hydrobromic acid and red phosphorus break down with the formation of methylhydrazine, as has been shown in the case of the fluorene adduct[150]:



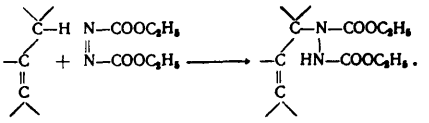
gem-Dialkylbutadienes react similarly to aromatic hydrocarbons with azocarboxylic ester; for example, 2,5-dimethylhexa-2,4-diene gives the corresponding adduct in 70–75% yield[177]:



These addition products had previously been regarded as diethyl 1,2,3,6-tetrahydropyridazine-1,2-dicarboxylates[178,179], since the reaction was assumed to follow the usual mechanism of diene synthesis. However, Levina *et al.* have shown[177] that it represents a substitutive addition. The double bonds in the adduct can be hydrogenated over a platinum catalyst in the cold, an alkylhydrazine being obtained after hydrolysis[177]:

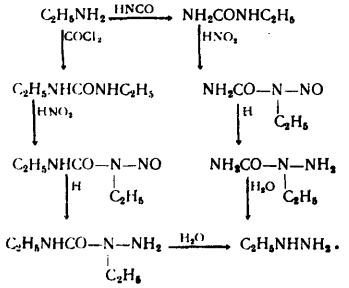


Azocarboxylic ester reacts not only with dienes but also with monoalkenes containing at least one hydrogen atom attached to an α-carbon atom [180-183], and this can also be used to obtain the corresponding alkylhydrazines:



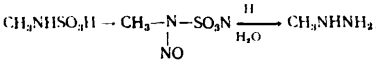
2. Synthesis Involving Formation of the N–N Bond

Nitrosation of an amino-group followed by reduction. The first information on monoalkylhydrazines was published as long ago as 1876 by Fischer [184], who found a route to their synthesis from primary amines *via* urea derivatives. Actually, reaction of nitrous acid with primary amines, which served as a method for the synthesis of arylhydrazines, was impossible with aliphatic amines because of rapid deamination. In order to avoid this, alkylamines are converted by means of cyanic acid or carbonyl chloride into mono- or di-alkylureas, which can now be nitrosated with nitrous acid. On careful reduction (with zinc and acetic acid) the nitroso-group is converted into a hydrazino-group. Acid hydrolysis yields alkylhydrazine, carbon dioxide, and alkylamine [185,186]:



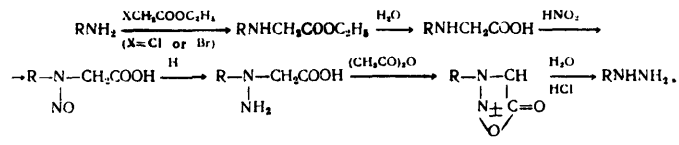
For a long time this classical method was the only one which could be considered for the preparation of alkylhydrazines, and was employed for the synthesis both of the simplest hydrazines (the methyl and ethyl derivatives [184,187]) and of more complicated products, for example hexamethylene-1,6-dihydrazine [44]. A substantial disadvantage of the method is the number of stages and the resulting low overall yield of monoalkylhydrazine.

Another method used to protect the amino-group before nitrosation was introduction of a sulpho-group. Thus nitrosation of methylsulphamic acid followed by reduction gave methylhydrazine [188]:

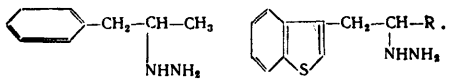


Alkylurethanes have been employed for the same purpose [189].

Finally, alkylhydrazines have been obtained during recent years by the acid hydrolysis of sydnones, which also are synthesised from primary amines [190-195]:

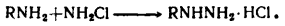


Originally used only in isolated cases, this method has subsequently been considerably extended, and can now be regarded as a fairly general procedure for the synthesis of monoalkylhydrazines [3,196-199]. It has been used in particular to synthesise α-methylphenethylhydrazine‡, which has an inhibiting effect on monoamine oxidase and is employed in the treatment of mental illness [3,198], and a series of 2-benzothienylethylhydrazines, which possess a hypotensive, analgesic, and sedative action [197]:



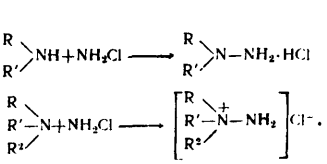
The reduction has also been reported of the comparatively stable nitramines for the preparation of methyl- and ethyl-hydrazines [200].

Reaction of amines with chloramine. A comparatively simple and extremely promising method developed in recent years for the synthesis of alkylhydrazines is based on the reaction of chloramine with primary amines [201-206]:



It is a modification of Raschig's well-known synthesis of hydrazine [207,208] from chloramine (hypochlorite and ammonia in the presence of aqueous alkali) and excess of ammonia.

