MONOCYCLIC AZEPINES

The Syntheses and Chemical Properties
of the Monocyclic Azepines

This is the Fifty-sixth Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR

Editor

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The Syntheses and Chemical Properties of the Monocyclic Azepines

GEORGE R. PROCTOR
University of Strathclyde

JAMES REDPATH
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Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g. pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic, medicinal and biochemistry, and for this reason we initiated several years ago a parallel series entitled *General Heterocyclic Chemistry* which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

The present volume extends our previous coverage of seven-membered nitrogen-containing rings to the parent monocyclic azepines. It is an

authoritative, exhaustive and most welcome contribution to the literature of heterocyclic chemistry.

Edward C. Taylor

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Princeton University
Princeton, New Jersey 08544

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XIII. 4,5-Dihydro[3*H*]azepine-3,5-diones* –

XIV. 3,6-Dihydro[2*H*]azepine-3,6-diones* –

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* Compounds marked with asterisks are not mentioned in the literature.

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List of Abbreviations

DMAD	Dimethyl acetylenedicarboxylate
DMSO	Dimethyl sulphoxide
DDQ	Dichlorodicyanobenzoquinone
DMF	*N*,*N*-Dimethylformamide
HMPA	Hexamethylphosphoric triamide
THF	Tetrahydrofuran
TCE	Tetracyanoethylene
GLC	Gas–liquid chromatography
Tos	Toluene-*p*-sulphonyl
PPA	Polyphosphoric acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
NBS	*N*-Bromosuccinimide
Meerwein's reagent	Triethyloxonium borofluoride
LDA	Lithium diisopropylamine
Dibal	Diisobutyl aluminium hydride
DPPA	Diphenylphosphoryl azide
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine

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George R. Proctor, James Redpath
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CHAPTER 1

Introduction

Although tricyclic and bicyclic azepines have been presented in this series,[1] monocyclic azepines have not been reviewed. Previous azepine compilations have included mono-, di- and tricyclic azepines[2,3] in some detail. In this volume we have collated all relevant data on monocyclic azepines in the style customary for this series. Where certain aspects of the subject have been satisfactorily reviewed previously,[3] we have summarised in an effort to avoid unhelpful duplication.

The subject is conveniently divided according to the state of oxidation of the heterocycle. Thus hexahydroazepines (azepanes) and their keto derivatives can be distinguished from tetrahydro- and dihydroazepines and their keto derivatives. Finally, azepines and azepinones provide examples at the highest state of oxidation (or dehydrogenation). Tables are provided where a significant number of examples justify this.

In order to systematise the presentation of the many possible structures containing carbonyl groups, we have referred to these compounds as di- or tetrahydroazepinones or -diones as appropriate, thereby maintaining the convention of naming the parent compounds according to the substituent with the highest oxidation state. For example, there are 26 distinct structures for tetrahydroazepinediones which are subdivided into 11 categories, depending on the position of the carbonyl groups: tetrahydroazepine-2,3-dione, tetrahydroazepine-2,4-dione, and so on. Of these possible structures, 18 are unknown at the present time. Similarly many of the possible dihydroazepinones and diones are not represented in the literature. For the sake of completeness, and to highlight the areas which have still to be explored, all the possible structural types have been included in the Contents list, but within the appropriate chapters we shall deal only with those structures for which compelling evidence has been adduced in the literature. Compounds for which no physical

data were cited are only included in the tables when there is definite evidence of their existence.

Literature was searched via *Chemical Abstracts* up to late 1994 fairly exhaustively, and selectively for 1995. The nomenclature used is that currently seen in *Chemical Abstracts*.[4]

Table 1 Overview of monocyclic azepine structures

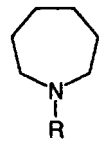
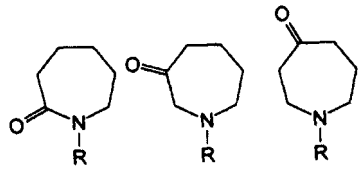
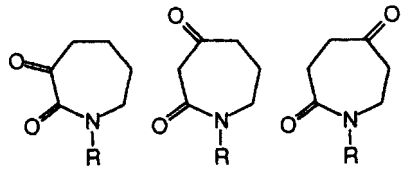
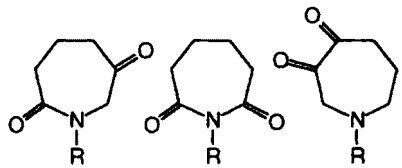
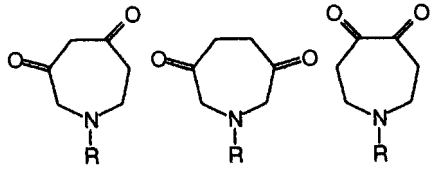
Chapter No.	Compound name	Structure
2	**Azepanes** (hexahydroazepines)	
3	**Azepanones**	
	I. Azepan-2-ones II. Azepan-3-ones III. Azepan-4-ones	
4	**Azepanediones**	
	I. Azepane-2,3-diones II. Azepane-2,4-diones III. Azepane-2,5-diones	
	IV. Azepane-2,6-diones V. Azepane-2,7-diones VI. Azepane-3,4-diones	
	VII. Azepane-3,5-diones VIII. *azepane-3,6-diones* IX. Azepane-4,5-diones	

Table 1 (continued)

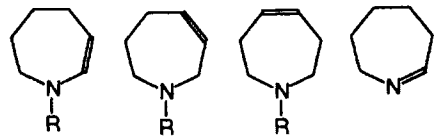
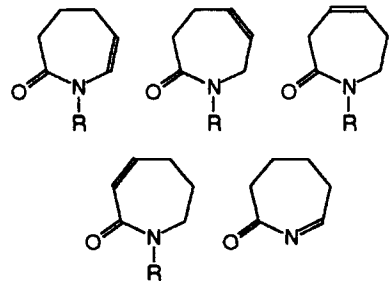
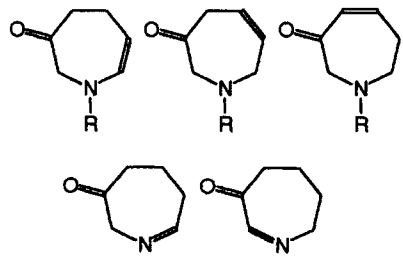
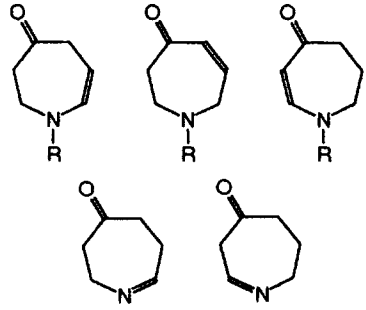
Chapter No.	Compound name	Structure
5	**Tetrahydroazepines**	
	I. 2,3,4,5-Tetrahydro[1*H*]-azepines II. 2,3,4,7-Tetrahydro[1*H*]-azepines III. 2,3,6,7-Tetrahydro[1*H*]-azepines IV. 3,4,5,6-Tetrahydro[2*H*]-azepines	
6	**Tetrahydroazepinones**	
	I. 1,3,4,5-Tetrahydro[2*H*]-azepin-2-ones II. 1,3,4,7-Tetrahydro[2*H*]-azepin-2-ones III. 1,3,6,7-Tetrahydro[2*H*]-azepin-2-ones IV. 1,5,6,7-Tetrahydro[2*H*]-azepin-2-ones V. *3,4,5,6-Tetrahydro[2H]-azepin-2-ones*	
	VI. *1,2,4,5-Tetrahydro[3H]-azepin-3-ones* VII. *1,2,4,7-Tetrahydro[3H]-azepin-3-ones* VIII. 1,2,6,7-Tetrahydro[3*H*]-azepin-3-ones IX. *2,4,5,6-Tetrahydro[3H]-azepin-3-ones* X. *4,5,6,7-Tetrahydro[3H]-azepin-3-ones*	
	XI. *1,2,3,5-Tetrahydro[4H]*-azepin-4-ones XII. 1,2,3,7-Tetrahydro[4*H*]-azepin-4-ones XIII. 1,5,6,7-Tetrahydro[4*H*]-azepin-4-ones XIV. 2,3,5,6-Tetrahydro[4*H*]-azepin-4-ones XV. 3,5,6,7-Tetrahydro[4*H*]-azepin-4-ones	

Table 1 (continued)

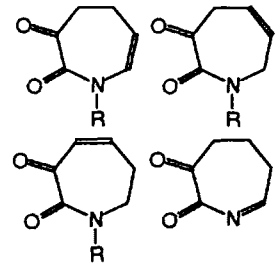
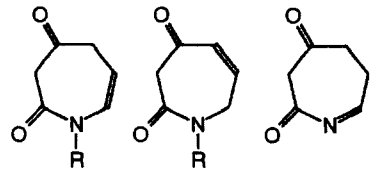
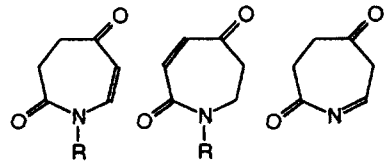
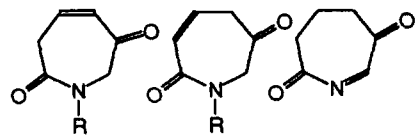
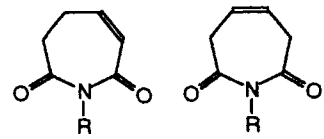
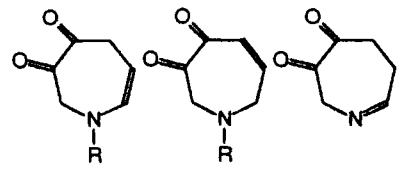
Chapter No.	Compound name	Structure
7	**Tetrahydroazepinediones**	
	I. 2,3,4,5-Tetrahydro[1*H*]-azepine-2,3-diones II. *2,3,4,7-Tetrahydro[1H]-azepine-2,3-diones* III. *2,3,6,7-Tetrahydro[1H]-azepine-2,3-diones* IV. *3,4,5,6-Tetrahydro[2H]-azepine-2,3-diones*	
	V. 2,3,4,5-Tetrahydro[1*H*]-azepine-2,4-diones VI. *2,3,4,7-Tetrahydro[1H]-azepine-2,4-diones* VII. *3,4,5,6-Tetrahydro[2H]-azepine-2,4-diones*	
	VIII. 2,3,4,5-Tetrahydro[1*H*]-azepine-2,5-diones IX. 2,5,6,7-Tetrahydro[1*H*]-azepine-2,5-diones X. *3,4,5,6-Tetrahydro[2H]-azepine-2,5-diones*	
	XI. *2,3,6,7-Tetrahydro[1H]-azepine-2,6-diones* XII. *2,5,6,7-Tetrahydro[1H]-azepine-2,6-diones* XIII. *3,4,5,6-Tetrahydro[2H]-azepine-2,6-diones*	
	XIV. 2,3,4,7-Tetrahydro[1*H*]-azepine-2,7-diones XV. 2,3,6,7-Tetrahydro[1*H*]-azepine-2,7-diones	
	XVI. *2,3,4,5-Tetrahydro[1H]-azepine-3,4-diones* XVII. *2,3,4,7-Tetrahydro[1H]-azepine-3,4-diones* XVIII. *3,4,5,6-Tetrahydro[2H]-azepine-3,4-diones*	

Table 1 (continued)

