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THE SYNTHESIS AND PROPERTIES OF
SOME HYDRAZINES

by

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SUMMARY

A new synthetic method, applicable to the preparation of a wide range of hydrazine derivatives, is described. This involves the diborane reduction of a hydrazone, or, more conveniently, the reductive-condensation of a hydrazine and the appropriate aldehyde (or ketone). The method gives high yields and provides a particularly simple route to the relatively inaccessible 1,2-disubstituted hydrazines bearing a different group on each nitrogen.

The new method has also been applied to the preparation of 1,2-disubstituted hydrazines with the same group on both nitrogens (via the azine), the very rare 1,2-disubstituted hydrazines bearing a tert-butyl group, trisubstituted hydrazines and monosubstituted hydrazines. Application of the reaction to the preparation of diaziridines has also been investigated.

A mechanism for the reduction, supported by the isolation of a boron-containing intermediate, is suggested. Some limitations of the procedure are discussed.

A general i.r. method of distinguishing the isomeric disubstituted hydrazines, as stable salts, has been developed. This has the advantages of speed and simplicity over previous methods.

The mass spectra of a series of monosubstituted hydrazines, a series of 1,2-disubstituted hydrazines and some 1-benzoyl 2-alkylhydrazines have been examined in detail. The spectra are

generally dominated by α -cleavage processes and the compounds show a variety of interesting rearrangement reactions. The mass spectra of some 1,1-disubstituted hydrazines and some trisubstituted hydrazines have also been examined.

Rearrangement processes occurring in the mass spectrum of tropylium fluoroborate have been examined. Similar rearrangements have been found in the spectrum of trityl fluoroborate and may be of general occurrence in the mass spectra of aromatic fluoroborates.

Chemical shift values for some groups on hydrazine nitrogen are recorded and the results of tumour inhibitory tests on some hydrazines are also given.

This work was carried out between October, 1967 and October, 1970 at the University of Aston in Birmingham. The work is independent and has not been submitted for any other degree.

R. J. Gardner

R. J. GARDNER

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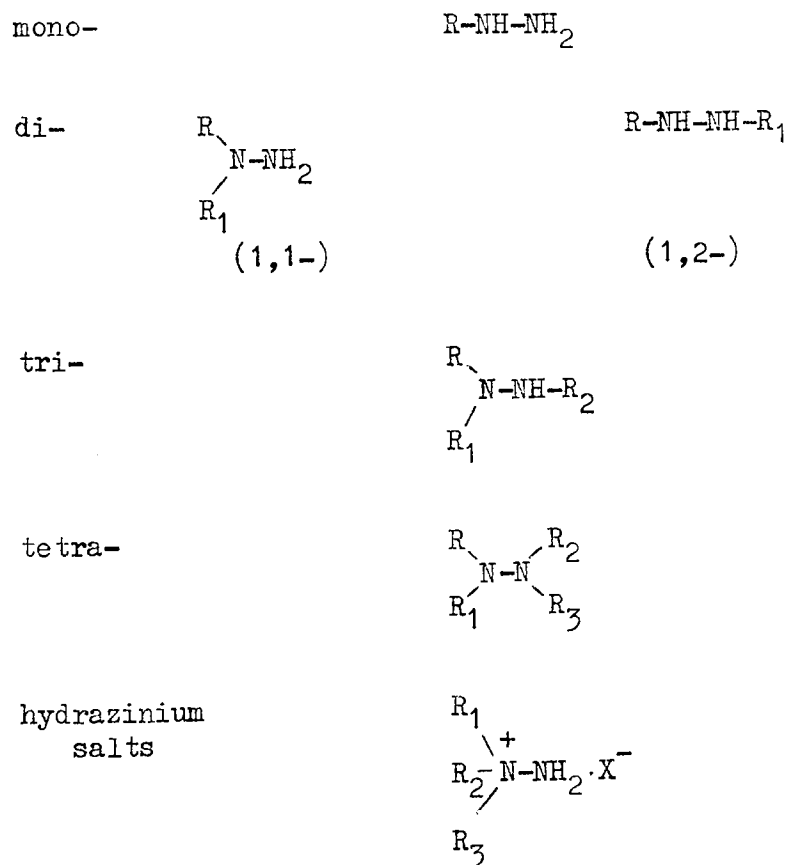
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Introduction.

The group of compounds known as hydrazines are sub-divided into the mono-, di-, tri- and tetra-substituted derivatives and hydrazinium salts. The disubstituted hydrazines are further subdivided into the isomeric 1,1- and 1,2-derivatives. (Fig.I).

Fig I.

The hydrazine group.



R_1, R_2 and R_3 may, or may not be the same; generally alkyl, aryl etc.

The hydrazines have found use as intermediates in the synthesis of heterocyclic compounds, agricultural chemicals, textile chemicals, photographic developers and explosives. Recent interest has centred around their use as propellants and medicaments.¹ In the latter field they have found particular use as tuberculostats.²⁻⁵ (isonicotinic acid hydrazide), anti-depressants⁴⁻⁶ (Iproniazid) and carcinostats⁷⁻¹¹ (Natulan).

Of the simple alkyl and aryl substituted hydrazines the least well known are 1,2-disubstituted derivatives with a different group on both nitrogens. The various routes to hydrazine derivatives are reviewed below and a new method for the synthesis of 1,2-disubstituted derivatives with different groups on the nitrogens is described (page 40). The new method has been used to prepare a series of 1-benzyl 2-alkylhydrazines and is of particular interest because it provides a route to 1-tert-butyl 2-alkylhydrazines.

The new method also appears to be applicable to the preparation of monosubstituted hydrazines, 1,2-disubstituted hydrazines with the same group on both nitrogens, trisubstituted hydrazines and, by altering the ratios of the reactants, to the preparation of diaziridines.

The synthesis of alkyl and aryl hydrazines

The synthesis of monosubstituted hydrazines¹² and hydrazinium salts¹³ has been extensively reviewed and preparative methods for other substituted hydrazines have been discussed in a number of general reviews.¹⁴⁻¹⁷ These only contain, however, references to work prior to 1966.

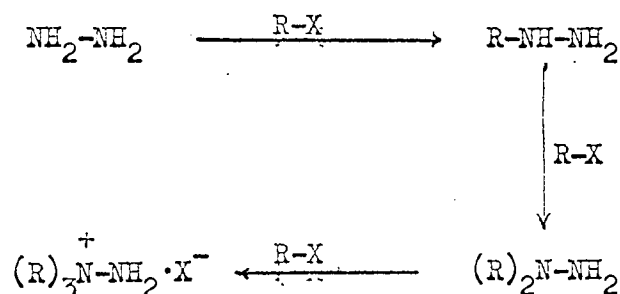
Preparative methods for hydrazines fall into ten groups :-

- 1 Alkylation and arylation of hydrazine(s).
- 2 The amination of amines.
- 3 The reduction of hydrazones, azines and semicarbazones.
- 4 The reduction of hydrazides.
- 5 The reduction of diazonium salts.
- 6 The reduction of nitrosamines and related compounds.
- 7 The cleavage of heterocyclic compounds.
- 8 Via azo-compounds.
- 9 The use of organo-metallic reagents.
- 10 Reactions of sodium hydrazide.

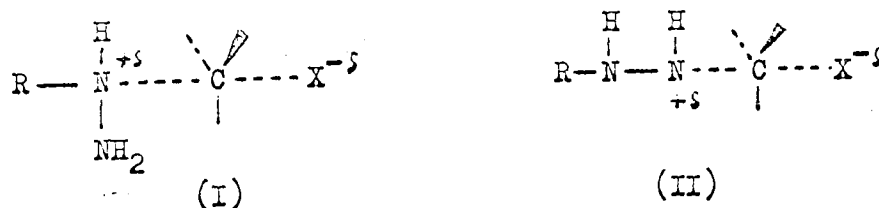
These methods are discussed below in a general fashion with emphasis on the preparation of mono-, 1,2-di- and tri-substituted hydrazines.

1 Alkylation and arylation of hydrazine(s).

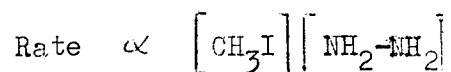
Hydrazine will react with the usual alkylating agents,¹⁸⁻²¹ e.g. alkyl halides and alkyl sulphates. The reaction is complicated by the formation of a mixture of products. The major products are generally those involving alkylation at the nitrogen atom which already bears a substituent :-



The route taken in alkylation was originally assumed to be a result of an increase in base strength, paralleled by nucleophilicity, at the alkylated nitrogen. Hinman has suggested²² an alternative explanation in terms of the relative stabilities of the two possible transition states. The developing positive charge will be better stabilized at the nitrogen which carries the larger number of alkyl groups, hence transition state (I), leading to the mode of alkylation observed, will form in preference to transition state (II) :-



The same argument applies to the formation of more highly substituted products and has recently received support from kinetic studies. Hasty has shown²³ that in the alkylation of hydrazine with low concentrations of methyl iodide a bimolecular rate law is followed :-



The exact route taken in a given alkylation depends on various factors and, by varying the conditions, a number of hydrazines have been prepared in good yield :-

a) The nature of X in the alkylating agent.

The rates of reaction of halides with hydrazine is generally in the order $\text{I} > \text{Br} > \text{Cl}$, thus iodides give quaternary salts directly and almost exclusively on reaction with hydrazine.²⁴ After formation of the hydrazinium salt reaction ceases; the second amino-group remains unsubstituted. For example reaction¹⁸ of methyl iodide with trimethylhydrazinium iodide at 130°C results in cleavage of the nitrogen-nitrogen bond.

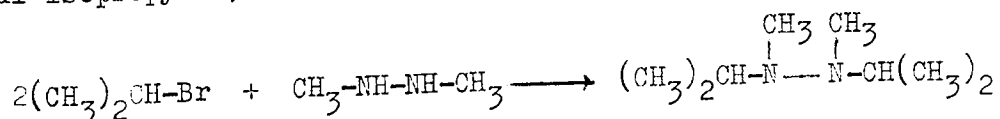
The difference in reactivity may be due to the fact that the carbon-nitrogen bond length, in the transition state, is larger for good leaving groups, with the result that the transition state is not so sensitive to destabilization.

A change from an iodide to a chloride may make it possible to stop the reaction at the mono-, or di-, stage of substitution, but the advantage may be offset by the slowness of reaction of the chlorides.

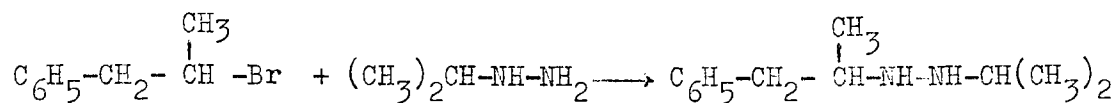
b) The steric effects of substituents.

Sterically hindered substituents may force the incoming group onto the unsubstituted nitrogen, i.e. substitution by transition state (II). This only occurs when steric hindrance is extreme; even tertiary butylhydrazine methylates on the substituted nitrogen.²⁵ With the higher 1-chloroalkanes, (above C₈), practically no quaternary salt is formed and with alkyl chlorides containing twelve or more carbon atoms monosubstituted and unsymmetrically disubstituted hydrazines are the only products.^{20,21} It is only when forcing conditions are used that the incoming group will actually substitute on the primary nitrogen.

Franzen and Kraft^{26,27} prepared tribenzylhydrazine by subjecting hydrazine hydrate to prolonged treatment with benzyl chloride. Further reaction of tribenzylhydrazine with benzyl bromide yields tetrabenzylhydrazine.²⁸ By exploiting similar favourable steric factors Klages^{29,30} synthesised tri-isopropylhydrazine and 1,2-di-isopropyl-1,2-dimethylhydrazine :-



1-(1-methyl)phenethyl-2-iso-propylhydrazine³¹ has also been prepared by direct alkylation :-



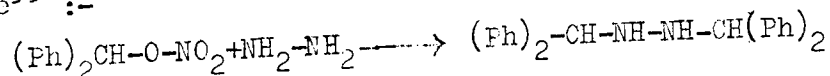
The use of forcing conditions to bring about substitution on the primary nitrogen is limited by the elimination of the hydrocarbon from tertiary halides.³²

c) Electronic effects of the substituents.

Any base-weakening substituent should destabilize transition-state (I) (page 4) with respect to transition state (II) and hence give increased yields of the 1,2-disubstituted hydrazine. Thus phenylhydrazine gives some 1-alkyl-2-phenylhydrazine on alkylation,²² but, contrary to earlier reports,³³ it also alkylates on the substituted nitrogen.²²

When the base-weakening effect is extreme and/or combined with steric hindrance, some useful products can be obtained. For example triphenylmethylhydrazine,³² 1-phenyl-2-triphenylmethylhydrazine³⁴ and 1,2-diphenylfluorenylhydrazine³² have been obtained in high yield by direct alkylation.

An interesting example of the base-weakening effect of the diphenylmethyl-group is shown in the preparation of 1,2-diphenylmethylhydrazine by reaction of diphenylnitrate with hydrazine³⁵ :-



The use of nitric acid esters in alkylation of hydrazines is limited by the formation of complex reduction products.³⁶

d) The concentration of hydrazine.

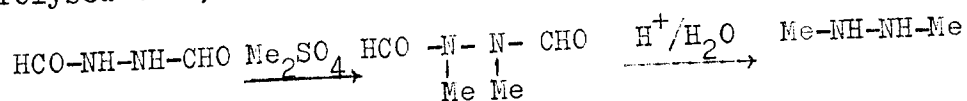
Polyalkylation is considerably diminished by slow addition of the alkyl halide to a tenfold excess of hydrazine hydrate with vigorous stirring.^{31,37} The complete removal of the monoalkylhydrazine from the resulting mixture may be difficult and can often only be achieved by prolonged extraction.

The best examples of the use of excess hydrazine are the preparation of benzylhydrazine,³¹ (Experiment No. 9) and ethylhydrazine,³⁸ in yields of 80% and 32% respectively.

By utilizing special features alkylation lends itself to the preparation of examples of all the classes of substituted hydrazines and monoaryl hydrazines can be prepared quite successfully by direct arylation of hydrazines activated towards nucleophilic attack.^{14,39}

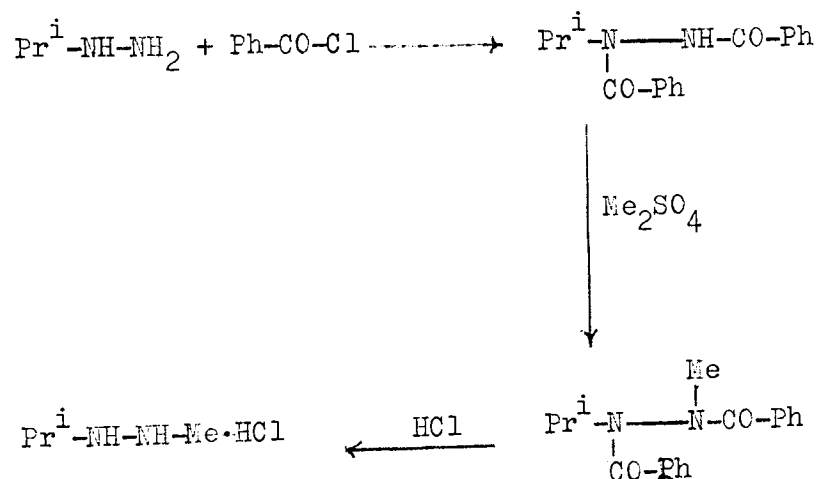
When it is not possible to utilise steric, or base-weakening effects to cause alkylation to take place at the unsubstituted nitrogen, blocking groups can be used to achieve the same end.

Symmetrical diformylhydrazine, for example, can be methylated once on each nitrogen and the resulting 1,2-diformyl-1,2-dimethylhydrazine hydrolysed to 1,2-dimethylhydrazine⁴⁰ :-

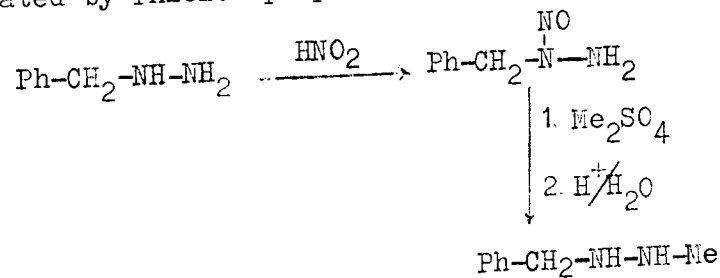


1,2-benzoylhydrazine can be used in a similar fashion^{41,42} and is reported as giving better yields of the hydrazine. This method suffers from the disadvantage that it is only applicable to the synthesis of hydrazines with identical groups on each nitrogen.

Monosubstituted hydrazines can be acylated twice to produce a 1,2-diacyl-1-alkylhydrazine, which, on further alkylation and hydrolysis, yields a 1,2-dialkylhydrazine with a different group on each nitrogen. Using this route 1-methyl-2-iso-propylhydrazine has been synthesised in 50% yield :-⁴³

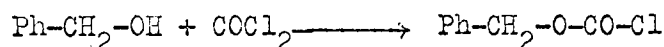


The nitroso-group can be used in the same way, as is illustrated by Thieles preparation⁴⁴ of 1-benzyl-2-methylhydrazine :-

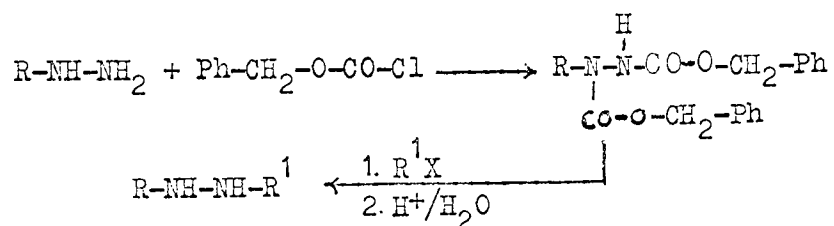


The nitrosation step gives variable results; ⁴⁵ acid conditions give benzaldehyde and benzyl alcohol, the nitrosation being favoured by neutral, or alkaline, conditions. ⁴⁶

Benzyl chloroformate, prepared by the action of phosgene on benzyl alcohol ⁴⁷ :-

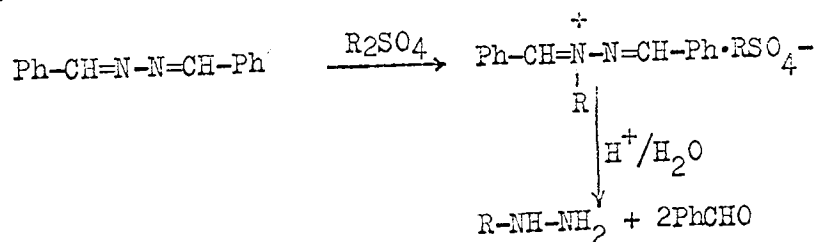


has been used as a blocking-group by Zeller and his co-workers ⁷ :-



The use of blocking-groups gives a possible route to any 1,2-disubstituted hydrazine, but the method is tedious and the large number of steps makes the overall yield of hydrazine rather low.

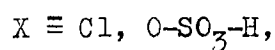
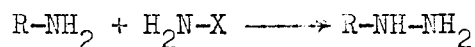
A further successful modification of direct alkylation involves the reaction of benzalazine with the alkylating agent, followed by hydrolysis of the hydrazone salt to the corresponding alkylhydrazine ⁴⁸ :-



Unfortunately azines are poor nucleophiles and only fairly active alkylating agents will alkylate them.

2 Amination of amines.

Chloramine and hydroxylamine-O-sulphonic acid have been found to be capable of aminating amines to give hydrazines :-



The reaction can be extended to the preparation of a variety of hydrazine derivatives, hence each reagent is considered in detail.

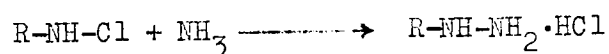
(a) Chloramine.

The use of chloramine to prepare monoalkylhydrazines is analogous to the well known Raschig⁴⁹ synthesis of hydrazine from chloramine and excess ammonia. The method was first reported by Audrieth and Diamond⁵⁰ who prepared all the simple hydrazines up to $\text{Bu}^t\text{-NHNH}_2\cdot\text{HCl}$, and later⁵¹ extended the reaction to cyclohexyl-, allyl-, β -hydroxyethyl- and β -aminoethyl-hydrazines.

The yield of alkyl hydrazine depends on the presence of a metal inhibitor, the amine/chloramine ratio and the presence of a base.⁵⁰ Increased yields can be obtained, without the use of gelatin or a base, if anhydrous amines are used⁵² and the yields are also increased if the reaction is carried out in the presence of a tertiary amine equivalent in amount to the free hydrazinium ions formed by the action of chloramine on the amine.⁵³

By reacting ammonia and sodium hypochlorate in the presence of a suitable reagent, (acid water-soluble salt or a water soluble neutral salt containing Mg, Zn, or Ca ions), which will remove 90% of the OH^- ions formed during the reaction, very high concentrations of chloramine can be obtained.⁵⁴ Greater than 85% yields of hydrazine, or alkylhydrazines, are claimed from the reaction of these higher concentrations of chloramine with ammonia, or primary amines, in the presence of metal hydroxides.

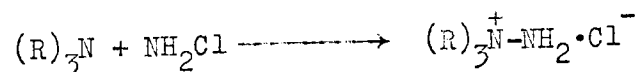
The reaction of ammonia with substituted chloramines has also been noted⁵⁵ :-



Amination with chloramine has been successfully extended to the preparation of 1,1-disubstituted hydrazines^{52,53} :-



and to hydrazinium salts^{56,57} :-



Attempts to extend the reaction to the preparation of 1,2-disubstituted hydrazines produced⁵⁸ very low yields.

(b) Hydroxylamine-O-sulphonic acid.

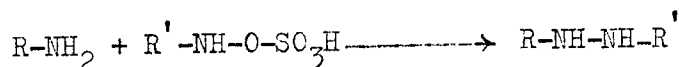
In 1925 Sommer and his co-workers⁵⁹ prepared a number of alkylhydrazines by amination of primary amines with the more complex analogue of chloramine, hydroxylamine-O-sulphonic acid :-



The method was not further investigated until 1949, when Gever and Heyes⁶⁰ prepared a series of monoalkylhydrazines with this reagent. Meuwson and Gosl^{61,62} have extended the reaction to include 1,1-disubstituted hydrazines, monoarylhydrazines and monoheterocyclic hydrazines.

In analogy to the chloramine synthesis metal ions retard the reaction.⁶² Better yields are obtained in the presence of potassium hydroxide at elevated temperatures.^{60,62}

Recent attempts⁶³ to prepare 1,2-disubstituted hydrazines by the reaction of N-alkyl-sulphonic acid derivatives and primary amines :-



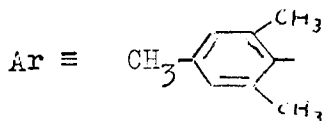
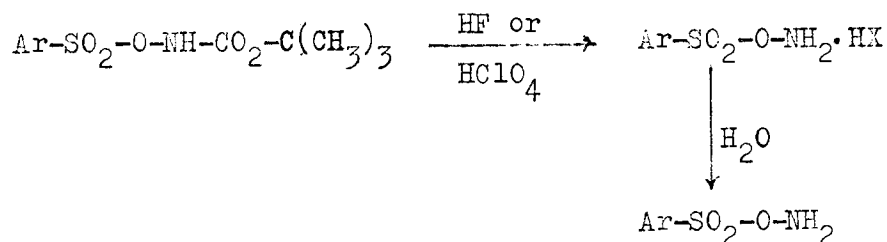
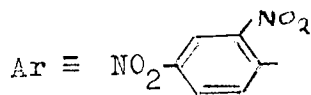
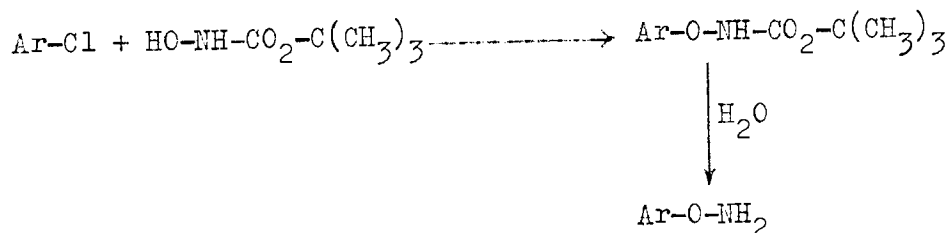
have given very low yields.

Hydroxylamine-O-sulphonic acid is easily prepared,^{59,64,65} but widespread use of this reagent is limited by its low stability, which makes it unsuitable for storage.

(c) Newer aminating agents.

O-mesitylene sulphonylhydroxylamine,⁶⁶ and O-(2,4-dinitrophenyl) hydroxylamine⁶⁷⁻⁶⁹ are two potentially useful aminating agents which have received only limited attention in the hydrazine field.^{66,68}

The preparation of these compounds is also of interest and is outlined below :-

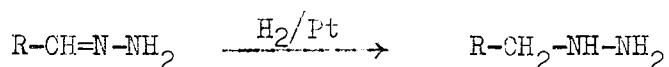
O-mesitylene sulphonylhydroxylamine :-O-(2,4-dinitrophenyl) hydroxylamine :-

Thus use is made of the easily cleaved carb-tert-butoxy-group, which has potential use as a blocking-agent.⁷⁰

3 The Reduction of hydrazones, azines and semicarbazones.

The carbon-nitrogen double-bond of hydrazones has been reduced by a range of reagents to give mono-, 1,2-di- and trisubstituted hydrazines.

In the preparation of monosubstituted hydrazines, from hydrazones, catalytic hydrogenation^{14,71,72} over a platinum catalyst is generally used.

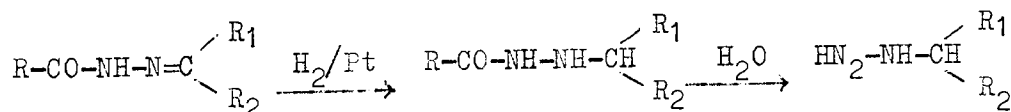


Raney Nickel ruptures the nitrogen-nitrogen bond.⁷³

The conditions must be very carefully controlled.

Hydrogenation of the hydrazone of benzyl methyl ketone can yield, depending on the conditions, four products:- the azine of the ketone, 1,2-bis- α -methylphenethylhydrazine, α -methylphenethylhydrazine, or α -methylphenethylamine.³¹

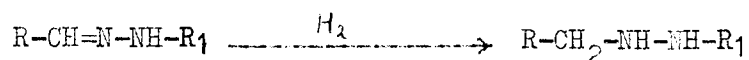
The nitrogen-nitrogen bond of acylhydrazones is rather more stable and it is often preferable to reduce these and then hydrolyse the resulting acyl derivative to the free monoalkyl hydrazine :-



The reduction has been achieved with platinum catalyst,^{71,72} Raney Nickel⁷³ and lithium aluminium hydride.^{74,75} With lithium aluminium hydride the reduction may go all the way to the 1,2-disubstituted

hydrazine. Predominant formation of 2-alkyl hydrazides can be achieved, as the carbonyl group is more stable to reduction.⁷⁶ (See page 19).

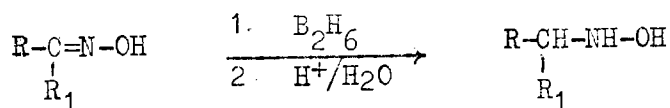
The reduction of the hydrazones of aldehydes, or ketones, is one of the better routes to 1,2-disubstituted hydrazines :-



The usual method of reduction is catalytic hydrogenation,^{77,78} but the reaction is not always successful and side reactions may be numerous.^{79,80}

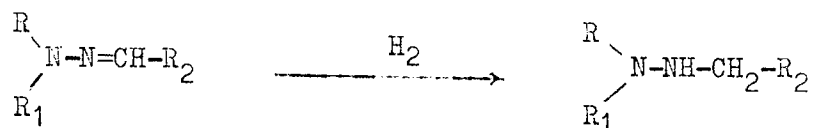
Other methods of reducing the carbon-nitrogen double-bond of hydrazones include the use of a variety of dissolving metals,^{79,81-83} di-imide⁸⁴ sodium borohydride^{85,86} and lithium aluminium hydride.⁸⁷⁻⁹⁰

Diborane has been used to reduce the carbon-nitrogen double-bond of aldoximes and ketoximes,⁹¹⁻⁹⁴ :-



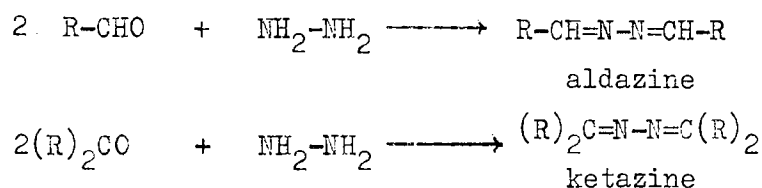
but reduction of hydrazones with this reagent has been reported to be unsuccessful.^{86,95-97} The reduction of hydrazones with diborane and the attempted reduction of benzaldehyde methylhydrazone with lithium aluminium hydride will be discussed later in the text (page 38).

Reduction of hydrazones is also applicable to the preparation of trisubstituted hydrazines :-



Lithium aluminium hydride⁸⁹ and sodium borohydride⁸⁵ have both been used to bring about the reduction.

The easily prepared aliphatic and aromatic azines :-



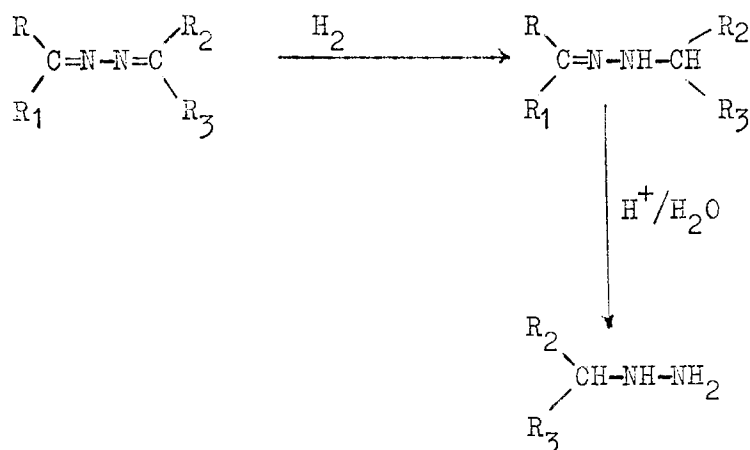
can be used to prepare 1,2-disubstituted hydrazines or monosubstituted hydrazines.

The most widely used method of reducing azines to 1,2-disubstituted hydrazines is hydrogenation over a platinum catalyst.⁹⁸⁻¹⁰⁰ Hydrazines with aliphatic,^{100,101} aromatic^{80,102} or acyclic^{103,104} substituents have been obtained. The method is only applicable to the preparation of disubstituted hydrazines with the same group on both nitrogens and the nitrogen-nitrogen bond is sensitive to cleavage during hydrogenation.

Lithium aluminium hydride is a useful reagent for reducing azines,¹⁰⁵ as it gives good yields of hydrazine which are generally free from amine impurities. Attempted reduction of benzophenone azine,⁸⁰

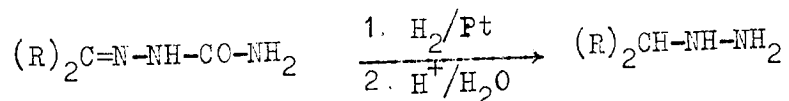
with lithium aluminium hydride at 90-100°C, leads to cleavage of the nitrogen-nitrogen bond.

The use of aldazines and ketazines as starting materials for the preparation of monoalkylhydrazines is often useful when the azine is more readily prepared than the hydrazone. The general route is illustrated below :-



The initial reduction has been achieved with lithium aluminium hydride,¹⁰⁵ sodium amalgam¹⁰⁶ and by catalytic hydrogenation. Various nuclear substituted hydrazines¹⁰⁶ have been prepared by this method. Extension of the reaction to purely aliphatic hydrazines is limited, by the greater resistance of aliphatic azines to reduction.¹⁰⁷

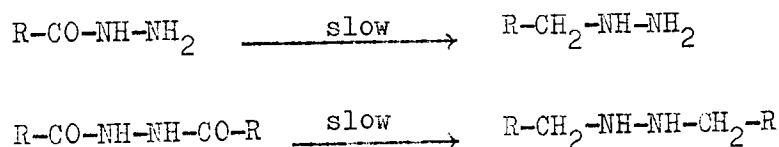
Catalytic hydrogenation of semicarbazones, followed by hydrolysis of the resulting semicarbazide, also yields monosubstituted hydrazines¹⁰⁸ :-



4 The reduction of hydrazides.

The reduction of acid hydrazides offers a potential route to the whole family of hydrazines, but, in practice, is only applicable to the preparation of 1,1-disubstituted, trisubstituted and tetrasubstituted hydrazines.

Lithium aluminium hydride has been used to reduce a number of hydrazides to the corresponding hydrazines,^{75,88,89,109-111} but secondary hydrazide groups, (-CO-NH-), are reduced much more slowly than tertiary hydrazide groups, (-CO-N(R)-).¹¹² This effect is particularly pronounced with benzoylhydrazines,¹¹² and makes the preparation of monosubstituted and 1,2-disubstituted hydrazines impracticable by this route :-

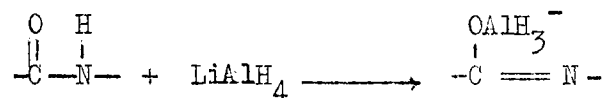


Similarly tertiary amides, (R-CO-NR₂), are much more readily reduced than secondary amides, (R-CO-NH-R),^{113,114} and benzamide takes-up lithium aluminium hydride at a relatively slow rate.¹¹⁴

The reduction is thought to proceed by the aluminate replacing the active hydrogens of the substrate, resulting in the evolution of hydrogen and the formation of a complex between the substrate and reducing agent. The differences in reactivity have been suggested as arising from one, (or both), of two causes :-

i) The insolubility of the complex and/or the hydrazides in the solvents used, (ether or tetrahydrofuran), hinders, or prevents, reduction of the functional group.¹¹⁵

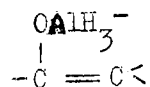
ii) The inactivation of the functional group by the formation of a stable complex¹¹² :-



Spialter et. al.¹¹¹ have found that 1-acyl-2-alkylidenehydrazines can be reduced to the corresponding 1,2-dialkylhydrazines in good yield if the reaction is carried out with constant extraction of the substrate in, for example, a Soxhlet extractor. The method probably works by increasing the amount of substrate available for reduction by increasing its concentration in the ethereal phase.

Spialter's work would indicate that the low solubility of the substrate, or complex, (point(i)), is the cause of the resistance of secondary hydrazide structures to reduction, but other work indicates that this is not the only factor involved. Thus some compounds, for example 1-benzoyl-2,2-dimethylhydrazine, are not reduced even in homogeneous solution,¹¹⁰ whereas others, for example 1,2-diformyl-1,2-dimethylhydrazine, are rapidly reduced even in heterogeneous solution.⁸⁹

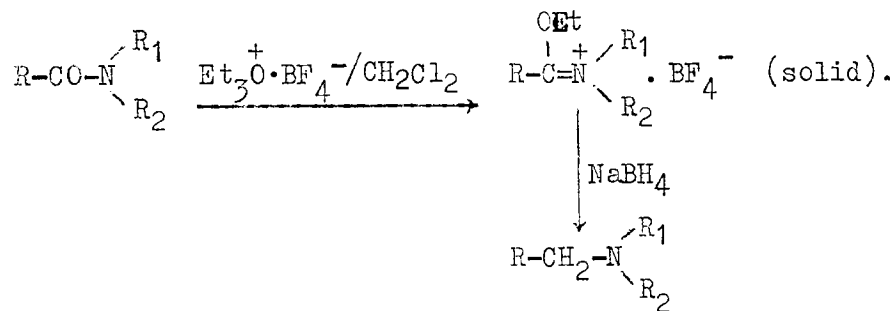
There is also a striking similarity between the structure of the suggested stable intermediate (point (ii)), and the enolate ion :-



which is reported to be resistant to attack by lithium aluminium

hydride.¹¹⁵ Point (ii) thus offers the best explanation of the resistance of the -CO-NH- group to reduction, but, in certain cases, the solubility factor may play a part.

Triethyloxonium fluoroborate,¹¹⁶ ($\text{Et}_3\text{O}^+\cdot\text{BF}_4^-$), has recently been found to react with amides to give solid salts. Previous workers have noted⁸⁵ the ease with which sodium borohydride reduces the -C=N^+ group and these new compounds are no exception. Thus the salts are readily reduced by sodium borohydride in ethanol to the corresponding amines.¹¹⁶



Yields are excellent and the method reduces both tertiary and secondary amides with equal facility. The method is thus of potential use for the reduction of hydrazides, particularly those of secondary structure.

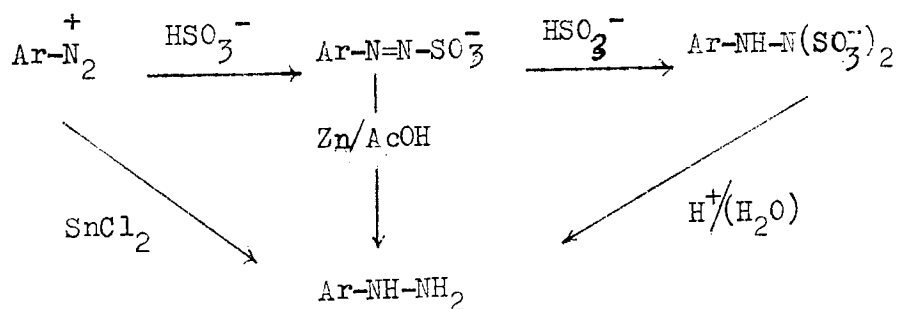
In a recent paper Feur and Brown¹¹⁷ have reported the successful reduction of a number of hydrazides with diborane. Hydrazides with a tertiary amido-group were readily reduced in refluxing tetrahydrofuran, but hydrazides with secondary amido-groups required heating to 129-135°C, in diglyme, and partially reduced and cleavage products were also isolated.

Our own attempts to reduce 1,2-dibenzoylhydrazine, with lithium aluminium hydride and diborane, are described later in the text (page 38).

5 The reduction of diazonium salts.

The reduction of diazonium salts is a major source of mono-aryl hydrazines,¹¹⁸ but is not useful for the corresponding alkyl derivatives.

The reduction has been achieved with a number of reagents.¹¹⁹ Stannous chloride^{118,120} is a convenient method, but zinc/acetic acid has also been used. Both these reagents suffer from the drawback that reduction is rather slow. The low stability of diazonium salts prevents heating of the reduction mixture, to speed-up the reaction, and it is often necessary to employ Fischer's¹²¹ device of converting the diazonium salt to the more stable arylazosulphate, by reaction with sulphurous acid or sodium bisulphate, and then reducing this by more vigorous methods.



Davies¹²², using ammonium sulphite, has isolated the intermediate ammonium hydrazine sulphonate.

Reduction with sodium or potassium sulphite has also been utilised.^{123,124}

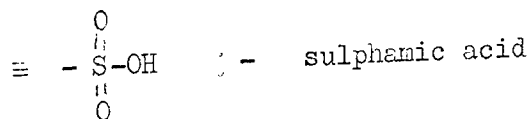
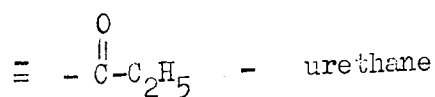
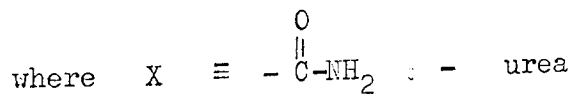
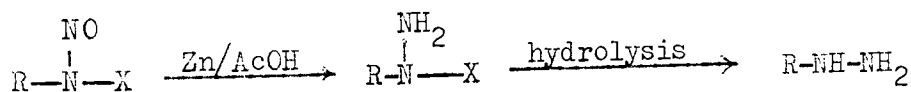
6 The reduction of nitrosamines, nitroso-ureas and related compounds.

The best practical method for the preparation of 1,1-disubstituted hydrazines is the reduction of the corresponding nitrosamines :-

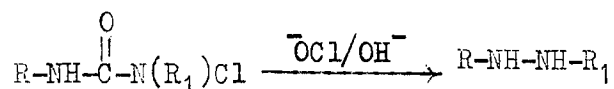


Nitrosamines have been successfully reduced with zinc in acetic acid,^{125,126} lithium aluminium hydride,^{31,126-129} sodium in ethanol,¹²⁸ sodium in liquid ammonia,¹²⁸ aluminium amalgam¹²⁹ and, on an industrial scale, by hydrogenation over a palladium catalyst.¹³⁰

The direct nitrosation and reduction of primary amines is impracticable for the preparation of monoalkyl hydrazines, however, N-substituted ureas, urethanes and sulphamic acids, can be readily nitrosated. Reduction and hydrolysis of the resulting N-nitroso-compound yields the corresponding monosubstituted hydrazine¹³¹⁻¹³⁴ :-



A reaction, which is formally analogous to the Hoffman rearrangement of N-halo-amides, may also be used to convert ureas to hydrazines. Thus hydrazine,^{135,136} monoalkyl,^{136,137} monoaryl¹³⁸ and 1,2-disubstituted^{136,137} hydrazines have been prepared by treatment of chloroureas with hypochlorite and base :-

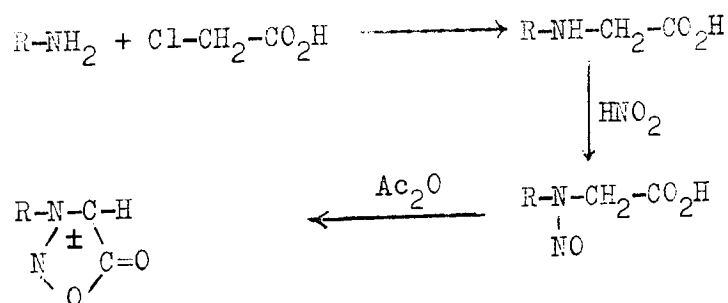


7 The cleavage of heterocyclic compounds.

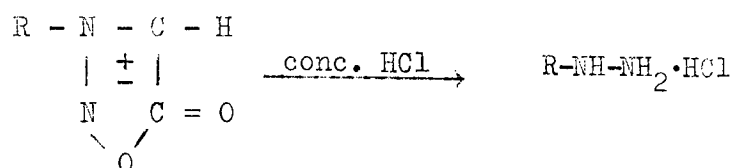
If a heterocyclic compound containing two adjacent nitrogen atoms can be cleaved at some point other than the nitrogen-nitrogen bond a hydrazine may be obtained. The various classes of heterocycle which have been used for this purpose are discussed separately below.

a Sydnones.