The first paper on the use of Raschig's synthesis to obtain monoalkylhydrazines appeared in 1954 [201], when it was found that conditions for the preparation of methylhydrazine resembled in many respects those required for the synthesis of hydrazine itself (the addition of gelatin was needed, this being a deactivator of heavy metals; the alkalinity had to be maintained constant; etc.). The maximum yield of methylhydrazine was 64%. However, important differences were also found: firstly, the molar ratio of amine to chloramine required for the maximum yield of alkylhydrazine was considerably lower than that of ammonia to chloramine; and secondly, the temperature required for good yields of alkylhydrazines was considerably lower than was required for hydrazine. In the reaction of methylamine with chloramine, for example, considerable quantities of methylhydrazine are formed even at 0° and with a molar ratio of $CH_3NH_2 : NH_2Cl = 5$ (at room temperature, however, the process is complete in 20 min); whereas, if satisfactory yields of hydrazine are to be obtained, a molar ratio of $NH_3 : NH_2Cl = 20$ is necessary, and the ammonia–chloramine mixture must be heated to 60°. Subsequently, this method was extended to secondary and tertiary amines, and enabled unsymmetrical dialkylhydrazines [202-205,209] and tri-substituted hydrazinium salts [210-218] respectively to be obtained:



A useful improvement in the above method of obtaining alkylhydrazines is to carry out the reaction in the presence

‡ Obtained also by reduction of the hydrazone of benzyl methyl ketone [1].

of a tertiary amine, equivalent in amount to the free hydrazinium ions formed by the action of chloramine on the primary (or secondary) amine[205]. Addition of triethylamine in the preparation of methylhydrazine, for example, raises the yield of the latter from 55% to 75% (based on the chloramide).

There is also a reference in the patent literature to the production of alkylhydrazines by a process which is in some sense the opposite of the above method: amines are first converted into substituted chloramines, which then react with ammonia to form alkylhydrazines[219]:

$$RNHCl + NH_3 \longrightarrow RNHNH_2 \cdot HCl.$$

Thus this reaction represents ammonolysis of the chloramine.

Reaction of amines with hydroxylamine hydrogen sulphate. In 1925, long before Raschig's synthesis was extended to amines, several alkylhydrazines were produced in Germany by a similar method, in which the more complicated analogue of chloramine, hydroxylamine hydrogen sulphate, was employed[220,221]:

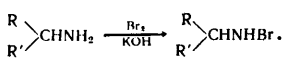
$$RNH_2 + NH_2OSO_3H \longrightarrow RNHNH_2 \cdot H_2SO_4.$$

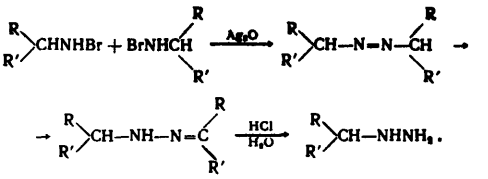
Under these conditions secondary amines give unsymmetrical dialkylhydrazines, and the reaction with tertiary amines yields quaternary 1,1,1-trialkylhydrazinium salts[222], so that the analogy with the Raschig synthesis is maintained in these cases too. For a long time this method failed to attract the attention of organic chemists, and it was only in 1949 that a second paper appeared on the use of this method to obtain a series of alkylhydrazines[223].

Recently a more detailed study of the reaction has been made by Gösl and Meuwsen[222,224], who found that better yields (up to 65%) of both mono- and di-alkylhydrazines are obtained in the presence of caustic potash, at elevated temperatures, and with molecular proportions of amine : NH_2OSO_3H : KOH = 2 : 1 : 2. Further increase in the proportion of amine produces only a slight increase in the yield of hydrazine. The presence of copper ions has a deleterious effect on the synthesis of monoalkylhydrazines. These workers consider that the production of hydrazines from amines and hydroxylamine hydrogen sulphate is to be regarded as a substitution, analogous to alkylation, for example methylation with dimethyl sulphate.

Hydroxylamine hydrogen sulphate itself is not produced in large quantities, which somewhat impedes widespread use of the method. The acid can be obtained from hydroxylamine sulphate and chlorosulphuric acid or oleum[220,225].

Action of silver oxide on bromamines. An interesting method for the synthesis of monosubstituted hydrazines was suggested by Kizhner[118,226-230]. The starting materials were primary amines in which the amino-group occupied a secondary position, and these were converted by the action of bromine and alkali into the corresponding bromamines. With silver oxide the latter gave azo-compounds, which immediately isomerised into hydrazones, on hydrolysis of which with hydrochloric acid the alkylhydrazines separated:

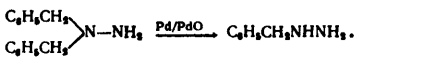




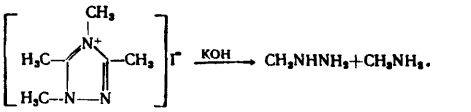
This method was employed by Kizhner for the preparation of hydrazines from 1-methylpentylamine, 1-propylbutylamine, 1-methylheptylamine, 3-methylcyclohexylamine, and *laevo*-menthylamine. However, this method is fairly complicated, and cannot be extended to the simplest radicals, since amines in which the amino-group occupies a primary position are oxidised by bromine to the corresponding nitriles.

