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A STUDY OF THE DIRECT CYCLIZATION OF HYDRAZINE DERIVATIVES TO 1,3,4-TRISUBSTITUTED-Δ^2-1,2,4-TRIAZOLIN-5-ONES

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ABSTRACT

SALEM DANIEL

A STUDY OF THE DIRECT CYCLIZATION OF HYDRAZINE DERIVATIVES TO 1,3,4-TRISUBSTITUTED-Δ^2-1,2,4-TRIAZOLIN-5-ONES

The ring closure reaction of a number of 1-benzoyl-2,4-disubstituted semicarbazides and aldehydic 2,4-disubstituted semicarbazones has been investigated. Cyclizations of the first type of derivatives were performed in an alkaline medium or, alternatively, by dehydration using zinc chloride, polyphosphoric acid or molecular sieves in benzene. An oxidation process was involved for the semicarbazone derivatives employing such oxidants as alkaline potassium ferricyanide, ferric chloride hexahydrate, isoamyl nitrite and lead tetraacetate.

The starting semicarbazide chains were synthesized through reactions of the appropriate monosubstituted hydrazines with aliphatic or aromatic isocyanates followed by benzoylation of the products according to the Schotten-Baumann method. Semicarbazones were obtained by condensation of isocyanates with monosubstituted hydrazones, the latter resulting from the reaction of hydrazines with aldehydes.

The structures of the intermediates, products and side products were verified and studied by spectroscopic methods.

TO MY MOTHER AND FATHER

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to his research director Prof. Jacques Lenoir. He is also sincerely grateful to Dr. Thomas J. Adley for providing him with mass spectra as well as going over that section of the thesis and to Dr. Oswald S. Tee for several appreciated discussions. Thanks are also due to the members serving on his committee, Dr. Zacharias Hamlet and Dr. Roderick E. Townshend, and to the Chemistry Department for its financial support. He would also like to thank his fellow students for showing true friendship and making this experience a much more meaningful one.

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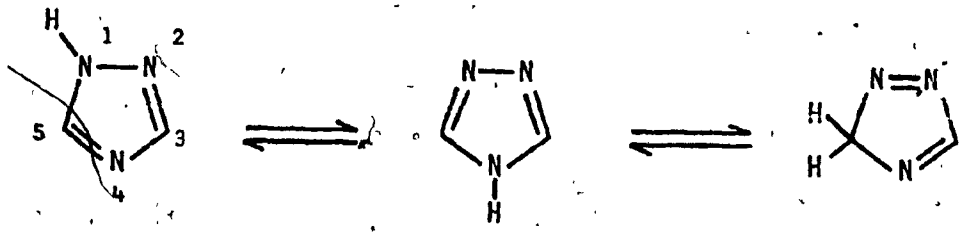
GENERAL INTRODUCTION

THE 1,2,4-TRIAZOLE RING SYSTEM

Nomenclature

The fully unsaturated five-membered heterocycle containing three nitrogen atoms and two carbon atoms is known as a triazole. Two types are possible; 1,2,3-triazole or v-triazole (vicinal) and 1,2,4-triazole or s-triazole (symmetric).[1-5] It is derivatives of the second type which are the subject of this thesis.

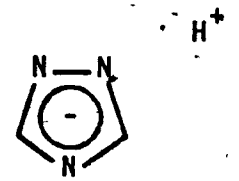


I II III

1,2,4-Triazole

The name triazole was given to this ring system by Bladin[6,7] who was responsible for the synthesis of the first such derivative. An alternative name for the ring, introduced by Andreocci,[8,9] is pyrrodiazole, which regards it as a member of a class of compounds analogous to pyrrole.

In the presence of N-substituents the relationship to the parent form is signified by describing them as 1,2,4-1H-triazole (Structure I) or as 1,2,4-4H-triazole (Structure II). This method of nomenclature is based on the assumption that the 1,2,4-triazole is capable of existing as two tautomeric forms I and II. Another representation of the system assumes that the imino hydrogen atom exists as a proton closely bound to the triazole anion as follows.



However, in the light of more recent spectroscopic evidence this representation is inappropriate.

Structure and Tautomeric Forms

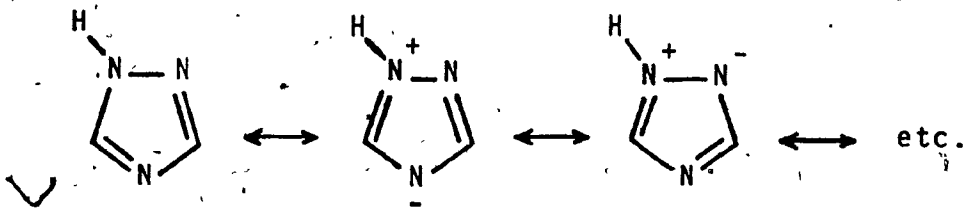
Energies of formation of azoles, based on Slater calculations,[10] predict that there is a decrease in thermodynamic stability as the number of ring nitrogen atoms increases.

Total energies of formation (eV)

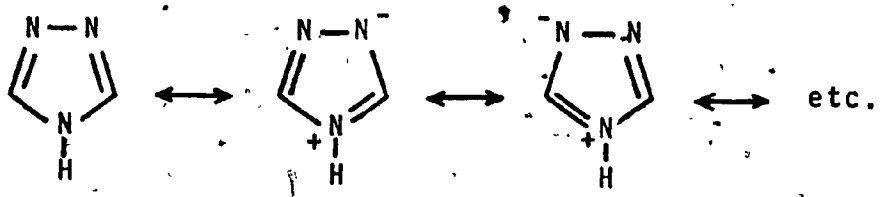
Molecule	Energy
Pyrrole	20.62
Imidazole	12.23
1,2,4-Triazole	5.02
Tetrazole*	-0.88
Pentazole	-6.37

A more accurate prediction of the stability of these structures, however, must also involve the consideration of the contributions of resonance forms as dictated by the number and positions of the heteroatoms involved and the electronic distribution in the ring. In the case of 1,2,4-triazole, the following resonance hybrids are possible.

Tautomer I



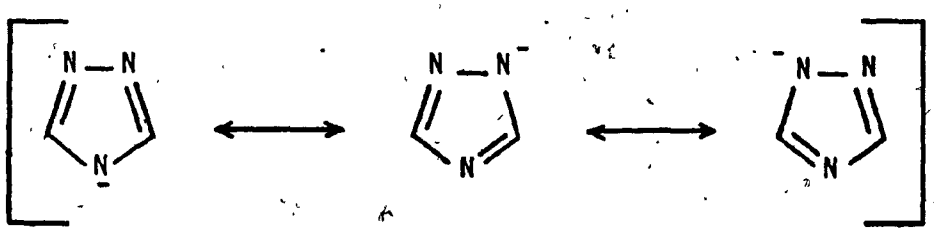
Tautomer II



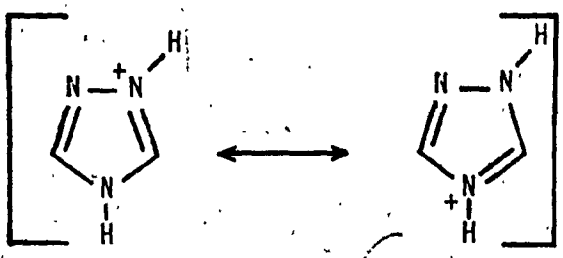
* 1,2,3,5- and 1,2,3,4-tetrazole

The existence of two kinds of nitrogen atoms, $\geq N$ and -NH which are interconvertible by the rapid proton exchange phenomenon is known for various five-membered N-heterocycles. Although an appreciable difference of ^{14}N chemical shifts should be noticed between the two, only a single ^{14}N resonance peak was observed by Saito, Tanaka, and Nagata[11] in the spectra of imidazole, pyrazole and 1,2,4-triazole in acetone, on the basis of the coalescence of ^{14}N peaks by the rapid N-H proton exchange. The inability to distinguish between the ring heteroatoms suggests that n.m.r. spectroscopy is not a useful technique for studying the tautomeric structures involved. In a proton n.m.r. study of s-triazole carried out in acetonitrile at 21°C, Potts and Crawford[12] observed one intense singlet at τ-value 1.82 corresponding to the C-3 and C-5 ring protons. This result, however, has been interpreted by these authors as being indicative of the predominance of Tautomer II with a chemical shift overlap being attributed to the presence of a symmetry element, rather than a rapid proton exchange.

On the basis of infrared studies of triazole and its derivatives containing an unsubstituted NH, it has been suggested[13,14] that the solid state structure contains a pair of ions, each of which is stabilized by resonance as shown below.

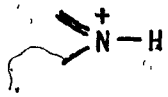


Anion



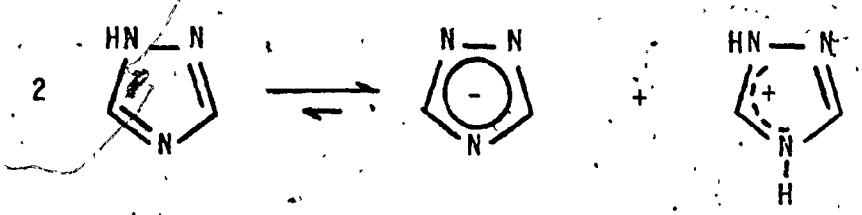
Cation

The state of affairs in the above representation being an intermolecular association in which the hydrogen atom of the imino group protonates an unsaturated nitrogen of an adjacent molecule. This suggestion was made as a result of the presence of two bands in the infrared spectrum. Both, a broad ammonia-type band at 3.5ν - 4.0ν and an immonium band at 5.5ν were present.[15] The immonium band is characteristic of the following structural element.



Furthermore, these bands are not present in the gas phase spectrum.

This suggestion may be further verified by comparing the values of acid and base dissociation constants in the following equilibrium.



pKa not reported

pKa 2.30 (25°C)[16]

A conclusion cannot be derived on such a basis since the acid dissociation constant of 1,2,4-triazole is not reported. However the amphoteric nature of the ring, as described in a subsequent section, implies that the values are of a similar order of magnitude.

Of the two likely Tautomers I and II, x-ray crystallographic determinations by Goldstein and coworkers[17] and by Deuschl[18] favour the unsymmetrical Structure I as the more stable in the solid phase at -155°C. The unsymmetrical tautomer was also found to predominate in the vapour phase as indicated by microwave spectroscopy.[19]

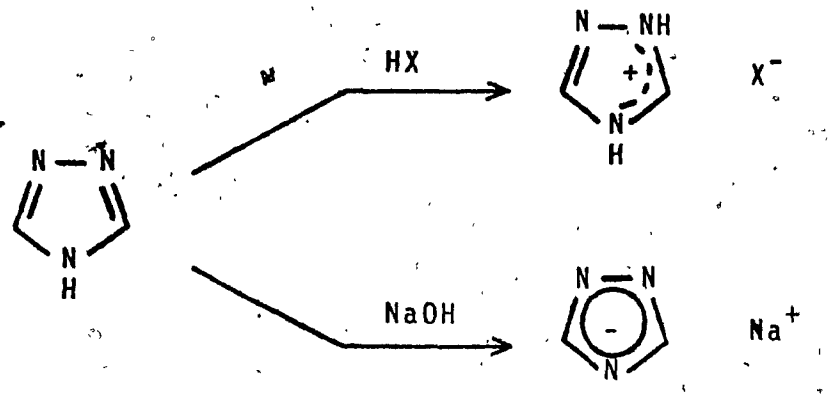
The tautomeric contribution of 1,2,4-triazole was estimated by Kroeger and Freiberg[20] from potentiometrically

determined ionization constants of the 1- and 4-alkyl derivatives. The tautomeric ratio of 1H- (unsymmetrical) to 4H- (symmetrical) 1,2,4-triazole was found to be about 5-10 : 1.

Physical Properties and Uses

The considerable polar nature of 1,2,4-triazole and its ability to hydrogen-bond is suggested by physical evidence such as melting points and dipole moments[21] and is emphasized for azoles in general as compared with other five-membered rings such as furan, thiophene and pyrrole. For example, the introduction of a methyl group in the 1-position of 1,2,4-triazole lowers the boiling point by 82°C, whereas the introduction of a 3-methyl substituent shows no appreciable difference. Likewise, the melting point of the 1-methyl substituent is nearly 100°C lower, and that of the 1-phenyl derivative 77°C lower than those of the parent compounds, while the melting points of 3-substituted 1,2,4-triazoles are not altered greatly. Solubility patterns also parallel these results as increasing the substitution on the nitrogen atoms increases the solubility in non-polar solvents. This feature of the ring was of particular importance during the isolation of the final cyclic products synthesized during the present study and is described in detail in the experimental section.

1,2,4-Triazoles are also amphoteric, forming salts with acids and bases.



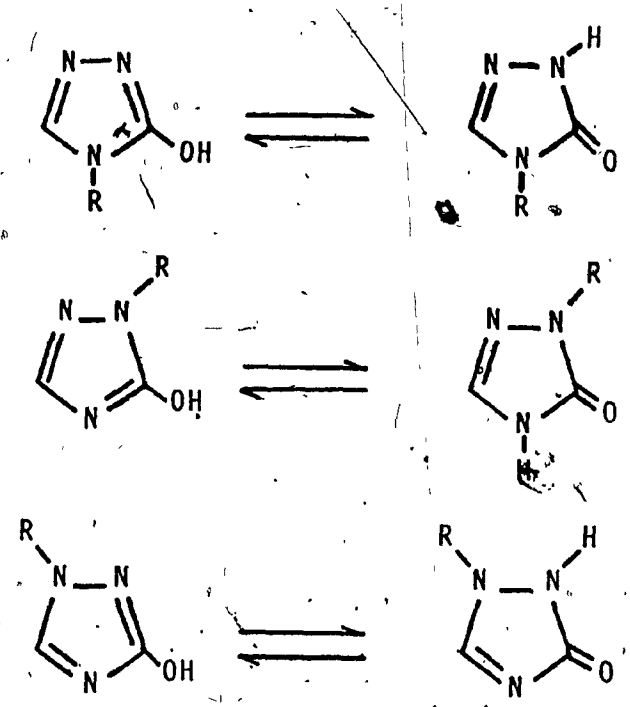
These compounds are very weak bases capable of forming quaternary salts.[1,2] Both steric and electronic effects will dictate the pattern of N-substitution with Structure (A) being the more likely product.

(A) (B)

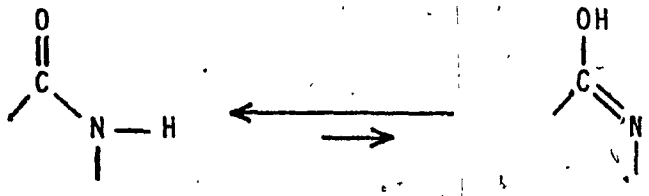
The wide scope of applications of 1,2,4-triazoles has been covered in numerous publications[1,2] and includes pharmaceutical, agricultural, photographic and various other areas.

MONO- AND DISUBSTITUTED ARYL AND ALKYL HYDROXY TRIAZOLES

5-Hydroxy-1,2,4-triazoles are potentially tautomeric. With one substituent on nitrogen, three different systems are possible.



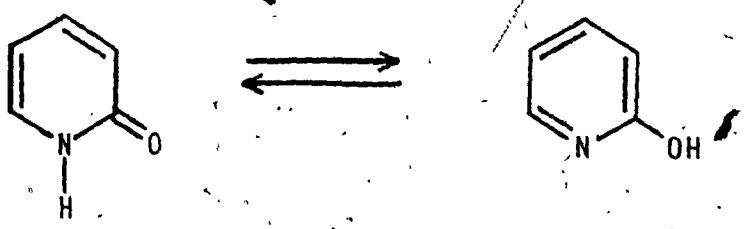
The above structures represent particular examples of lactam-lactim tautomerization which is well known in the field of heterocyclic chemistry. In general, protomeric equilibria between a wide variety of amides, Structure (1) and the corresponding iminols, Structure (2) have been shown to favour the amide form.[22]



(1) (2)

The position of the equilibrium, however, may be substantially influenced by the molecular environment as

exemplified by the classical keto-enol equilibrium between 2-pyridone (1a) and 2-hydroxypyridine (2a).

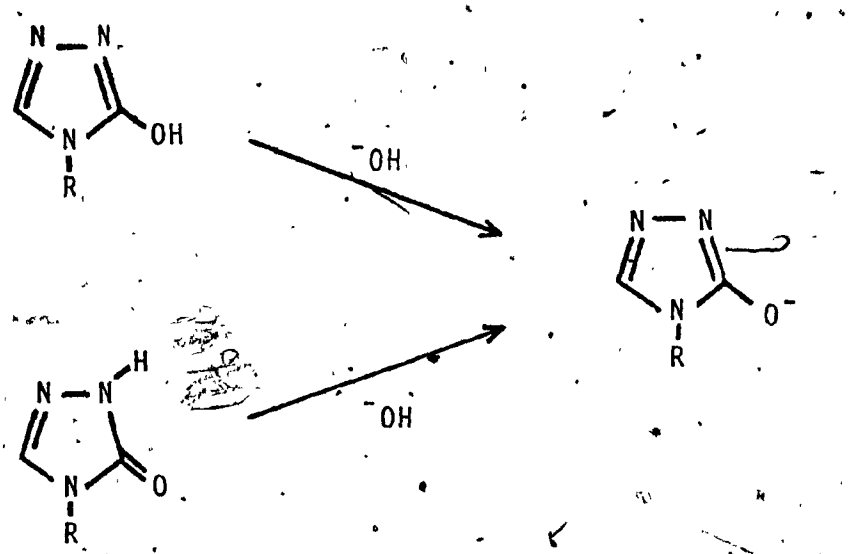


(1a) (2a)

The system represented above is one of the more thoroughly studied examples in the literature and, furthermore, is representative of the class of compounds under discussion. Katritzky and Lagowski strongly favour (1a) over (2a) in solution.[23] Structure determination by x-ray crystallography also supports (1a) in the solid state.[24] In contrast, (2a) has been reported to predominate in the vapour phase by infrared studies,[25,26] by mass spectrometric analysis[27] and by ultraviolet spectroscopy over a temperature range of 120-140°C.[25;28] These results have been included with the intention of serving as a model and offering some insight to protomeric equilibria between triazolinones and hydroxytriazoles.

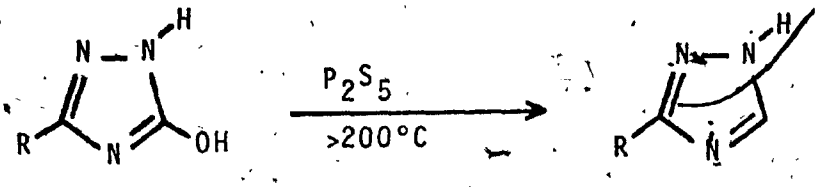
The presence of a hydroxyl or a mercapto group on the ring carbon partially removes the basic character of the

parent skeleton. In addition, these derivatives are soluble in alkaline medium, presumably through anion formation.



Finally, these compounds are important synthetic intermediates since they can be readily converted to the parent structure with such reagents as phosphorus pentoxide.[29]

Eg.



(80%)

Synthetic methods

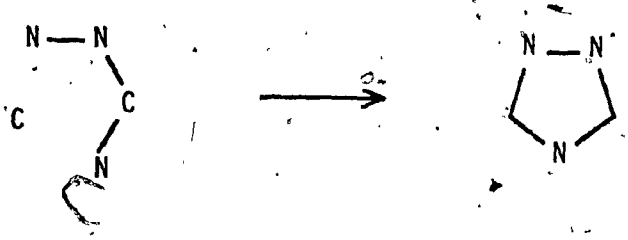
Mono- and disubstituted alkyl and aryl 5-hydroxy-1,2,4-triazoles have been obtained from a variety of methods. These can be classified under three major pathways:

I. Intermolecular condensation
II. Intramolecular condensation
III. N-Alkylation of hydroxy triazoles

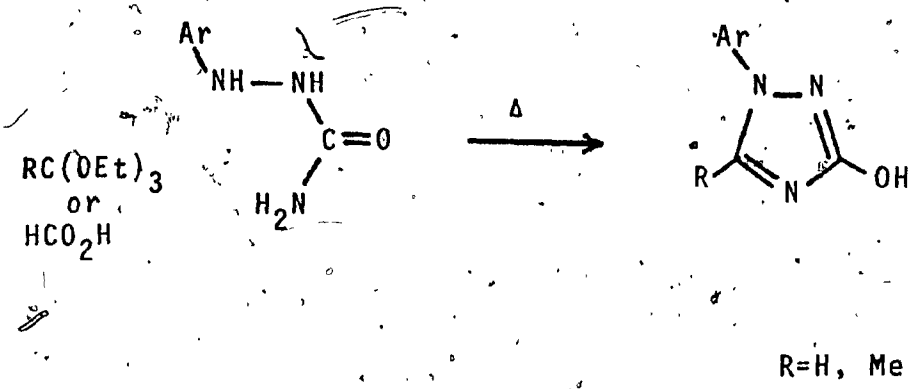
I. Intermolecular condensation

To briefly review this method, three distinct catagories are described.

i)

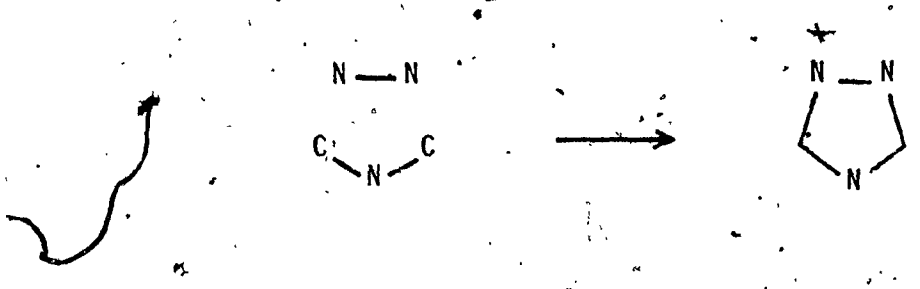


Two such examples include the treatment of 1-aryl semi-carbazides with ortho esters to yield 1,5-disubstituted-3-hydroxy triazoles,[30] and with anhydrous formic acid to give 1-aryl-3-hydroxy triazole.[31]

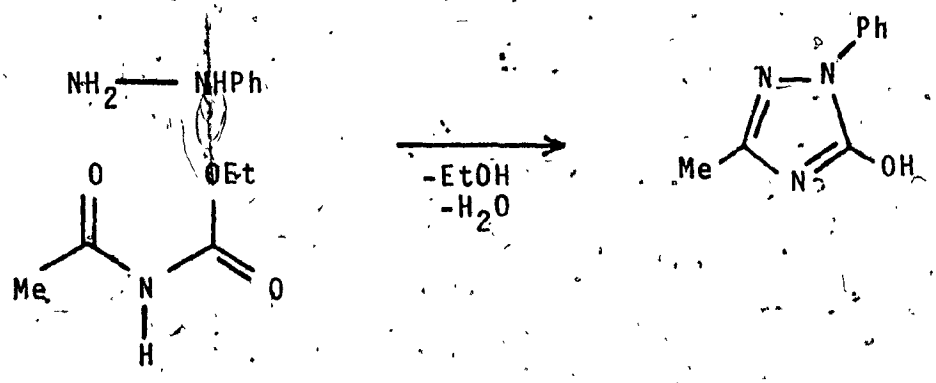


R=H, Me

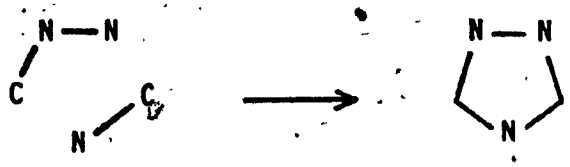
ii)



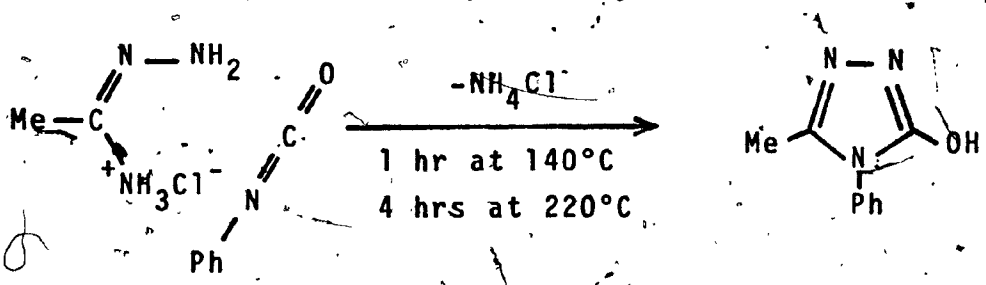
This mode is limited by the availability of substituted hydrazines, and is exemplified by the condensation of phenylhydrazine with N-acetyl urethane to give 1-phenyl-3-methyl-5-hydroxy triazole[8] as shown below.



iii)

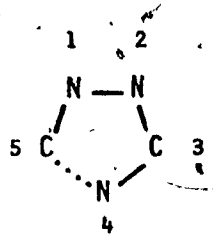


This method is exemplified by the action between amidrazone hydrochlorides and an excess of aliphatic or aromatic isocyanates.[32]

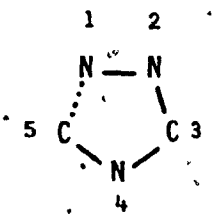


II. Intramolecular condensation

Direct cyclization into 1,2,4-hydroxy triazoles has been achieved through C-N bond formation only, and as a result, the starting chain has been restricted to one of two types shown below.

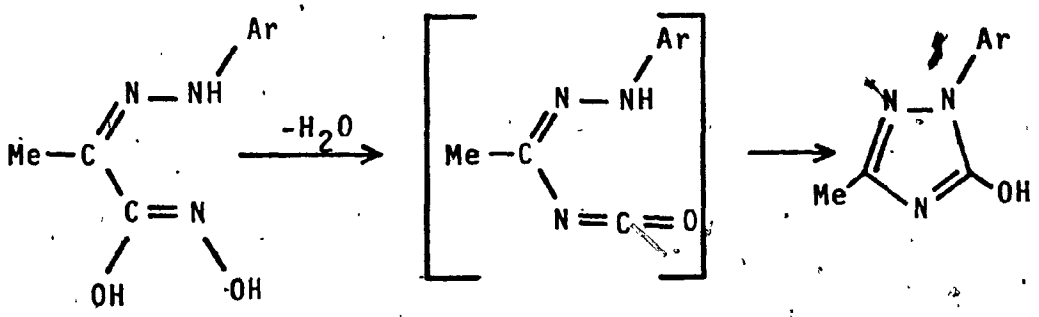


(A)

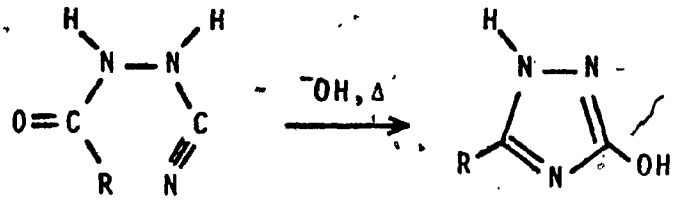


(B)

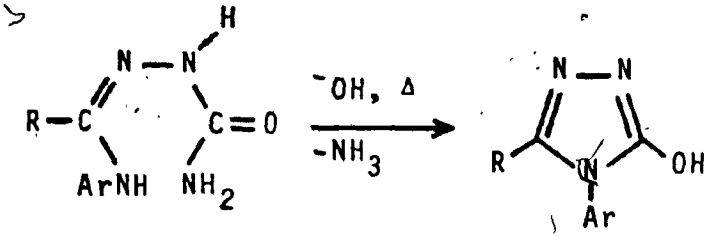
For both (A) and (B) a semicarbazide derivative may serve as the starting material. Approach (A) requires a suitable substituent on N-1, whereas approach (B) requires a substituent on N-4. An example of (B) is the cyclization of arylhydrazones of pyruvylhydroxamic acid to 1-aryl-3-methyl-5-hydroxy triazole by heating the contents in the presence of acetic anhydride and sodium acetate.[33] The reaction is expected to proceed via a Beckmann-type rearrangement leading to an isocyanate intermediate as follows.



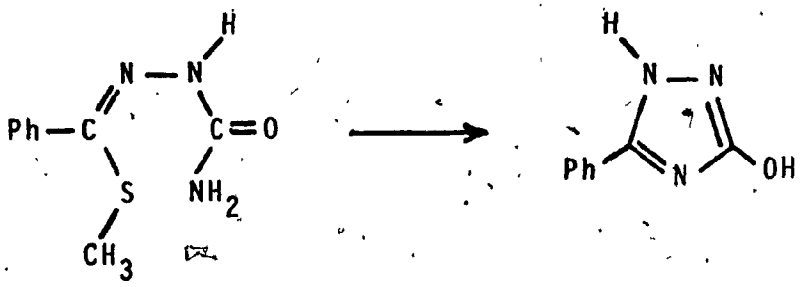
Cyclizations of type (A) are discussed in this thesis and may be achieved by refluxing cyanohydrazide derivatives[34] and N-aryl-N'-uredo amidines[35] in base. The latter proceeds with the evolution of ammonia.



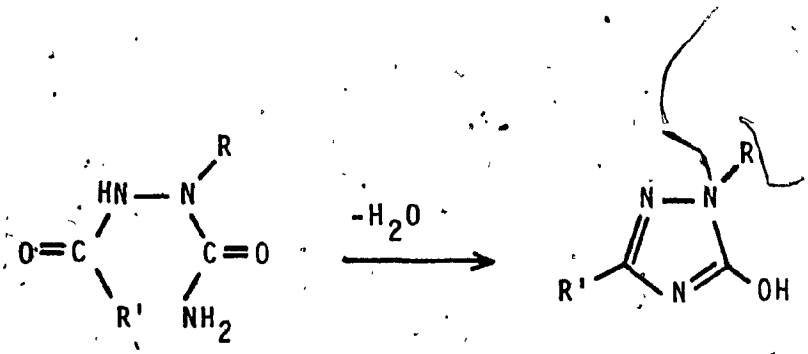
R = H
methyl
β-naphthyl
isopropyl
phenyl
benzyl

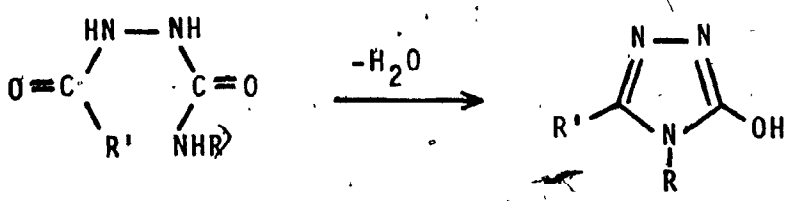


Another cyclization that may be regarded as belonging to type (A) occurs when 1-[α-(methylthio) benzylidene]-semicarbazide is pyrolyzed at 210°C. Methyl mercaptan is readily eliminated with the formation of 3-phenyl-5-hydroxy-1,2,4-triazole.[36]



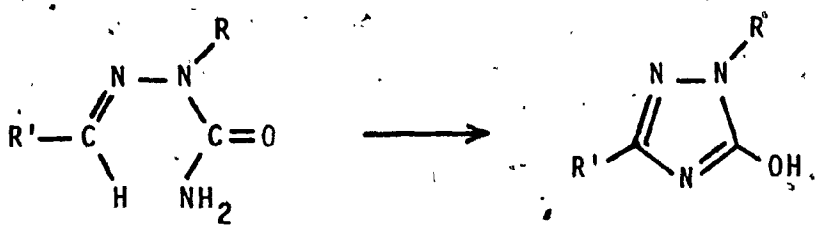
This method has also been applied for acid derivatives of semicarbazides. The reaction is normally carried out in alkaline medium at refluxing temperatures.

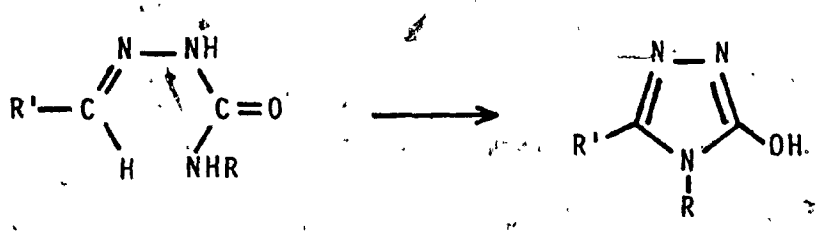




R and R' = H, alkyl or aryl

An analog of the above reaction is the oxidation of substituted semicarbazones.

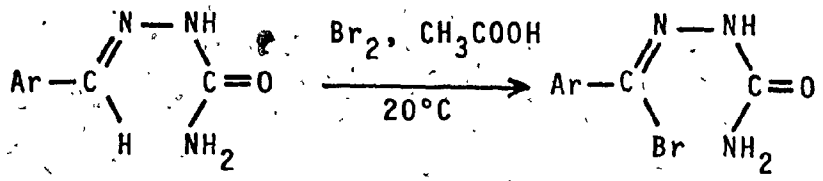




R and R' = H, alkyl or aryl

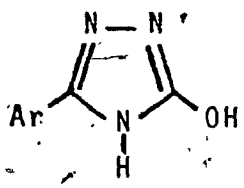
The above oxidation reaction has previously been carried out using such oxidizing agents are ferric chloride,[29,37,38,39] isoamyl nitrite,[40] potassium ferricyanide[41,42,43] and bromine in anhydrous acetic acid.[44,45]

In the last case, however, cyclizations to the hydroxy triazole and to the isomeric amino oxadiazole were observed. These results are shown below.

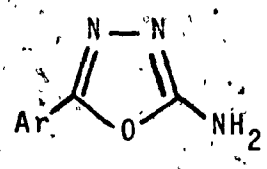


Ar = C_6H_5
$p\text{-}ClC_6H_4$
$p\text{-}BrC_6H_4$
$p\text{-}MeC_6H_4$
$p\text{-}MeOC_6H_4$

dependent on pH of medium



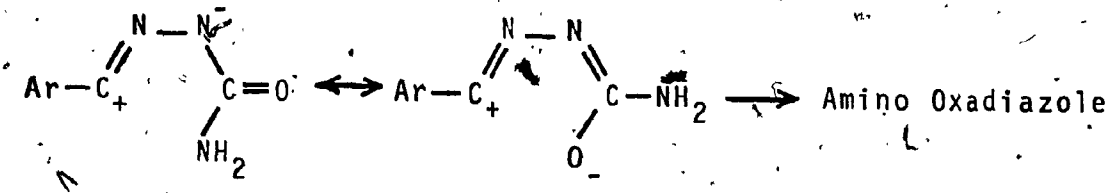
(41-51%)



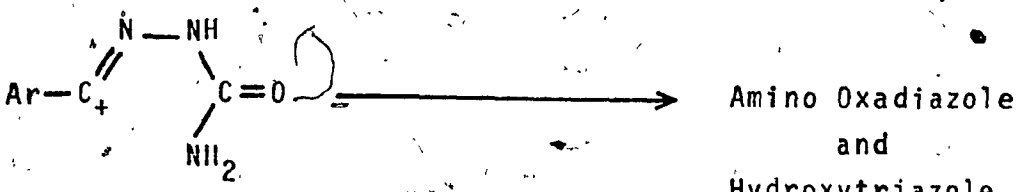
(3-7%)

The yields of hydroxy triazoles were somewhat increased when the reaction was carried out under refluxing conditions. When the 2-methyl derivatives of the above semicarbazones were refluxed in anhydrous acetic acid, they produced the corresponding hydroxy triazoles in greater than 70% yields. The authors envisage a nitrilimine as an intermediate for

the ring closure at the oxygen atom and a carbonium ion for ring closure at both the nitrogen and the oxygen atoms.



Nitrilimine

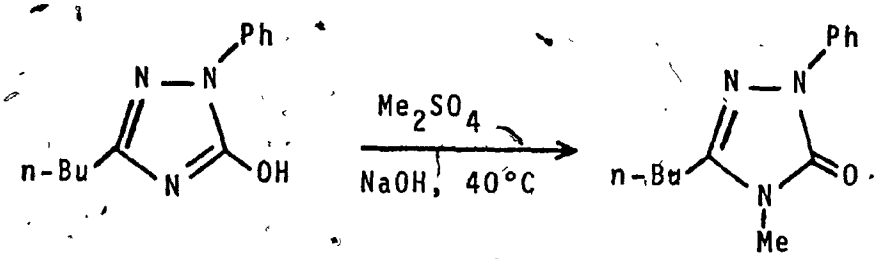


Carbonium Ion

Other oxidants which yield oxadiazoles from the reaction with semicarbazones are sodium hypobromite,[46] iodine-potassium iodide in aqueous sodium carbonate[47] and lead tetraacetate.[45,48] It is clear, therefore, that the choice of oxidizing agent used in this reaction is of a particular importance in the type of the cyclic product obtained.

III. N-Alkylation of hydroxy triazoles

This method has been limited in its applicability to alkylating agents containing alkyl groups such as methyl and ethyl. Methylation of a 1,3-disubstituted-5-hydroxy triazole is demonstrated in the following example.[49]



1,3,4-TRISUBSTITUTED ARYL-AND ALKYL-Δ^2-1,2,4-TRIAZOLIN-5-ONES

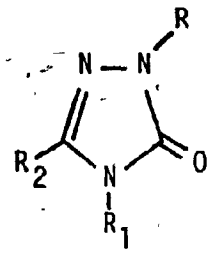
The name triazolin specifies partial saturation and Δ^2 indicates the second bond from N-1 to be unsaturated. Unlike their mono- and disubstituted analogues, these derivatives are restricted to the keto form and as a result are completely insoluble in base. This property facilitates isolation of the triazolinones when the reaction leading to them is carried out in alkali as has been encountered in the present study. Details are described in the experimental section of the thesis.

The reactions yielding the derivatives under discussion

are similar to those in which mono- and disubstituted hydroxy triazoles are obtained. However, the degree of difficulty in achieving the previously described reactions is expected to be higher in this case due to steric hindrance in the final product. i.e. the increased bulkiness of the ring substituents.

To date, only five such derivatives have been obtained by a direct cyclization reaction. Furthermore, of all 1,3,4-trisubstituted-Δ^2-1,2,4-triazolin-5-ones described in the literature, only four are substituted by a phenyl group at C-3 of the ring. These results are summarized in Table I. A ring closure reaction to yield the C-phenyl analogues has been considered in this project.