The mesionic sydnones can be prepared,^{139,140} in good yields, from primary amines and chloroacetic acid in three steps :-



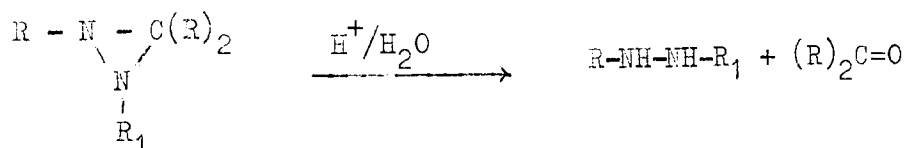
The hydrolysis of sydnones with concentrated hydrochloric acid gives monoalkyl hydrazines, (as hydrochlorides) :-



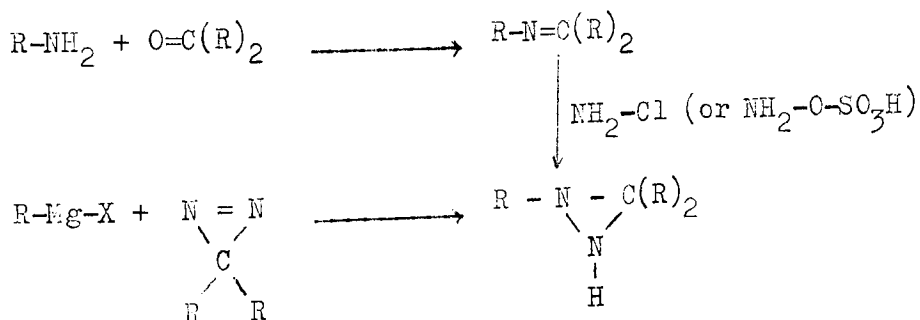
The method is applicable to the preparation of a range of monosubstituted hydrazines,¹⁴⁰⁻¹⁴² including some of medical interest.¹²

b Diaziridines.

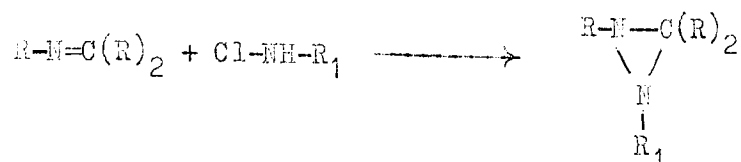
Acid cleavage of diaziridines yields monosubstituted, or 1,2-disubstituted, hydrazines :-



Diaziridines may be prepared^{143,144} by the action of chloramine, (or hydroxylamine- θ -sulphonic acid), with Schiff bases, or by the addition of Grignard reagents to diazirine^{143,145}



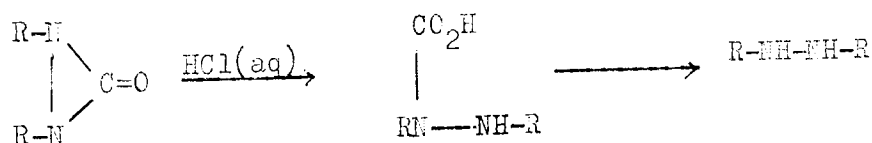
Reaction of an N-alkyl chloramine and a Schiff base gives the substituted diaziridines necessary for the preparation of 1,2-disubstituted hydrazines¹⁴³ :-



Utilizing these compounds Schmitz and his co-workers have synthesised a range of monosubstituted hydrazines^{144,145} and 1,2-disubstituted hydrazines.^{143,146} Side reactions only occur with the extremely stable diaziridines derived from formaldehyde,¹⁴⁷ but cleavage with HCl in carbon tetrachloride leads to rupture of the N-N bond in all cases.¹⁴⁶

c Diaziridinones.

In analogy to the cleavage of diaziridines, diaziridinones¹⁴⁸ have been hydrolysed to give 1,2-disubstituted hydrazines^{149,150} :-

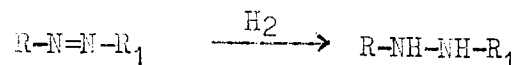


d Cleavage of other heterocycles.

Alkaline hydrolysis of the isomeric iodo-derivatives of dimethylpyrazole are reported¹⁵¹ as giving 1,2-dimethylhydrazine and 1,1-dimethylhydrazine. Similarly alkaline hydrolysis of 1,3,4,5-tetramethyl-1,2,4-triazolium iodide gives methylhydrazine.^{152,153} Neither of these methods are of any practical importance.

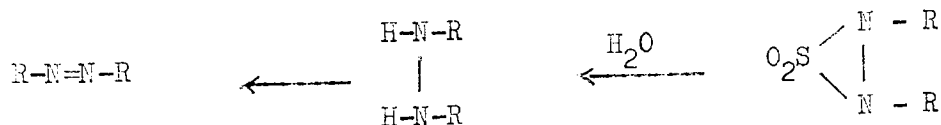
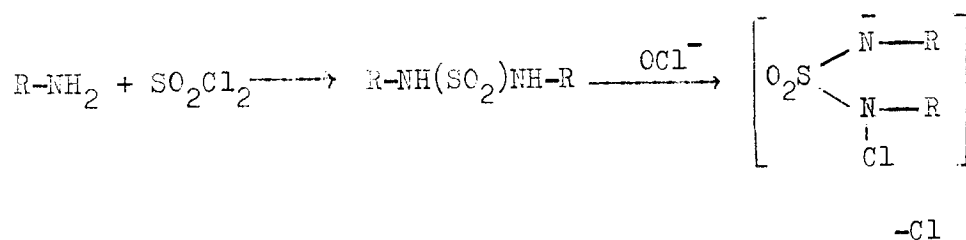
8 Via. azo-compounds

The reduction of azo-compounds :-



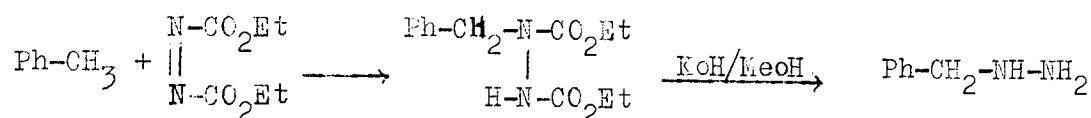
has been achieved with sodium metal,¹⁵⁴ sodium ethanol,^{71,155} zinc-dust¹⁵⁶ and di-imide.¹⁵⁷ The reduction is an obvious route to hydrazines, but is rarely useful; the azo-compounds are generally prepared via. 1,2-disubstituted hydrazines.

Recently the reaction of thionyl chloride and amines has been used to prepare azo compounds^{158,159} :-

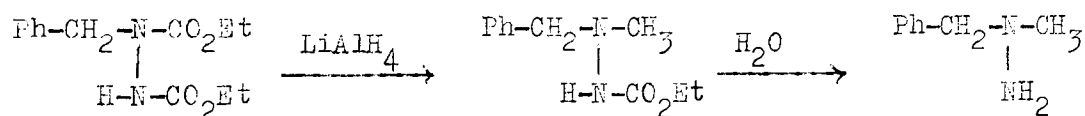


The azo-compounds can be hydrogenated (Pd/C) in acetic acid to give the 1,2-disubstituted hydrazines as the acetates¹⁵⁸ and the reaction promises to be a useful route to 1,2-disubstituted hydrazines.

Azo-carboxylic ester may be used as a precursor to a number of hydrazines. Thus the compound will add to aromatic hydrocarbons containing alkyl radicals to form 1-alkylhydrazine-1,2-carboxylates,¹⁶⁰ which on heating with methanolic hydroxide give aralkylhydrazines :-

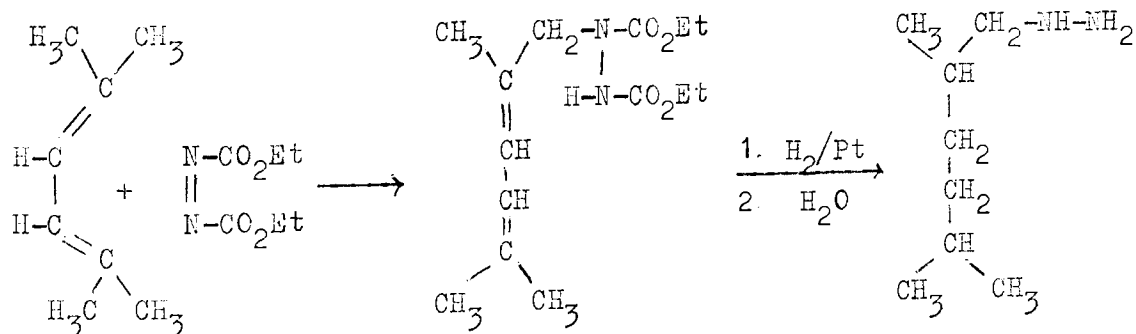


Alternatively treatment of the intermediate with lithium aluminium hydride, which preferentially reduces the ester group on the substituted nitrogen (page 19) followed by hydrolysis gives 1-alkyl-1-methylhydrazine¹⁶⁰ :-



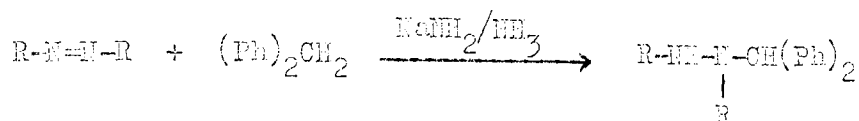
Gen-dialkylbutadienes react similarly to aromatic hydrocarbons.¹⁶¹

The double-bonds of the adduct can be hydrogenated and an alkylhydrazine obtained after hydrolysis :-



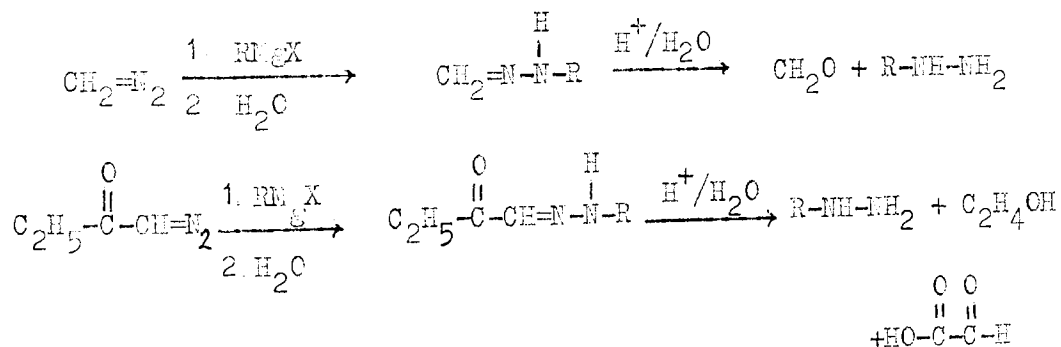
Mono-alkenes, containing at least one hydrogen atom on the α -carbon, can be used in an analogous manner.¹⁶²

Recently Kaiser and Bartling¹⁶³ have reported the preparation of trisubstituted hydrazines by the addition of carbanions to azo-compounds :-



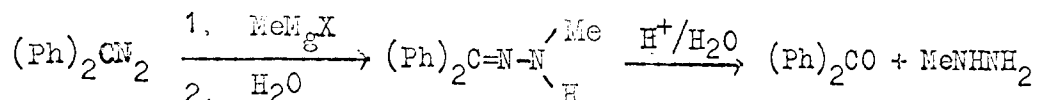
9 The use of organo-metallic reagents.

Grignard reagents will add to the diazo-group of such compounds as diazomethane and ethyl diazoacetate. Hydrolysis of the resulting hydrazone produces the monosubstituted hydrazine corresponding to the Grignard reagent :-



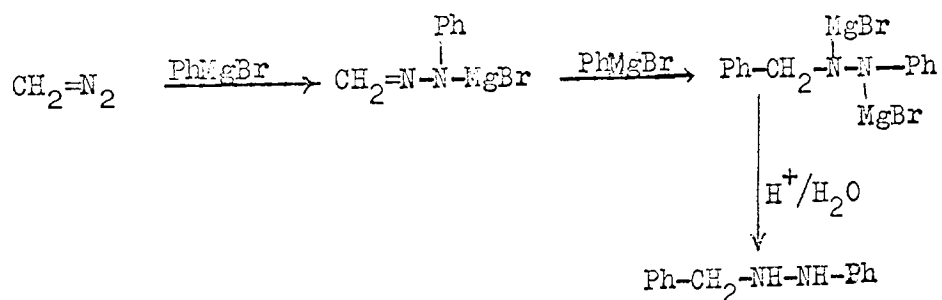
Thus Zerner¹⁶⁴ obtained methylhydrazine and ethylhydrazine by reaction of ethyl diazoacetate with methyl magnesium iodide and ethyl magnesium iodide respectively. Benzylhydrazine was prepared by the analogous reaction with diazomethane.

In extension of this work Coleman¹⁶⁵ treated diphenyl-diazomethane with methylmagnesium iodide and hydrolysed the resulting hydrazone to benzophenone and methylhydrazine :-



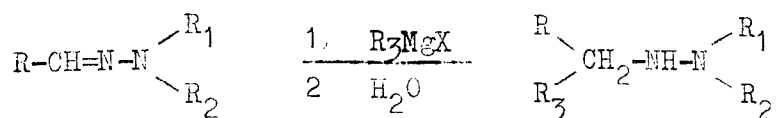
The analogous reaction with tert-butyl magnesium chloride gives tert-butylhydrazine.¹⁶⁶

On treating diazomethane with a large excess of a Grignard reagent Coleman¹⁶⁵ found that reduction of the azo-methine linkage occurred, as well as addition to the diazo-group :-

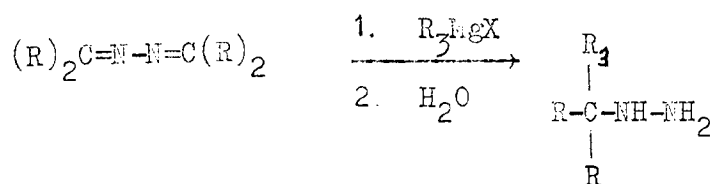


When benzyl magnesium chloride was substituted for phenyl magnesium bromide, the product was reported¹⁶⁵ to be 1-methyl 2-benzylhydrazine, rather than the expected 1-phenethyl 2-benzylhydrazine. In an analogous fashion diazomethane and n-butylmagnesium bromide gave a product showing the properties of 1-n-butyl 2-methylhydrazine. Foxall⁴⁵ was unable to repeat Coleman's preparation of 1-benzyl 2-methylhydrazine, despite the use of identical conditions.

Grignard reagents can also be added to the carbon-nitrogen double bond(s) of hydrazones :-



and azines :-

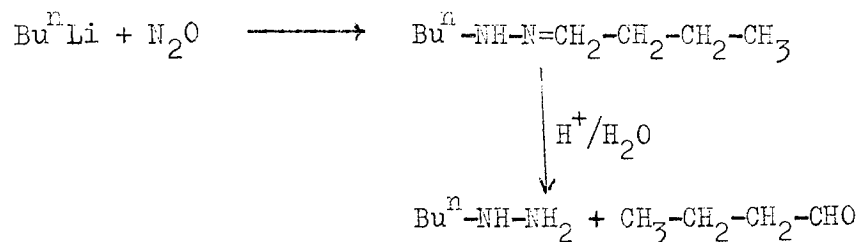


Thus Ioffe and Poroshin¹⁶⁷ have prepared a range of trisubstituted hydrazines by the reaction of alkyl Grignards with hydrazones. Earlier work has reported the preparation of 1,1-dimethyl 2-ethylhydrazine¹⁶⁸ and triethylhydrazine¹⁶⁹ by the reaction of methyl magnesium bromide with formaldehyde dimethylhydrazone and formaldehyde diethylhydrazone respectively. Alkyl lithium will add to hydrazones in a manner analogous to Grignard reagents, but yields are rather low.¹⁷⁰

Addition of Grignard reagents to azines has been used¹⁷⁰ to prepare monosubstituted and trisubstituted hydrazines. A report²⁹ that reaction of methyl magnesium bromide with acetone azine yields tert-butylhydrazine, after hydrolysis, has, however, been refuted.²⁵

Reaction of Grignard reagents with azo-compounds gives hydrazo-derivatives after hydrolysis.¹⁷¹ Addition of phenyllithium to azo-compounds has been observed¹⁷² to give hydrazobenzene, or triphenylhydrazine, depending on the conditions. Alkyl and aryl zinc have been observed¹⁷³ to give cleavage of the N-N bond.

Finally, monosubstituted hydrazines have been prepared¹⁷⁴ by the reaction of alkyl lithium with nitrous oxide, followed by alkaline hydrolysis of the alkylalkylidenehydrazine which is formed :-

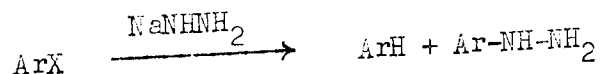


Aryl lithium gives a mixture of products and Grignard reagents do not react.¹⁷⁴

10 The reactions of sodium hydrazides.

The preparation and reactions of sodium hydrazides have been recently reviewed.¹⁷⁵ For the preparation of hydrazines the most useful reactions would appear to be those with activated carbon-carbon double-bonds, aromatic nitrogen heterocycles and aryl sulphonates.¹⁷⁶

In the reaction of aryl halides with sodium hydrazide substitution of the halogeno-group by the hydrazo-group compete with reductive dehalogenation :-



Experimentally adopted procedures.Monosubstituted hydrazines.

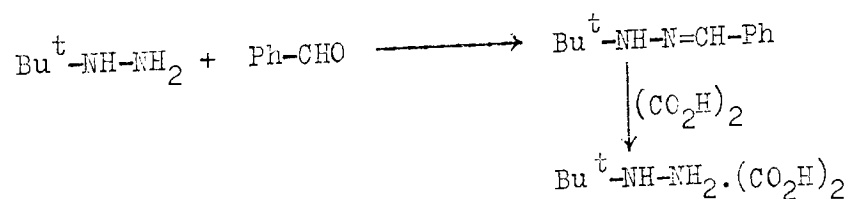
Benzylhydrazine and tert-butylhydrazine were required in fairly large quantities as precursors to 1,2-disubstituted hydrazines. The methods used to prepare these compounds are discussed below.

a. Benzylhydrazine

The direct alkylation of a ten-fold excess of hydrazine with benzyl chloride, using the procedure described by Biel and his co-workers,³¹ gave benzylhydrazine in excellent yield (80%), (Experiment No. 9).

b. tert-butylhydrazine.

Gever and Heyes have prepared⁶⁰ a number of hydrazines by amination of an excess of the appropriate amine with hydroxylamine-O-sulphonic acid. Using an analogous procedure Foxall⁴⁵ prepared tert-butylhydrazine. The hydrazine was isolated from the excess tert-butylamine by treatment of the reaction mixture with benzaldehyde to give benzaldehyde tert-butylhydrazone. Hydrolysis of the hydrazone with oxalic acid gave the required hydrazine as the oxalate :-



Using this method tert-butylhydrazine oxalate was prepared in 34% yield, in terms of the hydroxylamine-C-sulphonic acid (Experiment No. 19a). This only represents a yield of about 4% in terms of the total amount of tert-butylamine used.

Gever and Heyes have reported⁶⁰ that the amount of amine required for the preparation of hydrazines may generally be lowered if base (KOH) is added to the reaction mixture. The preparation of tert-butylhydrazine oxalate in the presence of base (Experiment No. 19b) gave a yield of only 1% in terms of the tert-butylamine, hence no saving was possible on the amount of amine used.

Conversion of tert-butylhydrazine oxalate to the free base¹⁶⁶ was readily achieved by refluxing the salt with sodium hydroxide solution (approx. 70%) and distilling over the mixture of free base and water (Experiment No. 22). Extensive drying failed to remove all the water, but the 'crude' hydrazine-water mixture was used quite successfully to prepare further compounds.

1,2-disubstituted hydrazines.

Of the general methods available for the synthesis of 1,2-disubstituted hydrazines reduction of hydrazides (page 19) and the reduction of hydrazones (page 15) offer the widest range of possible products.

To test these possibilities 1,2-dibenzoylhydrazine was chosen as a model compound. 1,2-dibenzoylhydrazine contains two secondary amido-groups, both flanked by phenyl-groups, and should form a particularly stable intermediate. Any reagent capable of reducing this compound would be expected to reduce other hydrazides quite successfully.

Reduction with lithium aluminium hydride.

Extreme conditions were provided by refluxing 1,2-dibenzoylhydrazine in diglyme (bis 2-methoxyethyl ether) with a three-fold excess of lithium aluminium hydride. Twentyfour hour reflux gave benzylamine hydrochloride as the only isolated product (Experiment No. 2a). Shorter reflux times (eighteen and nine hours) gave benzaldehyde benzoylhydrazine (Experiment No. 26). The results of a number of experiments are summarized in Table I (page 37).

Addition of the aluminate to a cold suspension of 1,2-dibenzoylhydrazine in diglyme gave a dark red solution. As reflux proceeded the solution turned green and then colourless. Benzaldehyde benzoylhydrazine was obtained in greatest yield when the reaction mixture was 'worked-up' whilst it was still green. A reasonable mechanism for the reaction is formulated below :-

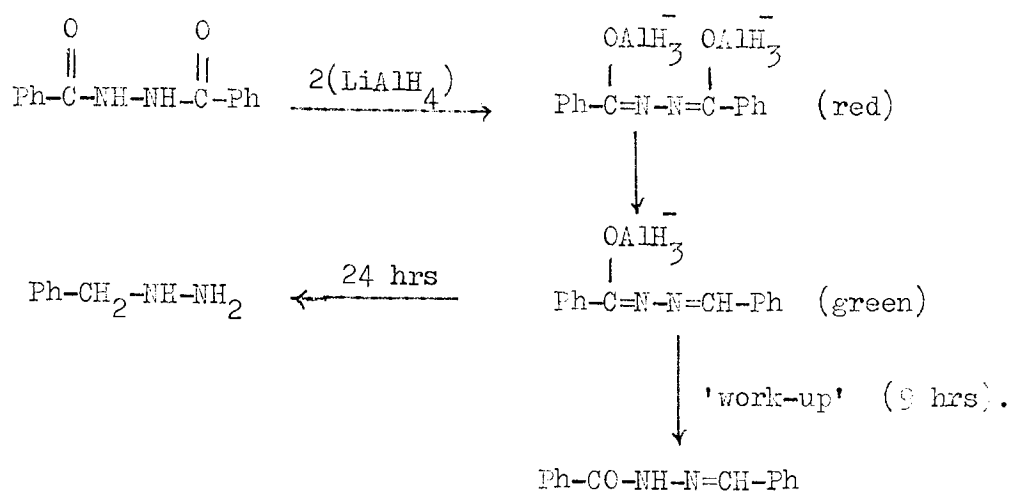


TABLE I.

Lithium Aluminium Hydride Reductions.

<u>Substrate</u>	<u>Reflux</u> (hrs.)	<u>LiAlH₄</u> (moles)	<u>Product</u>	<u>Yield</u> *
Ph-CO-NH-NH-CO-Ph	24	3	Ph-CH ₂ -NH ₂ ·HCl	2%
Ph-CO-NH-NH-CO-Ph	24	3	Ph-CH ₂ -NH ₂ ·HCl	4%
Ph-CO-NH-NH-CO-Ph	24	3	Ph-CH ₂ -NH ₂ ·HCl	10%
Ph-CO-NH-NH-CO-Ph	18	3	Ph-CO-N=CH-Ph	9%
Ph-CO-NH-NH-CO-Ph	9	3	Ph-CO-N=CH-Ph	45%
Ph-CH=N-NH-Me	18	2	Ph-CH ₂ -NH ₂ ·HCl	12%
Ph-CH=N-NH-Me	1.5	1.5	Ph-CH ₂ -NH ₂ ·HCl (Ph-CH=N-NH-Me·HCl)	5%
Ph-CH=N-NH-Me	0.5	1	Ph-CH=N-NH-Me·HCl	-

* Recrystallized yield.

Reductive-cleavage of the carbon-nitrogen double-bond of tosylhydrazones has been observed¹⁷⁷ in the presence of lithium aluminium hydride and reductive-cleavage of the carbon-nitrogen bond of amides, in the presence of alkoxyaluminumhydrides, has also been noted.¹⁷⁸ The cleavage of the nitrogen-nitrogen bond has been previously noted in the reduction of an azine⁸⁰ and may be of thermal origin.

b. Reduction with diborane.

Passage of diborane, at ambient temperature, into a suspension of 1,2-dibenzoylhydrazine in dry diglyme, followed by saturation with dry HCl gas, gave only unchanged starting material. (Experiment No. 3). Feur and Brown have recently reported¹¹⁷ the successful reduction of a number of diacylhydrazines with diborane. Diacylhydrazines containing a tertiary amido-group $R-CO-N(R')-N(R')-CO-R$ were readily reduced in refluxing tetrahydrofuran (THF) but hydrazides containing a secondary amido-group $R-CO-NH-NH-CO-R$ were much more resistant to reduction and required lengthy reflux at elevated temperatures (129-135°C).

2. The reduction of hydrazones.

The preparation and reduction of hydrazones (page 15) represents a potential two stage route to monosubstituted, 1,2-disubstituted or trisubstituted hydrazines. In particular a general method of reducing hydrazones would provide a simple

synthesis of the relatively inaccessible 1,2-disubstituted hydrazines with a different group on each nitrogen.

To test various methods of reducing hydrazones to hydrazines, benzaldehyde methylhydrazone was chosen as a model compound. This compound was chosen for the following reasons :-

1. The carbon-nitrogen double-bond of benzaldehyde methylhydrazone is conjugated with the phenyl ring and for this reason may be rather stable to reduction. A suitable method for reducing this compound should be capable of extension to a wide range of hydrazones.

2. 1-benzyl 2-methylhydrazine is known to be a powerful carcinostat. A route to other hydrazines of general structure $\text{Ph-CH}_2\text{-NH-NH-R}$ would provide a means of examining the structure-activity relationships within a series of closely related compounds.

The various methods available for the reduction of hydrazones have already been discussed (page 15) The methods used in the present work are discussed below.

a. Hydrogenation.

Hydrogenation of hydrazones, usually over a platinum catalyst has been extensively used to prepare hydrazines, but the results are variable and side reactions are common (see page 15). Hydrogenation of benzaldehyde methylhydrazone, over platinum oxide, gave a mixture of products; the major component being benzaldehyde methylhydrazone (Experiment No. 5).

Similarly an attempt to reduce benzaldehyde tert-butylhydrazone, over a palladium catalyst, has been reported⁴⁵ as giving a mixture of products with benzaldehyde tert-butylhydrazone as the major component.

b. Reduction with lithium aluminium hydride.

The results of a number of attempts to reduce benzaldehyde methylhydrazone with lithium aluminium hydride are summarised in Table I. The reductions were carried out in boiling diglyme and lengthy reflux times gave only benzylamine; shorter reflux gave unchanged hydrazone or a mixture of both products. (Experiment No. 6.).

c. Reduction with diborane.^{179,180}

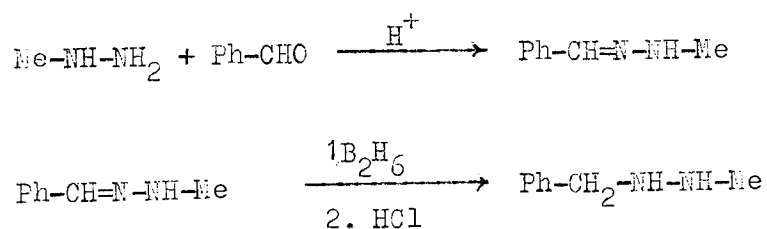
Diborane reduction of hydrazones has been reported,^{86,95-97} to be unsuccessful in a number of cases, but reduction of oximes with this reagent gives high yields of the corresponding hydroxylamines.⁹¹⁻⁹⁴ Feur and his co-workers have noted⁹² that in the reduction of aromatic oximes acid hydrolysis of the intermediate gave high yields of the corresponding hydroxylamine, but alkaline hydrolysis gave a mixture of products, the major component of which was generally the starting oxime. In reductions of hydrazones of 2,4-dinitrophenylhydrazine, with diborane, McMurry⁹⁶ used an alkaline 'work-up' procedure. Although they give no experimental details Nulu and Nematollahi⁸⁶ refer to the earlier work of McMurry and it is likely that they also used an alkaline hydrolysis of the boro-intermediate.

In the light of the above results it seemed reasonable to attempt the diborane reduction of benzaldehyde methylhydrazone using acid hydrolysis of the boro-intermediate. This procedure also has the advantage that it traps any hydrazine formed as a salt before oxidation to the hydrazo-, or azo-, derivative can occur.

Utilizing the general method and apparatus described by Zweifel and Brown¹⁸¹ diborane was passed into a solution of benzaldehyde methylhydrazone in dry diglyme at ambient temperature. Saturation of the reaction mixture with dry HCl gas gave the required 1-benzyl 2-methylhydrazine as a mixture of mono- and di-hydrochlorides (Experiment No. 7).

Simplification and extension of the diborane reduction method.

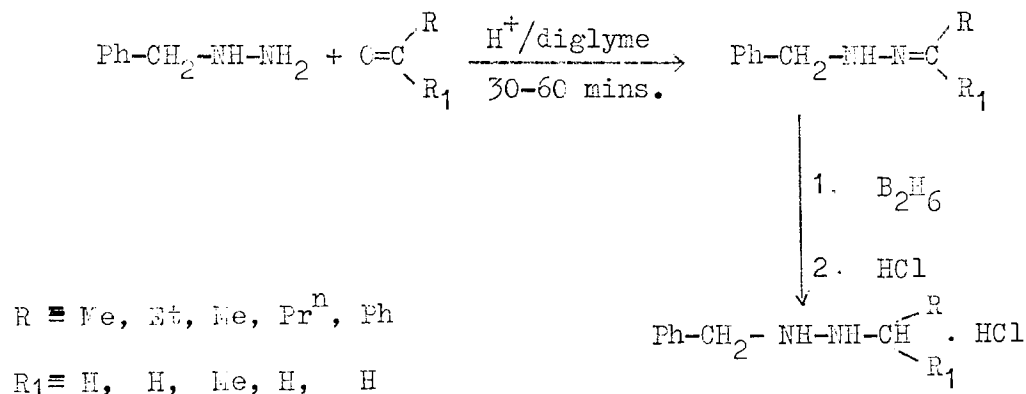
The route to 1-benzyl 2-methylhydrazine described above involves the preparation and isolation of the intermediate hydrazone :-



To reduce the total number of stages a one-step condensation-reduction procedure was developed (Experiment No. 8). Thus an equimolar mixture of benzaldehyde, methylhydrazone and a few spots of acetic acid, in diglyme, was put aside for a short period under nitrogen and treated with two mole equivalents of diborane.

Subsequent saturation of the mixture with dry HCl gas gave 1-benzyl 2-methylhydrazine as a mixture of mono- and di-hydrochlorides. The crude yield of hydrazine was unaffected by the change in technique.

Using this procedure, with either dry diglyme or dry T.H.F. solvent, a range of 1-benzyl 2-alkylhydrazines was prepared (Experiment No. 11-16).



The 1,2-disubstituted hydrazines were generally obtained as a mixture of mono- and di-hydrochlorides, for this reason analytically pure samples were only obtained after extensive recrystallization. 1-benzyl 2-methylhydrazine hydrochloride and 1-benzyl 2-n-propylhydrazine hydrochloride were never obtained as pure mono- salts.

In an attempt to prepare pure 1-benzyl 2-methylhydrazine dihydrochloride the mixture of salts was dissolved in the minimum quantity of methanol and treated with a large excess of dry HCl gas. The product, a low melting solid which rapidly discoloured on exposure to air, had the spectral properties expected for the dihydrochloride,

but consistent analyses could not be obtained. Recrystallization of this material gave a mixture of mono- and di-hydrochlorides. (Experiment No. 7).

An attempt was also made to prepare a mono-salt directly from the reduction mixture (Experiment No. 15). Thus in a preparation of 1-benzyl 2-n-butylhydrazine hydrochloride a mixture of butyraldehyde and benzylhydrazine was treated with diborane in the usual manner and the resulting solution divided into four parts. The first aliquot was treated with excess dry HCl gas to give 1-benzyl 2-n-butylhydrazine as a mixture of mono- and di-hydrochlorides. The second portion was diluted with dry solvent and dry HCl gas passed slowly into the stirred solution. This also gave a mixture of mono- and di-hydrochlorides.

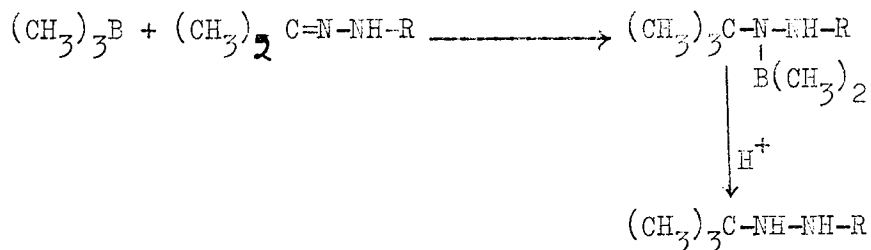
The third and fourth portions were treated with concentrated sulphuric acid and glacial acetic acid respectively. The former gave only an intractable tar and the latter gave no solid product.

1,2-disubstituted hydrazines containing a tert-butyl group are rare. Cleavage of 1,2-di-tert-butyldiaziridone has provided¹⁵⁰ 1,2-di-tert-butylhydrazine, but the literature contains no other reference to this class of compound. Three routes to 1-benzyl 2-tert-butylhydrazine were investigated :-

1. Diborane reduction of benzaldehyde tert-butylhydrazine hydrochloride
2. Addition of trimethylboron to acetone benzylhydrazone and
3. Condensation-reduction of tert-butylhydrazine and benzaldehyde.

Benzaldehyde tert-butylhydrazone hydrochloride was readily prepared (Experiment No. 20) by treatment of an aqueous solution of tert-butylhydrazine oxalate with strong base, followed by addition of acetic acid to neutrality and then addition of benzaldehyde. Extraction of the solution with ether and saturation of the dried extracts with HCl gas gave the required hydrazone hydrochloride in 50% yield. Treatment of a suspension of benzaldehyde tert-butylhydrazone hydrochloride in dry diglyme with diborane failed to bring about any reduction. The only isolated solid was starting material (60%), (Experiment No. 21).

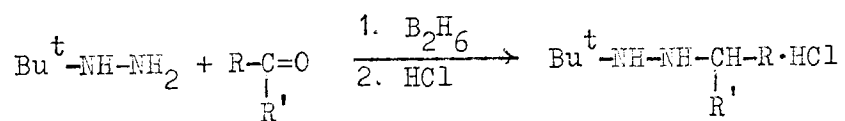
Trimethylboron might be expected to add to a hydrazone in a manner similar to alkyl lithium :-



To test this possibility trimethylboron, prepared by the method described by Brown,¹⁸² was passed into a solution of acetone benzylhydrazone in diglyme at ambient temperature. Subsequent passage of HCl gas gave only benzylhydrazine hydrochloride (Experiment No. 25a). Tert-butylhydrazine is reported¹⁶⁶ as eliminating the tert-butyl group in the presence of acid. It was thus possible that the required hydrazine had been formed, but that

decomposition had occurred during the passage of HCl. Repetition of the experiment using an identical procedure, except that the solution was kept below 0°C during the passage of HCl, also resulted in formation of benzylhydrazine hydrochloride (Experiment No. 25b).

The use of two mole equivalents of diborane in the condensation-reduction of tert-butylhydrazine and benzaldehyde did not result in reduction to the 1,2-disubstituted hydrazine. The only isolated product was benzaldehyde tert-butylhydrazine hydrochloride (Experiment No. 23a). As noted earlier (page 33) the tert-butylhydrazine contained a high proportion of water and it seemed likely that most of the diborane reacted with this. With this in mind the reduction was repeated using a larger excess (four mole equivalent) of diborane. This technique gave a high yield of 1-benzyl 2-tert-butylhydrazine monohydrochloride (Experiment No. 23b). Similarly condensation-reduction of 'crude' tert-butylhydrazine and acetone, using four moles of diborane, gave 1-iso-propyl 2-tert-butylhydrazine monohydrochloride (Experiment No. 24).

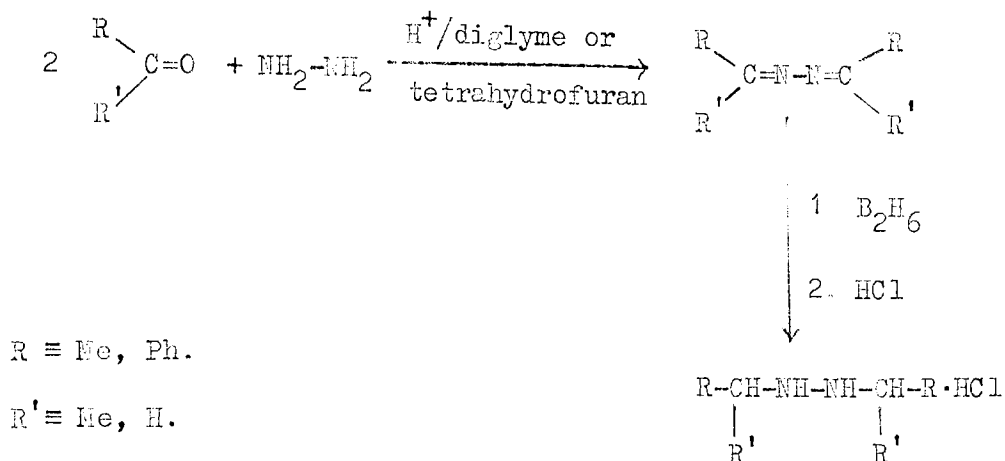


R = Ph, Me

R' = Ph, Me

The condensation-reduction procedure was also found to be applicable to the preparation of 1,2-disubstituted hydrazines with

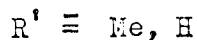
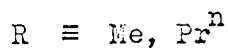
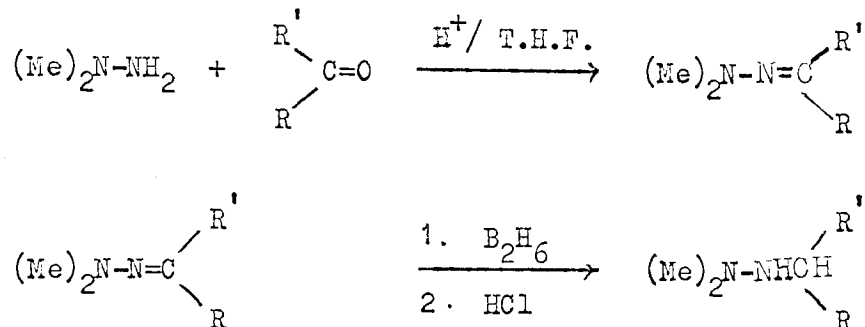
the same group on both nitrogens, i.e. via the azine (Experiments 16b and 17):-



Direct application of the condensation-reduction method to the synthesis of monosubstituted hydrazines was not found to be possible. Thus slow addition of acetone (1 mole) to hydrazine hydrate (1 mole) in a large excess of tetrahydrofuran solvent followed by passage of diborane gave, on saturation with dry HCl gas, a mixture of iso-propylhydrazine hydrochloride and 1,2-di-iso-propylhydrazine hydrochloride, with the latter compound as the major component. (Experiment No. 26). When the acetone was replaced by benzaldehyde only 1,2-dibenzylhydrazine hydrochloride was obtained. (Experiment No. 27).

Reduction of the isolated hydrazone with diborane would appear to be possible. Thus benzaldehyde hydrazone was reduced to benzylhydrazine in 60% yield (Experiment No. 28).

Extension of the reaction to trisubstituted hydrazines has also been possible (Experiment Nos. 29 and 30) :-



The 1,1-dimethyl 2-n-butylhydrazine did not form a crystalline hydrochloride and attempts to isolate the free base resulted in decomposition, hence evidence for its formation is spectral only.

The various hydrazines prepared are summarised in Table II.

TABLE II

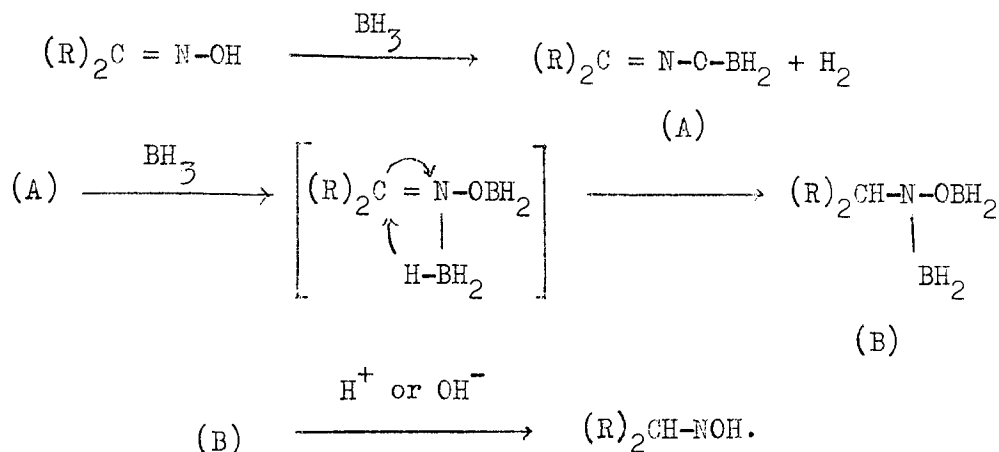
Hydrazines prepared by diborane reduction of hydrazones.