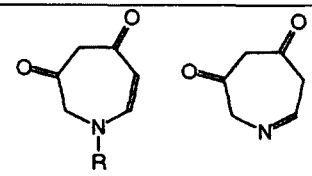
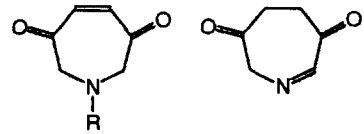
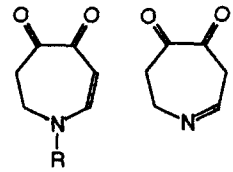
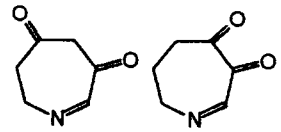
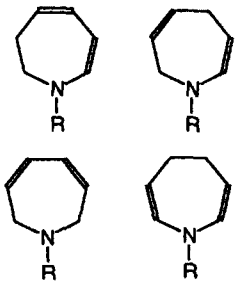
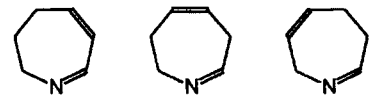
Chapter No.	Compound name	Structure
	XIX. *2,3,4,5-Tetrahydro[1H]-azepine-3,5-diones* XX. *3,4,5,6-Tetrahydro[2H]-azepine-3,5-diones*	
	XXI. *2,3,6,7-Tetrahydro[1H]-azepine-3,6-diones* XXII. *3,4,5,6-Tetrahydro[2H]-azepine-3,6-diones*	
	XXIII. 2,3,4,5-Tetrahydro[1*H*]-azepine-4,5-diones XXIV. 3,4,5,6-Tetrahydro[2*H*]-azepine-4,5-diones	
	XXV. *3,4,5,6-Tetrahydro[2H]-azepine-4,6-diones* XXVI. *3,4,5,6-Tetrahydro[2H]-azepine-5,6-diones*	
8	**Dihydroazepines**	
	I. 2,3-Dihydro[1*H*]-azepines II. 2,5-Dihydro[1*H*]-azepines III. 2,7-Dihydro[1*H*]-azepines IV. 4,5-Dihydro[1*H*]-azepines	
	V. 3,4-Dihydro[2*H*]-azepines VI. 3,6-Dihydro[2*H*]-azepines VII. 5,6-Dihydro[2*H*]-azepines	

Table 1 (continued)

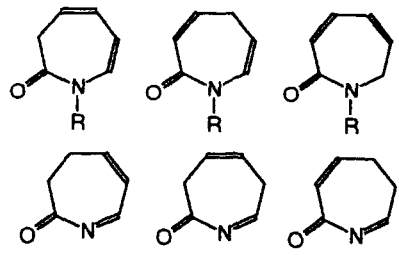
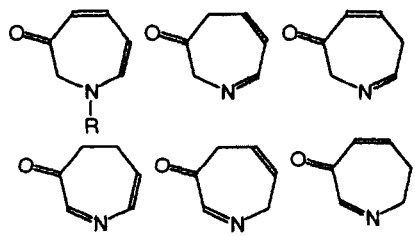
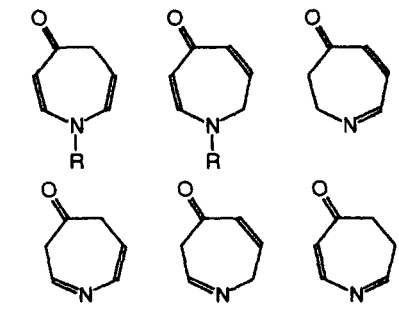
Chapter No.	Compound name	Structure
	VIII. 4,5-Dihydro[3*H*]-azepines	
9	**Dihydroazepinones**	
	I. 1,3-Dihydro[2*H*]-azepin-2-ones II. 1,5-Dihydro[2*H*]-azepin-2-ones III. 1,7-Dihydro[2*H*]-azepin-2-ones IV. 3,4-Dihydro[2*H*]-azepin-2-ones V. 3,6-Dihydro[2*H*]-azepin-2-ones VI. *5,6-Dihydro[2H]-azepin-2-ones*	
	VII. 1,2-Dihydro[3*H*]-azepin-3-ones VIII. *2,4-Dihydro[3H]-azepin-3-ones* IX. *2,6-Dihydro[3H]-azepin-3-ones* X. *4,5-Dihydro[3H]-azepin-3-ones* XI. *4,7-Dihydro[3H]-azepin-3-ones* XII. *6,7-Dihydro[3H]-azepin-3-ones*	
	XIII. *1,5-Dihydro[4H]-azepin-4-ones* XIV. *1,7-Dihydro[4H]-azepin-4-ones* XV. 2,3-Dihydro[4*H*]-azepin-4-ones XVI. *3,5-Dihydro[4H]-azepin-4-ones* XVII. *3,7-Dihydro[4H]-azepin-4-ones* XVIII. *5,6-Dihydro[4H]-azepin-4-ones*	

Table 1 (continued)

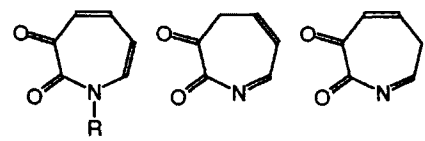
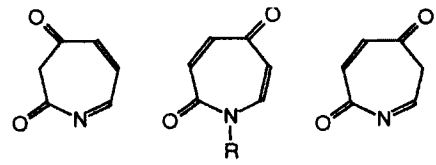
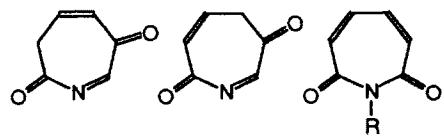
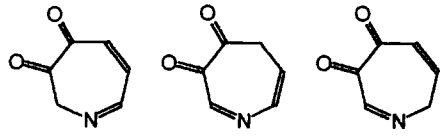
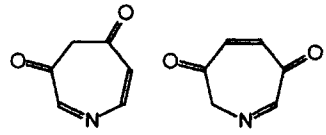
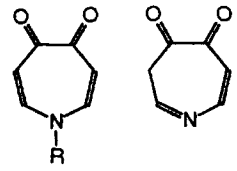
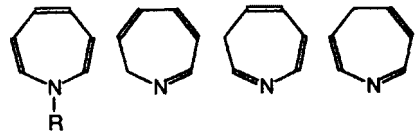
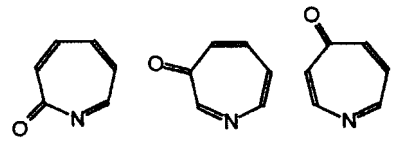
Chapter No.	Compound name	Structure
10	**Dihydroazepinediones**	
	I. 2,3-Dihydro[1*H*]-azepine-2,3-diones II. *3,4-Dihydro[2H]-azepine-2,3-diones* III. *3,6-Dihydro[2H]-azepine-2,3-diones*	
	IV. *3,4-Dihydro[2H]-azepine-2,4-diones* V. 2,5-Dihydro[1*H*]-azepine-2,5-diones VI. *5,6-Dihydro[2H]-azepine-2,5-diones*	
	VII. *3,6-Dihydro[2H]-azepine-2,6-diones* VIII. *5,6-Dihydro[2H]-azepine-2,6-diones* IX. 2,7-Dihydro[1*H*]-azepine-2,7-diones	
	X. *3,4-Dihydro[2H]-azepine-3,4-diones* XI. *4,5-Dihydro[3H]-azepine-3,4-diones* XII. *4,7-Dihydro[3H]-azepine-3,4-diones*	
	XIII. *4,5-Dihydro[3H]-azepine-3,5-diones* XIV. *3,6-Dihydro[2H]-azepine-3,6-diones*	
	XV. *4,5-Dihydro[1H]-azepine-4,5-diones* XVI. *4,5-Dihydro[3H]-azepine-4,5-diones*	

Table 1 (continued)

Chapter No.	Compound name	Structure
11	**Azepines**	
	I. [1*H*]azepines II. [2*H*]azepines III. [3*H*]azepines IV. [4*H*]azepines	
12	**Azepinones**	
	I. [2*H*]Azepin-2-ones II. [3*H*]Azepin-3-ones III. [4*H*]Azepin-4-ones	

In Table 1, structures which are theoretically possible but which have not been found in the literature are shown in *italics*. For the sake of completeness, these structures are shown in the above diagrams, but they are not referred to further in the text. The authors hope that by highlighting the missing structures in this manner, other researchers who are involved in synthetic heterocyclic chemistry may be inspired to fill the gaps.

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1. B. Renfroe, C. Harrington and G.R. Proctor, 'Azepines, Part 1', in A. Rosowski (Ed.), *The Chemistry of Heterocyclic Compounds*, Wiley, Chichester, 1984.
2. J.A. Moore and E. Mitchell, in R.C. Elderfield (Ed.), *Heterocyclic Compounds*, Vol. 9, Wiley, Chichester, 1967.
3. R.K. Smalley, *Comprehensive Heterocyclic Chemistry*, Vol. 7, Pergamon Press, Oxford, 1984, pp. 491–546.
4. *Naming and Indexing of Chemical Substances for Chemical Abstracts, Appendix IV from the Chemical Abstracts 1977 Index guide*, American Chemical Society, Columbus, OH, 1977.

Chemistry of Heterocyclic Compounds, Volume 56
George R. Proctor, James Redpath
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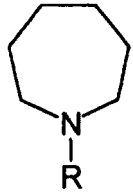
CHAPTER 2

Azepanes (Hexahydroazepines)

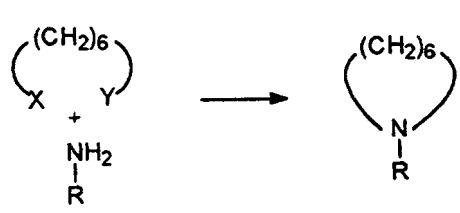


Originally the parent (R = H) of this series was referred to as 'hexamethyleneimine.' Later, and more correctly, these substances were seen as hexahydroazepines, but recently the name azepane has been preferred. The literature contains several thousand references to azepanes since it has been popular, particularly in the patent literature, to attach the azepane nucleus to very many structures in the same way as piperidine and pyrrolidine have been used. We are, therefore, obliged to restrict coverage to those cases in which the azepane portion comprises the major part of a molecule.

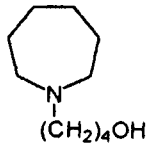
PREPARATION

Early work has been very adequately covered in a previous review.[1]

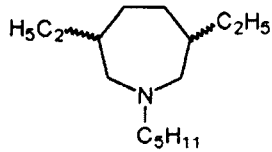
1. Reaction of 1,6-Difunctional Hexanes with Ammonia or Amines



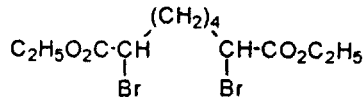
This approach, introduced in 1928,[2] has continued to be employed from time to time with some variations.[3] In the latter case, 1,6-diaminohexane reacted with butane-1,4-diol in the presence of Raney nickel giving **1**, although Adkins and co-workers had developed high-pressure treatment of various diols with amines in the presence of hydrogen and 'CuCrO' 20 years earlier.[4,5] From the appropriate diols azepanes such as **2** were obtained in moderate yields.[5] The use of 1,6-dihalohexanes[2] has limitations, side reactions tending to intervene.



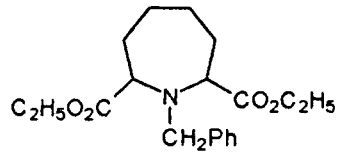
(1)



(2)

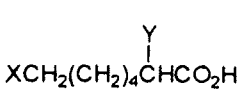


(3)

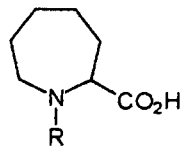


(4)

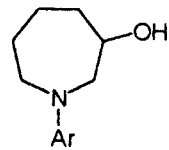
However, the presence of electron-withdrawing groups α- to halogen atoms has a beneficial effect. Thus, following a precedent,[6] Italian chemists developed a mild reaction of benzylamine with the dibromo diester **3** which provided the azepane diester **4** in slightly impure form.[7] On the other hand, in Russia, α,ω-dihalo-monocarboxylic acids **5** reacted with a variety of amines yielding the α-amino acid derivatives **6**.[8]



(5)



(6)



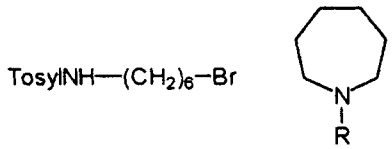
(7)

Organometallic chemistry has more recently had an impact on this type of azepane synthesis. Tetracarbonyl hydridoferrate [$HFe(CO)_4^-$], used stoichiometrically, promoted the reductive cyclisation of adipodialdehyde with primary amines,[9] but an improvement involves catalytic ruthenium halide plus triphenyl- or tributylphosphine promotion of reactions between primary amines and hexane-1,6-diol[10,11] at 180 °C under an inert atmosphere. This gives reasonable, somewhat variable, yields of 1-substituted azepanes: in general, $RuCl_3.3H_2O + Ph_3P$ is advised for aromatic amines, whereas $RuCl_3.3H_2O + Bu_3P$ is favoured for reactions involving aliphatic amines. A further useful development demonstrated the use of hexane-1,2,6-triol which gave passable