Table I. Literature Concerning 1,3,4-trisubstituted-Δ^2-1,2,4-triazolin-5-ones



R	R_1	R_2	Method	Ref.
Me	Me	Ph	Methylation of the 3-phenyl-4-methyl derivative using dimethyl sulphate	50
Me	Et	Ph	Methylation of the 3-phenyl-4-ethyl derivative using dimethyl sulphate	50
Me	Ph	Ph	Methylation of the 3,4-diphenyl derivative using dimethyl sulphate, and condensation of 1-methyl benzamidrazone hydrochloride with phenyl isocyanate at 160-220°C	50, 32
Ph	Me	n-Bu	Alkaline ring closure of 1-n-valeryl-2-phenyl-4-methyl semicarbazide	49

Table I Cont.

R	R_1	R_2	Method	Ref.
Ph	Ph	Me	Alkaline ring closure of 1-acetyl-2,4-diphenyl semicarbazide	51
Ph	Ph	Et	Alkaline ring closure of 1-propionyl-2,4-diphenyl semicarbazide	51
Ph	Ph	i-Pr	Alkaline ring closure of 1-i-butyryl-2,4-diphenyl semicarbazide	51
Ph	Ph	Ph	Oxidative ring closure of benzaldehyde-2,4-diphenyl semicarbazone using isoamyl nitrite	40

EXPERIMENTAL

The melting points of the synthesized compounds were determined using a Gallenkamp melting point apparatus and are uncorrected.

Infrared spectra were measured with a Perkin-Elmer 457 infrared spectrometer. The spectra of the solid samples were obtained through potassium bromide discs, while liquid samples were run neat using a silver chloride cell. The assigned bands were corrected according to a polystyrene standard 0.05 mm in thickness.

Nuclear magnetic resonance spectra were recorded on a Varian A-60A instrument operating at 60 MHz with a probe maintained at ambient temperature. Tetramethylsilane was used as an internal reference unless otherwise specified and chemical shifts are reported in δ values.

Elemental analyses were carried out by Galbraith Laboratories Inc., Knoxville, Tennessee for those compounds not described in the literature. Analyses were not performed in the case of non-benzoylated semicarbazides as their structures were studied through their benzoylated derivatives. Prior to analyses, samples were dried in a drying pistol (Abderhalden type) under vacuum over phosphorus pentoxide at a temperature corresponding to the heat carrier solvent used.

The identity of all intermediates and by-products were verified by n.m.r. spectroscopy used in conjunction with i.r. spectrometry. Structural assignments were based on

n.m.r., i.r., CHN analyses, mass spectrometry and thin layer chromatography.

The starting materials used are listed below.

Materials	Suppliers	Grades
Isopropyl bromide	M.C. & B.	Reagent
Hydrazine hydrate, 85%, 99%	Anachemia	Technical
Methylhydrazine	Aldrich	Reagent
Phenylhydrazine	Aldrich	Technical
(distilled four times under vacuum, once using a fractionating column. A yellow colored impurity could not be completely removed, b.p. 130°C/18 mm.)		
Ethyl isocyanate	Aldrich	Reagent
Isopropyl isocyanate	Aldrich	Reagent
tert-Butyl isocyanate	Aldrich	Reagent
Phenyl isocyanate	Baker	Reagent
" "	Anachemia	Practical
" "	Eastman	Practical
α,α,α -Trifluoro-o-tolyl isocyanate	Aldrich	Reagent
1-naphthyl isocyanate	Eastman	Reagent
Acetaldehyde	Baker	Reagent
Propionaldehyde	Eastman	Reagent
Benzaldehyde	B.D.H.	Analar
(distillation range not less than 95% between 178-181°C)		
Benzoyl chloride (distilled)	Anachemia	Reagent
Benzamide	M.C. & B.	Practical

Oxidative, dehydrative and other agents were used from the following sources.

Agents	Suppliers	Grades
Ferric chloride hexahydrate	M.C. & B.	Reagent
Potassium ferricyanide	Fisher	Technical
Isoamyl nitrite	M.C. & B.	Reagent
Zinc chloride	B.D.H.	Reagent
Polyphosphoric acid	K & K	Technical
Sodium hydroxide, pellets	Anachemia	Reagent A.C.S.
Pyridine (distilled over barium oxide and kept dried over molecular sieves, type 4A)	Anachemia	Reagent

Deuterated solvents used for n.m.r. were obtained from Merck, Sharp & Dohme (Canada) and all solvents were of minimum isotopic purity of 99.5% or better, such as: dimethyl-d_6 sulfoxide, deuterium oxide, chloroform-d and acetone-d_6.

SYNTHESES OF INTERMEDIATES AND PRODUCTS

Phenylurea

This product was prepared from aniline hydrochloride and potassium cyanate according to the method of Weith.[52] Potassium cyanate was used in 20% excess and the product obtained was recrystallized from water to give white crystals melting at 143-146° (dec.) (lit.[52] 147° dec.).

Acethydrazide

(a) The preparation was attempted using acetamide and an excess of hydrazine hydrate in water. This procedure was discontinued because of the difficulties encountered in the separation process.

(b) Forty four grams of ethyl acetate (0.5 mole) were added dropwise to 25 g. of hydrazine hydrate (85%) (0.5 mole) followed by addition of absolute ethanol until the contents went completely into solution. The resulting solution was refluxed for 18 hours. Distillation removed the unreacted ester (about 10 ml.) and part of the solvent. The concentrated solution, upon cooling, yielded a white solid which was filtered, washed with ethyl acetate and ether, and dried.

M.p. 58-68° (lit.[53] 77°).

Benzhydrazide

One hundred and twenty one grams of benzamide (1.0 mole) were refluxed with 65 g. of hydrazine hydrate (1.1 mole, 10% in excess) in 170 ml. of water for a period of 12 days, the reflux period being dictated by the intensity of the ammonia fumes given off during the course of the reaction. The white solid separating out upon cooling to room temperature was filtered and washed with water. Concentrating and cooling the filtrate gave a further amount of benzhydrazide. Yield 83%.

M.p. 110-114° (lit.[54] 112°).

Isopropylhydrazine

Following the method of Kost and Sagitullin,[55] 369 g. of isopropyl bromide (3.0 mole) were added with vigorous stirring to 624 g. of hydrazine hydrate (85%) (10.7 mole, the above authors used a four-fold excess of 99% hydrazine hydrate). With the use of a dropping funnel, the addition was extended over a period of three hours while maintaining the reaction temperature between 55° and 60°. The resulting clear solution was stirred for two additional hours at this temperature range, cooled down and extracted with ether (dried over metallic sodium ribbons) using a continuous extraction apparatus for forty four hours. No further extraction was noticed after the first thirty hours upon repetition of the preparation. The ether was then distilled off and the residue distilled from barium oxide. Yield 142 g. (64%).

B.p. 101-107°/atm.

After redistillation the product had a boiling range of 102.5-105°/atm. (lit.[55] 106-107°/748 mm.).

N.m.r.(CCl_4, δ): 3.49 (3 H, singlet, N-1(H) and N-2(H) protons), 2.73 (1 H, septet, J = 6 Hz, methine proton), 0.99 (6H, doublet, J = 6 Hz, isopropyl protons). The NH protons appear at δ3.51 for the commercially available methylhydrazine.

1-Benzoyl-2-methylhydrazine

Fifteen grams of benzamide (0.12 mole) were completely

dissolved in 50 ml. of warm water. A solution of 5.70 g. of methylhydrazine (0.12 mole) in 30 ml. of water was added. The mixture was refluxed for 71 hr. with only starting benzamide (10.30 g., 68.7%) melting at 125-129° being recovered.

1-Benzoyl-2-phenylhydrazine

A mole to mole ratio of benzamide and phenylhydrazine were subjected to the conditions described above. Once again benzamide (74.4%), melting at 125-129° was recovered.

1-Benzoyl-2-isopropylhydrazine

This product was prepared by a three-step procedure involving the reduction of the appropriate isopropylidene hydrazide with varying melting points reported for it: 109-110°,[56] 106°[57] and 117°.[58] The product obtained from the two-step procedure described in the following paragraph was identified as N-isopropyl-N,N'-dibenzoylhydrazine.

To a solution of 5.00 g. of isopropylhydrazine (67.4 mmole) in 20 ml. of cyclohexane containing 5 drops of dry pyridine, 8.58 g. of benzoyl chloride (61.0 mmole) were added slowly while cooling to -5°. The formation of a hard gum resulted. The solvent was decanted and another 30 ml. of cyclohexane were added, the gum eventually transforming to a solid. Filtration of the solid followed by water and ether washings and recrystallization from ethanol-water (7:4) gave a considerable yield of cotton-like needles melting at 164.5-165.5°.

Attempt at hydrolysis of the above product to 1-benzoyl-2-isopropylhydrazine

An amount of the above product was refluxed in 5% sodium hydroxide for 30 min. The clear solution was cooled down and precipitation was induced by acidification with hydrochloric acid. Only the starting material, melting at 162-163.5°, was isolated. Increasing the alkali concentration and reaction time did not produce positive results.

SEMICARBAZIDES

4-Phenyl semicarbazide (Compound 1-1)

A mixture of 65.05 g. of hydrazine sulfate (0.50 mole), 75.50 g. of phenylurea (0.50 mole) and 40 g. of sodium hydroxide (1.0 mole) in 200 ml. of ethanol (80%) was refluxed on a steam bath for 12 hr. The mixture was cooled, filtered and the precipitate was washed with water. Purification of the product by conversion to the hydrochloride and then to the free base in an ethanolic medium gave 24 g. (32%) of the pure product melting at 117-119°. (lit.[59] 37-40% yield melting at 120-123°).

The hydrochloride melts at 217°, the melting varies with the rate of heating (lit.[59] 215°).

I.r. (KBr, cm^{-1}): 3306-3366 (ν NH), 1680 (ν CO).

2-Methyl-4-ethyl semicarbazide (Compound 1-2)

A 200-ml. round-bottomed flask containing 15.00 g. of methylhydrazine (0.32 mole) in 40 ml. of anhydrous ether

was fitted with a stirrer, thermometer, dropping funnel and a reflux condenser mounted with a calcium chloride drying tube. 22.75 g. Of ethyl isocyanate (0.32 mole) in 30 ml. of ether were added dropwise over a period of 45 min., the reaction temperature being maintained close to 0°. Solvent removal under reduced pressure left a yellow oil which was kept under vacuum at 87° for 45 min. in order to completely remove all traces of starting material. (No biurea was formed as a by-product in this reaction). Yield 33.21 g. (88.6%).

Preparation of 2-methyl-4-ethyl semicarbazide hydrochloride

Ethanolic hydrochloric acid was added to a 1.00 g. solution of the oil (8.55 millimole) in absolute ethanol. The solid which precipitated was filtered and washed with ethanol and ether. The small, very hygroscopic needles were stored under vacuum over sodium hydroxide pellets. Yield 0.89 g. (69.0%)
M.p. 147.5-151.0° (lit.[60] 154-155°).

2-Methyl-4-isopropyl semicarbazide (Compound 1-3)

A solution of 25.50 g. of isopropyl isocyanate (0.30 mole) in 35 ml. of anhydrous ether was added to a solution of 14.00 g. of methylhydrazine (0.33 mole) in 50 ml. of ether over a period of 50 min. at 0°. The solution was then stirred at room temperature for one hour. A slight turbidity was observed due to 1,6-di-isopropyl-3-methyl biurea (compound 2-3) and removed by filtration. The

filtrate was evaporated to give a residue which was kept under vacuum to remove all traces of solvent and starting materials. Yield 38.0 g. (96.4%).
M.p. 40-47°.

The product was further purified by extraction with a minimum amount of cold ether affording colorless, transparent, crystalline plates melting at 49.5-53°. Decomposition accompanied by brown coloration occurs when the product is left exposed to the atmosphere. Attempts to form the corresponding hydrochloride failed.

2-Methyl-4-t-butyl semicarbazide (Compound 1-4)

A solution of 24.78 g. of t-butyl isocyanate (0.25 mole) in 25 ml. of ether was added to a solution of 11.52 g. of methylhydrazine (0.25 mole) in 75 ml. of ether over a period of 1 hr. at -5 to 0°, followed by stirring for 75 min. at room temperature. Filtration and concentration of the filtrate gave a crude product. Yield 32 g. (88%) melting at 93-100.5°. Even after repeated extractions with ether the degree of purity could not be improved. Recrystallization from water resulted in transparent needles melting at 91-97.5°.

Biurea derivative (Compound 2-4)

1,6-Di-t-butyl-3-methyl biurea, 0.4 g. (1.4% based on the isocyanate used) melting at 171.5-172.5° was also

recovered and dried for 5.5 hr. (ether).*

I.r. (KBr, cm^{-1}): 3341 (ν NH), 2973 (aliphatic ν CH), 1660 (ν CO).

Anal. calcd. for $C_{11}H_{24}N_4O_2$: C, 54.04; H, 9.89; N, 22.91. Found: C, 54.04; H, 9.90; N, 22.88.

2-Methyl-4-phenyl semicarbazide (Compound 1-5)

A solution of 88.0 g. of phenyl isocyanate (0.74 mole) in 50 ml. of ether was added to a solution of 34.0 g. of methylhydrazine (0.74 mole) in 65 ml. of ether over a period of 30 min. with cooling. The solid obtained was filtered cold. The insoluble biurea derivative was separated from the semicarbazide by extraction with boiling isopropyl alcohol. The filtrate was concentrated and salting out with ether produced a pure semicarbazide. Conversion of the semicarbazide to the hydrochloride and back to the free base did not improve its melting point.

Yield 37 g. (30%).

M.p. 87-91.5° (lit.[60] 93-94°).

I.r. (KBr, cm^{-1}): 3346, 3306, 3206 (ν NH), 2950 (aliphatic ν CH), 1625-1655 (ν CO).

The nature of the product was further confirmed by conversion to its semicarbazone derivative melting at 106-108° (lit.[60] 108°).

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* indicates drying temperature to be that of refluxing ether.

Biurea derivative (Compound 2-5)

Yield 18 g. (9% based on the isocyanate used).
M.p. 202-206° (lit.[60] 204°).
I.r. (KBr, cm^{-1}): 3381, 3276 (ν NH), 2920 (aliphatic ν CH), 1665 (ν CO).

2-Methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide (Compound 1-6)

A solution of 11.06 g. of α,α,α-trifluoro-o-tolyl isocyanate (59.1 mmole) in 20 ml. of ether was added to 2.72 g. of methylhydrazine (59.1 mmole) in 45 ml. of anhydrous ether over a period of 30 min. at -10 to -3°. After stirring for 90 min. at room temperature, the white solid which formed was filtered and identified as 1,6-di-(α,α,α-trifluoro-o-tolyl)-3-methyl biurea. The filtrate was evaporated to dryness under vacuum and the solid thus obtained was further separated from traces of the biurea derivative by recrystallization from water. A slight decomposition was noticed during the recrystallization process.

The semicarbazide, in the form of white needles, had a naphthalene-like odor and was dried for 21 hr. (ether). The yield was 11.6 g. (84.4%) prior to recrystallization.
M.p. 97.5-99° (from water).
Anal. calcd. for $C_9H_{10}N_3OF_3$: C, 46.36; H, 4.32; N, 18.02.
Found: C, 46.47; H, 4.26; N, 18.13.

Biurea derivative (Compound 2-6)

Further purified by recrystallization from benzene along with charcoal treatment. The final product was in the form of white needles with the same characteristic odor as that of the semicarbazide. The derivative was dried for 12 hr. (ether). Yield 1.5 g. (5.9% based on the isocyanate used). M.p. 166-167°.

I.r. (KBr, cm^{-1}): 3446, 3296 (ν NH), 1702, 1667 (ν CO).

Anal. calcd. for $C_{17}H_{14}N_4O_2F_6$: C, 48.58; H, 3.36; N, 13.33. Found: C, 48.64; H, 3.50; N, 13.25.

2-Isopropyl-4-ethyl semicarbazide (Compound 1-7)

A solution of 19.2 g. of ethyl isocyanate (0.27 mole) in 35 ml. of ether was added to 20.0 g. of isopropyl-hydrazine (0.27 mole) in 45 ml. of ether over a period of 105 min. with cooling below 0°. The slurry was stirred for another 90 min. then filtered leaving behind the biurea derivative which was washed with ten 10-ml portions of ether. Evaporation of the filtrate and the washings under reduced pressure yielded a yellow oil which, on standing, yielded a waxy solid. An n.m.r. spectrum of the product shows the possible existence of two isomers while T.L.C. using a silica gel plate and ethanol as eluent shows only one spot. The yield of semicarbazide was 29.7 g. (75.9%). Vacuum distillation gave a major fraction, b.p. 96-99°/0.75 mm., melting at 50-63° and a minor fraction, b.p. 124-126°/0.75 mm. Attempts to prepare the hydrochloride salt failed, however a pure benzoyl derivative was

obtained.

The crude biurea derivative (compound 2-7) was recrystallized from isopropyl alcohol and dried for 10.5 hr. (ether). Yield 5.9 g. (10% based on the isocyanate used). M.p. 178-179°.

I.r. (KBr, cm^{-1}): 3306 (ν NH), 2986, 2943 (aliphatic ν CH), 1648 (ν CO).

Anal. calcd. for $C_9H_{20}N_4O_2$: C, 49.94; H, 9.31; N, 25.88. Found: C, 50.01; H, 9.39; N, 26.01.

2,4-Di-isopropyl semicarbazide (Compound 1-8)

A solution of 25.5 g. of isopropyl isocyanate (0.30 mole) in 25 ml. of ether was added to a solution of 22.2 g. of isopropylhydrazine (0.30 mole) in 75 ml. of ether over a period of 50 min. at a temperature range between -8 and -2°. The mixture was then stirred at room temperature for 40 min. The 1,3,6-tri-isopropyl biurea which separated out of the solution was filtered and washed thoroughly with ether. The crude product was purified by extraction with hot ethyl acetate while the filtrate and washings, upon concentration and cooling, gave the semicarbazide. Both products were then recrystallized from ethyl acetate. The semicarbazide was further recrystallized from 95% ethanol. Yield 29.7 g. (62.2%, crude).

M.p. 104-109°.

The conversion of the product to the benzaldehyde semicarbazone derivative was carried out by the addition of benzaldehyde to the ethyl acetate solution and heating.

The product precipitated out as transparent needles by the addition of aqueous ethanol and had a melting range of 86.5-89.5°.

Anal. calcd. for $C_{14}H_{21}N_3O$: C, 67.93; H, 8.55; N, 16.98. Found: C, 67.89; H, 8.61; N, 16.84.

The biurea derivative (compound 2-8) was dried for 18.5 hr. (ether). Yield 3.8 g. (5.2% based on the isocyanate used).

M.p. 187-188°.

Anal. calcd. for $C_{11}H_{24}N_4O_2$: C, 54.04; H, 9.89; N, 22.91. Found: C, 54.14; H, 10.02; N, 22.83.

2-Isopropyl-4-t-butyl semicarbazide (Compound 1-9)

A solution of 24.78 g. of t-butyl isocyanate (0.25 mole) in 45 ml. of ether was added to a solution of 18.53 g. of isopropylhydrazine (0.25 mole) in 90 ml. of ether over a period of 1 hr. at 0°. Stirring of the reaction mixture was continued for 2 hr. at room temperature. Filtration of the suspension followed by washings with three 20-ml portions of ether gave 35 g. of a mixture of the semicarbazide and the biurea derivative melting at 115-140°. Extraction with a Soxhlet apparatus using ether as solvent eliminated most of the biurea. The product melted at 122-137°.

Further attempts at separation of the two components by extraction with different solvents, by preparation of the hydrochloride and sulfate salts of the semicarbazide, and by recrystallization all failed. A small amount of the nitrate salt was successfully prepared and its structure was

confirmed by n.m.r. spectroscopy. The nitrate salt melted at 111-113°.

Biurea derivative (Compound 2-9)

1,6-Di-isopropyl-3-t-butyl biurea was recovered upon recrystallization of the crude product from ethanol. The solid, in the form of shiny white needles, was dried for 13 hr. (ether).

M.p. 155-155.5°.

Anal. calcd. for $C_{13}H_{28}N_4O_2$: C, 57.30; H, 10.36; N, 20.56. Found: C, 57.28; H, 10.39; N, 20.36.

2-Isopropyl-4-phenyl semicarbazide (Compound 1-10)

A solution of 31.7 g. of phenyl isocyanate (0.27 mole) in 35 ml. of ether was added to 20.0 g. of isopropyl-hydrazine (0.27 mole) in 55 ml. of ether over a period of 2 hr. while cooling in ice. Further stirring with slight heating was required since the odor of the isocyanate was still persistent. The resulting suspension was filtered cold, washed with nine 10-ml portions of cold ether and extracted with ethanol and acetone. Evacuation of the extracts to dryness afforded the semicarbazide. Yield 26 g. (50%).

M.p. 91.5-95°.

The biurea derivative (compound 2-10) was dried for 10.5 hr. (ether). Yield 12 g. (14% based on the isocyanate used).

M.p. 185.5°.

Anal. calcd. for $C_{17}H_{20}N_4O_2$: C, 65.34; H, 6.45; N, 17.93. Found: C, 65.28; H, 6.52; N, 17.93.

When the addition of the two reagents was made over a period of 20 min. and stirring was continued for 75 min. at room temperature, under the same conditions, the ratio of semicarbazide to biurea was reduced from 78:22 to 64:36.

2-Isopropyl-4-α,α,α-trifluoro-o-tolyl semicarbazide (Compound 1-11)

A solution of 8.00 g. of α,α,α-trifluoro-o-tolyl isocyanate (42.8 mmole) in 10 ml. of ether was added to 3.18 g. of isopropylhydrazine (42.9 mmole) in 15 ml. of ether over a period of 75 min. at a temperature range from -10 to 0°, followed by stirring at room temperature overnight. The solid which precipitated out of the solution was filtered, washed with cold ether and found to consist solely of the corresponding biurea. The filtrate was evaporated under vacuum and the solid left behind was treated with cyclohexane. The suspension was filtered and the insoluble residue was extracted with warm ethanol. The insoluble fraction was the biurea derivative while the alcohol solution, after concentration, gave crystals of a product melting at 69-74°. The product did not correspond to the expected semicarbazide. The n.m.r. spectrum of the crystals in carbon tetrachloride contained the following bands: 9.04 δ(1 H, singlet, N-4(H) proton), 6.84-8.58 δ (5 H, multiplet), 3.90 δ (1 H, broad singlet), 3.10 δ (1 H,

septet, J = 6.5 Hz, methine proton), 1.08 δ (6 H, doublet, J = 6 Hz, isopropyl protons). The total integration is correct for 14 H, however, the spectrum does not compare with that of the 2-methyl analog of the above semicarbazide derivative in DMSO-d_6.

Biurea derivative (Compound 2-11)

Recrystallized from dilute alcohol and yielded shiny crystalline needles with the characteristic naphthalene-like odor of the trifluoro derivatives. The product was dried for 6 hr. (ether).

M.p. 149.5-150°.

Anal. calcd. for $C_{19}H_{18}N_4O_2F_6$: C, 50.90; H, 4.05; N, 12.50. Found: C, 50.82; H, 4.24; N, 11.98.

2-Phenyl-4-ethyl semicarbazide (Compound 1-12)

A solution of 19.77 g. of ethyl isocyanate (0.28 mole) in 25 ml. of ether was added to 31.00 g. of phenylhydrazine (0.29 mole) dissolved in 45 ml. of ether over a period of 1 hr. with the temperature kept below 20°. Stirring was continued for an additional 30 min. at room temperature and the resulting suspension was filtered and washed with ten 40-ml portions of ether to yield 45.10 g. (90.6%) of a white powder corresponding to the semicarbazide.

M.p. 150.5-152°.

The biurea derivative was not present as a by-product in the reaction mixture.

1-BENZOYL SEMICARBAZIDES

1-Benzoyl-4-phenyl semicarbazide (Compound 3-1)

(a) To a solution of 3.00 g. of 4-phenyl semicarbazide (19.9 mmole) in 18 ml. of anhydrous pyridine, 2.80 g. of benzoyl chloride (19.9 mmole) were added dropwise. The resulting solution was stirred for an additional 90 min. at room temperature and the precipitate formed upon dilution with water was filtered, washed with water and then with isopropyl alcohol. Further purification was achieved through filtration of the dilute alkaline solution of the product. The final product was then recovered in a pure form by acidification of the alkaline filtrate. Yield 4.00 g. (78.9%).

M.p. 201.5-203° (lit. 209-210°,[61] 192-193°[62]).

(b) An attempt at benzoylation of 4-phenyl semicarbazide by the classical Schotten-Baumann method failed.

(c) A solution of 40.0 g. of phenylurea (0.29 mole) and 50.0 g. of benzhydrazide (0.37 mole) in 120 ml. of absolute ethanol was refluxed for 12 hr. The precipitate formed was filtered and washed with isopropyl alcohol to yield ~10 g. of a product melting at 228-233°. The crude product was dissolved in 5% sodium hydroxide, an insoluble portion was filtered off, and the yellow filtrate gave a white solid which was filtered, washed with water, drained well and washed with ether.

M.p. 233.5-237°; 237-239.5° (from ethanol).

The formation of a brown color was observed during melting. The structure of the product was elucidated as 1,2-dibenzoylhydrazine (~23%) and confirmed by comparison with an authentic sample prepared as follows:

To a cold solution of 2.5 g. hydrazine hydrate 99% (.05 mole) in 80 ml. pyridine, 12.6 g. benzoyl chloride (0.09 mole) were added dropwise. This was followed by stirring at room temperature for 5 min. and diluting with 150 ml. of water. The white product precipitating out was filtered and washed with ten 50-ml. portions of water, two 20-ml. portions of isopropyl ether and finally with 20 ml. of ethyl ether. The yield was 6.8 g. (63% based on the starting hydrazine).

M.p. 237.5-238.5°; 239-240° (from ethanol).

The mixed melting point of the two products acquired by both methods was 239.5-240.5°.

Arndt, Loewe and Ergener[63] obtained the product (m.p. 241°) by starting with hydrazine sulfate and benzoyl chloride in potassium hydroxide solution. When preparation of the product was initially attempted according to this method, negative results were obtained.

1-Benzoyl-2-methyl-4-ethyl semicarbazide (Compound 3-2)

The turbid solution resulting from dissolving 10.00 g. of 2-methyl-4-ethyl semicarbazide (85.3 mmole, the crude product in the form of an oil was used without further purification) in 45 ml. of dry pyridine was filtered. The

clear solution was cooled in ice and 11.99 g. of benzoyl chloride (85.3 mmole) were added followed by further stirring of the contents for 90 min. at room temperature. Upon dilution of the reaction mixture a white product was formed, filtered and washed thoroughly with water. Yield 12.38 g. (65.5%).

M.p. 164-166°.

Working up the mother liquor gave 8.3% (based on benzoyl chloride used) of benzoic acid (m.p. 117-122.5° confirmed from n.m.r. and i.r. spectra). The resulting filtrate, upon acidification, gave an additional 8% of the semicarbazide derivative. Recrystallization of the semicarbazide from isopropyl alcohol followed by drying for 8 hr. (ether) afforded a white shiny crystalline product melting at 163.5-165°.

Anal. calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.80; H, 6.85; N, 18.97.

Similar results were obtained when 2-methyl-4-ethyl semicarbazide hydrochloride (the purified form) was used.

1-Benzoyl-2-methyl-4-isopropyl semicarbazide (Compound 3-3)

To a cooled solution of 16.00 g. of 2-methyl-4-isopropyl semicarbazide (0.122 mole, m.p. 40-47°) in 50 ml. of dry pyridine, 17.15 g. of benzoyl chloride (0.122 mole) were added followed by stirring for 90 min. at room temperature. Filtration of the pyridine hydrochloride formed and evacuation of the filtrate under reduced pressure resulted in a yellow oil. Addition of 25 ml. of water to the oil

gave an oily suspension which was once again evacuated to dryness. Repetition of the previous step two more times resulted in a complete azeotropic stripping of the pyridine and a white solid which was washed thoroughly with water, filtered and re-washed with ether (the above procedure has been followed in all cases where dilution of the pyridine reaction solution with water produced an oil). Yield 18.10 g. (63.1%).

M.p. 153-157°.

Recrystallization using isopropyl alcohol and ethyl acetate afforded shiny, sugar-like crystals which were dried for 11.5 hr. (ether).

M.p. 155.5-157.5°.

Anal. calcd. for $C_{12}H_{17}N_3O_2$: C, 61.26; H, 7.28; N, 17.86. Found: C, 61.39; H, 7.34; N, 17.80.

1-Benzoyl-2-methyl-4-t-butyl semicarbazide (Compound 3-4)

To a cold solution of 4.07 g. of 2-methyl-4-t-butyl semicarbazide (28.0 mmole, m.p. 89-94.5°) in 15 ml. of pyridine, 3.94 g. of benzoyl chloride (28.0 mmole) were added. The mixture was stirred for 2 hr. and 15 min. at room temperature. Filtration of the suspended pyridine hydrochloride and dilution of the filtrate with water gave a solid which was filtered, washed with ten 10-ml. portions of water followed by three 5-ml. portions of ether. Yield 5.83 g. (83.5%).

M.p. 142-146.5°.

Recrystallization from benzene yielded small white needles which were dried for 12 hr. (ether) and melted at 143.5-145.5°.

Anal. calcd. for $C_{13}H_{19}N_3O_2$: C, 62.61; H, 7.68; N, 16.85. Found: C, 62.90; H, 7.86; N, 16.79.

1-Benzoyl-2-methyl-4-phenyl semicarbazide (Compound 3-5)

To a solution of 8.00 g. of 2-methyl-4-phenyl semicarbazide (48.5 mmole, m.p. 87-91.5°) in 45 ml. of pyridine, 6.82 g. of benzoyl chloride (48.5 mmole) were added. The mixture was stirred for 2 hr. and 15 min. at 25-30°. Upon dilution with 110 ml. of water a white suspension was formed, filtered and washed with water to yield 12.10 g. (92.8%) of the product.

M.p. 144-145.5°.

Recrystallization from isopropyl alcohol gave white needles melting at 144.5-145.5°.

1-Benzoyl-2-methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide (Compound 3-6)

Isolation of the pure form of this product was extremely difficult. To a solution of 0.38 g. of 2-methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide (1.63 mmole, m.p. 97-98.5°) in 5 ml. of pyridine, 0.23 g. of benzoyl chloride (1.63 mmole) were added. The mixture was refluxed with precautions against humidity from the air for 1 hr. and 50 min. The color of the solution gradually changed from pink to a deep yellow. Upon dilution of the solution with

water, a yellow oil formed which turned into a gum and was eventually converted to a solid by stripping off all traces of pyridine and stirring in cold water. Extraction of this residue with 20 ml. of boiling water left behind an oil which was converted to a solid upon cooling. This solid proved to be the expected product. The yield (~85% crude) could not be precisely determined due to difficulty encountered in the isolation process.

M.p. 117-123°.

When the above procedure was repeated with a reflux period of 3 hr. a product corresponding to the benzoylated semicarbazide was isolated and had a melting range of 121-126°. The n.m.r. spectrum of this solid was identical to the one above (see Table X of Discussion), however the singlet at δ 10.14 was missing.

N.m.r. (CCl_4 + 3 drops of acetone, δ): 6.86-7.63, 7.76-8.40 (10 H, multiplet), 3.17 (3 H, singlet, methyl protons).

1,6-Di-(α,α,α-trifluoro-o-tolyl)-3-methyl biurea was isolated as well and after recrystallization from ethanol had an m.p. 169-170°.

N.m.r. (DMSO-d_6, δ): 9.04 (1 H, singlet, N-3(H) proton), 8.40, 8.54 (2H, two singlets, N-1(H) and N-6(H) protons), 7.12-8.23 (8H, multiplet, phenyl protons), 3.14 (3 H, singlet, methyl protons).

I.r. (KBr, cm^{-1}): 3446, 3294 (ν NH), 1703, 1665 (ν CO).

When the above reaction was attempted with only slight heating in ether containing a trace of pyridine, a mixture

of products was once again obtained.

1-Benzoyl-2-isopropyl-4-ethyl semicarbazide (Compound 3-7)

To a cooled solution of 15.22 g. of 2-isopropyl-4-ethyl semicarbazide (0.105 mole, the distilled oil was used) in 60 ml. of pyridine, 15.50 g. of benzoyl chloride (5% in excess of 0.105 mole) were added. At the end of the reaction, the resulting salt was filtered and the filtrate was concentrated to a yellow oil which hardened to a transparent glass on standing. Extraction of this material with 70 ml. of ether left behind a white powder which was filtered and washed thoroughly with water and ether. The product obtained, still somewhat crude, was extracted with a Soxhlet apparatus using di-isopropyl ether for 5 hr. The ether was evaporated and the product was dried for 12 hr. (methanol). Yield 11 g. (42%).

M.p. 112-114°.

Anal. calcd. for $C_{13}H_{19}N_3O_2$: C, 62.61; H, 7.68; N, 16.85. Found: C, 62.65; H, 7.69; N, 16.65.

An attempt to purify the product by distillation resulted in decomposition to 1-benzoyl-2-isopropylhydrazine, the structure of which was confirmed by n.m.r. and i.r. spectra and found to be analogous to the by-product obtained during the reflux of 1-benzoyl-2-isopropyl-4-t-butyl semicarbazide in 5% sodium hydroxide as described in a subsequent synthesis. The decomposition product had b.p. 132-134°/0.55 mm. and m.p. 107-112° (lit.109-110°[56], 106°[57]).

N.m.r. (DMSO-d_6 + CCl_4, δ): 7.80-8.16, 7.24-7.60 (multiplet, phenyl protons), 4.90-6.40 (broad singlet, N-2(H) proton), 3.16 (septet, J = 6.5 Hz, methine proton), 1.04 (doublet, J = 6.5 Hz, isopropyl protons).

I.r. (KBr, cm^{-1}): 3296 (ν NH), 2976 (aliphatic ν CH), 1642 (ν CO).

1-Benzoyl-2,4-di-isopropyl semicarbazide (Compound 3-8)

To a cooled solution of 9.00 g. of 2,4-di-isopropyl semicarbazide (56.6 mmole, m.p. 105-112°) in 35 ml. of pyridine, 8.04 g. benzoyl chloride (57.2 mmole) were added. The reaction mixture was then stirred for 90 min. at room temperature. Filtration of the pyridine hydrochloride and repeated evacuation and dilution of the filtrate followed by maceration gradually converted the oily product into a white solid. Thorough washings with 100 ml. of warm water followed by 110 ml. of ether yielded 3 g. (20%) of product. M.p. 151-157°.

The ether extracts showed a considerable amount of unreacted starting material still present. This suggests that optimization of the yield would necessitate a longer reaction period and/or lower reaction temperatures. Recrystallization from benzene followed by drying of the solid for 6.5 hr. (ether) gave m.p. 149.5-152°.

Anal. calcd. for $C_{14}H_{21}N_3O_2$: C, 63.73; H, 8.02; N, 15.92. Found: C, 64.09; H, 8.17; N, 16.00.

1-Benzoyl-2-isopropyl-4-t-butyl semicarbazide (Compound 3-9)

To a solution of 11.0 g. of crude 2-isopropyl-4-t-butyl

semicarbazide (22% in excess over 52 mmole, m.p. 122-137°) in 35 ml. of pyridine, 7.3 g. of benzoyl chloride (52 mmole) were added. The pink suspension was stirred for 2 hr. at room temperature and the product that separated out of the solution was filtered and extracted with 50 ml. of water in order to remove all traces of pyridine. Dilution of the filtrate with water resulted in the isolation of a second crop of product. Recrystallization from ethyl acetate yielded ∿11 g. (∿70%) of a crude product with a melting range of 10°. This product was extracted with a Soxhlet apparatus using di-isopropyl ether for 1 hr. Upon filtration of the extract a white, sugar-like crystalline product was obtained and dried for 11 hr. (ether).

M.p. 162-166.5° (varies somewhat with the rate of heating).

Anal. calcd. for $C_{15}H_{23}N_3O_2$: C, 64.86; H, 8.35; N, 15.13. Found: C, 65.05; H, 8.40; N, 14.97.

1-Benzoyl-2-isopropyl-4-phenyl semicarbazide (Compound 3-10)

To a solution of 8.50 g. of 2-isopropyl-4-phenyl semicarbazide (44.0 mmole, m.p. 91.5-95°) in 10 ml. of pyridine, 6.10 g. of benzoyl chloride (43.4 mmole) were added. The initial solution was turbid and was therefore filtered prior to the addition of the acid chloride. The mixture was then stirred for 5 hr. at 40°. Dilution with 15 ml. of water caused the separation of an oil which gradually solidified upon the addition of 10 ml. of ethanol. 10.37 g. (81.2%) of the product melting at 148-155° were recovered.

Acidification of the original filtrate with hydrochloric

acid precipitated 9.7% of a product confirmed from its n.m.r. spectrum (CCl_4) to be benzoic acid (m.p. 111-120°).

The semicarbazide derivative was recrystallized from 60 ml. of 95% ethanol containing some activated charcoal. The white shiny crystalline solid was then dried for 11 hr. (ether).

M.p. 152.5-155.5°.

Anal. calcd. for $C_{17}H_{19}N_3O_2$: C, 68.61; H, 6.43; N, 14.12. Found: C, 68.85; H, 6.51; N, 14.09.

1-Benzoyl-2-phenyl-4-ethyl semicarbazide (Compound 3-11)

To a solution of 5.00 g. of 2-phenyl-4-ethyl semicarbazide (27.9 mmole, m.p. 150.5-152°) in 15 ml. of pyridine, 4.02 g. of benzoyl chloride (28.6 mmole) were added. The temperature was brought up to 50-65° due to the incomplete solubility of the starting semicarbazide at room temperature. The milky suspension which resulted was left at that temperature range for another 6 hr., filtered and washed with water and ether. More product was secured by concentration and dilution of the filtrate with water. Yield 5.71 g. (72.1%).

M.p. 219-221° (dec., decomposes to a yellow-brown liquid).

Recrystallization from isopropyl alcohol yielded small white needles which were dried for 12.5 hr. (ether), and melted at 224.5-226° (dec.).

Anal. calcd. for $C_{16}H_{17}N_3O_2$: C, 66.67; H, 6.17; N, 15.27. Found: C, 67.83; H, 6.05; N, 14.83.

When the reaction was carried out at room temperature only starting material, contaminated with a trace of the expected product, was recovered.