<u>Aldehyde/ketone</u>	<u>Hydrazine</u>	<u>Diborane</u> ¹ (mol.)	<u>Product</u> ² (crude yield)
MeNHNH ₂ (1.1g.)	PhCHO (2.4g.)	1	MeNHNHCH ₂ Ph (3.1g.)
MeNHNH ₂ (1.1g.)	PhCHO (2.4g.)	2	MeNHNHCH ₂ Ph (3.1g.)
PhCH ₂ NHNH ₂ (3.3g.)	MeCHO (2.4g.)	2	EtNHNHCH ₂ Ph (1.8g.)
PhCH ₂ NHNH ₂ (1.4g.)	EtCHO (3.0g.)	2	Pr ⁿ NHNHCH ₂ Ph (2.8g.)
PhCH ₂ NHNH ₂ (2.4g.)	Me ₂ CO (1.2g.)	2	Pr ⁱ NHNHCH ₂ Ph (2.6g.)
PhCH ₂ NHNH ₂ (3.0g.)	Pr ⁿ CHO (1.8g.)	2	Bu ⁿ NHNHCH ₂ Ph (2.9g.)
PhCH ₂ NHNH ₂ (4.4g.)	PhCHO (3.9g.)	2	PhCH ₂ NHNHCH ₂ Ph (4.2g.) ³
NH ₂ NH ₂ ·H ₂ O (1.2g.)	PhCHO (5.0g.)	4	PhCH ₂ NHNHCH ₂ Ph (2.8g.)
NH ₂ NH ₂ ·H ₂ O (1.7g.)	Me ₂ CO (4.2g.)	4	Pr ⁱ NHNHPr ⁱ (4.1g.)
Bu ^t NHNH ₂ (4.5g.)	PhCHO (5.4g.)	4	Bu ^t NHNHCH ₂ Ph (10.3g.) ³
Bu ^t NHNH ₂ (3.8g.)	Me ₂ CO (2.5g.)	4	Bu ^t NHNHPr ⁱ (3.5g.) ³
Me ₂ NNH ₂ (2.4g.)	Me ₂ CO (2.4g.)	2	Me ₂ N-NH-Pr ⁱ (4.2g.) ³
Me ₂ NNH ₂ (1.2g.)	Pr ⁿ CHO (1.5g.)	2	Me ₂ N-NH-Bu ⁿ (-) ⁴
Ph-CH=N-NH-Me (2.9g.)		2	MeNHNHCH ₂ Ph (3.8g.) ⁵
Ph-CH=N-NH ₂ (7.5g.)		2	PhCH ₂ NHNH ₂ (5.8g.) ⁵

- 1 Calculation assumes only one proton is available for reduction.
- 2 As a mixture of mono- and dihydrochlorides.
- 3 Mainly monohydrochloride.
- 4 Hydrochloride was not isolated.
- 5 Prepared by reduction of isolated hydrazone.

Mechanism of the reaction.

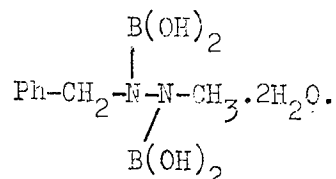
In the reduction of oximes with diborane Feuer and his co-workers⁹² isolated a boron containing intermediate and suggested the following mechanism for the reaction:-



Feuer et. al suggest⁹² that the compounds (A) and (B) are probably polymeric in nature.

A similar intermediate has been obtained in the condensation-reduction of methylhydrazine and benzaldehyde (Experiment No. 8c). The material obtained by stopping the reaction at the halfway stage appeared to be a mixture of two components. The major component was an involatile boron-containing material, (presence of boron shown by 'flame-test'; Experiment No. 8c). Passage of HCl gas into a suspension of the intermediate in dry tetrahydrofuran gave the expected 1-benzyl 2-methylhydrazine hydrochloride.

Analysis gives the approximate composition as $C_8H_{14}B_2N_2O_4 \cdot 2H_2O$. Spectral data suggests that the major component has the formula :-



Thus the i.r. spectrum shows a broad peak $3500-2700 \text{ cm.}^{-1}$. ($B(OH)_2$ -hydrogen bonded), a strong broad peak $1475-1370$ (aromatics and B-O) and two strong sharp peaks at 695 cm.^{-1} and 780 cm.^{-1} (aromatics). N.m.r. data on the intermediate are given in Table III. Discussion of the side-product is deferred until the next section.

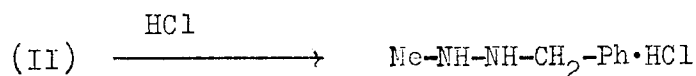
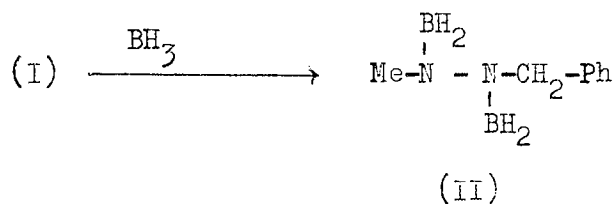
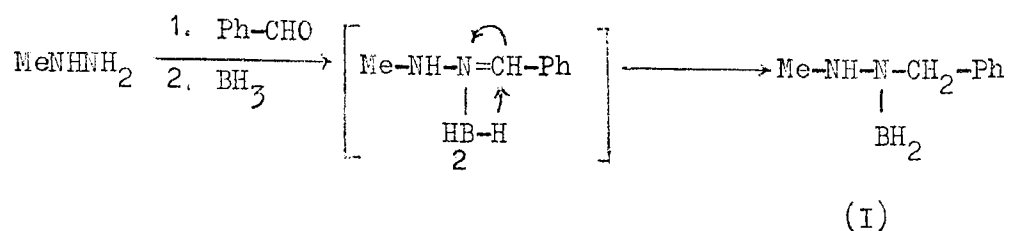
Table III

N.m.r. data for boron intermediate.

<u>Solvent and Spectrometer used.</u>	<u>τ</u>	<u>Interpretation.</u>
D ₂ O (Perkin-Elmer R10).	(2.5	aromatic protons.
	(5.9	benzylic protons of boro-adduct.
	(7.1	side product.
	(7.24	CH ₃ of boro-adduct.
Dimethyl Sulphoxide (Perkin-Elmer R.14).	(2.53	aromatics of side product.
	(2.6	aromatics of boro-adduct.
	(<u>c.a.</u> 5.2	B-(OH) ₂ -broad.
	(5.45	side product.
	(5.9	benzylic protons of boro-adduct.

Determination of the molecular weight of the intermediate by Rast's Method, (depression of m.p. of camphor), gave a value between 188 and 225. Hence the isolated material is not polymeric, but as suggested⁹² by Feuer and his co-workers the intermediate may be.

A possible mechanism for the reduction of hydrazones with diborane is outlined below :-



This mechanism is similar to that proposed,⁹² by Feuer and his co-workers, for the reduction of oximes, but initial attack of diborane at the carbon-nitrogen bond, rather than the substituted nitrogen, is suggested. This is not unreasonable in the light of the work of Ioffe and his co-workers,⁹³ which suggests that the initial point of diborane attack may vary with the structure of the substrate. Intermediate (I) can be used to rationalize the formation of the side product (see page 53).

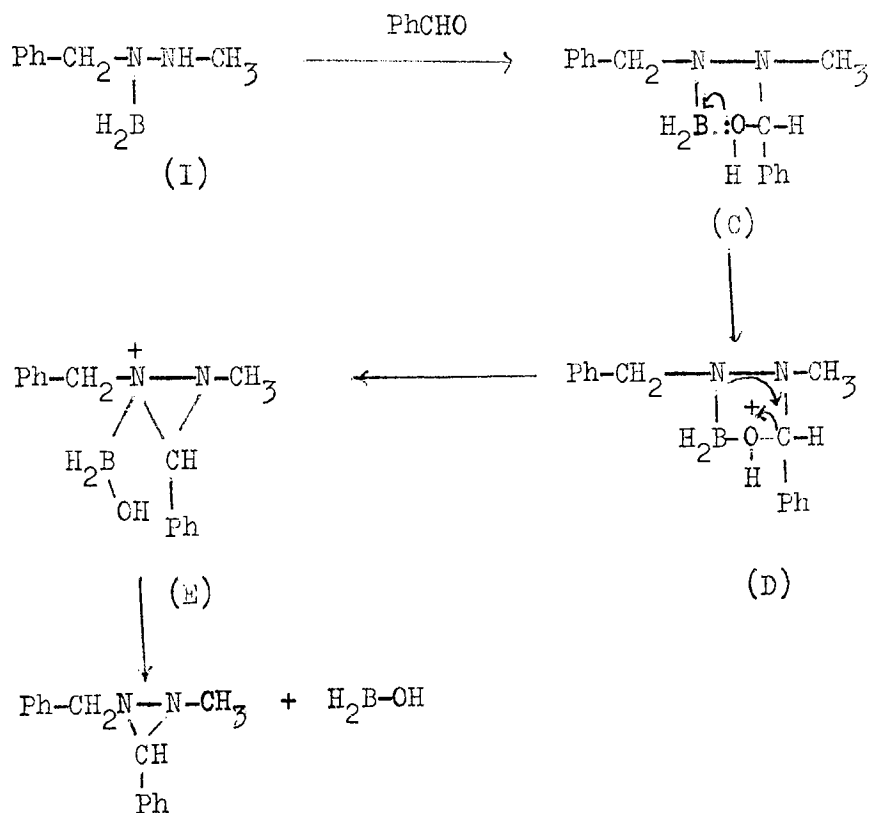
The intermediate $\text{Ph-CH}_2\text{-NB(OH)}_2\text{-NB(OH)}_2\text{-H.e.}\cdot 2\text{H}_2\text{O}$ was isolated without any special precautions, hence its formation by hydrolysis of intermediate (II) is quite reasonable.

The preparation of diaziridines.

As described in the last section a boron-containing intermediate was isolated during the course of the condensation-diborane-reduction of methylhydrazine and benzaldehyde which contained a small amount of a more volatile material. Although the boron-intermediate was too involatile to give a mass spectrum the side-product gave a high mass peak at m/e 224 and fairly intense peaks at m/e 209, m/e 91, m/e 65 and m/e 39. Accurate mass measurement gives the formula of the m/e 224 peak as $\text{C}_{15}\text{H}_{16}\text{N}_2$. The loss of fifteen mass units suggests cleavage of a methyl group and the m/e 91, 65 and 39 peaks suggest a benzylic group.

The mass spectral and n.m.r. data indicate that the side product is 1-benzyl 2-methyl 3-phenyldiaziridine. The n.m.r. data (Table III) for the side-product can be rationalized thus :- for the spectrum in D_2O τ 7.1 (CH_3 of diaziridine) and for the spectrum in dimethyl sulphoxide τ 2.53 (aromatics of diaziridine) and τ 5.45 (benzylic protons of diaziridine).

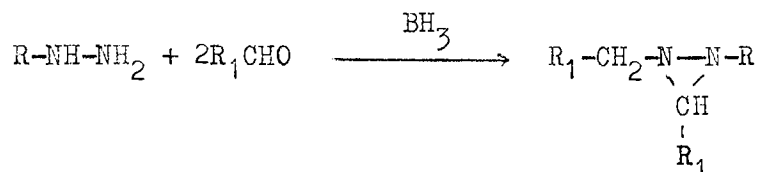
A feasible mechanism for the formation of the diaziridine is suggested below :-



Initial attack of benzaldehyde on intermediate (I) produces the carbanolamine (c). The hydroxyl group is labilized by co-ordination of the oxygen lone pairs with the boron atom and internal nucleophilic attack (D) gives the quaternary nitrogen of compound (E). Loss of H_2BOH then produces the diaziridine.

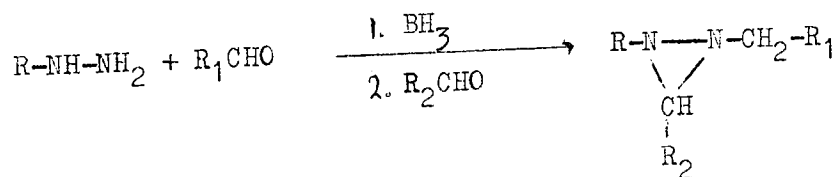
This reaction is of great interest. Thus, if the mechanism outlined is correct, then the use of excess aldehyde should lead to

an increased yield of the diaziridine. Hence the reaction is potentially a simple one-step method of synthesising diaziridines.



Methods of synthesis and properties of diaziridines have been reviewed.^{143,183} The more common routes to diaziridines (reaction of chloramine, substituted chloramines or hydroxylamine-*O*-sulphonic acid with Schiff bases) have already been noted (page 25). Reaction with hydroxylamine-*O*-sulphonic acid appears to be the most successful method, giving yields of 50-80%¹⁴³

As *N*-substituted hydroxylamine-*O*-sulphonic acids and *N*-substituted chloramines have to be prepared separately the synthesis of diaziridines with three different groups attached to the ring is rather lengthy. The possible route outlined above offers a convenient method for the synthesis of these compounds. In further extension of the method the use of 'mixed' aldehydes, or ketones, with diborane and a hydrazine offers a simple route to any desired diaziridine i.e :-



It is also noteworthy that the suggested mechanism for the formation of the diaziridine involves the use of boron to co-ordinate with the lone-pair of the hydroxyl oxygen. This method of labilizing the hydroxyl group may be applicable to other cyclization reactions.

To examine the formation of the diaziridine further the condensation-diborane-reduction of a mixture of benzaldehyde and methylhydrazine was repeated using a 2:1 mole equivalent of benzaldehyde to methylhydrazine. After passage of diborane the solution was treated with strong sodium hydroxide solution to give two layers. The upper layer was extracted with ether. Evaporation of the extracts produced a golden yellow oil. When a small sample of this oil was warmed with acidified potassium iodide in the presence of copper sulphate iodine was produced. This is a reaction which is characteristic of diaziridines.¹⁸³ Accurate mass measurement of the molecular ion (m/e 224) in the compounds mass spectrum gave the formula $C_{15}H_{16}N_2$. The n.m.r. data is consistent with the diaziridine structure (see Experiment No. 31). The crude yield was approximately 60%, but attempts to distil the compound, at reduced pressure, resulted in a large degree of decomposition.

Similar condensations using two moles of propionaldehyde, or two moles of acetone, with methylhydrazine gave mixtures of products, but spectral data did not indicate the presence of the appropriate diaziridine. (Experiments Nos. 32 and 33). The failure of these reactions may be due to one of two causes :-

1. Non-formation of the carbanolamine(C). The initial site

of diborane attack on a hydrazone may vary with the structure of the hydrazone. If initial attack occurs at the saturated nitrogen-atom then further formation of a carbonolamine will be blocked. The presence of broad bands (3500 cm^{-1}) in the i.r. spectra of the products from the reaction of both acetone and propionaldehyde suggest that the aldehydes have, at least in part, been converted to the corresponding alcohols, *i.e.* condensation to the carbonolamine did not occur.

2. Cyclization of the intermediate may not have occurred even if it was formed. The benzylic structure may be necessary to stabilize the hydroxy group.

An attempt was also made to prepare 1-methyl 2-*n*-propyl 3-benzyl diaziridine which constituted a test of point 2. above. Thus methylhydrazine (1 mole) and propionaldehyde (1 mole) were condensed, in dry tetrahydrofuran, in the presence of a few spots of glacial acetic acid. Benzaldehyde (1 mole) was then added and diborane passed into the resulting mixture (Experiment No. 34).

The product appeared to be a mixture of compounds and did not release iodine when heated with acidified potassium iodide in the presence of copper sulphate. The mass spectrum shows peaks up to m/e 253. Peaks at m/e 176 and 174 peak-match to the formulae $C_{11}H_{16}N_2$ and $C_{11}H_{14}N_2$ respectively, but n.m.r. data does not indicate the presence of a diaziridine, at least not in large amounts.

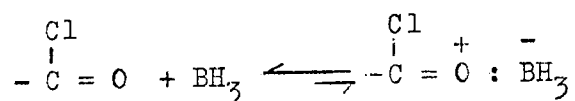
These experiments were very exploratory in nature and have not been repeated. Hence the reaction requires a great deal more

investigation, but may prove a useful preparation of diaziridines.

Limitations to the diborane reduction of hydrazones.

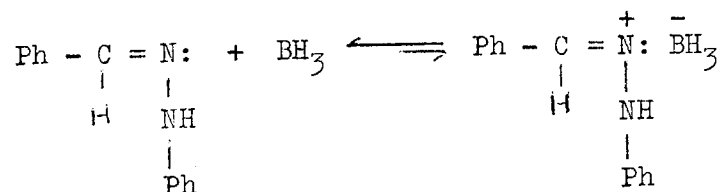
Attempts to prepare 1-benzyl 2-phenylhydrazine by the condensation-reduction of benzaldehyde and phenylhydrazine have met with consistent failure (Experiment No. 18a). The only material isolated from these reactions was a dark-green solid the exact composition of which has not been determined. This material is also obtained when a mixture of benzaldehyde and phenylhydrazine, in dry ether, is saturated with HCl gas, hence it would appear that diborane is failing to reduce the intermediate hydrazone.

Diborane attacks as a Lewis acid,¹⁸⁴ In compounds, such as acid chlorides the strongly electronegative chlorine reduces the basicity of the carbonyl oxygen and the intermediate boro-adduct is not very stable. Hence in the equation below the equilibrium lies to the left and compounds such as acid chlorides are resistant to reduction by diborane^{184,185} :-



In a similar manner the equilibrium between diborane and benzaldehyde phenylhydrazone may lie to the left and hence no reduction

occurs :-



Sodium borohydride attacks as a Lewis base¹⁸⁵ and this reagent rapidly reduces acid chlorides. In analogy sodium borohydride might be expected to reduce hydrazones of the type $R-CH=N-NH-R_1$, where R and R_1 are electron-withdrawing groups. It is thus of interest that Nulu and Nematollahi have reported⁸⁶ that imidazolecarboxyhydrazones are not reduced by diborane, but that reduction with sodium borohydride gives good yields of the corresponding hydrazines.

Other reports⁹⁵⁻⁹⁷ of the non-reduction of hydrazones by diborane have all involved attempts to reduce hydrazones bearing an aromatic group on the saturated nitrogen. It is thus likely that compounds of the type $R-CH=N-NH-Ph$ are not amenable to reduction with diborane.

Some care must be taken in choosing the hydrazine and aldehyde, or ketone, when attempting to prepare a particular hydrazine by the condensation-reduction procedure. For example the yield of 1-benzyl 2-ethylhydrazine hydrochloride (Experiment No. 11) was rather lower than the yields observed in the preparation of other 1-benzyl 2-alkylhydrazines. The method used involved the condensation-reduction of benzylhydrazine and acetaldehyde. Acetaldehyde is very volatile and the condensation reaction is rather exothermic, hence losses of acetaldehyde may be quite large. This will necessarily reduce the overall yield of hydrazine. Better yields of 1-benzyl 2-alkylhydrazine might be obtained by condensation-reduction of ethylhydrazine and benzaldehyde.

Similarly 1-methyl 2-alkylhydrazines are probably best prepared by the condensation-reduction of methylhydrazine and the appropriate aldehyde (e.g. Experiment No. 3). Their preparation by the condensation-reduction of formaldehyde and an hydrazine might give rather lower yields. Thus losses would occur because of the volatility of formaldehyde and the use of formalin solution is prohibited by the large percentage of water present. Water will both cut down the efficiency of the condensation and react with diborane.

Physical Properties.

The physical chemistry of hydrazines is of special interest because of the close proximity of the unshared electron pairs. This has been suggested¹⁸⁶ as the cause of the abnormally large spacing of the N-H stretching frequencies observed in the i.r. spectra of hydrazines and was thought¹⁸⁷ to account for the increased nucleophilic character of the hydrazines compared to the amines, (the ' α -effect'). It has recently been suggested,¹⁸⁸ however, that in compounds such as hydrazine and hydroxylamine, the preferred conformation is such as to minimise $\overline{p\pi}$ - $\overline{p\pi}$ overlap, hence the increased nucleophilicity of these compounds is not due to an ' α -effect', but arises from some other cause. In the particular case of the hydroxamic acids the apparent increase in nucleophilicity appears to be due to intermolecular catalysis.¹⁸⁹

The conformation of hydrazines is also of interest. Much recent work has been devoted to low temperature n.m.r. studies. The results have been discussed¹⁹⁰⁻¹⁹³ in terms of restricted rotation about the N-N bond and slow nitrogen inversion.

In the present work the i.r. spectroscopy has been found to be particularly useful for distinguishing the isomeric disubstituted hydrazines¹⁹⁴ (page 61). The mass spectral fragmentation patterns for a series of mono-substituted hydrazines,¹⁹⁵ a series of 1-benzyl 2-alkylhydrazines,¹⁹⁶ some 1-benzoyl 2-alkylhydrazines, some 1,1-disubstituted hydrazines and some trisubstituted hydrazines are presented (page 68) and n.m.r. τ -values for various groups, bonded to the nitrogen are given (page 121).

1. Infra-red Spectra

In general the infra-red of alkylhydrazines resembles those of amines in the N-H stretching and bending regions.^{197,198} The hydrazines show, however, a larger spacing of the N-H stretching bands, a fact which has recently been interpreted in terms of the close proximity of the unshared electron pairs.¹⁸⁶

The prepared 1,2-disubstituted hydrazine hydrochlorides give infra-red spectra characterised by a strong single band in the range 3190-3220 cm.^{-1} , (Table V). The constant nature of this band makes infra-red a quick and simple technique for distinguishing isomeric disubstituted hydrazines as salts.¹⁹³

The isomeric disubstituted hydrazines are generally distinguished by catalytic hydrogenation,^{73,199} or by their differing reactivity towards carbonyl compounds.¹⁶ The methods are tedious and the latter may give unexpected results.¹⁶

Bis(organosilyl)hydrazines have been distinguished by n.m.r.²⁰⁰ The N-H protons of the 1,1-isomer are equivalent and give a singlet, but the 1,2-isomer gives two resonance signals. The method is inapplicable to 1,2-isomers with the same group on each nitrogen and the width and lack of fine structure^{201,202} of the N-H resonance reduces the methods general usefulness.

Isomeric bis(organosilyl)hydrazines have also been distinguished by examining the N-H stretching, ($\nu\text{-NH}$), bands in the i.r. spectra of the free bases.²⁰⁰ The frequency shift between the symmetric and anti-

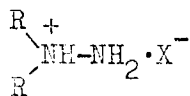
symmetric ν -NH bands for the 1,1-isomer is very constant, (76-88 cm.^{-1}), but the corresponding shift for the 1,2-isomer is small, (approx. 23 cm.^{-1}), and may not be observed. The method suffers from a number of drawbacks.

Free hydrazines are unpleasant to handle, easily oxidised and difficult to free from residual water. Oxidation has been shown to be responsible for discrepancies in the i.r. spectrum of a hydrazine²⁰³ and residual water makes observation of the important region above 3100 cm.^{-1} rather difficult. More important, however, is the fact that 1,2-dialkylhydrazines show a much larger shift than the 23 cm.^{-1} observed in the bis(organosilyl)hydrazines. For example gaseous 1,2-dimethylhydrazine shows a shift of 117 cm.^{-1} and solid 1,2-diphenylhydrazine a shift of 66 cm.^{-1} . The corresponding 1,1-isomers show shifts of 181 cm.^{-1} and 122 cm.^{-1} respectively,¹⁸⁶ hence spectra of both isomers must be compared before unambiguous structural assignments can be made.

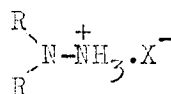
Partial deuteration of primary amino groups has been used²⁰⁴ to classify the structures of isomeric disubstituted ureas. The technique could be applied to the isomeric hydrazines, but is rather tedious.

Evans and Kynaston¹⁹⁷ have developed an elegant method of determining the site of protonation of a substituted hydrazine salt. This can be extended to give a general method of distinguishing isomeric hydrazines as stable salts.

Mono salts of 1,1-disubstituted hydrazines will have either structure (I) or (II): -



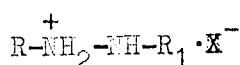
(I)



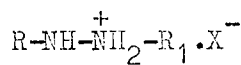
(II)

The $\overset{+}{\text{N}}\text{H}$ and $\overset{+}{\text{N}}\text{H}_3$ moieties do not show strong ν N-H bands above 3100 cm.^{-1} ^{205,206} (See Table IV for examples). Hence structure (I) will show the typical symmetric and antisymmetric ν N-H bands, above 3100 cm.^{-1} , of the primary amino group and structure (II) will show no strong bands in this region.

Mono-salts of 1,2-disubstituted hydrazines will have either structure (IIIa) or structure (IIIb) :-



(IIIa)



(IIIb)

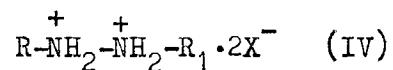
$\overset{+}{\text{N}}\text{H}_2$ does not ^{205,206} absorb above 3100 cm.^{-1} (See Table IV), hence either structure will show only one strong ν N-H band.

Table IV
 ν N-H bands for various compounds ^{205,206}

<u>Compound</u>	<u>Highest strong absorption (cm.^{-1})</u>	<u>Assignment</u>
Amino-acids	3100	$\overset{+}{\text{N}}\text{H}_3$
$\text{Me}\overset{+}{\text{N}}\text{H}_3 \cdot \text{Cl}$	3075	$\overset{+}{\text{N}}\text{H}_3$
$(\text{Me})_2\overset{+}{\text{N}}\text{H}_2 \cdot \text{Cl}^-$	2965	$\text{>}\overset{+}{\text{N}}\text{H}_2$
$(\text{Ph})_2\overset{+}{\text{N}}\text{H}_2 \cdot \text{Cl}^-$	2755	$\text{>}\overset{+}{\text{N}}\text{H}_2$
$(\text{Me})_3\overset{+}{\text{N}}\text{H} \cdot \text{Cl}^-$	2735	$\text{>}\overset{+}{\text{N}}\text{H}$
$(\text{Et})_3\overset{+}{\text{N}}\text{H} \cdot \text{Cl}^-$	2540	$\text{>}\overset{+}{\text{N}}\text{H}$

1,1-disubstituted hydrazine salts thus show two or no strong ν N-H bands and the corresponding 1,2-disubstituted hydrazine salts will show one ν N-H band. Table V illustrates this difference.

Di-salts of 1,2-disubstituted hydrazines, structure (IV) :-



like structure (II) will not show bands above 3100 cm.^{-1} (See Table V). Structure (II) only occurs, however, when electron-withdrawing groups are present.¹⁹⁷ With these conditions the 1,2-isomer is not likely to form a di-salt.

Table V.

⁺
N-H bands in isomeric disubstituted hydrazine salts.

Compound	(N-H) (above 3,100 cm. ⁻¹)		Structural Type
(CH ₃) ₂ N-NH ₂ ·(CO ₂ H) ₂	3240(s)	3130(s)	(I)
(CH ₃) ₂ N-NH ₂ ·HCl ¹⁹⁷	3290(s)	3131(s)	(I)
CH ₃ -NH-NH-CH ₃ ·2HCl	—		(IV)
(Et) ₂ N-NH ₂ ·(CO ₂ H) ₂	3250(s)	3120(s)	(I)
Et-NH-NH-Et·HCl ²⁰⁷	3205(s)		(III)
(Pr ⁱ) ₂ N-NH ₂ ·HCl ¹⁹⁷	3260(s)	3150(s)	(I)
Pr ⁱ -NH-NH-Pr ⁱ ·HCl	3195(s)		(III)
CH ₃ -NH-NH-CH ₂ -Ph·HCl	3200(s)		(III)
CH ₃ -NH-NH-CH ₂ -Ph·2HCl	—		(IV)
Et-NH-NH-CH ₂ -Ph·HCl	3200(s)		(III)
Pr ⁿ -NH-NH-CH ₂ -Ph·HCl	3200(s)		(III)
Pr ⁱ -NH-NH-CH ₂ -Ph·HCl	3190(s)		(III)
Bu ⁿ -NH-NH-CH ₂ -Ph·HCl	3200(s)		(III)
Bu ^t -NH-NH ₂ ·HCl ⁴⁵	3320(s)	3230(s) 3170(s)	(I)
Ph-CH ₂			
Bu ^t -NH-NH-CH ₂ -Ph·HCl	3200(s)		(III)
Ph-CH ₂ -NH-NH-CH ₂ -Ph·HCl	3195(s)		(III)
(Ph) ₂ N-NH ₂ ·HCl	—		(II)
Bu ^t -NH-NH ₂ ·HCl ²⁵	3220(s)	3120(m)	(I)
neo-pentyl			
Bu ^t -NH-NH-Pr ⁱ ·HCl	3220(s)		(III)

s = strong m = medium
* weak band at 3158 cm.⁻¹.¹⁹⁷

2. Mass Spectra.

Introduction.

Electron-induced fragmentation studies of hydrazines are limited to hydrazine,^{208, 209} tetraphenylhydrazine,²¹⁰ the methylhydrazines,^{210,212} nitrophenylhydrazines²¹³ and some N-toluene-p-sulphonyl-N¹-acylhydrazines.²¹⁴ Mass spectrometric examination of the photo-ionisation of hydrazine,²¹⁵⁻²¹⁷ benzylhydrazine,²¹⁵ methylhydrazine^{216,217} and some 1,1-disubstituted hydrazines;^{215,217} has been reported. Detailed fragmentation patterns have only been worked-out for the nitrophenylhydrazines.²¹³

The mass spectra of many organic compounds containing two linked nitrogen atoms have been examined.²¹⁸ Most of these, for example hydrazones and azines, contain carbon-nitrogen, or other, double-bonds. The presence of unsaturation has great influence on the mass spectral fragmentation modes of these compounds, hence direct analogy with the fully saturated hydrazine derivatives is impossible.

Mass spectral fragmentation of amines has received detailed examination.²¹⁸⁻²²² As will be indicated later in the text the amines and hydrazines show very similar effects in their mass spectra.

The limited available information on the mass spectrometry of hydrazines will be discussed further at appropriate points in the text.

Notes on the determination and presentation of the spectra.

Unless otherwise stated all the spectra were determined on an A.E.I. M.S.9 spectrometer at a source temperature of 250°C. and electron energies of 70 e.v. Liquids were inserted via the "hot-box" and solids on the direct-inlet probe.

The spectra are presented as bar graphs, plotting relative abundance (R.A.), vs. m/e. The spectra are not all drawn to the same scale, but when direct comparisons are made the appropriate spectra are drawn to the same scale.

For comparative purposes it has been necessary in some spectra to extend peaks above the arbitrary R.A. 100% base peak. This has been indicated by placing an arrow-head on top of the appropriate bar and writing the R.A. in brackets beside it. Peaks of R.A. less than 5% are only considered if they are of special significance.

Transitions observed with an appropriate metastable peak are indicated by the symbol * or m. The symbol * indicates that the metastable is observed in the spectrum; the symbol m indicates that the metastable has been found by the metastable-defocusing technique.²²³ For the sake of clarity only metastables observed in the spectra are drawn on the figures.

Calculated and measured masses for various ions are given in Appendix I. Appendix 2 gives calculated and observed values for metastables and the transition from which they arise.

Comparison of the mass spectra of hydrazine free bases and hydrazine salts.

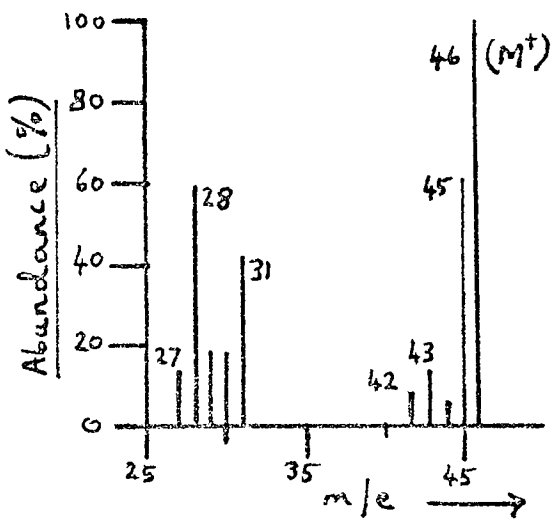
The stability and availability of hydrazine salts makes them more attractive for spectral studies than the relatively unstable free bases. The mass spectrum of aniline has been reported²²⁴ as showing little difference to the spectrum of aniline hydrochloride above m/e 40, but hydrazines and hydrazine salts have not previously been compared.

Tert-butylhydrazine, tert-butylhydrazine hydrochloride and tert-butylhydrazine oxalate, (Figs. 14, 15 and 16 respectively; page 81) give qualitatively similar spectra, with only small quantitative differences.

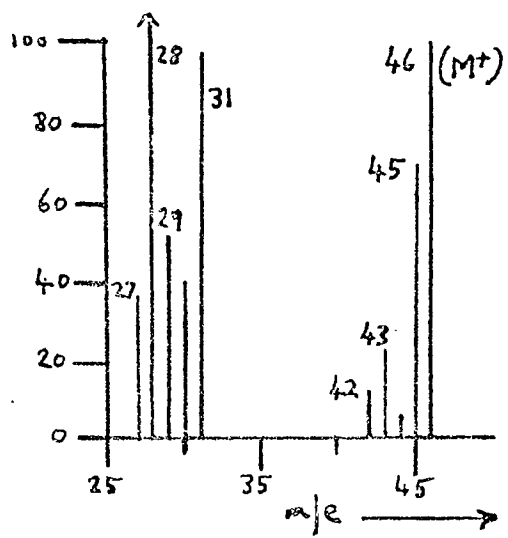
With methylhydrazine, (Fig. 2), and methylhydrazine hydrochloride, (Fig. 3), the quantitative differences are rather more pronounced, but the spectra are still qualitatively the same. Methylhydrazine oxalate, (Fig. 4), and methylhydrazine sulphate, (Fig. 6), give spectra dominated by fragments from the salt moiety. This was found to be generally true for the sulphates and hence oxalates and hydrochlorides were used for this study.

(Note :- Figs. 2 to 6 are shown on page 69).

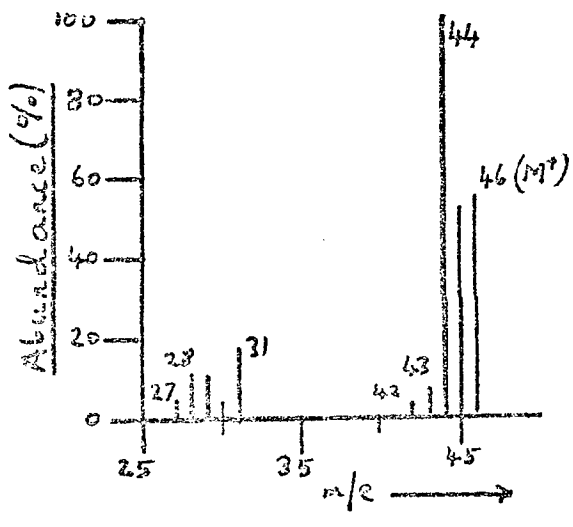
M_2NHNH_2 (Fig. 2)



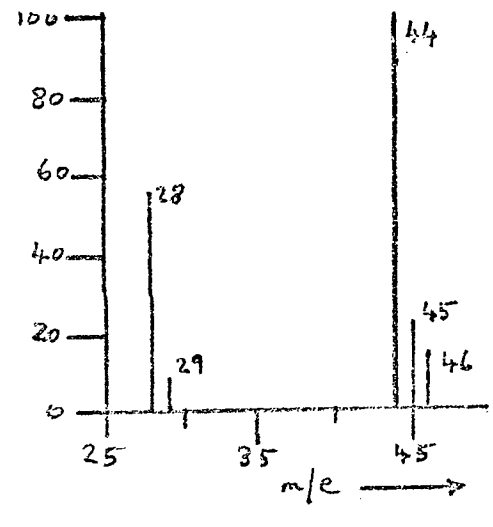
$M_2NHNH \cdot HCl$ (Fig. 3)



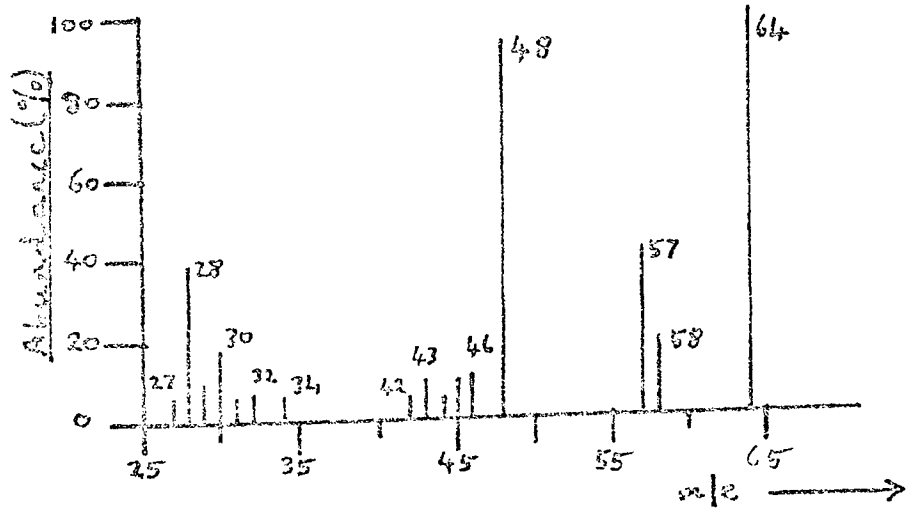
$M_2NHNH_2 \cdot (CO_2H)_2$ (Fig. 4)



Oxalic Acid (Fig. 5)



$M_2NHNH_2 \cdot H_2SO_4$ (Fig. 6)



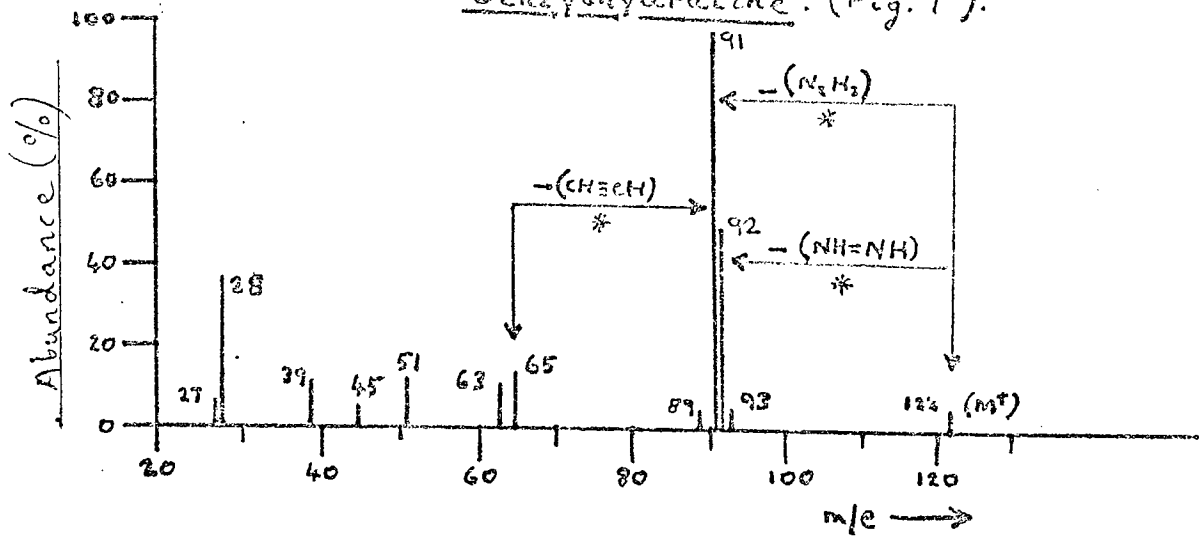
The oxalate moiety (compare oxalic acid, Fig. 5), gives intense peaks (m/e 46, 45 and 44) in a region containing important fragments from the hydrazine. Examination of high resolution spectra enables the removal of peaks due to the oxalate moiety. The spectra of ethylhydrazine oxalate (Fig. 10; page 77), n-propylhydrazine oxalate (Fig. 11; page 77), iso-propylhydrazine oxalate (Fig. 12; page 78) and n-butylhydrazine oxalate (Fig. 13; page 78) have been corrected in this fashion. Where comparison has been drawn between the hydrazine oxalate and the free base the spectra have not been corrected, but examination of the appropriate spectra (e.g. tert-butylhydrazine, Fig. 14, page 81 and tert-butylhydrazine oxalate, Fig. 16, page 81), clearly indicates the oxalate moiety as the source of the m/e 44-46 peaks.

The hydrochlorides give peaks in a region which does not contain important fragments from the hydrazines. Thus the peaks at m/e 35 (^{35}Cl), m/e 36 (H^{35}Cl), m/e 37 (^{37}Cl) and m/e 38 (H^{37}Cl) are not included in figures showing hydrazine hydrochlorides.

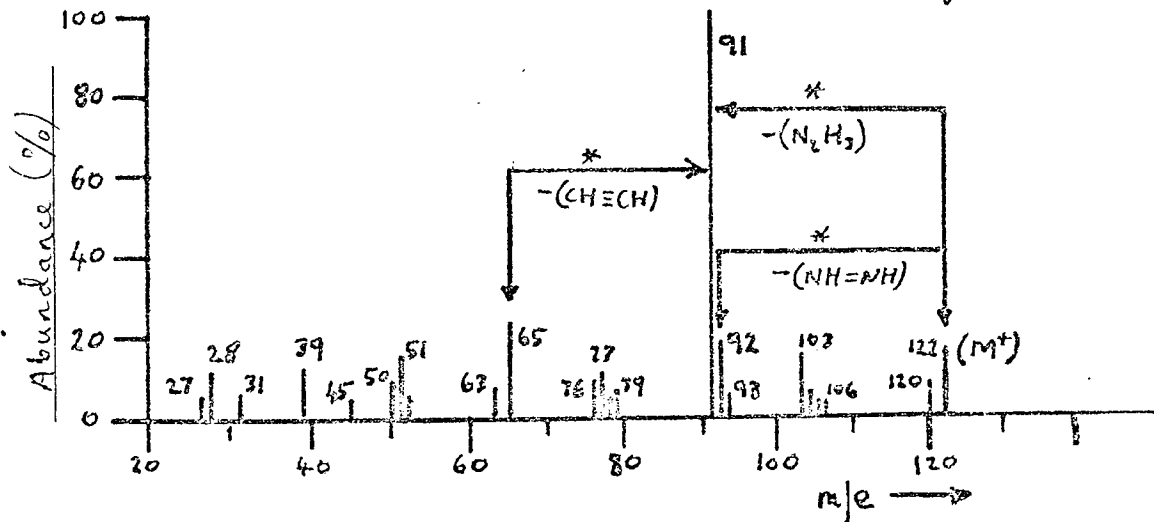
Comparison of the mass spectra of 1,2-dimethylhydrazine (Fig. 23; page 101) and 1,2-dimethylhydrazine dihydrochloride (Fig. 24; page 101) and 1,1-dimethylhydrazine (Fig. 31; page 116) and 1,1-dimethylhydrazine oxalate (Fig. 32; page 116) also indicate that the spectra of the free bases and the salts are qualitatively similar.

The spectra of benzylhydrazine, benzylhydrazine hydrochloride and benzylhydrazine oxalate (Figs. 7, 8 and 9 respectively; page 71) show more pronounced differences; particularly in the peaks m/e 120, m/e 107-103 and m/e 79-74.