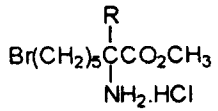
yields of 3-hydroxy-*N*-arylazepanes **7**, but unfortunately failed for benzylamine and furfurylamine.[12]

2. Cyclisation of 1,6-Haloamines and Related Molecules

This has been a popular and successful approach which could be regarded as a stepwise variation of the previously discussed direct reaction of 1,6-dihalohexanes with amines. The first and relatively inefficient preparation of azepane,[13] later improved,[1] involved treating 1,6-haloamines with aqueous alkali, but the modification involving cyclisation of 6-bromo-*N*-tosylamine (**8**) to *N*-tosylazepane (**9**, R = tosyl) was an improvement.[14]



(8) (9)



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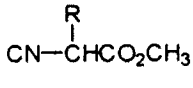
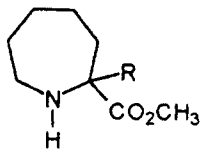


(11)



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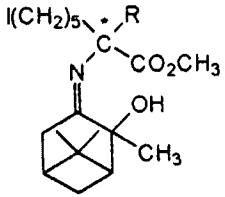
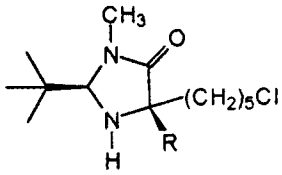


(13)



(14)

Access to useful intermediate bromoamino esters (**10**, R = CH_3, Ph, CH_2Ph) was gained by reaction of 1,5-dibromopentane with the isocyano esters (**11**, R = CH_3, Ph, CH_2Ph) and sodium hydride followed by treatment with hydrochloric acid. Cyclisation was effected with triethylamine, the overall yields of azepane esters (**12**) were good and the corresponding amino acids were obtained in good to excellent yield by alkaline hydrolysis.[15]

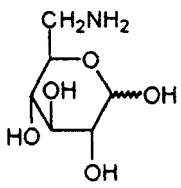
The amino acids **6** (R = H, CH_3, C_2H_5) have been obtained by cyclising the acyclic haloamino acids **5** (X = Cl, Y = NH_2, $NHCH_3$, NHC_2H_5 etc.) by boiling aqueous solutions of their alkali metal salts for 10 h along with some potassium iodide (~10%).[16] However, this approach did not appear to offer advantages over the direct method alluded to previously.[8] A chiral version has been reported[17] in which the chiral haloamino esters required for cyclisation (NaH/THF/RT) (RT = room temperature) were obtained by chirally induced substitution on imines **13** using (−)-2-hydroxypinan-3-one. The enantiomeric excess (ee) obtained was better than 95% in products **12**; in the case of **12** (R = CH_3) the absolute configuration was considered to be R.

Another interesting chiral synthesis proceeded by cyclisation on to a chiral imidazolidinone (**14**): aqueous acid treatment of the bicyclic product removed the auxiliary and provided the (*S*)-2-methylazepine-2-carboxylic acid (acid from **12**, R = CH_3).[18]

The electrophilic alkyl halide component of these cyclisations can be replaced by an alcohol. Thus amino alcohols **15** (R = CH_3, C_2H_5, C_3H_7, C_4H_9) were transformed into the respective azepanes (**9**) by heating over alumina at 275 °C.[19] On occasion the alcohol portion required for cyclisation has been

$RNH(CH_2)_6OH$

(15)



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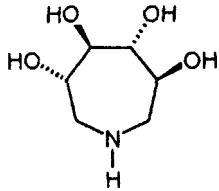

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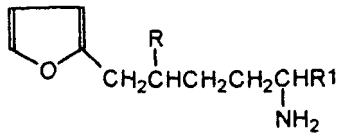
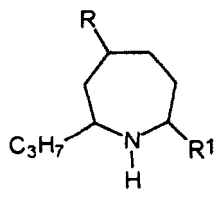


(18)

generated *in situ* from a carbonyl component. For example, catalytic hydrogenation of 6-amino-6-desoxy-D-glucose (**16**) yielded the tetrahydroxyazepane (**17**).[20] The equivalence of furans to 1,4-diones has been exploited by catalytic (H_2/Pt–C/220 °C) reduction of some furan amines (**18**, R, R^1 = H or CH_3) which led to 2-propylazepanes (**19**, R, R^1 = H or CH_3).[21]



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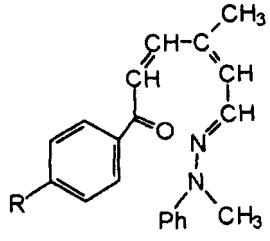

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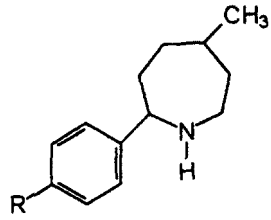
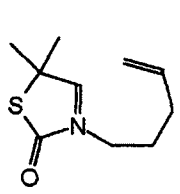


(21)

A further variation on this theme allowed reductive cyclisation of keto hydrazones (**20**, R = H, OCH_3) over nickel to produce 2-arylazepanes (**21**, R = H, OCH_3).[22]

The electrophilic iminium ion cyclisation technique of Hamersma and Speckamp[23,24] has been adapted most ingeniously for synthesis of azepinothiazolidine compounds (e.g. **23** from **22**) from which sulphur removal leads to azepane **24**.[25]



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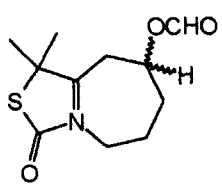

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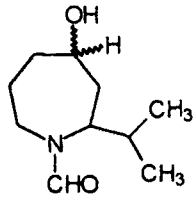
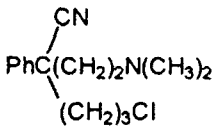


(24)

Cyclisation of ω-halo-tertiary amines leads to the production of cyclised quaternary salts: this approach has been extensively exploited for azepane synthesis, particularly in connection with the search for analgesic substances.



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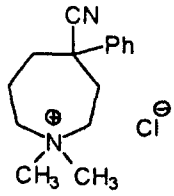

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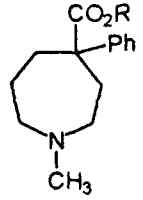
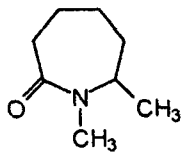


(27)

The latter requirement provided the stimulus for syntheses of 3,3- and 4,4-disubstituted azepane derivatives. Accordingly the haloamine **25** (available by sequential alkylations of phenylacetonitrile) on heating gave **26**, which was demethylated on pyrolysis[26] to the corresponding 4-cyano-4-phenyl-1-methyl-azepane from which various esters (**27**) became accessible. In similar fashion, many analogous materials have been obtained.[27–30]

3. Reduction of Caprolactams and Other Ketoazepanes

This is arguably the most popular method for obtaining azepanes. Caprolactams (Chapter 3, Section I) being widely available, their chemistry, including various reductive processes, has been well studied. The reagent of choice for direct reduction of the lactams is $LiAlH_4$ and it was used more than 40 years ago for conversions (**28** → **29**,[31] **30** → **31**,[32] **32** → **33**[33]).



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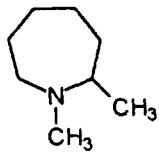

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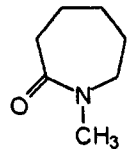

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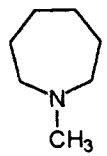

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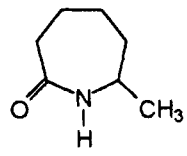

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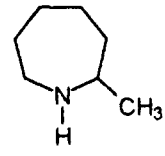
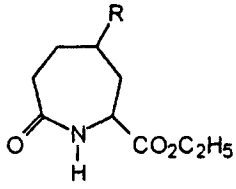


(33)

Simultaneous or consecutive reduction of two carbonyl functionalities is known: thus the lactam-ester **34** (R = H) was converted into the hydroxymethyl azepane **35** (R = H).[34] In another example the conversion **34** → **35** (R = Ph) allowed access eventually to a homobenzomorphan (**36**).[35]



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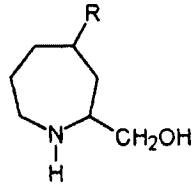

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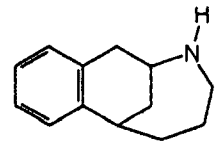

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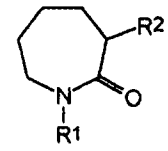
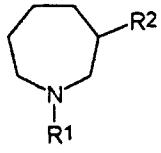


(37)

Since caprolactams can be alkylated at C-3, subsequent $LiAlH_4$ reduction of the products makes 3-substituted azepanes available. Thus alkylation of caprolactam gave **37** ($R^1 = CH_2Ph$, $R^2 = CH_3$)[36] and **37** ($R^1 = CH_3$, $R^2 = CO_2C_2H_5$,[37] which on reduction yielded **38** ($R^1 = CH_2Ph$, $R^2 = CH_3$ and $R^1 = CH_3$, $R^2 = CO_2C_2H_5$, respectively). A variation on this theme involves exploitation of the 2,3-diketoazepane **39** (from caprolactam), which underwent Grignard addition at C-3 followed by reduction to give **40**.[38]



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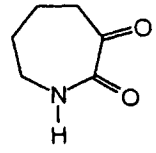

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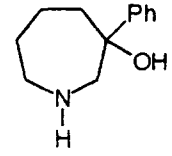
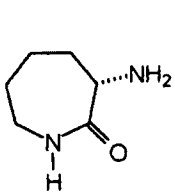


(40)

$LiAlH_4$ reduction of chiral lactams produces chiral azepanes. The former have been obtained either by direct cyclisation as in the case of methyl L-lysinate, which led to **41**,[39] or by Beckmann rearrangement of a chiral oxime (**42**),[40] which gave **43**. Reductions proceeded to **44** and **45**, respectively, in fair optical purity.



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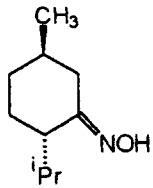

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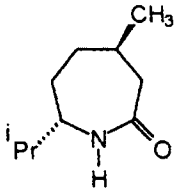

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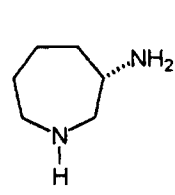

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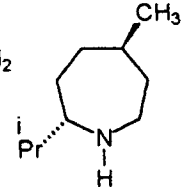
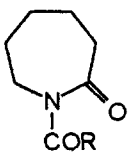


(45)

Sodium borohydride in acidified ethanol is known to reduce caprolactams to 2-ethoxyazepanes[41] provided the nitrogen atom was protected as a urethane, that is, lactams **46** (R = OC_2H_5, OCH_2Ph, O^tBu) gave the products **47** (R = OC_2H_5, OCH_2Ph, O^tBu) at −6 to 0 °C. This method complements those generally employed for these synthetically useful substances via imides[42] or by anodic oxidation.[43] Thus displacement of the ethoxy group at C-2 could be effected by various nucleophiles leading to structures **48** (R = CN, N_3 and 3-indolyl).[44]



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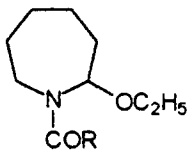

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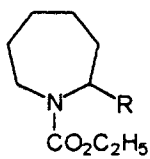

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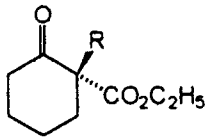

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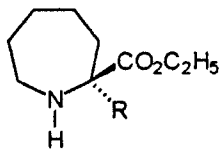
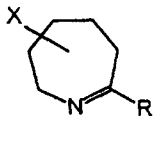


(50)

Reduction of caprolactams using a borane–dimethyl sulphoxide combination has been reported.[45] Capitalising on the successful Schmidt reaction on chiral β-keto esters (**49**), the authors reduced the chiral products (lactams) to chiral azepane esters (**50**, R = $PhCH_2$, etc.; see Table 1) in generally good optical purity.