HYDRAZONES

Propionaldehyde methylhydrazone (Compound 4-2)

This compound was prepared according to the method of Ioffe, Stopskii and Sergeeva.[64] To a solution of 46.07 g. of methylhydrazine (1.00 mole) in 100 ml. of freshly distilled ether, 58.08 g. of propionaldehyde (1.00 mole) were added over a period of 3 hr. and 15 min. while maintaining the reaction mixture at a temperature range between -8 and -5°. The two phase reaction mixture was transferred to a separatory funnel. After discarding the 9 ml. of water formed as by-product (100% yield is equivalent to 18 ml. of water), the ether layer was dried over anhydrous sodium sulfite. The ether was then removed by distillation and the resulting residue purified through fractional distillation. Two colorless fractions were collected. Yield 38.20 g. (44.4%). B.p. 120.0-120.5°/atm. (lit.[64] 124.6-124.7°/763 mm.); the other fraction, ∿9 g. and b.p. 94.5-95.5°/atm. was not identified.

Benzaldehyde methylhydrazone (Compound 4-3)

A mixture of 17.0 g. of methylhydrazine (0.37 mole) and 39.22 g. of benzaldehyde (0.37 mole) in 30 ml. of 95% ethanol was refluxed for 4 hr. over a steam bath. The

ethanol was then removed under vacuum, the residual oil (yellow) dissolved in 40 ml. of ether, the solution dried and the ether distilled off. The dry residue was distilled under reduced pressure to give a pale-yellow oil with a camphoraceous basic odor. Yield 20.43 g. (41.2%). B.p. 132-135°/18.5 mm. (lit. 81°/0.8 mm.,[65] 129-133°/20 mm.[66]). I.r. (neat) (AgCl cell, cm^{-1}): broad band at 3326-3426 (ν NH), 2876-2986 (aliphatic ν CH).

Acetaldehyde phenylhydrazone (Compound 4-4)

This compound was prepared according to the method of Laws and Sidgwick.[67] To a solution of 57.33 g. of acetaldehyde (1.30 mole) in 160 ml. of 80% ethanol, 82.35 g. of freshly distilled phenylhydrazine (0.76 mole) were added dropwise over a period of 50 min. The solution was stirred for 90 min. at room temperature with a gradual formation of a solid (the condenser was kept very cold throughout the reaction; the b.p. of acetaldehyde being 22°). The solid was filtered and washed with ethanol to yield yellowish needles. Second and third crops were recovered by concentration of the filtrate (the product was found to be appreciably soluble in acetaldehyde). Yield 65 g. (64%). M.p. 65-81°.

The melting range undoubtedly depends on the relative proportions of the α and β isomerides present. The hydrazone decomposes in air to a dark, reddish-brown oil and is best stored under vacuum over sodium or potassium hydroxide.

An attempt to separate the α and β isomers according to the method reported in the literature[67] was unsuccessful. The reported melting points for the α and β forms are: 93-98° and 56°;[67] 93-100° and 57-59°.[68]

I.r. (KBr, cm^{-1}): 3301 (ν NH).

Benzaldehyde phenylhydrazone (Compound 4-5)

This product was prepared according to standard laboratory text procedure from benzaldehyde and phenylhydrazine.

M.p. 152-154.5°.

I.r. (KBr, cm^{-1}): 3313 (ν NH).

SEMICARBAZONES

Benzaldehyde semicarbazone (Compound 5-1)

This product was prepared according to standard procedure from hydrazine hydrochloride, potassium cyanate and benzaldehyde added in that order in aqueous ethanol.

M.p. 222°.

I.r. (KBr, cm^{-1}): 3483, 3311 (ν NH), 1695 (ν CO).

Benzaldehyde 2-methylsemicarbazone (Compound 5-2)

This product was prepared by standard procedure from methylhydrazine hydrochloride, potassium cyanate and benzaldehyde in aqueous ethanol added in that order at ambient temperature. The crystalline product was recrystallized from isopropyl alcohol.

M.p. 158-160° (lit.[37] 159-160°).

I.r. (KBr, cm^{-1}): 3456, 3283, 3216 (ν NH), 1660 (ν CO).

Benzaldehyde 2-methyl-4-ethyl semicarbazone (Compound 5-3)

A solution of 2.4 g. of ethyl isocyanate (34 mmole) in 15 ml. of ether was added to 4.6 g. of benzaldehyde methylhydrazone (34 mmole) in 25 ml. of ether over a period of 20 min. while cooling in an ice bath. A precipitate formed during 3 hr. at ambient temperatures while maintaining very dry conditions. Filtration of the solid at -5° (the solid being appreciably soluble in the reaction solvent) and washing with two portions of cold ether yielded 5 g. (70%) of a pure product melting at 88.5-92°. Recrystallization from ethanol-water (2:1) gave transparent needles which were dried for 6.5 hr. (ether).

M.p. 89.5-92°.

Anal. calcd. for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47.
Found: C, 64.28; H, 7.29; N, 20.48.

Propionaldehyde 2-methyl-4-phenyl semicarbazone (Compound 5-4)

To an ice-cold solution of 3.10 g. of propionaldehyde methylhydrazone (36.0 mmole) in 25 ml. anhydrous ether were added 4.30 g. of phenyl isocyanate (36.1 mmole). The product was precipitated by cooling the reaction mixture in a dry ice-acetone bath, filtered and washed twice with ether at dry ice-acetone bath temperature. It should be emphasized that a considerable loss of product is due to the high solubility of the product in ether. The crystalline white solid was dried for 17 hr. at room temperature.

Yield 3.50 g. (48.8%).

M.p. 38.5-40°.

Anal. calcd. for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.26; H, 7.31; N, 20.54.

Benzaldehyde 2-methyl-4-phenyl semicarbazone (Compound 5-5)

(a) This product was prepared by stirring a solution containing 2.72 g. of 2-methyl-4-phenyl semicarbazide (16.5 mmole) and 2.12 g. of benzaldehyde (20.0 mmole, 21% excess) in 25 ml. of 95% ethanol containing 0.3 g. of sodium acetate for 45 min. at ambient temperature. The product crystallized out from the reaction mixture and was filtered and washed with dilute alcohol. Dilution of the filtrate with water resulted in a further amount of the white powder. Yield 3.79 g. (80.0%).

M.p. 106-108° (lit.[60] 108°).

I.r. (KBr, cm^{-1}): 3366 sharp band (ν NH), 1685 (ν CO).

(b) Alternatively, the above semicarbazone may be prepared by the addition, with slight cooling, of 11.9 g. of phenyl isocyanate (0.10 mole) to 13.40 g. of benzaldehyde 2-methylhydrazone (0.10 mole) in 100 ml. of anhydrous ether. The addition is made over a period of 40 min. and the resulting mass is filtered and washed with four portions of ether.

Yield 16.24 g. (64.7%).

M.p. 106.5-108.5°.

Benzaldehyde 2-isopropyl-4-ethyl semicarbazone (Compound 5-6)

A solution of 3.00 g. of 2-isopropyl-4-ethyl semi-

carbazide (20.6 mmole, distilled oil used, b.p. 96-99°/ 0.75 mm.) and 2.23 g. of benzaldehyde (21.0 mmole) in 15 ml. of ethanol, containing 0.3 g. of sodium acetate, was stirred at ambient temperature for one hour resulting in a milky suspension. Dilution with 55 ml. of water induced precipitation of more product, first as an oil which was converted to a solid on scratching the walls of the vessel. The product was then filtered and washed with warm water. Yield 3.5 g. (71.4%).

M.p. 82-84°.

Recrystallization from ethanol-water (1:1) containing decolorizing charcoal afforded shiny, silvery crystals which were dried for 6 hr. (ether) and gave m.p. 82-83.5°. Anal. calcd. for $C_{13}H_{19}N_3O$: C, 66.83; H, 8.20; N, 17.98. Found: C, 66.84; H, 8.27; N, 17.98.

Benzaldehyde 2,4-di-isopropyl semicarbazone (Compound 5-7)

The preparation of this product was described under the heading of 2,4-di-isopropyl semicarbazide on p. 37.

Benzaldehyde 2-phenyl-4-ethyl semicarbazone (Compound 5-8)

A solution containing 3.00 g. of benzaldehyde phenylhydrazone (15.3 mmole, m.p. 152-154.5°) and 1.07 g. of ethyl isocyanate (15.1 mmole) in 40 ml. of benzene was refluxed for 65 hr. under rigorously dry conditions (length of the refluxing time was dictated by the persistence of the isocyanate odor) with a gradual change of the solution color to a deep red. A solid (0.13 g.) melting at

178-179° (dec.) was isolated but not identified. Attempts to solidify the residual red oil failed.

Acetaldehyde 2,4-diphenyl semicarbazone (Compound 5-9)

A solution of 0.89 g. of phenyl isocyanate (7.46 mmole) in 5 ml. of anhydrous ether was added to a solution of 1.00 g. of acetaldehyde phenylhydrazone (7.46 mmole, m.p. 78-90°, isomeric) in 20 ml. of ether. The solution color became orange-red after 70 hr. of stirring at room temperature and the solid which precipitated out was filtered and washed with ether. Yield 0.55 g. M.p. 232-238°.

Two recrystallizations from aqueous ethanol gave a yellowish, cotton-like material melting at 233.5-235.5°. The structure was elucidated from the n.m.r. and mass spectra as 1,3-diphenylurea (70.0% based on isocyanate used) (lit.[16] 238°, 240°).

When the reaction was repeated in refluxing benzene for 3.5 hr., the product isolated from the orange-red solution had a melting point range of 202-207°. The n.m.r. spectral data are not in agreement with the expected structure.

N.m.r. (DMSO-d_6, δ): 9.44-9.84 (1H, 3 peaks), 7.20-8.26 (5.5H, multiplet).

I.r. (KBr, cm^{-1}): 3401, 3366, 3211, 3131, 3071, 2906, 1678, 1607, 1598, 1292.

Benzaldehyde 2,4-diphenyl semicarbazone (Compound 5-10)

A solution of 8.42 g. of benzaldehyde phenylhydrazone (43.0 mmole) and 5.75 g. of phenyl isocyanate (48.3 mmole, 12% in excess) in 55 ml. of anhydrous benzene was refluxed for 4.5 hr. The brown-red reaction mixture was filtered and the solid recrystallized once from methanol and twice from ethanol with charcoal treatment. A pink powder was obtained. Yield 2 g. (15%)
M.p. 164-166° (lit.[40] varies between ~163-175°).

Benzaldehyde 2-phenyl-4-(1-naphthyl) semicarbazone (Compound 5-11)

A mole:mole ratio of benzaldehyde phenylhydrazone and 1-naphthyl isocyanate in anhydrous benzene refluxed for 5.5 hr. under very dry conditions gave only benzaldehyde phenylhydrazone (50%) as the recoverable product.
M.p. 148.5-150° (from aqueous ethanol).

TRIAZOLINONES

1H-3,4-Diphenyl-Δ^2-1,2,4-triazolin-5-one (3,4-diphenyl-5-hydroxy-1,2,4-triazole (Compound 6-1)

Alkaline ring closure (Method A)

This procedure was attempted according to the method of Gehlen and Schade[51] for disubstituted semicarbazides. A solution containing 2.50 g. of 1-benzoyl-4-phenyl semicarbazide (9.80 mmole; m.p. 213-216°) in 27 ml. of 3.8% sodium hydroxide was refluxed for 8.5 hr. at 106°. The colorless solution was cooled to room temperature then

neutralized with 10% hydrochloric acid to give a solid which was filtered and redissolved in 80 ml. of 1 N sodium hydroxide. The alkaline solution was then filtered and the filtrate acidified with dilute hydrochloric acid. This process was repeated twice to yield 0.7 g. (30%) of product. Recrystallization of 0.5 g. of the triazolinone from 17 ml. of isopropyl alcohol containing a trace of ethanol afforded white needles which were dried for 12 hr. (ether).
M.p. 256.5-258° (dec. with the formation of a brown liquid) (lit. 258-260°,[69] 252°,[70] 262°,[51] 254°[71]). No decomposition was reported by these authors.

Intermolecular condensation

This process was attempted by refluxing 2.00 g. of 4-phenyl semicarbazide (13.2 mmole, m.p. 117-119°) and 2.21 g. of benzoic acid (18.1 mmole, 37% in excess) in 30 ml. of ethanol for 5.5 hr. Concentration of the reaction mixture to 10 ml. under reduced pressure yielded a solid which was filtered and washed with ethanol and di-isopropyl ether. The product, melting at 232-236°, was identified as 1,6-diphenyl biurea by comparison of its i.r. spectrum with that of an authentic sample (lit.[72] m.p. 242-243°).
I.r. (KBr, cm^{-1}): 3216-3301 (ν NH), 1670 (ν CO).

4H-1-Methyl-3-phenyl-Δ^2-1,2,4-triazolin-5-one (1-methyl-3-phenyl-5-hydroxy-1,2,4-triazole) (Compound 6-2)

Oxidative ring closure using potassium ferricyanide (Method E)

The procedure of oxidative cyclization of Srinivasan

and co-workers[41,42,43] was followed. To a warm solution of 1.0 g. of benzaldehyde 2-methyl semicarbazone (5.65 mmole, m.p. 158-159°) in 30 ml. of ethanol, 2.4 g. of sodium hydroxide (60 mmole) in 35 ml. of water were added. The solution temperature was brought up to reflux and 19.7 g. of potassium ferricyanide (60 mmole) in 150 ml. of water were added by portions. The solid precipitating out during the addition of the oxidant redissolved as the reflux temperature reached 91° (its maximum). After heating for 39 hr. the cloudy orange-brown solution was cooled in ice, filtered and the solid was purified by extraction with ether. A second crop was recovered by concentration of the filtrate. The solid consisted of the starting material (46% recovery) melting at 156-159°. The cyclic product, melting at 218-219°, was previously obtained using ferric chloride as oxidizing agent.[37]

1-Methyl-3-phenyl-4-ethyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-3)

Alkaline ring closure (Method A)

The turbid solution obtained by dissolving 7.00 g. of 1-benzoyl-2-methyl-4-ethyl semicarbazide (31.6 mmole, m.p. 163-166°) in 60 ml. of 5.0% sodium hydroxide was filtered and then brought to reflux by heating in an oil bath (reflux temperature, 102°). The oil bath temperature was kept at 118-120° and heating was maintained for 2 hr. with the formation of an oily turbidity appearing after the

first thirty minutes. Fumes of ammonia-like odor, strongly alkaline to a dampened litmus paper, were present throughout the duration of the reaction. These fumes were trapped in ethanol and identified as ethylamine.

Isolation of ethylamine - The reaction mixture, composed of a clear alkaline layer and a lower colorless oil, was heated slowly in a fractional distillation apparatus. The first few drops collected between room temperature and 55°, were diluted in D_2O and confirmed by n.m.r. spectroscopy to contain ethylamine (lit.[73] b.p. 16.6°). N.m.r.[*] (D_2O, δ): 2.66 (quartet, J = 6.5 Hz, methylene protons), 1.02 (triplet, J = 6.5 Hz, methyl protons).

Isolation of the triazolinone - The product, in the form of a yellow tinted viscous liquid, was extracted with twelve 5-ml. portions of ether, washed with sixteen 5-ml. portions of water to remove all traces of base, dried over anhydrous sodium sulfite and evaporated under reduced pressure with the precipitation of a flaky white solid. The solid was converted back to a viscous liquid with a faint, but characteristic odor of the trapped solvent being detectable. Yield 1.65 g. (25.7%).

Isolation of benzoic acid hydrolysis product - The alkaline layer was concentrated under vacuum and made slightly acidic to litmus using 1:1 HCl (~11.5 ml.). The resulting solid was filtered, washed thoroughly with water,

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[*] TMS was used as external reference.

extracted with ether and the extracts evaporated, leaving behind yellow needles, the structure of which was confirmed by n.m.r. Yield 0.23 g. (6.0%).

M.p. 114-118°.

Isolation of unreacted starting material - This fraction was the insoluble portion contained in the above extraction procedure. Yield 0.06 g. (0.9%).

M.p. 158-164°; 163-166° (from isopropyl alcohol).

Reducing the reflux time to 90 min. resulted in a recovery of 6.3% of starting material with no change in the yields of the triazolinone and benzoic acid. The yield of the triazolinone was not improved even when the reflux time was extended to 26 hr.

Purification of the triazolinone - Attempts to convert the viscous liquid to a solid product failed. The product was purified by filtering the hot ether solution through activated charcoal followed by evaporating the solvent in a rotatory evaporator for 6.5 hr. and finally drying in the Abderhalden apparatus under vacuum for 2 hr. (acetone) and then for 15 hr. (ether). The viscous liquid was colorless and odorless.

Anal. calcd. for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.67. Found: C, 64.88; H, 6.43; N, 20.60.

Slight decomposition was observed during vacuum distillation of the oil.

B.p. 134-140°/~0.2 mm. (lit.[50] 130°/0.2 mm. The compound was obtained by methylation of 3-phenyl-

4-ethyl-5-hydroxy-1,2,4-triazole). The distillate did not solidify.

Oxidative ring closure using potassium ferricyanide (Method E)

The requisite quantity of benzaldehyde 2-methyl-4-ethyl semicarbazone was dissolved in ethanolic sodium hydroxide (10-fold excess) and an aqueous solution of potassium ferricyanide (10-fold excess) was added to the refluxing solution. Heating was continued for 94 hr. with only starting material melting at 87-91° having been recovered. When the reaction was carried out in a pressure bomb immersed in an oil bath (140°) for 4 hr. the starting material, 44% recovery m.p. 88-89.5°, was again obtained.

Oxidative ring closure using ferric chloride (Method F)

A solution of 0.60 g. of the semicarbazone (2.93 mmole) and 2.03 g. of ferric chloride hexahydrate (7.50 mmole) in 75 ml. of ethanol was heated in a bomb at 120-165° for three hours and fifteen minutes. The resulting green suspension was evaporated under vacuum to give a solid which was extracted with acetone. The extract was concentrated down to a brown oil (0.36 g.) consisting of both the triazolinone and semicarbazone (58%:42%). This ratio was measured from the n.m.r. integration curve of the methyl protons. Based on the oil obtained, this represents a yield of 36% in triazolinone and a recovery of 25% in semicarbazone.

N.m.r. (CCl_4, δ): 7.20-7.62 (multiplet with the strongest peak centered at δ7.42, phenyl protons, starting material and triazolinone), 3.70 (quartet, methylene protons, J = 7 Hz, triazolinone), 3.38 (singlet, methyl protons, triazolinone), 3.23 (singlet, methyl protons, starting material), 1.19 (distorted triplet, J = 7 Hz, $-CH_2-\underline{CH_3}$ protons of the starting material and triazolinone).

Because of their identical solubility patterns separation of the two compounds was very cumbersome and as a result further isolation attempts were discontinued.

Oxidative ring closure using isoamyl nitrite (Method G)

Refluxing the semicarbazone with isoamyl nitrite (10-fold excess) in anhydrous benzene for 113 hr. and evaporating the solvent and most of the oxidizing agent under reduced pressure resulted in a solid being produced which was shown by n.m.r. (CCl_4) to contain the starting semicarbazone contaminated with a trace of isoamyl nitrite.

1-Methyl-3-phenyl-4-isopropyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-4)

Alkaline ring closure (Method A)

Osing an oil bath, 5.00 g. of 1-benzoyl-2-methyl-4-isopropyl semicarbazide (21.3 mmole, m.p. 153-157°) were refluxed in 50 ml. of 6.0% sodium hydroxide for 13 hr. with the formation of an oil having been observed after the first 5 hr. The basic isopropylamine fumes which formed were trapped in ethanol and the resulting solution was

analyzed by thin-layer chromatography on a silica gel plate and found to be identical with that of an authentic sample of isopropylamine in ethanol. Furthermore, the amine traces were isolated from the reaction mixture by fractional distillation.

B.p. 32-35° (lit.[73] 33-34°).

The nature of the amine was also recognized from n.m.r. N.m.r. (CCl_4, δ): 2.93 (septet, J = 6.25 Hz, methine proton), 0.91 (doublet, J = 6.25 Hz, isopropyl protons).

An authentic sample gave the identical spectrum.

Extraction of the reaction mixture with twelve 10-ml. portions of ether followed by washing with fifteen 5-ml. portions of water, drying with anhydrous sodium sulfite, and evaporating under reduced pressure afforded a yellow tinted oil. Yield 1.19 g. (25.8% in triazolinone). From the acidified alkaline layer 37.5% of benzoic acid was recovered and purified by extractions with ether.

M.p. 119.5-122°.

The nature of this product was confirmed by n.m.r.

Increasing the reflux time to 38 hr. resulted in no apparent increase in the cyclization reaction.

Purification of the cyclic product - Repeated cooling in liquid nitrogen, evacuating, and scratching of the oil against the walls of the vessel produced transparent crystals which were washed five times with cyclohexane and dried for 15 hr. (room temperature) and 4.5 hr. (ether). The product had m.p. 44-46° and b.p. 120-121°/0.05 mm.

Anal. calcd. for $C_{12}H_{15}N_3O$: C, 66.30; H, 6.95; N, 19.33. Found: C, 66.29; H, 7.02; N, 19.31.

1-Methyl-3-phenyl-4-t-butyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-5)

Alkaline ring closure (Method A)

Refluxing a solution of 1-benzoyl-2-methyl-4-t-butyl semicarbazide (m.p. 142-146.5°) in 4.3% sodium hydroxide for 3 hr. gave unreacted starting material only. Increasing the sodium hydroxide concentration to 5.0% and the refluxing time to 30 hr. yielded a film of oil which was isolated by extractions with ether. The n.m.r. spectrum of the oil in CCl_4 shows a singlet at δ7.40 which may correspond to the phenyl protons of the cyclic product. The low availability of the product, however, prevented further identification. Increasing the alkaline concentration to 10% and prolonging the refluxing time resulted in a 65% recovery of benzoic acid melting at 119-122°.

1-Methyl-3-ethyl-4-phenyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-6)

Oxidative ring closure using potassium ferricyanide (Method E)

The procedure using ethanolic sodium hydroxide (10-fold excess) and an aqueous solution of potassium ferricyanide (10-fold excess) was repeated using propionaldehyde 2-methyl-4-phenyl semicarbazone (m.p. 38.5-40°) with no apparent traces of ring closure having been observed even

after a prolonged reflux period. Treatment of the semicarbazone with the same oxidizing agent, using a higher boiling solvent (e.g., bis-(2-methoxyethyl) ether, b.p. 161-163°, 70% in water) resulted in decomposition of the semicarbazone accompanied by green coloration.

Oxidative ring closure using lead tetraacetate

(Method H)

Lead tetraacetate (in excess over 1.46 mmole) in 5 ml. of acetic acid was added to a solution of 0.30 g. of the semicarbazone (1.46 mmole) in 8 ml. of acetic acid. This was stirred for 20 min. at room temperature with the solution color turning wine red. Addition of water resulted in a brown oil which could not be further purified. The same results were obtained when the reaction was repeated in methylene chloride.

The required lead tetraacetate was prepared by the action of acetic acid on lead oxide (red lead) in acetic anhydride medium. Lead oxide was added by portions with each fresh addition being made only after the color due to preceding portion had largely disappeared. The temperature was kept below 65°. The product was recrystallized from acetic acid-acetic anhydride (4:1) containing decolorizing charcoal and was stored in acetic acid.

1-Methyl-3,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-7)

This derivative was previously synthesized by heating a mixture of the corresponding amidrazone hydrochloride

with a 10-20% excess of the appropriate isocyanate for 1 hr. at 140° and 4 hr. at 220°. 50% of a product melting at 181-181.5° were obtained.[32] The triazolinone was also prepared by direct methylation of 3,4-diphenyl-5-hydroxy-1,2,4-triazole using dimethyl sulfate and anhydrous calcium carbonate. The reported yield of the alkylation reaction is 44%, m.p. 180°,[42] 174-175°.[50]

Alkaline ring closure (Method A)

The turbid solution obtained by dissolving 9.00 g. of 1-benzoyl-2-methyl-4-phenyl semicarbazide (33.5 mmole) in 65 ml. of 5.0% sodium hydroxide was filtered prior to refluxing in an oil bath. The refluxing was continued for 3 hr. with an oil turbidity forming after the first 30 min. of heating. The product, in the form of an oil, gradually transformed to a white solid on standing and was filtered and washed with water. Yield 1.04 g. (12.4%).

Work-up of the reaction mixture afforded a 20% recovery in benzoic acid (m.p. 118-121.5°), 2% of starting material (m.p. 141.5-144°) and an amount of methylhydrazine. The latter was confirmed through its n.m.r. spectrum.

The crude triazolinone (0.7 g.) was recrystallized from 17 ml. of absolute ethanol containing decolorizing charcoal. On cooling to room temperature, the solution gave small needles which were filtered, washed with absolute ethanol and dried for 3.5 hr. (acetone) and for 18 hr. (room temperature).
M.p. 177.5-178°

Anal. calcd. for $C_{15}H_{13}N_3O$: C, 71.52; H, 5.20; N, 16.68. Found: C, 71.71; H, 5.40; N, 16.73.

The yield of triazolinone was not improved by increasing the reflux time to 8 hr.

Dehydrocyclization using zinc chloride (Method B)

Seven grams of anhydrous zinc chloride were well mixed with 0.70 g. of the semicarbazide (2.60 mmole) and the container was immersed in an oil bath at 180-190° for 2 hr. The molten mixture which hardened to a solid mass was dissolved in 20 ml. of water. The resulting suspension was extracted with seven 8-ml. portions of ether and the combined ether extract was washed with water and dried over anhydrous sodium sulfite. Concentrating under reduced pressure gave a yellow solid which was identified as the crude triazolinone contaminated with a trace of starting material. The contaminant was completely removed by washing with dilute sodium hydroxide. Yield 0.05 g. (9%). M.p. 168-174°.

Reducing the oil bath temperature to 150-155° resulted in a slightly better yield in triazolinone (~15%).

Dehydrocyclization using polyphosphoric acid (Method C)

Employing this reagent resulted in the cyclization to 2-phenyl-4-methyl-Δ^2-1,3,4-oxadiazolin-5-one with elimination of aniline. One gram of 1-benzoyl-2-methyl-4-phenyl semicarbazide (3.72 mmole) was completely dissolved in 10 g. of warm polyphosphoric acid. The solution was

left in an oil bath at 60-65° for 2 hr. and at 75-80° for 2.5 hr. The white solid which precipitated by diluting with water was filtered and washed with dilute sodium hydroxide and then with water. Yield 0.5 g. (77%), m.p. 97-100°. Starting material (5%) was recovered from the sodium hydroxide washings. The crude oxadiazole was recrystallized from 95% ethanol containing decolorizing charcoal and the crystalline transparent prisms obtained were dried for 5 hr. (ether) and for 2 days (room temperature), m.p. 99.5-100°.

When the above reaction was repeated with stirring at room temperature for 74 hr., 94% starting material was recovered.

Oxidative ring closure using potassium ferricyanide (Method E)

To a solution of 9.00 g. of benzaldehyde 2-methyl-4-phenyl semicarbazone (35.6 mmole, m.p. 106.5-108.5°) in 250 ml. of 95% ethanol, 14.2 g. of sodium hydroxide (356 mmole) in 45 ml. of water were added. The mixture was brought to reflux and 81.9 g. of potassium ferricyanide (249 mmole, 7-fold excess) in 410 ml. of water were slowly added with the formation of a black turbidity after each addition. The final orange solution was then refluxed (reflux temperature being 85°) for 8.5 hr. with the basic fumes given off trapped in D_2O. The resulting suspension was filtered cold and extracted, first with 350 ml. of

water, then with 150 ml. of water and finally with three 80-ml. portions of water. A white cotton-like solid contaminated with a brown inorganic impurity was obtained. Yield 7.72 g. (86.5%).
M.p. 177-179°.

The filtrate of the initial reaction mixture was concentrated to 350 ml. by distillation (the distillate was slightly basic to litmus) to give an extra 4.3% yield of the triazolinone.

Recrystallization of the crude triazolinone from 95% ethanol containing decolorizing charcoal gave an 89.2% recovery of a pure product in the form of small white needles, m.p. 177.5-178°.

Oxidative ring closure using ferric chloride (Method F)

A solution of the semicarbazone containing ferric chloride hexahydrate in ethanol, heated in a bomb for 90 min. at 135°, gave back the starting material.

Oxidative ring closure using isoamyl nitrite (Method G)

Refluxing the semicarbazone in benzene containing a 5-fold excess of isoamyl nitrite for 7.5 hr. yielded a non-identified mixture melting at 130-165° together with the crude starting material, m.p. 96-103°. The latter structure was verified from the i.r. spectrum.

Intermolecular condensation

Two grams of 2-methyl-4-phenyl semicarbazide (12.1 mmole) were refluxed with 1.9 g. of benzoic acid (15.6 mmole, 29%

in excess) in 30 ml. of 95% ethanol over a period of 24 hr. Dilution of the reaction mixture with an equal volume of water and cooling gave a solid which was filtered and washed with dilute alcohol. Yield 1.3 g., m.p. 59-99°. Extraction of this crude product using isopropyl alcohol gave 1,6-diphenyl-3-methyl biurea melting at 182-184.5° as the insoluble portion.

N.m.r. (DMSO-d_6, δ): 8.76, 8.88 (2H, two singlets, N-1(H) and N-6(H) protons), 8.20 (1H, singlet, N-3(H) proton), 6.82-7.76 (10H, multiplet, phenyl protons), 3.06 (3H, singlet, methyl protons).

The combined alcoholic extracts, by evaporation to dryness, gave a wide melting range solid (50-102°) which appeared to consist of crude starting material and biurea according to the n.m.r. spectroscopic evidence.

A second variation was attempted. Molar ratios of 2-methyl-4-phenyl semicarbazide and benzoic acid were refluxed in xylene for 45 hr. in an apparatus equipped with a Dean and Stark trap. Only a minimal amount of water was isolated (100% condensation reaction corresponds to 0.5 ml. of water). The solid precipitating out on cooling was filtered, washed with water and recrystallized three times from toluene, m.p. 155.5-158.5°. The structure of this product was not identified.

I.r. (KBr, cm^{-1}): 3340 (ν NH); 1655 (ν CO).

1-Isopropyl-3-phenyl-4-ethyl-Δ^2-1,2,4-triazolin-5-one

(Compound 6-8)

Alkaline ring closure (Method A)

The slightly turbid solution obtained by dissolving 2.75 g. of 1-benzoyl-2-isopropyl-4-ethyl semicarbazide (11.0 mmole, m.p. 102-110°) in 50 ml. of 5.0% sodium hydroxide was filtered. Upon refluxing the solution for 2.5 hr., a colorless oily turbidity occurred rapidly as the reaction temperature reached 94°. The ammonia-like fumes were trapped in ethanol throughout the course of the reaction and were subsequently identified by n.m.r. as ethylamine. The reaction mixture was then extracted with six 5-ml. portions of ether. The combined ether extracts were washed with ten 5-ml. portions of water, dried over anhydrous sodium sulfite and concentrated under reduced pressure to give a faint yellowish oil. Yield 1.65 g. (64.7%). Repeated preparation of the triazolinone gave consistent yields of 75% in crude product.

Besides ethylamine, benzoic acid melting at 119.5-121° was isolated from the reaction mixture.

Purification of the triazolinone - The crude oil gradually solidified by repetative cooling in liquid nitrogen and evacuating. The solid thus obtained, melting at 52-65°, was further purified by filtering its cyclohexane solution, while hot, through decolorizing charcoal and letting stand overnight. The transparent, cubic prisms which

precipitated out were filtered, washed with cyclohexane and dried for 10.5 hr. (ether).

M.p. 66.5-68.5°.

Anal. calcd. for $C_{13}H_{17}N_3O$: C, 67.45; H, 7.40; N, 18.15. Found: C, 67.59; H, 7.52; N, 18.11.

Dehydrocyclization using molecular sieves (Method D)

This attempt at ring closure was carried out by refluxing the semicarbazide in benzene containing molecular sieves for 13 hr., while maintaining anhydrous conditions. Only starting material was recovered.

Oxidative ring closure using potassium ferricyanide (Method E)

To a solution of 2.0 g. of benzaldehyde 2-isopropyl-4-ethyl semicarbazone (8.57 mmole) in 100 ml. of ethanol, 3.4 g. of sodium hydroxide (86 mmole) in 25 ml. of water were added. The mixture was heated during the addition of 28.3 g. of potassium ferricyanide (86 mmole) in 200 ml. of water. The dark-orange solution obtained was then refluxed for 28 hr., cooled down somewhat, filtered, and the filtrate concentrated down to 180 ml. The residue was extracted with twenty 5-ml. portions of ether and the combined ether extracts were washed with eight 10-ml. portions of water, dried over anhydrous sodium sulfite and evaporated to dryness. A trace of yellow solid was obtained and shown by n.m.r. to consist of a mixture of starting material and triazolinone.

N.m.r. (CCl_4, δ):

semicarbazone: 7.00-8.20 (multiplet, phenyl protons)
4.64-5.14 (multiplet, methine proton)
3.14-3.36 (multiplet, methylene protons)

triazolinone: 7.46 (strong peak within multiplet, phenyl protons)
4.22-4.64 (multiplet, methine proton)
3.36-4.02 (multiplet, methylene protons)

The remaining spectrum was overlapped.

1,4-Di-isopropyl-3-phenyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-9)

Alkaline ring closure (Method A)

A mixture of 1.40 g. of 1-benzoyl-2,4-di-isopropyl semicarbazide (5.32 mmole, m.p. 151-157°) was refluxed with 30 ml. of 5.0% sodium hydroxide for 2 hr. and 45 min. resulting in the formation of oil droplets after the first 5 min. of reflux. The oil which solidified on cooling was filtered, washed with water, extracted with ether and the extract, when evacuated to dryness, gave a yellow solid. Yield 0.22 g. (17%).
M.p. 68-81°.

Because of its low yield, further purification of the crude triazolinone was discontinued.

The filtrate obtained from the initial reaction mixture was extracted with six 10-ml. portions of ether. The combined ether extract was washed with seven 10-ml. portions

of water, dried over anhydrous sodium sulfite and evaporated to dryness. The yellow solid left behind was identified as crude N-benzoyl-N'-isopropylhydrazine. Yield 0.3 g. (32%).

M.p. 102-108° (lit. 109-110°[56], 106°[57], 117°[58]).

N.m.r. (CCl_4, δ): 7.23-7.53, 7.68-7.95 (3 H and 2H respectively, multiplet, phenyl ring protons), 6.88 (2 H, broad peak, NH and N'H protons), 3.18 (1 H, septet, J = 6.5 Hz, methine proton), 1.07 (6 H, doublet, J = 6.5 Hz, isopropyl protons).

Isolation of benzoic acid was not attempted.

1-Isopropyl-3-phenyl-4-t-butyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-10)

Alkaline ring closure (Method A)

A solution of 1.50 g. of 1-benzoyl-2-isopropyl-4-t-butyl semicarbazide (5.41 mmole, m.p. 166-172.5°) in 30 ml. of 5.0% sodium hydroxide containing 5 ml. of ethanol (the solid was not completely soluble in the absence of ethanol; reflux temperature, 90°) was refluxed for a period of 30 hr. On cooling, the reaction mixture gave a precipitate which was filtered, washed thoroughly with water and extracted with acetone (the starting material being insoluble in acetone). The acetone extracts were evaporated to dryness to give white needles of N-benzoyl-N'-isopropylhydrazine. Yield 0.5 g. (5.2%).

M.p. 111-113°.

The n.m.r. spectrum was identical to the one above. I.r. (KBr, cm^{-1}): 3298 (ν NH), 2978 (aliphatic ν CH), 1643 (ν CO).

The filtrate from the initial reaction mixture was shown to contain benzoic acid (40.9% recovery) and tert-butylamine. The amine was isolated by fractional distillation and identified using thin layer chromatography (silica gel plates, ethanol as eluent) by comparison with an authentic sample.

Dehydrocyclization using molecular sieves (Method D)

One gram of the semicarbazide (3.61 mmole) in benzene containing 15 g. of molecular sieves was refluxed for 67 hr. The solution was filtered and the filtrate evaporated to dryness to give a mixture of the initial semicarbazide and N-benzoyl-N'-isopropylhydrazine. Recrystallization of the mixture from carbon tetrachloride containing decolorizing charcoal gave 0.11 g. (17%) of the benzoyl-isopropylhydrazine melting at 102-110° (i.e., this result seems to indicate that the reaction system was not completely dry, otherwise, decomposition is a thermal process). N.m.r. and i.r. spectra were the same as in previous cases.

1-Isopropyl-3,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-11)

Alkaline ring closure (Method A)

One gram of 1-benzoyl-2-isopropyl-4-phenyl semicarbazide

(3.40 mmole, m.p. 151.5-156°) refluxed in 16 ml. of 5.0% NaOH for 20 min. afforded an oily film which solidified upon cooling. The mixture was filtered and the solid washed with water. Yield ~0.1 g., m.p. 107-180°. Recrystallization from EtOH gave a product melting at 185-188°.

N.m.r. (DMSO-d_6 + CCl_4, δ): 8.66, 8.54 (two singlets), 6.76-8.20 (multiplet, strong band at δ7.44 may be due to phenyl ring protons of the triazolinone), 4.42-4.87 (broad, unresolved septet, methine proton), 1.15 (doublet, J = 6 Hz, methyl protons).

Workup of the filtrate afforded unreacted starting material.

Extending the reaction time to 2 hr. yielded 0.28 g. (initial amount being 0.70 g., 2.35 mmole) of a yellowish oil which was isolated from the reaction solution by extractions with ether.

N.m.r. (CCl_4, δ): 7.66-7.92 (2.7 H, multiplet), 6.36-7.44 (19.7 H, multiplet), 4.65 (7.5 H, singlet), 3.16 (1 H, septet, J = 6.5 Hz, methine proton), 1.44 (2 H, doublet, J = 7 Hz, methyl protons possibly due to a trace of triazolinone), 1.00 (7.5 H, doublet, J = 6 Hz, methyl protons, starting material?).

10% benzoic acid was also recovered.

Carrying out the reaction using sodium bicarbonate and sodium carbonate separately, at various concentrations and heating times and temperatures, resulted in the

isolation of starting material, benzoic acid and products with a wide range in m.p.