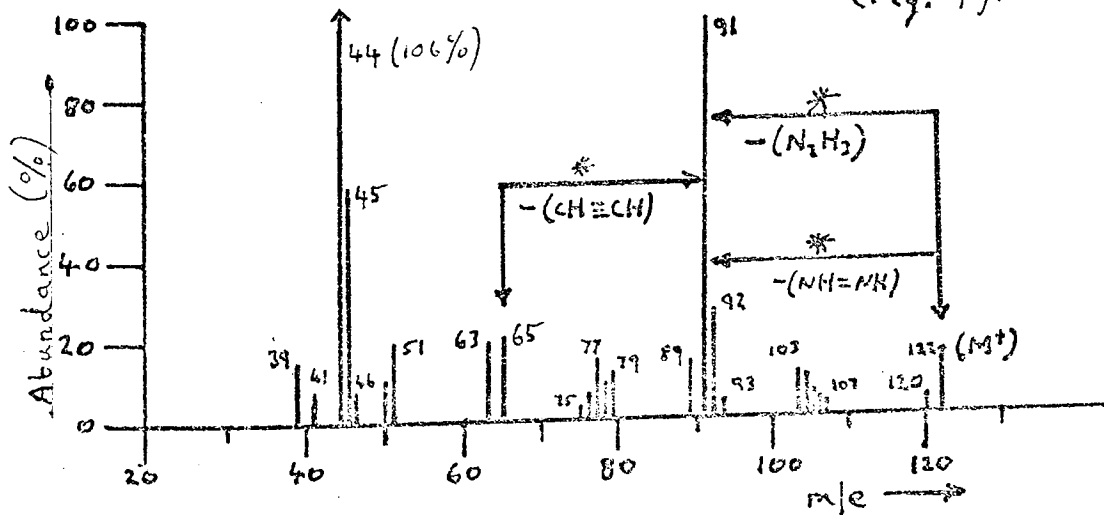
Benzylhydrazine. (Fig. 7).



Benzylhydrazine Hydrochloride (Fig. 8).



Benzylhydrazine Oxalate (Fig. 9).



Accurate mass measurement indicates the formulae $C_6H_5-CH_2-NH_2$, $C_6H_5-CH=NH_2$, $C_6H_5-CH=NH$ and $C_6H_5-C\equiv N$ for the peaks at m/e 107, 106, 105 and 103 respectively. The lower masses in the spectra of benzylhydrazine salts are not inconsistent with the known fragmentation of benzylamine (m/e 107) and phenylcyanide (m/e 103), hence the structures given above for the m/e 107-103 peaks are reasonable. The peaks m/e 107-103 do not appear to arise, however, by electron bombardment induced fragmentation of benzylhydrazine hydrochloride. Loss of the $-NH-$ moiety from the molecular ion would be a most unusual process and it is unlikely that the benzylhydrazine salts would differ in such a marked fashion from the free base. There is no indication of a $(H-NH)^+$ peak in the spectra of any of the other hydrazines, nor has this been noted by other workers.

The intensities of the m/e 107-103 peaks increase with the time the hydrochloride is allowed to remain on the probe. This would indicate that they arise either by thermolysis, or from an impurity of lower volatility than benzylhydrazine hydrochloride.

Benzylhydrazine was prepared by the benzylation of hydrazine (Experiment No. 9) and the hydrochloride precipitated by passing dry HCl gas into an ethereal solution of benzylhydrazine. Benzylhydrazine hydrochloride was also prepared directly by the diborane reduction of benzaldehyde hydrazone (Experiment No. 28). 1,1-dibenzylhydrazine hydrochloride may be expected as a contaminant in the first method and 1,2-dibenzylhydrazine hydrochloride in the second. Samples prepared by either route show similar mass spectra and the degree of recrystallization has little effect on them.

Use of the metastable defocusing technique to examine metastable transitions in the field free region does not reveal a source for the peaks m/e 106-103, but the m/e 107 peak apparently arises by the transition $135 \xrightarrow{m} 107$. A small peak, (R.A. 1%), occurs at m/e 135 in the spectrum of benzylhydrazine hydrochloride and in 1,2-dibenzylhydrazine hydrochloride, (R.A. 4%; Fig. 22). Benzylhydrazine hydrochloride does not, however, show a peak at m/e 212, although this is quite intense, (R.A. 15%), in 1,2-dibenzylhydrazine hydrochloride, hence this impurity cannot explain the observed spectra.

As both 1,1-dibenzylhydrazine and benzylamine itself are not likely to be impurities in the diborane reduction of benzaldehyde hydrazone these compounds are unlikely to be the source of the extra peaks.

Thermolysis of benzylhydrazine hydrochloride, (160°C for 30 minutes in vacuo), gives a mixture of solid and liquid products. The mass spectrum of these products obtained via the "hot-box" shows major peaks at m/e 120, 118, 85 and 83, whilst the spectrum obtained on the probe shows additional intense peaks at m/e 107-103 and m/e 79-74. The m/e 122 and m/e 91 peaks are greatly reduced.

The ratios of the abundances of the peaks 107, 106, 105, 104 and 103, for three sequential mass spectra of a sample of benzylhydrazine hydrochloride are given with the same ratios for the thermolysis product, (obtained on the direct inlet probe), in Table VI. The ratios are all very similar.

Table VI

Comparison of m/e 107-103 peaks in benzylhydrazine
hydrochloride and its thermolysis products.

<u>Compound</u>	Ratio m/e 107: 106: 105: 104: 103
$C_6H_5CH_2NHNH_2.HCl$ (2 mins. on probe)	1.0:1.8:1.0:2.1:2.1
$C_6H_5CH_2NHNH_2.HCl$ (4 min. on probe)	1.0:1.8:1.0:2.1:2.1
$C_6H_5CH_2NHNH_2.HCl$ (10 min. on probe)	1.0:1.8:1.1:1.7:1.8
Thermolysis products (on probe)	1.0:2.1:1.0:1.3:2.0

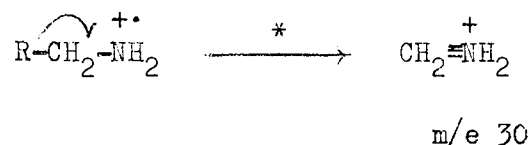
The evidence thus suggests that the m/e 107-103 peaks in the mass spectra of benzylhydrazine salts are of thermal origin. The changes in passing from the free base to the salt may be due to differences in technique and temperatures of volatilisation.

As thermolysis may occur in the other salts only major transitions, accompanied by well defined metastable peaks are considered in detail.

The mass spectra of monoalkylhydrazines. 195

a. Straight-chain alkylhydrazines.

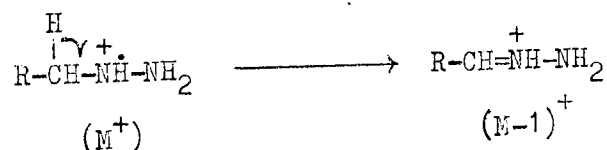
The mass spectra of primary amines are characterised²¹⁹⁻²²² by an intense peak at m/e 30. This peak is formed by an α -cleavage process:-



Similarly the mass spectra of the straight chain alkylhydrazines Me-NH-NH₂ (Fig. 2; page 69), Et-NH-NH₂·(CO₂H)₂ (Fig. 10; page 77), Prⁿ-NH-NH₂·(CO₂H)₂ (Fig. 11, page 77), and Buⁿ-NH-NH₂·(CO₂H)₂ (Fig. 13; page 78), are dominated by an intense m/e 45 peak formed by an α -cleavage analogous to that occurring in the primary amines :-



The alternative α -cleavage of a proton :-



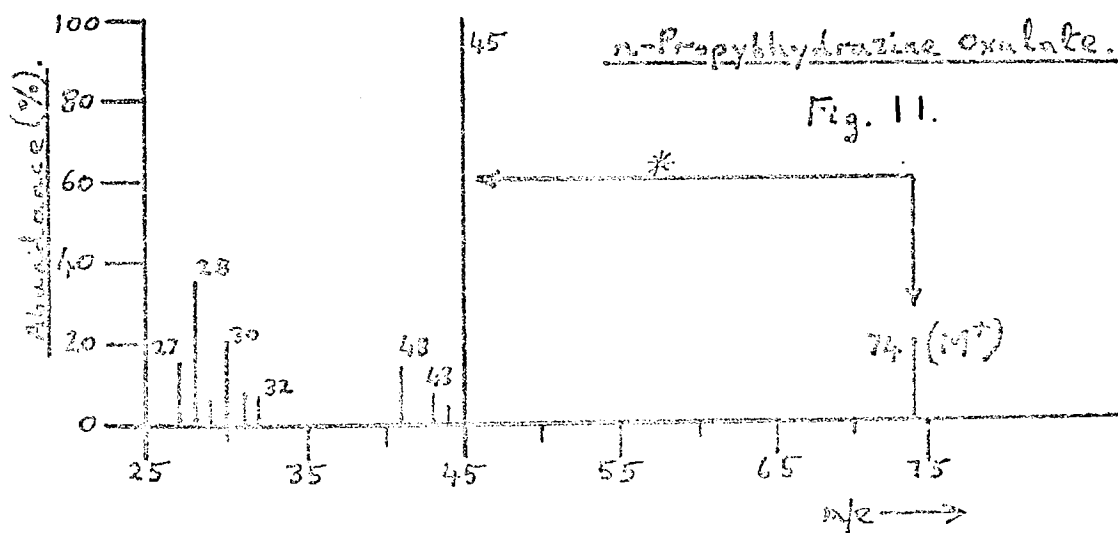
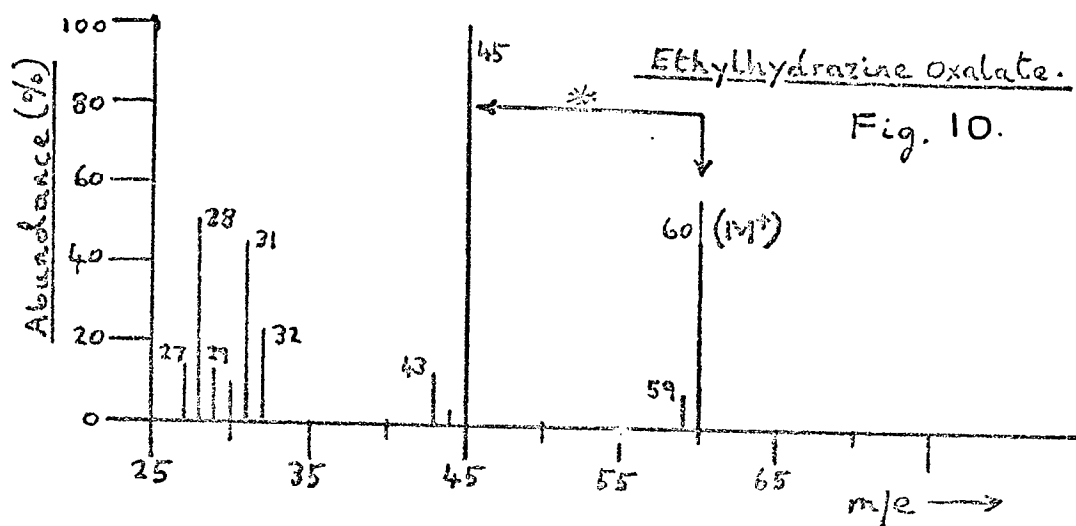
occurs to only a small extent. Loss of the C-H proton, rather than the N-H proton, is indicated by the absence of a (M-1) peak in the spectrum of tert-butylhydrazine. In analogy to the amines the ratio (M-1)/(M-R) falls with increasing chain length. The ratio values for methyl, ethyl,

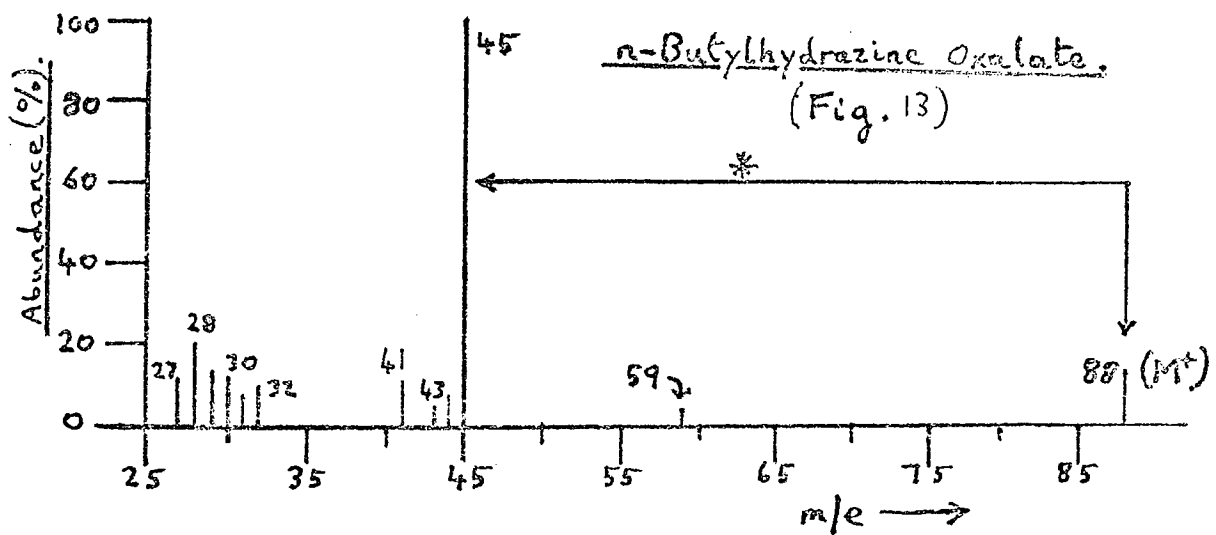
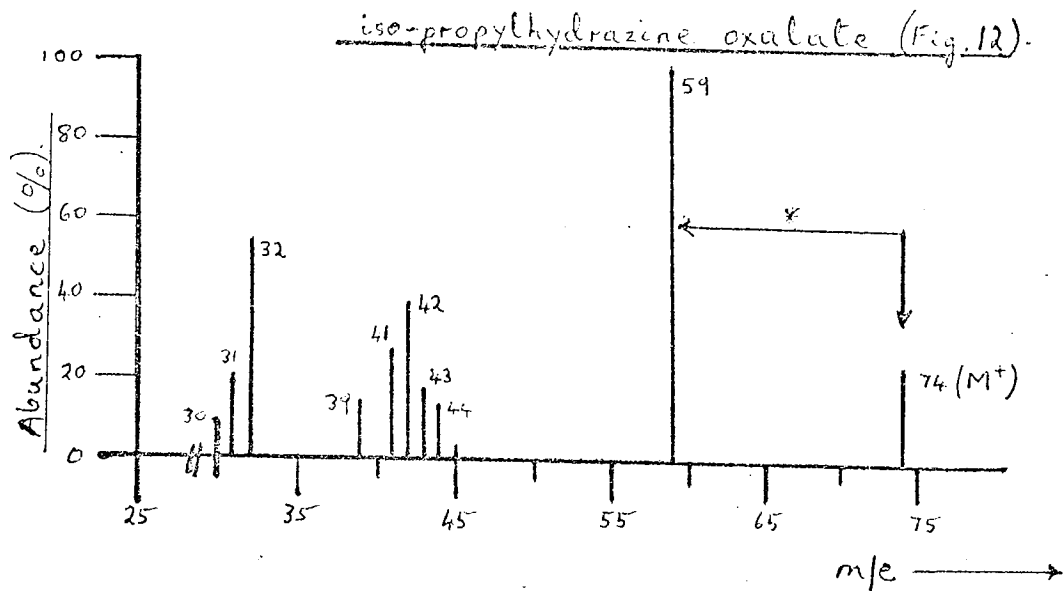
iso-propyl, n-propyl and n-butyl hydrazines are 1.0, 0.054, 0.035, 0.023 and 0.007 respectively. The corresponding²²⁰ values for methyl, ethyl, iso-propyl, n-propyl and n-butyl amines are 1.0, 0.2, 0.09, 0.03 and 0.001 respectively. The change reflects the increasing stability of the leaving radical (R), with increasing chain length, compared to the alternative loss of H.

In both ethylhydrazine and iso-propylhydrazine the competing processes are loss of a methyl radical or loss of a hydrogen. Although the energetics of the processes will be the same for both compounds the ratio of (M-1)/(M-R) is greater for ethylhydrazine than for iso-propylhydrazine. This difference is probably statistical in origin. Ethylhydrazine has a choice of two protons to lose, but iso-propylhydrazine has only one. The same argument applies to ethylamine and iso-propylamine.

In further analogy with the primary amines the intensity of the molecular ion, in the hydrazine spectra, falls with increasing chain length. Thus for methyl, ethyl, n-propyl and n-butyl hydrazines the R.A. of the molecular ion is 100%, 57%, 20% and 12.5% respectively.

It is also noteworthy that the hydrazine salts give molecular ions corresponding to the free bases and that β - and γ -cleavages occur to only a minor extent; (e.g. 59; R.A. 2.5%, in n-butylhydrazine corresponds to a β -cleavage product.)

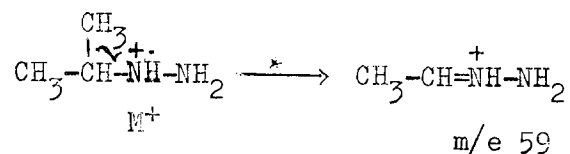




b. α -branched monoalkyl hydrazines.

Iso-propylhydrazine oxalate (Fig. 12; page 78) and tert-butylhydrazine, (Fig. 14; page 81), are representative of hydrazines with branching at the α -carbon.

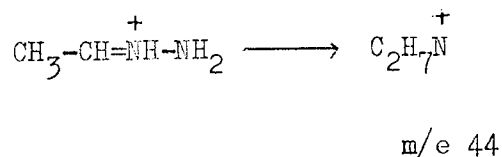
The dominant process occurring in the fragmentation of iso-propylhydrazine is again an α -cleavage :-



In analogy with the amines we would expect more complex α -branched hydrazines to show preferential loss of the larger α -group.

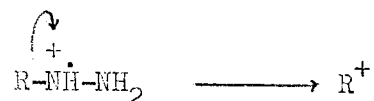
α -cleavage also occurs in tert-butylhydrazine, but the base peak (m/e 32) is formed by rearrangement of the molecular ion to "hydrazine" (N_2H_4) (Scheme 1; page 82). The m/e 32 is also fairly intense in the spectrum of iso-propylhydrazine and a similar fragmentation may be occurring here, but an appropriate metastable peak has not been observed.

The α -cleavage product from tert-butylhydrazine (m/e 73) shows an interesting loss of -NH- to give m/e 58. A similar fragmentation appears to occur in iso-propylhydrazine oxalate :-

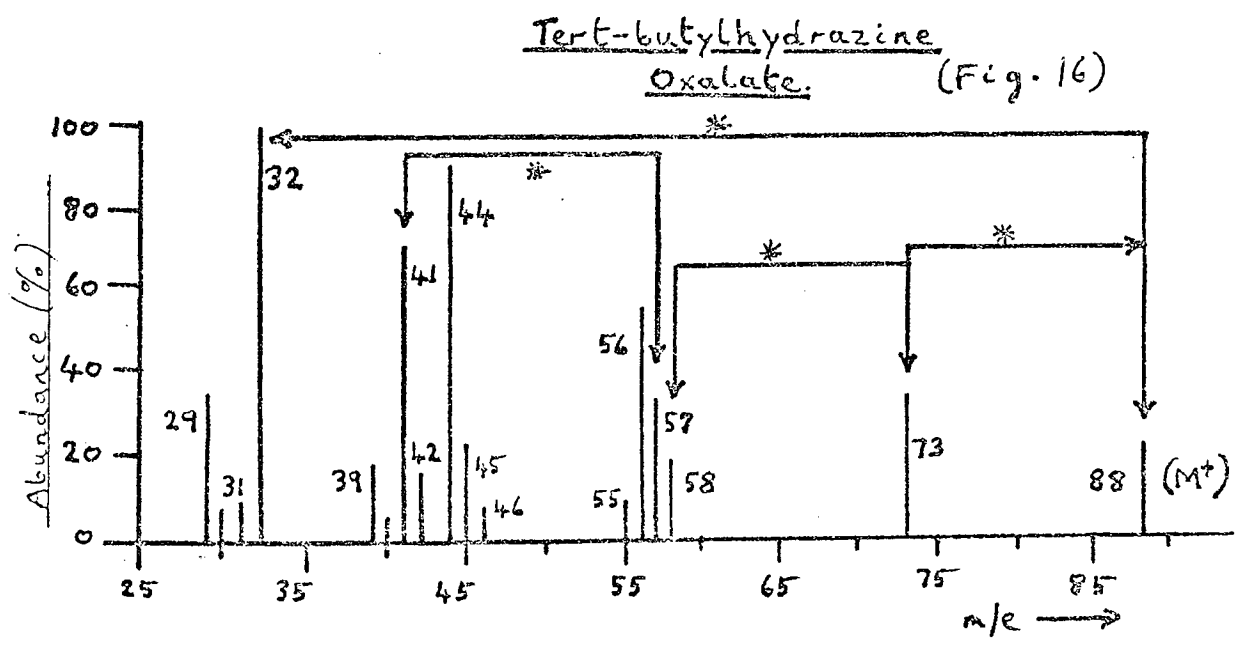
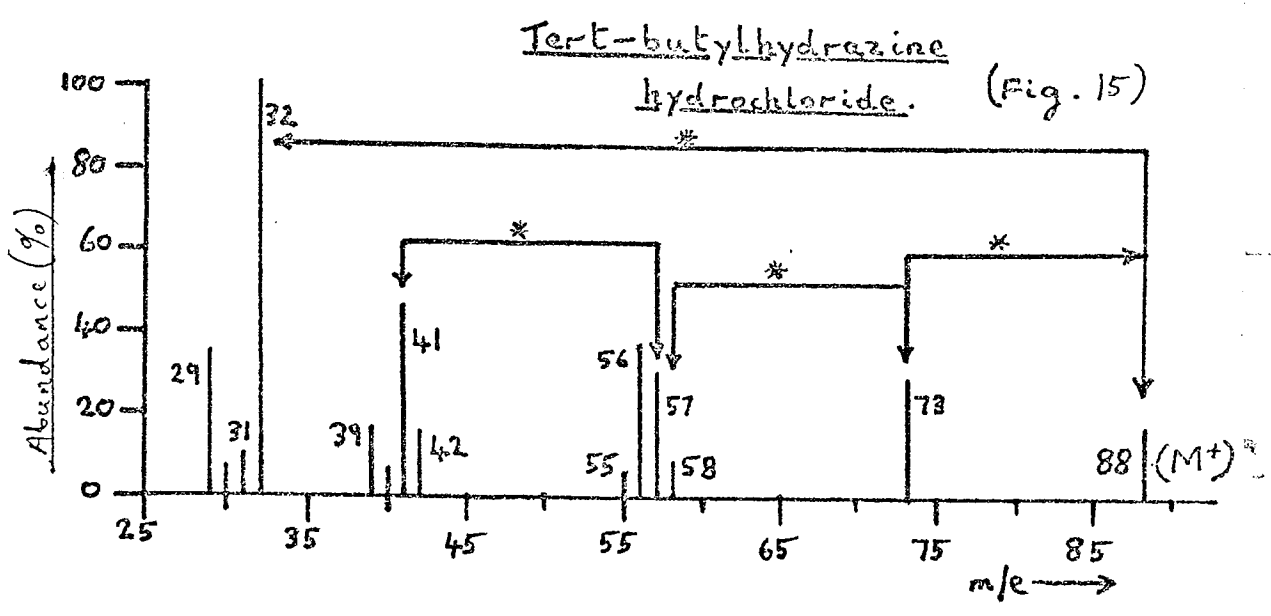
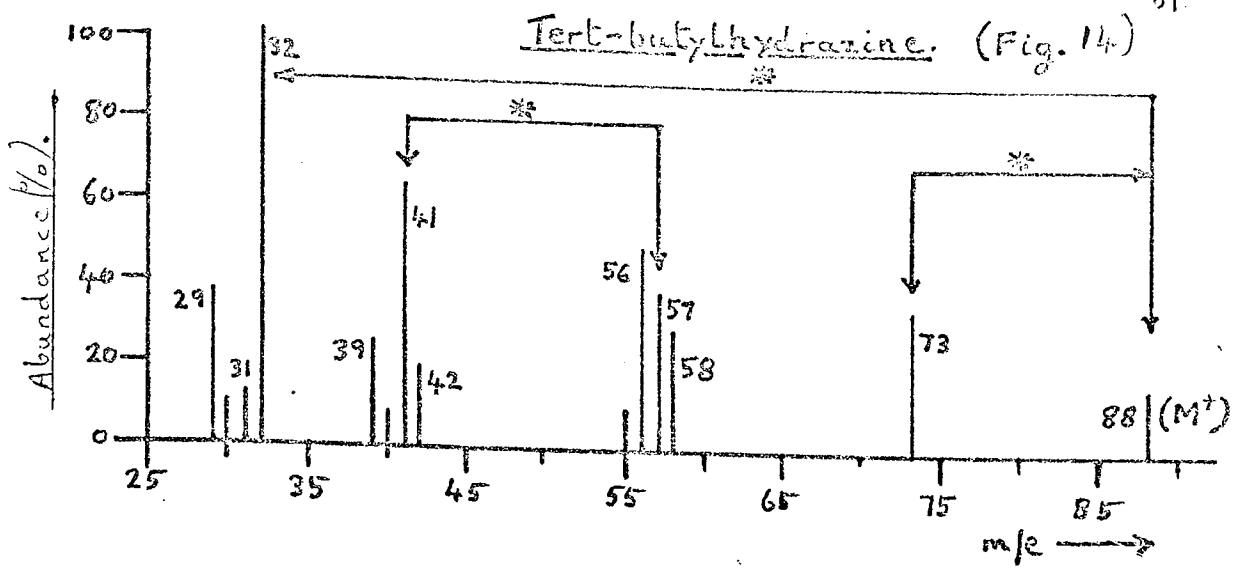


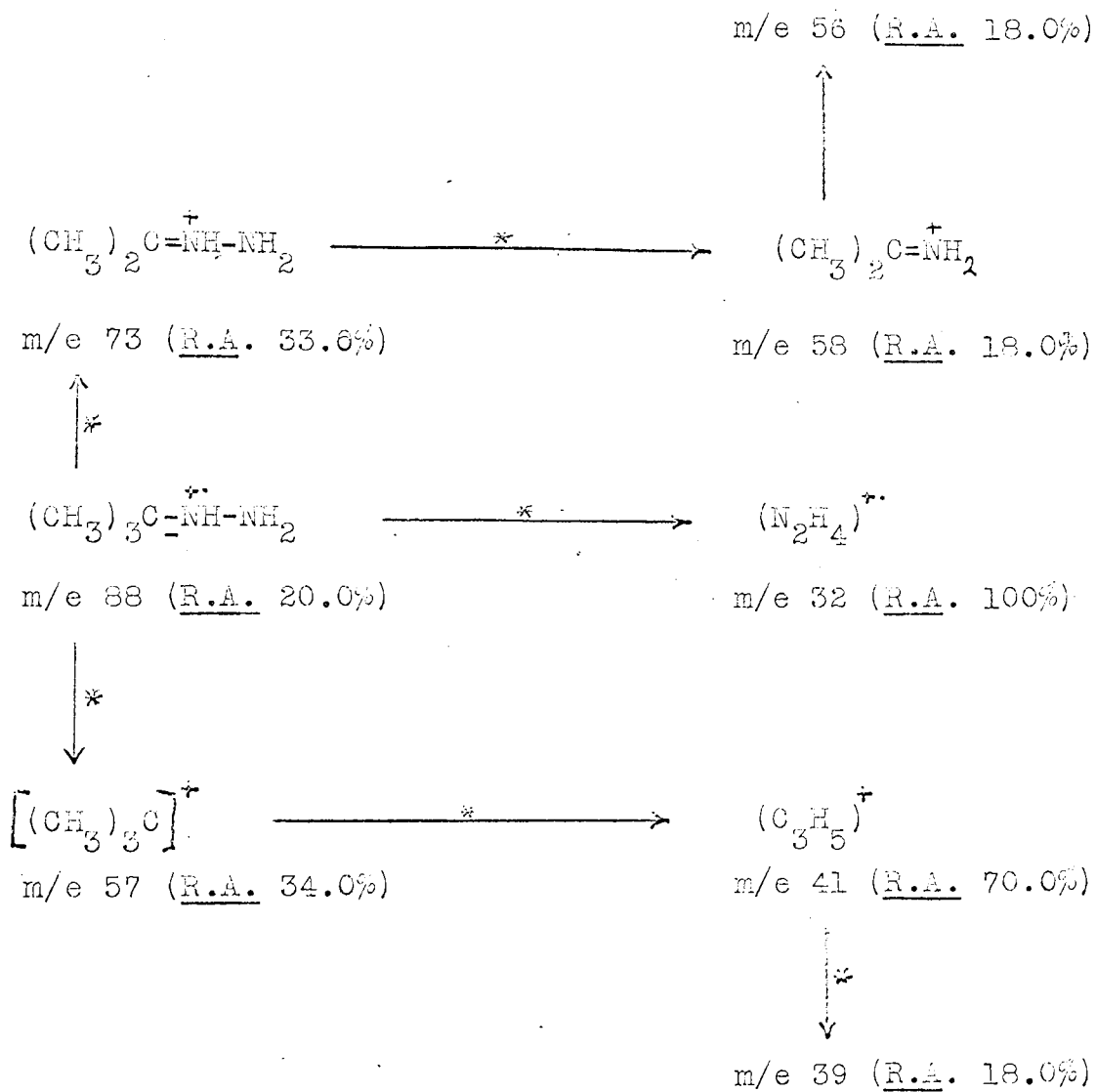
and may occur in the other hydrazines. An appropriate metastable has only been found, however, in the case of tert-butylhydrazine.

With the alkylhydrazines cleavage of the C-N bond to give the alkyl carbonium ion, (compare benzylhydrazine below) :-



only occurs to any great extent in the case of iso-propylhydrazine and tert-butylhydrazine. The former yields the secondary ion $(\text{CH}_3)_2\text{CH}^+$ (m/e 43; R.A. 33.0%), and the latter the tertiary ion $(\text{CH}_3)_3\text{C}^+$ (m/e 57; R.A. 38.0%). This is in agreement with the generalization that carbonium ion stability runs tertiary > secondary > primary.

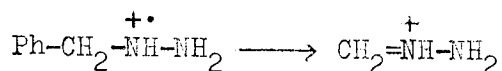


Scheme 1.Fragmentation of tert-butylhydrazine.

c. Benzylhydrazine

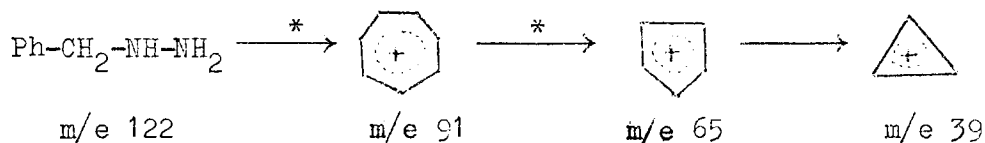
The spectra of benzylhydrazine, benzylhydrazine hydrochloride and benzylhydrazine oxalate are shown in Figs. 7, 8 and 9, respectively, (page 71). The peaks m/e 107-103 and m/e 79-74, occurring in the salts have already been discussed, (page 70).

Benzylhydrazine yields a small peak due to α -cleavage :-

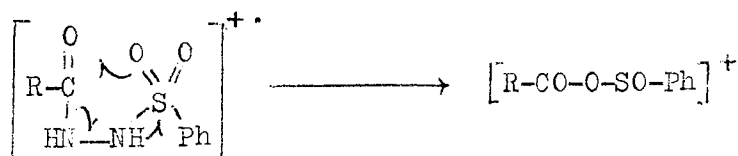


(m/e 45; R.A. 5.0 %)

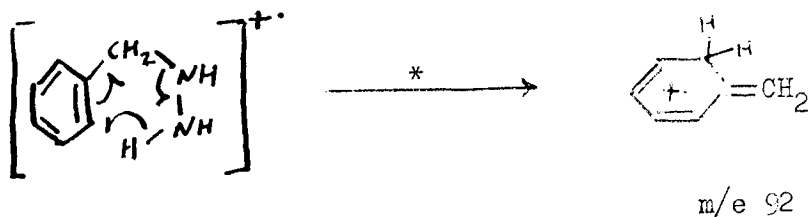
but the major process is the formation and cleavage of the tropylium ion:



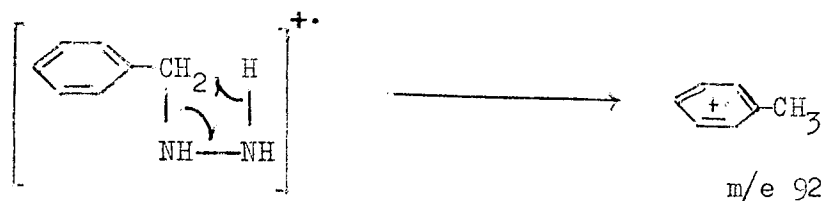
N-toluene-*p*-sulphonyl-*N'*-acylhydrazines have been reported²¹⁴ as eliminating di-imide from the molecular ion :-



Of the hydrazines examined only benzylhydrazine shows elimination of di-imide :-

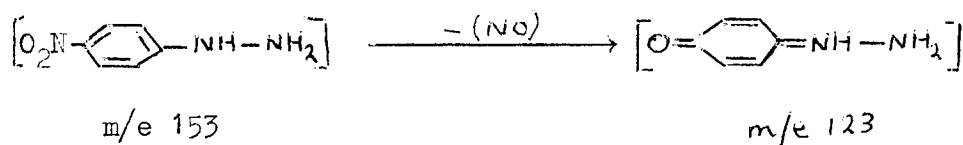


Alternatively the m/e 92 peak may be written with a toluene structure, but formation of this would involve a four membered transition state :-



A five-membered transition state for the rearrangement seems more reasonable.

m-Nitro-phenylhydrazine also shows a peak corresponding to loss of 30 mass units. Recent investigation²¹³ has shown that this involves loss of NO rather than N_2H_2 :-



The mass spectra of 1,2-disubstituted hydrazines.¹⁹⁵

a) General Preamble.

The mass spectra of the following 1-benzyl 2-alkylhydrazine hydrochlorides were determined:- Me-NH-NH-CH₂-Ph (Fig. 17; page 88), Et-NH-NH-CH₂-Ph (Fig. 18; page 91), Prⁿ-NH-NH-CH₂-Ph (Fig. 19; page 91), Prⁱ-NH-NH-CH₂-Ph (Fig. 20; page 94), Buⁿ-NH-NH-CH₂-Ph (Fig. 21; page 94), Ph-CH₂-NH-NH-CH₂-Ph (Fig. 22; page 99) and Bu^t-NH-NH-CH₂-Ph (Fig. 25; page 105). The mass spectra of Me-NH-NH-Me·2HCl (Fig. 24; page 101) and Bu^t-NH-NH-Prⁱ·HCl (Fig. 26; page 105) have also been recorded.

Fragmentation schemes for 1-benzyl 2-n-propylhydrazine hydrochloride (Scheme 2; page 92), 1,2-dibenzylhydrazine hydrochloride (Scheme 3; page 100) 1-benzyl 2-tert-butylhydrazine hydrochloride (Scheme 4; page 106) and 1-iso-propyl 2-tert-butylhydrazine hydrochloride (Scheme 5; page 107) are given in detail. The reaction pathways shown are supported by observation of appropriate metastables and, except for 1-iso-propyl 2-tert-butylhydrazine hydrochloride, by accurate mass measurement of all the peaks discussed.

b) Variation of the spectra with time.

Of the hydrochlorides examined only 1-benzyl 2-n-butylhydrazine hydrochloride and 1,2-dibenzylhydrazine hydrochloride give mass spectra which are unchanged with the time the compounds are allowed to remain on the inlet probe. The effect is particularly pronounced with 1-benzyl 2-methylhydrazine hydrochloride, (Fig. 17a and Fig. 17b; page 88).

The peaks giving the greatest time effect are generally a product of an α -cleavage (m/e 45 in Fig. 17; page 88) and the tropylium ion (m/e 91). Use of the metastable-defocusing technique indicates that both these peaks, (at least in part), arise by electron-induced fragmentation of higher masses.

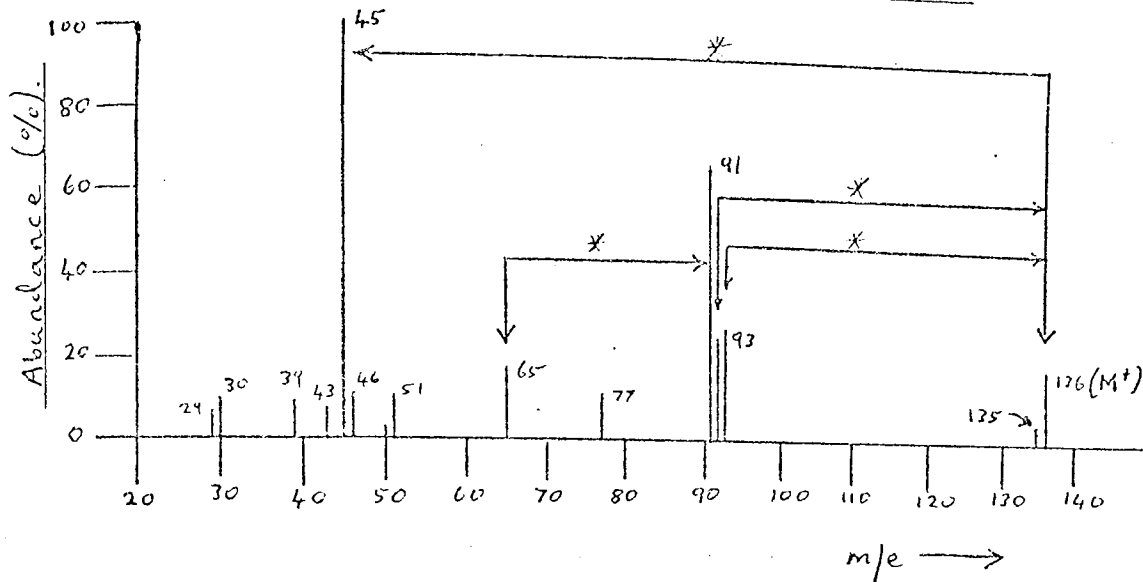
The compounds showing the largest time effects, (the methyl and n-propyl derivatives), have only been obtained as mixtures of mono- and di-hydrochlorides, (Experiment No. 8 and Experiment No. 12) and the other compounds probably contain varying amounts of the di-salt. The observed variation may thus be a function of the differing volatility and thermal stability of the mono- and di-hydrochlorides.

1-tert-butyl 2-benzylhydrazine monohydrochloride shows a different type of variation with time. The initial spectrum of this compound shows relatively intense peaks at m/e 176, 161 and 120, but in subsequent spectra these are shifted to m/e 178, 163 and 122 respectively. The peaks below m/e 106 remain unchanged.

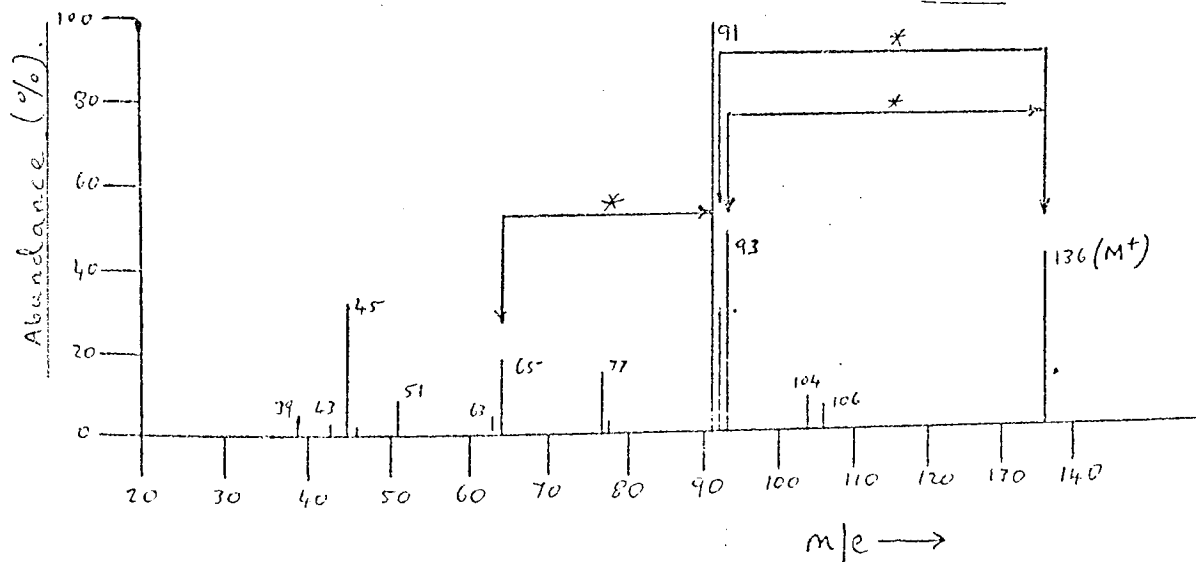
The most reasonable explanation of the effect is oxidation of the hydrazine to the more volatile hydrazone, or azo-compound, either prior to the determination of the spectrum or on the inlet probe. The similarity of the spectra below m/e 106, the fact that metastables are observed for processes $176 \rightarrow 161$ and $176 \rightarrow 120$ in the initial spectrum and for $178 \rightarrow 163$ and $178 \rightarrow 122$, (see scheme 4), in later spectra, is consistent with this view.

Similar effects are observed in the spectra of 1-benzyl 2-iso-propylhydrazine and 1-iso-propyl 2-tert-butylhydrazine.

1-benzyl 2-methylhydrazine hydrochloride (Fig. 17a).
run 1.



1-benzyl 2-methylhydrazine hydrochloride (Fig. 17b)
run 2.

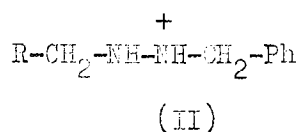
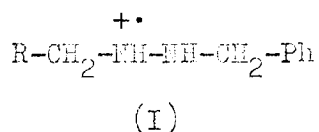


c) α -cleavage processes.