Very useful preparations of both 2-alkyl- and 2,2-dialkylazepanes have arisen from the work of Yamamoto and co-workers, who have studied combined Beckmann rearrangement–reductive alkylation protocols applied to the *O*-sulphonyl derivatives of cyclohexanone oximes.[46–48] In the first place it was



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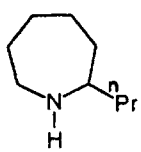

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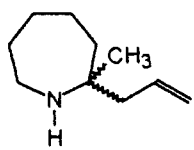

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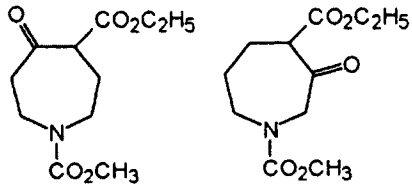

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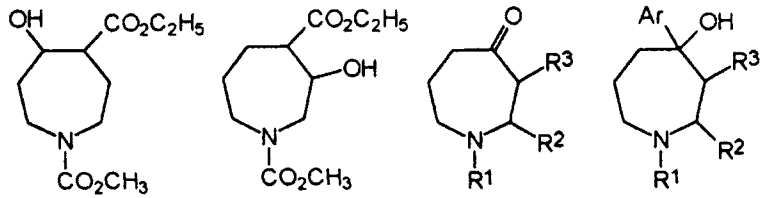
shown that trialkylaluminium reagents converted oxime sulphonates to tetrahydroazepines alkylated at C-2 (**51**), which were reduced *in situ* by diisobutylaluminium hydride. A full recipe has been published for the case of 2-propylazepane (**52**).[49] It was furthermore demonstrated that if simple Grignard reagents in non-polar solvents replaced $^{i}Bu_2AlH$ in this sequence, then the products were 2,2-dialkylamines.[50] This has the clear advantage of giving access to substitution by two different alkyl groups (e.g. **53**). It has long been known that caprolactams react with Grignard reagents to give 2,2-homodisubstituted azepanes.[32b]

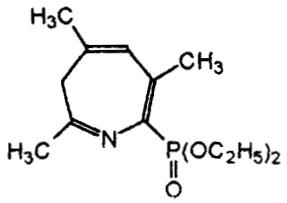
Other azepanones have been reduced to azepanes. For example, the β-keto esters **54** and **55** have been catalytically hydrogenated over Raney Ni to give the corresponding hydroxy esters (**56**, **57**)[51] and several 4-ketoazepanes (**58**) have been reacted with aryllithium or -magnesium reagents to yield products (**59**) of pharmacological interest.[52]



(56) (57) (58) (59)

4. Reduction of Azepines and Dihydro- and Tetrahydroazepines

The catalytic hydrogenation of azepines has been used on several occasions, principally to demonstrate that these molecules contained three double bonds in a seven-membered cyclic assembly. This was particularly useful in the early days of azepine synthesis by nitrene insertion to benzene by photolytic and thermal means.[53–55] The ring expansion work of Johnson and co-workers (Chapter 8) was supported by evidence obtained by catalytic hydrogenation.[56,57] All of these involved reduction of [1*H*]azepine derivatives, but the [3*H*]azepine **60** has also been likewise reduced to the azepanyl phosphonate **61**.[58] Catalysts used have usually been platinum or palladium supported on carbon or occasionally Adam's platinum oxide.



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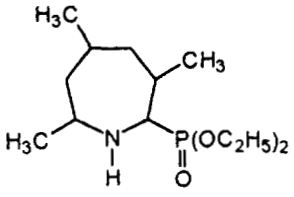

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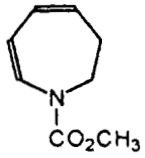

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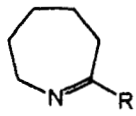
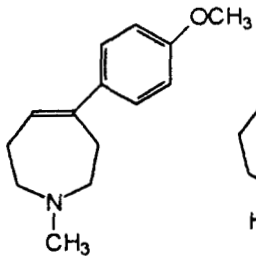


(63)

Not surprisingly, dihydroazepines (e.g. **62**) can be reduced catalytically[59] and several examples of tetrahydroazepine hydrogenations are known. Both 2-alkyl-[60] and 2-aryl-[61] 3,4,5,6-tetrahydro[2*H*]azepines (**63**, R = alkyl, aryl) have given substituted azepanes, as have 2,3,6,7-tetrahydro[2*H*]azepines (**64**[62] and **65**[51,63]). 2,3,4,7-Tetrahydroazepine (**66**) was both reduced and hydrolysed using palladium on charcoal.[72]



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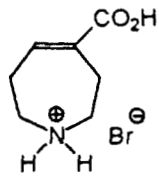

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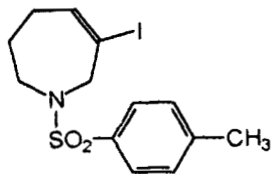


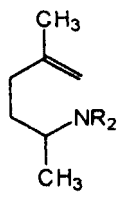
(66)

Nitrones (e.g. *N*-oxide of **63**) prepared recently by hydroxylamine–alkyne cyclisations (Chapter 5, Section IV) react with Grignard reagents (e.g. vinylmagnesium bromide) to give 2,2-disubstituted *N*-hydroxyazepanes[234,235] which are convertible to azepanes with $TiCl_3$.

5. C–C Bond Cyclisations

Syntheses of azepanes by cyclisations involving carbon–carbon bond formation are of relatively recent origin for the most part. Apparently Cope and Burrows[64] were the first to recognise that iminium ions generated during

'Clarke–Eschweiler' methylation could lead to azepanes. In this way the alkenamine **67** (R = H) treated with formaldehyde and formic acid yielded the azepane **68** in 39% yield, along with the expected *N*,*N*-dimethyl starting



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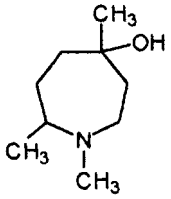

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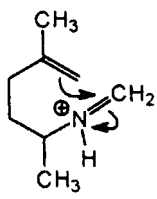

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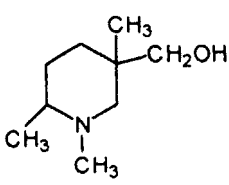
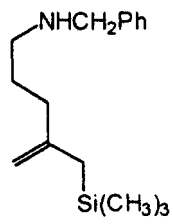


(70)

material (**67**, R = CH_3). This cyclisation would appear to proceed via the iminium ion **69** in the *endo* mode; it is surprising that none of the alternative *exo* mode product (**70**) was found. Twenty years later[65] a similar type of reaction was applied (CH_2O/CF_3CO_2H) to the silylamine **71** to give a very good yield of the azepane **72**. An alkynylsilane (**73**) was also shown[66] to participate via an iminium ion, leading to the interesting allenic structure **74**.



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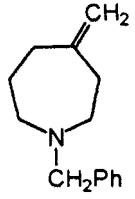

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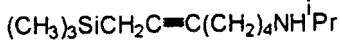

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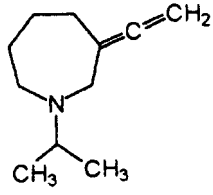
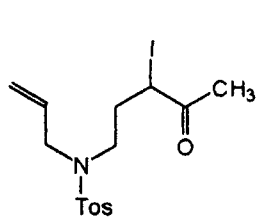


(74)

Palladium chemistry has helped in promoting radical-like cyclisations of α-halo esters and ketones. Thus the iodoketone **75** gave the *N*-tosyl azepanes **76** along with isomeric piperidines (**77**) using $Pd(PPh_3)_4$ (10%) in dioxane at room temperature.[67] The radical-like features of this type of reaction were revealed by Curran and Chang,[68] who demonstrated that identical product mixtures were obtained from unsaturated α-iodocarbonyls using either Pd^0 or $(Bu_3Sn)_2$; compound **78** along with several others was isolated from the iodo



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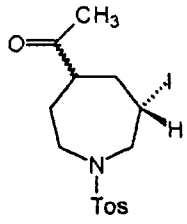

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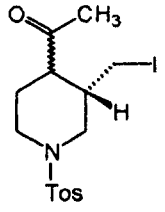

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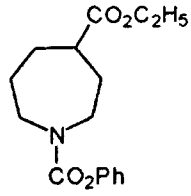

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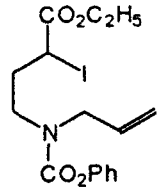
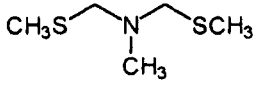


(79)

ester **79**. As yet these interesting studies could not be said to constitute viable syntheses for medium-scale work.

A [4 + 3] reaction is known[69] whereby the bis(methylthiomethyl)amine **80** reacted with diketene silyl acetal (**81**) in the presence of trimethylsilyl triflate to give an acceptable (63%) yield of the azepane **82**.



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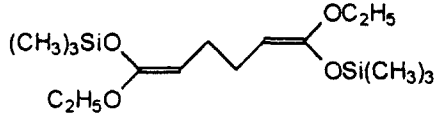

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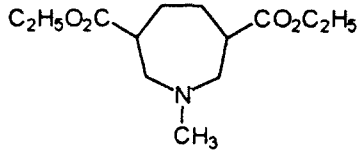
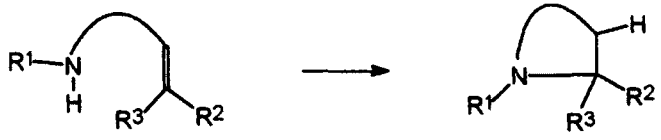


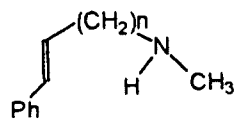
(82)

6. C–N Bond Cyclisations

In this section we consider processes which are effectively described as intramolecular hydroamination:



Photochemically induced versions are known: styrylamines (**83**; $n = 4$, 5) give azepanes but not as major products. Thus **83** ($n = 4$) did give **84** especially in



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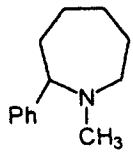

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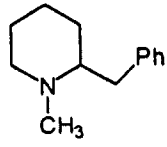

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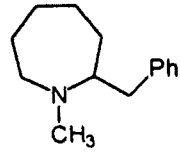
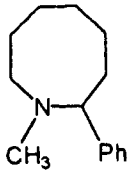


(86)

acetonitrile solution but the major product was the piperidine **85**.[70] Perversely **83** ($n = 5$) showed a reversal of these ratios, the azepane **86** being a minor product detected with the azocine **87**. One of the products formed by irradiating **88** was the azepane **89** (35%).[71] However these processes do not yet have the status of useful syntheses.



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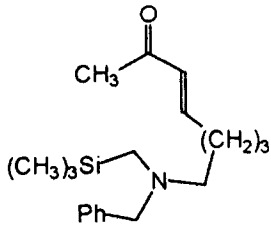

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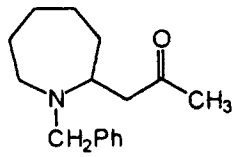

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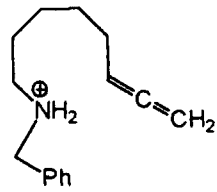
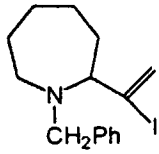


(90)

Allenic amines are showing some promise. Treatment of the allenic salt **90** with I_2 in CH_2Cl_2 followed by triethylamine gave the product **91** in 20% yield.[72] Cyclisation of the base (from **90**) was effected using $PdCl_2(PhCN)_2/CO/MeOH/Et_3N$, the product (**92**) being obtained in 23% yield.[73,74]. The *N*-tosyl analogues



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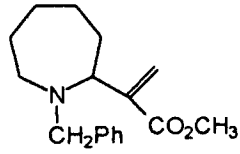

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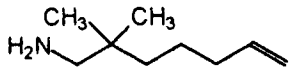

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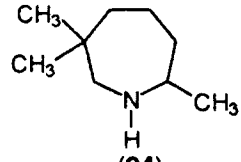
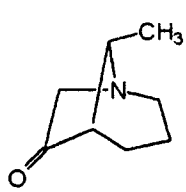


(94)

could not be cyclised. An organolanthanide-induced cyclisation of the alkenamine **93** to the azepane **94** has been reported;[75] hopefully this type of process could be adapted for working on a moderate scale.