Dehydrocyclization using zinc chloride (Method B)

One gram of the semicarbazide (3.40 mmole) was uniformly mixed with 8 g. of anhydrous zinc chloride and the contents were immersed in an oil bath at 210° for 20 min. and 160° for 21 hr. Cooling of the contents followed by the addition of 10 ml. of water and filtration of the suspended solid yielded 0.90 g. of a white solid melting at 170-193°. After recrystallization from 15 ml. of 95% EtOH the product melted at 211-217.5° (dec.). The n.m.r., i.r., and mass spectral results obtained for this product are described on pp. 127-128.

Repeating this procedure at 115-125° for 2.5 hr. in one attempt and at 170-185° for 4.5 hr. in another did not alter the results.

1,3-Diphenyl-4-ethyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-12)

Alkaline ring closure (Method A)

One gram of 1-benzoyl-2-phenyl-4-ethyl semicarbazide (3.53 mmole, m.p. 219-221°) was refluxed with 30 ml. of 5.0% sodium hydroxide for 1 hr. and 45 min. The resulting orange solution was cooled and filtered. The precipitate was washed with water and then with ether to give 0.16 g. (25.4%) of 2-phenyl-4-ethyl semicarbazide melting at 144.5-150°.

N.m.r. (DMSO-d_6, δ): 7.54, 7.72 (two singlets, 2 N-1(H) protons), 6.62-6.96, 7.04-7.44 (multiplet, phenyl protons), 6.44 (triplet, J = 6 Hz, N-4(H) proton), 1.00 (triplet, J = 7 Hz, methyl protons).

I.r. (KBr, cm^{-1}): 3386, 3236 (ν NH), 2972 (aliphatic ν CH), 1652 (ν CO).

Workup of the reaction filtrate provided a mixture of products, one of which being benzoic acid (47%).

1,3,4-Triphenyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-13)

Oxidative ring closure using potassium ferricyanide (Method E)

This reaction has been carried out previously using isoamyl nitrite as oxidizing agent.[40] A solution containing 0.70 g. of benzaldehyde 3,4-diphenyl semicarbazone (2.22 mmole, m.p. 164-166°) and 0.9 g. of sodium hydroxide (22 mmole) in 60 ml. of 80% ethanol was brought to reflux and 7.20 g. of potassium ferricyanide (22 mmole) in 65 ml. of water were slowly added. The refluxing was continued for 1 hr. followed by filtration of the yellow solid formed and washing with water. Repeated recrystallizations from ethanol (four times) using decolorizing charcoal gave pale orange needles which were dried for 13 hr. (ether).

Yield 0.15 g. (23%, not optimized).

M.p. 220-221° (lit.[40] yield 23%, m.p. 221.5-223°).

This procedure is far more convenient than the previous method using isoamyl nitrite.

DISCUSSION

SYNTHETIC APPROACH AND MECHANISTIC PATHWAYS LEADING TO THE INTERMEDIATES AND PRODUCTS

The possibility of encountering biological activity in the title compounds, particularly in view of the claims[49,50] regarding their applicability as drugs possessing very low toxicity and high antipyretic, antinflamatory, analgesic, analeptic, sedative, as well as hypnotic actions was one of the reasons for promoting an investigation into this area from a synthetic point of view. The approach considered for the synthesis is one involving a direct ring closure.

1,3,4-Trisubstituted-Δ^2-1,2,4-triazolin-5-ones, specifically the derivatives carrying a phenyl moiety at the 3-position are not numerous, although the synthetic routes leading to them are similar to those from which hydroxy triazoles are obtained. Consequently it was our aim to further define the scope of oxidative cyclization, alkaline cyclization and cyclization by various dehydrative processes of semicarbazide-type chains containing different functional groups. As mentioned earlier, the structure of the product requires this chain to contain a semicarbazide array. Unsymmetrically substituted aryl(phenyl) and alkylhydrazines comprised the starting material from which these semicarbazides were obtained. When position 1 of the heterocyclic ring contains

No substituents, hydrazine, in form of a hydrate or a salt is clearly the starting material.

During the course of this work a literature survey of monoalkylhydrazines (methylhydrazine being commercially available) showed that the methods for preparing the series from ethyl through amyl are few and are either, tedious and complicated, or give poor yields.[74]

Derivation of these compounds by direct and indirect replacement of hydrogen atoms in hydrazine (eg. by reaction with alkyl halides) is an appealing method, however when applied to the lower alkyl halides it leads chiefly to di-, tri-, and tetrasubstituted hydrazines as well as quaternary ammonium salts.

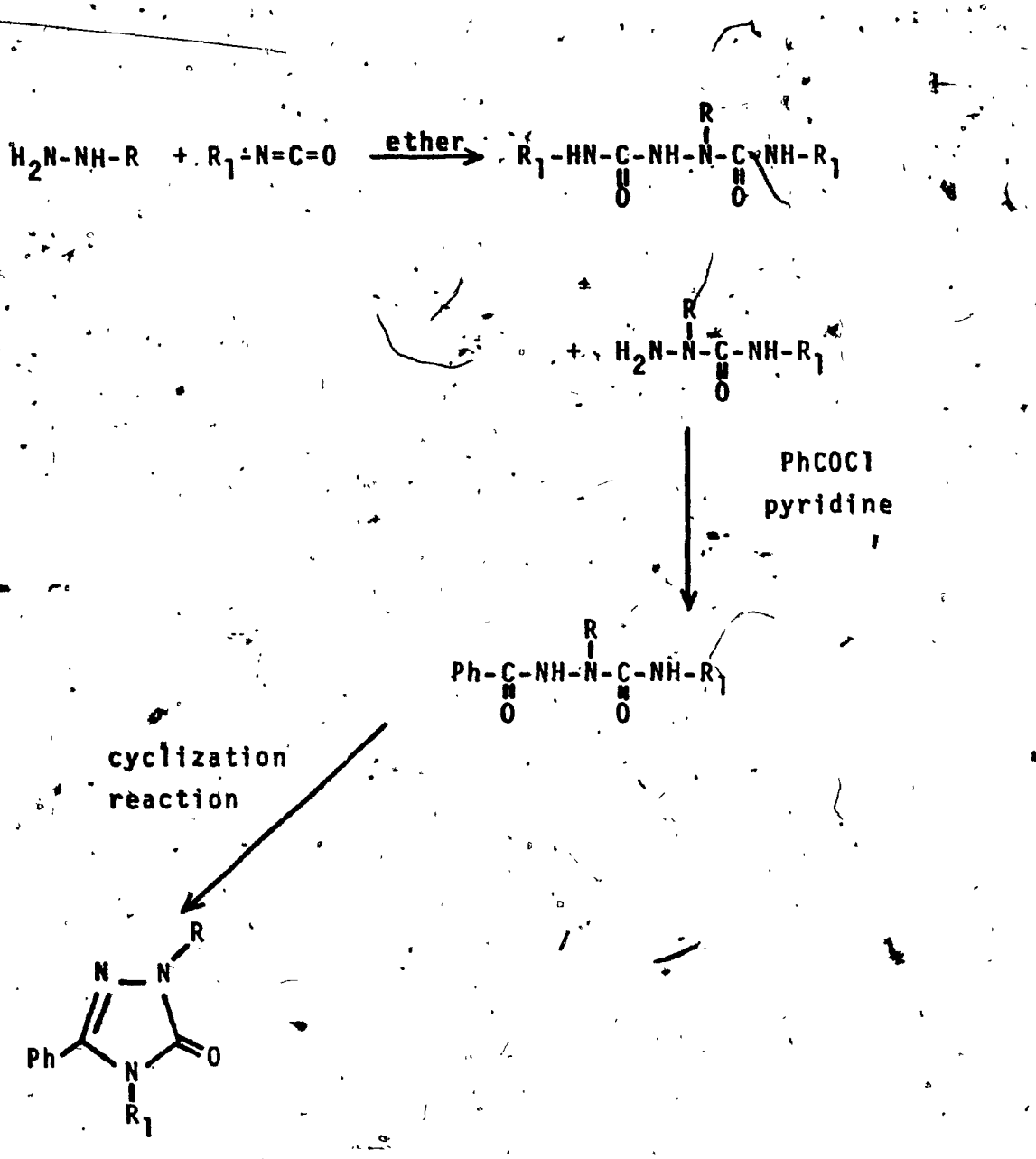
$$H_2N\text{-}NH_2 \cdot H_2O + RX \longrightarrow RHN\text{-}NH_2,\ R_2N\text{-}NH_2,\ RHN\text{-}NHR,\ R_2N\text{-}NHR,\ R_2N\text{-}NR_2$$

These facts make it clear why the view has become established in the literature that such direct alkylations cannot serve for the preparation of unsymmetrical monoalkylhydrazines.[75,76] Nevertheless, the results published by Kost and Sagitullin[55,77] indicate that polyalkylation is considerably diminished by slow addition of the alkyl halide to a ten-fold excess of hydrazine hydrate with vigorous stirring of the reaction mixture. Complete removal of the resulting monoalkylhydrazine, however, is achieved only by continuous and prolonged extraction in a

suitable apparatus. It has been suggested by these authors that the usual partition of alkylhydrazine between solvent and hydrazine hydrate is accompanied by equilibrium between a salt of the alkylhydrazine and the hydrazine itself, preventing rapid extraction of the alkylhydrazine.

Isopropylhydrazine has been prepared according to the method described[55] using isopropyl bromide and a 3.5-fold excess of hydrazine hydrate with the relatively high yield claimed by these authors having been obtained. Phenylhydrazine, the only aromatic member considered in this project, is a commercial product.

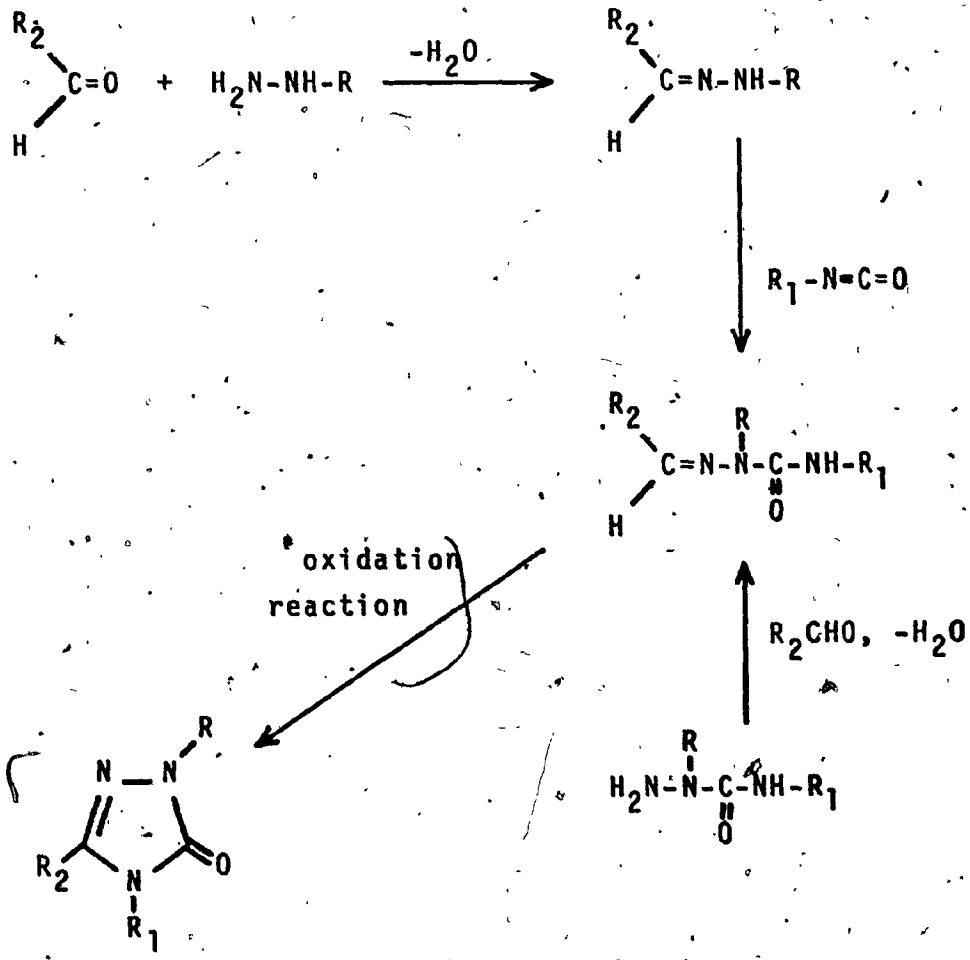
In the case of alkaline ring closure and ring closure using dehydrating agents, the starting hydrazine was generally reacted with the appropriate isocyanate yielding a semicarbazide as the major product accompanied in most cases by 1,3,6-trisubstituted biurea. The extent to which the biurea is present depends on the nature of the substituents on both starting materials. Isolation of the semicarbazide and its subsequent benzoylation afforded the starting chain as shown in Scheme 1.



Scheme 1. Synthetic approach via semicarbazides

Oxidative cyclizations were carried out using aldehydic semicarbazones which were obtained by action of the appropriate aldehydes on the non-benzoylated semicarbazides described in Scheme 1. Alternatively, these intermediates

were obtained by the initial formation of hydrazones followed by their treatment with aliphatic or aromatic isocyanates as shown below.

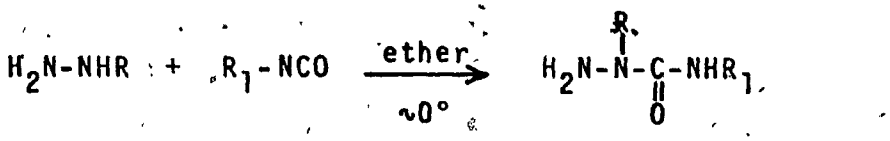


Scheme 2. Synthetic approach via semicarbazones

In a number of instances the approach to the intermediates and heterocycles was somewhat varied. Such cases will be outlined individually.

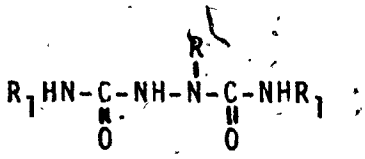
The Reaction of Isocyanates with Hydrazines

The classical reaction was carried out in ether, under anhydrous conditions with cooling, and dropwise addition of the isocyanate. To assure completion of the reaction the resulting mixture was further stirred at room temperature.



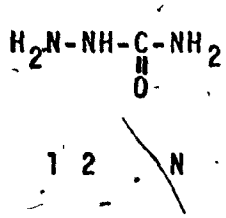
2,4-disubstituted semicarbazide

+



1,3,6-trisubstituted biurea

An alternative method of nomenclature for semicarbazide is hydrazine carboxyamide with the following numbering system.[78]



The results of this reaction are summarized in Table II.

Table II. Results of the Reaction of Isocyanates with Hydrazines

R	R_1	$H_2N-\underset{R}{N}-\underset{O}{C}-NHR_1$ M.P. °C	Yield %	Compd.	$R_1HN-\underset{O}{C}-NH-\underset{R}{N}-\underset{O}{C}-NHR_1$ M.P. °C	Yield %	Compd.
H	C_6H_5	117-119	~32	1-1[a]	-	-	2-1
CH_3	CH_2CH_3	Faint yellow oil, hydrochloride 147.5-151	88.6	1-2	-	-	2-2
CH_3	$CH(CH_3)_2$	49.5-53	96.4	1-3	-	trace	2-3
CH_3	$C(CH_3)_3$	91-97.5	88	1-4	171.5-172.5	1.4	2-4
CH_3	C_6H_5	87-91.5	30	1-5	202-206	9	2-5
CH_3	$o\text{-}CF_3C_6H_4$	97.5-99	84.4	1-6	166-167	5.9	2-6

Table II Cont.

R	R_1	$H_2N-\underset{R}{N}-\underset{O}{C}-NHR_1$ M.P. °C	Yield %	Compd.	$R_1HN-\underset{O}{C}-NH-\underset{R}{N}-\underset{O}{C}-NHR_1$ M.P. °C	Yield %	Compd.
$CH(CH_3)_2$	CH_2CH_3	50-63 (isomeric?)	75.9	1-7	178-179	10.0	2-7
$CH(CH_3)_2$	$CH(CH_3)_2$	104-109	62.2	1-8	187-188	5.2	2-8
$CH(CH_3)_2$	$C(CH_3)_3$	122-137 biurea contaminant; nitrate salt, 111-113.	-	1-9[b]	155-155.5	-	2-9[b]
$CH(CH_3)_2$	C_6H_5	91.5-95	50.	1-10	185.5	14	2-10
$CH(CH_3)_2$	o-$CF_3C_6H_4$	-	-	1-11[b,c]	149.5-150	-	2-11[b]

Table II Cont.

R	R_1	$H_2N-\underset{\underset{O}{\|}}{\overset{\overset{R}{\|}}{N-C}}-NHR_1$ M.P. °C	Yield %	Compd.	$R_1HN-\underset{\underset{O}{\|}}{C}-NH-\underset{\underset{O}{\|}}{\overset{\overset{R}{\|}}{N-C}}-NHR_1$ M.P. °C	Yield %	Compd.
C_6H_5	CH_2CH_3	150.5-152	90.6	1-12	-	-	2-12

a Prepared by refluxing hydrazine sulphate and phenylurea in alkaline EtOH. All other reactions were carried out using the appropriate isocyanates and hydrazines in cold ether.

b Yields are not reported due to the inability to achieve complete separation.

c The product melting at 69-74° was not consistent with the assigned structure.

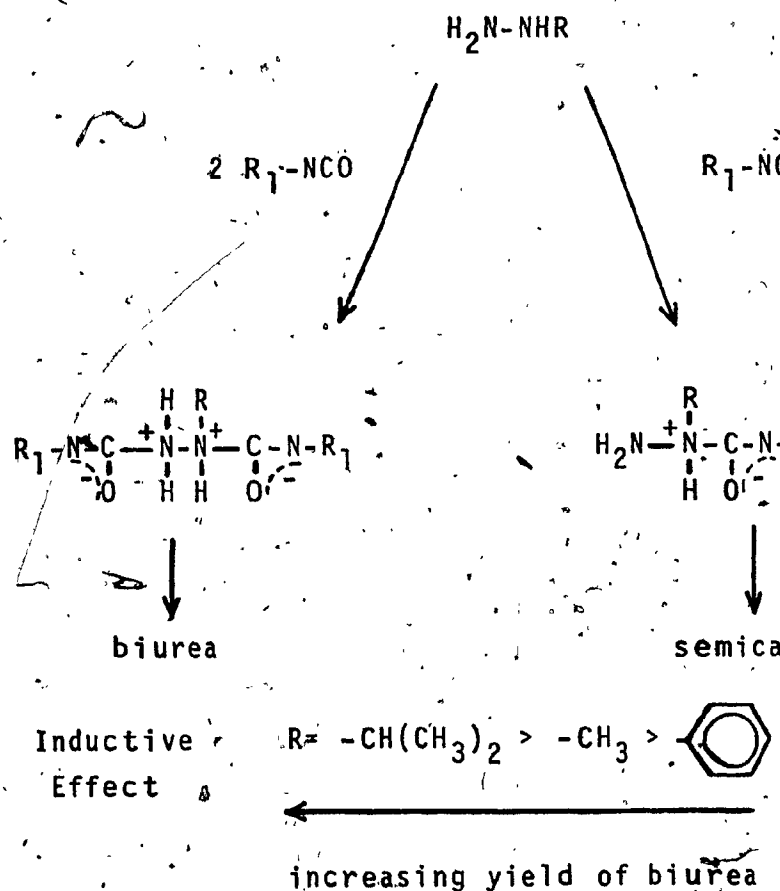
A number of reviews concerning organic isocyanate chemistry have been written.[79,80,81] The reactions and reactivity of isocyanates can best be understood by considering the electronic structure of the isocyanate group and the effect on this structure of various groups attached to the nitrogen atom. Consideration of the resonance structures according to molecular orbital theory indicates the electron or charge density is greatest on the oxygen and least on the carbon, the nitrogen being intermediate with a net negative charge. Potential nucleophiles such as the nitrogen atom of a hydrazine molecule will add in a predicted manner to the polarized azomethane linkage of the isocyanate group, with the most basic compounds being most reactive. The following is a representation of the valence bond structures.

$$R\text{-}\overset{-}{N}\text{-}\overset{+}{C}\text{=}O \longleftrightarrow R\text{-}N\text{=}C\text{=}O \longleftrightarrow R\text{-}N\text{=}\overset{+}{C}\text{-}\overset{-}{O}$$

minor major

If steric factors are neglected, any electron withdrawing groups attached to NCO will increase the positive charge on the carbon atom, thereby increasing the reactivity of the isocyanate towards nucleophilic attack. Conversly, electron donating groups will reduce the reactivity of the NCO group. Likewise, the reactivity of the reagent attacking the electrophilic carbon of the isocyanate group

will increase as its nucleophilicity increases. The latter is demonstrated in Table II where it is evident that the extent of involvement of the ß-nitrogen of the hydrazine in the reaction, with the formation of the corresponding biurea, is a function of substituent R. This effect reflects the stability of the Zwitterionic intermediate and may be summarized as follows.



Scheme 3. The effect of R substituents on the condensation of isocyanates with monosubstituted hydrazines

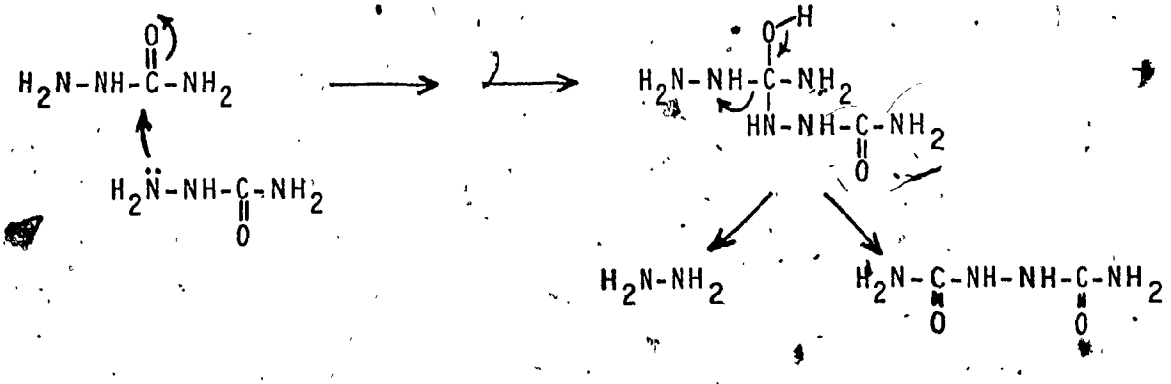
The intermediates in both processes rearrange via a proton migration to the final products. In the case where R is substituted by a phenyl group the side reaction is absent, while only traces of biurea were present in the reaction mixture when R was a methyl group. The yield of the by-product was most predominant with the presence of an isopropyl group at the hydrazine.

It may also be concluded from the results gathered that, regardless of the electronic nature of the substituent, the reaction of monoalkylhydrazines with aliphatic and aromatic isocyanates takes place primarily at the substituted (α) nitrogen atom of the hydrazine molecule. These results extend the study of Shevchenko, Vasil'evskaya and Grekov[82] who reported a similar influence of a number of electron-accepting and electron-donating substituents on the order of reactivity of monoalkylhydrazines in their reaction with phenyl isocyanate. None of the derivatives synthesized by these authors correspond to the ones obtained in the present study. Moreover, only compounds 1-1, 1-2, 1-5 and 2-5 of this series were encountered in the literature.

The yield of biurea in all cases was minimized by carrying out the reaction at low temperatures. Furthermore, the high reactivity of isocyanates with active hydrogen compounds necessitated anhydrous conditions throughout. The products resulting from the condensation of isocyanates with water are carbon dioxide and the corresponding amines,

which in turn may further react with the isocyanate to yield compounds not easily separated from the semicarbazides in question.

Separation of the biureas from the desired products was made possible by the different solubility patterns of the two. However, it was found that when R = isopropyl and R_1 = t-butyl, phenyl and α,α,α-trifluoro-o-tolyl (substituents with increasingly higher molecular weights) this task was more tedious owing to the similarity in the solubilities of the two products. Moreover, semicarbazides are known to undergo decomposition on exposure to prolonged heating. This was observed to a slight extent when an attempt was made to isolate 2-methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide from its biurea analog by recrystallization from aqueous solution. The following scheme has been postulated for the thermal decomposition of unsubstituted semicarbazide.[83]



Scheme 4. Mechanism for the thermal decomposition of semicarbazide

Benzoylation Reaction

The Schotten-Baumann reaction which is the most widely used method in the benzoylation of amides was employed. Acylation is generally carried out using the acid anhydride while benzoylation is normally achieved with benzoyl chloride. An attempt to benzoylate 4-phenyl semicarbazide via the classical Schotten-Baumann technique using sodium hydroxide failed. Anhydrous pyridine gave good results and was therefore used in all cases as solvent (refer to Scheme 1).

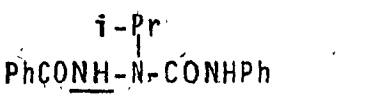
A study carried out by Grekov and Shevchenko[84] discloses that the most convenient method for the preparation of 1,4-disubstituted semicarbazides is the reaction between carboxylic acid hydrazides with isocyanates. Application of this reaction to yield 1,2,4-trisubstituted derivatives requires that the starting carboxylic acid hydrazide contain a substituent at the β-nitrogen. For this reason the synthesis of N-benzoyl-N'-isopropylhydrazine(1-benzoyl-2-isopropylhydrazine) by benzoylation of isopropylhydrazine was attempted. Only the dibenzoylated product, of which two isomeric structures (I) or (II) are possible, was recovered.

$$H_2N\text{-}NH\text{-}i\text{-}Pr \xrightarrow[\text{pyridine}]{PhCOCl} PhCONH\text{-}N(iPr)\text{-}COPh \quad (I)$$

$$(PhCO)_2N\text{-}NH\text{-}i\text{-}Pr \quad (II)$$

N.m.r. (DMSO-d_6, δ): 10.44 (1H, singlet, NH proton), 7.24-7.96 (10H, multiplet, phenyl ring protons), 4.76 (1H, septet, J = 6.5 Hz, methine proton), 1.20 (6H, doublet, J = 7 Hz, methyl protons).

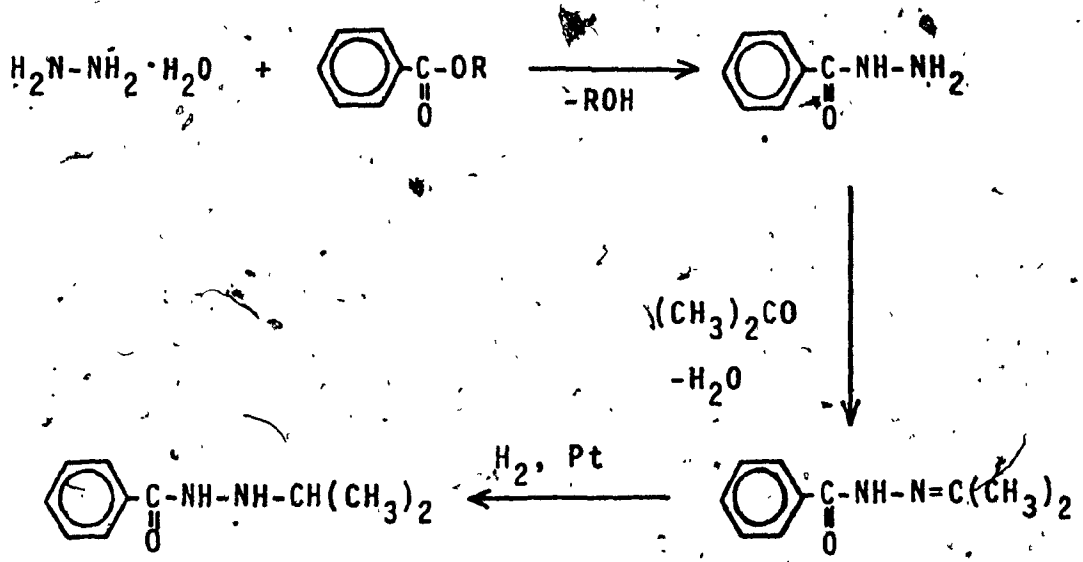
(I) was assigned as the correct structure on the basis of the position of the NH signal. The environment experienced by this proton is somewhat similar to that experienced by N-1(H) of 1-benzoyl-2-isopropyl-4-phenyl semicarbazide (compound 3-10).



The n.m.r. spectrum of compound 3-10 contains two singlets at δ10.22 and δ8.54 due to the N-1(H) and N-4(H) protons respectively. It is also evident from Table X that all compounds containing an -NH-i-Pr group consist of a doublet in the region between δ5.75 and δ6.34 due to coupling between the NH and methine protons. This further justifies elimination of structure (II). Further benzoylation of (I) is not expected since the remaining amide NH group is only weakly nucleophilic. Attempts at partial hydrolysis of (I) to 1-benzoyl-2-isopropylhydrazine using sodium hydroxide failed.

The preparation of this and of similarly substituted carboxylic acid hydrazides is rather involved and is usually a three-step process. The derivative under discussion has been previously synthesized according to

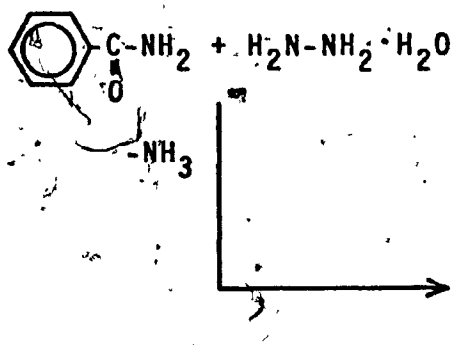
Scheme 5:[56,57,58]

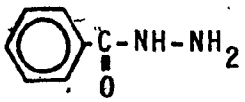


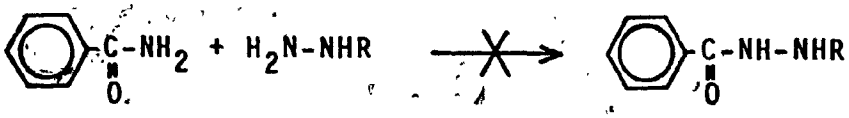
Scheme 5. Synthetic route leading to 1-benzoyl-2-isopropylhydrazine

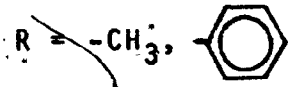
In view of the difficulty encountered in obtaining such intermediates, this method was discontinued.

In a different approach the synthesis of N-benzoyl-N'-methylhydrazine and N-benzoyl-N'-phenylhydrazine was attempted by prolonged refluxing of benzamide with methyl and phenylhydrazines in aqueous medium. Starting material, only, was isolated in both cases. In contrast, benzhydrazide was obtained, as expected, from the reaction of benzamide with hydrazine hydrate.

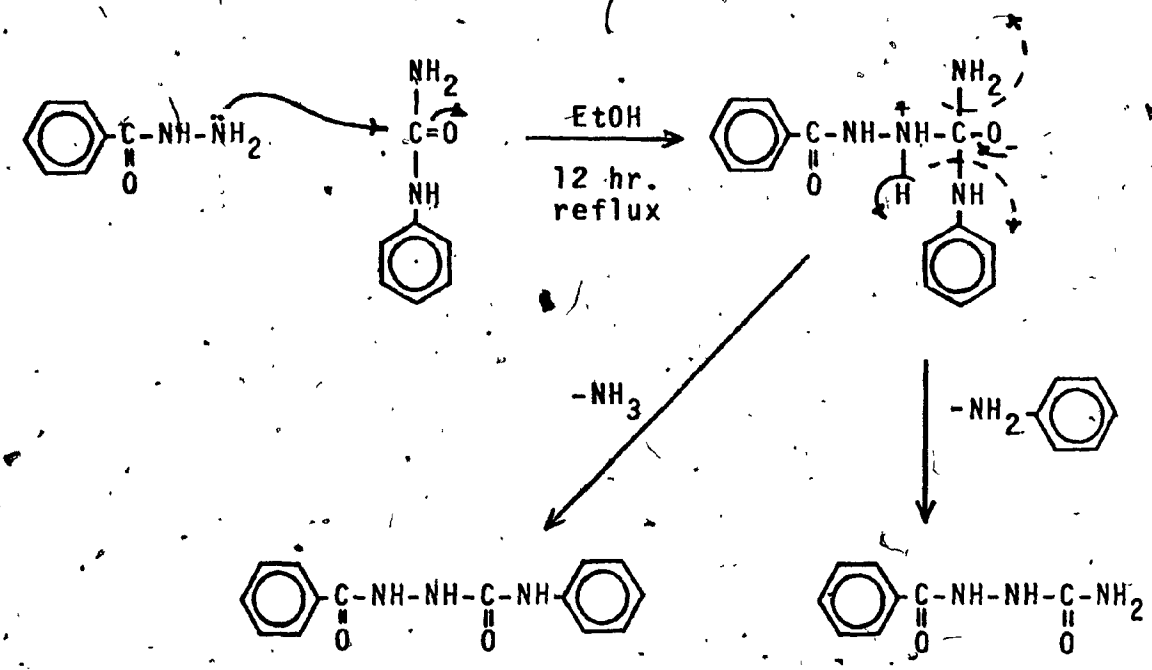






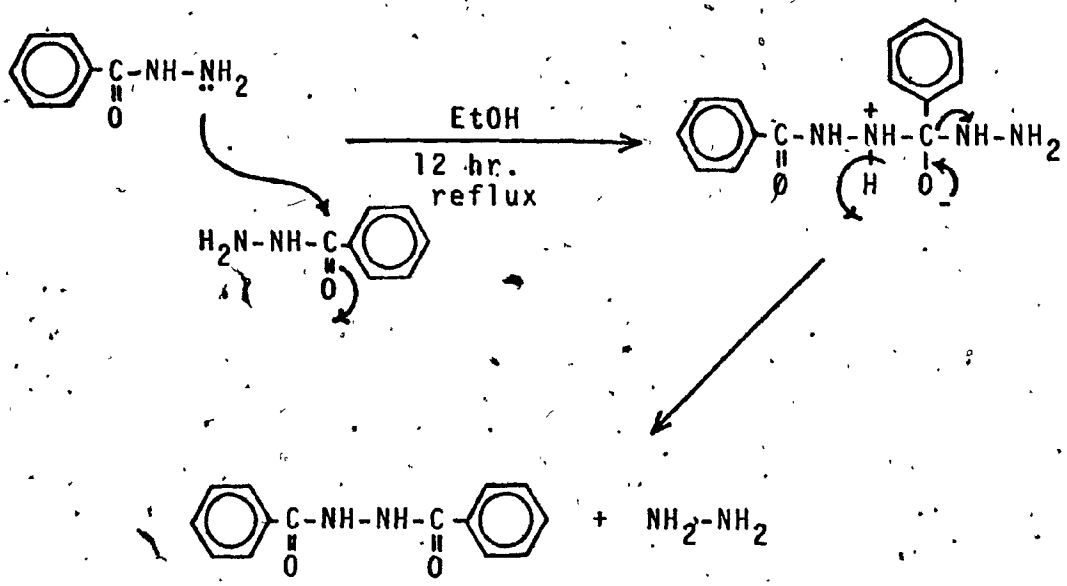


Another attempt extended the condensation of hydrazine sulfate with phenylurea to benzhydrazide and phenylurea. The desired reaction which leads to 1-benzoyl-4-phenyl semicarbazide may proceed with a side reaction producing 1-benzoyl semicarbazide.



Scheme 6. Possible mechanism for the condensation of benzhydrazide with phenylurea

The high melting solid (237-239.5°) collected from the reaction mixture was assigned the structure of 1,2-dibenzoylhydrazine indicating that the reaction proceeds via neither one of the above mechanisms. Instead, a bimolecular reaction between two benzhydrazide molecules may be envisaged.



Scheme 7. Suggested mechanism for the bimolecular condensation of benzhydrazide

N.m.r. (DMSO-d_6, δ): 10.52 (2H, singlet, two NH protons), 7.83-8.16 (4H, multiplet, ortho ring protons), 7.35-7.74 (6H, multiplet, meta and para ring protons).

I.r. (KBr, cm^{-1}): 3206 (νNH), 1670, 1635 (νCO).

The expected molecular ion at m/e 240 is absent in the mass spectrum. The reason for this is ascribed to the decomposition of the non-volatile solid prior to electron impact. The predominant fragments in the spectrum with abundances relative to the base peak are: m/e 106.0 (12.0%); $PhCO^+$, m/e 105.0 (100.0%); $PhCN^+$, m/e 103.0 (5.7%);

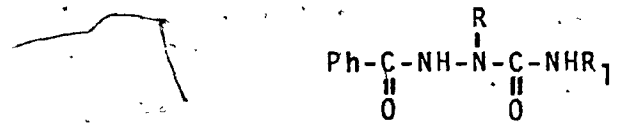
$C_6H_5^+$, m/e 77.0 (71.8%); $C_4H_3^+$, m/e 51.0 (20.3%).

The identity of the symmetrical hydrazine is supported both by physical as well as spectroscopic evidence. A preparation of an authentic sample using hydrazine sulfate and benzoyl chloride in potassium hydroxide solution[63] was unsuccessful. In contrast, when benzoyl chloride was added to a pyridine solution of hydrazine hydrate, 1,2-dibenzoyl hydrazine melting at 239-240° was isolated in 63% yield. The n.m.r. and i.r. data are identical with the above. This reaction proceeded in the same manner as the benzoylation of isopropylhydrazine described on p. 95.

It was concluded on the basis of the various methods attempted that the most appropriate approach at deriving 1-benzoyl-2,4-disubstituted semicarbazides is the one described in Scheme 1, involving benzoylation of the products obtained from the reaction of monosubstituted hydrazine with isocyanates. The products, most of which have not been previously described in the literature, are classified in Table III, pp. 102-103.