In analogy to the amines²¹⁹⁻²²² and the monosubstituted hydrazines the 1,2-disubstituted hydrazines might be expected to give intense peaks due to α -cleavage :-



In applying the concept of charge localization to the 1-benzyl 2-alkylhydrazines two structures may be written for the molecular ion (structure (I) and structure (II)) :-

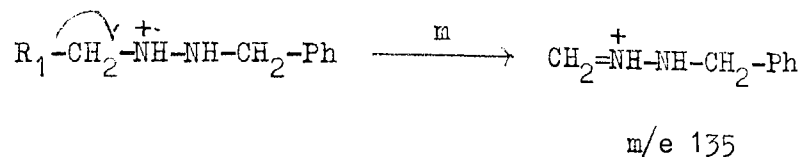


Ground state arguments would suggest that the inductive effect of the alkyl group (R) would stabilize structure (I) with respect to structure (II). The major fragmentation modes observed in the series of 1-benzyl 2-alkylhydrazines examined are best interpreted in terms of structure (I).

Thus all the compounds examined show an intense peak due to α -cleavage of the benzylic group :-

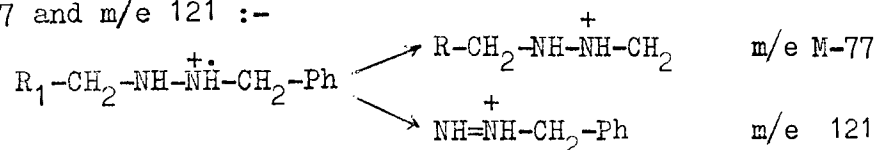


The alternative α -cleavage of R_1 to m/e 135 :-



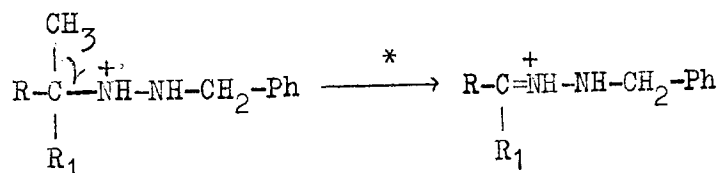
appears from the spectra to be of little importance, but the low intensity of this peak may be due to the ease with which it undergoes further fragmentation (see page 97).

Structure (II) would be expected to give α -cleavage products at m/e M-77 and m/e 121 :-



Both peaks are observed in low abundance, but metastable-defocusing does not indicate that they are a source of the more intense fragments at lower mass values.

Structure (I) may also be invoked to explain the loss of the branching group in α -branched hydrazines :-

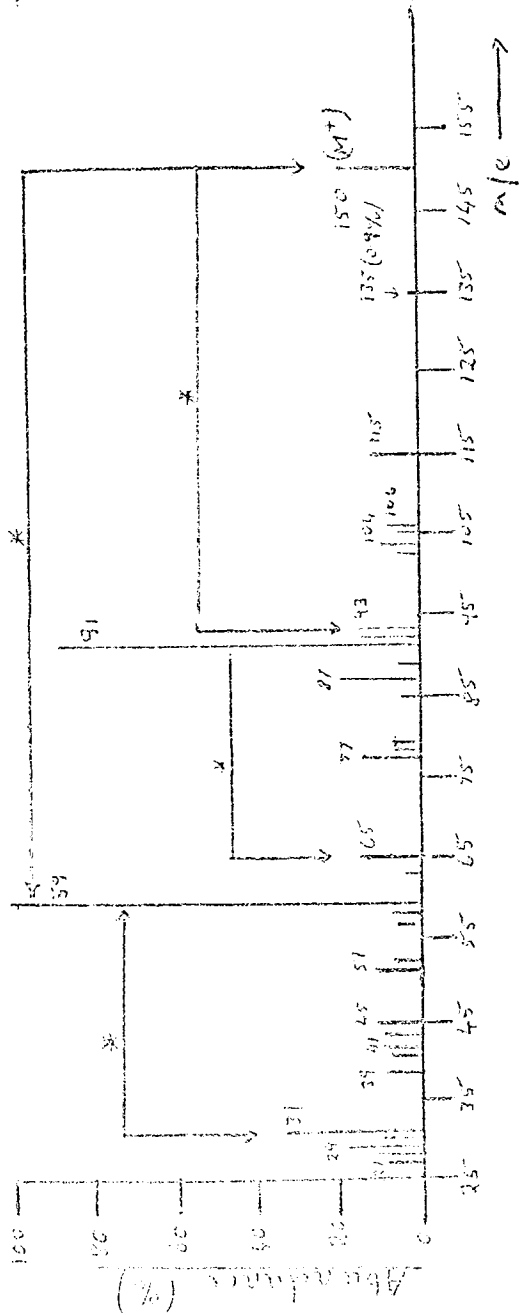


(observed where $\text{R}=\text{CH}_3$, $\text{R}_1=\text{H}$ and $\text{R}=\text{R}_1=\text{CH}_3$).

The major α -cleavage processes are thus most consistent with structure (I); it is therefore likely that the greater part of the molecular ion is ionized in this fashion. Cleavages consistent with structure (II) occur to a much smaller extent.

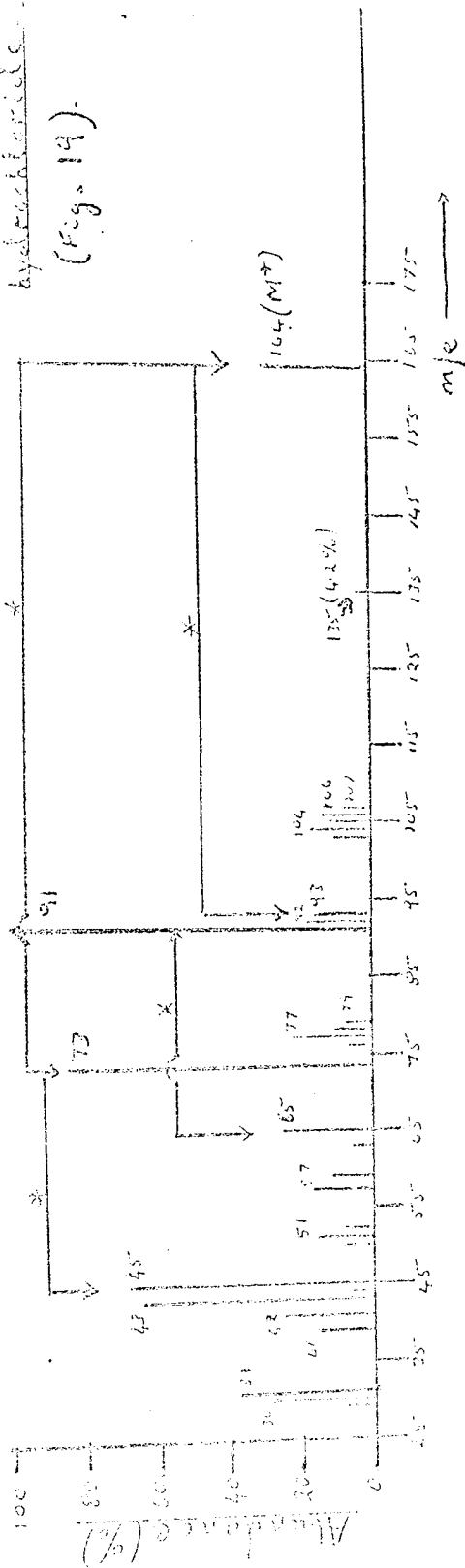
1-Benzyl-2-ethylhydrazine
hydrochloride

(Fig. 18)



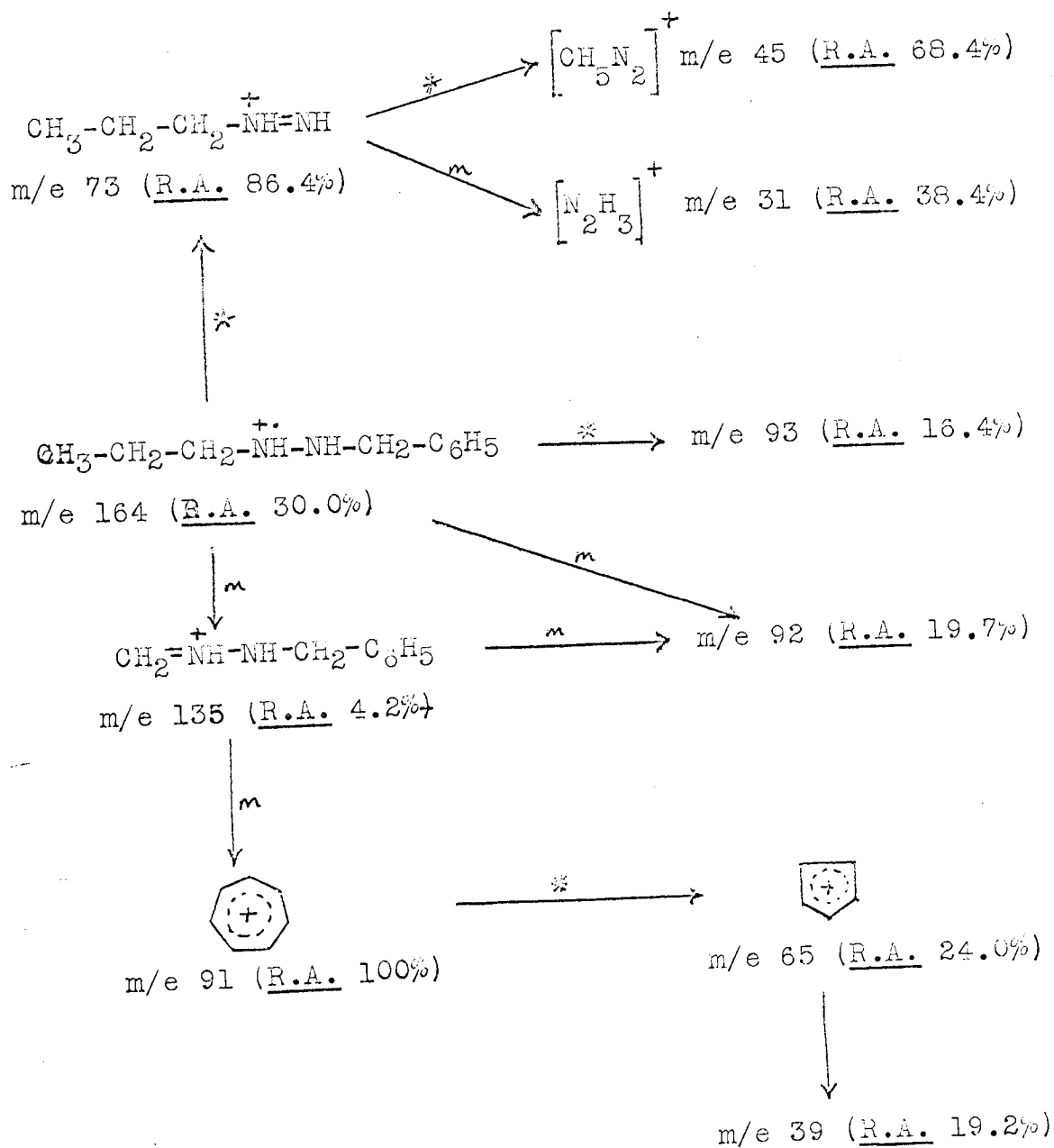
1-Benzyl-2-n-propylhydrazine
hydrochloride

(Fig. 19)



Scheme 2.

Fragmentation of 1-benzyl 2-n-propylhydrazine
hydrochloride.



d) Heterolysis of the C-N⁺ bond.

Heterolysis of the C-N⁺ bond of structure (I) has been observed in derivatives in which this process gives a reasonably stable carbonium ion :-

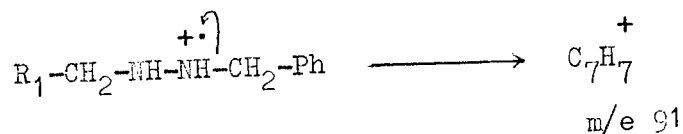


ie. for R=Prⁱ:- m/e 43 (R.A. 60.1%)

R=Bu^t:- m/e 57 (R.A. 100.0%)

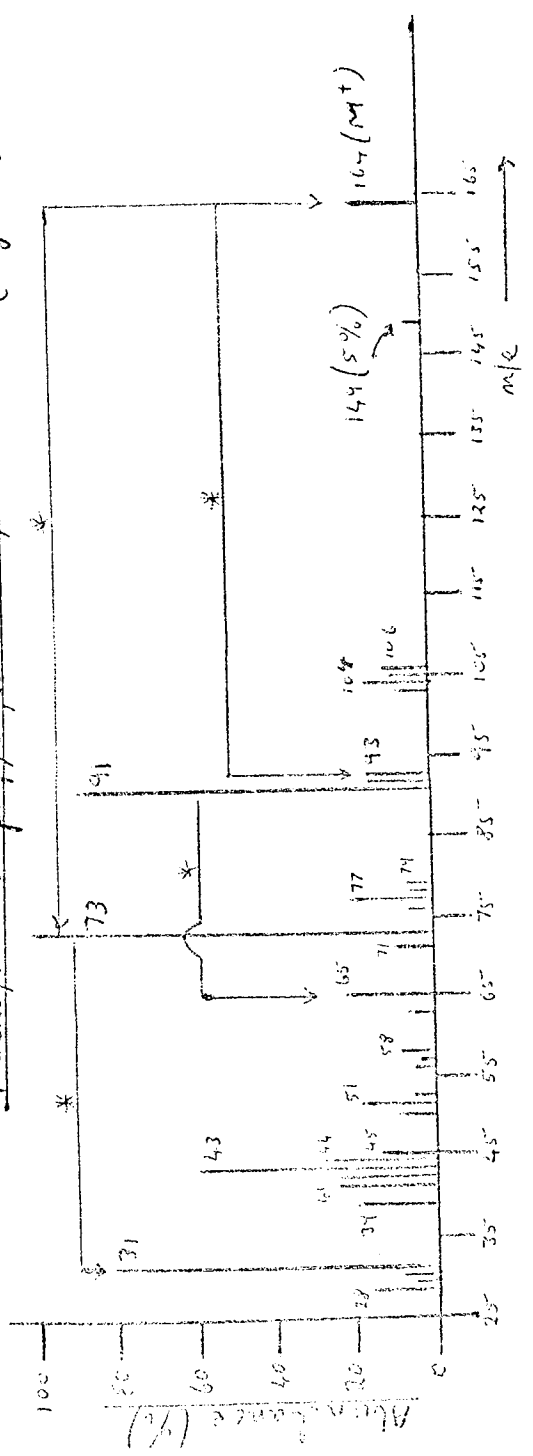
R=Ph-CH₂:- m/e 91 (R.A. 100.0%)

Charge localization in the molecular ion in the manner shown in structure (II) would be expected to lead to an intense tropylium ion peak (m/e 91) by heterolysis of the C-N⁺ bond :-

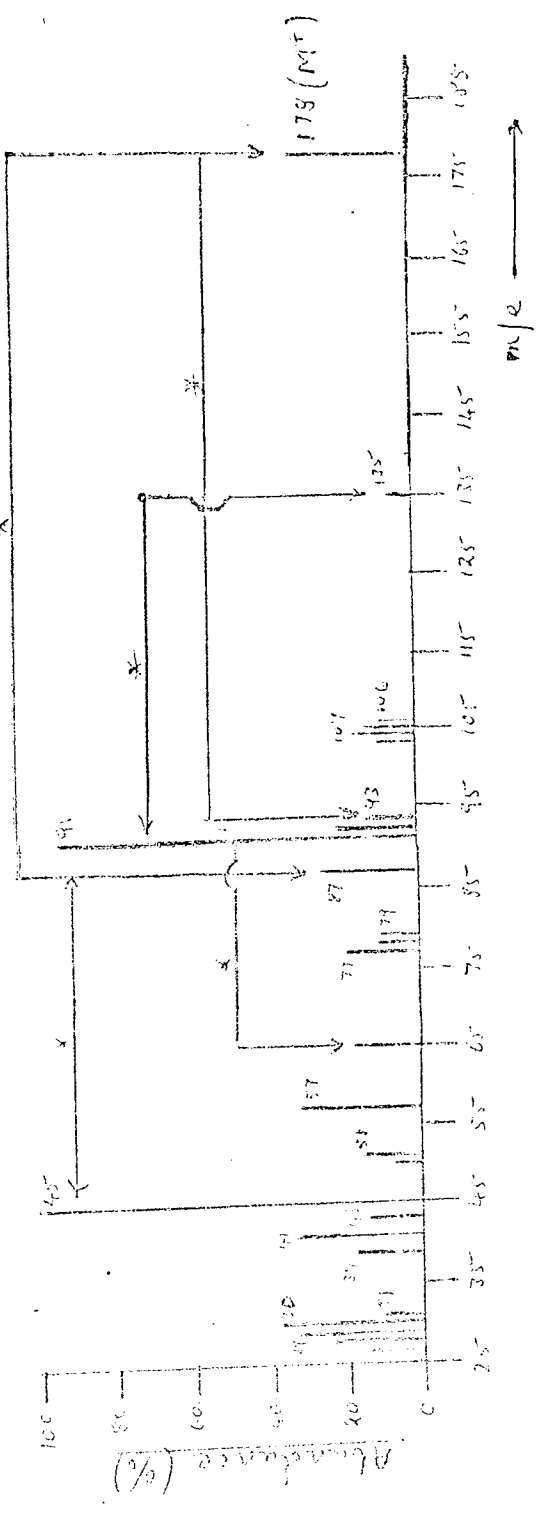


All the spectra show intense m/e 91 peaks, but only in 1,2-dibenzylhydrazine (Scheme 3) and 1-benzyl 2-n-butylhydrazine does metastable-defocusing indicate the molecular ion as the source of the tropylium ion. The non-observance of a metastable peak does not necessarily indicate that the transition involved is not occurring. The general appearance of a metastable for the process $\text{M}^+ \rightarrow \text{R}_1\text{-CH}_2\text{-}\overset{+}{\text{NH-NH}}$, but not for $\text{M}^+ \rightarrow 91$, does, however, fit the pattern of fragmentation if the bulk of the parent ion is present in the form of structure (I).

1-Benzyl 2-iso-propylhydrazine hydrochloride (Fig. 20)



1-Benzyl 2-n-butylhydrazine hydrochloride (Fig. 21)



e) Further fragmentation of the α -cleavage products.

(i) The M-91 fragment:- $R-NH=NH^+$.

The M-91 fragment (m/e 45, 59, 73, 87 and 121 for the methyl, ethyl, propyl (n- and iso-), butyl (n- and tert-) and benzyl respectively) undergoes a variety of cleavages depending on the nature of the group R.

Thus accurate mass measurement and metastables are consistent with :-

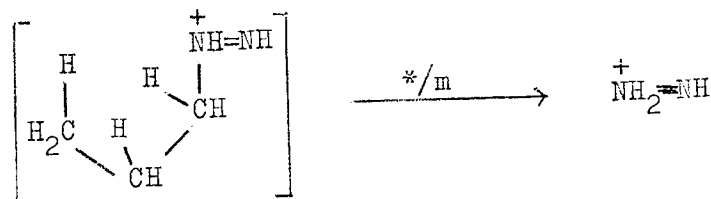
1) Rearrangement to $N_2H_3^+$ (m/e 31)

2) Rearrangement to $CH_5N_2^+$ (m/e 45)

and 3) Loss of di-imide

1) Rearrangement to $N_2H_3^+$

The M-91⁺ peak in the ethyl, n-propyl and iso-propyl derivatives rearranges to $N_2H_3^+$:-

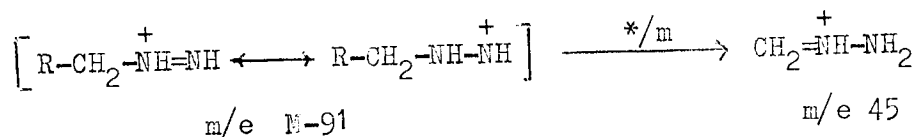


The m/e 31 peak has R.A. of 33.8%, 38.4% and 80.1% in Et-NH-NH-CH₂-Ph, Prⁿ-NH-NH-CH₂-Ph and Prⁱ-NH-NH-CH₂-Ph respectively. In the other derivatives competing reactions keep the m/e 31 peak below R.A. 5%.

2) Rearrangement to CH_5N_2^+

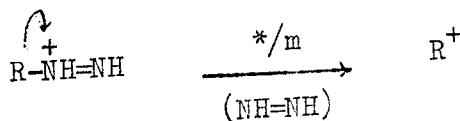
Rearrangement of the M-91⁺ peak to m/e 45 (CH_5N_2^+) is observed in the spectra of the n-propyl (m/e 68.4%) and n-butyl (R.A. 100%) derivatives. This rearrangement is probably best rationalized in terms of the alternative resonance structure for the M-91⁺ peak, i.e.

$\text{R-CH}_2\text{-NH-NH}^+$:-



The structures for m/e M-91 and m/e 45 are of course hypothetical, but they give a reasonable interpretation of the observed fragmentation modes.

A m/e 45 peak (R.A. 10.0%) occurs in the mass spectrum of 1-benzyl 2-ethylhydrazine, but the corresponding metastable is not observed. The change in the mode of rearrangement in changing from the ethyl, through the n-propyl, to the n-butyl derivative is rather surprising. Hydrogen transfer in even-electron ions usually occurs from the β , γ and δ positions with equal facility, with a smaller contribution from the α -position (approx. 10%).²²⁵

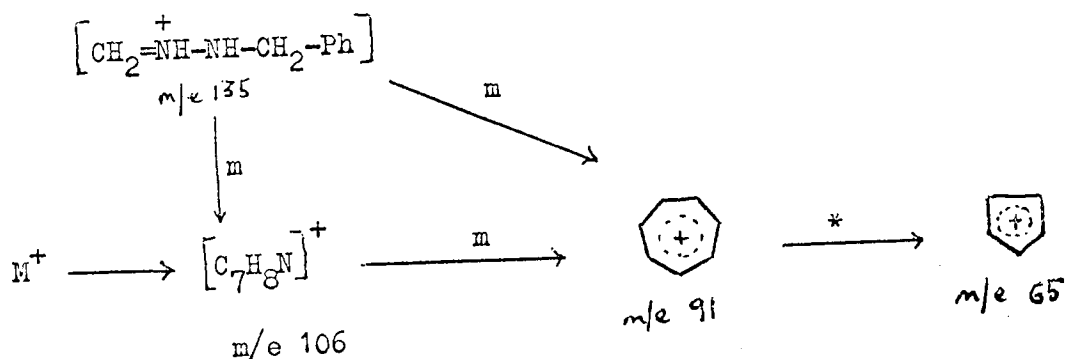
3) Loss of di-imide.

Loss of di-imide from the M-91 peak is observed in the iso-propyl, tert-butyl and benzyl derivatives, i.e. the derivatives capable of

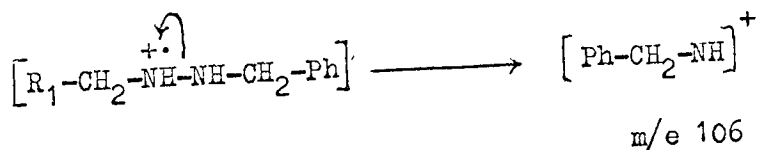
forming relatively stable carbonium ions.

(ii) The m/e 135 and corresponding peaks.

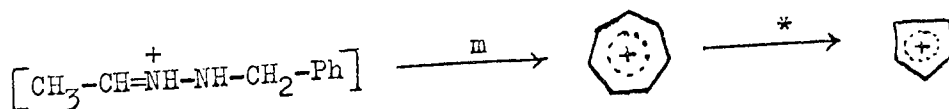
Metastable-defocusing indicates that the low abundance m/e 135 peak in the mass spectra of the straight chain alkyl hydrazines is both directly and indirectly a source of the tropylium ion :-



The formation of $\text{C}_7\text{H}_8\text{N}^+$ (m/e 106) from the parent ion is also consistent with charge localisation on the nitrogen adjacent to the alkyl group, i.e. by heterolysis of the N-N bond :-

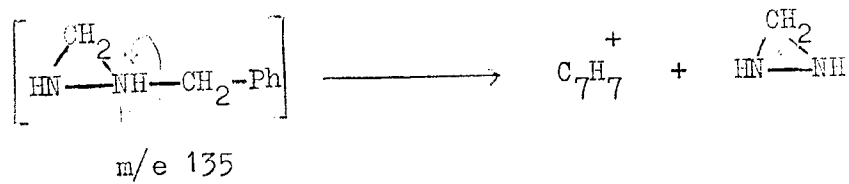


The corresponding α -cleavage products in 1-benzyl 2-iso-propylhydrazine :-

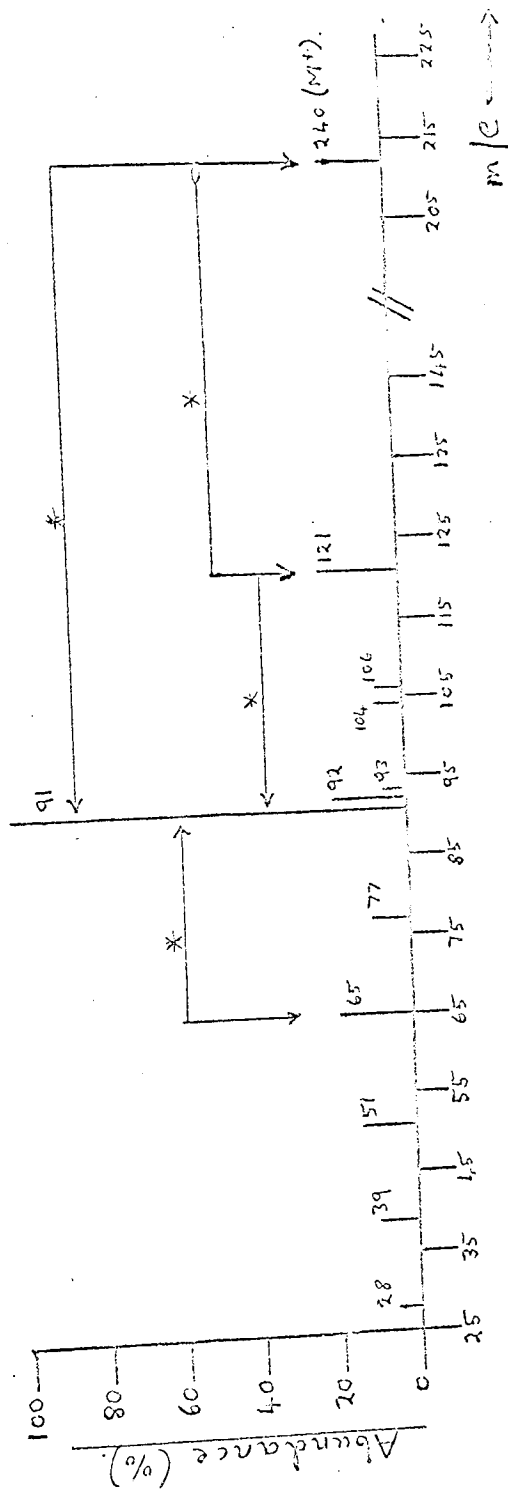


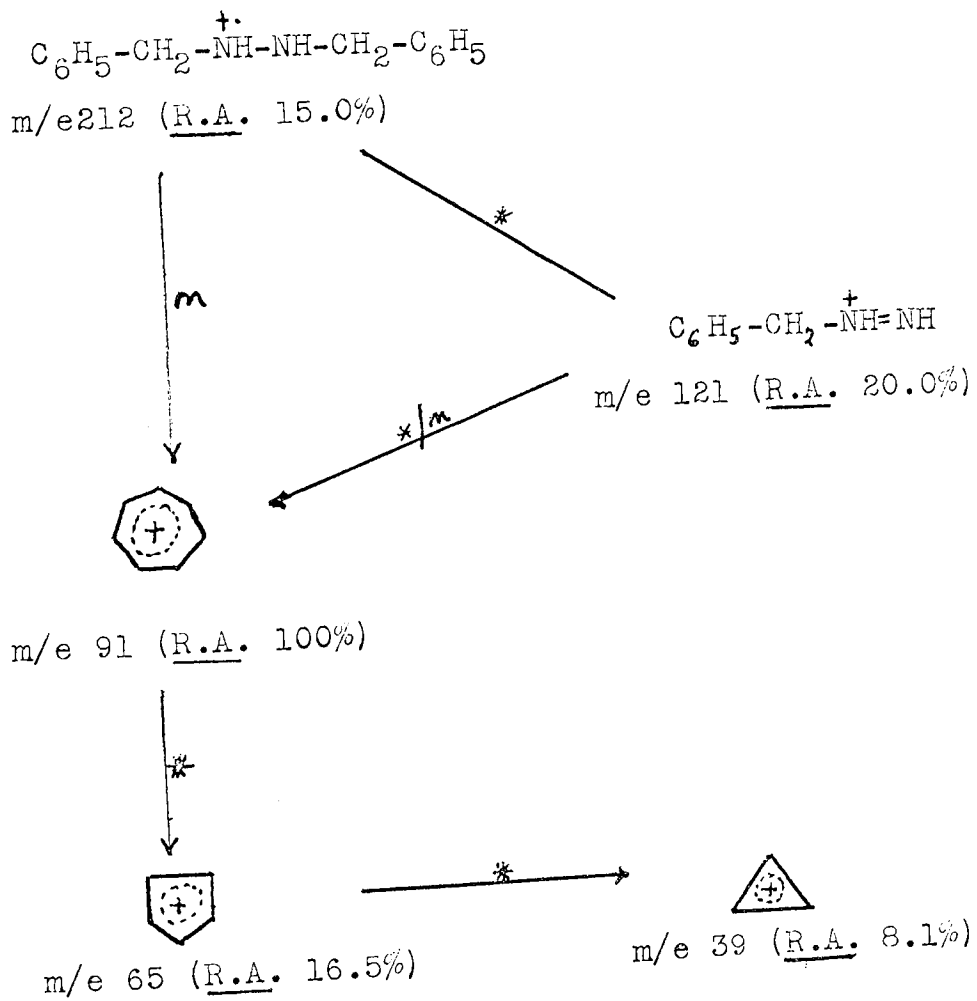
and 1-benzyl 2-tert-butyl-hydrazine (Scheme 4) also yield the tropylium ion.

The formation of tropylium from m/e 135 is best rationalized in terms of a cyclic structure i.e. -

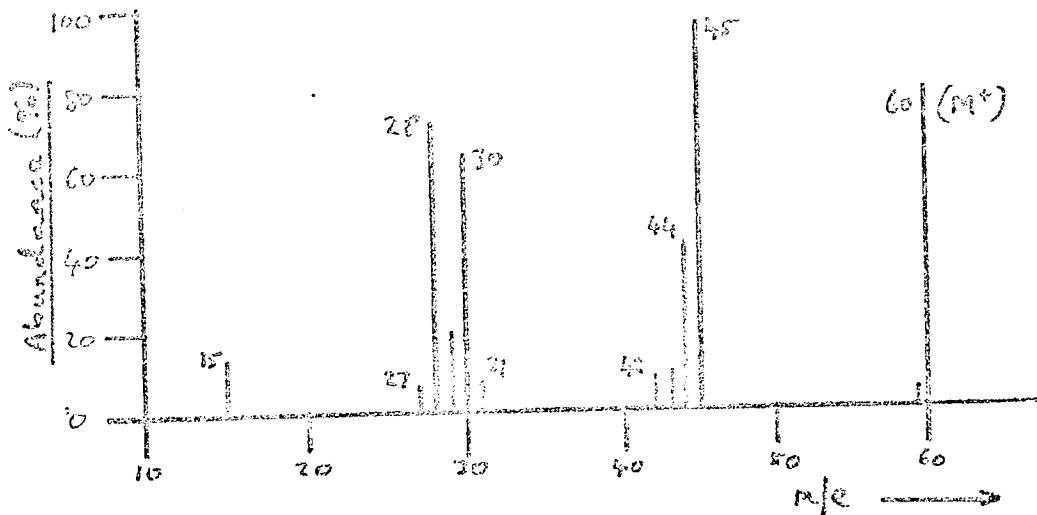


1,2-dibenzylhydrazine (Fig. 22)

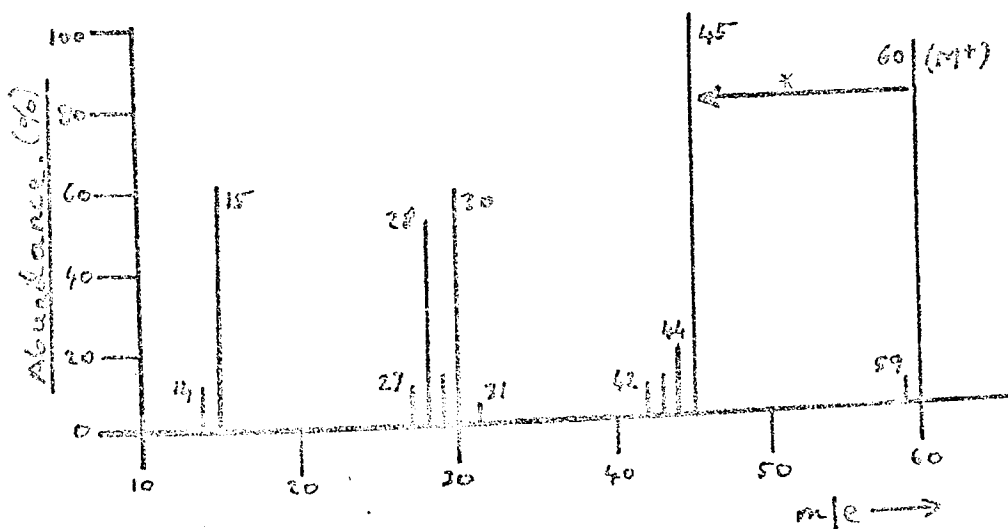


Scheme 3.Fragmentation of 1,2-dibenzylhydrazine
hydrochloride.

1,7-dimethylhydrazine
(Fig. 23)

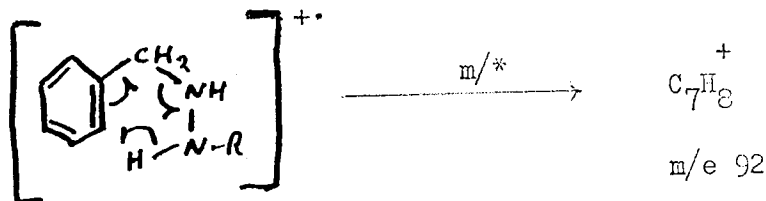


1,7-dimethylhydrazine dihydrochloride.
(Fig. 24).

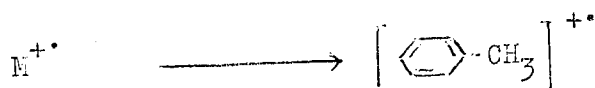


f) Rearrangement Processes.

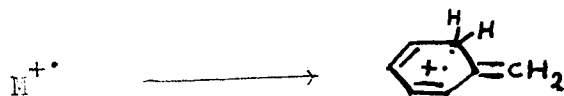
All the 1-benzyl 2-alkylhydrazine hydrochlorides give intense m/e 92 peaks ($C_7H_8^+$). Metastables and accurate mass measurement indicate that this is formed by rearrangement of the molecular ion :-



The $C_7H_8^+$ may be formed via a **four** membered ring :-



or via a six membered ring :-



The transition states are equally feasible.

In the straight chain derivatives metastable-defocusing indicates that the m/e 92 peak also arises by rearrangement of the m/e 135 peak.

The intensity of the m/e 93 peak suggests that it is not entirely due to isotopic ^{13}C and accurate mass measurement indicates that the major ion present is $C_7H_9^+$.

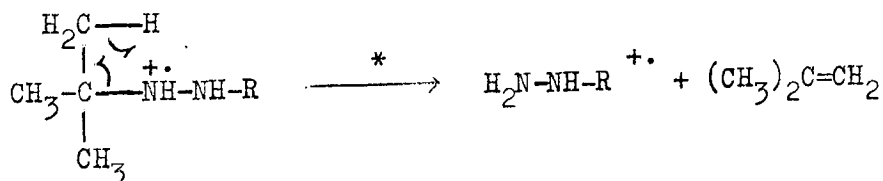
This apparently arises by a double-hydrogen rearrangement of the molecular ion :-



(* observed for R=Me, Et, Prⁿ, Prⁱ and Buⁿ)

As noted previously N-toluene-p-sulphonyl-N¹-acylhydrazines have been reported²¹⁴ to eliminate di-imide from the molecular ion. The 1,2-dialkylhydrazines do not give an analogous elimination. In all cases the M-30 peak was of R.A. < 5% and metastable-defocusing does not indicate this peak as a source of any of the intense peaks at lower m/e.

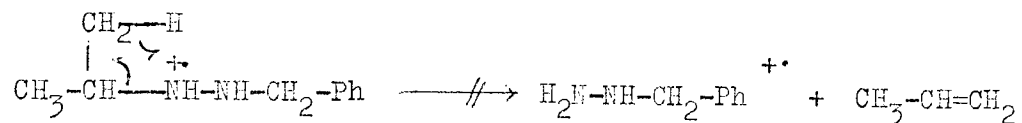
1-Benzyl 2-tert-butylhydrazine and 1-iso-propyl 2-tert-butylhydrazine show interesting rearrangements to 'benzylhydrazine' (C₇H₁₀N₂^{+•}) and 'iso-propylhydrazine' (C₃H₁₀N₂^{+•}) respectively. These rearrangements are best regarded as occurring via a four-membered transition state :-



R = Ph-CH₂-, Prⁱ ; see schemes 4 and 5.

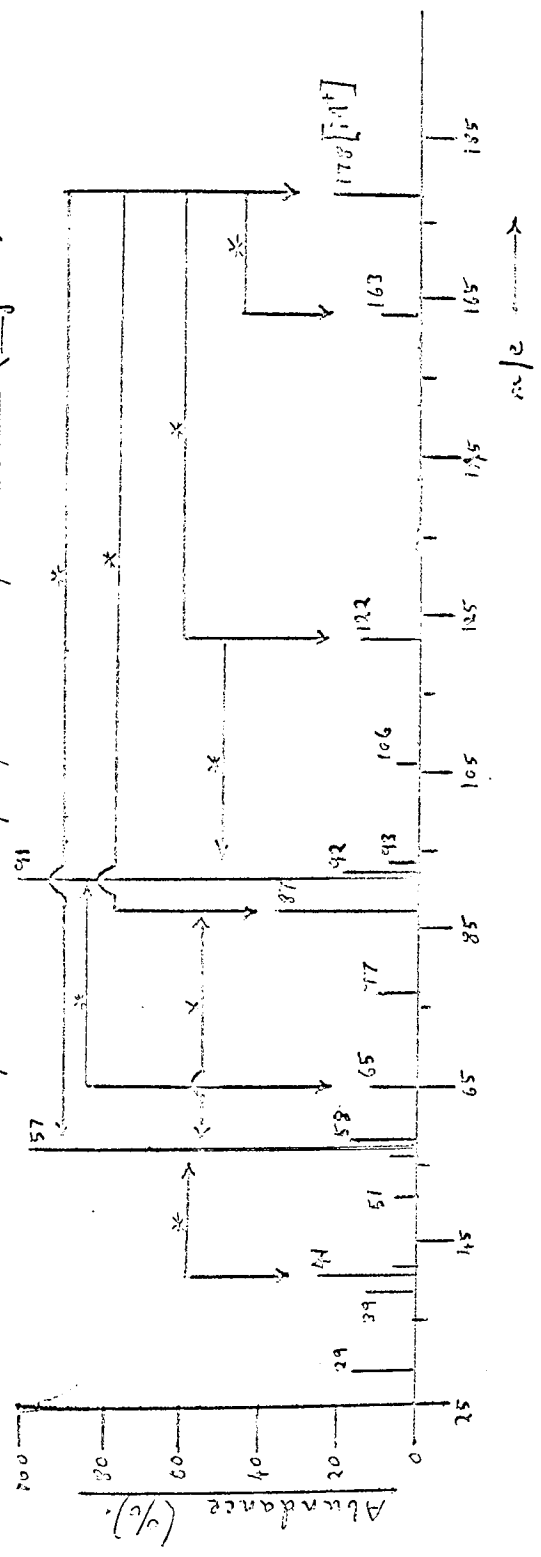
Mass spectral rearrangements proceeding via four-membered transition states are relatively uncommon.