3. Other Methods

It has already been mentioned that symmetrical dialkylhydrazines can be converted into monoalkylhydrazines by oxidation to azo-compounds followed by hydrolysis[147]. The preparation of benzylhydrazine from the unsymmetrical dibenzylhydrazine by decomposition over a palladium catalyst has been described:

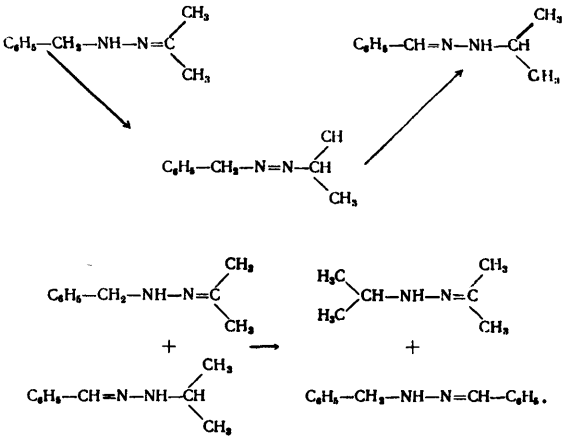


Methylhydrazine is obtained, together with methylamine, when 1,3,4,5-tetramethyl-1,2,4-triazolium iodide is heated in 50% caustic potash solution[232,233]:



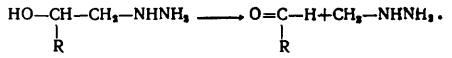
It has also been reported that methylhydrazine is formed as a secondary product in the preparation of diazomethane from hydrazine and chloroform[234].

When acetone benzylhydrazone is heated with hydrogen chloride to 200°, acetone isopropylhydrazone is formed, together with hydrocarbons and pyrazole and pyrazoline bases. Probably the double bond first migrates to a conjugated position (decomposition of the intermediate azo-compound gives rise to the hydrocarbons), and then the two hydrazones undergo double decomposition[235]:

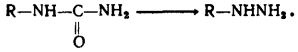


The benzaldehyde benzylhydrazone which is thus formed is unstable under the conditions of the reaction.

Several 2-hydrazinoethanols, on being heated to 200–215°, split off a molecule of methylhydrazine [236], the yields reaching 30%:



By analogy with Hofmann's method for the preparation of amines, substituted ureas could probably be converted by hypochlorites into the corresponding hydrazines:



This suggestion was made by Shestakov as long ago as 1903 [237], but has received no experimental confirmation.

III. PROPERTIES OF MONOALKYLHYDRAZINES

Among all the numerous class of monoalkylhydrazines and monoaralkylhydrazines, the properties of the two simplest members, methylhydrazine and benzylhydrazine respectively, have been most thoroughly investigated.

The lower monoalkylhydrazines are very hygroscopic, mobile, colourless liquids having a characteristic unpleasant odour, soluble in water, alcohol, and ether, and unstable in air. Much heat is evolved when they are mixed with water, and, like hydrazine itself, they can be freed from the latter only with difficulty. The boiling points of the first two members of the homologous series (methylhydrazine and ethylhydrazine) are lower than that of hydrazine itself. Like hydrazine, they are strong bases, but no quantitative estimate of the basic strengths of the alkylhydrazines has been made. It is only recently that the dissociation constants of some of the simplest hydrazines, including the methyl and ethyl derivatives, have been determined by potentiometric titration [238].

The simplest aralkylhydrazines (benzylhydrazine and phenethylhydrazine) possess similar properties [33,160].

The free bases of the higher alkylhydrazines are quite stable. From C_{12} they are solid at room temperature. Since they are strong bases, they absorb carbon dioxide, forming carbonates [18].

With acids, alkylhydrazines can give two series of salts, acid and normal. The former are obtained by reaction of the bases with excess of acid, and the latter by dissolving the acid salts in water and evaporating the solutions. The acid sulphates, oxalates, and picrates usually crystallise well. Hydrochlorides of the lower monoalkylhydrazines are extremely hygroscopic, and have no definite melting points. Those of the aralkylhydrazines are obtained in crystalline form without great difficulty.

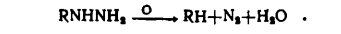
The free bases are obtained from the salts by repeated distillation with concentrated and solid alkali or even with barium oxide [11,160,185,187]. There is also an indication of the possibility of isolating the base from methylhydrazine sulphate by the action of liquid ammonia [239].

Alkylhydrazines are extremely corrosive substances, strongly attacking skin, rubber, corks, and even glass to some extent [187]. Data have been published [240] on the infrared spectrum of methylhydrazine.

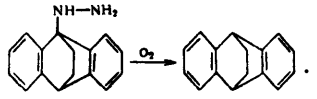
The lower alkylhydrazines are extremely toxic. Thus even at a concentration of 0.01%, methylhydrazine in the form of the free base destroys the lower forms of animal life, bacteria, and fungi [241].

Oxidation and Reduction

Like hydrazine itself, alkylhydrazines are readily oxidised, and immediately reduce Fehling's solution and ammoniacal silver oxide, nitrogen being evolved and the corresponding hydrocarbon being formed [11,185,187]:

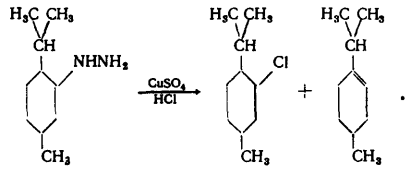


Sometimes oxidation in air occurs so readily that the free base cannot be isolated at all from the salt, as has been shown in the case of 9-hydrazino-9,10-dihydro-9,10-ethanoanthracene [195]:

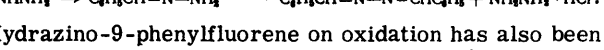


The oxidative breakdown of aralkylhydrazines of this type involves free radicals [242].