Refluxing was required during the benzoylation reaction of 2-methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide (compound 1-6). Furthermore, isolation of the desired product from the reaction mixture proved to be a tedious procedure, with different products being recovered upon repetition of the reaction while maintaining similar conditions. One such product was assigned, on the

Table III. Results of the Benzoylation Reaction



R	R_1	Reaction Conditions	M.P. °C	Yield %	Compound
H	C_6H_5	r.t.	201.5-203	78.9	3-1
CH_3	CH_2CH_3	r.t.	163.5-165	73.5	3-2[a]
CH_3	$CH(CH_3)_2$	r.t.	155.5-157.5	63.1	3-3
CH_3	$C(CH_3)_3$	r.t.	143.5-145.5	83.5	3-4
CH_3	C_6H_5	25-30° for 2.25 hr.	144.5-145.5	92.8	3-5
CH_3	o-$CF_3C_6H_4$	reflux for 110 min.	117-123	~85 (crude)	3-6
$CH(CH_3)_2$	CH_2CH_3	r.t.	112-114	42	3-7
$CH(CH_3)_2$	$CH(CH_3)_2$	r.t.	149.5-152	20 (not optimized)	3-8
$CH(CH_3)_2$	$C(CH_3)_3$	r.t.	162-166.5	~70	3-9

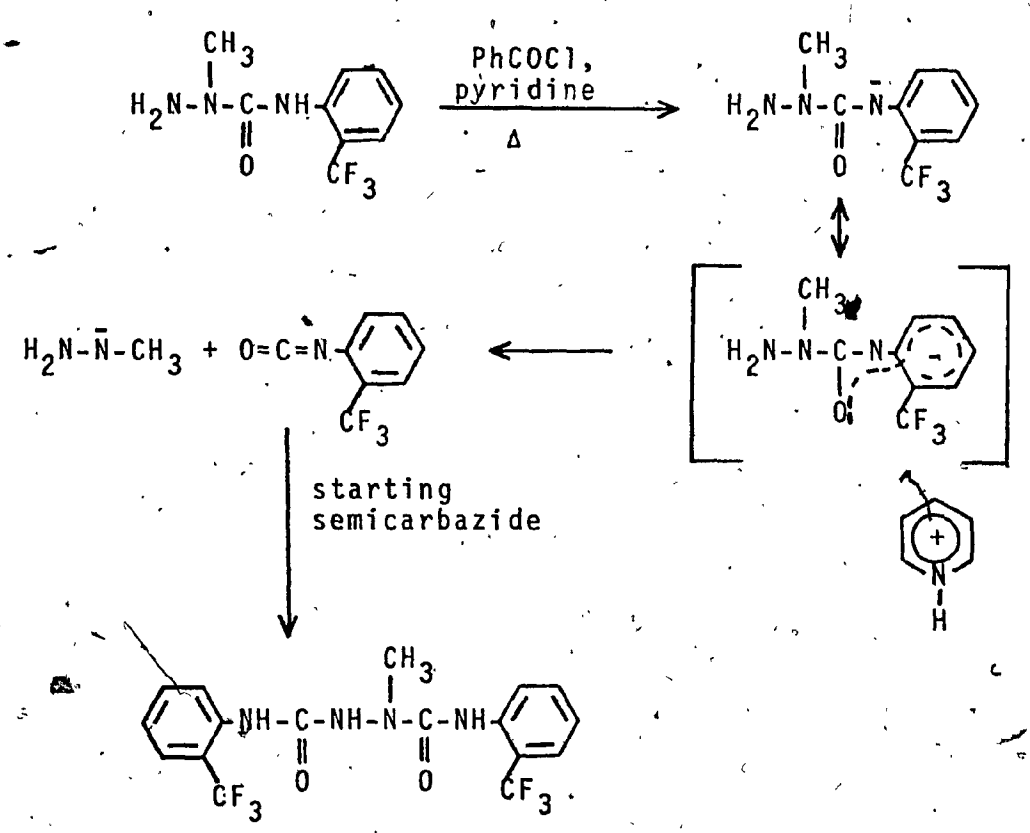
Table III Cont.

R	R_1	Reaction Conditions	M.P. °C	Yield %	Compound
$CH(CH_3)_2$	C_6H_5	40° for 5 hr.	152.5-155.5	81.2	3-10[a]
C_6H_5	CH_2CH_3	50-65° for 6 hr.	224.5-226 (dec.)	72.1	3-11

Pyridine was used as solvent.

[a] Benzoic acid was also recovered.

basis of its n.m.r. spectrum, the structure of 1,6-di-(α,α,α-trifluoro-o-tolyl)-3-methyl biurea. This product arises probably by the initial cleavage to the isocyanate as shown below.

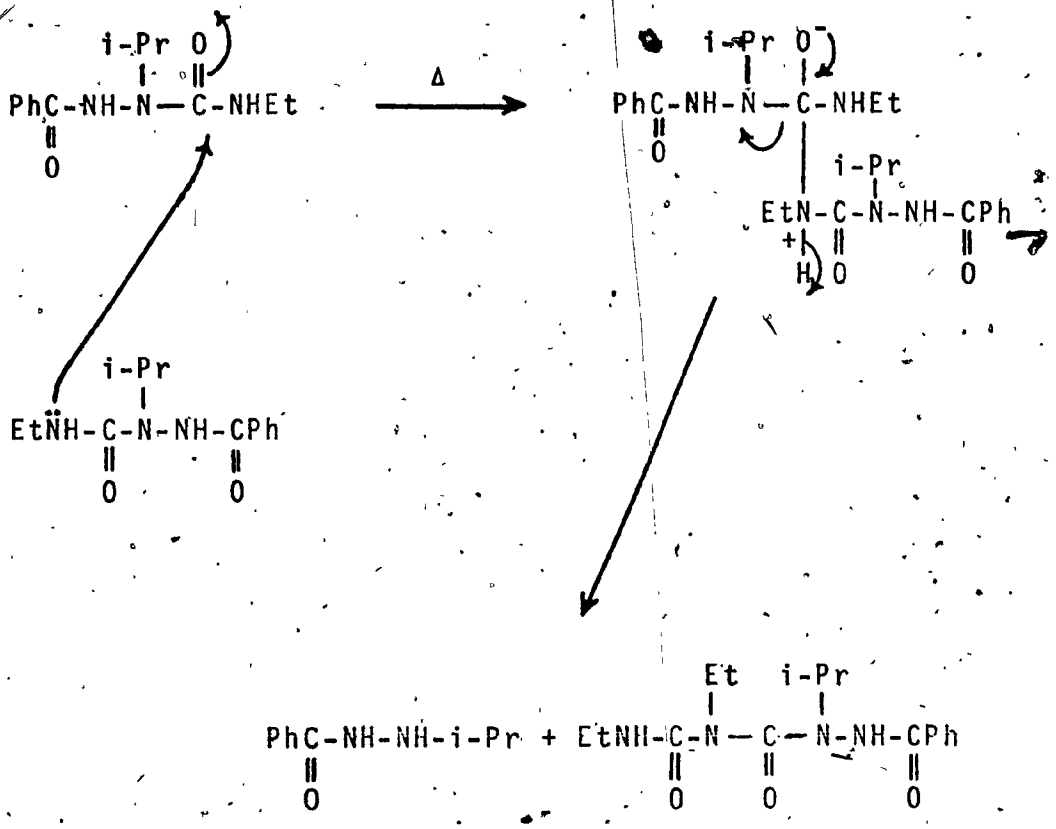


Scheme 8. Suggested mechanism for the product obtained during the benoylation of 2-methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide

The presence of both an o-trifluoromethyl group as well as a carbonyl group makes the proton at N-4 strongly acidic, and exposure of this site to nucleophilic attack results in

the resonance stabilized anion shown above. The absence of this side product in all the other benzoylation reactions may be accounted for by the following factors: i) The reaction always proceeded without the requirement of refluxing temperatures. ii) An o-trifluoromethyl is, undoubtedly, a much stronger electron-withdrawing group than an ethyl, isopropyl, t-butyl or a phenyl group.

A purification attempt of the 1-benzoyl-2-isopropyl-4-ethyl derivative (compound 3-7) by distillation under reduced pressure resulted in decomposition to 1-benzoyl-2-isopropylhydrazine. The material which was distilled at 132-134°/0.55 mm. solidified to crystalline needles melting at 107-112° (lit. 109-110°,[56] 106°,[57] 117°[58]). The n.m.r. spectrum of the product was identical to that of the hydrolysis product obtained during the alkaline reaction of 1-benzoyl-2-isopropyl-4-t-butyl semicarbazide (see cyclization reaction of compound 3-9). The decomposition most probably involves a bimolecular mechanism of the following sequence. Isolation of the biuret was not attempted as this is likely to undergo further thermal decomposition into more complicated fragments.



1-benzoyl-2-isopropyl-hydrazine

1,3-diethyl-5-isopropyl-5-benzamido biuret

Scheme 9. Suggested mechanism for the thermal decomposition of 1-benzoyl-2-isopropyl-4-ethyl semicarbazide

Reactions Leading to Substituted Semicarbazones

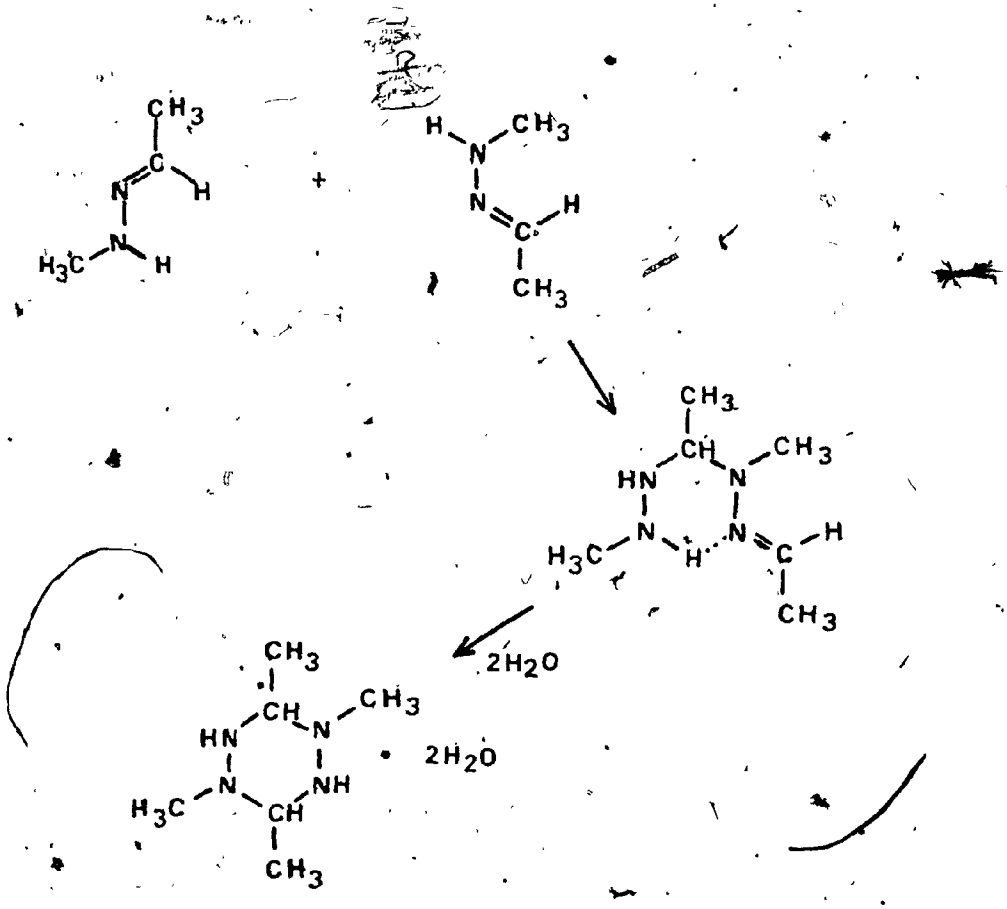
These intermediates were prepared by the reaction of suitable isocyanates with the corresponding hydrazones. The latter were readily prepared by condensation of the appropriate carbonyl compounds with monosubstituted

hydrazines in an ether or ethanolic medium. In some cases the semicarbazones were synthesized directly, without initial isolation of the hydrazones. In three instances substituted semicarbazones were obtained by the reaction of an aldehyde with non-benzoylated semicarbazides. A summary of the data follows in Tables IV and V, pp. 117-120.

A preparation of benzaldehyde methylhydrazone by Harries and Haga[85] yielded a colorless, crystalline solid with a high melting point (179°) and analytical data which were not in good agreement with the calculated values. One would expect the compound to be in the form of an oil of lower boiling point (because of weaker intermolecular hydrogen bonding) than the liquid benzaldehyde hydrazone. The same product has been obtained and identified as a pale-yellow oil by Wiley and Irick,[65] b.p. 81°/0.8 mm. and by Todd,[66] b.p. 129-133°/20 mm. The product we obtained is in good agreement in its physical and spectroscopic properties with the assigned structure.

Monoalkylhydrazones, in general, are known to be colorless or slightly yellowish mobile liquids which assume a green or yellow color in the presence of atmospheric oxygen.[64] Todd[66] reports a large amount of non-distillable oil formation when benzaldehyde methylhydrazone is allowed to stand at room temperature in alcohol-water solution, and attributes this to polymerization. This is further verified by Ioffe, Stopskii and Sergeeva[64] who claim that one direction of the side reactions associated with simpler

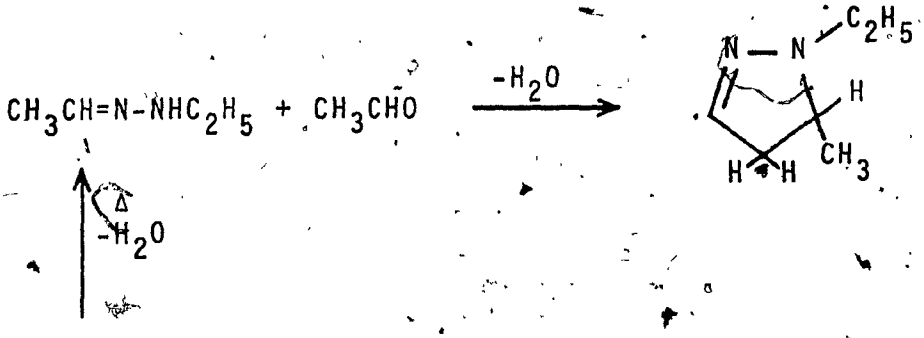
monoalkylhydrazones is its tendancy to dimerize. Based on n.m.r. and i.r. assignments, these authors identified the crystalline solid which gradually deposited during storage of the liquid methylhydrazone of acetaldehyde as a dimer. Moreover, they described the dimer to be a hygroscopic solid which is immediately converted to the dihydrate, and can be assigned the structure of 1,3,4,6-tetramethylhexahydro-1,2,4,5-tetrazine.



Scheme 10. The dimerization of acetaldehyde methylhydrazone

The phenomenon was also observed for the isopropylhydrazone of formaldehyde. In contrast, the methylhydrazone of propionaldehyde prepared during this study was clear with no apparent solid formation when stored for 24 months. An n.m.r. spectrum of the liquid was rerun after the indicated interval and found to be identical to the original spectrum, with the exception of an additional uninterpreted singlet at 1.99δ.

Another side reaction is postulated by the same authors when the reaction temperature is elevated. Thus, 5-methyl-1-ethyl-Δ^2-pyrazoline was the product accounted for when a mixture of acetaldehyde and ethylhydrazine was subjected to reflux.



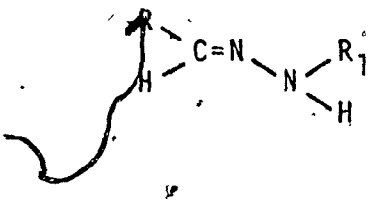
Scheme 11. The reaction between acetaldehyde and ethylhydrazine at elevated temperatures

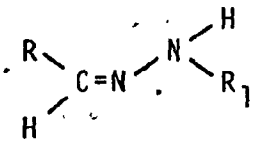
In view of these results the preparation of propionaldehyde methylhydrazone was carried out between

-8° and -5° with addition of the reagents made over 3.25 hours. The synthesis of benzaldehyde methylhydrazone, on the other hand, required refluxing in ethanol. 1-Methyl-5-phenyl-Δ^2-pyrazoline, if formed, is expected to have a higher boiling point than the hydrazone and remain in the non-distilled residue.

Isomeric Structures of Hydrazones

The following isomers are known to exist for mono-substituted hydrazones.





<u>syn</u> isomer (aldehydic hydrogen and NHR_1 group <u>cis</u>)

<u>anti</u> isomer (aldehydic hydrogen and NHR_1 group <u>trans</u>)

The type of solvent alters the relative proportions of the two isomers to a slight extent as indicated by the following examples.[86]

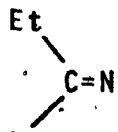
Syn/anti Ratios of Phenylhydrazones in Solution (RHC=N-NHPh)

R	% syn/anti at equilibrium
Me	64/36[b]; 63/37[c]; 65/35[d,g]; 61/39[e]
Et	89/11[a]; 82/18[c]
i-Pr	95/5[a,d]; 96/4[c]; 94/6[f,g]

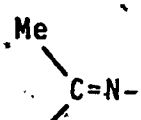
[a]neat, [b]acetone, [c]benzene, [d]carbon tetrachloride, [e]dimethyl sulfoxide, [f]methanol, [g]methylene bromide.

The values were determined from the integration of n.m.r. peak areas and are accurate to ± 5%.

Of the hydrazones prepared during this work, only those of propionaldehyde methylhydrazone and acetaldehyde phenylhydrazone were observed to exist as isomers. In both cases the syn isomer was the thermodynamically more stable one.



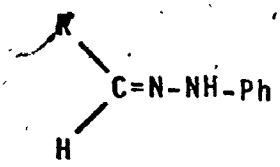
syn/anti calculated:	82/18	(neat liquid)
reported:[64]	82/18	(solvent not indicated)



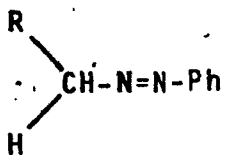
syn/anti calculated:	61/39	(CCl_4)
reported:[86]	65/35	(CCl_4)

Autoxidation of Phenyl Substituted Hydrazones

It has been concluded from spectroscopic studies[87] that in neutral solutions phenyl hydrazone (I) readily isomerizes to the azo form (II).

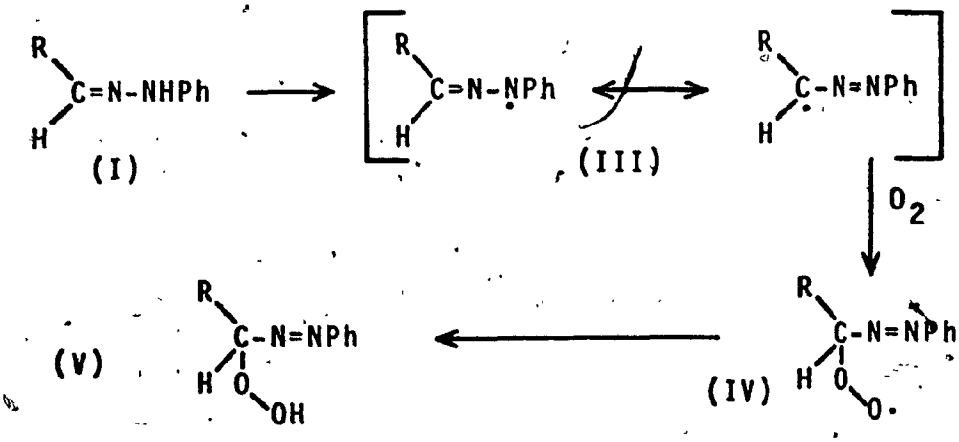


(I)



(II)

A reinvestigation by Bellamy and Guthrie[68,88] showed no evidence for the tautomerism and attributed the observations of the other authors to autoxidation. A radical mechanism seems to be plausible for such a process.



1-hydroperoxy-1-phenylazoalkane

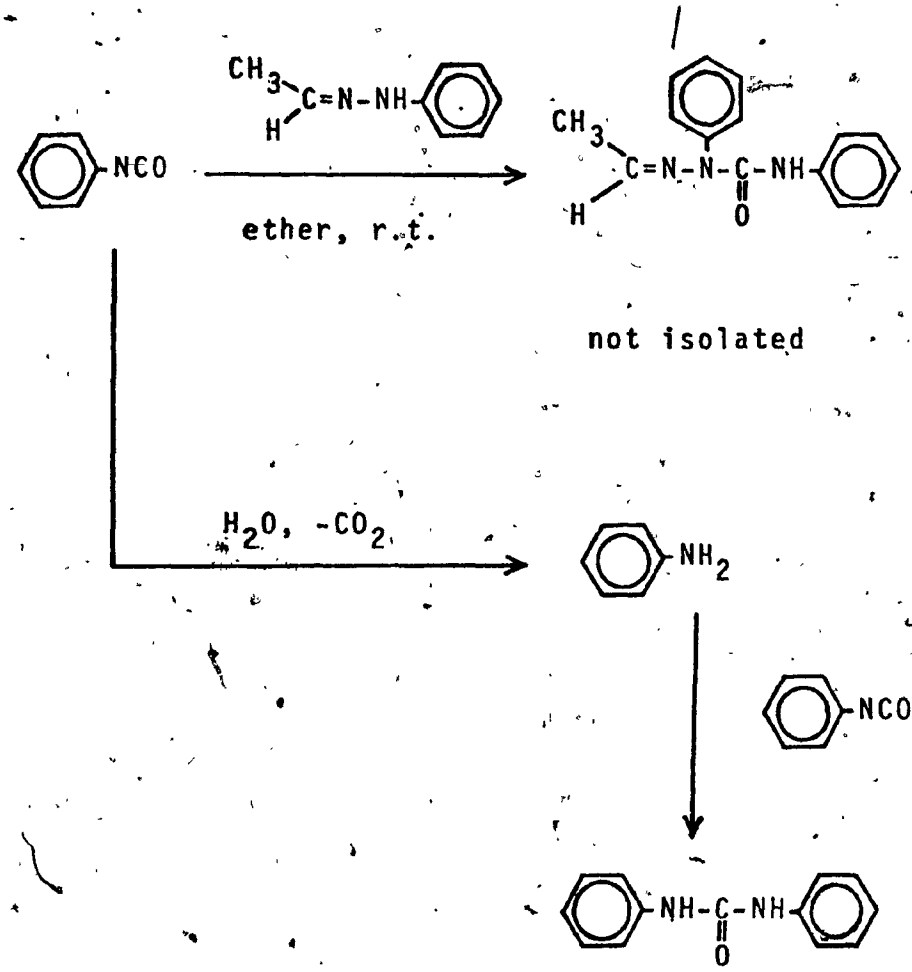
Scheme 12. Mechanism for the autoxidation of phenylhydrazones

The generation of a pseudo-allylic radical (III) from a phenylhydrazone using a radical initiator whose source is uncertain may result in the phenylazoalkane (V), if the radical reacts at the carbon. This is expected to occur through intermolecular hydrogen abstraction provided that there is no other reactive species present in the medium. Chain propagation via nitrogen rather than carbon is disproved according to n.m.r. data.[86] Phenylhydrazones of ketones are also known to undergo the above autoxidation process.

Exposure of acetaldehyde phenylhydrazone (Compound 4-4) to the atmosphere resulted in a progressive darkening of sample to a deep-red oil. Autoxidation of the product was eliminated by its storage under vacuum over sodium hydroxide. The same behaviour was observed for non-polar solutions of benzaldehyde phenylhydrazone (Compound 4-5).

The reaction of isocyanates with monosubstituted hydrazones was most difficult to achieve for phenyl substituted hydrazones as suggested in Table V. More rigorous conditions were required in these cases than in the cases where monoalkylhydrazones constituted the starting materials. The workup of the reaction mixture of ethyl isocyanate and benzaldehyde phenylhydrazone afforded a red oily residue purification of which was difficult. The color formation may be attributed to autoxidation of the starting phenylhydrazone, with the resulting hydroperoxide probably reacting further to yield more

complicated products. Refluxing a solution of benzaldehyde phenylhydrazone and phenyl isocyanate in benzene gave the expected semicarbazone (compound 5-10), however, only in a low yield. The synthesis of this compound was thoroughly studied by Guglielmino[40] who also obtained a low yield of the pink colored product. Finally, the reaction between acetaldehyde phenylhydrazone and phenyl isocyanate in ether was accompanied by the orange-red autoxidation color, the solid isolated being characterized as sym-diphenylurea rather than the expected acetaldehyde 2,4-diphenyl semicarbazone. This alternative pathway indicates that the reaction conditions were not completely anhydrous, thus allowing for the initial formation of aniline via condensation of the isocyanate with water, followed by its reaction with a second isocyanate molecule in the following manner. The n.m.r. spectrum of this product is identical to that of an authentic sample of 1,3-diphenylurea.



Scheme 13. Suggestion for the side reaction occurring during the attempted condensation of acetaldehyde phenylhydrazone and phenyl isocyanate

N.m.r. (DMSO-d_6, δ): 8.64 (2H, singlet, N-1(H) and N-3(H) protons), 6.74-7.66 (10H, multiplet, phenyl protons).

The more abundant fragments in the mass spectrum have been assigned as follows:

m/e	Relative Intensity (%)*	Fragment
212.0	52.7	M^+
120.0	10.5	$PhNHCO^+$
119.0	50.8	$PhNCO^+$ ($PhNHCO^+$-H)
94.0	55.3	$PhNH_3^+$ (via ion molecule collision)
93.0	100.0	$PhNH_2^+$ (M^+-PhNCO)
92.0	56.4	$PhNH^+$
91.0	38.7	PhN^+
77.0	65.5	$C_6H_5^+$
67.0	10.4	$PhNH_3^+$-HCN
66.0	63.6	$PhNH_2^+$-HCN
65.0	66.9	$PhNH^+$-HCN
64.0	36.2	PhN^+-HCN
51.0	45.5	$C_4H_3^+$
39.0	48.9	$C_3H_3^+$

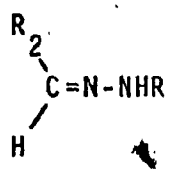
Metastable bands were observed for the following decompositions:

m/e 212.0 → 93.0 (40.8 calcd.)

m/e 93.0 → 66.0 (46.8 calcd.)

*Relative to the base peak.

Table IV. Results of the Condensations to Hydrazones

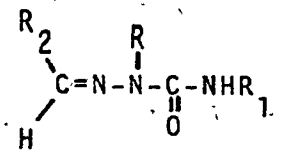


R	R_2	Reaction Conditions	M.P., B.P., °C	Yield %	Compound
H	C_6H_5	-	-	-	4-1[a]
CH_3	CH_2CH_3	Ether, addition over 3.25 hr. at -8 to -5°	B.P. 120.0-120.5/ atm.	44.4	4-2[b]
CH_3	C_6H_5	95% EtOH, reflux for 4 hr.	B.P. 132-135/ 18.5 mm.	41.2	4-3
C_6H_5	CH_3	80% EtOH, 90 min. at r.t.	M.P. 65-81	64	4-4[b]
C_6H_5	C_6H_5	95% EtOH, ambient temps.	M.P. 152-154.5	-	4-5

[a] Not isolated prior to its condensation with the isocyanates.

[b] Isomeric.

Table V. Results of the Condensations to Semicarbazones



R	R_1	R_2	Reaction Conditions	M.P. °C	Yield %	Compound
H	H	C_6H_5	Aqueous EtOH, ambient temps.	222	-	5-1[a]
CH_3	H	C_6H_5	Aqueous EtOH, ambient temps.	158-160	-	5-2[a]
CH_3	CH_2CH_3	C_6H_5	Ether, addition made with cooling	89.5-92	70	5-3
CH_3	C_6H_5	CH_2CH_3	Ether, addition made with cooling	38.5-40	48.8	5-4
CH_3	C_6H_5	C_6H_5	Ether, addition made with cooling	106.5-108.5	64.7	5-5

Table V Cont.

R	R_1	R_2	Reaction Conditions	M.P. °C	Yield %	Compound
CH_3	C_6H_5	C_6H_5	95% EtOH, ambient temps. for 45 min.	106-108	80	5-5[b]
$CH(CH_3)_2$	CH_2CH_3	C_6H_5	95% EtOH, ambient temps. for 60 min.	82-83.5	71.4	5-6[b]
$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_5	Ethyl acetate, ambient temps.	86.5-89.5	-	5-7[b]
C_6H_5	CH_2CH_3	C_6H_5	Benzene, reflux for 65 hr.	Solid m.p. 178-179° (dec.)?		5-8
C_6H_5	C_6H_5	CH_3	Ether, 70 hr. at r.t.	70.0% 1,3-diphenylurea isolated		5-9
C_6H_5	C_6H_5	C_6H_5	Benzene, reflux for 4.5 hr.	164-166	15	5-10

Table V Cont.

R	R_1	R_2	Reaction Conditions	M.P. °C	Yield %	Compound
C_6H_5	1-naphthyl	C_6H_5	Benzene, reflux for 5.5 hr.	Starting material recovered		5-11

[a] Obtained without initial isolation of the hydrazone.

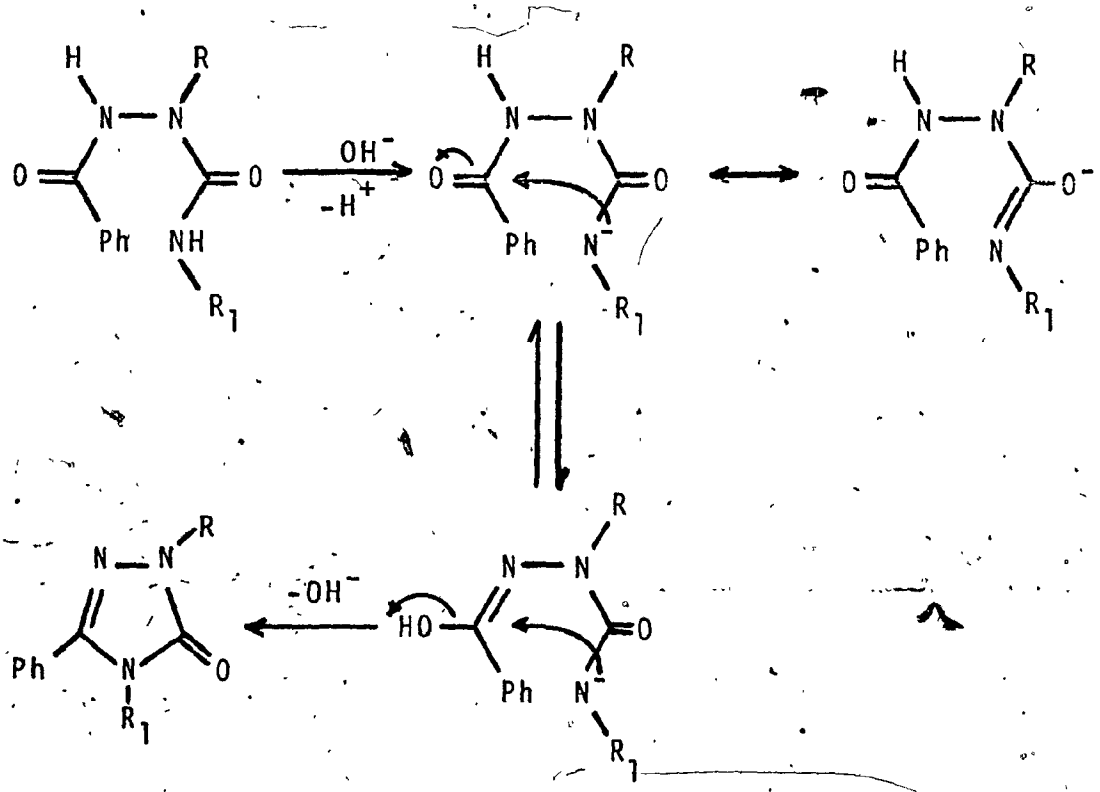
[b] Prepared by condensation of the non-benzoylated semicarbazide with benzaldehyde.

Cyclization Reactions

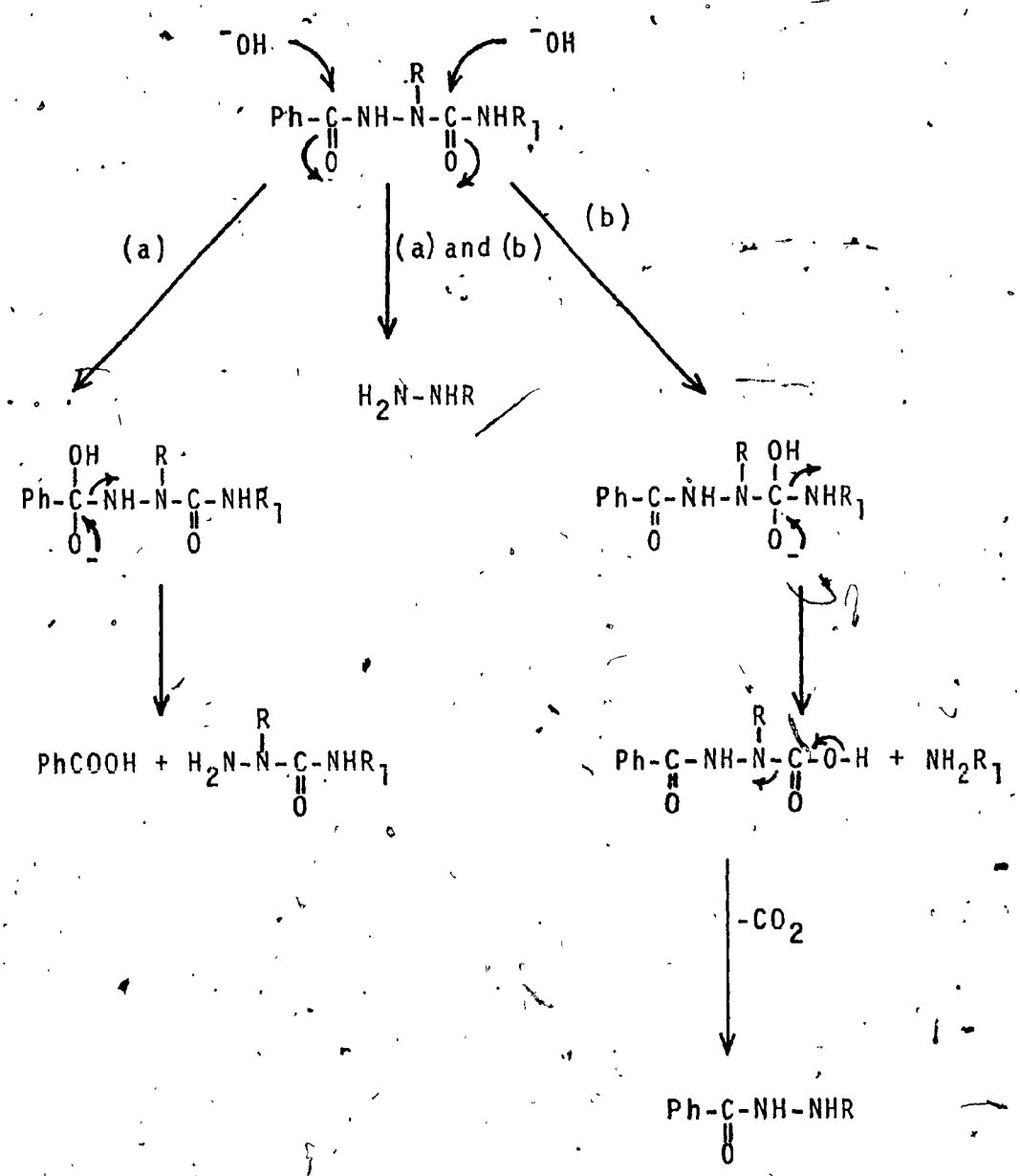
I. Ring closure of 1-benzoyl-2,4-disubstituted semicarbazides

i) Alkaline ring closure (Method A)

It is evident from the results in Table VI that two competing reactions are taking place in this mode of cyclization. One of these is the desired cyclization and the other is hydrolysis.



Scheme 14. Suggested mechanism for the alkaline cyclization of 1-benzoyl-2,4-disubstituted semicarbazides



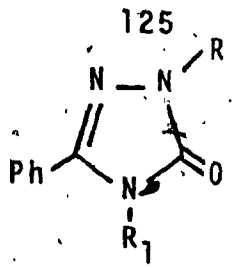
Scheme 15. Suggested mechanism for the alkaline hydrolysis of 1-benzoyl-2,4-disubstituted semicarbazides

Hydrolysis of the benzoyl moiety (Scheme 15-a) produces benzoic acid and the corresponding non-benzoylated chain in the form of sodium salts. Hydrolysis of the carbonyl function of the semicarbazide unit (Scheme 15-b) on the other hand is indicated by expulsion of a β-substituted benzhydrazide, the appropriate amine and carbon dioxide in the form of a carbonate. In one instance, during the cyclization reaction of 1-benzoyl-2-methyl-4-phenyl semicarbazide (Compound 3-5), the original monoalkylhydrazine was isolated during workup of the reaction mixture demonstrating that hydrolysis may also proceed via Schemes 15-a and 15-b simultaneously.

Because of their stronger acidic character, the hydrolysis of arylamido groups (ArCONH-; cf. benzamido group, Scheme 15-a) is easier to achieve than the hydrolysis of alkylamido groups (RCONH-). Base induced cyclizations to the 3-phenyl derivatives of 1,4-disubstituted-Δ^2-1,2,4-triazolin-5-ones are not reported in the literature. In fact, 3-phenyl-5-hydroxy- and 1,3-diphenyl-5-hydroxy-triazoles obtained from the cyclizations of 1-benzoyl semicarbazide[89] and 1-benzoyl-2-phenyl semicarbazide[51] were the only two encountered during this study. The yields are unsatisfactory being 36% and 6% respectively. No mention is made in these publications regarding the hydrolysis side reactions. Cyclizations leading to derivatives containing alkyl groups at the 3-position of the ring are more common.[49,51,90]

Intramolecular condensation yielding the heterocycles is likely to be dictated by both steric and electronic factors. Bulky groups will tend to hinder the process while the presence of strongly electron-withdrawing substituents at N-4 will favour abstraction of the adjacent proton rather than hydrolysis of either or both carbonyl groups. The overall effect of the latter is enhancement of the cyclization reaction and moderation of the undesired hydrolysis reaction. The validity of such a presumption could have been demonstrated by the relative yields of cyclic and hydrolysis products obtained in the alkaline reaction of 1-benzoyl-2-methyl (isopropyl)-4-α,α,α-trifluoro-o-tolyl semicarbazides. Attempts to isolate such products, however, were unsuccessful. The unexpected biurea formation during the benzoylation of 2-methyl-4-α,α,α-trifluoro-o-tolyl semicarbazide (Compound 1-6) is an indication that deprotonation of N-4(H) is, in fact, a facile one as expected; the benzoylation reaction being performed in pyridine.