7. Ring Contractions and Fragmentations

Some interesting azepane structures have been reported arising from the above approaches. The 1-aza[3.2.1]bicyclooctanone **95** (originating from the diester **96**) was reduced (Wolff–Kishner) and subjected to Hofmann degradation



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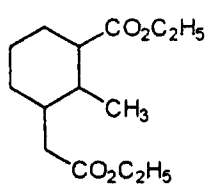

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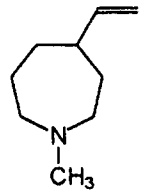

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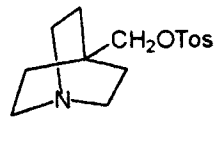
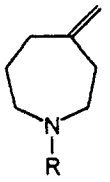


(98)

(MeI/Ag_2O) to give the 4-vinylazepane **97**, which was converted into several other azepanes.[76] The tosyloxy quinuclidene **98** underwent fragmentation with alkali yielding the methylene azepanes **99** (R = H, CH_3).[77]



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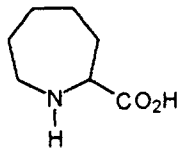

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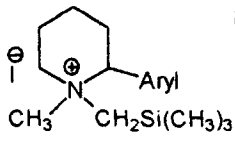

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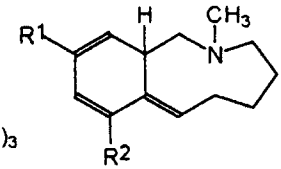
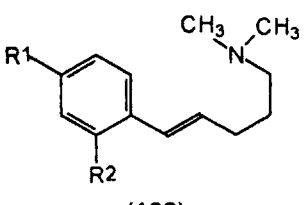


(102)

Favorskii rearrangement of α-halolactams allowed access to several cyclic α-amino acids including the azepane acid **100**.[78,79] Certain 2-arylpiperidinium methylides, generated from silanes **101** by CsF treatment, yielded interesting structures (**102**, R^1, R^2, various: H, CH_3, OCH_3), thermolysis of the latter generating mainly styrylamines (**103**) with azepanes (**104**) as the minor products, produced presumably by a Stevens type of rearrangement.[80]



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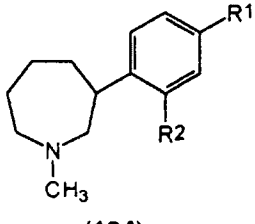

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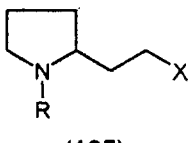

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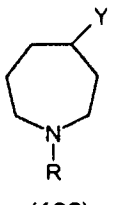
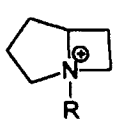


(106)

8. Ring Expansion Processes

The earliest example of pyrrolidine ring expansion dates from 1964 when it was shown[81] that the haloamine **105** (R = CH_3, X = Cl) reacted with nucleophiles

(OH^-, NH_2CH_2Ph) to give some of the normal displacement products **105** (R = CH_3, X = OH or $NHCH_2Ph$) along with azepanes **106** (R = CH_3, Y = OH or $NHCH_2Ph$). It was considered that these reactions involved the azetidinium ion (**107**, R = CH_3).



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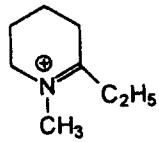

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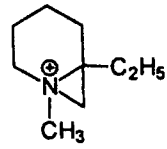

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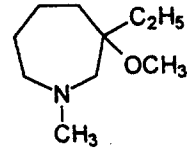
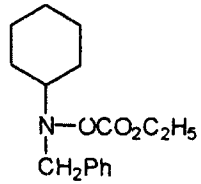


(110)

More recently, a thermal version has been reported in which radicals are implicated. Thus, conversion of the alcohol **105** (R = CH_2Ph, X = OH) to certain thiono- and dithionocarbonates (e.g. **105**, R = CH_2Ph, X = OCS.OPh, OCSSPh) allowed thermal reactions to proceed which relied on the ease of carbonyl sulphide (COS) elimination. This led to the production of azepanes (**106**, R = CH_2Ph, Y = OPh or SPh) probably via the ion **107** (R = CH_2Ph): again pyrrolidine derivatives (**105**, R = CH_2Ph, Y = OPh or SPh) intruded.[82]

Expansion of the tetrahydropyridinium salt **108** through the aziridinium salt **109** gave the 3-substituted azepane **110**.[83] The extensive researches of Yamamoto and co-workers into organoaluminium reagents uncovered a ring expansion/nitrogen insertion reaction involving hydroxylamine carbonates.[84] For example, the carbonate **111** reacted with the appropriate organoaluminium



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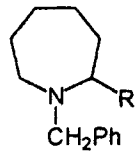

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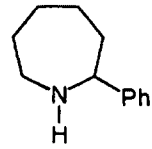


(113)

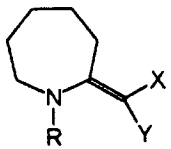
reagent (R = CH_3 or $^nBuC{\equiv}C$) giving azepanes (**112**, R = CH_3 or $^nBuC{\equiv}C$) in good yields.

As discussed in Section 3, derivatives of cyclohexanone oximes undergo Beckmann rearrangement/reduction in 'one-pot' processes which overall could be regarded as ring expansions. In addition to those already mentioned,[45–60] we should comment here on the fact that azepanes have been found, along with several other products, when a number of cyclohexenone oximes were treated with $LiAlH_4$.[85] Indeed, oximes themselves have been subjected to the trialkylaluminium/diisobutylaluminium hydride protocol previously (Section 3) described for oxime sulphonates. In this way oxime **42** gave the azepane **45**, although no figure was given for the optical rotation.[46] A variation is known in which the mesyl derivative of cyclohexanone oxime can be

treated sequentially with diethylaluminium iodide, phenylmagnesium bromide and diisobutylaluminium hydride to give an 81% yield of 2-phenylazepane (**113**).[86] Aluminium hydride has also been shown to induce ring expansion/reduction of the *O*-methyl ethers of cyclohexenone oximes.[87,88]

9. Alkenyl-Substituted Azepanes

2-Alkenyl-substituted azepanes (**114**) have received a good deal of attention, partly because of their accessibility and partly for their synthetic utility and structural relation to biologically active molecules.[89]



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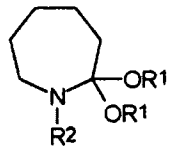

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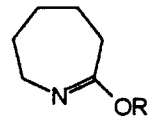

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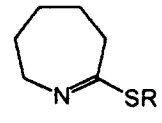

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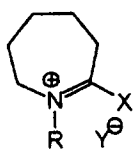
Caprolactam acetals (**115**, $R^1 = CH_3$, C_2H_5) react with various activated methylene compounds such as malonates, β-keto esters and 1,3-diones, the products (**114**) being generally obtained in fair to good yield.[89–96] Enol ethers (**116**) have also been used;[96] this reaction may be promoted by piperidinium acetate,[97] although catalysis by nickel salts seems now to be favoured.[98–100] Thio analogues (**117**) appear to be more reactive; they give products (**114**) with activated methylene compounds in presence of triethylamine[101] or pyridine.[102] In some cases, heating the components together brings about the formation of products **114**; in this respect malononitrile is particularly reactive.[103] Iminium salts (**118**, R = CH_3, CH_2Ph; X = OCH_3, SCH_3, Cl) have been shown to react with Meldrum's acid in the presence of triethylamine giving the useful products **119**.[104,105]



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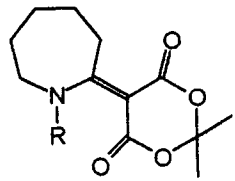

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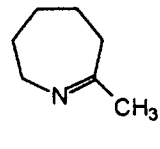

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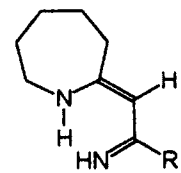
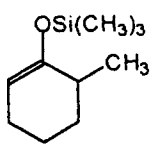


(121)

It is possible to deprotonate (LDA) the tetrahydroazepine **120** and to react the anion so formed with nitriles to yield azadienes (**121**, R = Ph or cyclohexyl).[106] In the presence of diethylaluminium chloride, silyl enol ethers react with cyclohexanone oxime mesylates giving 2-alkenylazepanes. For example, silyl enol ether **122** reacted with cyclohexanone oxime mesylate **123** providing the product **124** in 82% yield.[107]



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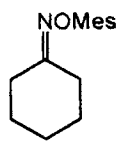

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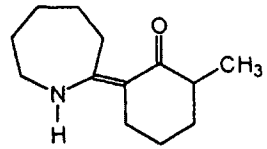

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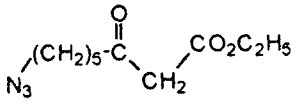

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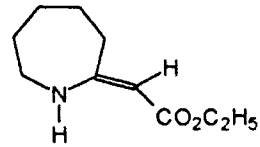
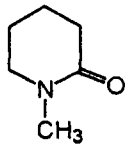


(126)

An interesting intramolecular aza-Wittig Reaction is recorded;[108] for instance triphenylphosphine treatment of the diketoazide **125** gave the 2-alkenylazepane



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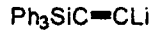

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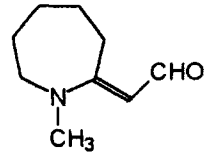

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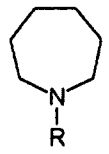
126. When piperidone **127** reacted with lithium triphenylsilylacetylide (**128**), a ring expansion reaction ensued;[109] the structure of the product was later corrected[110] to **129**.

PROPERTIES AND REACTIONS

Azepanes, as one would expect, are moderately strong bases, forming stable salts such as hydrochlorides, picrates, fumarates and hydrobromides. The tertiary bases (*N*-alkylazepanes) also form methiodides. pK_a values have been recorded for azepane (10.30),[156] *N*-methylazepane (10.19) and *N*-propylazepane (10.45).[111] The azepane bases are, in general, stable distillable liquids, oils or low-melting solids (see tables). Bifunctional bases have been shown to form metal complexes; for example, 3-aminoazepane (**38**, $R^1 = H$, $R^2 = NH_2$; and **44**) forms Cu^{2+} complexes[39] and 1-azepanylacetic acid (**9**, $R = CH_2CO_2H$) forms Pd^{2+} and Pt^{2+} complexes.[112] *N*-Alkylation of *N*-unsubstituted azepanes is easily brought about by reaction with alkyl halides in the presence of Et_3N[113] or sodium hydroxide solution.[114] Acylation is also carried out using Et_3N[113] and sulphonation using pyridine.[61] *N*-Unsubstituted azepanes take part in the usual Michael-type additions with acrylonitrile[115] or ethylene sulphide[116] giving **9** ($R = CH_2CH_2CN$ and CH_2CH_2SH, respectively). Reaction of azepane with



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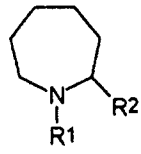

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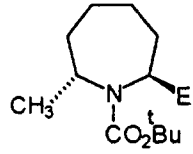

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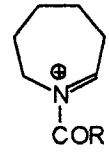


(132)

hydrogen peroxide gave the hydroxylamine (**9**, R = OH).[117] *N*-Arylation has been achieved by use of benzynes[118] or with *o*- or *p*-nitrohalobenzenes.[119]

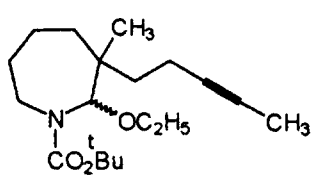
1. Substitution at 2-Position

This area has been extensively investigated. Seebach *et al.*[120] showed that *N*-nitrosoazepane (**9**, R = NO) could be deprotonated at C-2 (LDA/THF/−80 °C) and reacted with electrophiles; for example benzophenone gave **130** [R^1 = NO, R^2 = $CH(OH)Ph_2$]. In a similar vein, Meyers and co-workers demonstrated that t-butylformamidines (**9**, R = $CH{=}N^tBu$) could be deprotonated (^{n}BuLi) and reacted with electrophiles (PhSeSePh, $ClCO_2CH_3$, n-heptyl and n-propyl) to yield the corresponding 1,2-disubstituted azepanes (**130**, R^1 = $CH{=}N^tBu$, R^2 = PhSe, CO_2CH_3, C_7H_{15}, C_3H_7). Removal of the *N*-protecting groups (KOH/CH_3) gave 2-substituted azepanes in acceptable yields.[121,122] The *N*-t-butoxycarbonyl group has also been shown to fulfil a similar role: in this case **9** (R = $CO_2{}^tBu$) reacted in diethyl ether with sec-butyllithium/TMEDA and then treatment with dimethyl sulphate gave the product (**130**, R^1 = $CO_2{}^tBu$, R^2 = CH_3); alternatively, addition to the lithio salt of DMF led to isolation of **130** (R^1 = $CO_2{}^tBu$, R^2 = CHO).[123] Interestingly, repetition of this protocol can provide 2,7-disubstituted azepanes in which the substituents are mutually *trans* [**131**, E = CH_3, $Si(CH_3)_3$ and CHO].[123] It had previously been shown[124] that tributyltin chloride participated in these reactions leading to the isolation of **130** (R^1 = $CO_2{}^tBu$, R^2 = Bu_3Sn). It has been pointed out that the successful lithiation of all of these *N*-substituted azepanes depends upon the formation of dipole-stabilised carbanions.[120–125] The *o*-iodobenzyl group [in **9**, R = $CH_2C_6H_4I(o)$] has been used in samarium iodide-mediated C–C bond formation: thus, reaction with pentan-3-one led to **130** [R^1 = *o*-iodobenzyl, R^2 = $C(OH)(C_2H_5)_2$].[125]