It is interesting to note that the rearrangement only occurs for hydrazines carrying a tert-butyl group. A similar rearrangement is feasible for 1-benzyl 2-iso-propylhydrazine :-

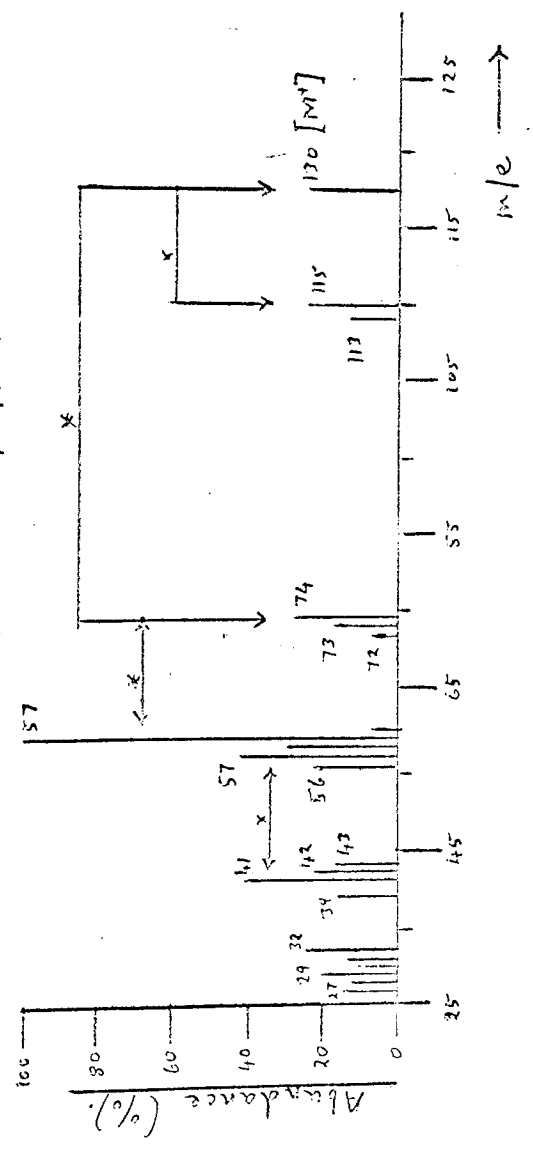


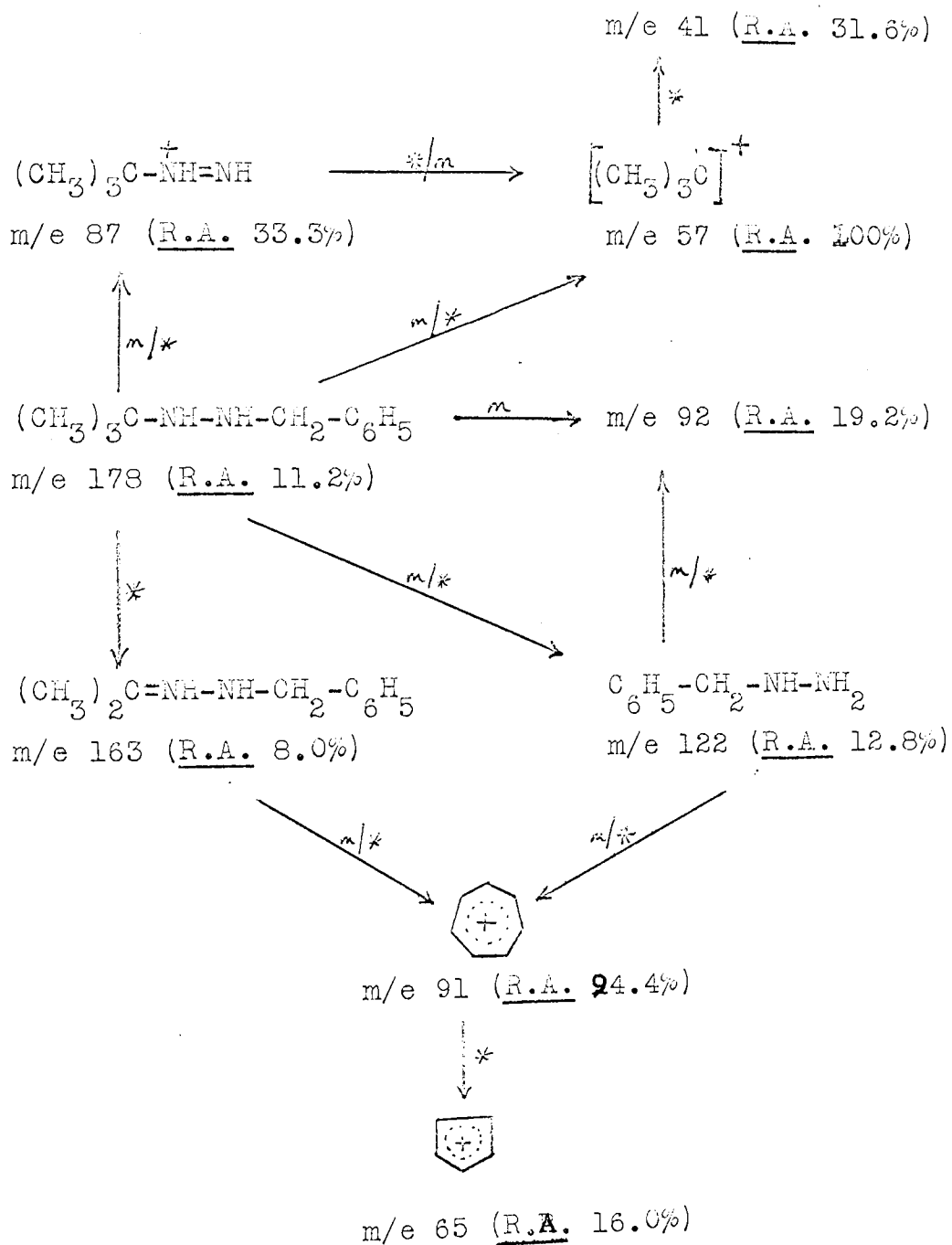
but does not occur. The situation is analogous to that in the monosubstituted hydrazines where the base peak in tert-butylhydrazine occurs at m/e 32 and arises by a four-membered transition state (page 79).

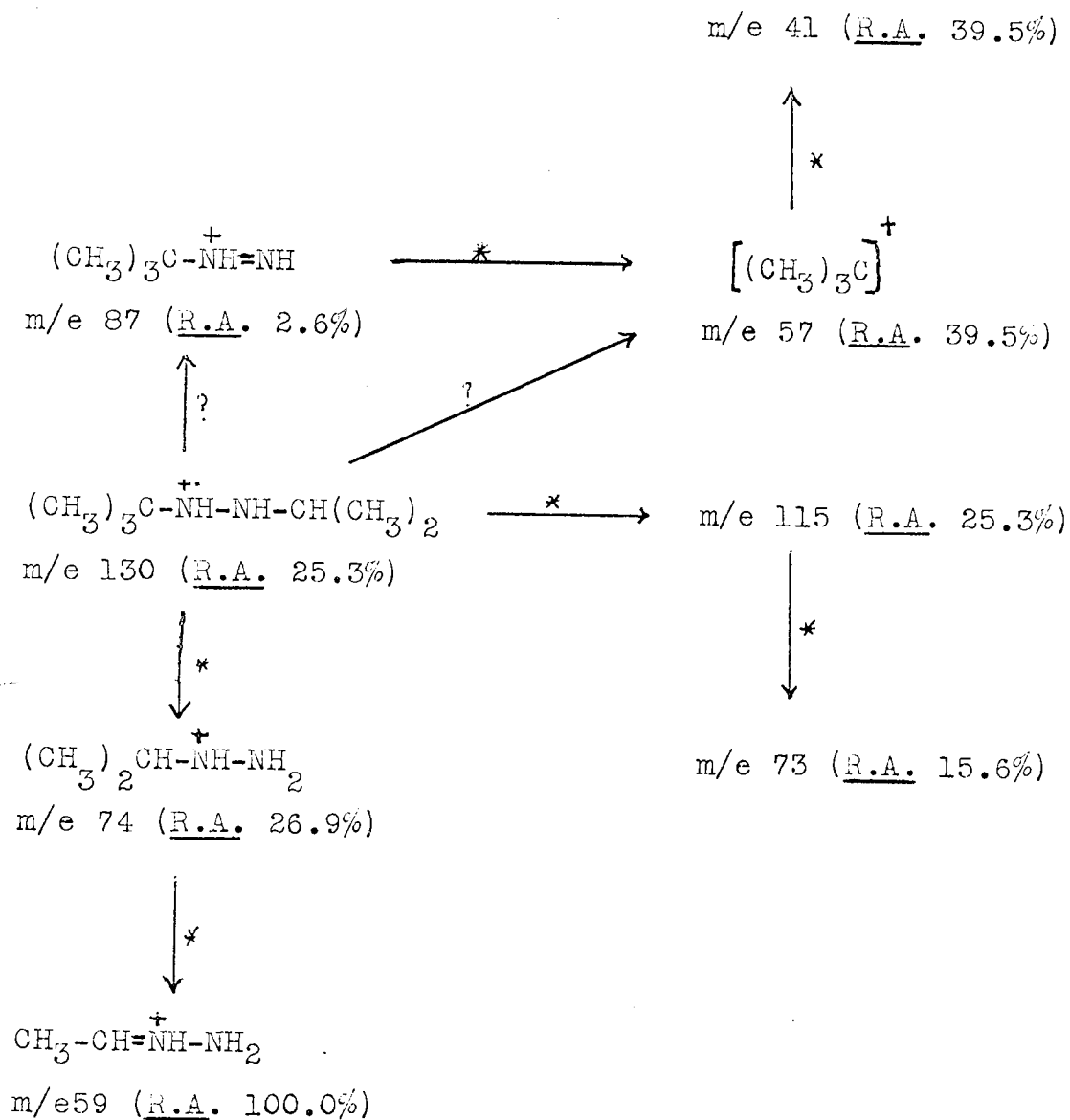
1-tert-butyl-2-cyanoethylhydrazine hydrochloride (Fig. 25).



1-tert-butyl-2-iso-propylhydrazine hydrochloride (Fig. 26).



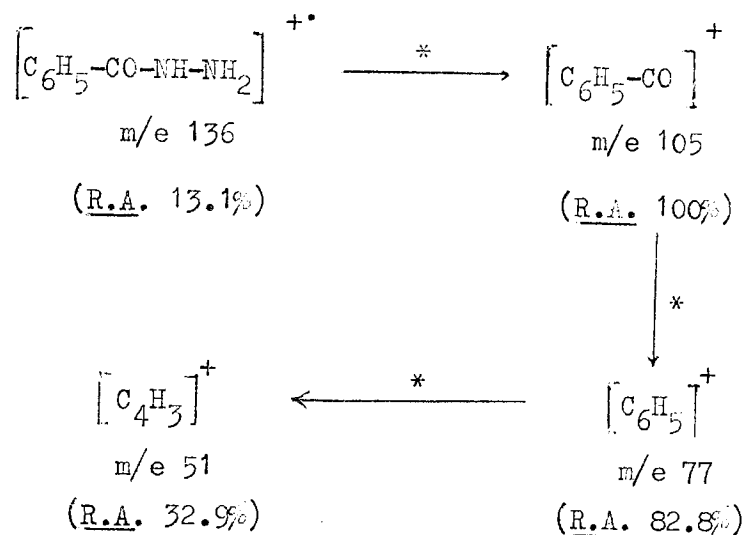
Scheme 4.Fragmentation of 1-benzyl 2-tert-butylhydrazine hydrochloride.

Scheme 5.Fragmentation of 1-tert-butyl 2-iso-propyl-
hydrazine hydrochloride.

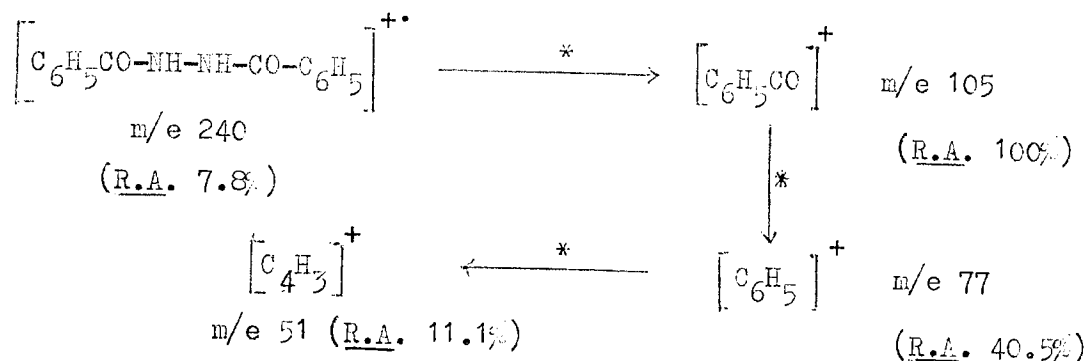
The mass spectra of 1-benzoyl 2-alkylhydrazines.

Four hydrazines containing the benzoyl group have been examined :- benzhydrazide (Fig. 27; page 111), 1,2-dibenzoylhydrazine (Fig. 28; page 111), 1-benzoyl 2-methylhydrazine (Fig. 29; page 112) and 1-benzoyl 2-tert-butylhydrazine (Fig. 30; page 112). The detailed fragmentations of 1-benzoyl 2-methylhydrazine and 1-benzoyl 2-tert-butylhydrazine are given in schemes 6 and 7 respectively, (pages 113 and 114).

The spectra of all the benzoyl hydrazines examined are dominated by an intense m/e 105 peak ($C_7H_7O^+$). In benzhydrazide the major fragments arise thus :-

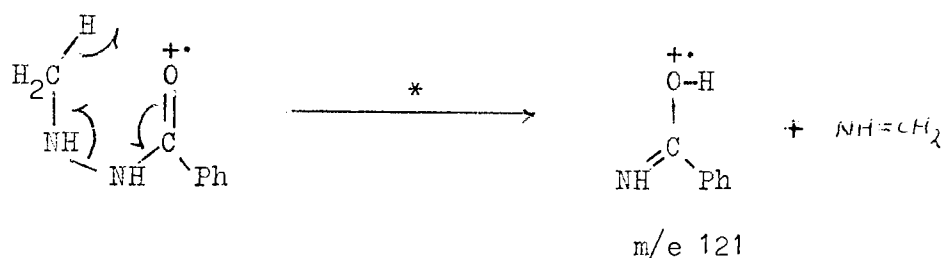


The major fragments in the spectrum of 1,2-dibenzoylhydrazine arise in an analogous manner :-

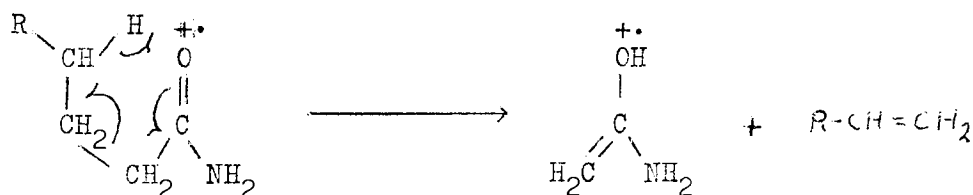


The introduction of an alkyl group on the terminal nitrogen of benzhydrazide causes an interesting change in the mode of formation of the base peak (m/e 105). Thus m/e 105 arises via a rearrangement product (see schemes 6 and 7).

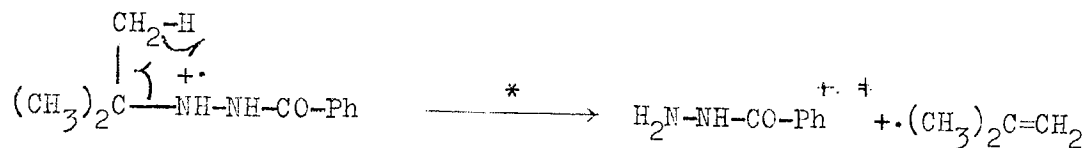
The rearrangement product, m/e 121, in 1-benzoyl 2-methylhydrazine presumably arises by a McLafferty rearrangement of the parent ion :-



The process is analogous to the formation of the base peak (m/e 59) in primary amides^{218,226} :-

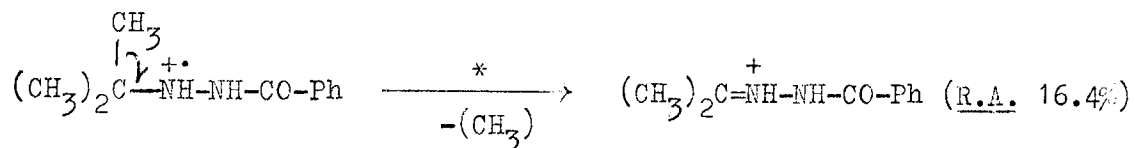


In the particular case of 1-benzoyl 2-tert-butylhydrazine the initial step is best written as a rearrangement to the nitrogen adjacent to the tert-butyl group :-

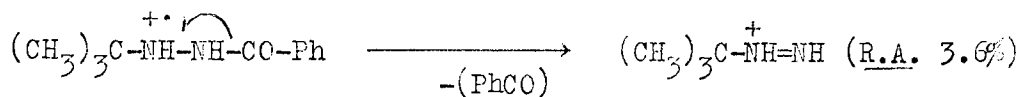


Such a rearrangement is analogous to the four-centre rearrangements already noted for tert-butylhydrazine (page 79) and the 1-alkyl 2-tert-butylhydrazines (page 103). The structure for the molecular ion of 1-benzoyl 2-tert-butylhydrazine in which the charge is localised on the nitrogen adjacent to the tert-butyl group can also be used to rationalise the various α -cleavage processes which are observed.

Thus α -cleavage of a methyl group :-

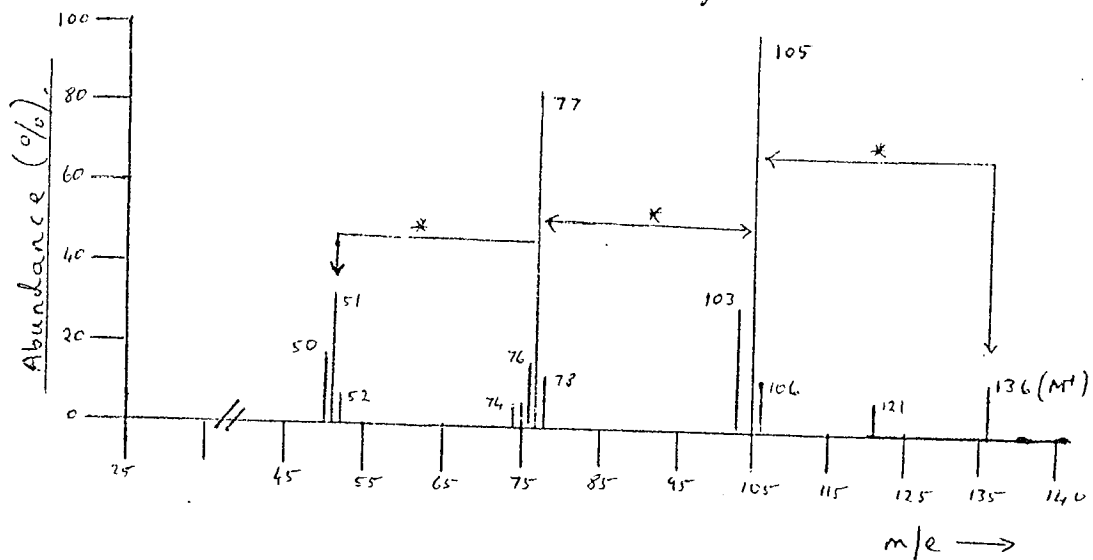


and of the benzoyl group :-

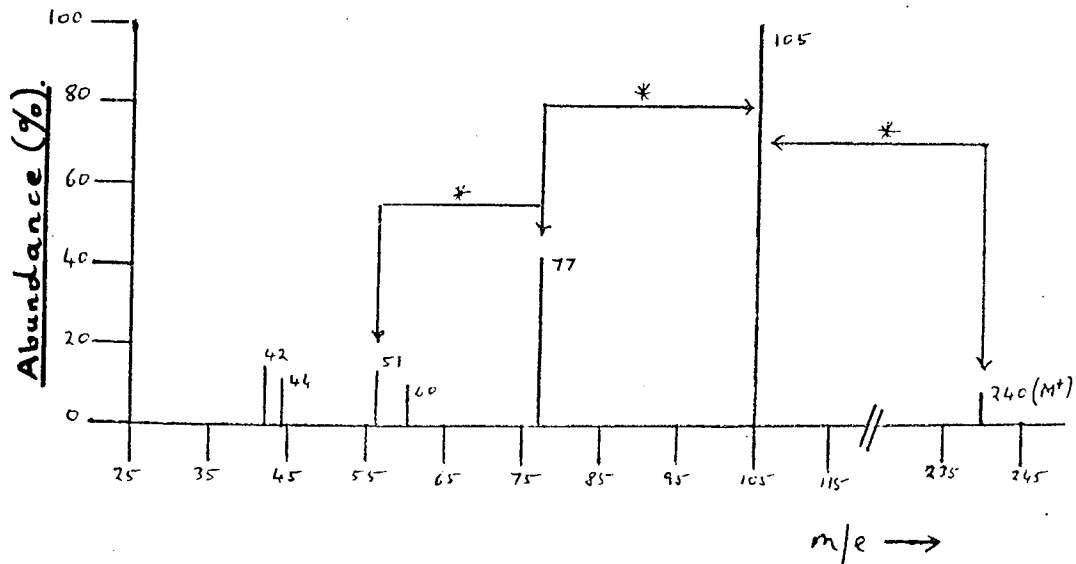


are also observed.

Benzhydrazide (Fig. 27).

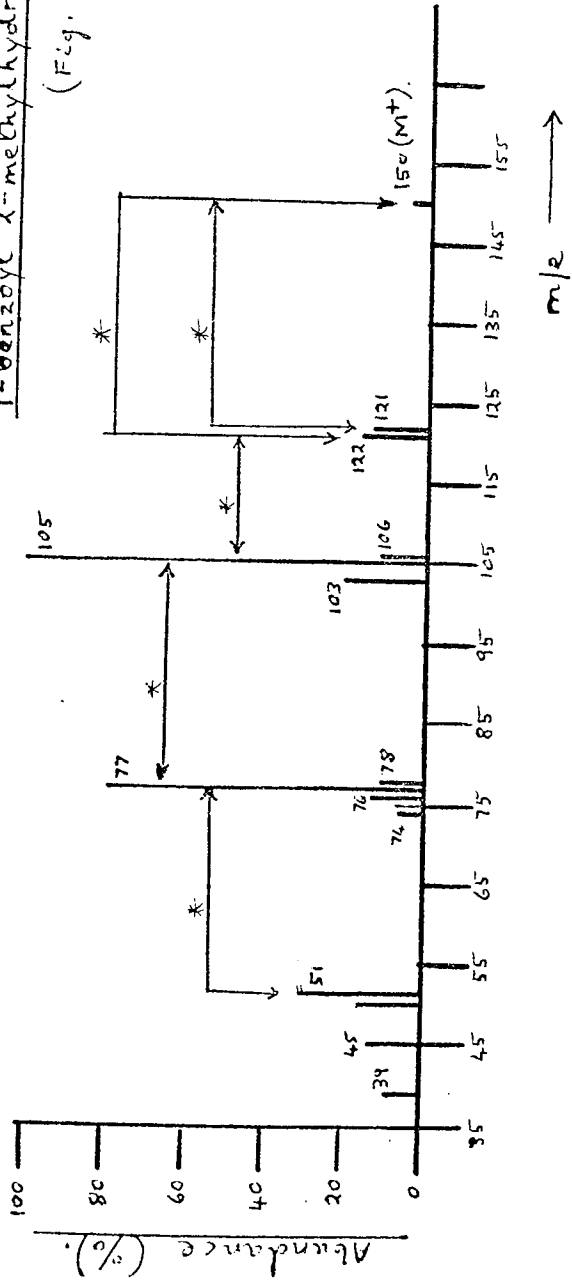


1,2-dibenzoylhydrazine (Fig. 28).

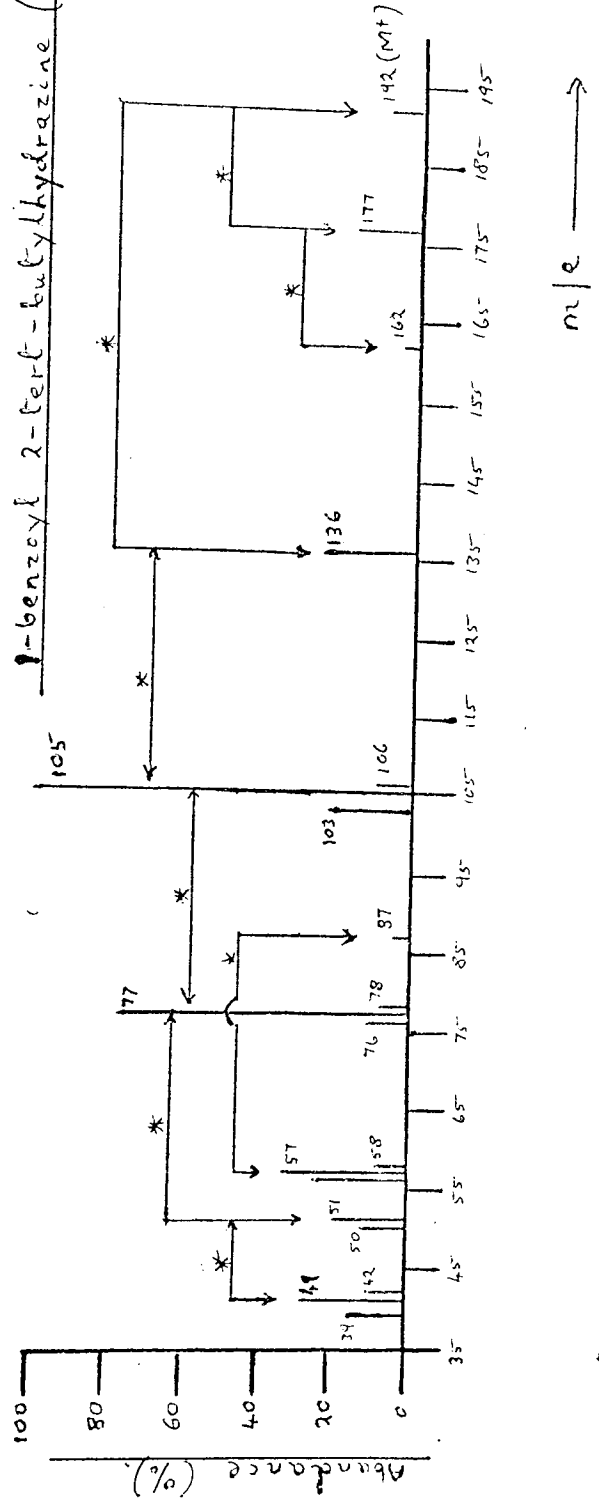


1-benzoyl 2-methylhydrazine.

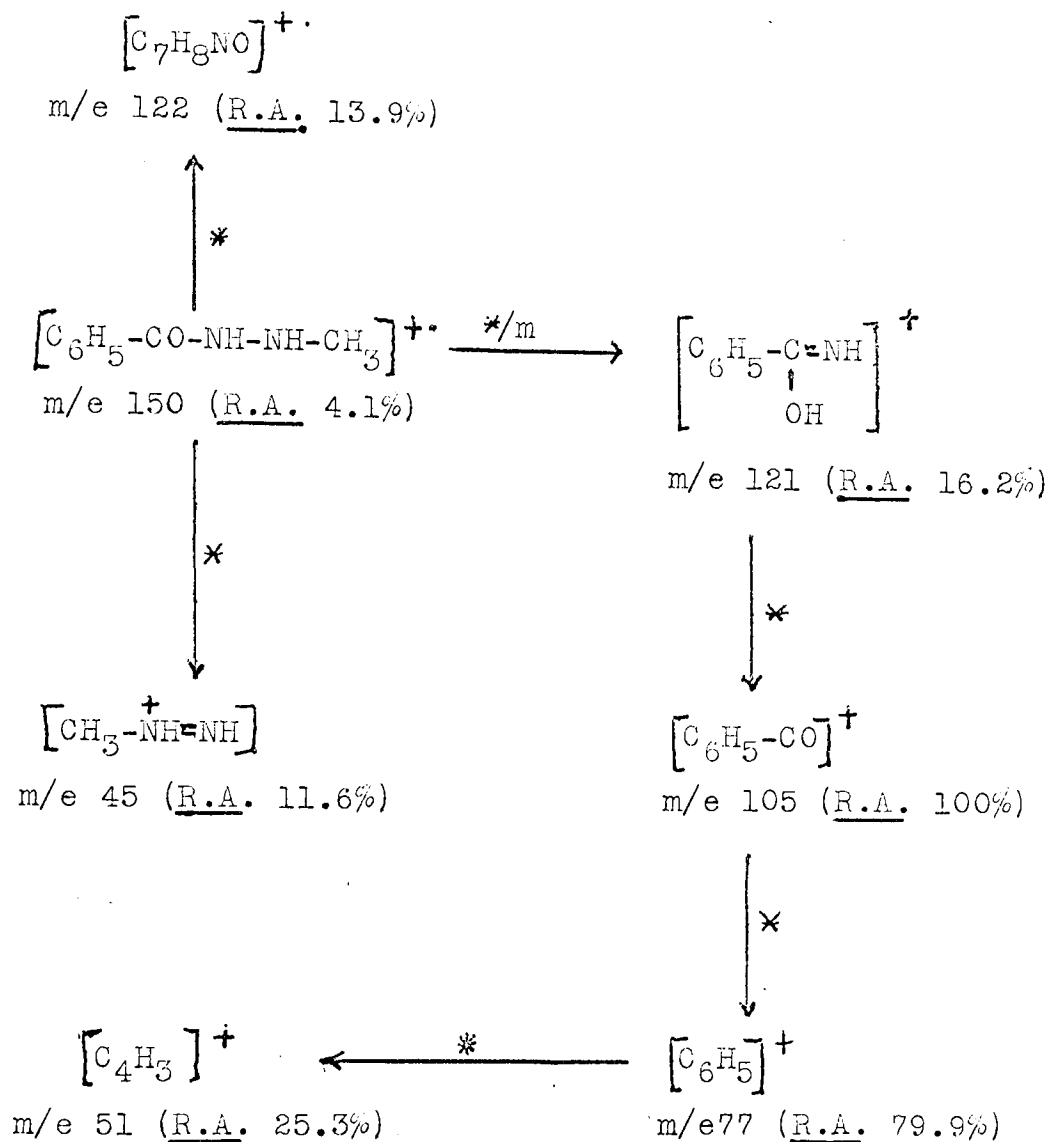
(Fig. 29).

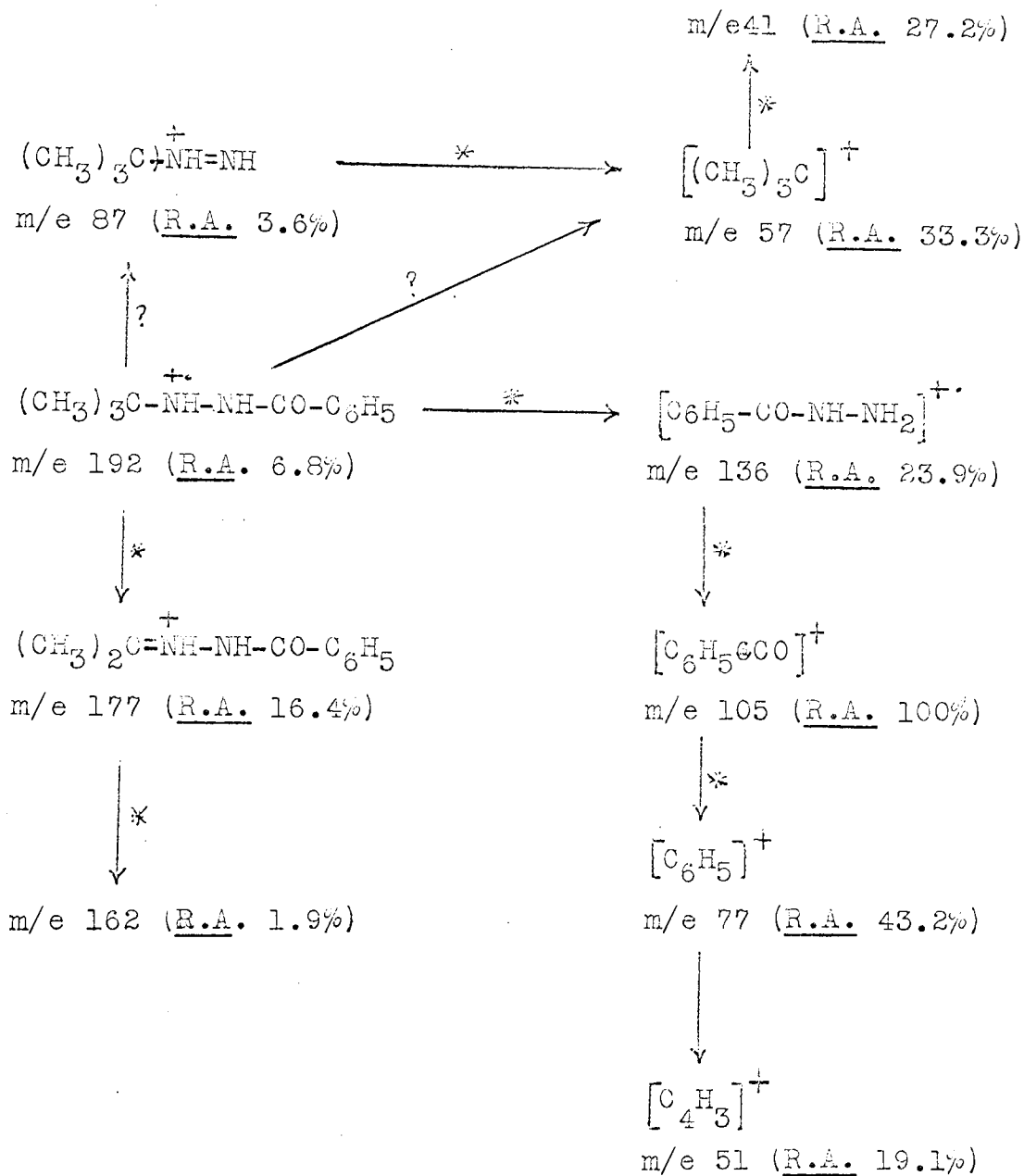


1-benzoyl 2-tert-butylhydrazine (Fig. 30).



Scheme 6.

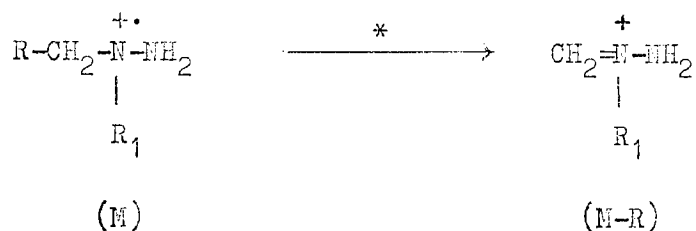
Fragmentation of 1-benzoyl 2-methylhydrazine.

Scheme 7.Fragmentation of 1-benzoyl 2-tert-butylhydrazine hydrochloride.

The mass spectra of some 1,1-disubstituted hydrazines.

The mass spectra of 1,1-dimethylhydrazine,²¹¹ 1,1-dimethylhydrazine oxalate, 1,1-diethylhydrazine oxalate and 1-benzyl 1-tert-butylhydrazine hydrochloride are shown in Figs. No. 31, 32, 33 and 34 respectively (pages 116 and 117).

No accurate mass measurements have been carried out on these materials, but some general conclusions concerning their fragmentation modes may be drawn. Thus all the compounds show intense peaks due to α' -cleavage :-

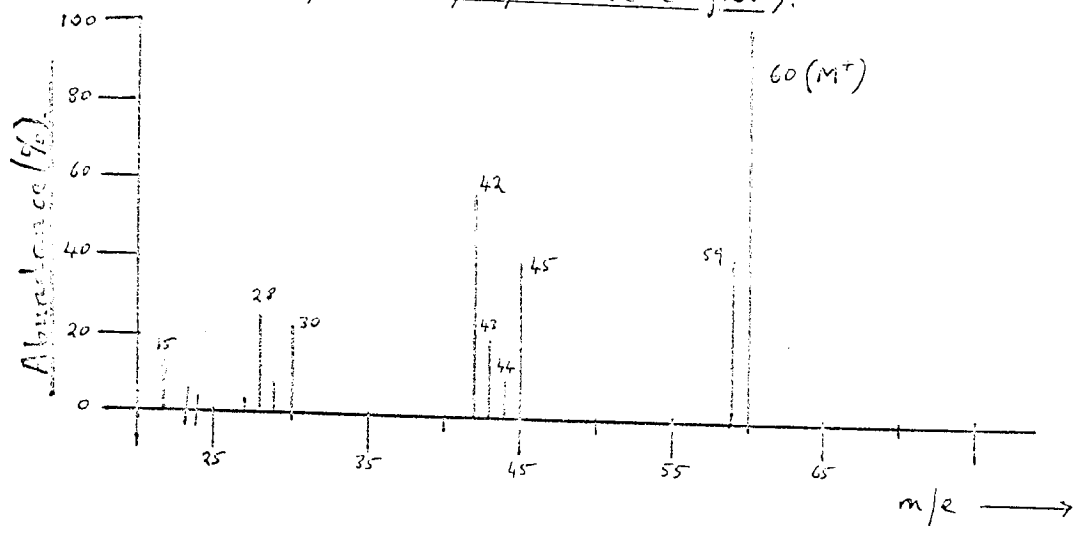


where R = Me and R₁ = H:- M-R₁ is R.A. 44.1%

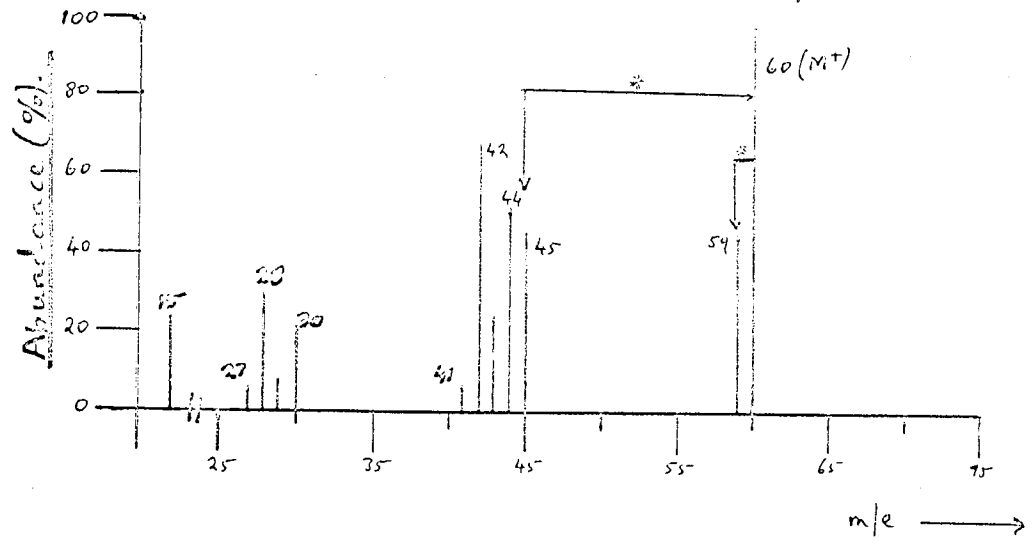
and where R = Et and R₁ = Me:- M-R₁ is R.A. 100.0%

In the particular case of 1-benzyl 1-tert-butylhydrazine the observation of a number of metastables in the spectrum enables the construction of a reasonable picture of the fragmentation processes occurring (scheme 8). It is interesting to note the overall similarity between the mass spectra of the isomeric benzyl, tert-butylhydrazines.

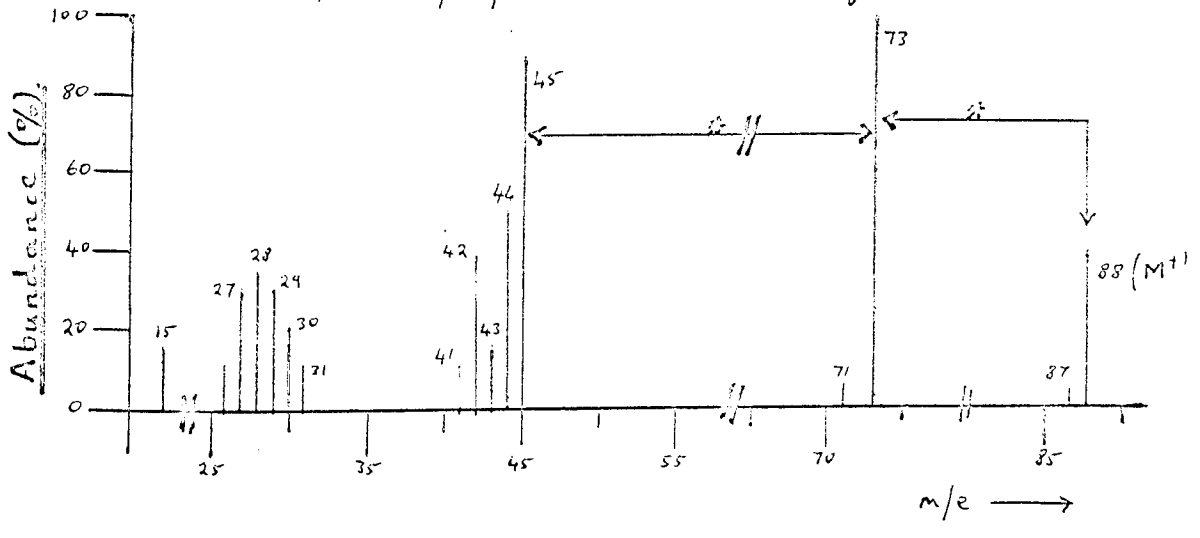
1,1-dimethylhydrazine (Fig. 31).



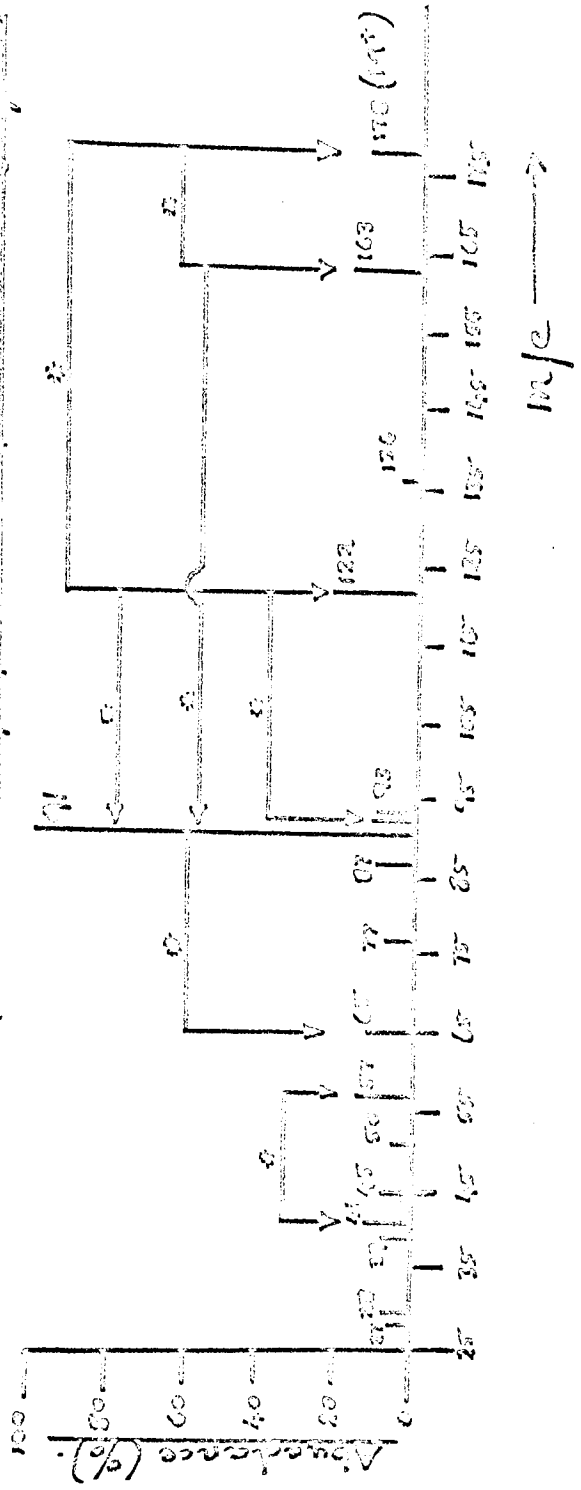
1,1-dimethylhydrazine oxalate (Fig. 32).