Ring closure by this method was carried out in refluxing sodium hydroxide, normally 5.0% concentration. Increasing the alkaline concentration was found to increase the hydrolysis reaction and to have no effect on the intramolecular condensation reaction. The cyclic products were obtained from trace amounts to 30% yield, with the exception of compound 6-8 which was recovered in a high yield.



R = H,	R_1 = Ph (30%)	(Compound 6-1)
R = Me,	R_1 = Et (25.7%)	(Compound 6-3)
	i-Pr (25.8%)	(Compound 6-4)
	t-Bu (trace?)	(Compound 6-5)
	Ph (12.4)	(Compound 6-7)
R = i-Pr,	R_1 = Et (65-75%)	(Compound 6-8)
	i-Pr (17% crude)	(Compound 6-9)
	t-Bu (0%)	(Compound 6-10)
	Ph (trace?)	(Compound 6-11)

A complete summary of the results including the extent of the side reactions is given in Table VI. It is interesting to note the physical characteristics of this class of compounds in relation to an earlier discussion. The 1,4-dialkyl-3-phenyl cyclic derivatives are considerably lower melting than their open chain analogs. In fact, the one with the lowest molecular weight (Compound 6-3) is a viscous oil. This property may be attributed to a decrease in the polar nature of the molecule brought about by the absence of a free NH group. Furthermore, hydrogen bonding is absent in these heterocycles. In contrast, the presence of a free NH is associated with a substantial increase in melting point as

indicated by 3,4-diphenyl-5-hydroxy-1,2,4-triazole (Compound 6-1).

ii) Dehydrocyclization using zinc chloride (Method B)

Matei and Comanita[71] successfully obtained 3,4-diphenyl-5-hydroxy-1,2,4-triazole by heating a mixture of 1-benzoyl-4-phenyl semicarbazide in the presence of anhydrous zinc chloride at 200°, but report no yield for the reaction.

Dehydrocyclization proceeded to a certain extent when a homogeneous mixture of this reagent and 1-benzoyl-2-methyl-4-phenyl semicarbazide (Compound 3-5) was heated in an oil bath at 180-190°. However, when a similar procedure was attempted for the 2-isopropyl derivative (Compound 3-10), a solid melting at 211-217.5° (dec.) was isolated but not identified. Aside from the isopropyl group resonance, the n.m.r. integration curve of this product suggests the presence of two NH(OH) protons and five protons due to a single phenyl ring. Furthermore, cyclization to either a triazole or an oxadiazole is doubtful on the basis of the chemical shift of the isopropyl group. Alkyl R and R_1 substituents have been found during this study to resonate further downfield for such cyclic products. This aspect is described in the n.m.r. section. The highest molecular weight fragment in the mass spectrum of the solid is at m/e 178 (13.1%). According to the n.m.r. spectral data this ion may correspond to either N-benzoyl-N'-isopropyl-

hydrazine (PhCONHNH-i-Pr) or 1-phenyl-3-isopropylurea (PhNHCONH-i-Pr). The former compound has been described earlier as a by-product and is not in agreement, according to its melting point and n.m.r. spectrum, with the product under discussion. The latter is also disproved by its melting point (lit. 154-155°[91]). It stands to reason, however, that partial decomposition of the sample occurs prior to electron impact in the mass spectrometer with the formation of either or both these fragments.

Spectral data of the product are given below.

N.m.r. (DMSO-d_6, δ): 10.12 (1H, singlet), 7.42-7.66 and 7.78-8.07 (2H and 3H respectively, multiplet, phenyl ring protons), 5.16 (1H, singlet), 3.16 (1H, septet, J = 6 Hz, methine proton), 1.04 (6H, doublet, J = 6 Hz, methyl protons).

I.r. (KBr, cm^{-1}): 3154, 2969-3078, 2873, 1605-1632.

The most significant peaks in the mass spectrum are listed below.

m/e	Relative Intensity (%)*	Possible fragment
178.0	13.1	
163.0	69.1	
122.0	82.1	$PhCOOH^+$
106.0	54.9	$PhCOH^+$
105.0	100.0	$PhCO^+$
104.0	39.6	$PhHCN^+$
103.0	19.0	$PhCN^+$
79.0	26.8	

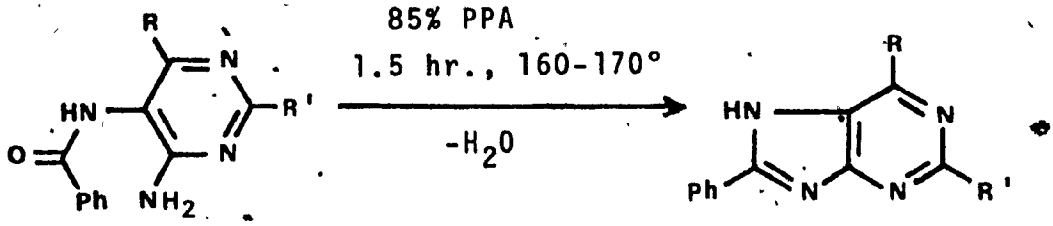
m/e	Relative Intensity (%)*	Possible fragment
78.0	29:9	
77.0	87.9	$C_6H_5^+$
76.0	25.1	
73.0	56.4	
58.0	81.0	NH-i-Pr$^+$
57.0	15.0	
56.0	17.6	
51.0	62.6	$C_4H_3^+$
44.0	27.3	
43.0	60.8	i-Pr$^+$
42.0	41.4	
41.0	45.8	
39.0	25.5	$C_3H_3^+$
31.0	48.7	
28.0	28.6	
27.0	32.7	

*Relative to the base peak

iii) Dehydrocyclization using polyphosphoric acid (Method C)

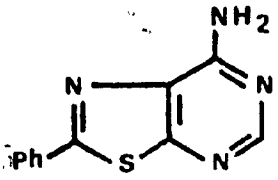
Polyphosphoric acid (PPA), previously used for the cyclization of a number of ring systems,[92] was found by Fu, Chinoporos and Terzian[93] to be an outstanding dehydrocyclization agent for the formation of purines from 4-amino-5-benzamidopyrimidines. The authors report the

synthesis of a number of 8-phenylpurines by this procedure in high yields and purity.



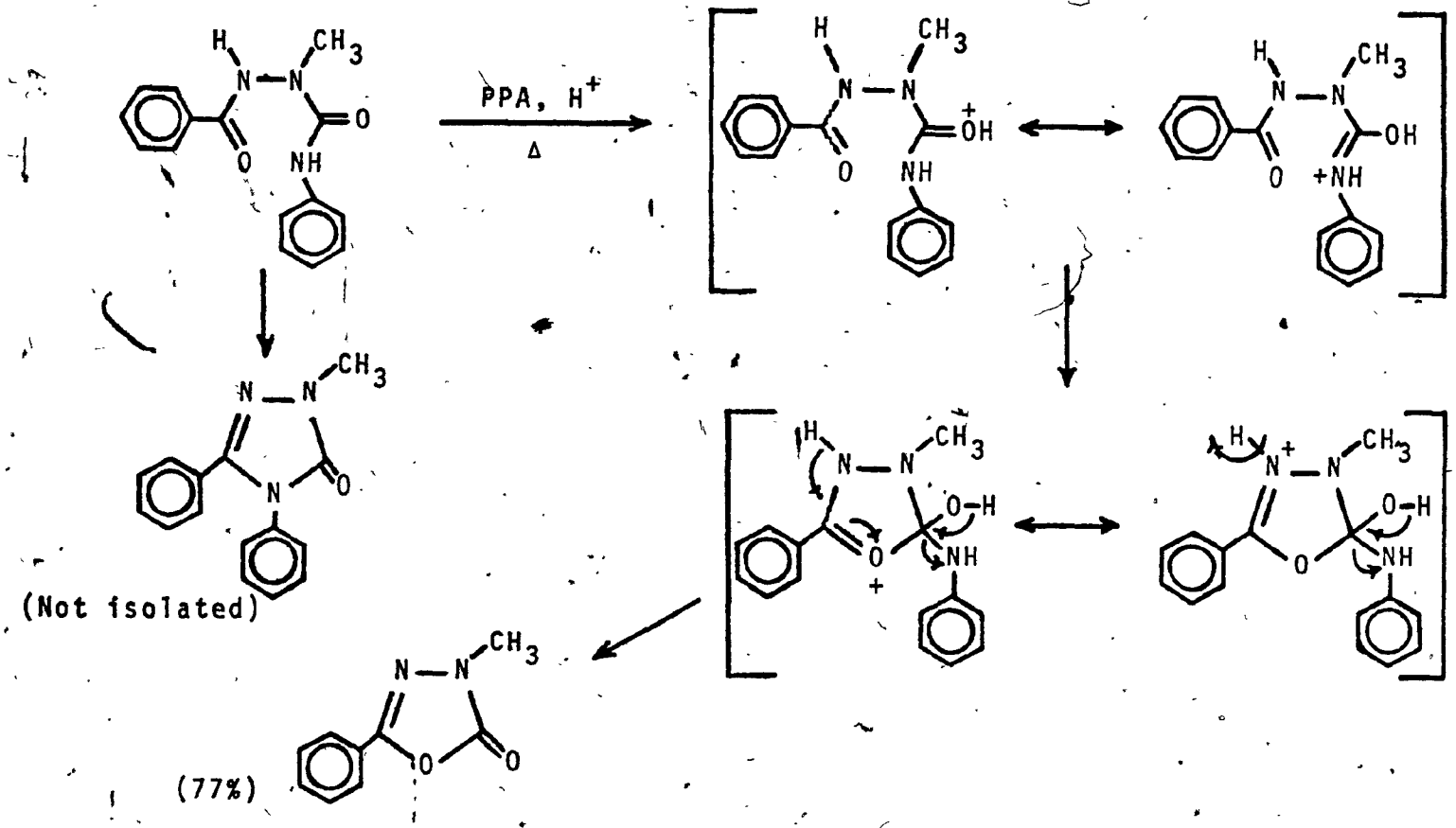
R	R'
$-CH_3$	-H
-H	-H
$-NH_2$	-H
-OH	$-CH_3$
-SH	-SH

Substitution on the C-2 and C-6 positions of the pyrimidine ring had little or no influence on the cyclization with the exception of the 6-mercapto derivative (R=SH, R'=H), where cyclization through the thio group occured to yield the isomeric 2-phenyl-7-amino-thiazolo-[5,4-d]pyrimidine shown below.



The effect of PPA is expected to be the same for these compounds as for the benzoylated semicarbazide derivatives prepared during this study. In both cases benzamido and anilino terminal groups are involved in the dehydrocyclization reaction. The major difference between the two is the presence of a functional group R_1 at N-4 of the semicarbazides. Cyclization to an oxadiazolinone rather than the expected triazolinone occured when 1-benzoyl-2-methyl-4-phenyl semicarbazide (Compound 3-5) was heated to 60-80° in PPA. The identity of the product was postulated from the n.m.r., i.r., and mass spectral data. The alternative O-cyclization reaction is somewhat similar to that of the thio derivative described.

The nuclear magnetic resonance spectrum of the solid consists of a multiplet rather than a singlet in the phenyl region which is contrary to the case where the ring oxygen is replaced by N-Ph (see n.m.r. spectrum of 1-methyl-3,4-diphenyl-Δ^2-1,2,4-triazolin-5-one, Compound 6-7).

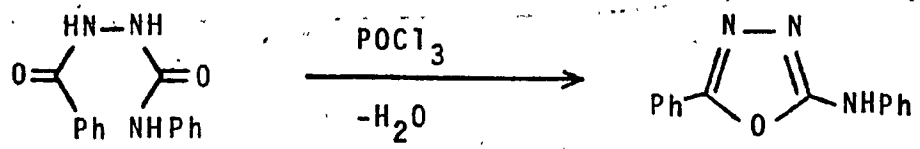


Scheme 16. Suggested Mechanism for the Direct Cyclization to 2-Phenyl-4-Methyl-Δ^2-1,3,4-Oxadiazolin-5-one Using PPA

N.m.r. (CCl_4, δ): 7.66-7.98 (2H, multiplet, ortho ring protons), 7.22-7.56 (3H, multiplet, meta and para ring protons), 3.42 (3H, singlet, methyl protons).
I.r. (KBr, cm^{-1}): 2936 (aliphatic νCH), 1752-1780 (lactone-type νCO), 1025 (νC-O-C).

The molecular ion occurs at m/e 176. A detailed analysis of the mass spectrum follows in a later section.

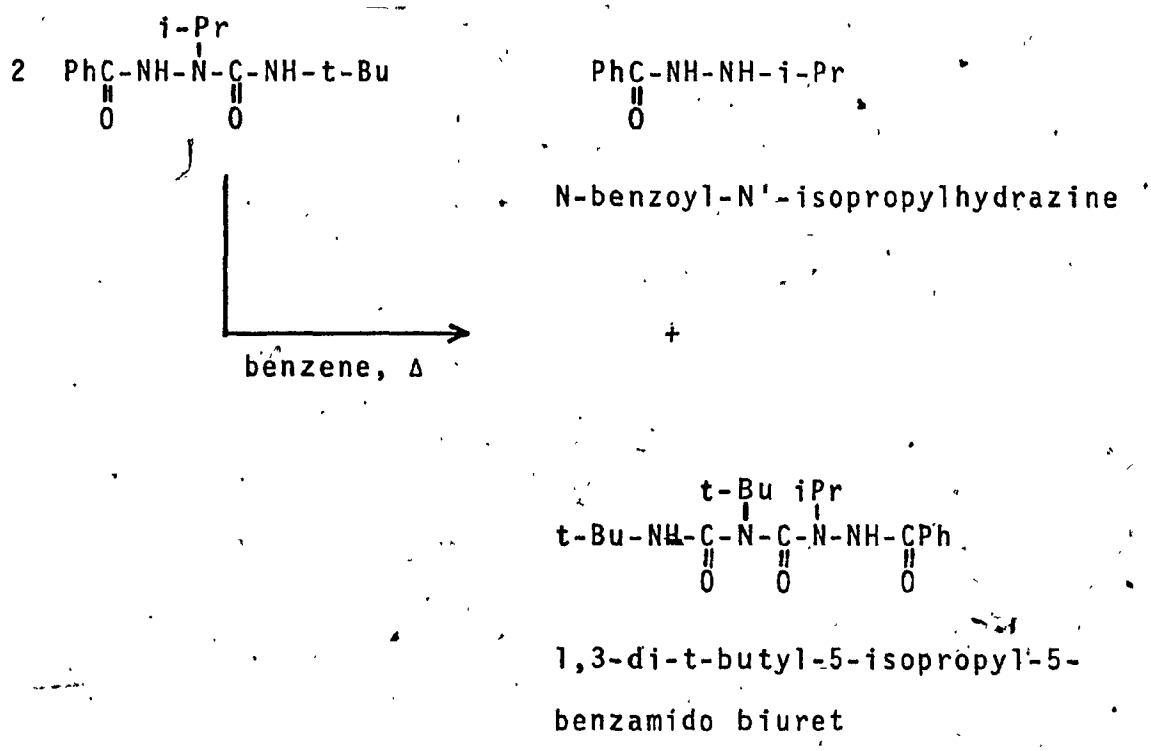
Oxadiazolinone formation is favoured over the formation of anilino oxadiazole since an anilino anion is a better leaving group than a hydroxyl anion. A reaction leading to the product of the latter type has been reported in the case of 1-benzoyl-4-phenyl semicarbazide and phosphorus oxychloride.[62]



iv) Dehydrocyclization using molecular sieves (Method D)

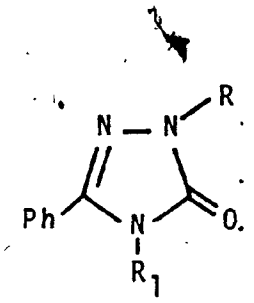
The desired reaction was not observed for Compounds 3-7 and 3-9 even after a prolonged reflux period in benzene. N-Benzoyl-N'-isopropylhydrazine was the only product

isolated in the latter case, possibly by a bimolecular thermal decomposition in the following manner.



An analogous effect was observed earlier during the vacuum distillation of 1-benzoyl-2-isopropyl-4-ethyl semicarbazide (see Scheme 9). Alternatively, the formation of N-benzoyl-N'-isopropylhydrazine may be due to a hydrolysis reaction brought about by the presence of traces of water. Results of the cyclization reaction of 1-benzoyl-2,4-disubstituted semicarbazides are summarized in Table VI.

Table VI. Results of the Semicarbazide Ring Closure



R	R_1	Method	Reaction Conditions	M.P. °C	Yield %	Side Products	Compd.
H	C_6H_5	A	3.8% NaOH, reflux for 8.5 hr.	256.5-258(dec.)	30	-	6-1
CH_3	CH_2CH_3	A	5.0% NaOH, reflux for 2 hr.	colorless viscous oil	25.7	Ethylamine Benzoic acid Starting material	6-3
CH_3	$CH(CH_3)_2$	A	6.0% NaOH, reflux for 13 hr.	44-46	25.8	isopropyl-amine Benzoic acid	6-4
CH_3	$C(CH_3)_3$	A	5.0% NaOH, reflux for 30 hr.	-	trace?	-	6-5[a]

Table VI Cont.

R	R_1	Method	Reaction Conditions	M.P. °C	Yield %	Side Products	Compd.
CH_3	C_6H_5	A	5.0% NaOH, reflux for 3 hr.	177.5-178	12.4	Benzoic acid Methyl-hydrazine Starting material	6-7
CH_3	C_6H_5	B	180-190° for 2 hr.	168-174	9	-	6-7
CH_3	C_6H_5	C	60-65° for 120 mjn., 75-80° for 2.5 hr.	-	-	oxadiazo-linone starting material	6-7
$CH(CH_3)_2$	CH_2CH_3	A	5.0% NaOH, reflux for 2.5 hr.	66.5-68.5	65-75	Ethylamine Benzoic acid	6-8

Table VI Cont.

R	R_1	Method	Reaction Conditions	M.P. °C	Yield %	Side Products	Compd.
$CH(CH_3)_2$	CH_2CH_3	D	Benzene, reflux for 13 hr.	-	-	Starting material	6-8
$CH(CH_3)_2$	$CH(CH_3)_2$	A	5.0% NaOH, reflux for 2.75 hr.	68-81	17 (crude)	1-benzoyl-2-isopropyl-hydrazine	6-9
$CH(CH_3)_2$	$C(CH_3)_3$	A	5.0% NaOH-95% EtOH (6:1), reflux for 30 hr.	-	-	t-Butylamine Benzoic acid 1-benzoyl-2-isopropyl-hydrazine	6-10
$CH(CH_3)_2$	$C(CH_3)_3$	D	Benzene, reflux for 67 hr.	-	-	1-benzoyl-2-isopropyl-hydrazine Starting material	6-10

Table VI Cont.

R	R_1	Method	Reaction Conditions	M.P. °C	Yield %	Side Products	Compd.
$CH(CH_3)_2$	C_6H_5	A	5.0% NaOH, 1)reflux for 20 min. 2)reflux for 2 hr.	-	Trace	Product m.p. 185-188 Benzoic acid Starting material	6-11
$CH(CH_3)_2$	C_6H_5	B	210° for 20 min. 160° for 21 hr.	-	-	Product m.p. 211-217.5 (dec)	6-11
C_6H_5	CH_2CH_3	A	5.0% NaOH, reflux for 105 min.	-	-	Benzoic acid 2-phenyl-4-ethyl semi-carbazide	6-12

Method A Alkaline ring closure
Method B Dehydrocyclization using zinc chloride
Method C Dehydrocyclization using polyphosphoric acid
Method D Dehydrocyclization using molecular sieves

[a] Benzoic acid (65%) was obtained when the reaction was carried out in 10.0% NaOH for 5 hr.

II. Oxidative Ring Closure of Aldehydic 2,4-Disubstituted Semicarbazones

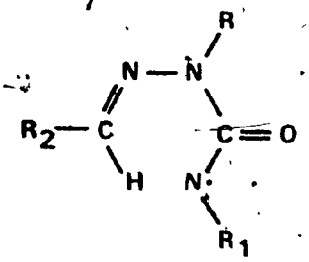
i) Using potassium ferricyanide (Method E)

Alkaline ferricyanide oxidation was attempted according to the method of Srinivasan and co-workers[41,42,43] who obtained 3-alkyl-4-aryl- and 3,4-diaryl-5-hydroxy-1,2,4-triazoles in high yields at ordinary temperatures and pressures, in contrast with the standard ferric chloride reaction which requires high pressures.

Potassium ferricyanide (potassium hexacyanoferrate III) falls into a class of oxidizing agents in which the oxidizing species is a complex electron-abstracting ion.[94] Consequently, ferricyanide has been used in systems which favour the extraction of an electron from an electron-rich site. The overall reaction being:

$$2[Fe(CN)_6]^{3-} + 2e \longrightarrow 2[Fe(CN)_6]^{4-}$$

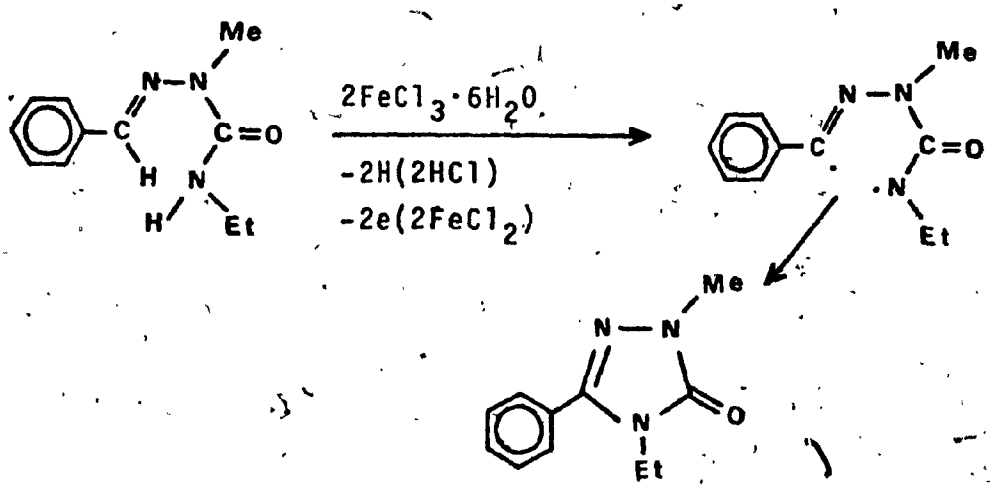
When used in conjunction with sodium hydroxide the oxidizing species is reduced to potassium mono-sodium ferrocyanide, $K_3NaFe(CN)_6$. The one-electron reaction results in the generation of the following semicarbazone radical.



The formation of this radical and its subsequent addition to yield the heterocycle is likely to be favoured by the presence of an aromatic substituent adjacent to it. Alkyl, unlike aryl groups, are not conducive to resonance stabilization of radicals and would not be expected to enhance the reaction. This has been verified to a certain extent by the absence of ring closure when R_1 was equivalent to either a hydrogen atom or an ethyl group. Only a trace of cyclic product was isolated during one of these attempts. In contrast, when the reaction was repeated for three different derivatives containing a phenyl substituent at N-4, cyclization proceeded in two of the three attempts. The 1-methyl-3,4-diphenyl-Δ^2-1,2,4-triazolin-5-one (Compound 6-7) was obtained quantitatively and the 1,3,4-triphenyl derivative (Compound 6-13) was obtained in a similar yield as previously reported for it using isoamyl nitrite as the oxidizing species.[40] The inertness of 4-alkyl semicarbazones to alkaline ferricyanide oxidation was also reported by Srinivasan and co-workers.[43]

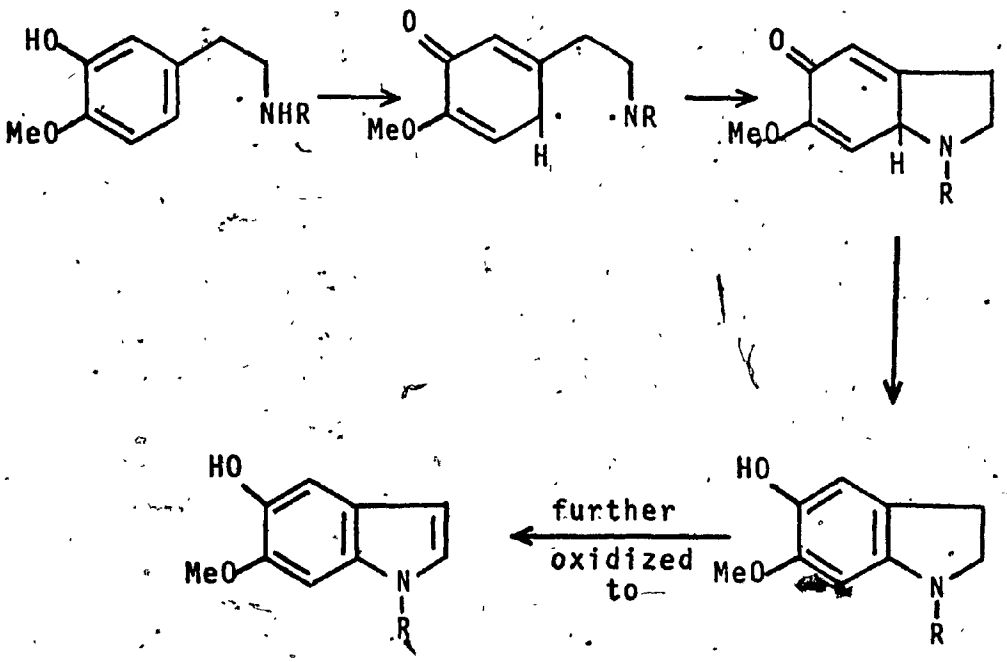
ii) Using ferric chloride hexahydrate (Method F)

The pressure reaction was carried out in an ethanolic medium.[37,38,39] Ring closure was not achieved in the case of benzaldehyde 2-methyl-4-phenyl semicarbazone (Compound 5-5) while oxidation of the benzaldehyde 2-methyl-4-ethyl derivative (Compound 5-3) yielded a brown oil consisting, according to its n.m.r. spectrum, of the desired triazole contaminated with starting material. The cyclic compound was present in a satisfactory yield, however its separation from the contaminant was difficult in view of the similar solubilities of the two. This represents the only successful cyclization of a semicarbazone derivative containing an alkyl group at N-4. A one-electron transfer resulting in an intramolecular oxidative coupling may be envisaged.



Scheme 17. Oxidative ring closure of benzaldehyde 2-methyl-4-ethyl semicarbazone using ferric chloride hexahydrate

Contrary to the rationalization in a previous page, the above scheme suggests a radical formation next to an alkyl group. Somewhat similar is the cyclization reported by Kametani and co-workers.[95] The authors describe the formation of two indole derivatives via oxidation of the appropriate amine analogs using ferric chloride hexahydrate at room temperature, over a period of 20 hours.



R=H(10.5%)

=Et (crude)

Scheme 18. The direct cyclization to indole derivatives by oxidation with ferric chloride hexahydrate

Although the structures under discussion are not identical to the ones studied by these authors, there is an obvious resemblance between the two cases.

iii) Using isoamyl nitrite (Method G)

1,3,4-Triphenyl-Δ^2-1,2,4-triazolin-5-one is the only trisubstituted derivative having been synthesized by direct cyclization of a semicarbazone.[40] The reaction was carried out in refluxing benzene containing isoamyl nitrite with a yield of 23% reported for it. An NO radical may initiate the process. Only the starting materials were recovered when oxidation using isoamyl nitrite was attempted for Compounds 5-3 and 5-5.

iv) Using lead tetraacetate (Method H)

A general description of this oxidative procedure is the transformation of lead tetraacetate (LTA) into lead acetate by the expulsion of two acetoxy groups.[96] The process may proceed in various ways.

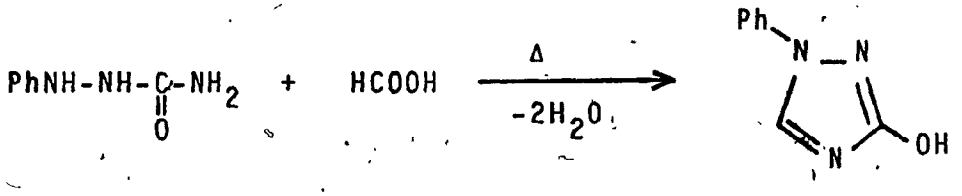
1. Two acetoxy radicals can be released.
2. An acetoxy anion and an acetoxy cation (in which case the latter is the oxidative species) can be released.
3. Two acetate anions can be removed by the addition of two electrons.

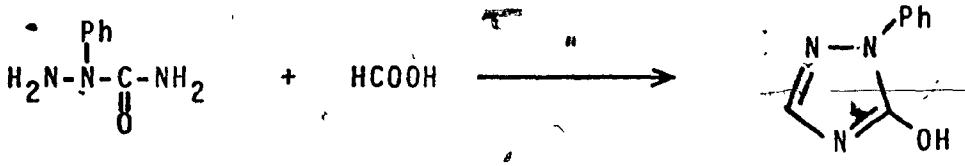
A brown oil consisting of various products was obtained when propionaldehyde 2-methyl-4-phenyl semicarbazone (Compound 5-4) was subjected to LTA oxidation. Attempts at

isolation of a pure component were unsuccessful. It was suspected prior to the undertaking that O-attack leading to an oxadiazole would take preference over N-attack, considering the type of reagent used.[45,48] As discussed earlier however (refer to pages 19 and 20), substituents at N-2 of the starting semicarbazone are known to hinder formation of the nitrilimine intermediate which is believed to result in O-cyclization. Results of the oxidation reactions are given in Table VII, pp. 145-147.

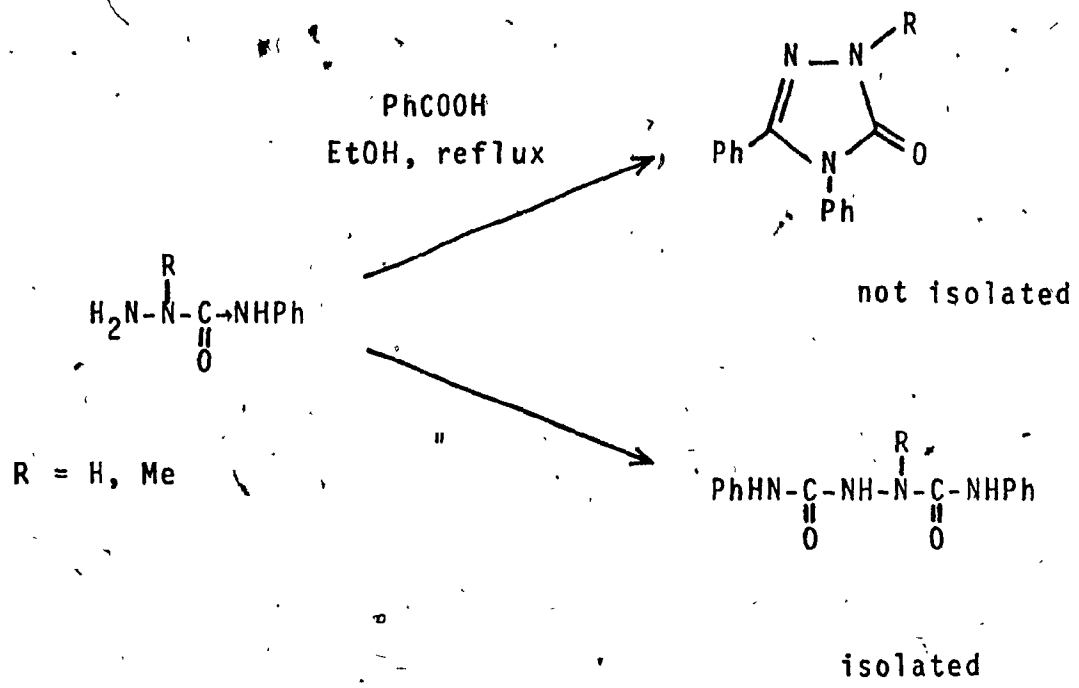
Attempted Intermolecular Condensations

Condensations of 1-phenyl and 2-phenyl semicarbazides with formic acid are known to yield 1-phenyl-3-hydroxy- and 1-phenyl-5-hydroxy-1,2,4-triazoles respectively.[31,97]



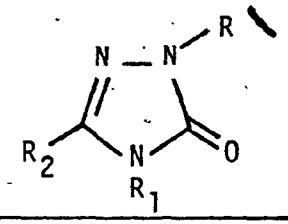


Extending this method to 4-substituted semicarbazides and benzoic acid resulted in bimolecular condensation with the formation of the corresponding biureas.



The 1,6-diphenyl biurea was identified by comparing its i.r. spectrum with that of an authentic sample while the 3-methyl derivative was assigned according to the spectral data of Compound 2-5. When 2-methyl-4-phenyl semicarbazide and benzoic acid were subjected to prolonged reflux in xylene, a solid melting at 155.5-158.5° was isolated. The nature of this product was not elucidated.

Table VII. Results of the Oxidative Ring Closure of Semicarbazones



R	R_1	R_2	Method	Reaction Conditicns	M.P. °C	Yield %	Side Products	Compd.
CH_3	H	C_6H_5	E	Reflux for 39 hr.	-	-	Starting material	6-2
CH_3	CH_2CH_3	C_6H_5	E	Reflux for 94 hr.	-	-	Starting material	6-3
CH_3	CH_2CH_3	C_6H_5	E	140° for 4 hr. under pressure	-	-	Starting material	6-3
CH_3	CH_2CH_3	C_6H_5	F	120-165° for 3.25 hr. under pressure	Brown oil	36 (crude)	Starting material	6-3
CH_3	CH_2CH_3	C_6H_5	G	Reflux for 113 hr.	-	-	Starting material	6-3

Table VII Cont.

R	R_1	R_2	Method	Reaction Conditions	M.P. °C	Yield %	Side Products	Compd.
CH_3	C_6H_5	CH_2CH_3	E	Prolonged reflux period	-	-	?	6-6
CH_3	C_6H_5	CH_2CH_3	H	Acetic acid, 20 min. at r.t.	-	-	Brown oil	6-6
CH_3	C_6H_5	CH_2CH_3	H	Methylene chloride, 20 min. at r.t.	-	-	Brown oil	6-6
CH_3	C_6H_5	C_6H_5	E	Reflux for 8.5 hr.	177.5-178	81.0	-	6-7
CH_3	C_6H_5	C_6H_5	F	135° for 90 min. under pressure	-	-	Starting material	6-7

Table VII Cont.

R	R_1	R_2	Method	Reaction Conditions	M.P. °C	Yield %	Side Products	Compd.
CH_3	C_6H_5	C_6H_5	G	Reflux for 7.5 hr.	-	-	Starting material	6-7
$CH(CH_3)_2$	CH_2CH_3	C_6H_5	E	Reflux for 28 hr.	-	Trace	Starting material	6-8
C_6H_5	C_6H_5	C_6H_5	E	Reflux for 60 min.	220-221	23	-	6-13

Method E Using potassium ferricyanide, $K_3Fe(CN)_6$
Method F Using ferric chloride hexahydrate, $FeCl_3 \cdot 6H_2O$
Method G Using isoamyl nitrite, $(CH_3)_2CHCH_2CH_2ONO$
Method H Using lead tetraacetate, $Pb(OCOCH_3)_4$

NUCLEAR MAGNETIC RESONANCE AND INFRARED STUDIES

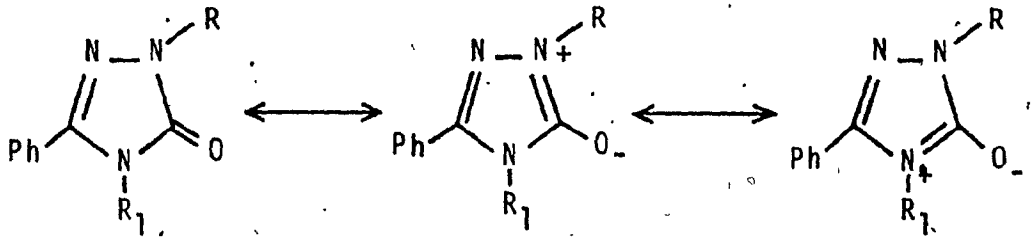
Nuclear Magnetic Resonance Spectra

The experimental conditions have been described previously. The distinguishing features in the n.m.r. spectra of the cyclic products as compared with the starting chains are i) the nature of the C-phenyl signal, ii) the chemical shifts of alkyl R and R_1 protons, and iii) absence of the signals due to the two NH protons (an NH and a benzylidene proton in the case of the semicarbazones).

The phenyl ring resonance of the benzoyl moiety, in the case of 1-benzoyl-2,4-dialkyl substituted semicarbazides, consists of a multiplet where the relative shift ($\delta m,p - \delta o$) between the resonance of the meta and para protons (integrates to area 3), and that of the ortho protons (integrates to area 2) is within a range of 0.15 to 0.20δ. The multiplet due to the meta and para protons is more shielded and appears further upfield, 7.38-8.08δ then the multiplet associated with the ortho protons, 7.82-8.50δ. Where R_1 corresponds to a phenyl group the two multiplets integrate as 8:2 and the chemical shift separation is reduced to $\sim$0.10δ. The presence of a phenyl substituent at N-2 (Compound 3-11) causes an overlap of the two multiplets. Ring closure results in coalescence to a more or less sharp singlet for the C-phenyl protons with resonance confined between 7.23δ and 7.48δ. The environment experienced by

the phenyl substituent prior to and following ring closure must be considered in the interpretation of such results. This may be rationalized in terms of coplanarity of the phenyl and triazole rings.[98]

The second characteristic n.m.r. feature is the downfield shift of the alkyl groups at N-2 and N-4 brought about by the cyclization reaction. For example, the chain N-2 methyls resonate at a range of 3.02-3.17δ, while cyclization results in a downfield shift of the corresponding signal to 3.34-3.53δ. Likewise, the doublet due to the methyl groups of the isopropyl substituent, when at N-2 of the chain, is shifted from 1.05-1.16δ to 1.37-1.38δ, and when at N-4 of the chain, is shifted from 1.06-1.07δ to 1.44-1.47δ. This observed difference may possibly be interpreted by deshielding caused by a weak resonance effect in the cyclic structure.



Although the n.m.r. spectra of the starting chains were performed in DMSO-d_6 while CCl_4 was the solvent used

for the cyclic products, the validity of the above results is not in doubt. This was concluded by examining the effect of the two solvents on the chemical shifts of Compound 6-7 (see Table XIII).