Anodic electrolytic oxidation of *N*-formyl- and *N*-acetylazepanes has proved to be a very fruitful operation.[126,127] The products are C_2-alkoxy-*N*-formyl- or -*N*-acetylazepanes (**130**, R^1 = CHO, $COCH_3$, R^2 = OCH_3 or OC_2H_5) depending on which alcohol was employed. These methoxy- or ethoxyazepanes can be perceived as precursors to *N*-acyl iminium salts (**132**) and, as such, react with nucleophiles *in situ* giving C-2-substituted products; usually $AlCl_3$ has been used as promoter. In this way arenes and β-keto esters have been made to react giving a variety of products [**130**, R^1 = CHO,

R^2 = aryl or $XC(CO_2C_2H_5)COY$] which are listed in the tables.[128–131] This type of protocol has been extended to the production of 2-alkynylazepanes using bis-trimethylsilylacetylene.[132–134]

Intramolecular versions of *N*-acyliminium ion reactions have allowed cyclisations to be developed. Thus several 3-alkenyl- and alkynylalkyl-substituted 2-ethoxyazepanes have been cyclised under the influence of $SnCl_4$ at −23 °C (e.g. **133** → **134**).[135] The required iminium ions have also been reached by a decarboxylative process:[136] acid **135** was treated with $POCl_3$ at 100 °C to yield the 1-azabicyclo[5.4.0]undecane **136**.



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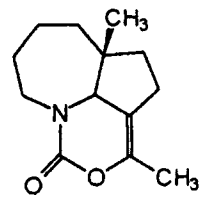

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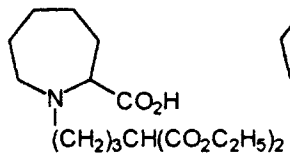

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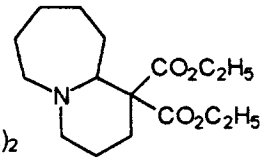

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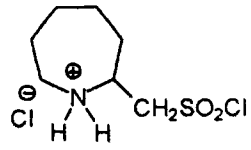
2. Annulation to the Azepane Ring

In addition to the intramolecular iminium ion cyclisations referred to above, there are only a few other examples of ring annulation to azepanes. Thiazetidine dioxide (**138**) was isolated when sulphonyl chloride hydrochloride **137** was treated in chloroform with ammonia at 0 °C.[137] A Dieckmann cyclisation



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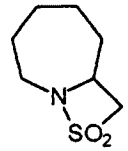

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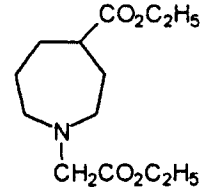

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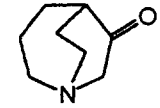
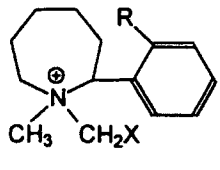


(140)

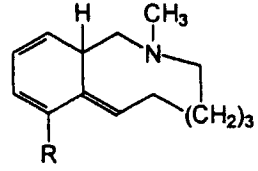
applied to the diester **139** was reported to give (after hydrolysis) the expected ketone (**140**); unfortunately, no experimental details were provided.[138]

3. Ring-Expansion, Contraction or Fission

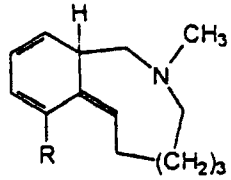
Certain ylids (**141**, R = H or CH_3, X = −), obtained by desilylation of **141** [R = H or CH_3, X = $Si(CH_3)_3$] by CsF in DMF, led to a mixture of products (**142** and **143**) which reacted with KOH or HCl giving **144** (R = H or CH_3).[139]



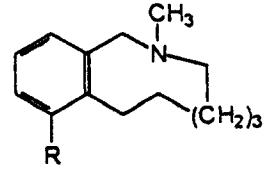
(141)



(142)

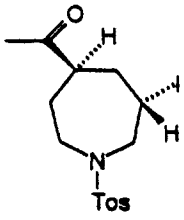


(143)

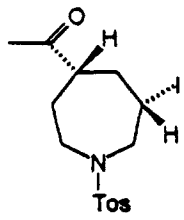


(144)

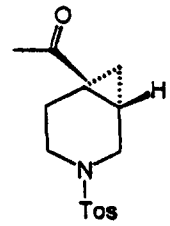
On the other hand, a contraction was seen when compound **76a** was treated with DBU in benzene at room temperature. The product (**145**) was also



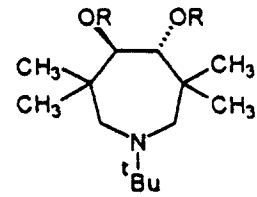
(76a)



(76b)



(145)

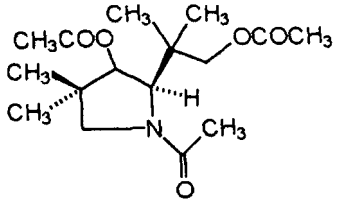


(146)

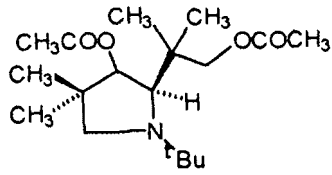
obtained from **76b** but more slowly and in poorer yield. The *cis*-isomer of **77** also provided **145** on treatment with DBU or KOtBu.[67]

It has been reported that the *trans*-diol **146** (R = H) or its acetate (R = CH_3CO) undergo ring contraction to **147** and **148** on treatment with various acetic acid/acetic anhydride combinations,[140] depending upon the temperature used. Compound **148** was shown to lie on the path between **146** and **147** and a plausible mechanism (involving **149**) was suggested.[140]

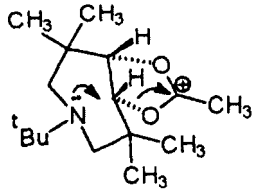
The N–C-2 bond of some azepanes has been shown to be vulnerable. Thus, when compound **150** was treated with methyl iodide, one of the products was



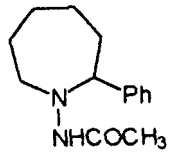
(147)



(148)

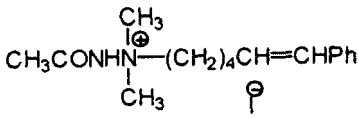


(149)

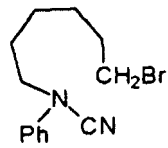


(150)

a ring-opened salt (**151**).[141] Not surprisingly, *N*-phenylazepane[142] reacted with cyanogen bromide to give the bromocyanide **152**.



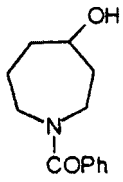
(151)



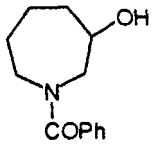
(152)

4. Oxidation

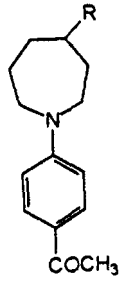
The azepane ring appears to be stable to oxidation by permanganate, **97** being oxidised at the side-chain alkenyl group to yield the corresponding *N*-methylazepane-4-carboxylic acid (**106**, R = CH_3, Y = CO_2H).[76] Biological oxidation



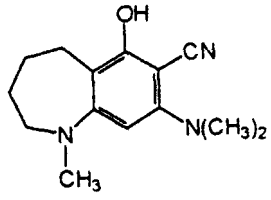
(153)



(154)



(155)



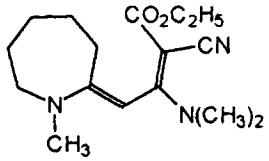
(156)

using a strain of *Beauveria sulfurescens* has been reported by two groups of workers.[143,144] *N*-Benzoylazepane (**9**, R = PhCO) yielded a mixture of 4- and 3-hydroxy compounds (**153** and **154**),[143] while **155** (R = H) gave the alcohol (**155**, R = OH) in good yield.

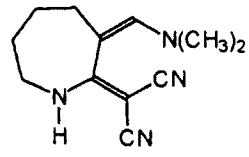
5. 2-Alkenylazepanes

The ready availability of these compounds has allowed their chemistry to be thoroughly investigated. Protonation occurs on the exocyclic carbon atom (β-atom of an enamine) as one might expect.[93] In a few cases, the precise stereochemistry of the compounds **114** has been established:[93,100,148] however, it is well known that isomerisation is facile, particularly with heating, especially in cases where neither X nor Y (in **114**) is hydrogen.[93] In Table 4, we present the structures of 2-alkenylazepanes as recorded in the literature, but their accuracy cannot be guaranteed.

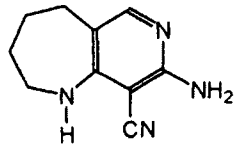
2-Alkenylazepanes have proved useful for annulation of other rings on to the azepane. A 1-benzazepine (**156**) arose when **157** was heated[95] and treatment of



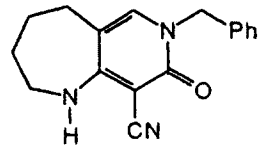
(157)



(158)



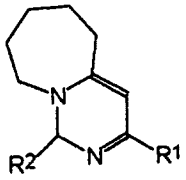
(159)



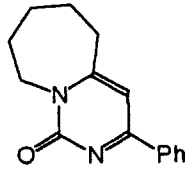
(160)

158 with ammonia in a bomb yielded the pyrimido[3,4-*b*]azepine structure (**159**);[96] a variant of the latter[145] gave **160**.

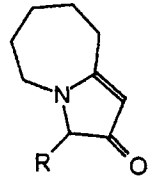
Pyrimido[1,6-*a*]azepines (**161**, R^1 = Ph, cC_6H_{11}; R^2 = *p*-tolyl, ^{i}Pr, ^{i}Bu) were prepared from compounds **121** and aldehydes under the influence of



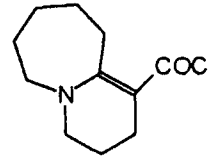
(161)



(162)



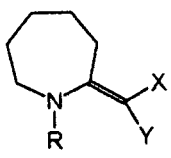
(163)



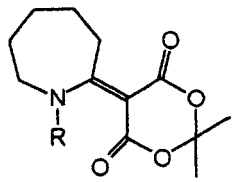
(164)

$BF_3(C_2H_5)_2O$;[106] alternatively a pyrimidine structure (**162**) can be obtained from **121** using 'triphosgene' ($Cl_3COCOOCCl_3$).[106] Meldrum's acid derivatives (**119**) have proved very useful. Thus, flash vacuum pyrolysis of **119** (R = CH_3, CH_2Ph) gave the pyrroloazepine **163** (R = H, Ph),[105] whilst compound **119** [R = $(CH_2)_3Cl$] produced the acid chloride **164**, which could be converted

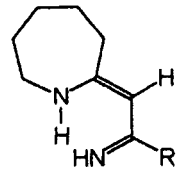
further.[146] Furthermore, pyrolysis of Meldrum's acid derivative **119** (R = H) in the presence of alcohols, ethanethiol and diethylamine yielded other alkenylazepanes [**114**, R = X = H, Y = CO_2R, $COSC_2H_5$, $CON(C_2H_5)_2$].[147] *N*-Methyl analogue **119** (R = CH_3) gave similar results.[104]



(114)



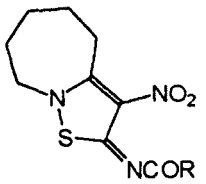
(119)



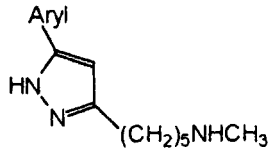
(121)

Alkylation (CH_3I/K_2CO_3) of **114** (R = X = H, Y = $CO_2C_2H_5$) yielded exclusively **114** (R = H, X = CH_3, Y = $CO_2C_2H_5$)[148] and acylation with both aliphatic and aromatic acid chlorides gave products **114** (R = H, X = $CO_2C_2H_5$, Y = CH_3CO, $CH_3CH_2CH_2CO$, PhCO).[149] Decarboxylation of the latter proceeds in fair to good yields using boric acid.[99]

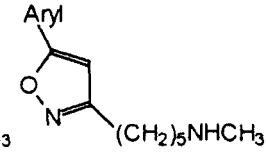
Isothiazolo[2,3-*a*]azepines (**165**, R = Ph, OC_2H_5) were shown[150,151] to arise when isothiocyanate adducts (**114**, R = H, X = NO_2, Y = CSNHCOR) were



(165)



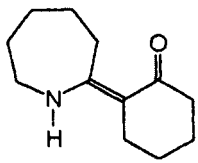
(166)



(167)

treated with bromine in chloroform or acetic acid. Pyrazoles or isoxazoles arose by reaction of certain alkenylazepanes (**114**, R = CH_3, X = COAryl, Y = H) with hydrazines or hydroxylamine. Thus **166** and **167** were obtained.[90]

Long-chain ω-amino acids were obtained by treating ketoenamines with aqueous sodium hydroxide.[152] When this useful protocol was applied to the



(168)

$H_2N(CH_2)_5CO(CH_2)_5CO_2H$

(169)

alkenylazepane ketone **168**, the product **169** was obtained in 77% yield; reduction (Wolff–Kishner) of the carbonyl group allowed the isolation of the ω-amino acid [$NH_2(CH_2)_{11}CO_2H$] in 93% yield.