Potassium ferricyanide effects especially smooth oxidation of alkyl- and cycloalkyl-hydrazines [118]. An attempt to effect the autoxidation of menthylhydrazine by means of copper sulphate in hydrochloric acid medium gave a mixture of menthene and menthyl chloride [243]:



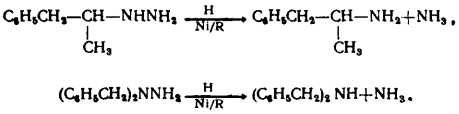
Wohl and Oesterlin [160] oxidised benzylhydrazine with ferric chloride in acid medium, and obtained benzylidene azine and a salt of hydrazine. The primary process probably consists in the formation of benzaldehyde hydrazone, which then undergoes disproportionation:



9-Hydrazino-9-phenylfluorene on oxidation has also been converted into the corresponding azo-compound [27].

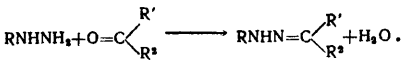
The oxidation of monoalkylhydrazines has been used for their quantitative determination [244,245].

Monoalkylhydrazines are not reduced by mild reducing agents. Under severe conditions, for example catalytic hydrogenation over Raney nickel, however, the N–N bond undergoes hydrogenolysis. This reaction was studied by Hinman [146,147,246], which enabled it to be used subsequently even for the preparation of some primary and secondary amines [1]:

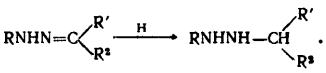


Reactions Involving the NH_2 Group

Alkylhydrazines react with aldehydes and ketones (including sugars) to form the corresponding alkylhydrazones [12,20,33,60,115,159,160,194,234,247-251]:

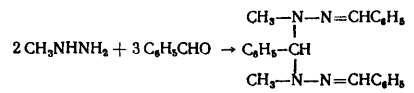


Reduction of alkylhydrazones can be used for the preparation of 1,2-dialkylhydrazones [252-256]:

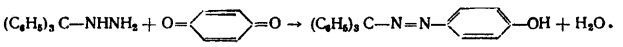


Attempts to employ alkyl- or aralkyl-hydrazines for the identification of carbonyl compounds were made long ago by Fischer, but most of the hydrazones obtained were liquid or did not crystallise readily.

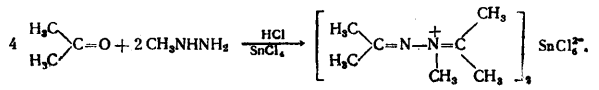
Sometimes the reaction between an alkylhydrazine and a carbonyl group takes an unusual course. Thus methylhydrazine, which gives a hydrazone of normal structure on treatment with an equimolecular quantity of benzaldehyde, forms "tribenzylidenemethylhydrazine" with excess of benzaldehyde [20]:



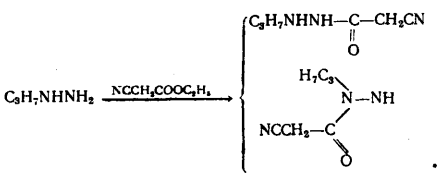
Triphenylmethylhydrazine and *p*-benzoquinone form not a hydrazone but *p*-triphenylmethylazophenol [26]:



In the presence of tin(IV) chloride and hydrochloric acid, methylhydrazine gives with many aldehydes and ketones crystalline *N*-methylketazinium and *N*-methylaldazinium hexachlorostannates [257,258]:

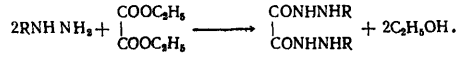


Alkylhydrazines undergo acylation at either the NH or the NH_2 group depending on the reagent and the reaction conditions. With mild acylating agents, for example esters, alkylhydrazines are monoacylated at the NH_2 group [125,259-262]. Depending on the temperature, propylhydrazine gives with ethyl cyanoacetate either a symmetrically substituted (on cooling) or an unsymmetrically substituted (on heating) *N*-propylcyanoacetohydrazide [259]:



Alkylhydrazines which have been acylated with isonicotinic acid possess antitubercular activity [132,133,262-264] (see p. 171). The analogous products obtained with nicotinic acid have an antidepressive action [265].

Alkylhydrazines react in the normal manner with esters of dibasic acids, oxalic ester, for example, yielding *N*-alkyloxalohydrazides [33,185,187], in which the NH_2 group has been acylated:



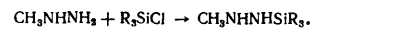
Equimolecular quantities of ethylene carbonate and alkylhydrazines form 2-hydroxyethyl alkylhydrazinecarboxylates [266]:



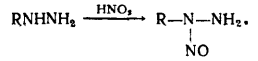
Acylation of the NH group is discussed below.