The NH resonances of the non-benzoylated and benzoylated semicarbazides, and of the biureas are discussed separately.

i) Non-benzoylated Semicarbazides Two N-1(H) and N-4(H).

The two N-1(H) protons give rise to a singlet at 3.40-4.97δ except when R=Ph where they are split into two singlets at 7.46δ and 7.64δ.

The N-4(H) resonance appears at 6.08-6.52δ with a downfield shift to 8.70-9.08δ when R_1 = Ph and 9.55δ when R_1=o-$CF_3C_6H_4$.

ii) Benzoylated Semicarbazides N-1(H) and N-4(H)

N-1(H)	doublet	10.38δ	when R=H
	singlet	10.00-10.96δ	when R=alkyl
	singlet	8.90δ	when R=Ph
N-4(H)		5.33-7.08δ	when R_1=alkyl with a progressive upfield shift with increasing size of the alkyl group
		8.54-8.91δ	when R_1=Ph

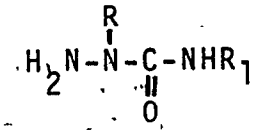
iii) Biureas N-1(H), N-4(H) and N-6(H)

The chemical shifts of the N-1(H) and N-6(H) protons are observed within the same region upfield from the N-4(H) signal, except when R_1=Ph where the opposite is true. A distinction between the two (N-1(H) and N-6(H)) may be established by deuterium labelling.

N-1(H) and N-6(H)	5.41-6.58δ	when R_1=alkyl
	8.54-8.96δ	when R_1=Ph
	8.30-8.54δ	when R_1=o-$CF_3C_6H_4$
N-4(H)	7.54-7.63δ	when R_1=alkyl
	8.04δ, 8.26δ	when R_1=Ph
	9.03δ, 9.08δ	when R_1=o-$CF_3C_6H_4$

The nuclear magnetic resonance data is summarized in Tables VIII through XIII with coupling constants reported where possible. The chemical shifts of the isomeric hydrazones were sufficiently different permitting estimation of their relative concentrations from the n.m.r. integration curves. These assignments are made in Table XI.

Table VIII. N.m.r. Spectral Parameters of the Non-benzoylated Semicarbazide Derivatives



R	R_1	Solvent	N-1(H) Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
H	Ph	DMSO-d_6	4.42, 2H(s)	Overlapped with N-4(R_1)	8.70, 1H(s)	6.76-7.74, 6H(m)	1-1
Me	Et	CCl_4 ≠	4.10, 2H(s)	2.95,3H(s)	6.39, 1H (t, J = 6.5 Hz)	methyl - 1.01, 3H (t, J = 7.0 Hz) methylene - 3.07, 2H (quintet, J= 7.0 Hz),	1-2

Table VIII Cont.

R	R_1	Solvent	N-1(H) Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
Me (Hydrochloride salt)	Et	D_2O	H-D exchange 4.63	3.17, 3H(s)	Overlapped with N-1(H)'s	methyl - 1.08, 3H (t, J = 7.0 Hz) methylene - 3.18, 2H (q, J= 7.5 Hz)	153
Me	1-Pr	CCl_4	4.43, 2H(s)	3.01, 3H(s)	6.34, 1H (d, J = 7.5 Hz)	methyls - 1.08, 6H (d, J = 6.5 Hz) methine - 3.79, 1H (septet, J= 7.0 Hz)	1-3

Table VIII Cont.

R	R_1	Solvent	N-1(H) Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
Me	t-Bu	CCl_4	3.92, 2H(s)	2.99, 3H(s)	6.34, 1H(s)	1.27, 9H(s)	1-4
Me	Ph	DMSO-d_6	4.72, 2H(s)	3.02, 3H(s)	9.08, 1H(s)	6.76-7.63, 5H(m)	1-5
Me	o-$CF_3C_6H_4$	DMSO-d_6	4.97, 2H(s)	3.06, 3H(s)	9.55, 1H(s)	7.00-7.80, 3H(m) 8.30 and 8.43, 1H (two singlets)	1-6
i-Pr	Et	CCl_4	3.83(s)	<u>methyls</u> - overlapped with N-4(R_1) <u>methine</u> - 4.56,(septet, J = 7.0 Hz)	6.52, (t, J = 6.0 Hz)	<u>methyls</u> - 0.78-1.30(m) <u>methylene</u> - 3.15, (quintet, J = 7.0 Hz)	1-7[a]

Table VIII Cont.

R	R_1	Solvent	N-1(H) Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
i-Pr	i-Pr	CCl_4	3.40, 2H(s)	methyls - 1.10, 6H (d, J = 7.0 Hz) methine - 4.63, 1H (septet, J = 7.0 Hz)	6.08, 1H (broad peak) also 5.61 (isomer?)	methyls - 1.06, 6H (d, J = 7.0 Hz) methine - 3.86, 1H (septet, J = 7.0 Hz)	1-8
i-Pr (nitrate salt)	t-Bu	D_2O	H-D exchange 4.60	methyls - 1.18, 6H (d, J = 7.0 Hz) methine - 4.18, 1H (septet, J = 6.5 Hz)	Overlapped with N-1(H)'s	1.26, 9H(s)	1-9

Table VIII Cont.

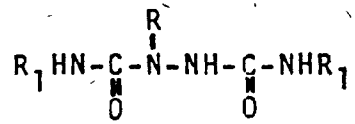
R	R_1	Solvent	N-1(H) Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
i-Pr	Ph	DMSO-d_6	4.37, 2H(s)	methyls - 1.08, 6H (d, J = 7.0 Hz) methine - 4.58, 1H (septet, J = 7.0 Hz)	9.03, 1H(s)	6.75-7.70, 5H(m)	1-10
Ph	Et	DMSO-d_6	7.46, 1H(s) 7.64, 1H(s)	6.56-6.86, 3H(m) 7.01-7.40, 2H(m)	6.38, 1H (t, J = 6.0 Hz)	methyl - 0.98, 3H (t, J = 7.0 Hz) methylene - 3.03, 2H (quintet, J = 6.5 Hz)	1-12

Table VIII Cont.

[f] TMS was used as external reference.

[a] Integration was complicated due to the following bands (isomer?): Triplet at 5.68δ, J = 6.0 Hz and two singlets at 1.89δ and 2.08δ.

Table IX. N.m.r. Spectral Parameters of the Biurea Derivatives



R	R_1	Solvent	N-1(H) and N-6(H) Protons	N-1(R_1) and N-6(R_1) Protons	N-3(R) Protons	N-4(H) Proton	Compd.
Me	t-Bu	DMSO-d_6	5.58, 1H(s)	1.22, 9H(s)	2.84, 3H(s)	7.60, 1H(s)	2-4
			5.85, 1H(s)	1.24, 9H(s)			
Me	Ph	DMSO-d_6	8.82, 1H(s)	6.82-7.78,	3.08, 3H(s)	8.26, 1H(s)	2-5
			8.96, 1H(s)	10H(m)			
Me	o-$CF_3C_6H_4$	DMSO-d_6	8.40, 1H(s)	7.44-8.29,	3.14, 3H(s)	9.03, 1H(s)	2-6
			8.54, 1H(s)	8H(m)			

Table IX Cont.

R	R_1	Solvent	N-1(H) and N-6(H) Protons	N-1(R_1) and N-6(R_1) Protons	N-3(R) Protons	N-4(H) Proton	Compd.
i-Pr	Et	DMSO-d_6	6.19-6.58, 2H (broad multiplet)	methyls - 0.77-1.18, 12H(m) methylenes - 3.07, 4H (quintet, J = 6.75 Hz)	methyls-overlapped with R_1's methine - 4.42, 1H (septet, J = 7.0 Hz)	7.63, 1H(s)	2-7
i-Pr	i-pr	DMSO-d_6	5.75, 1H (d, J = 8.0 Hz) 6.05, 1H (d, J = 8.0 Hz)	methyls-0.82-1.19, 18H(m) methines-3.77, 2H (septet, J = 7.0 Hz)	methyls-overlapped with R_1's methine-4.41, 1H (septet, J = 6.5 Hz)	7.54, 1H(s)	2-8

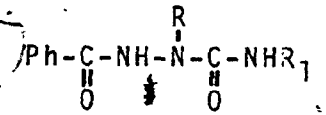
Table IX Cont.

R	R_1	Solvent	N-1(H) and N-6(H) Protons	N-1(R_1) and N-6(R_1) Protons	N-3(R) Protons	N-4(H) Proton	Compd.
i-Pr	t-Bu	DMSO-d_6	5.41, 1H(s) 5.67, 1H(s)	1.23, 18H(s)	methyls-0.97, 6H (d, J = 6.5 Hz) methine-4.40, 1H (septet, J = 6.5 Hz)	7.55, 1H(s)	2-9
i-Pr	Ph	DMSO-d_6 + CCl_4	8.54, 1H(s) 8.67, 1H(s)	6.76-7.72, 10H(m)	methyls-1.14, 6H (d, J = 7.0 Hz). methine-4.63, 1H (septet, J = 7.0 Hz)	8.04, 1H(s)	2-10

Table IX Cont.

R	R_1	Solvent	N-1(H) and N-6(H) Protons	N-1(R_1) and N-6(R_1) Protons	N-3(R) Protons	N-4(H) Proton	Compd.
i-Pr	o-$CF_3C_6H_4$	DMSO-d_6	8.30, 1H(s) 8.36, 1H(s)	7.15-8.26, 8H(m)	<u>methyls</u>-1.16, 6H (d, J = 6.5 Hz) <u>methine</u>-4.64, 1H (septet, J = 6.5 Hz)	9.08, 1H(s)	2-11

Table X. N.m.r. Spectral Parameters of the Benzoylated Semicarbazide Derivatives



R	R_1	Solvent	C-Ph Protons	N-1(H) Proton	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
H	Ph	DMSO-d_6	Overlapped with N-4(R_1)	10.38, 1H (d, J = 2.0 Hz)	8.25, 1H (d, J = 2.0 Hz)	8.91, 1H (s)	6.81-7.71, 8H(m). 7.80-8.16, 2H(m)	3-1
Me	Et	DMSO-d_6	7.76-8.08, 3H(m) 8.28-8.50, 2H(m)	10.96, 1H(s)	3.17, 3H (s)	7.08, 1H (t, J = 6.0 Hz)	methyl-1.04, 3H (t, J = 7.5 Hz) methylene- 3.18, 2H (q, J = 7.0 Hz)	3-2

Table X Cont.

R	R_1	Solvent	C-Ph Protons	N-1(H) Proton	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
Me	i-Pr	DMSO-d_6	7.43-7.70, 3H (m) 7.85-8.16, 2H (m)	10.39, 1H(s)	3.03, 3H (s)	6.30, 1H (d, J = 7.5 Hz)	methyls- 1.07, 6H (d, J = 7.0 Hz) methine- 3.89, 1H (septet, J = 7.0 Hz)	3-3
Me	t-Bu	DMSO-d_6	7.53-7.71, 3H (m) 7.86-8.05, 2H (m)	10.38, 1H(s)	3.02, 3H (s)	5.71, 1H (s)	1.27, 9H(s)	3-4

Table X Cont.

R	R_1	Solvent	C-Ph Protons	N-1(H) Proton	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
Me	Ph	DMSO-d_6	Overlapped with N-4(R_1)	10.60, 1H(s)	3.14, 3H (s)	8.77, 1H (s)	6.83-7.74, 8H(m) 7.84-8.16, 2H(m)	3-5
Me	o-$CF_3C_6H_4$	CCl_4 + acetone- d_6	Overlapped with N-4(R_1)	10.14, 1H(s)	3.10, 3H (s)	Over-lapped with N-4 (R_1)	6.76-7.60 and 7.70-8.30, 10H(m)	3-6
i-Pr	Et	DMSO-d_6	7.38-7.70, 3H(m) 7.90-8.16, 2H(m)	10.03, 1H(s)	methyls-overlapped with N-4(R_1) methine-4.54,1H (septet, J= 6.5Hz)	6.48, 1H (t, J = 6.0 Hz)	methyls-0.80-1.20, 9H(m) methylene-3.03, 2H (quintet, J = 6.5 Hz)	3-7

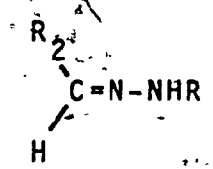
Table X Cont.

R	R_1	Solvent	C-Ph Protons	N-4(H) Proton	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
i-Pr	i-Pr	DMSO-d_6	7.42-7.70, 3H(m) 10.00 7.88-8.14, 2H(m) 1H(s)		methyls-overlapped with N-4(R_1) methine-4.56, 1H (septet, J = 7.0 Hz)	6.00, 1H (d, J = 7.0 Hz)	methyls-1.06, 12H (d, J = 6.5 Hz) methine-3.88, 1H (septet, J = 7.0 Hz)	3-8
i-Pr	t-Bu	DMSO-d_6	7.45-7.65, 3H(m) 10.00, 7.82-8.02, 2H(m) 1H(s)		methyls-1.05, 6H (d, J = 7.0 Hz) methine-4.50, 1H (septet, J = 6.5Hz)	5.33, 1H (s)	1.24, 9H(s)	3-9

Table X Cont.

R	R_1	Solvent	C-Ph Protons	N-4(H) Proton	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
i-Pr	Ph	DMSO-d_6	Overlapped with N-4(R_1)	10.22, 1H(s)	methyls-1.16, 6H (d, J = 6.5 Hz) methine-4.62, 1H (septet, J = 7.0 Hz)	8.54, 1H (s)	6.80-7.75, 8H(m) 7.89-8.20, 2H(m)	3-10
Ph	Et	DMSO-d_6	Overlapped with N-2(R)	8.90, 1H(s)	7.00-7.71, 10H(m)	6.48, 1H (t, J = 6.5 Hz)	methyl-0.90, 3H (t, J = 7.0 Hz) methylene-2.92, 2H (quintet, J = 6.5 Hz)	3-11

Table XI. N.m.r. Spectral Parameters of the Hydrazone Derivatives[a]



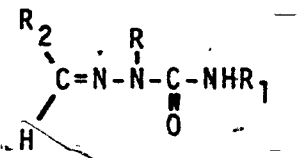
R	R_2	Solvent	C-H Proton	R_2 Protons	N-H Proton	R Protons	Compd.
Me	Et	neat	1H syn-6.53, (t, J = 5.0 Hz) anti-5.95, (t, J = 5.0 Hz)	methyl-0.70, 3H (t, J = 7.5 Hz) methylene-1.50-2.20, 2H (two quintets)	5.28, 1H (broad singlet)	3H syn-2.38(s) anti-2.53(s)	4-2
Me	Ph	CCl_4	Overlapped with R_2	6.87-7.42, 6H(m)	5.38, 1H (s)	2.54, 3H(s)	4-3
Ph	Me	CCl_4	Overlapped with R	Total-6H syn-1.87, (d, J = 5.0 Hz) anti-1.70, (d, J = 5.0 Hz)	Overlapped with R	Total-14H syn and anti-6.33-7.37(m)	4-4

Table XI Cont.

R_1	R_2	Solvent	C-H Proton	R_2 Protons	N-H Proton	R Protons	Compd.
Ph	Ph	CCl_4	Overlapped with R	Overlapped with R	Overlapped with R	6.57-7.68(m)	4-5[a]

[a] CCl_4 solution rapidly autoxidizes with the formation of a purple color.

Table XII. N.m.r. Spectral Parameters of the Semicarbazone Derivatives



R	R_1	R_2	Solvent	C-H Proton	R_2 Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
H	H	Ph	DMSO-d_6	8.06, 1H (s)	7.28-8.00, 5H(m)	10.64, 1H(s)	Overlapped with N-4(R_1)	6.62, 2H(s)	5-1
Me	H	Ph	DMSO-d_6	Overlapped with R_2	7.10-7.38, 3H(m) 7.48-7.85, 3H(m)	3.09, 3H(s)	"	6.62, 2H (broad singlet)	5-2
Me	Et	Ph	CCl_4	"	7.13-7.69, 6H(m)	3.21, 3H(s)	6.58, 1H (t, J = 6.5 Hz)	methyl-1.13, 3H (t, J = 7.5 Hz) methylene-2H, overlapped with N-2(R)	5-3

Table XII Cont.

R	R_1	R_2	Solvent	C-H Proton	R_2 Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
Me	Ph	Et	CCl_4	Overlapped with N-4(R_1)	methyl-1.11, 3H (t, J = 7.0 Hz) methylene-2.31, 2H (quintet, J = 6.5 Hz)	3.11, 3H(s)	8.60, 1H(s)	6.70-7.60, 6H(m)	5-4[a]
Me	Ph	Ph	CCl_4	"	Overlapped with N-4(R_1)	3.48, 3H(s)	9.14, 1H(s)	7.18-8.24, 11H(m)	5-5[a]
Me	Ph	Ph	$CDCl_3$	"	"	2.94, 3H(s)	8.66, 1H(s)	6.66-7.74, 11H(m)	5-5[a]

Table XII Cont.

R	R_1	R_2	Solvent	C-H Proton	R_2 Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
i-Pr	Et	Ph	CCl_4	7.73, 1H(s)	7.18-7.68, 5H(m)	methyls-1.43, 6H (d, J = 7.0 Hz) methine-4.87, 1H (septet, J = 6.5 Hz)	6.45, 1H (broad singlet)	methyl-1.20, 3H (t, J = 7.0 Hz) methylene-3.30, 2H (quintet, J = 7.0 Hz)	5-6
i-Pr	i-Pr	Ph	CCl_4	7.73, 1H(s)	7.20-7.67, 5H(m)	methyls-overlapped with N-4(R_1) methine-4.86, 1H (septet, J = 6.5 Hz)	6.32, 1H (d, J = 7.5 Hz)	methyls-1.0-1.6, 12H(m) methine-3.99, 1H (septet, J = 6.5 Hz)	5-7[b]

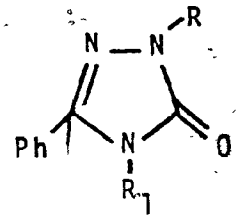
Table XII Cont.

R	R_1	R_2	Solvent	C-H Proton	R_2 Protons	N-2(R) Protons	N-4(H) Proton	N-4(R_1) Protons	Compd.
Ph	Rb	Rh	CCl_4	Overlapped with N-4(R_1)	Overlapped with N-4(R_1)	Overlapped with N-4(R_1)	9.24, 1H (s)	7.14-8.20, 16H(m)	5-10

[a] Distinction between the C-H and N-4(H) protons was based on the assignments of Compound 3-5.

[b] Distinction between the two methine protons was made according to that of Compound 5-6.

Table XIII. N.m.r. Spectral Parameters of the Heterocyclic Derivatives



R	R_1	Solvent	Method	N-1(R) Protons	N-4(R_1) Protons	C-Ph Protons	Compd.
H	Ph	DMSO-d_6	A	12.16, 1H(s)	Overlapped with C-Ph	7.32(7.14-7.60), 10H (near-singlet)	6-1
Me	Et	CCl_4	A	3.40, 3H(s)	methyl-1.19, 3H (t, J = 7.0 Hz) methylene-3.75, 2H (q, J = 7.0 Hz)	7.48(7.30-7.68), 5H (near-singlet)	6-3
Me	Et	CCl_4	F	3.38, (s)	methyl-1.19, (t, J = 7.0 Hz) methylene-3.70, (q, J = 7.0 Hz)	7.42(7.20-7.62), (near-singlet)	6-3

Table XIII Cont.

R	R_1	Solvent	Method	N-1(R) Protons	N-4(R_1) Protons	C-Ph Protons	Compd.
Me	i-Pr	CCl_4	A	3.34, 3H(s)	methyls-1,44, 6H (d, J = 7.0 Hz) methine-4.15, 1H (septet, J = 7.0Hz)	7.42, 5H(s)	6-4
Me	Ph	CCl_4	A	3.53, 3H(s)	Overlapped with C-Ph	7.27(7.19-7.40), 10H (near-singlet)	6-7
Me	Ph	CCl_4	B	3.51, 3H(s)	Overlapped with C-Ph	7.23(7.14-7.38), 10H (near-singlet)	6-7
Me	Ph	CCl_4	E	3.53, 3H(s)	Overlapped with C-Ph	7.26(7.15-7.39), 10H (near-singlet)	6-7
Me	Ph	DMSO-d_6	E	3.50, 3H(s)	Overlapped with C-Ph	7.36(7.20-7.54), 10H (near-singlet)	6-7

Table XIII Cont.

R	R_1	Solvent	Method	N-1(R) Protons	N-4(R_1) Protons	C-Ph Protons	Compd.
i-Pr	Et	CCl_4	A	methyls-1.38, 6H (d, J = 6.5 Hz) methine, 4.47, 1H (septet, J = 6.75 Hz)	methyl-1.25, 3H (t, J = 7.0 Hz) methylene-3.78, 2H (q, J = 7.0 Hz)	7.48(7.29-7.72), 5H (near-singlet)	6-8
i-Pr	i-Pr	CCl_4	A	methyls-1.37, (d, J = 7.0 Hz) methine-4.43, (septet, J = 7.0Hz)	methyls-1.47 (d, J = 7.0 Hz) methine-4.13 (septet, J = 7.0 Hz)	7.40(s)	6-9[a]
Ph	Ph	CCl_4	E	Overlapped with C-Ph	Overlapped with C-Ph	7.38(7.21-7.49), 10H (near-singlet)	6-13

[a] Assignment of the two isopropyl groups was based on the n.m.r. data of Compounds 6-4 and 6-8.

Infrared Spectra

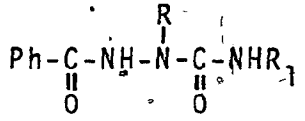
The infrared spectra were recorded on a Perkin-Elmer 457 spectrometer using potassium bromide discs and corrected according to a polystyrene standard 0.05 mm. in thickness. The data of the benzoylated semicarbazide derivatives and triazolinones are discussed while fundamental assignments of the various other intermediates and by-products synthesized are included in the experimental section of the thesis.

The following ring deformation bands have been calculated for unsubstituted 1,2,4-triazole using a modified Urey-Bradley force field method,[99] 962 cm^{-1} (calcd.); 965 cm^{-1} (obs.) and 936 cm^{-1} (calcd.); 930 cm^{-1} (obs.). The pair of bands in the spectra of the triazolinones, observed at 964-978 cm^{-1} (absent in Compounds 6-4 and 6-9) and 921-936 cm^{-1} may be related in origin to ring deformation although more conclusive evidence is required.

Three factors characterizing the semicarbazide ring closure are as follows: i) Elimination of the NH stretching vibration of the substituted chain at 3211-3470 cm^{-1}, ii) Absence of the associated amide I vibration (νCO) in the cyclic products as opposed to the starting chain. This occurs between $\sim$1600 to $\sim$1650 cm^{-1} and is brought about by the complete substitution in the heterocycle (intermolecular association is also non-existent for 2,4-diphenyl-5-hydroxy triazole, Compound 6-1, as indicated by the absence of this

band in the spectrum). Moreover, the frequency associated with the free amide is displaced from approximately 1650-1705 cm^{-1} prior to cyclization, to 1690-1710 cm^{-1}, iii) The amide II absorption in the region between 1505 to 1565 cm^{-1} of the semicarbazides is reduced from a strong broad band to a weak to moderate intensity band at 1542-1557 cm^{-1}. This absorption is ascribed to a C-N-H vibration comprising of an NH deformation and a C-N stretch.[22] The i.r. data is tabulated in the following pages.

Table XIV. Significant i.r. Frequencies in the Spectra of the Benzoylated Semicarbazide Derivatives



R	R_1	νNH cm^{-1}	Aliphatic νCH cm^{-1}	Amide I[a] (νCO) cm^{-1}	Amide II cm^{-1}	Amide III (νCN) cm^{-1}	Compd.
H	Ph	3286	-	1680	1584(w)	1314(m)	3-1
				1645	1535-1565	1303(m)	
				1605			
Me	Et	3414	2986(m)	1683	1587(w)	1309(m)	3-2
		3259		1620	1520-1553	1292	
Me	i-Pr	3378	2986(m)	1700(m)	1587(w)	1302-1319(m)	3-3
		3246	2946(w)	1685	1525-1544		
				1645			
Me	t-Bu	3451(m)	2979	1690	1585(w)	1292-1312	3-4
		3386	2939(w)	1665	1520-1550		
		3266		1643			
		3211					

Table XIV Cont.

R	R_1	νNH cm^{-1}	Aliphatic νCH cm^{-1}	Amide I[a] (νC0) cm^{-1}	Amide II cm^{-1}	Amide III (νCN) cm^{-1}	Compd.
Me	Ph	3336	2986(w)	1675	1587	1307(m)	3-5
				1605	1530-1546	1280-1292	
Me	o-$CF_3C_6H_4$	3470	-	1705	1593	1303	
		3286		1667	1585	1287	3-6
				1615(w)	1515-1535		
i-Pr	Et	3436	2988	1692	1588(w)	1282-1312	3-7
		3256	2946(m)	1645	1505-1538		
				1609(w)			
i-Pr	j-Pr	3446(m)	2983	1689	1582(w)	1292-1303	3-8
		3246	2933	1625	1505-1535		
i-Pr	t-Bu	3453(m)	2976	1690	1582(w)	1312(m)	3-9
		3266	2936(w)	1630	1515-1525	1281	

Table XIV Cont.

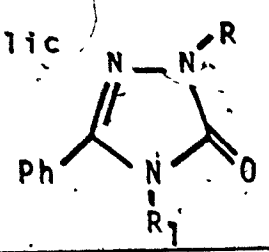
R	R_1	νNH cm^{-1}	Aliphatic νCH cm^{-1}	Amide I[a] (νCO) cm^{-1}	Amide II cm^{-1}	Amide III (νCN) cm^{-1}	Compd.
i-Pr	Ph	3301	2993	1695	1585	1307(m)	3-10
			2946(w)	1668	1505-1537	1292	
				1635			
				1605			
Ph	Et	3386(m)	2983(w)	1665	1590(w)	1305(m)	3-11
		3246		1640	1538		

(w) Of weak intensity

(m) Of moderate intensity

a Bands above ν1650 cm^{-1} are due to free amide I and those below ν1650 cm^{-1} to associated amide I.

Table XV. Significant i.r. Frequencies in the Spectra of the Heterocyclic Derivatives



R	R_1	νNH cm^{-1}	Aliphatic νCH cm^{-1}	Amide I[a] (νCO) cm^{-1}	Amide II cm^{-1}	Amide III (νCN) cm^{-1}	Compd.
H	Ph	3146(m)	-	1689	1593(w) 1547(m)	1313(m)	6-1
Me	Et	-	2986 2953	1685- 1725	1589(w) 1550(m)	1317 1281	6-3
Me	i-Pr	-	2996(m) 2976(w)	1695- 1715	1550(w)	1322(w) 1282(m)	6-4
Me	Ph	-	-	1710	1561(w) 1545(w)	1315(m)	6-7[b]

Table XV Cont.

R	R_1	νNH cm^{-1}	Aliphatic νCH cm^{-1}	Amide I[a] (νCO) cm^{-1}	Amide II cm^{-1}	Amide III (νCN) cm^{-1}	Compd.
i-Pr	Et	-	2991	1675-	1543(m)	1322	6-8
			2946(m)	1705		1289(w)	
i-Pr	i-Pr	-	2986	1705	1583(w)	1320(m)	6-9
			2941(m)	1685	1542(m)	1285(m)	
Ph	Ph	-	-	1705	1596(m)	1316(m)	6-13[b]
					1557(w)	1291(w)	

[a] Free amide I.

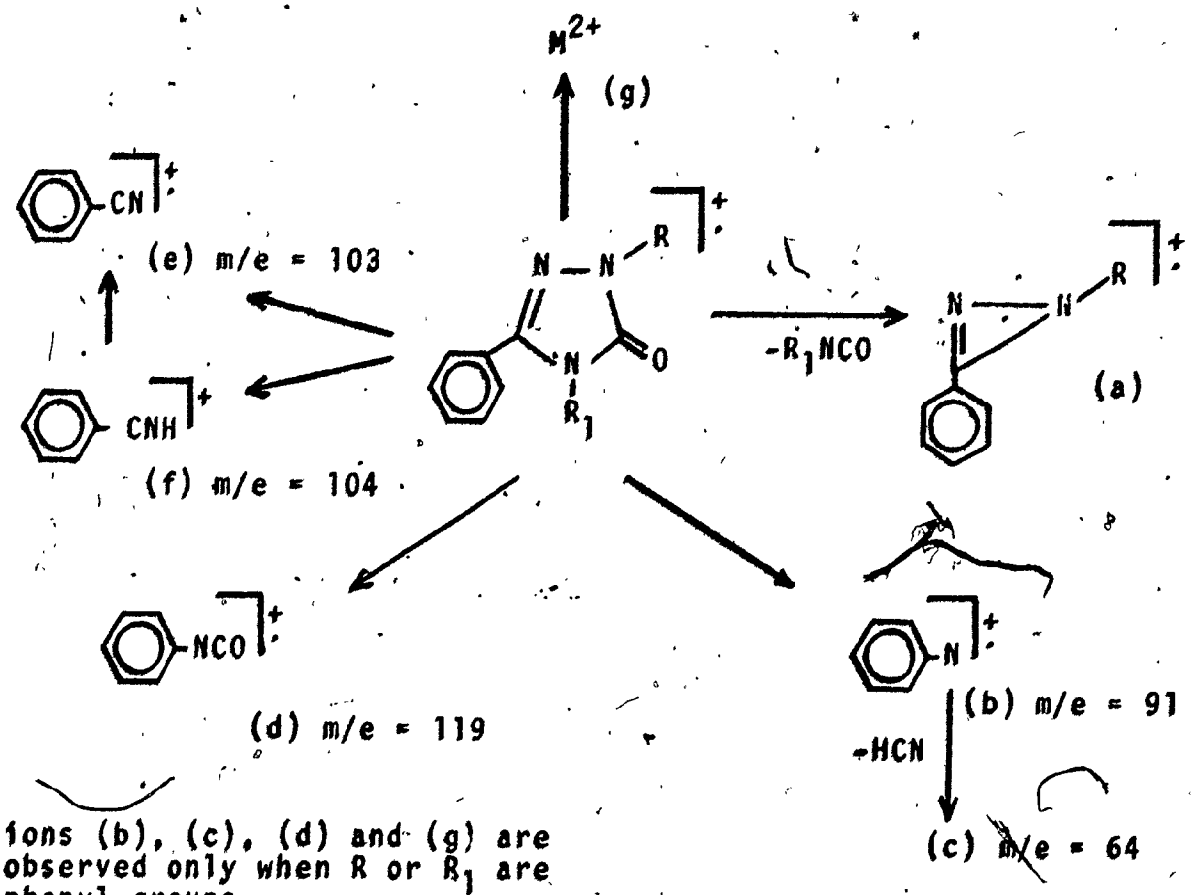
[b] In good agreement with the literature values[32].

MASS SPECTRAL STUDY OF THE CYCLIC COMPOUNDS

The mass spectra of the samples were generated using a Hitachi Perkin-Elmer RMU-7 double-focusing mass spectrometer employing the direct introduction technique. An ionizing voltage of 70 eV. and a source and inlet system of 100-150°C were used. The spectrometer has a maximum resolving power of 1 part in 20,000 at m/e 28. Intensities relative to the base peak (%) and relative to the total ion current (%Σ) were calculated using a 2114A Hewlett Packard computer in conjunction with a 2020 digital tape unit. Plots of intensities (%) vs. m/e values were obtained on line with a Houston Instrument digital plotting system. The program was written by Dr. Robin T.B. Rye of this Department.

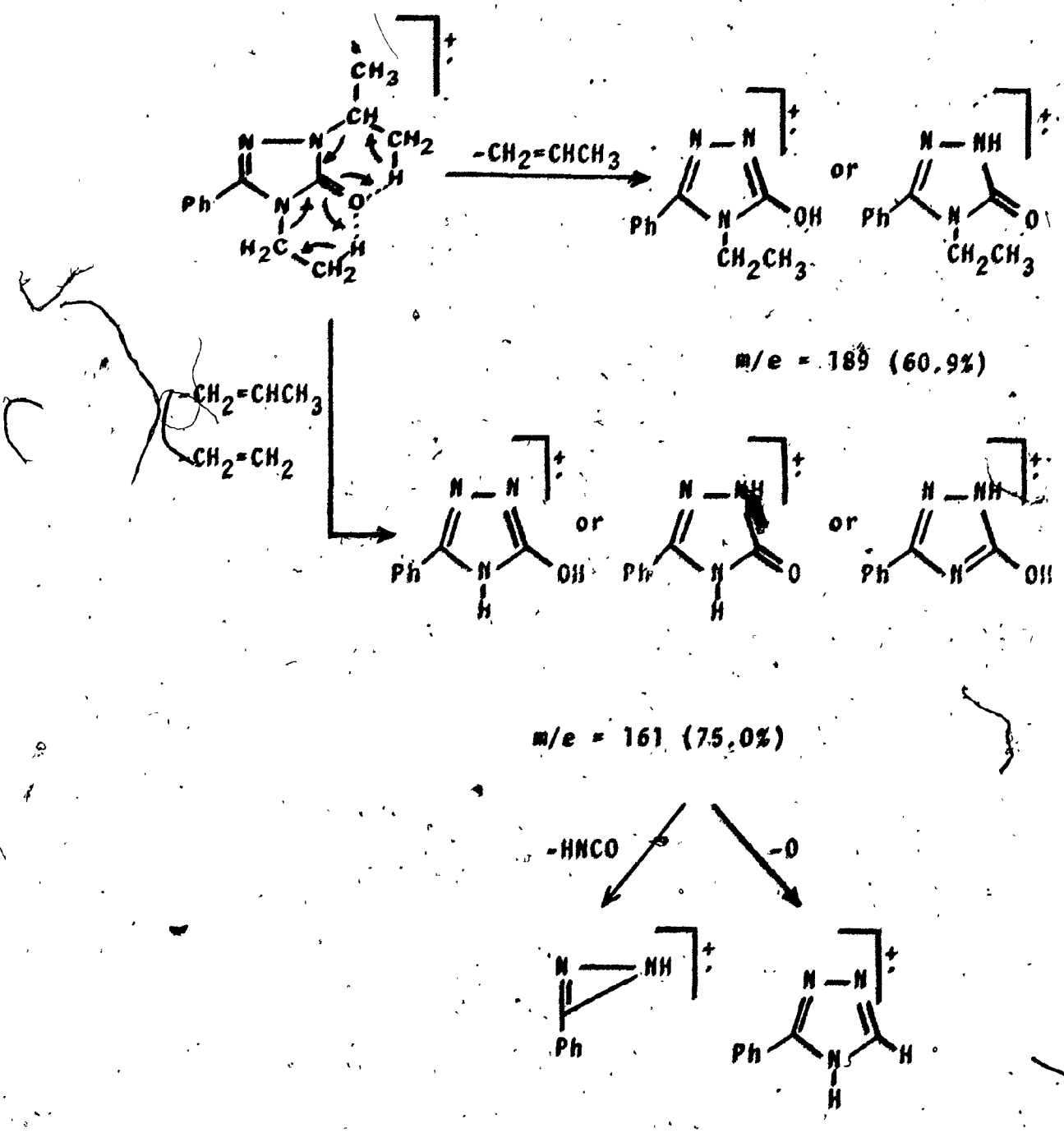
The investigations into the electron impact of 1,2,4-triazoles are only of a recent nature.[100-106] A group of Japanese authors[107] have examined the fragmentation patterns of a number of 1-phenyl-3-alkyl-Δ^2-1,2,4-triazolin-5-ones (as well as the 1,4-diphenyl-3-methyl derivative) and 2-alkyl-4-phenyl-Δ^2-1,3,4-oxadiazolin-5-ones. The study which has been carried out in view of the pharmacological importance is the only one reported for triazolinones. The modes of fragmentation of the 1,4-disubstituted-3-phenyl triazolin-5-ones and of the oxadiazolinone by-product obtained during this study are analogous to those demonstrated.[107] Modifications must be considered, however,

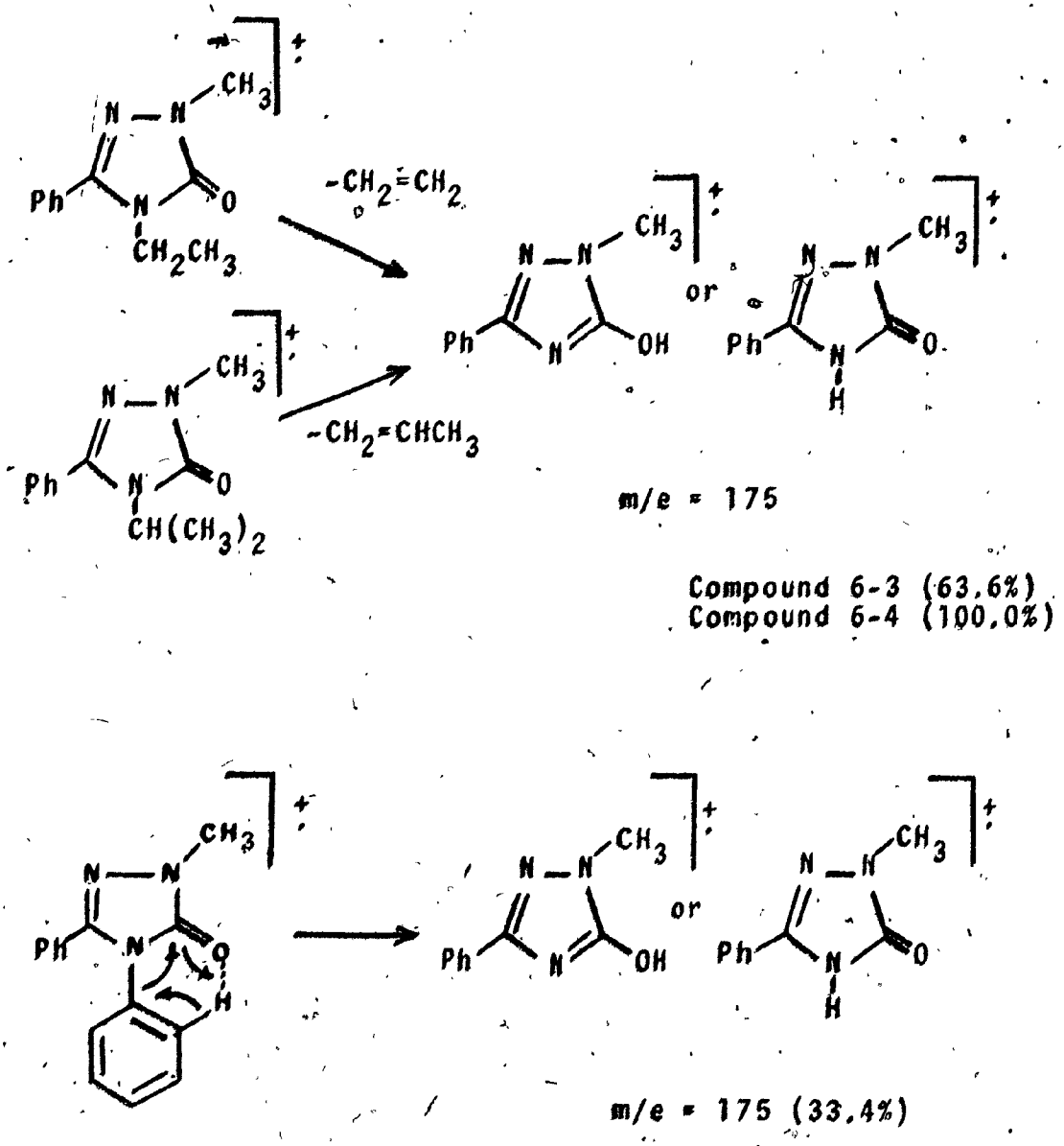
owing to the presence of an additional functional group at the 4-position of the ring. One such modification takes the form of an initial rearrangement of the substituents prior to the ring fragmentation. The major cleavages taking place in the triazole nucleus produce fragment ions (a) to (f) as shown in Scheme 19.