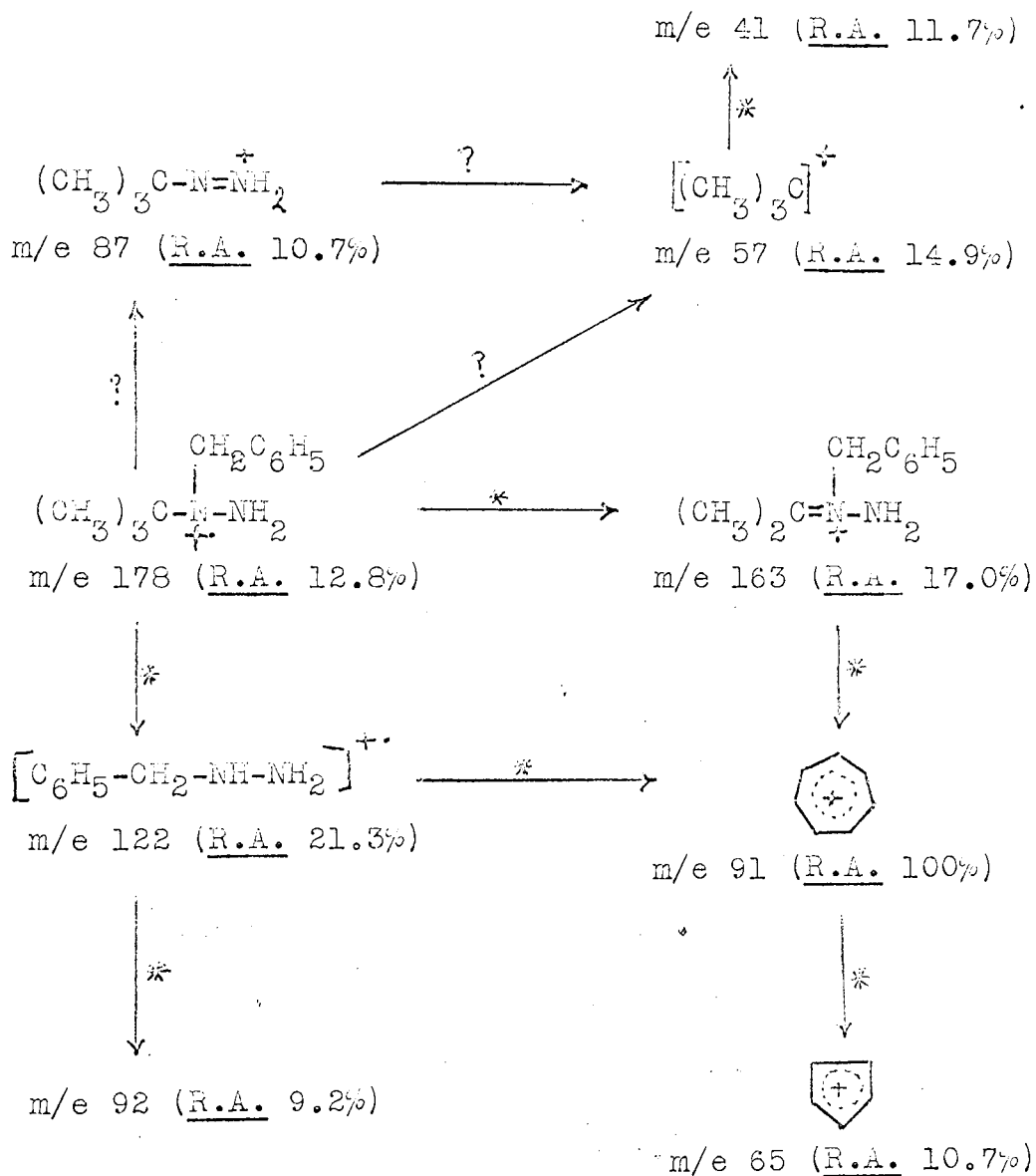


1,1-diethylhydrazine oxalate (Fig. 33).



1-Benzyl 1-tert-butylhydrazine hydrochloride (Fig. 31).



Scheme 8.Fragmentation of 1-benzyl 1-tert-butylhydrazine hydrochloride.

The mass spectrum of trisubstituted hydrazines.

The mass spectra of trimethylhydrazine,²¹² 1,1-dimethyl 2-iso-propylhydrazine hydrochloride and 1,1-dimethyl 2-n-butylhydrazine are shown in Figs. No. 35, 36 and 37 respectively (page 120).

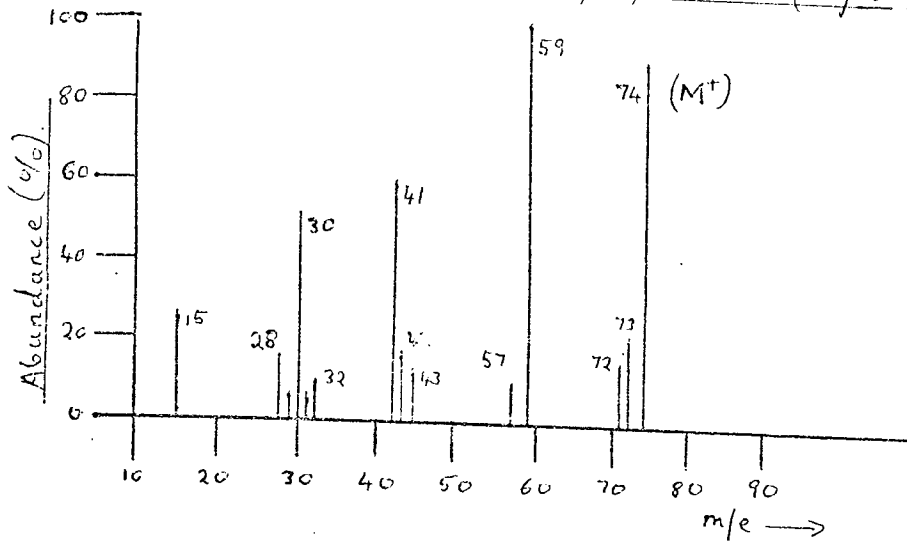
Detailed studies of these compounds have not been made, but the major fragmentation process again appears to be α -cleavage :-



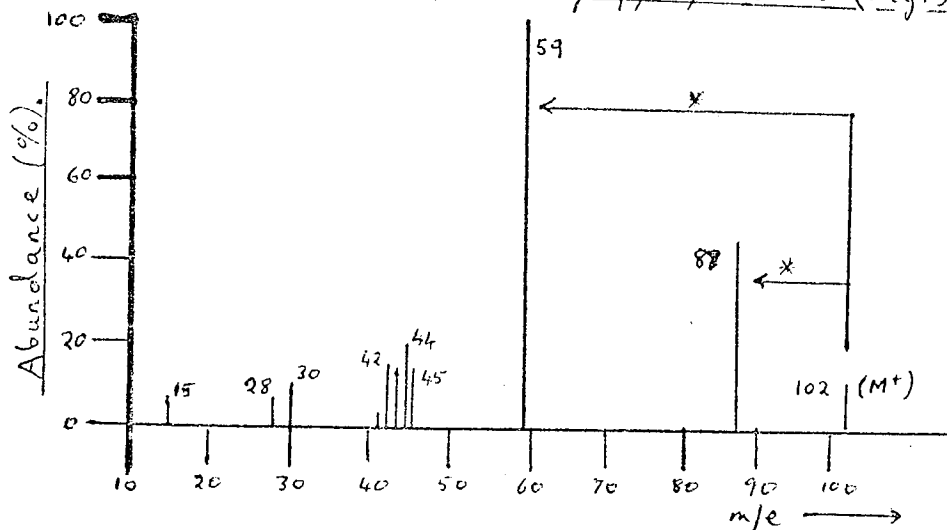
m/e 59 (100.0%)

Trimethylhydrazine (Fig. 35).

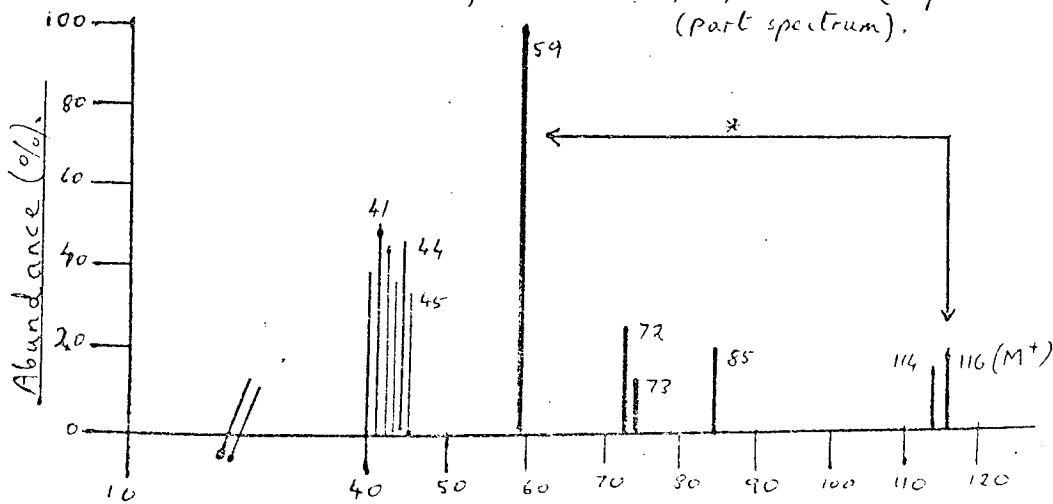
120



1,1-dimethyl-2-isopropylhydrazine (Fig. 36).



1,1-dimethyl-2-n-butylhydrazine (Fig. 37).
(part spectrum).



3) N.m.r. spectra.

The n.m.r. signals of the H-N group of hydrazines are characterised by great width and lack of fine structure.^{227, 228} This is caused by rapid exchange of the protons on the nitrogens, and/or by interference from the quadrupole moment of the nitrogen. In general we have not observed n.m.r. signals from the H-N-N moiety of the 1,2-disubstituted hydrazine hydrochlorides.

N.m.r. has proved, however, a powerful tool for the determination of the structures of alkyl components of the new hydrazines. τ -values for various groups in the series of 1-benzyl 2-alkylhydrazine hydrochlorides are recorded in Tables VII and VIII (page 122)

The new 1-tert-butyl 2-alkylhydrazines may be particularly useful for the synthesis of trisubstituted hydrazines showing restricted rotation about the N-N bond.

Table VII

τ -values for aromatic and benzylic protons in 1-benzyl 2-alkylhydrazine hydrochlorides (R-NH-NH-CH₂-Ph).

R.	Ph (τ)	Ph-CH ₂ -NH(τ)	Solvent
Me	2.28	5.55	D ₂ O
Me	3.51	5.49	T.F.A.
Et	2.44	5.74	D ₂ O
Et	3.51	5.52	T.F.A.
Pr ⁿ	2.42	5.72	D ₂ O
Pr ⁿ	3.51	5.43	T.F.A.
Pr ⁱ	2.43	5.75	D ₂ O
Pr ⁱ	3.54	5.60	T.F.A.
Bu ⁿ	2.54	5.84	D ₂ O
Bu ⁿ	2.56	5.56	T.F.A.
Bu ^t	2.54	5.64	T.F.A.
Ph-CH ₂	3.18	6.1	T.F.A.

Table VIII

τ -values for alkyl protons adjacent to nitrogen in 1-benzyl 2-alkylhydrazine hydrochlorides (R-NH-NH-CH₂-Ph).

R	τ	Solvent	Group
Me	7.0	D ₂ O	CH ₃ -NH
Me	6.83	T.F.A.	CH ₃ -NH
Et	<u>c.a.</u> 6.2	D ₂ O	CH ₂ -NH
Et	<u>c.a.</u> 6.54	T.F.A.	CH ₂ -NH
Pr ⁿ	<u>c.a.</u> 6.8	D ₂ O	CH ₂ -NH
Pr ⁿ	<u>c.a.</u> 6.6	T.F.A.	CH ₂ -NH
Bu ⁿ	<u>c.a.</u> 6.75	D ₂ O	CH ₂ -NH
Bu ⁿ	<u>c.a.</u> 6.55	T.F.A.	CH ₂ -NH
Pr ⁱ	<u>c.a.</u> 6.45	D ₂ O	(CH ₃) ₂ CH-NH
Pr ⁱ	<u>c.a.</u> 6.20	T.F.A.	(CH ₃) ₂ CH-NH
Bu ^t	8.51	T.F.A.	Bu ^t

EXPERIMENTAL

Preamble

Melting points were determined on a Kofler Hot-stage apparatus. Physical constants quoted as "lit.", without qualification are from the "Dictionary of Organic Compounds"²²⁹ and the "Handbook of Chemistry and Physics".²³⁰ All melting and boiling points are quoted in °C.

N.m.r. were determined on Varian A60, Perkin-Elmer R.10 and Perkin-Elmer R.14 instruments, i.r. spectra on a Perkin-Elmer 237 spectrometer and mass spectra on an A.E.I. MS9.

I.r. assignments are based on the texts of Bellamy,²⁰⁵ Rao²⁰⁶ and Nakanishi²³¹ and for n.m.r. Jackman²³² and Mathieson.²³³ Where spectral data for specific compounds are available appropriate references are given.

Microanalyses were performed by Dr. F. B. Strauss, Oxford, and Mrs. B. Taylor, Chemistry Department, University of Aston.

Commercially available compounds.

Samples of the following compounds, for synthetic and/or spectral studies, were obtained by redistillation, or recrystallization, of laboratory reagents:- Methylhydrazine, b.p. 88-90°/760 mm. Hg (lit. 87°/745 mm. Hg); ethylhydrazine oxalate (EtOH), m.p. 169-170° (lit.⁶⁰ 170-171°); n-propylhydrazine oxalate (EtOH), m.p. 174-176° (lit.⁶⁰ 175°); iso-propylhydrazine oxalate (EtOH), m.p. 170-172° (lit.⁶⁰ 172°); n-butylhydrazine oxalate (EtOH), m.p. 164-165° (lit.⁶⁰ 165°);

phenylhydrazine b.p. 271-273° (lit. 273°); phenylhydrazine hydrochloride (EtOH), m.p. 239-241° (lit. 240°); para-nitro-phenylhydrazine (EtOH), m.p. 159-160° decomp. (lit. 159° decomp.); 2,4-dinitro-phenylhydrazine (EtOH), m.p. 194-196° (lit. 194°); benzhydrazide (EtOH), m.p. 111-112° (lit. 112°); 1,1-dimethylhydrazine b.p. 62-63° (lit. 63°).

Mono-hydrazine hydrochlorides, for mass spectral studies, were prepared by passing dry HCl gas into an ethereal solution of the free base.

1. 1,2-dibenzoylhydrazine.

1,2-dibenzoylhydrazine was prepared according to the method described by Hatt.⁴²

Recrystallization of the crude product ($\text{CH}_3\text{CO}_2\text{H}$) gave 1,2-dibenzoylhydrazine (85.0g; 70%); m.p. 240-241° (lit. 241°); M^+ found 240.0899 calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$ 240.0902; (Found C 69.60 H 5.03 N 11.70, $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_2$ requires C 69.97 H 5.03 N 11.67%) i.r. maxima (KBr) 3210s (NH) 1640s (C=O); n.m.r. (T.F.A.) τ c.a. 2.3 (m, ArH).

2. Reduction of 1,2-dibenzoylhydrazine with lithium aluminium hydride.

The aluminate (4 g.) was added, in small portions, to a cold suspension of 1,2-dibenzoylhydrazine in dry diglyme and the mixture refluxed for :-

a) 24 hrs. and 18 hrs., b) 9 hrs.

2.a) Excess lithium aluminium hydride was destroyed by the careful addition of water and the solution evaporated to dryness. Treatment of the solid with acid (pH.4) left a residue of inorganic salts which were removed by filtration. Addition of solid sodium hydroxide to the filtrate,

extraction with benzene, drying, (MgSO_4) of the extracts and saturation with dry HCl gas gave a white solid. This was shown to be identical (m.p. and mixed m.p. of benzoyl derivative; i.r. and n.m.r.) with benzylamine hydrochloride. (Yield 2-10%; see Table I).

2.b) Excess lithium aluminium hydride destroyed (H_2O) and the solution evaporated to dryness. Recrystallization (EtOH) gave benzaldehyde benzoylhydrazone; m.p. 205-207° (lit.²³⁴ 206°); mixed m.p.; (Found C 74.59 H 5.31 N 12.52, $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$ requires C 74.97 H 5.40 N 12.51%), i.r. maxima (KBr) 3200s (NH) 3020 (aromatic) 1640s (C=O) 1605s, 1550s, 760s 590s (aromatic) cm.^{-1} ; n.m.r. (T.F.A.) τ c.a. 0.8 (1H, s, CH=N) τ ca. 2.0 (5H, m, ArH).

3. Attempted reduction of 1,2-dibenzoylhydrazine with diborane.

Diborane¹⁸¹ (1.0 g.) was flushed with nitrogen into a well stirred suspension of 1,2-dibenzoylhydrazine (3.0g) in diglyme (200 ml.). The solid dissolved, but saturation with dry HCl gas gave only 1,2-dibenzoylhydrazine (2.5 g; 83% recovery).

4.a) Benzaldehyde methylhydrazone.²³⁵

Benzaldehyde (11.4 g) and acetic acid (2-3 drops) were added dropwise to a refluxing solution of methylhydrazine (5.1 g) in ethanol (50 ml.). After refluxing for 30 mins. the ethanol was removed under reduced pressure and the solution cooled. Ether was added (to increase the volume) and the solution dried (MgSO_4). Removal of the ether and

fractional distillation gave benzaldehyde methylhydrazone (6.0 g; 43.0%); b.p. 130-133°/18 mm. Hg., (lit.²³⁵ 131-134°/20 mm. Hg.).

4.b) Benzaldehyde methylhydrazone hydrochloride.

Passage of dry HCl gas into a cooled solution of benzaldehyde methylhydrazone gave benzaldehyde methylhydrazone hydrochloride.

Recrystallized (EtOH) sample had m.p. 175-177°; M^+ 134; i.r. maxima 3020 m, 760 s, 700 s (aromatic) cm.^{-1} ; n.m.r. (T.F.A.) τ 1.05 (H, s, $\text{CH}=\text{N}$) τ 1.2 (H, s, $\text{CH}=\text{N}$ isomer) τ c.a. 2.3 (m, ArH) τ 5.7 (s, CH_2-N) τ 6.95 (s, CH_2-N isomer).

5. Attempted hydrogenation of benzaldehyde methylhydrazone.

The hydrogenation at atmospheric pressure of benzaldehyde methylhydrazone over PtO_2 , in ethanol, resulted in the uptake of 1.05 equivalents of hydrogen after reduction of the catalyst. The catalyst was filtered off under a nitrogen atmosphere and the resulting filtrate freeze-dried for 24 hrs. This gave a yellow viscous oil which was taken up in dry ether and treated with dry HCl gas. A white precipitate was formed. Spectral data (i.r. and n.m.r.) indicated that this was mainly benzaldehyde methylhydrazone hydrochloride.

6. Reduction of benzaldehyde methylhydrazone with lithium

aluminium hydride.

The aluminate (5.0 g.) was added in small portions to a cold solution of benzaldehyde methylhydrazone (4.0 g.) in dry diglyme (150 ml.) and then refluxed for 18 hrs.

After reflux the solution was cooled, the excess hydride destroyed by the careful addition of water and the solution evaporated to dryness. Addition of sodium hydroxide to the filtrate, extraction with benzene, drying (H_2SO_4) of the extract and saturation with dry HCl gas gave a white solid. This was identical (m.p. and mixed m.p. of benzoyl derivative; i.r. and n.m.r.) with benzylamine hydrochloride (37.5% yield).

The reduction was repeated using 90 and 30 minute reflux times. Benzylamine hydrochloride, and benzaldehyde methylhydrazone hydrochloride were the only products isolated.

7. Reduction of benzaldehyde methylhydrazone with diborane.

Diborane (0.7 g.) was passed into a solution of benzaldehyde methylhydrazone (3.1 g.) in dry diglyme (150 ml.) at ambient temperature. Saturation of the solution with dry HCl gas gave a white solid (3.8 g.). Recrystallization (EtOH) gave a white powder showing the properties of 1-benzyl 2-methylhydrazine mono-hydrochloride m.p. 140-142° (lit.⁴⁴ 140° for the dihydrochloride); M^+ found 136.1000 calculated for $C_8H_{12}N_2$ 136.0990; i.r. maxima (KBr) 3200 s (NH) 3000-2500 ($\overset{+}{N}H_2$) 750 s, 700 s (aromatic) cm^{-1} ; n.m.r. (D_2O) τ 2.25 (5H, s, ArH) τ 5.6 (2H, s, benzylic) τ 7.0 (3H, s, N- $\underline{CH_3}$). Consistent analyses could not, however, be obtained. Values obtained were between those expected for the mono- and di-hydrochloride; e.g. (Found C 47.32 H 6.90 N 14.93, $C_8H_{13}ClN_2$ requires C 55.62 H 7.67 N 16.23, $C_8H_{14}Cl_2N_2$ requires C 45.94 H 6.70 N 13.41%).

Dissolution of the crude monohydrochloride in methanol followed by saturation with dry HCl gas produced a low melting ($86-89^{\circ}$) solid which rapidly turned yellow in air and had the spectral properties expected for 1-benzyl 2-methylhydrazine dihydrochloride; M^+ found 136.0980 calculated for $C_8H_{12}N_2$ 136.0990; (Found C 44.45 H 6.77 N 14.82 $C_8H_{14}Cl_2N_2$ requires C 45.95 H 6.70 N 13.41%); i.r. maxima (KBr) 3000-2500 (NH_2^+) 750 s, 700 s (aromatic) $cm.^{-1}$; n.m.r. (D_2O) τ 2.25 (5H, s, ArH) τ 5.6 (2H, s, benzylic) τ 7.0 (3H, s, $N-CH_3$).

Attempts to recrystallize the crude dihydrochloride gave a mixture of mono- and di-hydrochlorides.

8. 1-benzyl 2-methylhydrazine hydrochloride :- condensation-reduction method.

Experiment a. (1 mole equivalent of diborane).

Methylhydrazine (1.1 g.), benzaldehyde (2.4 g.) and acetic acid (2-3 drops) were allowed to stand under nitrogen with constant stirring (30 mins.) in dry diglyme (150 ml.). The passage of diborane (0.35 g.) at ambient temperature, followed by saturation with dry HCl gas gave a white precipitate (3.1 g.). Recrystallization (EtOH) gave a white crystalline solid with the same properties (m.p. and mixed m.p.; i.r., n.m.r. and intermediate analyses) as previously noted (Experiment No. 7) for 1-benzyl 2-methyl hydrazine 'hydrochloride'.

Experiment b. (2 mole equivalent of diborane).

Experiment 8a. was repeated using two mole equivalents of diborane (0.7 g.). Saturation of the reaction mixture with dry HCl gas gave a white precipitate (3.1 g.) showing the same properties (m.p.; i.r.; n.m.r. and intermediate analyses) as noted for 1-benzyl 2-methylhydrazine 'hydrochloride'.

Experiment c. (Isolation of boro-intermediate).

As described in Experiment No. 8b. methylhydrazine and benzaldehyde were treated with diborane. After passage of the diborane the reaction mixture was evaporated to dryness. A white powder was obtained, which gradually decomposed in air.

Treatment of this solid, in ether, with dry HCl gas gave 1-benzyl 2-methylhydrazine hydrochloride (m.p.; i.r.; n.m.r.) and the material gave a positive test for boron (ground with calcium fluoride, conc. sulphuric acid was added and the resulting slurry imparted a green colouration to a bunsen flame).

Spectral evidence suggests that the material was a mixture of a boron containing intermediate $\text{Ph-CH}_2\text{-NB(OH)}_2\text{-NB(OH)}_2\text{-CH}_3\cdot 2\text{H}_2\text{O}$ (major component) and 1-benzyl 2-methyl 3-phenyldiaziridine (minor component).

Thus we find :-

Analysis - found C 35.19 H 6.01 N 9.15%, $\text{C}_8\text{H}_{14}\text{B}_2\text{O}_4\text{N}_2\cdot 2\text{H}_2\text{O}$ requires C 36.16 H 6.92 N 10.76%; M^+ found 224.1316 calculated for $\text{C}_{15}\text{H}_{16}\text{N}_2$ 224.1313 (boro-adduct is too involatile to give a spectrum); i.r. maxima (KBr) 3500-2700 br. (B(OH)_2) 695 s, 780 s (aromatic) cm^{-1} ; n.m.r.

(D₂O) - Perkin-Elmer R10 instrument τ 2.5 (s, ArH, both compounds unresolved) τ 5.2 (s, H₂O impurity) τ 5.9 (s, benzylic protons of boro-adduct) τ 7.1 (s, CH₃ of diaziridine) τ 7.24 (s, benzylic protons of boro-adduct); n.m.r. (dimethyl sulphoxide) - Perkin-Elmer R14 instrument - τ 2.53 (s, ArH - boro-adduct) τ 2.6 (s, ArH of diaziridine) τ 5.2 (s, broad, OH of boro-adduct) τ 5.45 (s, of benzylic protons of diaziridine) τ 5.9 (s, benzylic protons of boro-adduct).

Attempts to wash the diaziridine out of the mixture with benzene, or ether, caused decomposition.

9. Benzylhydrazine

Adopting the general procedure of Biel³¹ and his co-workers, a solution of benzyl chloride (63 g.; 0.5 mole) in ethanol (300 ml.) was added over a period of one hour to a refluxing solution of 98% hydrazine hydrate (144 g.; 2.9 mole) in ethanol (1000 ml.), after which the mixture was refluxed for a further six hours. The ethanol was then removed by distillation at atmospheric pressure and the residue extracted with ether. Fractionation of the dried (K₂CO₃) extract through a 30 cm. Vigreux column gave benzylhydrazine (52.0 g.; 85%); b.p. 100°/5 mm. Hg. (lit.³¹ 98°/4 mm. Hg.).

10. Benzylhydrazine hydrochloride.

Saturation of a solution of benzylhydrazine in ether with dry HCl gas gave benzylhydrazine hydrochloride. Recrystallized (EtOH) sample had m.p. 110-112° (lit.¹⁴⁵ 110°); M⁺ found 122.0745 calculated

for $C_7H_{10}N_2$ 122.0844; (Found C 58.85 H 9.91 N 7.16, $C_7H_{11}ClN_2$ requires C 58.72 H 9.79 N 7.05%); i.r. maxima (KBr) 3250 s, 3140 s (NH_2) 1580 s, 1450 s, 750 s, 695 s (aromatic) cm^{-1} ; n.m.r. (D_2O) τ 2.75 (5H, s, ArH) τ 5.9 (2H, s, benzylic).

11. 1-benzyl 2-ethylhydrazine monohydrochloride.

Benzylhydrazine (3.3 g.), acetaldehyde (2.3 g.) and acetic acid (2-3 drops) were allowed to stand (40 mins.) in dry diglyme (200 ml.). Passage of diborane (0.8 g.) into the mixture, at ambient temperature, followed by saturation with dry HCl gas gave 1-benzyl 2-ethylhydrazine as a mixture of mono- and di-hydrochlorides (1.7 g.). Recrystallization (EtOH) gave 1-benzyl 2-ethylhydrazine monohydrochloride m.p. 100-104°; M^+ found 150.1157 calculated for $C_9H_{14}N_2$ 150.1157; (Found C 58.70 H 8.14 N 14.38 $C_9H_{15}ClN_2$ requires C 58.04 H 8.12 N 15.0%); i.r. maxima (KBr) 3200 s (NH) 3000-2500 (NH_2^+) 750 s 700 s (aromatic) cm^{-1} ; n.m.r. (D_2O) τ 2.48 (5H, s, ArH) τ 5.75 (2H, s, benzylic) τ c.a. 6.2 (2H, q, $NH-CH_2-CH_3$) τ 8.7 (3H, t, $NH-CH_2-CH_3$).

12. 1-benzyl 2-n-propylhydrazine hydrochloride.

Using the same procedure as for Experiment No. 11 benzaldehyde (1.4 g.) and propionaldehyde (3.0 g.) were reduced with diborane (0.8 g.) to give 1-benzyl 2-n-propylhydrazine as a mixture of mono- and di-hydrochlorides (2.8 g.). Extensive recrystallization (EtOH) failed to give pure monohydrochloride. The material obtained always gave intermediate analyses; m.p. 119-122°; M^+ found 164.1314 calculated for

$C_{10}H_{16}N_2$ 164.1313 ; (Found C 51.47 H 8.12 N 13.19, $C_{10}H_{17}ClN_2$ requires C 59.97 H 8.56 N 13.99% $C_{10}H_{16}Cl_2N_2$ requires C 50.64 H 7.60 N 11.81%); i.r. maxima (KBr) 3200 s (NH) 3000-2500 ($\overset{+}{N}H_2$) 770 s, (aromatic) cm^{-1} ; n.m.r. (D_2O) τ 2.5 (5H, s, ArH) τ 5.5 (2H, s, benzylic) τ c.a. 6.8 (2H, t, $NH-CH_2-CH_2-CH_3$) τ c.a. 8.0 (2H, m, $-CH_2-CH_2-CH_3$) τ c.a. 8.8 (3H, t, $-CH_2-CH_2-CH_3$)

13. 1-benzyl 2-iso-propylhydrazine monohydrochloride.

Using the same procedure as for Experiment No. 11 benzylhydrazine (2.4 g.) and acetone (1.2 g.) were reduced with diborane (0.6 g.) to give 1-benzyl 2-iso-propylhydrazine as a mixture of mono- and di-hydrochlorides (2.6 g.). Recrystallization (EtOH) gave 1-benzyl 2-iso-propylhydrazine monohydrochloride m.p. 171-172° (lit.⁷⁸ 170-172°) H^+ found 164.1316 calculated for $C_{10}H_{16}N_2$ 164.1313; (Found C 59.70 H 8.44 N 14.59, $C_{10}H_{16}ClN_2$ requires C 59.97 H 8.56 N 14.01%); i.r. maxima (KBr) 3190 s (NH) 3000-2500 ($\overset{+}{N}H_2$) 750 s, 700 s (aromatic) cm^{-1} ; n.m.r. (D_2O) τ 2.45 (5H, s, ArH) τ 5.78 (2H, s, benzylic) τ c.a. 6.46 (H, m, $-CH(CH_2)_2$) τ c.a. 8.7 (6H, d, $-CH(CH_2)_2$)).

14. 1-benzyl 2-n-butylhydrazine monohydrochloride.

Using the same procedure as for Experiment No. 11 benzylhydrazine (3.0 g.) and butyraldehyde (1.8 g.) were reduced with diborane (0.7 g.) to give 1-benzyl 2-n-butylhydrazine as a mixture of mono- and di-hydrochloride (2.9 g.). Recrystallization (EtOH) gave 1-benzyl 2-n-butyl-hydrazine monohydrochloride m.p. 147-149°; H^+ found 176.1460

calculated for $C_{11}H_{18}N_2$ 178.1470; (Found C 61.90 H 8.91 N 13.32, $C_{11}H_{19}ClN_2$ requires C 61.65 H 8.94 N 13.08%); i.r. maxima (KBr) 3200 s (NH) 3000-2500 (NH_2^+) 750 s, 700 s (aromatic) cm^{-1} ; n.m.r. (D_2O) τ 2.44 (5H, s, ArH) τ 5.72 (2H, s, benzylic) τ c.a. 6.75 (2H, m, $NH-CH_2$) τ c.a. 8.4 (4H, m, $NH-CH_2-CH_2-CH_2-CH_3$) τ c.a. 9.2 (3H, t, $(CH_2)_3-CH_3$)

15. Attempts to prepare mono-salts of 1-benzyl 2-n-butylhydrazine.

As for Experiment No. 11, but after passage of diborane the reaction mixture was divided into four parts. These were treated as follows :-

Part 1. Saturated with HCl as for Experiment No. 11; this gave 1-benzyl 2-n-butylhydrazine as a mixture of mono- and di-hydrochlorides.

Part 2. Slow saturation of the diluted (diglyme) solution with dry HCl gave the same product as for Part 1.

Part 3. Dropwise addition of sulphuric acid with constant stirring gave only an intractable tar.

Part 4. Dropwise addition of acetic acid gave no solid product.

16. 1,2-dibenzylhydrazine monohydrochloride.

a. Condensation-reduction of benzaldehyde and benzylhydrazine.

Benzylhydrazine (4.4 g.), benzaldehyde (3.9 g.) and acetic acid (2-3 drops) were allowed to stand (40 mins.) in dry THF (150 ml.). Passage of diborane (1.1 g.) at ambient temperature followed by saturation with dry HCl gas gave 1,2-dibenzylhydrazine as a mixture of

mono- and di-hydrochlorides (6.7 g.). Recrystallization (EtOH) gave 1,2-dibenzylhydrazine monohydrochloride; m.p. 182-195° (decomp.); M^+ found 212.1280 calculated for $C_{14}H_{16}N_2$ 212.1313; (Found C 67.55 H 7.14 N 11.65 $C_{14}H_{17}ClN_2$ requires C 67.59 H 6.86 N 11.27%); i.r. maxima, (KBr) 3200 s (NH) 3000-2500 (NH_2^+) 750 s, 700 s (aromatic) cm^{-1} ; n.m.r. (T.F.A.) τ 3.15 (5H, s, ArH) τ 6.1 (2H, s, benzylic).

b:- Condensation-reduction of benzaldehyde and hydrazine hydrate.

Using the same procedure as for Experiment No. 16a, hydrazine hydrate (1.2 g.) and benzaldehyde (5.0 g.) were reduced with diborane (1.4 g.) to give 1,2-dibenzylhydrazine as a mixture of mono- and di-hydrochlorides (2.8 g.). Recrystallization (EtOH) gave 1,2-dibenzylhydrazine monohydrochloride; (m.p. and mixed m.p.; i.r. and n.m.r.).

17. 1,2-di-iso-propylhydrazine monohydrochloride.

Acetone (4.2 g.), hydrazine hydrate (1.7 g.) and acetic acid (2-3 drops) were allowed to stand (35 mins.) in dry T.H.F. (200 ml.). Passage of diborane (2.1 g.) followed by saturation with dry HCl gas gave 1,2-di-iso-propylhydrazine as a mixture of mono- and di-hydrochlorides (6.7 g.). Recrystallization (water) gave 1,2-di-iso-propylhydrazine monohydrochloride m.p. 198-200° (lit. 198°); (Found C 47.60 H 11.11 N 18.41, $C_6H_{17}ClN_2$ requires C 47.34 H 11.26 N 17.91%); i.r. maxima, (KBr) 3195 s (NH) 3000-2500 (NH_2^+) 1600 s (NH) 1395 s, 1375 s (gem-dimethyl doublet) cm^{-1} ; n.m.r. (D_2O) τ c.a. 6.4 (2H, m, $CH(CH_3)_2$) τ c.a. 8.6 (12H, d, $CH(CH_3)_2$)

18a. Attempted preparation of 1-benzyl 2-phenylhydrazine hydrochloride.

Benzaldehyde (1.8 g.), phenylhydrazine (1.8 g.) and acetic acid (2-3 drops) were warmed (about 50°C) in dry diglyme (150 ml.) for ten minutes. After cooling diborane (0.5 g.) was passed into the mixture. Subsequent saturation with dry HCl gas gave a dark green solution. This gave no E.S.R. signal. Rotary-evaporation yielded a dark green solid m.p. indefinite; Mass spectrum - many peaks up to and above m/e 450 - polymeric, base peak at m/e 91; i.r. maxima (KBr) 3200 s (br.) (NH?) 1600 s, 1500-1400 (br.) (aromatic, NH etc.) 1195 m (C-N) 700 m, 750 m (aromatic) cm.⁻¹; n.m.r. (D₂O) τ c.a. 2.6 (m, ArH) τ 6.05 (s, benzylic?) τ 6.38 (s,?).

The material yields a green solution in water and a purple solution in TFA; its composition has not been determined.

18b. Passage of excess HCl into benzaldehyde phenylhydrazone.

Benzaldehyde (1.8 g.) and phenylhydrazine (1.8 g.) were stirred with acetic acid (2-3 drops) in dry ether. Saturation of the mixture with dry HCl gas followed by evaporation to dryness gave a green solid with the same properties as the product obtained in Experiment 18a.

19. Tertiary-butylhydrazine oxalate.

The procedure used was that described by Foxall.⁴⁵

a. Excess tert-butylamine.

Freshly distilled tert-butylamine (41.4 g; 0.5 moles) was mixed with water (15 ml.) and heated to reflux. The heat was removed and a solution of freshly prepared hydroxylamine-O-sulphonic acid (5.0 g.) in

water (5 ml.) was added dropwise over a period of fifteen minutes. On completion of the addition the solution was cooled, the white inorganic precipitate filtered off and discarded, and the filtrate acidified with glacial acetic acid (30 ml.), and then warmed to 50°C (10 mins.) with benzaldehyde (8.9 g.). The resulting emulsion was cooled and extracted with ether (3 x 50 ml.). The ether extracts were combined and added to an aqueous solution of oxalic acid dihydrate (7.9 g.) and the mixture steam distilled until no further benzaldehyde was collected. The residue was evaporated to dryness in vacuo and the resulting solid recrystallized, (90% EtOH) to give tert-butylhydrazine oxalate (1.8 g.); 4% in terms of the tert-butylamine); m.p. 185-187° decomp. (lit.⁴⁵ 187° decomp.); M⁺ found 88.0996 calculated for C₄H₁₂N₂ 88.1000; (Found C 40.30 H 7.76 N 15.57 C₆H₁₄N₂O₄ requires C 40.45 H 7.86 N 15.73%); i.r. maxima, (KBr) 3350 s, 3250 s (NH) cm.⁻¹; n.m.r. (TFA) τ 8.20 (s, (CH₃)₃C).

b. The effect of added base.

Freshly distilled tert-butylamine (37.0 g.) was mixed with a solution of potassium hydroxide (10.9 g.) in water (120 ml.) and the mixture refluxed. Hydroxylamine-O-sulphonic acid (10.1 g.) was added and the mixture worked-up as for Experiment 19a to give tert-butylhydrazine oxalate (1.1 g.; 1% yield in terms of butylamine); (m.p. and mixed m.p.; i.r. and n.m.r.).

20. Benzaldehyde tert-butylhydrazone hydrochloride.

Tert-butylhydrazine oxalate (6.0 g.) was dissolved in the minimum amount of water and sufficient sodium hydroxide (3.0 g.) added to neutralize the oxalate. The solution was brought back to neutrality with acetic acid and benzaldehyde (3.6 g.) added. Extraction with ether drying of the ether extracts (MgSO_4) followed by saturation with dry HCl gas gave a white precipitate of benzaldehyde tert-butylhydrazine hydrochloride (3.6 g; 50%). Recrystallized (C_6H_6) sample had m.p. 189-190°; (Found C 63.56 H 8.22 N 13.21, $\text{C}_{11}\text{H}_{17}\text{Cl N}_2$ requires C 63.50 H 8.04 N 13.25%); i.r. maxima, (KBr) 3000-2500 (NH_2^+) 1620 s (CH=NH; NH) 1600 m, 1580 m (aromatic) 1370 s, 1360 s (gem-dimethyl doublet) 695 s, 765 s (aromatic); n.m.r. (T.F.A.) τ 1.18 (1H, s, CH=N) τ c.a. 2.3 (5H, m, ArH) τ 8.38 (9H, s, $(\text{CH}_3)_3\text{C}$).

21. Attempted reduction of benzaldehyde tert-butylhydrazone hydrochloride with diborane.

Diborane (0.34 g.) was passed into a well stirred suspension of benzaldehyde tert-butylhydrazone hydrochloride (2.5 g.) in dry T.H.F. (150 ml.) at ambient temperature. Passage of dry HCl gas gave only benzaldehyde tert-butylhydrazone hydrochloride (1.5 g.; 60% recovery).

22. Tert-butylhydrazine.

Tert-butylhydrazine oxalate (29.1 g.) was refluxed with sodium hydroxide solution (approx. 70%). The supernatant tert-butylhydrazine and water was distilled off. Numerous dryings (NaOH) failed to remove all the residual water and the tert-butylhydrazine was used for further

reactions in this 'crude' form: M^+ found 88.0995 calculated for $C_4H_{12}N_2$ 88.1000; n.m.r. (neat) τ 8.8 (9H, s, $(CH_3)_3C-$) τ 5.2 (2H, s, H_2O).

23. 1-benzyl 2-tert-butylhydrazine monohydrochloride:- condensation-reduction method.

a) 2-moles of diborane.

Benzaldehyde (9.6 g.) and acetic acid (2-3 drops) were added to a solution of 'crude' tert-butylhydrazine (8.0 g.) in dry THF (200 ml.). Passage of diborane (2.6 g.) followed by saturation of the cooled ($0^\circ C$) solution with dry HCl gave benzaldehyde tert-butylhydrazone hydrochloride (13.8 g.); (m.p. and mixed m.p.; i.r. and n.m.r.).

b) 4-moles diborane.

Benzaldehyde, (5.4 g.) and a few spots of acetic acid (2-3 drops) were added to 'crude' tert-butylhydrazine (4.5 g.) in dry THF (200 ml.). Passage of diborane (5.7 g.) followed by saturation of the cooled ($0^\circ C$) solution gave crude 1-benzyl 2-tert-butylhydrazine monohydrochloride (10.3 g.). Recrystallization (EtOH) gave 1-benzyl 2-tert-butylhydrazine monohydrochloride (3.7 g.); m.p. $197-200^\circ$; M^+ found 178.1467 calculated for $C_{11}H_{18}N_2$ 178.1469; (Found C 61.65 H 8.81 N 13.08 $C_{11}H_{19}ClN_2$ requires C 61.85 H 8.94 N 13.08%); i.r. maxima (KBr) 3200 s (NH) 3010 w (aromatic) 3000-2500 (NH_2^+) 1400 s, 1375 s (gem-dimethyl) 1210 s (C-N) 760 s, 700 s, (aromatic) cm^{-1} ; n.m.r. (TFA) τ 2.54 (5H, s, ArH) τ 5.64 (2H, s, benzylic) τ 8.51 (9H, s, CH_3)₃C).

24. 1-tert-butyl 2-iso-propylhydrazine monohydrochloride.