Reactions Involving the NH Group

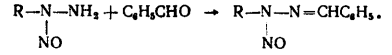
As already mentioned (see p. 160), alkylhydrazines undergo alkylation with alkyl halides at the substituted nitrogen atom (if this is not prevented by steric factors), with the successive formation of 1,1-dialkylhydrazines and trialkylhydrazinium salts [13,18-20]. When the alkyl halide contains a bulky radical, 1,2-dialkylhydrazines are obtained [267-269]. With a trialkylsilyl chloride, too, alkylhydrazines react at the NH_2 group [270]:



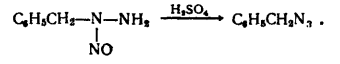
With nitrous acid, alkylhydrazines form nitroso-derivatives [11,30,119,160,194,271]:



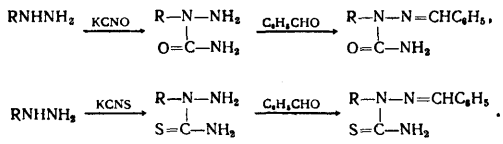
Alkylnitrosohydrazines are relatively stable, colourless, crystalline substances, and give a characteristic violet coloration with ferric chloride. The position of the nitroso-group is established by the fact that they give hydrazones with aldehydes, and therefore contain a free amino-group [11,119]:



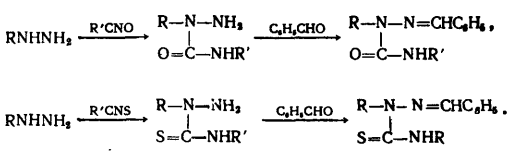
Benzylnitrosohydrazine is converted by dilute sulphuric acid into benzyl azide [119]:



Treatment of the salts of alkylhydrazines with potassium cyanate and thiocyanate gives respectively alkylsemicarbazides and alkylthiosemicarbazides, which yield the corresponding alkylsemicarbazones with aldehydes and ketones [32,185,187,223,272,273]:

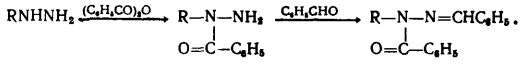


Similar reactions occur between alkylhydrazines and esters of isocyanic and isothiocyanic acids [32,185,187,272-279]:



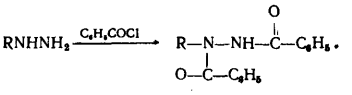
These reactions take place readily at room temperature, and thus there is no necessity to heat in order to speed them up [33].

Acylation of alkylhydrazines with the calculated quantity of acid anhydrides yields monoacyl derivatives in which the secondary nitrogen atom has been acylated, as can yet again be proved by the formation of hydrazones with benzaldehyde [78,273]:



Sometimes such acylation can be effected with esters and even with the acids themselves [259-261].

If acylation is carried out more rigorously, for example with acid halides by the Schotten–Baumann method or by heating with excess of the acid anhydride, the reaction can go further and affect the NH_2 group, with formation of diacyl derivatives [33,67,139,159]:

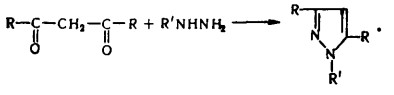


This last reaction is employed for the identification of alkylhydrazines.

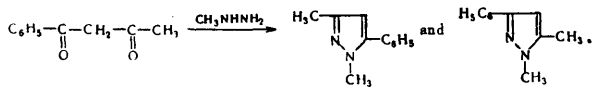
Reactions Involving Both Nitrogen Atoms

Reactions in which both nitrogen atoms of an alkylhydrazine take part usually result in heterocyclic compounds. They occur in the same way as with hydrazine itself, but the corresponding *N*-alkyl derivatives are obtained.

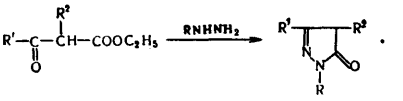
Reaction of alkylhydrazines with 1,3-difunctional compounds yields pyrazole derivatives. From 1,3-diketones or the corresponding acetals are obtained 1-alkylpyrazoles [280-290]:



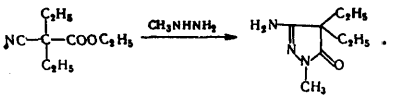
Unsymmetrical diketones give two isomeric pyrazoles with alkylhydrazines. Thus 1-phenylbutane-1,3-dione reacts with methylhydrazine to form 1,3-dimethyl-5-phenylpyrazole and 1,5-dimethyl-3-phenylpyrazole in the ratio 1 : 3: [291]



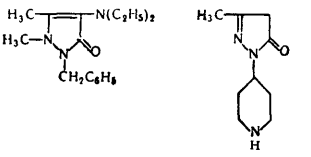
Similarly, acetoacetic ester and its homologues with alkylhydrazines yield 1-alkylpyrazol-5-ones [35,75,161,281,292-303]:



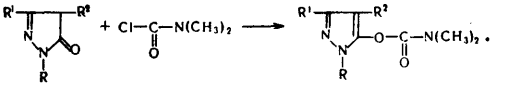
The corresponding aminopyrazolones are obtained from methylhydrazine and cyanoacetic or ethylcyanoacetic esters [300,304,305]:



Several of these pyrazolones, for example 1-benzyl--2,3-dimethyl-4-diethylaminopyrazol-5-one and 3-methyl--1-piperid-4'-ylpyrazol-5-one, exert an analgesic, antipyretic, spasmolytic, or antihistaminic action [296,297,303]:



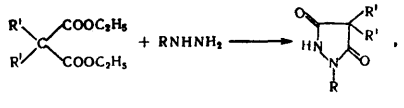
The 1-alkylpyrazolones obtained in this way are converted by dimethylcarbamoyl chloride into pyrazolyl dimethylcarbamates, which exert a strong anti-cholinesterase action [109,303-308]:



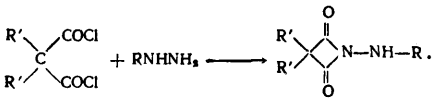
In particular, a compound of this type is used under the name "Isolan" [R = $(CH_3)_2CH$, $R^1 = CH_3$, $R^2 = H$] as a systemic insecticide for the control of suctorial insect pests of plants [307-309]. The preparation Indasol (R = $CNCH_2CH_2$, $R^1 = CH_3$, $R^2 = H$) is an efficient aphicide, and is less toxic to warm-blooded animals than is Isolan [109,306].