Table 1. Mono-*N*-substituted azepanes

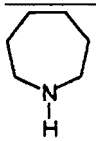
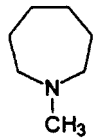
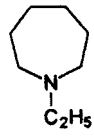
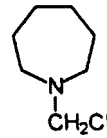
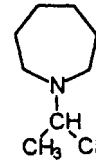
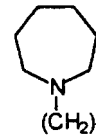
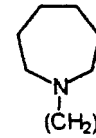
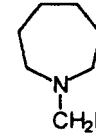
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			n_D^{23} 1.4654	153
	138–138.2/~760			154
	136/~760	HCl 235–236(d) Picrate 144.5		155
	136–137		n_D^{20} 1.4658	33
	146/~760	Picrate 202		156
	138–140/748	Picrate 217		32a
		HCl 180.5–182.5		157
		CH_3I 265		2
	90.5–91.5/90	Picrate 173–173.5	n_D^{20} 1.4571	158
	153.5/741	CH_3I 244.5–245.5(d)		
	107	Picrate 173	n_D^{23} 1.4541	19
	176–177		n_D^{20} 1.4555; d^{20} 0.8417	159
	102.5/77.5	Picrate 92.5	n_D^{23} 1.4538	19
			No data	160
	196–197		n_D^{20} 1.4573; d^{20} 0.8432	159
	94–95/13	HCl 217–218	n_D^{25} 1.4551	4
	130–132/12	HCl 158.5–159.5	n_D^{25} 1.5243	4
		HCl 163–165		115
	75/0.25		^1H, ^{13}C NMR, MS	9

Table 1 (continued)

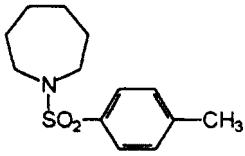
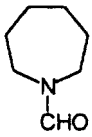
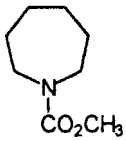
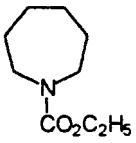
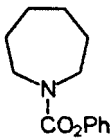
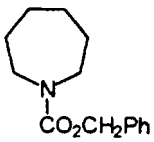
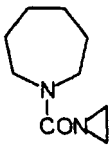
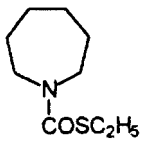
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	75 164/0.3			14
	102–103/5 127–130/23		n_D^{25} 1.4886 n_D^{20} 1.4903	117 162
	120–121/30 96–97/13		^{1}H NMR, IR	59 163
	46–49/0.1 118–120/20		n_D^{25} 1.4622 n_D^{21} 1.4635, IR	55 53, 54
	128–130/0.6		n_D^{25} 1.5328, IR	55
	Vac. dist.		^{1}H, ^{13}C NMR, MS	123
	114/3	HCl 104		113
	136.5–137		n_D^{25} 1.5156	164

Table 1 (continued)

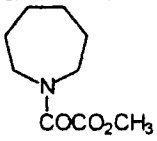
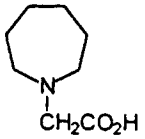
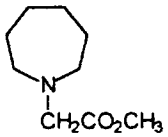
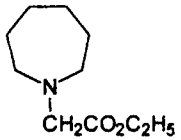
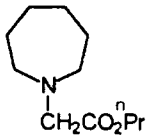
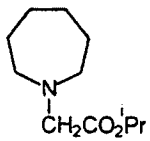
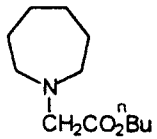
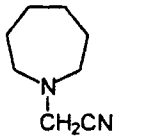
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	180–183/35		n_D^{25} 1.4839; d^{27} 1.1062	165
		HCl 187–188 HCl 185–187		166 112
	89–90/8	Picrate 111.5–113	n_D^{20} 1.4660; d^{20} 1.0066	159
	96–97/8	Picrate 87–88	n_D^{20} 1.4628; d^{20} 0.9852	159
	119–120/5	Picrate 104–105	n_D^{20} 1.4624	159
	115–115.5/11	Picrate 120–121	n_D^{20} 1.4590	159
	130–132/12	Picrate 77–77.5	n_D^{20} 1.4743	159
	102–103/14 110–112/15		n_D^{27} 1.4712	115 167

Table 1 (continued)

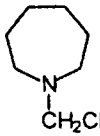
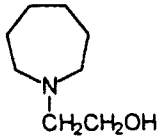
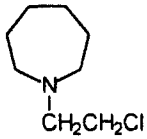
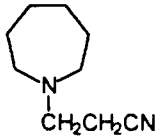
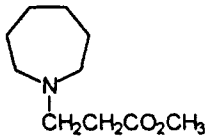
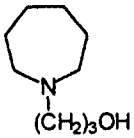
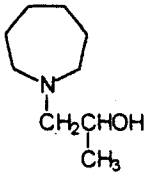
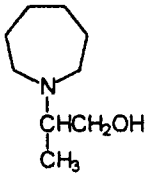
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	69–71/0.2	HCl 92–94	n_D^{27} 1.4821	115
	99–101/15 62–63/0.34	Picrate 105–109	^{1}H NMR, MS	168 9
		HCl 208–209		169
	121–123/14		n_D^{30} 1.4710	115
	125–132/14		n_D^{27} 1.4580	115
	112–114/9	HCl 153–154	n_D^{22} 1.4825	33
	97–100/11	HCl 131–132	n_D^{22} 1.4680	33
	110–112/17	HCl 111–112	n_D^{22} 1.4748	33

Table 1 (continued)

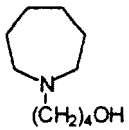
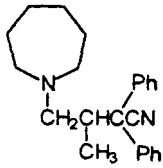
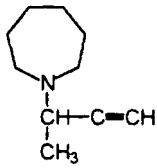
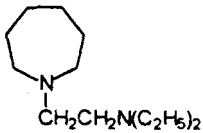
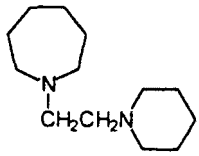
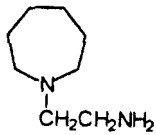
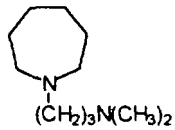
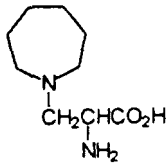
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	110–112/4 111–115/2.8	CH_3I 147.5–148.5	n_D^{20} 1.4813 d^{20} 0.9487, IR	171 170
	101.5–102.5	HBr 230–231.5 HI 228–229 HCl 218.5–220		157
	82–83/15			172
	122–126/14	2HCl 222–224 (d)		114
	151–153/17	2HCl 308–311 (d) 2HBr 315–317 (d)		114
	212/~760 71–73/5 66–67/1	 Dipicrate 207 2HCl 114–115		173 174 167 115
		2HCl 272–275		115
	167–168			166

Table 1 (continued)

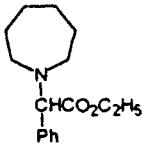
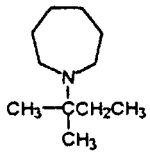
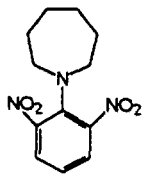
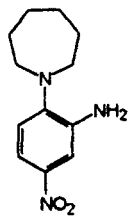
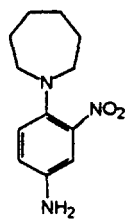
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	165/3		n_D^{26} 1.5360	175
	90–92/12	HCl 244–245		142
	66/0.18 146–148/12	 HCl 194 HBr 219	^{1}H NMR, MS	9 142
	73–74			119
	67–68.5 172.8–173.5/0.15			119
	76–77			119

Table 1 (continued)

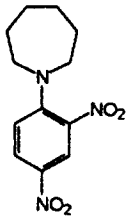
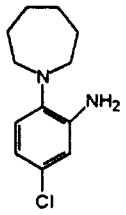
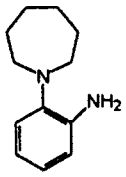
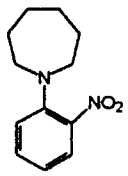
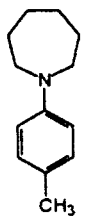
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	108–109			119
	198–200/20	HCl 200–202	n_D^{23} 1.5800	119
	160/10	HCl 165–166	$n_D^{23.5}$ 1.5640	119
	Yellow oil		$n_D^{22.3}$ 1.6010	119
	62/0.12		^1H,^{13}C NMR, MS	9

Table 1 (continued)

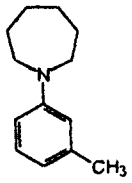
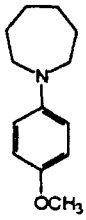
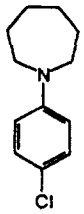
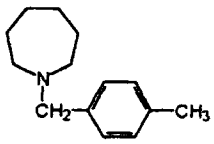
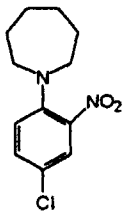
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	71/0.1		^{1}H NMR, MS	9
	87/0.24		^{1}H, ^{13}C NMR, MS	9
	75/0.16		^{1}H NMR, MS	9
	71–72/0.12		^{1}H,^{13}C NMR, MS	9
	56			119

Table 1 (continued)

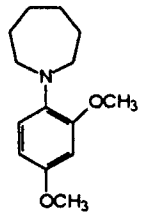
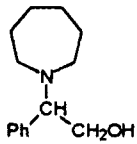
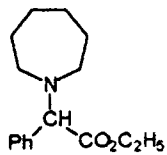
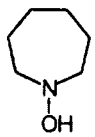
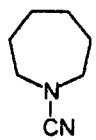
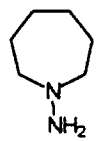
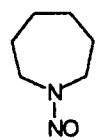
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	109–110/0.01	Picrate 141.5–142.5		118
	165/3		n_D^{26} 1.5360	175
	163/5		n_D^{31} 1.5300	175
	94–95/13 64–65/1.4		 n_D^{26} 1.4852	176 177
	110/0.1			177
	86–86.5/25			178
	83–86/2			178

Table 1 (continued)

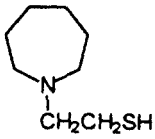
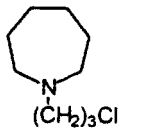
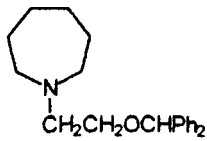
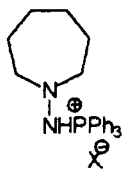
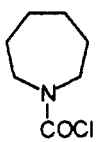
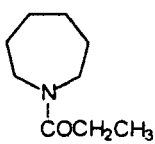
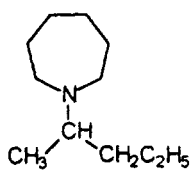
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	86/5		n_D^{20} 1.5076	116
		HCl 208–209		33
	158–160/0.01	HCl 144–146		179
	X = Br 178–180 X = Cl: 168–170		^{1}H NMR	180
	116–118/11			163
	123/9.5		n_D^{23} 1.4821	19
	65.5/12	Picrate 130–131	n_D^{20} 1.4523	161