Acetone (2.5 g.) and acetic acid (2-3 spots) were added to tert-butylhydrazine (3.8 g.), in dry T.H.F. (200 ml.) and the solution allowed to stand (30 mins.). Passage of diborane (1.2 g.; 4 moles) followed by saturation of the cooled (0°C) solution with dry HCl gas gave 1-tert-butyl 2-iso-propylhydrazine hydrochloride (3.5 g.). Recrystallized (EtOH) sample had m.p. 165-167°; M^+ found 130.1470 calculated for $C_7H_{18}N_2$ 130.1516; (Found C 50.24 H 11.20 N 16.91 $C_7H_9ClN_2$ requires C 50.46 H 11.41 N 16.82%); i.r. maxima (KBr) 3220 s (NH) 3000-2500 (NH_2^+) 1590 s (NH) 1390 s (gem-dimethyls) 1240 (C-N) cm^{-1} ; n.m.r. (D_2O) τ c.a. 8.85 (6H, d, $(CH_3)_2CH$) τ 8.5 (9H, s, $(CH_3)_3C^-$) τ c.a. 6.75 (1H, m, $(CH_3)_2CH$).

25. Attempted addition of trimethylboron to acetone benzylhydrazone.Experiment a.

Acetone (1.5 g.) and a few drops of acetic acid were added to benzylhydrazine (2.6 g.) in dry diglyme (200 ml.). The mixture was stirred under nitrogen for 45 mins.

Trimethylboron was prepared by the method described by Brown.¹⁸²

Magnesium turnings (3.0 g.) were placed in the generator and just covered with dry diglyme. Methyl iodide (15.2 g.) was added dropwise as the reaction proceeded. On completion of the reaction the mixture was allowed to cool and boron-trifluoride (6.6 g.) added dropwise. The resulting trimethylboron (1.3 g.) was flushed with nitrogen into the reaction flask. The last traces of trimethylboron were removed by heating the generator.

On completion of the addition of trimethylboron the reaction mixture was saturated with dry HCl gas. A white precipitate, of benzylhydrazine hydrochloride (m.p. and mixed m.p.; i.r. and n.m.r.) was obtained.

Experiment b.

The reaction was carried out as described in Experiment 1, but the saturation of the reaction mixture with HCl gas was carried out at 0°C. A white precipitate of benzylhydrazine hydrochloride (m.p. and mixed m.p.; i.r. and n.m.r.) was again obtained.

26. Attempted preparation of iso-propylhydrazine hydrochloride :-
condensation-reduction method.

Acetone (1.2 g.; 1 mole) was added dropwise to a solution of hydrazine hydrate (1.0 g.; 1 mole) and acetic acid (2-3 drops) in dry T.H.F. (200 ml.) and the solution allowed to stand (35 mins.). Passage of diborane (1.6 g.) followed by saturation with dry HCl gas gave a white hygroscopic solid (2.5 g.) consisting of a mixture of iso-propylhydrazine hydrochloride and 1,2-di-iso-propylhydrazine hydrochloride n.m.r. (D₂O) τ c.a. 8.35 (6H, d, CH(CH₃)₂ of di-substituted hydrazine) τ c.a. 8.41 (6H, d, CH(CH₃)₂ of iso-propylhydrazine) τ c.a. 6.2 (2H, m, methine protons of both compounds). Recrystallization, (EtOH), gave 1,2-di-iso-propylhydrazine mono-hydrochloride (m.p. & mixed m.p.; i.r. & n.m.r.).

27. Attempted preparation of benzylhydrazine hydrochloride :-
condensation-reduction method.

Benzaldehyde (2.5 g.; 1 mole) was added to a stirred solution of hydrazine hydrate (1.2 g.) and acetic acid (2-3 drops) in dry THF (200 ml.). After allowing to stand (35 mins.) the solution was treated with diborane (0.7 g.) and then saturated with dry HCl gas. A white precipitate (2.9 g.) was formed. Recrystallization (EtOH) gave 1,2-dibenzylhydrazine monohydrochloride (m.p. and mixed m.p.; M^+ , i.r. and n.m.r.).

28. Reduction of benzaldehyde hydrazone with diborane.

Benzaldehyde, (6.6 g.), was added dropwise to a refluxing mixture of hydrazine hydrate (10 ml.; three-fold excess), in ethanol (500 ml.). Solvent and excess hydrazine were removed under reduced pressure and the residual benzaldehyde hydrazone treated with diborane (1.8 g.) in dry THF (250 ml.). Subsequent passage of dry HCl gas gave a white precipitate. Recrystallization gave benzylhydrazine hydrochloride, (5.8 g; 60%) (m.p. and mixed m.p.; M^+ ; i.r. and n.m.r.).

29. 1,1-dimethyl 2-iso-propylhydrazine hydrochloride.

1,1-dimethylhydrazine (2.4 g.), acetone (2.3 g.) and acetic acid (2-3 drops) were warmed (20 mins.) in dry tetrahydrofuran (200 ml.). After cooling passage of diborane (1.1 g.) followed by saturation with HCl gas gave 1,1-dimethyl 2-iso-propylhydrazine hydrochloride (4.2 g.; 75%). Recrystallized (EtOH) sample had m.p. 136-140° (decomp.); M^+ found 102.1155

calculated for $C_5H_{14}N_2$ 102.1157; (Found C 43.43 H 11.01 N 20.22, $C_5H_{15}ClN_2$ requires C 43.22 H 10.83 N 20.83%); i.r. maxima (KBr) 3200 s (NH) 3000-2400 (NH) 1580 (NH) cm^{-1} ; n.m.r. (D_2O) τ c.a. 6.3 (H, m, $(CH_3)_2CH$) τ 6.85 (6H, s, $(CH_3)_2N$) τ c.a. 8.7 (6H, d $(CH_3)_2CH$).

30. 1,1-dimethyl 2-n-butylhydrazine

1,1-dimethylhydrazine (1.2 g.), butyraldehyde (1.5 g.) and acetic (2-3 drops) were allowed to stand (35 mins.), under nitrogen, in dry tetrahydrofuran (150 ml.). Passage of diborane (0.6 g.) followed by saturation with dry HCl gas gave a "plasticine-like" material. Treatment of this solid with concentrated sodium hydroxide solution, extraction with ether, drying ($MgSO_4$) of the extracts and finally removal of the ether at reduced pressure, gave a golden yellow solution (1.1 g.). The material showed the properties expected for 1,1-dimethyl 2-n-butylhydrazine; E^+ 116; i.r. maxima (neat) 3,200 s (NH) 1580 (NH) cm^{-1} ; n.m.r. ($CDCl_3$) τ c.a. 6.4 (2H, m, $NH-CH_2-$) τ 6.9 (6H, s, $N(CH_3)_2$) τ c.a. 7.8 (m, $-CH_2-$) τ c.a. 8.2 (m, $-CH_2-$) τ c.a. 9.05 (3H, t, $-CH_3$)

Attempted distillation of the crude 1,1-dimethyl 2-n-butylhydrazine resulted in decomposition to an intractable tar. Repetition of the experiment gave the same result.

31. Preparation of 1-benzyl 2-methyl 3-phenyldiaziridine.

Methylhydrazine (1.1 g.; 1 mole) benzaldehyde (4.8 g.; 2 moles) and acetic acid (2-3 drops) were allowed to stand (30 mins.), under nitrogen, in dry tetrahydrofuran (200 ml.). Diborane (0.7 g.) was then passed into the solution. Subsequent addition of a strong aqueous sodium

hydroxide solution gave two layers. The upper layer was extracted with ether, dried (NaOH) and solvent removed under reduced pressure to give a viscous golden yellow sample of 1-benzyl 2-methyl 3-phenyldiaziridine (3.5 g.; 60%); M^+ found 224.1313 calculated for $C_{15}H_{16}N_2$ 224.1313; i.r. maxima (neat) 3010 m, 1600 s, 1500 s, 750 s, 700 s (aromatic) cm^{-1} ; n.m.r. (neat) τ 2.8 (10H, m, aromatic) τ 5.45 (H, s, ring-CH-) τ 5.62 (2H, s, benzylic) τ 7.48 (3H, s, N-CH₃).; on warming with acidified potassium iodide, in the presence of a little copper sulphate, the sample gave iodine - a reaction characteristic of diaziridines. ¹⁸³

Attempts to distil the diaziridine, at reduced pressure, resulted in decomposition.

32. Attempted preparation of 1-n-propyl 2-methyl 3-ethyldiaziridine.

Experiment No. 31 was repeated, but the benzaldehyde was replaced by propionaldehyde (2 moles). A yellow liquid was obtained. This did not release iodine when warmed with acidified potassium iodide in the presence of copper sulphate, hence no diaziridine was present, Mass spectrum base peak m/e 59; i.r. maxima (neat) 3400 br (OH?); n.m.r. τ 2.0-4.0 (various low intensity CH=N?) τ 5.7 (s, OH ?) τ c.a. 6.4 (m, T.H.F.) The liquid appears to be a mixture of various components.

33. Attempted preparation of 1-iso-propyl 2,3,3-trimethyl diaziridine.

Experiment No. 31 was repeated, but the benzaldehyde was replaced by acetone (2 moles). A yellow liquid was obtained. This did not release iodine when warmed with acidified potassium iodide, in the presence of

copper sulphate, hence no diaziridine was formed. The material was not further investigated.

34. Attempted preparation of 1 n-propyl 2-methyl 3-phenyldiaziridine.

Propionaldehyde (1.4 g.; 1 mole) methylhydrazine (1.1 g.; 1 mole) and acetic acid (2-3 drops) were stirred together in tetrahydrofuran (200 ml.). Benzaldehyde (2.5 g; 1 mole) was added and the resulting mixture treated with diborane (0.6 g.). Subsequent addition of strong aqueous sodium hydroxide solution gave two layers. Extraction of the upper layer with ether and evaporation of the solvent gave a yellow liquid. This material did not release iodine from acidified potassium iodide, however small peaks in the mass spectrum at m/e 176 and m/e 174, were found, by accurate mass measurement, to correspond to the formulae $C_{11}H_{16}N_2$ (found 176.1311, calculated 176.1313) and $C_{11}H_{14}N_2$ (found 174.1156, calculated 174.1157) respectively. Small amounts of the required diaziridine may thus have been formed, but the mass spectrum showed numerous peaks up to m/e 253 and the material was probably a mixture of various compounds. The product was not further examined.

Appendix 1.Accurate mass measurement of various ions in mass
spectra examined.

Compound	Nominal Mass (m/e)	Mass Found	Mass Calculated ²³⁶	Formula
MeNHNH ₂ .HCl	46	46.0540	46.0531	CH ₆ N ₂
	45	45.0438	45.0453	CH ₅ N ₂
	44	44.0367	44.0374	CH ₄ N ₂
	43	43.0318	43.0296	CH ₃ N ₂
	31	31.0251	31.0295	N ₂ H ₃

(There are other m/e 31 fragments of lower abundance)

EtNHNH ₂ .(CO ₂ H) ₂	60	60.0685	60.0687	C ₂ H ₈ N ₂
	45	{ 45.0450	45.0453	CH ₅ N ₂
		{ 44.9974	44.9977	CO ₂ H
	44	{ 44.0378	44.0374	CH ₄ N ₂
{ 44.9975		44.9986	CO ₂	
Pr ⁿ NHNH ₂ .(CO ₂ H) ₂	74	74.0839	74.0844	C ₃ H ₁₀ N ₂
	45	{ 45.0450	45.0453	CH ₅ N ₂
		{ 44.9973	44.9977	CO ₂ H
	44	{ 44.9981	44.9986	CO ₂
{ 44.0499		44.0500	C ₂ H ₆ N	
		{ 44.0373	44.0374	CH ₄ N ₂

Compound	Nominal Mass (m/e)	Mass Found	Mass Calculated	Formula
$\text{Pr}^i\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	74	74.0845	74.0844	$\text{C}_3\text{H}_{10}\text{N}_2$
	59	59.0614	59.0609	$\text{C}_2\text{H}_7\text{N}_2$
	45	{ 45.0450	45.0453	CH_5N_2
		{ 44.9973	44.9977	CO_2H
	44	44.0500	44.0499	$\text{C}_2\text{H}_6\text{N}$
$\text{Bu}^n\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	88	88.1001	88.1000	$\text{C}_4\text{H}_{12}\text{N}_2$
	45	45.0452	45.0453	CH_5N_2
	44	{ 44.9975	44.9977	CO_2H
		{ 44.0501	44.0500	$\text{C}_2\text{H}_6\text{N}$
		{ 44.0378	44.0374	CH_4N_2
$\text{Bu}^t\text{NHNH}_2 \cdot$	88	88.0995	88.1000	$\text{C}_4\text{H}_{12}\text{N}_2$
	73	73.0767	73.0766	$\text{C}_3\text{H}_9\text{N}_2$
	58	58.0661	58.0657	$\text{C}_3\text{H}_8\text{N}$
	57	57.0711	57.0704	C_4H_9
	56	{ 56.0508	56.0500	$\text{C}_3\text{H}_6\text{N}$
		{ 56.0632	56.0626	C_4H_8 (small)
$\text{Bu}^t\text{NHNH}_2 \cdot \text{HCl}$	88	88.0999	88.1000	$\text{C}_4\text{H}_{12}\text{N}_2$
	73	73.0765	73.0766	$\text{C}_3\text{H}_9\text{N}_2$
	58	58.0651	58.0657	$\text{C}_3\text{H}_8\text{N}$
	57	57.0697	57.0704	C_4H_9
	56	{ 56.0494	56.0500	$\text{C}_3\text{H}_6\text{N}$ (small)
		{ 56.0620	56.0626	C_4H_9

Compound	Nominal Mass (m/e)	Mass Found	Mass Calculated	Formula
PhCH ₂ NHNH ₂ ·HCl	122	122.0845	122.0844	C ₇ H ₁₀ N ₂
	107	107.0735	107.0729	C ₇ H ₉ N
	106	106.0657	106.0653	C ₇ H ₈ N
	105	105.0578	105.0572	C ₇ H ₇ N
	103	103.0420	103.0420	C ₇ H ₅ N
	92	92.0626	92.0626	C ₇ H ₈
	91	91.0562	91.0548	C ₇ H ₇
	45	45.0452	45.0453	CH ₅ N ₂
Ph·CH ₂ NHNH ₂ ·HCl	136	136.0999	136.1000	C ₈ H ₁₂ N ₂
	106	106.0655	106.0657	C ₇ H ₈ N
	104	104.0533	104.0500	C ₇ H ₆ N
	92	{ 92.0626	92.0626	C ₇ H ₈
		{ 92.0498	92.0500	C ₆ H ₆ N (small)
	91	91.0563	91.0548	C ₇ H ₇
	77	77.0404	77.0391	C ₆ H ₅
	51	51.0247	51.0235	C ₄ H ₃
	45	45.0463	45.0453	CH ₅ N ₂
	31	{ 31.0423	31.0422	N ₂ H ₃
{ 31.0298		31.0296	CH ₅ N (small)	

Compound	Nominal Mass (m/e)	Mass Found	Mass Calculated	Formula
PhCH ₂ NHNHt.HCl	150	150.1157	150.1157	C ₉ H ₁₄ N ₂
	135	135.0921	135.0922	C ₈ H ₁₁ N ₂
	106	106.0640	106.0657	C ₇ H ₈ N
	93	93.0702	93.0704	C ₇ H ₉
	92	92.0624	92.0626	C ₇ H ₈
	91	91.0551	91.0548	C ₇ H ₇
	59	59.0594	59.0609	C ₂ H ₇ N ₂
	51	51.0225	51.0235	C ₄ H ₃
	45	45.0466	45.0453	CH ₅ N ₂
PhCH ₂ NHNHPr ⁿ .HCl	164	164.1316	164.1313	C ₁₀ H ₁₆ N ₂
	103	103.0405	103.0422	C ₇ H ₅ N
	93	93.0700	93.0704	C ₇ H ₉
	92	92.0607	92.0626	C ₇ H ₈
	73	73.0768	73.0766	C ₃ H ₉ N ₂
	45	45.0450	45.0453	CH ₅ N ₂

Compound	Nominal Mass	Mass Found	Mass Calculated	Formula
$\text{PhCH}_2\text{NHNHPr}^i \cdot \text{HCl}$	164	164.1316	164.1313	$\text{C}_{10}\text{H}_{16}\text{N}_2$
	106	106.0649	106.0657	$\text{C}_7\text{H}_8\text{N}$
	103	103.0417	103.0422	$\text{C}_7\text{H}_5\text{N}$
	93	93.0700	93.0704	C_7H_9
	92	(92.0626 92.0583	92.0630	C_7H_8
			92.0500	$\text{C}_6\text{H}_6\text{N}$ (small)
	73	73.0767	73.0766	$\text{C}_3\text{H}_9\text{N}_2$
	63	63.0246	63.0235	C_5H_3
	43	43.0557	43.0548	C_3H_7
	31	31.0297	31.0296	N_2H_3
	$\text{PhCH}_2\text{NHNHBU}^n \cdot \text{HCl}$	178	178.1460	178.1470
106		106.0657	106.0657	$\text{C}_7\text{H}_8\text{N}$
135		135.0951	135.0922	$\text{C}_8\text{H}_{11}\text{N}_2$
93		93.0702	93.0704	C_7H_9
92		92.0607	92.0630	C_7H_8
91		91.0547	91.0548	C_7H_7
87		87.0867	87.0922	$\text{C}_4\text{H}_{11}\text{N}_2$
45		45.0462	45.0453	CH_5N_2
$\text{Ph-CH}_2\text{NHNHBU}^t \cdot \text{HCl}$	178	178.1467	178.1470	$\text{C}_{11}\text{H}_{18}\text{N}_2$
	161	161.1079	161.1079	$\text{C}_{10}\text{H}_{13}\text{N}_2$
	91	91.0543	91.0548	C_7H_7
	87	87.0923	87.0922	$\text{C}_4\text{H}_{11}\text{N}_2$

Compound	Nominal Mass	Mass Found	Mass Calculated	Formula
PhCH ₂ NHNHCH ₂ Ph·HCl	212	212.1280	212.1313	C ₁₄ H ₁₆ N ₂
	93	93.0702	93.0626	C ₇ H ₉
	92	92.0631	92.0626	C ₇ H ₈
	91	91.0547	91.0548	C ₇ H ₇
Bu ^t NHNHFr ⁱ	130	130.1516	130.1470	C ₇ H ₁₈ N ₂
	59	59.0613	59.0614	C ₂ H ₇ N ₂
PhCONHNHLe	150	150.0794	150.0793	C ₈ H ₁₀ N ₂ O
	122	122.0601	122.0606	C ₇ H ₈ NO
	105	105.0332	105.0340	C ₇ H ₅ O
	45	45.0462	45.0453	CH ₅ N ₂
PhCONHNHBU ^t	192	192.1250	192.1263	C ₁₁ H ₁₆ N ₂ O
	177	177.1035	177.1028	C ₁₀ H ₁₃ N ₂ O
	162	162.0917	162.0919	C ₁₀ H ₁₂ NO
	136	136.0627	136.0637	C ₇ H ₈ N ₂ O
	105	105.0330	105.0340	C ₇ H ₅ O
	77	77.0398	77.0391	C ₆ H ₅
	57	57.0684	57.0704	C ₄ H ₉

Compound	Nominal Mass	Mass Found	Mass Calculated	Formula
PhCONHHCOPh	240	240.0902	240.0899	$C_{14}H_{12}N_2O_2$
	105	105.0351	105.0340	C_7H_5O
PhCONHNH ₂	136	136.0623	136.0637	$C_7H_8N_2O$
	105	105.0333	105.0340	C_7H_5O
	77	77.0387	77.0391	C_6H_5

Appendix 2.

Compound	Observed metastable [*] position	Calculated value ²³⁷	Transition
$\text{Et}^n\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	33.77	33.75	60 \longrightarrow 45
$\text{Pr}^n\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	27.36	27.36	74 \longrightarrow 45
$\text{Pr}^i\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	47.07	47.04	74 \longrightarrow 59
$\text{Bu}^n\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	23.0	23.01	88 \longrightarrow 45
Bu^tNHNH_2	60.5	60.56	88 \longrightarrow 73
	29.5	29.49	57 \longrightarrow 41
	11.6	11.64	88 \longrightarrow 32
$\text{Bu}^t\text{NHNH}_2 \cdot \text{HCl}$	60.59	60.56	88 \longrightarrow 73
	37.0	36.92	88 \longrightarrow 57
	29.48	29.49	57 \longrightarrow 41
	11.6	11.64	88 \longrightarrow 32
	46.1	46.08	73 \longrightarrow 58
$\text{Nu}^t\text{NHNH}_2 \cdot (\text{CO}_2\text{H})_2$	60.5	60.56	88 \longrightarrow 73
	29.5	29.49	57 \longrightarrow 41
	11.6	11.64	88 \longrightarrow 32

Compound	Observed metastable position	Calculated value	Transition
$\text{PhCH}_2\text{NHFH}_2$	69.5	69.38	122 \longrightarrow 92
	67.8	67.88	122 \longrightarrow 91
	46.5	46.43	91 \longrightarrow 65
$\text{PhCH}_2\text{NHCH}_2\cdot\text{HCl}$	69.5	69.38	122 \longrightarrow 92
	67.8	67.88	122 \longrightarrow 91
	46.4	46.43	91 \longrightarrow 65
$\text{PhCH}_2\text{NHCH}_2(\text{CO}_2\text{H})_2$	69.5	69.38	122 \longrightarrow 92
	67.8	67.88	122 \longrightarrow 91
	46.4	46.43	91 \longrightarrow 65
$\text{PhCH}_2\text{NHNHMe}\cdot\text{HCl}$	63.64	63.60	136 \longrightarrow 93
	62.22 (m)	62.24	136 \longrightarrow 92
	46.4	46.43	91 \longrightarrow 65
	33.80	33.78	77 \longrightarrow 51
	m	61.34	135 \longrightarrow 91
	m	77.93	106 \longrightarrow 91
	14.9	14.89	136 \longrightarrow 45

Compound	Observed metastable position	Calculated value	Transition
$\text{PhCH}_2\text{NHNHBBt} \cdot \text{HCl}$	57.7	57.66	150 \longrightarrow 93
	m	56.43	150 \longrightarrow 92
	m	62.70	135 \longrightarrow 92
	m	61.34	135 \longrightarrow 91
	23.4	23.21	150 \longrightarrow 59
	46.4	46.43	91 \longrightarrow 65
	16.3	16.29	59 \longrightarrow 31
	m	77.93	106 \longrightarrow 91
	$\text{PhCH}_2\text{NHNHPr}^n \cdot \text{HCl}$	52.75	52.74
m		51.61	164 \longrightarrow 92
m		62.70	135 \longrightarrow 92
m		61.34	135 \longrightarrow 91
32.5		32.49	164 \longrightarrow 73
46.3		46.43	91 \longrightarrow 65
27.7		27.74	73 \longrightarrow 45
m		13.17	73 \longrightarrow 31
$\text{PhCH}_2\text{NHNHPr}^i \cdot \text{HCl}$		52.7	52.74
	m	55.56	149 \longrightarrow 91
	m	68.44	121 \longrightarrow 91
	32.50	32.49	164 \longrightarrow 37
	46.5	46.43	91 \longrightarrow 65
	13.18	13.16	73 \longrightarrow 31
	39.1	39.09	45 \longrightarrow 41

Compound	Observed metastable position	Calculated value	Transition
$\text{PhCH}_2\text{NHNHtBu}^n \cdot \text{HCl}$	48.8	48.59	178 \rightarrow 93
	m	47.55	178 \rightarrow 92
	m	62.70	135 \rightarrow 92
	m	46.52	178 \rightarrow 91
	61.5 (m)	61.34	135 \rightarrow 91
	m	63.13	178 \rightarrow 106
	m	83.24	135 \rightarrow 106
	42.47 (m)	42.52	178 \rightarrow 87
	46.41	46.43	91 \rightarrow 65
	m	102.30	178 \rightarrow 135
	23.32 (m)	23.28	87 \rightarrow 45
	37.2	37.35	87 \rightarrow 57
	29.5	29.49	57 \rightarrow 41
	$\text{PhCH}_2\text{NHNHCH}_2\text{Ph} \cdot \text{HCl}$	68.44 (m)	68.43
69.0		69.06	212 \rightarrow 121
m		39.06	212 \rightarrow 91
m		61.34	135 \rightarrow 91
46.40		46.43	91 \rightarrow 65

Compound	Observed metastable position	Calculated value	Transition	
$\text{PhCH}_2\text{NHNHtBu}^{\dagger} \cdot \text{HCl}$	48.6	48.59	178 \rightarrow 93	
	m	47.55	178 \rightarrow 92	
	18.25 (m)	18.25	178 \rightarrow 57	
	42.5 (m)	42.52	178 \rightarrow 87	
	149.3	149.30	178 \rightarrow 163	
	83.6	83.62	178 \rightarrow 122	
	m	50.8	163 \rightarrow 91	
	m	70.89	122 \rightarrow 93	
	69.4 (m)	69.37	122 \rightarrow 92	
	67.9 (m)	67.88	122 \rightarrow 91	
	46.5	46.43	91 \rightarrow 65	
	37.4 (m)	37.34	87 \rightarrow 57	
	29.5	29.49	57 \rightarrow 41	
	$\text{MeNHNHMe} \cdot 2\text{HCl}$	33.8	33.75	60 \rightarrow 45
$(\text{Me})_2\text{NNH}_2 \cdot (\text{CO}_2\text{H})_2$		58.3	58.02	60 \rightarrow 59
		33.8	33.75	60 \rightarrow 45
	41.1	41.09	45 \rightarrow 43	
$(\text{Et})_2\text{NNH}_2 \cdot (\text{CO}_2\text{H})_2$	60.6	60.54	88 \rightarrow 73	
	27.7	27.74	73 \rightarrow 45	

Compound	Observed metastable position	Calculated position	Transition
Bu ^t -N-NH ₂ ·HCl	149.5	149.26	178 → 163
Ph-CH ₂	83.7	83.62	178 → 122
	69.4	69.38	122 → 92
	67.8	67.88	122 → 91
	50.8	50.80	163 → 91
	46.4	46.43	91 → 65
	29.5	29.49	57 → 41
PhCONHNH ₂	81.0	81.08	136 → 105
	56.50	56.46	105 → 77
	33.75	33.78	77 → 51
PhCONHNHCOPh	46.0	45.94	240 → 105
	56.5	56.46	105 → 77
	33.75	33.78	77 → 51
PhCONHNHMe	99.2 (m)	99.24	150 → 122
	97.6	97.61	150 → 121
	91.0	91.11	121 → 105
	56.5	56.46	105 → 77
	33.8	33.78	77 → 51
	m	13.50	150 → 45

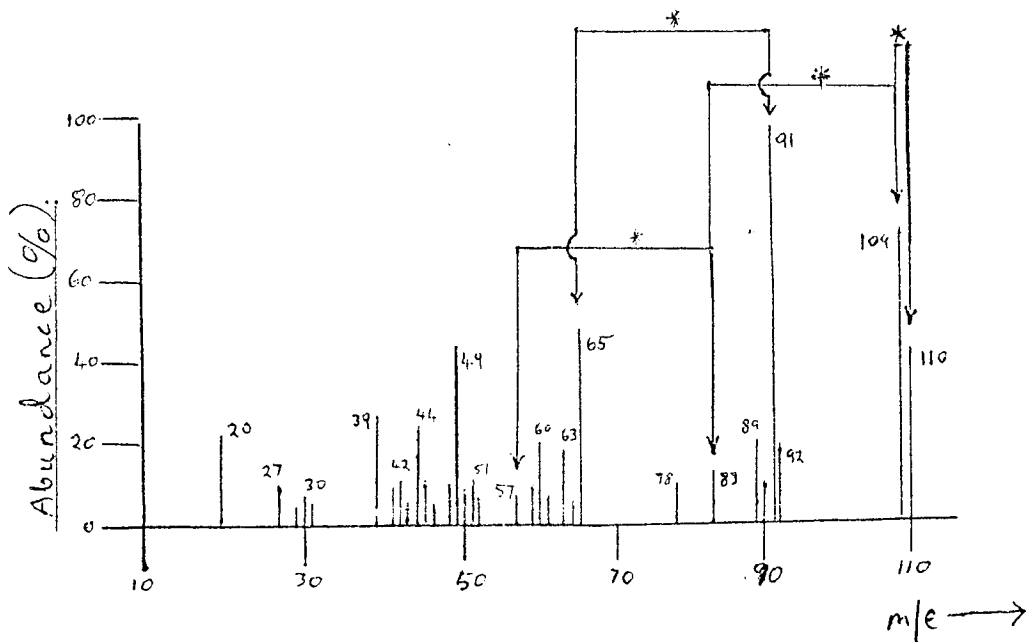
Compound	Observed metastable position	Calculated position	Transition
PhC(O)NHNHBu ^t	163.1	163.20	192 → 177
	96.4	96.31	192 → 136
	148.2	148.30	177 → 162
	81.0	81.08	136 → 105
	56.5	56.46	105 → 77
	37.2	37.36	87 → 57
	33.75	33.78	77 → 51
	29.5	29.49	57 → 41
(Me) ₂ NHNHPr ⁱ ·HCl	74.2	74.20	102 → 87
	34.2	34.06	102 → 59
(Me) ₂ NHNHBu ⁿ	29.5	29.57	116 → 59
Bu ^t NHNHPr ⁱ	101.7	101.73	130 → 115
	42.1	42.21	130 → 74
	47	47.04	74 → 59
	37.2	37.37	87 → 57
	29.5	29.49	57 → 41

* Observed metastable values quoted to two decimal places were measured on "expanded" spectra. Those quoted to one decimal place are approximate values obtained from normal scale spectra.

The symbol m indicates that the transition has been found, or checked, by the metastable defocusing technique described²²³ by Jennings.

Appendix 3The Mass Spectrum of Tropylium Fluoroborate.²³⁸

The $C_7H_7^+$ ion in the mass spectra of benzylic species has been postulated as having the fully symmetrical tropylium structure.²³⁸ As a series of 1-benzyl 2-alkylhydrazines was examined (see page 85), knowledge of the fragmentation of the tropylium ion was of particular interest. The literature contains no reference to the spectra of any tropylium salts and tropylium fluoroborate was chosen for study.

Tropylum Fluoroborate (Fig. 38).

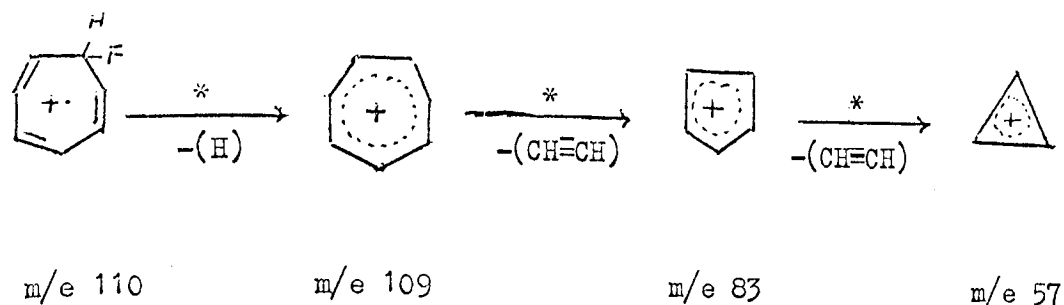
The mass spectrum of tropylium fluoroborate (Fig. 17; page 160) has the base peak at m/e 91, corresponding to the cationic portion of the salt, but also shows intense peaks eighteen (m/e 109) and nineteen (m/e 110) mass units higher. Accurate mass measurement indicates that these are due to $C_7H_6F^+$ and $C_7H_7F^+$ respectively (Table IX). In contrast tropylium hexachlorophosphate shows no intense peaks above the base m/e 91 peak.

Table IX

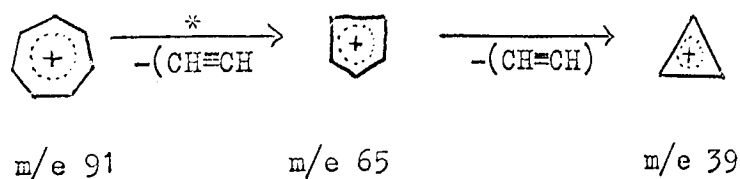
Accurate mass measurement in Tropylium Fluoroborate.

<u>Nominal Mass</u>	<u>Mass Found</u>	<u>Mass Calculated</u>	<u>Formula</u>
110	110.0527	110.0532	C_7H_7F
109	109.0451	109.0454	C_7H_6F
91	91.0546	91.0548	C_7H_7
83	83.0295	83.0297	C_5H_4F
65	65.0392	65.0391	C_5H_5
57	57.0094	57.0141	C_3H_2F
49	49.0062	49.0061	BF_2

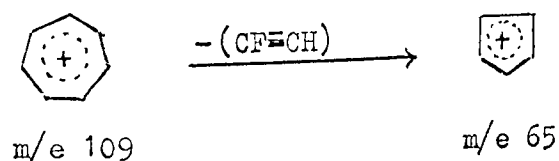
Accurate mass measurement of the other fluorine containing peaks and metastables are consistent with the following fragmentation :-



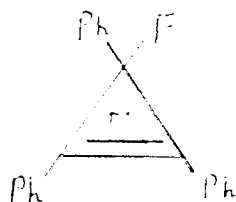
This is superimposed on the usual tropylium cleavage :-



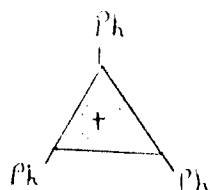
The ratio $\text{m/e } 65 : \text{m/e } 91$ in tropylium fluoroborate is 1 : 2.1. This is rather different to that observed^{239,240} in toluene (1 : 8) or ethylbenzene (1 : 11.8). The increased intensity of the $\text{m/e } 65$ peak is probably due to loss of fluoroacetylene from $\text{m/e } 109$:-



Unexpected high mass peaks, other than those due to impurities, are generally regarded as arising by thermolysis in the inlet system. Recently Battiste and Halton²⁴¹ have noted that in the mass spectrum of 1,2,3-triphenylcyclopropenyl fluoroborate the base peak occurs at $\text{m/e } 286$ (I), rather than the expected $\text{m/e } 267$ (II) :-



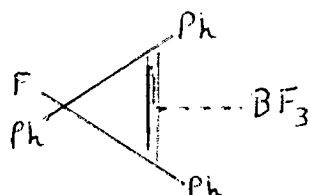
(I)



(II)

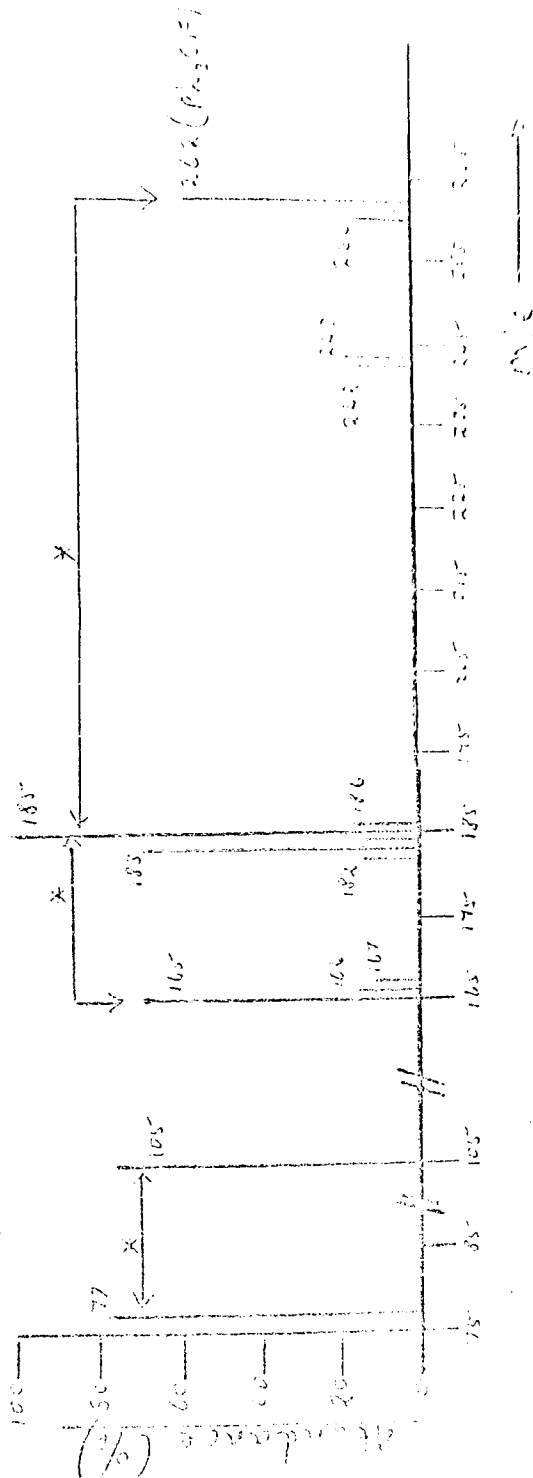
Other 3-halogeno 1,2,3-triphenylcyclopropanes give the base peak at m/e 267 (II). This behaviour is analogous to our own observations with tropylium fluoroborate and tropylium hexachlorophosphate.

Formation of m/e 286 by thermolysis of the 1,2,3-triphenylcyclopropenyl fluoroborate appears to be ruled-out by the fact that the compound sublimes unchanged at 200°C and pressures less than 10^{-2} torr. Battiste and Malton have suggested²⁴¹ that the high mass peak arises by electron-bombardment of the parent molecule in the form of "a slightly-polarised donor-acceptor complex" :-



Tropylium fluoroborate is not very likely to form a donor-acceptor complex of this type, but this explanation of the high mass peaks is feasible. To test the hypothesis further the mass spectrum of Trityl fluoroborate ($\text{Ph}_3\text{C}^+\text{BF}_4^-$) was obtained (Fig. 18, page 164). The 'propellor' shape of the cation in this salt makes the formation of a donor-acceptor complex rather unlikely.

Trikal Fluoroborate (Fig. 39). (part spectrum)



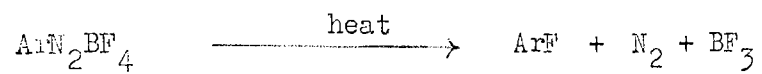
Triptyl fluoroborate was found to give a high mass peak at m/e 262 (R.A. 58.2%), nineteen mass units above the expected value for the cation m/e 243 (R.A. 18.7%). Accurate mass measurement of these peaks has not been carried out, but, in analogy to tropylium fluoroborate, they may reasonably be assigned the structures Ph_3CF^+ and Ph_3C^+ respectively. It would thus appear that this rearrangement is general to aromatic fluoroborates, but it is unlikely to be an electron-bombardment induced phenomena.

In the particular case of tropylium fluoroborate the high mass peaks are almost certainly formed by thermolysis. The following observations support this conclusion :-

1. Tropylium fluoroborate is reported²⁴² as decomposing slowly at temperatures above 210°C.
2. Metastable-defocusing does not indicate a source for either m/e 91 or m/e 110, which suggests (but does not prove) that they do not arise by an electron-bombardment process.
3. Tropylium fluoroborate gives a relatively intense m/e 49 peak; shown by accurate mass measurement to be BF_2^+ . This is the base peak in the mass spectrum of the other likely thermolysis product,²⁴³ i.e. boron trifluoride.

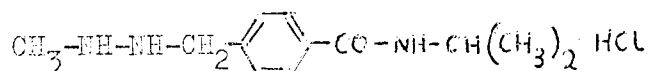
4. Older samples of tropylium fluoroborate show a large increase in the relative intensities of m/e 49, 109 and 110, suggesting that the rearrangement may occur slowly on standing even under normal conditions.

5. The rearrangement is formally analogous to the well-known Balz-Schiemann reaction²⁴⁴ :-



Appendix 4.Tumour inhibitory properties of hydrazines.

The work of Zeller, Bollag and their co-workers,^{78, 245} has shown that a number of hydrazines have tumour inhibitory properties. The most useful hydrazine carcinostat appears to be Natulan (N-iso-propyl- α (2-methylhydrazino)-p-toluamide), which is particularly effective in the treatment of Hodgkin's disease.



Natulan (Procarbazine)

Most of our present knowledge of the metabolism of hydrazines comes from work on Natulan. The metabolism and possible cytotoxic mechanisms of hydrazines have been reviewed.^{10, 45.}

Dr. T. A. Connors has undertaken the testing of the anti-tumour activity of a number of hydrazines. The general protocol employed has been described.²⁴⁶ The tests were carried out on the PC6 tumour (a solid plasma cell tumour) on groups of three animals for each dose level. The experiments were repeated for active compounds. The results obtained are shown in Table X.

Table X

Tumour inhibition of some hydrazines.

<u>Compound.</u> *	<u>LD₅₀</u> (mg./kg.)	<u>Anti-tumour effect.</u>
1. MeNHNH ₂ ·H ₂ SO ₄	60	Inactive
2. EtNHNH ₂ ·(CO ₂ H) ₂	30	Inactive
3. Pr ⁿ NHNH ₂ ·(CO ₂ H) ₂	25	Inactive
4. Pr ⁱ NHNH ₂ ·(CO ₂ H) ₂	24	Inactive
5. Bu ^t NHNH ₂ ·(CO ₂ H) ₂	40	Inactive
6. PhCH ₂ NHNH ₂ ·(H ₂ SO ₄)	25	83% inhibition at 32 mg./kg. (1/3 deaths).
7. Ph-CH ₂ -NHNH-CH ₃ ·HCl	300 (225)	100% inhibition at 160 " " " 80 " " " 40 73% " " 20 80% " " 10 (Therapeutic Index 6.4).
8. PhCH ₂ NHNHPr ⁿ	300	Inactive

* Compounds administered I.P. as a single dose (1-6 in oil and 7 and 8 in water).

It should be noted that many of the compounds were tested as oxalates. It was hoped that any carcinostatic effect would appear before the toxicity of the materials took effect.

The 1-benzyl 2-methylhydrazine (compound 7) has some activity, as would be expected from the work of Zeller and his co-workers,⁷ but the activity is of a low order.

Of interest is the fact that benzylhydrazine (compound 6) also has some activity. This has been noted previously,^{45, 247} and would indicate that the group $\text{CH}_3\text{-NHNH-CH}_2\text{-C}_6\text{H}_4\text{-R}$, considered by Zeller and his co-workers⁷ to be essential for any appreciable cytotoxic activity in hydrazines, is, in fact, not indispensable. It should be noted, however, that replacement of the N-CH_3 group of 1-benzyl 2-methylhydrazine by a N-Pr^n group apparently removes all activity, (Compound 9).

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