Scheme 19. Skelatal Fragmentation of the Heterocycles under Electron Impact

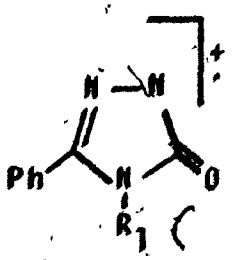
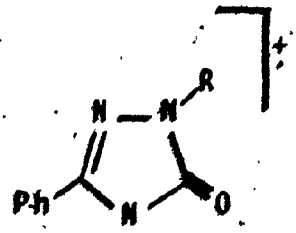
Expulsion of the neutral fragment R_1NCO from the ring produces the stable diazirine ion (a). A moderate to high abundance of this ion is observed, with the exception of the 1-isopropyl-4-ethyl derivative (Compound 6-8) where it constitutes only 1.8% of the base peak (0.12%Σ). This variation may be partially attributed to a modified McLafferty rearrangement involving the isopropyl and ethyl substituents and resulting in the 3-phenyl-4-ethyl-5-hydroxy- and 3-phenyl-5-hydroxy-1,2,4-triazole ions at m/e 189 and 161 respectively. These are demonstrated in Scheme 20. The presence of a phenyl group at N-1 or N-4 of the heterocycles gives rise to ions (b), (c), (d) and the doubly charged molecular ion (g). Ion (b) is also associated with a loss of HCN. The origin of the cyano fragment (e) may be traced back to either the molecular ion or alternatively to the diazirine ion (a). Rearrangement of the ring substituents as shown in Scheme 20 must clearly take place prior to fragmentation to ion (f), except for the disubstituted Compound 6-1. Finally, the base peak in the mass spectra of these compounds is the molecular ion. In the case of the 4-isopropyl derivative (Compound 6-4) the relative abundance of the M^+ ion is 98.0% of the base peak at m/e 175 (11.5%Σ). The latter is obtained by a loss of CH_2CHCH_3 from the parent ion as shown in Scheme 20.


-CH2=CHCH3
or
m/e = 189 (60.9%)
-CH2=CHCH3
-CH2=CH2
or
or
m/e = 161 (75.0%)
-HNCO
-O
m/e = 118 (38.8%)
m/e = 145 (44.1%)



Scheme 20. McLafferty-Type Rearrangements of the Substituents at N-1 and N-4 of the Rings

Other commonly occuring fragments are classified below.

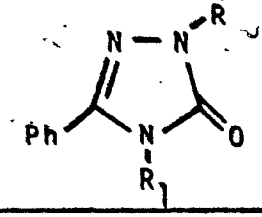
Fragment	Label
	(h)
R^+ (alkyl)	(i)
	(j)
R_1^+ (alkyl)	(k)
$C_6H_5^+$; $C_4H_3^+$; $C_3H_3^+$ (aromatic series)	(l); (m); (n)

The relative intensities of ions (a) through (n) are given in Table XVI followed by computer plots of the spectra. Copies of the digitized spectra in % and %I are available but have not been included in the thesis.

Mass Spectrum of 2-phenyl-4-methyl-Δ^2-1,3,4-oxadiazolin-5-one

The fragmentation pattern of this compound was similar to that of the substituted triazolinones already described with the exception of an additional fragment ion $PhCO^+$ at m/e 105 (73.4%). The molecular ion, unlike in the case of the triazolinones where it constitutes 98.0-100.0% of the base peak, comprised of only 60.1% of the base peak. Ions analogous to those observed in the spectra of the triazolinones are: $PhCNNCH_3^+$, m/e 132.0 (100.0%); $PhCNH^+$, m/e 104.0 (82.4%); $PhCN^+$, m/e 103.0 (28.6%); $C_6H_5^+$, m/e 77.0 (97.0%); $C_4H_3^+$, m/e 51.0 (80.3%); $C_3H_3^+$, m/e 39.0 (30.5%). Refer to p. 199 for the spectrum.

Table XVI. Summary of the Commonly Occurring Fragments in the Mass Spectra of the Heterocyclic Derivatives



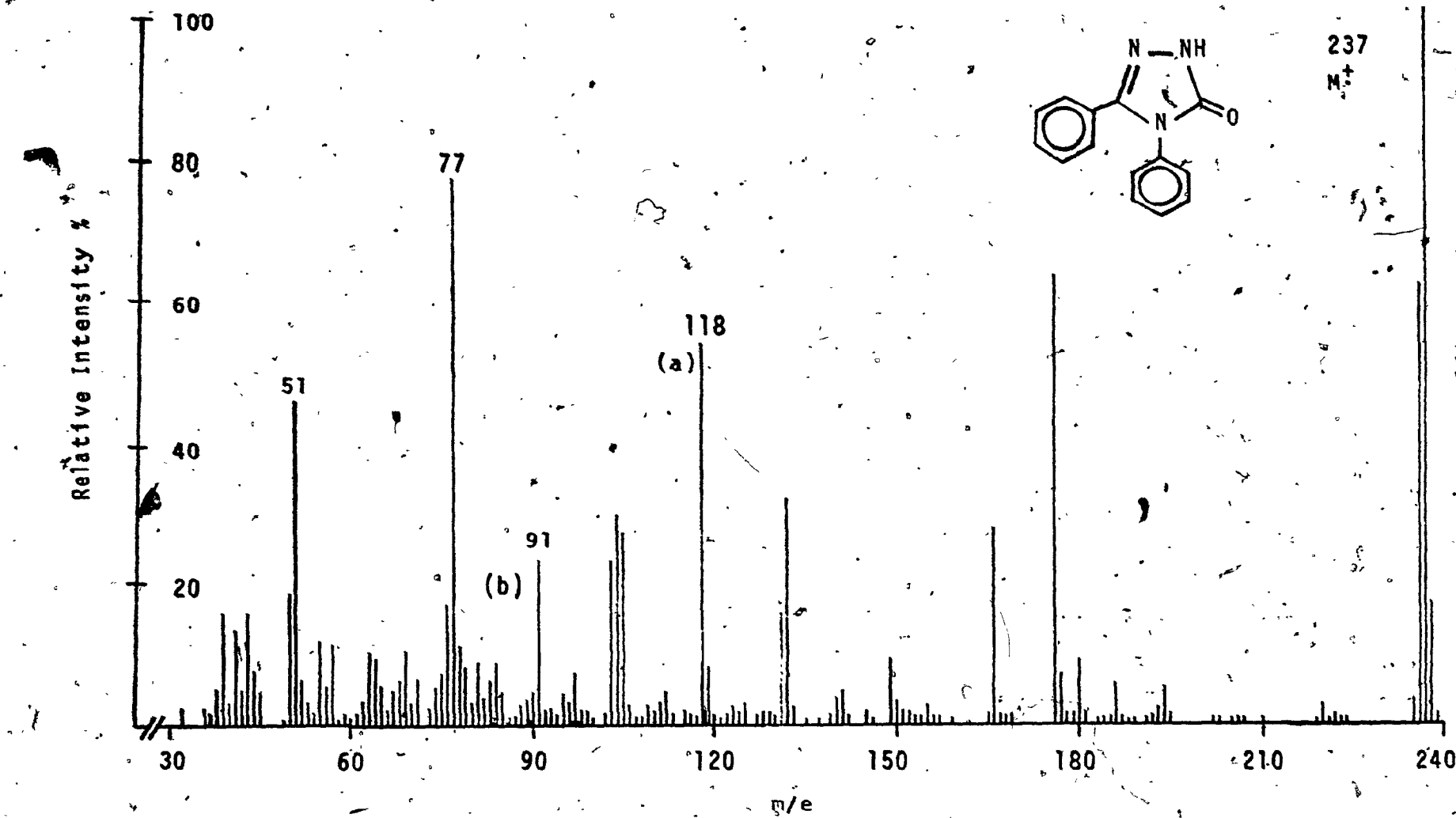
R	R_1	M^+ m/e (%)	$(M+1)^+$ m/e (% obs.) (% calcd.)	Ion a m/e (%)	Ion b m/e (%)	Ion c m/e (%)	Ion d m/e (%)	Ion e m/e (%)	Ion f m/e (%)	Compd.
H	Ph	237 (100.0)	238 (17.7) (16.7)	118 (53.7)	91 (23.1)	64 (9.4)	119 (8.5)	103 (22.9)	104 (29.8)	6-1
Me	Et	203 (100.0)	204 (15.4) (13.5)	132 (43.0)	-	-	-	103 (19.6)	104 (45.5)	6-3
Me	i-Pr	217 (98.0)	218 (37.4) (14.6)	132 (80.3)	-	-	-	103 (33.5)	104 (62.6)	6-4
Me	Ph	251 (100.0)	252 (17.8) (17.8)	132 (59.5)	91 (17.7)	64 (13.0)	119 (10.5)	103 (26.3)	104 (73.3)	6-7
i-Pr	Et	231 (100.0)	232 (20.3) (15.7)	160 (1.8)	-	-	-	103 (68.4)	104 (86.5)	6-8

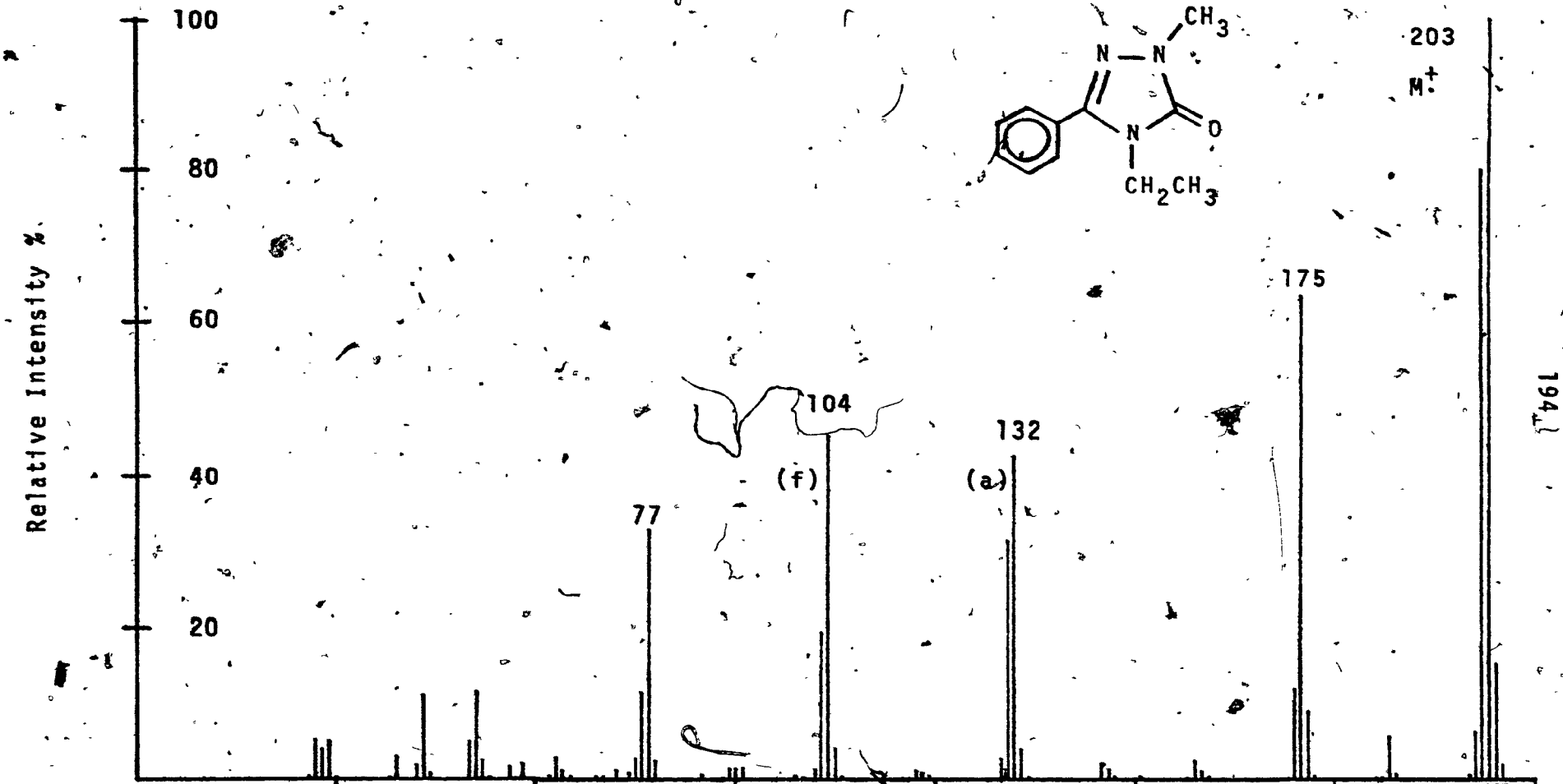
Table XVI Cont.

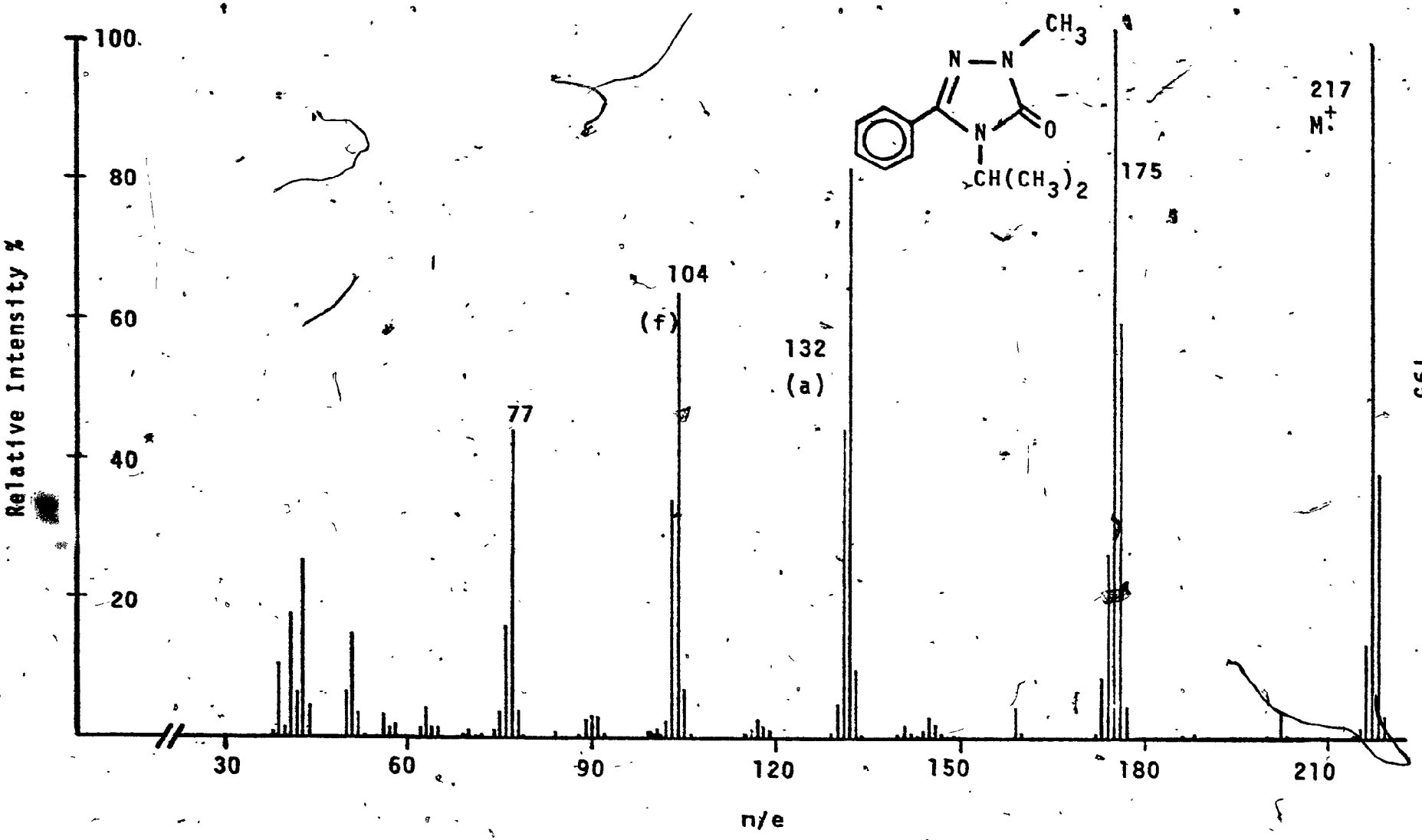
R	R_1	M^+ m/e (%)	$(M+1)^+$ m/e (% obs.) (% calcd.)	Ion a m/e (%)	Ion b m/e (%)	Ion c m/e (%)	Ion d m/e (%)	Ion e m/e (%)	Ion f m/e (%)	Compd.
Ph	Ph	313 (100.0)	314 (27.0) (23.4)	194 (28.7)	91 (93.9)	64 (56.5)	119 (11.0)	103 (19.2)	104 (12.9)	6-13

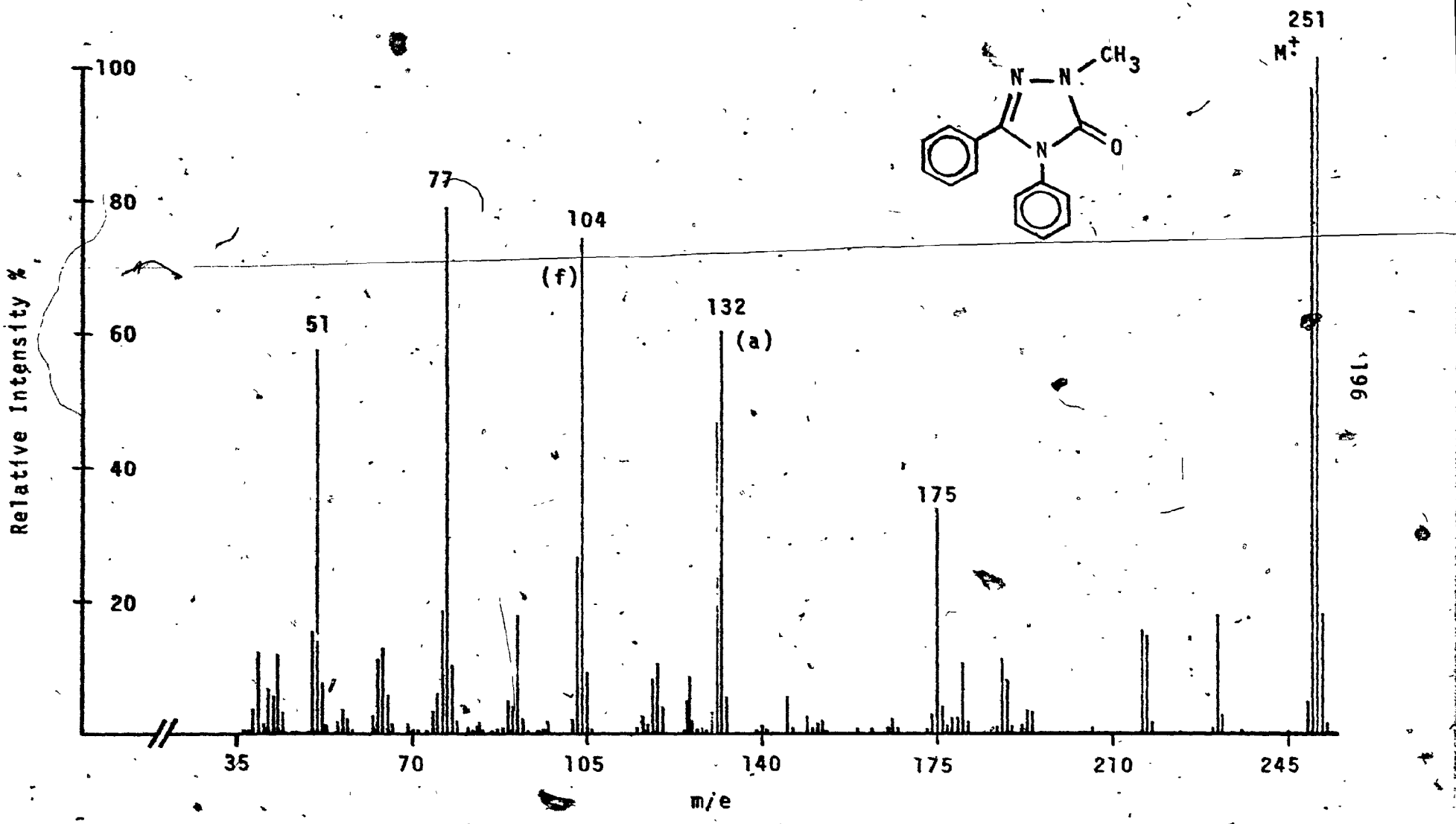
Table XVI Cont.

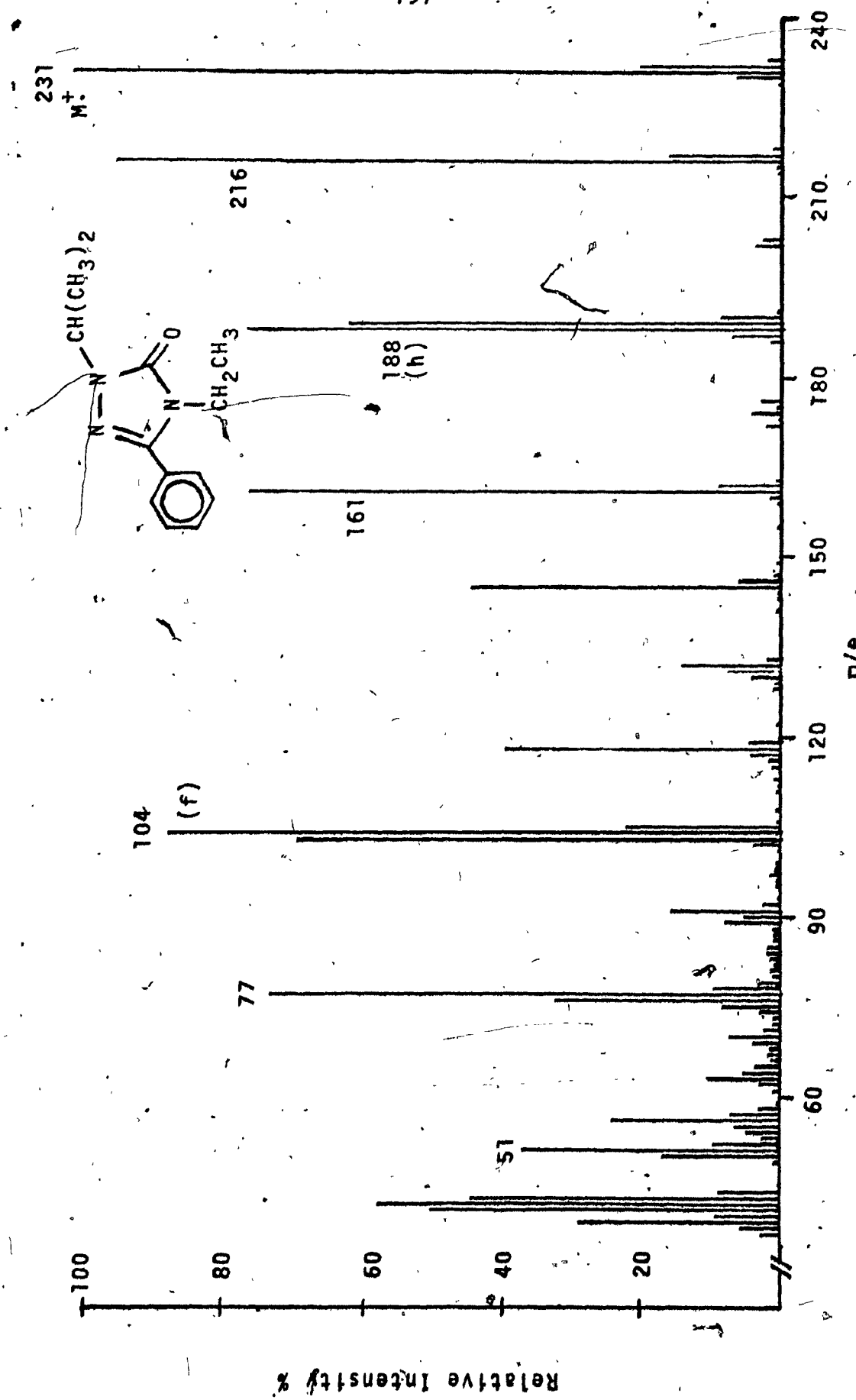
R	R_1	Ion g m/e (%)	Ion h m/e (%)	Ion i m/e (%)	Ion j m/e (%)	Ion k m/e (%)	Ion l m/e (%)	Ion m m/e (%)	Ion # m/e (%)	Compd.
H	Ph	118.5 (2.7)	236 (61.2)	-	-	-	77 (76.7)	51 (45.4)	39 (16.2)	6-1
Me	Et	-	188 (6.0)	-	174 (11.9)	29 (5.3)	77 (33.0)	51 (11.7)	39 (3.5)	6-3
Me	i-Pr	-	202 (3,8)	-	174 (25.7)	43 (24.9)	77 (43.5)	51 (14.7)	39 (10.4)	6-4
Me	Ph	125.5 (8.7)	236 (0.8)	-	-	-	77 (78.2)	51 (57.1)	39 (12.3)	6-7
i-Pr	Et	-	188 (75.3)	43 (44.1)	202 (3.9)	29 (36.8)	77 (72.0)	51 (36.8)	39 (28.8)	6-8
Ph	Ph	156.5 (1.9)	-	-	-	-	77 (73.0)	51 (57.6)	39 (18.1)	6-13

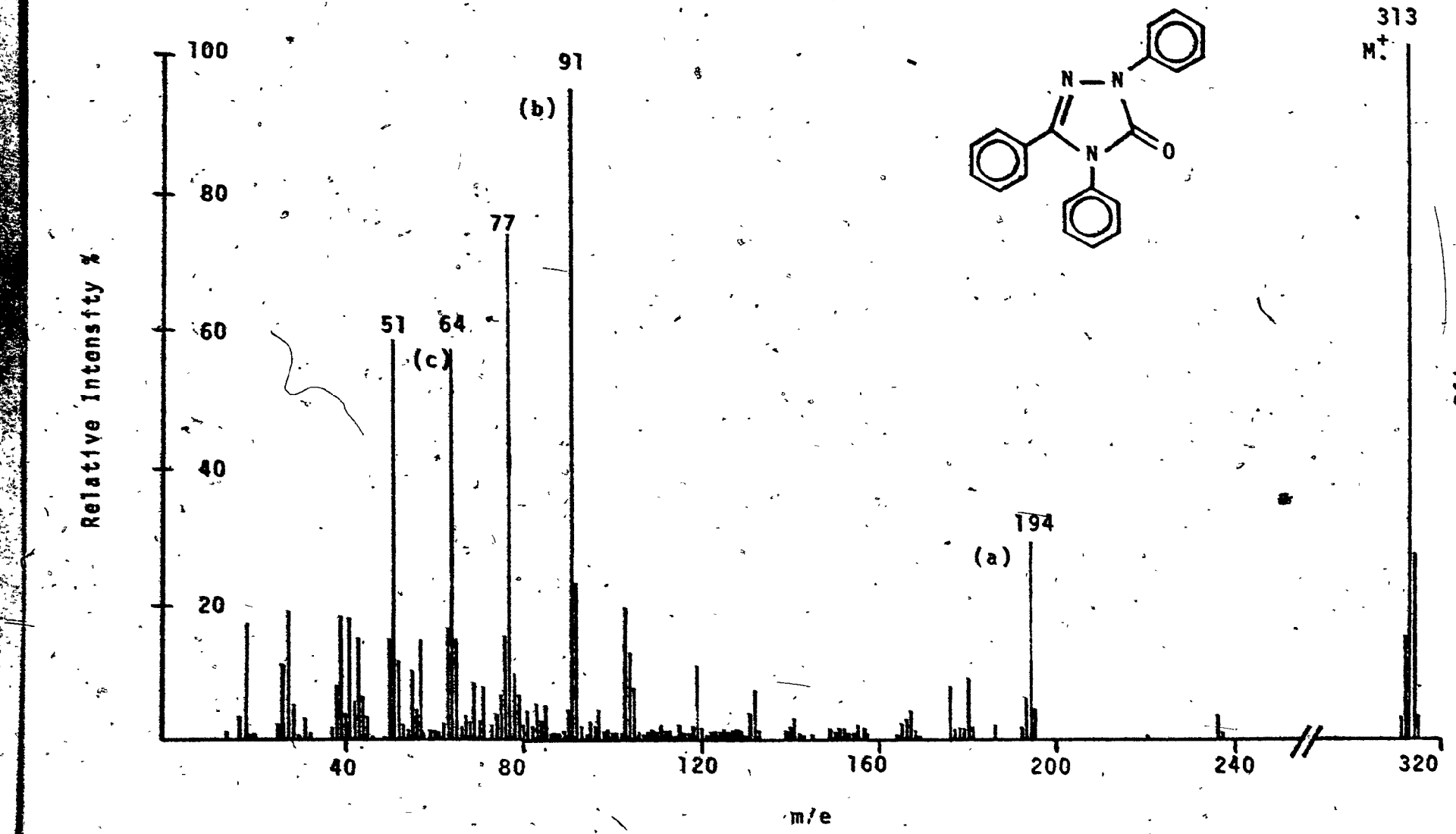

100
80
60
40
20
Relative Intensity %
77
51
118
(a)
91
(b)
193
237
M+
N—NH
N
O
30
60
90
120
150
180
210
240
m/e

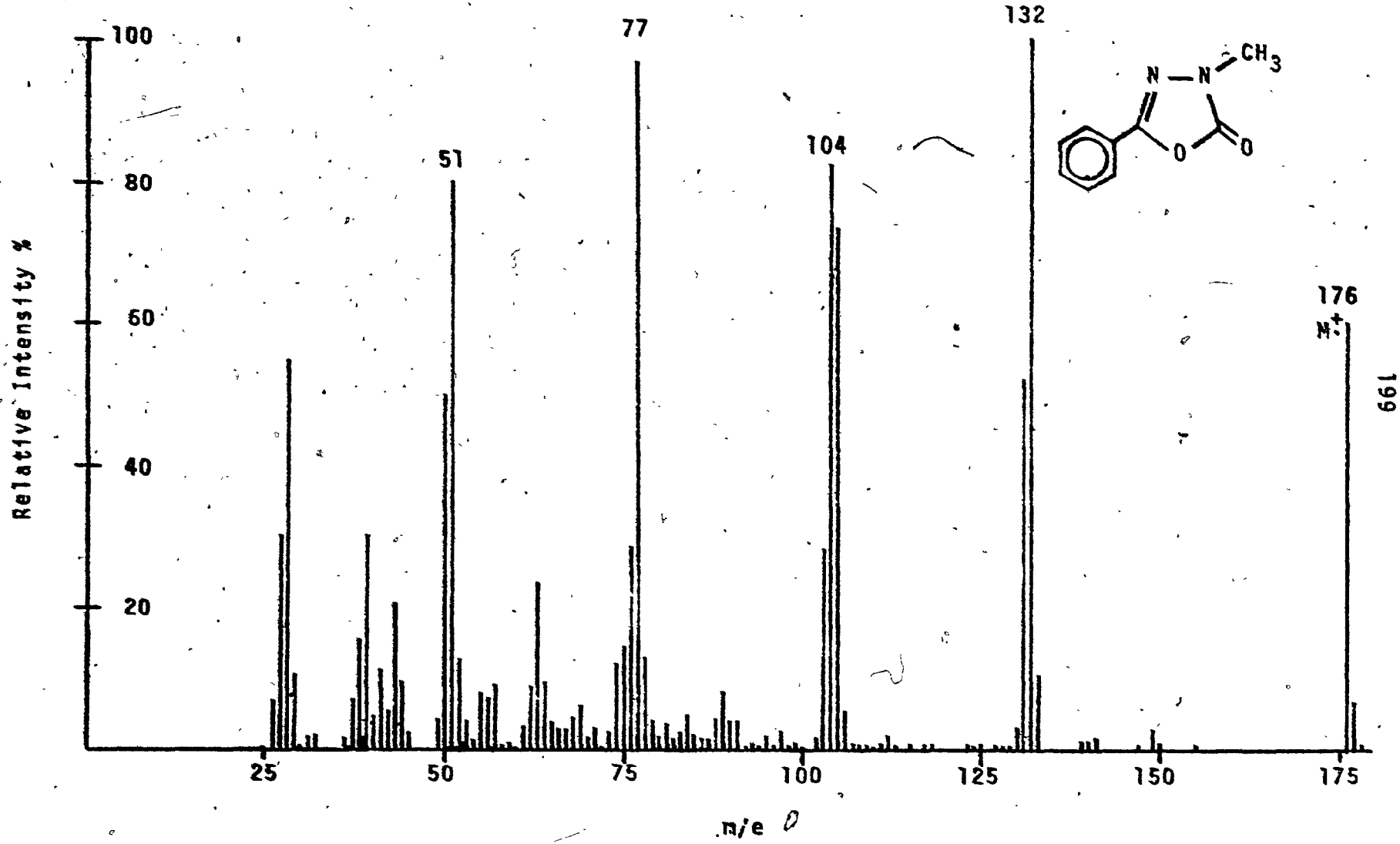

Relative Intensity %
100
80
60
40
20
30
60
90
120
150
180
210
m/e
77
104
(f)
132
(a)
175
203
M+
194
N
N
CH3
N
O
CH2CH3


100
80
60
40
20
Relative Intensity %
77
104
(f)
132
(a)
175
195
217
M+
CH3
N
N
O
CH(CH3)2
30
60
90
120
150
180
210
m/e


100
80
60
40
20
Relative Intensity %
77
104
(f)
51
132
(a)
175
251
M+
196
35
70
105
140
175
210
245
m/e
N
N
CH3
N
O

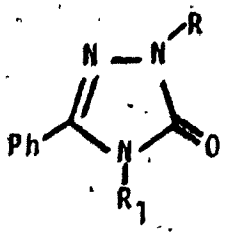

Relative Intensity %
100
80
60
40
20
m/e
240
210
180
150
120
90
60
231
M+·
216
188
(h)
161
104
(f)
77
51
CH(CH3)2
CH2CH3
O
N
N


Relative Intensity %
100
80
60
40
20
91
(b)
77
51
64
(c)
194
(a)
313
M.+
198
N
N
N
O
40
80
120
160
200
240
320
m/e


Relative Intensity %
100
80
60
40
20
25
50
75
100
125
150
175
m/e
77
132
51
104
176
M+
199
N
N
CH3
O
O

SUMMARY

The scope of the direct cyclization reaction yielding 1,3,4-trisubstituted-Δ^2-1,2,4-triazolin-5-ones has been extended to include the following series of derivatives.



R-	R_1	Semicarbazide ring closure	Semicarbazone ring closure
H	Ph	NaOH	-
Me	Et	NaOH	$FeCl_3 \cdot 6H_2O$ under pressure
Me	i-Pr	NaOH	-
Me	t-Bu	NaOH (trace?)	-
Me	Ph	NaOH $ZnCl_2$ PPA (oxadiazole)	$K_3Fe(CN)_6$
i-Pr	Et	NaOH	$K_3Fe(CN)_6$ (trace)
i-Pr	i-Pr	NaOH	-
i-Pr	Ph	NaOH (trace?)	-
Ph	Ph	-	$K_3Fe(CN)_6$

Direct ring closure yielding the 3-phenyl analogs is uncommon in the literature. In fact, the triphenyl derivative is the only such example reported. The yields of cyclic products obtained in this study are low, regardless of the method employed, and range from traceable amounts to approximately 36%, with the exception of two cases where yields as high as 81% were secured. The low yields may be attributed to steric factors and to the numerous side reaction. Alkaline ring closure of a semicarbazide-type chain was recognized as the most suitable method while potassium ferricyanide was the most effective among the various oxidizing agents when semicarbazones were used.

N.m.r. and i.r. assignments of the heterocyclic products have been made. Distinguishing n.m.r. features of the cyclization reaction are observed in the C-phenyl region and in the chemical shifts of the alkyl substituents at N-1 and N-4 of the ring. The absence of intermolecular association in the cyclic structures was deduced on the basis of the elimination of the amide I band in the i.r. region of approximately 1600-1650 cm^{-1}. A mass spectral study reveals the most prominent feature under electron impact to be ring fragmentation involving the elimination of R_1NCO along with fragments observed due to PhCN and PhHCN. Furthermore, the molecular ion is present as the base peak in all but one case where it constitutes 98% of the base peak. McLafferty-type rearrangement of the functional groups

prior to ring cleavage is also observed in certain cases. The mass spectrum of only one such derivative containing an alkyl rather than a phenyl group at the 3-position the ring, is described in the literature.

The various intermediates synthesized, most of which are not reported, were obtained in good yields by classical methods, and verified according to their spectroscopic evidence in conjunction with the elemental analyses results.

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