Pyrazolone dyes have also been described, obtained by coupling 1-alkylpyrazolones with various aromatic diazo--compounds [75,295,310,311].

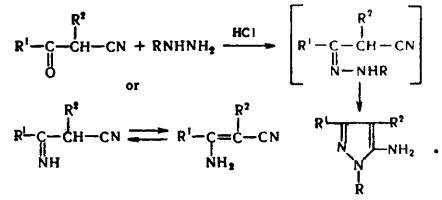
With substituted malonic esters, alkylhydrazines give pyrazolidinediones [312-315]:



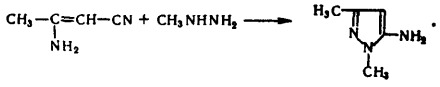
azetidine-2,4-dione being formed as a byproduct [312,315]. The latter can be obtained as the main product by treating the monoalkylhydrazine with a disubstituted malonyl chloride [316]:



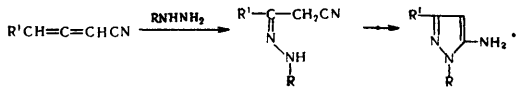
Aminopyrazole derivatives are obtained by the reaction of alkylhydrazines with malononitrile or its dimer [317], with ethoxymethylenemalononitrile and its homologues [317-319], and with α-cyano-β-ethoxyacrylic ester [6,318,320]. The most convenient method for obtaining 5-aminopyrazoles is reaction of alkylhydrazines with β-keto- or β-amino-nitriles [321,322]:



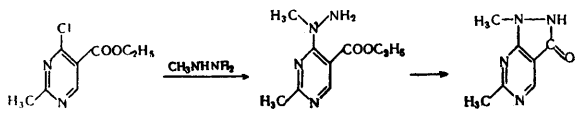
Thus, for example, a 97% yield of 1,3-dimethylpyrazol-5-amine has been obtained from methylhydrazine and the dimer of acetonitrile (β-aminocrotononitrile) [290,317]:



Pyrazolamines are formed also by the action of monoalkylhydrazines on 1-cyanoalka-1,2-dienes (cyanoallenes) [323]:

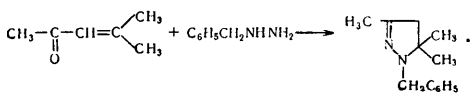


Fused ring systems containing a pyrazole ring, for example pyrazolopyrimidines, can be obtained by the condensation of monoalkylhydrazines with more complicated cyanides. With 4-chloro-5-cyano-2-dimethylaminopyrimidine, for example, isopropylhydrazine forms 3-amino-6-dimethylamino-2-isopropylpyrazolo[3,4-*d*]pyrimidine [6]. Similarly, the action of methylhydrazine on methyl 4-chloro-2-methylpyrimidine-5-carboxylate produces 1,6-dimethyl-3-oxopyrazolo[3,4-*d*]pyrimidine, in which case it is possible to isolate the primary product formed by replacement of the halogen by the hydrazino-group [324]:

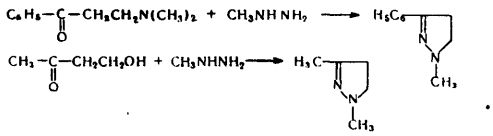


A series of such pyrazolopyrimidines have been synthesised recently, since among them have been discovered substances which possess an anticancer effect, as well as a stimulating action on the heart [6,318,320].

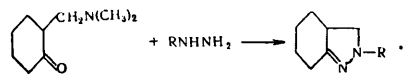
$\alpha\beta$-Unsaturated aldehydes and ketones react with monoalkylhydrazines to form 1-alkyl-Δ^2-pyrazolines [235,282,325-330]. For example, mesityl oxide reacts with benzylhydrazine to give 1-benzyl-3,5,5-trimethylpyrazoline [326]:



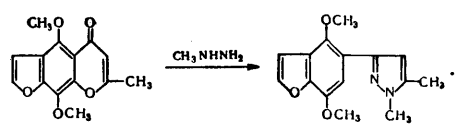
Pyrazolines are obtained also by the reaction of alkylhydrazines with several amino- and hydroxy-ketones. Thus 2-dimethylaminoethyl phenyl ketone [331] and 4-hydroxybutan-2-one [282] gave the corresponding pyrazolines with methylhydrazine:



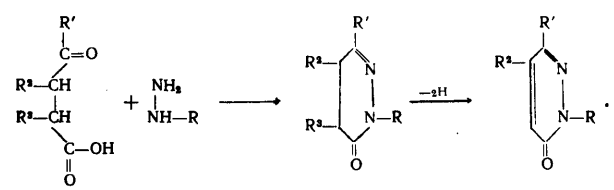
2-Dimethylaminomethylcyclohexanone forms, with methyl- and benzyl-hydrazines, pyrazolines which are substituted derivatives of hydrogenated indazoles [280]:



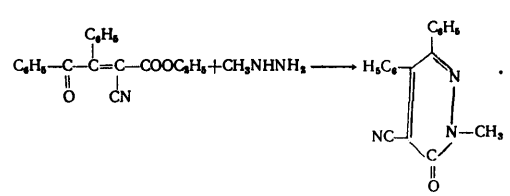
Alkylhydrazines, like phenylhydrazine and hydrazine itself, effect cleavage of the ring in several heterocyclic ketones, with subsequent formation of a pyrazole ring. Thus heating kellin with methylhydrazine opens the γ-pyrone ring and converts the compound into a pyrazolylbenzofuran [332]:



Condensation of γ-keto-acids or their reactive derivatives with monoalkylhydrazines gives 2,3,4,5-tetrahydro-3-oxopyridazines, which are readily dehydrogenated to the corresponding 2,3-dihydro-3-oxopyridazines [315,333]:

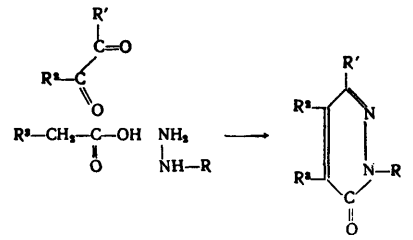


The latter compounds can be synthesised without a stage involving dehydrogenation if the corresponding unsaturated acid is used as starting material. For example, ethyl α-cyano-γ-oxo-$\beta\gamma$-diphenylcrotonate and methylhydrazine give 4-cyano-2,3-dihydro-2-methyl-3-oxo-5,6-diphenylpyridazine [334]:

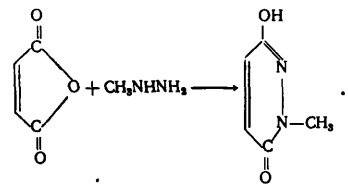


The method of Schmidt and Druey [335,336] effects in one stage the condensation of three components — a monoalkylhydrazine, an $\alpha\beta$-dicarbonyl compound or a reactive deri-

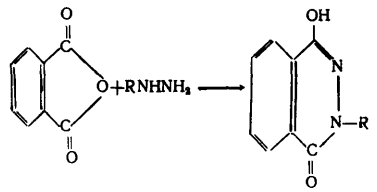
vative thereof, and an acid containing an α-methylene group or a reactive functional derivative thereof:



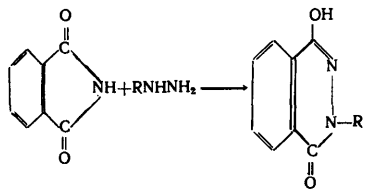
Dihydrohydroxyoxopyridazines can be obtained by the interaction of maleic anhydride and monoalkylhydrazines. Thus methylhydrazine yields 2,3-dihydro-6-hydroxy-2--methyl-3-oxopyridazine [337]:



Other alkylhydrazines react similarly [338,339]. On being heated with phthalic anhydride, monoalkylhydrazines form the corresponding hydroxyoxophthalazines [339-342]:



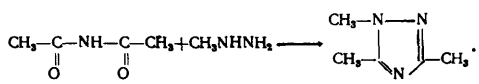
Phthalimide reacts similarly [341,343-347]:



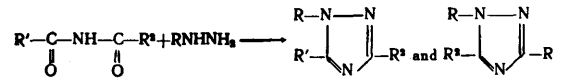
There are a fair number of publications in this field, since several pyridazine derivatives, for example 4-cyano-2,3--dihydro-2-methyl-3-oxo-5,6-diphenylpyridazine, possess analgesic and antipyretic properties [312,313,333,334,336].

1-Alkyl-4,5-dichlorodihydro-3-oxopyridazines have been patented as bacteriostatic and fungistatic compounds [348].

Condensation of monoalkylhydrazines with diacylamines, which represents a particular case of the Einhorn–Brunner reaction, results in substituted 1,2,4-triazoles [349-351]. For example, diacetimide and methylhydrazine yield 1,3,5-trimethyl-1,2,4-triazole [350]:



If the imide contains different acyl groups, the reaction gives a mixture of two isomeric triazoles [349]:



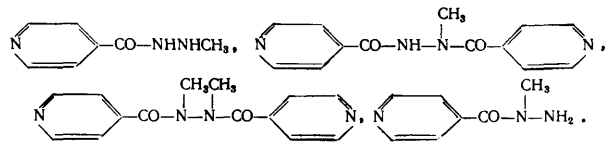
IV. BIOLOGICAL PROPERTIES OF ALKYL- AND ARALKYL-HYDRAZINES

As already mentioned, the lower monoalkylhydrazines are poisonous [241]. It has even been suggested [352] that research has been restricted by their toxicity. The higher alkylhydrazines, however, are far less toxic, and often have valuable pharmacological properties.

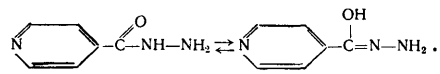
In view of the high antitubercular activity of the hydrazide of isonicotinic acid, many of its derivatives have been studied, as well as the hydrazides of other acids [132-134,262-264,353]. Since alkylidene and aralkylidene derivatives of isonicotinohydrazide possess high antitubercular activity, it has been suggested that such activity is due to their hydrolysis at the C : N bond, with formation of the above hydrazide in the organism [132]. In order to check this hypothesis, a series of 2-alkylhydrazides of isonicotinic acid having the general formula $4\text{-}C_5H_4NCONHNHR$ were synthesised, in which R represented CH_3, C_2H_5, C_3H_7, iso-C_3H_7, C_4H_9, iso-C_4H_9, C_6H_{13}, C_7H_{15}, C_8H_{17}, cyclohexyl, 4-methylcyclohexyl, 3-methylcyclohexyl, sorbit-1-yl, $C_6H_5CH_2$, p-$CH_3OC_6H_4CH_2$, $C_6H_5CH(CH_3)$, and $C_6H_5CH_2CH_2CH_2$. All of these compounds showed high antitubercular activity *in vivo* [132].

The analogous derivatives of nicotinic acid have an antidepressive effect [265].

It is interesting that the antitubercular activity of isonicotinohydrazide derivatives disappears when all the hydrogen atoms in the hydrazino-group have been replaced. Thus the methylhydrazides containing one and two isonicotinoyl groups exhibit antitubercular activity, whereas this is no longer present in 1,2-diisonicotinoyl-1,2-dimethylhydrazine. The 1-methylhydrazide of isonicotinic acid [262] and isonicotinoyl derivatives of various pyrazolines [354,355] are also inactive.



Thus the presence of an amide hydrogen atom is probably necessary for the appearance of antitubercular activity. This supports the hypothesis that such activity in isonicotinohydrazide is linked with the ability of the latter to pass into a pseudo-acid, which can form metal complexes [262]:

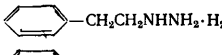


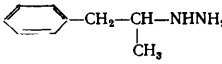
In the treatment of pulmonary tuberculosis with isonicotinohydrazide (Isoniazid) [356] it has been found that patients not only increase in weight but also overcome their state of depression and are in good spirits. The

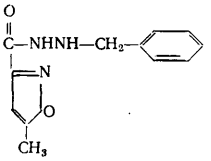
effect of the corresponding isopropylhydrazide (Marsilid) on the psychology of the patient is still more marked§. An intensive study has therefore been made of the psychopharmacological properties of various alkyl- and aralkyl--hydrazines and their acyl derivatives [1-3,49,100,123,128,129,143,145,198,253,268,357-368]. The antidepressant action of these compounds is due to suppression of the enzyne monoamine oxidase, which increases the concentration of serotonin in the human brain [357].

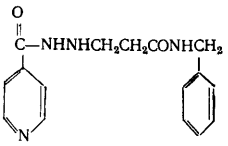
Hydrazines containing an α-methylphenethyl group have been proved to be good inhibitors of monoamine oxidase [1]. Such aralkylhydrazines are stronger inhibitors than the corresponding amines, their effect lasts longer, and they lower the blood pressure [1,362]. Substitution in the phenyl group, hydrogenation of the latter, alkylation or acylation at the nitrogen atoms, or replacement of phenyl by a heterocyclic radical produces a sharp fall in inhibiting activity.

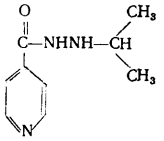
At the present time the following alkyl- and aralkyl--hydrazines are manufactured as monoamine oxidase inhibitors in various countries, and are employed for the treatment of mental illness [363]:


Phenethylhydrazine sulphate, phenelzine sulphate, Nardil


α-Methylphenethylhydrazine hydrochloride, Catron


2-Benzylhydrazide of 5-methylisoxazole-3--carboxylic acid, isocarboxazid, Marplan


2-Benzylcarbamoylethylhydrazide of pyridine-4--carboxylic acid, nialamide, Niamid


2-Isopropylhydrazide of pyridine-4-carboxylic acid, iproniazid phosphate, Marsilid

Various qualitative colour reactions have been worked out for all these preparations [363].

Among aralkylhydrazines have been found substances which resemble oxytocin in stimulating the smooth muscle of the uterus [7-9]. Thus benzylhydrazine and 2,5-dimethoxybenzylhydrazine hydrochlorides increase the duration of the spontaneous uterine contractions without changing their strength or tone. 3,4-Dimethoxybenzylhydrazine hydrochloride (Vetrazin), which has been developed by the present reviewers, is a strong stimulant of labour even at a dilution of 1 : 1 000 000 (in doses of 0.5–5 mg kg^{-1}).

During recent years many alkyl- and aralkyl-hydrazines and their simple derivatives have been patented as possessing a hypotensive, sedative, analgesic, local anaesthetic, spasmolytic, antirheumatic, or antiblastomic action [144,162,197,206,247,249,267].

§ Marsilid is no longer employed as an antitubercular remedy [356].

Finally, alkylhydrazines are widely used as intermediates in the synthesis of more complicated medicinals [6,116,219,250,296,297,303,312,313,315,318,320,333,335,336].

In the present review we have not discussed the chemistry of di-, tri-, and tetra-alkylhydrazines. Several methods for synthesising these substances are similar to those used for the preparation of monoalkylhydrazines, but the most important are specific to these structures. The differences in chemical reactions between mono- and poly--alkylhydrazines are still greater. The literature on these compounds, especially on dialkylhydrazines, is fairly extensive, so that it cannot be covered within the present review.

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