Table 1 (continued)

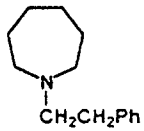
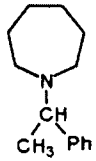
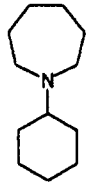
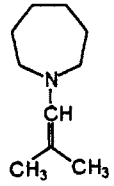
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	71.2/0.18		^1H,^{13}C NMR, MS	9
	64/0.07		^1H,^{13}C NMR, MS	9
	47/0.08		^1H NMR, MS	9
	85–86/12		n_D^{20} 1.4845	161

Table 2. Mono-2-substituted azepanes

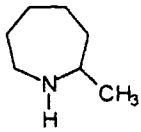
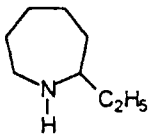
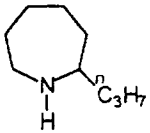
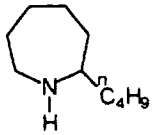
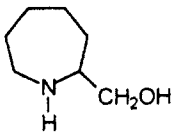
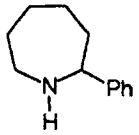
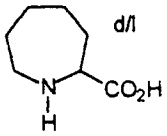
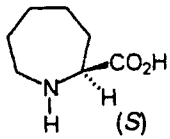
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	59–61/22	HCl 199–201	n_D^{27} 1.4569	60
		NSO_2Ph 75–77	n_D^{20} 1.4588	33
	148–150/748		^{1}H NMR	85
		HCl 156		31
			^{1}H NMR, IR claimed	48
	189–191	HCl 160–162	n_D^{20} 1.4580	118
			d^{20} 0.8574	21
	79–81/18		IR, ^{1}H NMR	49
	Chromatography			50
	90–95/1			34
	142–145/14	*N*-Acetyl 130–5/0.05		61
		N-Tosyl 101–103		182
	208–209	HCl 214–215		16
	205–208	Phenylthiohydantoin 165–166 + Tosyl acid		78
	183.3–184.4 (d)		α_D – 21 (c = 1.02/H_2O) IR, MS, ^{1}H NMR	18

Table 2 (continued)

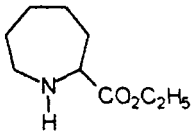
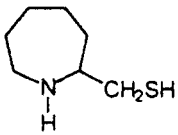
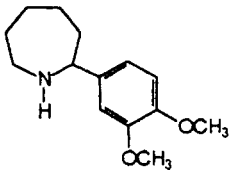
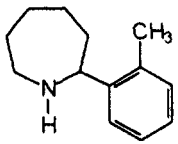
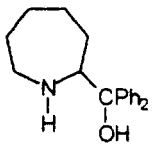
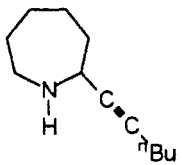
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	55–57/1.5	HCl 166–167		53 16
	60 (subl.)			137
	135–140/12	HCl 176–180 Picrate 178–182		61
	155/10	N-$CH_2Si(CH_3)_3$ 140/1.5	^{1}H NMR	139
	HCl 253–254			183
			Data in Registry	46, 49

Table 2 (continued)

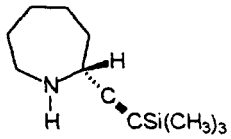
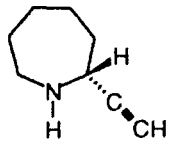
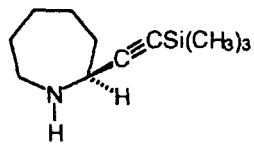
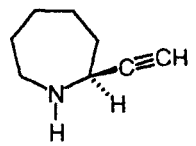
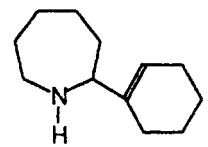
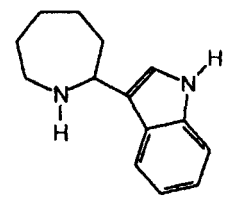
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
 (*R*)		Oxalate 145–146 *N*-Acetyl 72–74/0.02	$[\alpha]_D^{22}$ − 29.8 (c = 1.4, CH_3OH) $[\alpha]_D^{22}$ + 18.3 (c = 1.4, CH_3OH) $[\alpha]_D^{22}$ + 190 (c = 1.4, CH_3OH)	132, 134
 (*R*)		Oxalate 157–158 *N*-Acetyl 101–102	$[\alpha]_D^{22}$ + 12.8 (c = 1.4, CH_3OH) $[\alpha]_D^{22}$ + 197 (c = 1.4, CH_3OH)	132, 134
 (*S*)		Oxalate 145–146 *N*-Acetyl 70- 72/0.01	$[\alpha]_D^{22}$ + 29.9 (c = 1.4, CH_3OH) $[\alpha]_D^{22}$ − 18.7 (c = 1.4, CH_3OH) $[\alpha]_D^{22}$ − 190 (c = 1.4, CH_3OH)	132, 134
 (*S*)		Oxalate 157–158 *N*-Acetyl 101–102	$[\alpha]_D^{22}$ − 12.7 (c = 1.4, CH_3OH) $[\alpha]_D^{22}$ − 194 (c = 1.4, CH_3OH)	132, 134
	90–90.5/3	*N*-$COCHBrCH_3$ 230	IR, ^1H NMR	233
	202		IR	181

Table 3. Mono-3-substituted azepanes

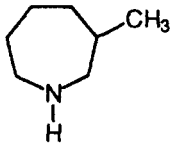
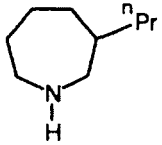
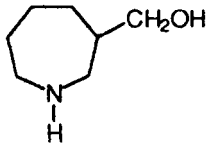
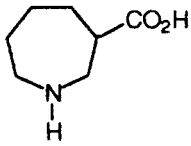
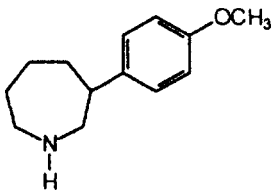
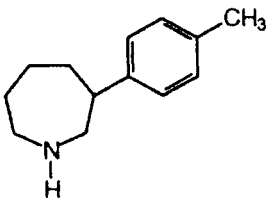
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			^{13}C NMR	85 87
	194–196/760		n_D^{20} 1.4620, d^{20} 0.8649	184
	97–98/1	HCl 122–124		154
		HBr 145–146.5	IR, ^{1}H NMR	185
			^{1}H NMR, MS	80
			^{1}H NMR, MS	80

Table 3 (continued)

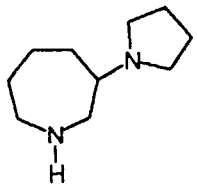
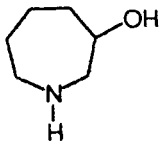
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Pale yellow oil	Fumarate 155–156 *N*-(3,4-Dichlorophenyl)acetyl 156–158	^{1}H NMR, MS	186
	GLC pure		IR	187

Table 4. Mono-4-substituted azepanes

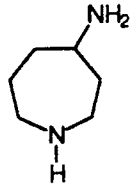
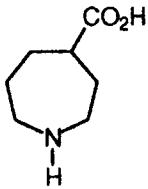
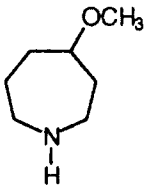
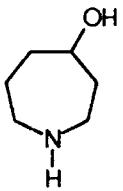
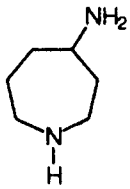
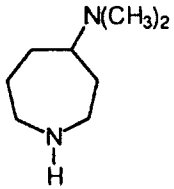
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	153–156/748	HCl 174–175 CH_3I 192 3,5-Dinitrobenzoate 125–126		33 77
		HBr 111.5–112.5	IR, $pK_a(H_2O)$ 3.87, 10.46	51
	75–75.6/15		n_D^{25} 1.4673	188
	82/0.5	Picrolonate 225		189, 190
	79–80/10	Chloroaurate 209 (d) Picrate 224 (d) Ring *N*-benzyl 105–106/0.4		189
	75/8		n_D^{25} 1.4750	188

Table 4 (continued)

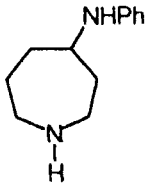
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	130–133/0.5 52–54	N^1-CH_3, N^2-acetyl 137–139 N^1-CH_2Ph, N^2-acetyl 169–171 N^1-CH_2–◁, N^2-acetyl 84–86	^{1}H NMR	191

Table 5. 1,2-Disubstituted azepanes

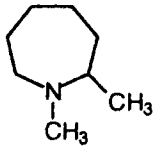
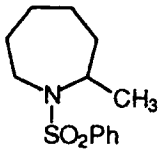
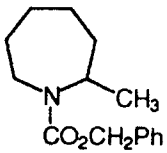
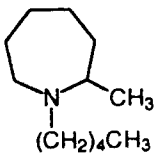
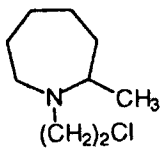
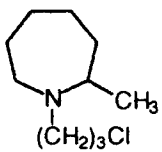
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	80–90/5	Picrate 233 Picrolonate 162–164 Picrate 237–238		31 192
	75–77			60
	Kugelrohr distilled		^{1}H NMR	123
	117–118/22	Picrate 79–80	n_D^{25} 1.4530	5
	177–181/25	2HCl 250–252 (d)		114
		Picrate 127–128		33
		HCl 113–114		33

Table 5 (continued)

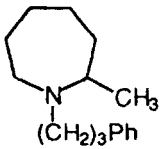
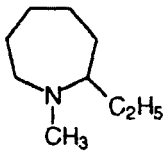
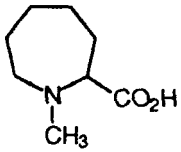
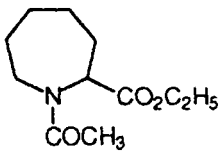
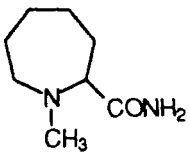
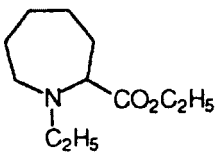
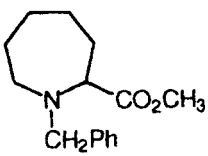
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	106–109/1	Picrate 105–106		5
	174–175/755	Picrate 166.5–167.5	n_D^{20} 1.4472	193
	183–184	Ethyl ester 44–50/1.5	n_D^{20} 1.4584	16
	107–109/1		n_D^{20} 1.4779	8
	74–75 119–121/1.5	*N*-CH_3 96/1.5	n_D^{20} 1.4888	8
	70–72/2		n_D^{24} 1.5420	16
			^1H, ^{13}C NMR, IR	194

Table 5 (continued)

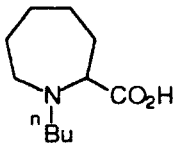
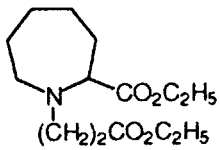
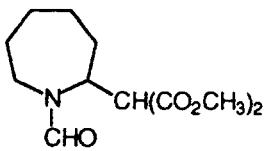
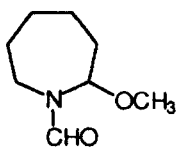
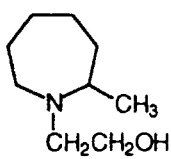
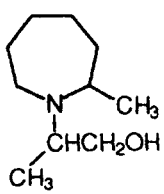
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	140–141	Ethyl ester 78–81/1.5	n_D^{24} 1.4544	16
	118–119/1.5			16
	79–81			195
	102–105/4			126
	94–97/7	CH_3I 213–215	n_D^{22} 1.4790	33
	113–116/11	HCl 121–122	n_D^{22} 1.4745	33

Table 5 (continued)

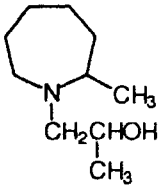
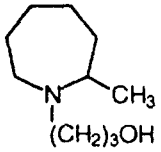
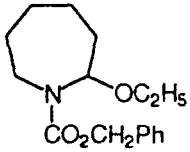
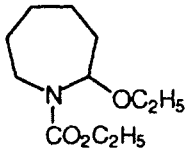
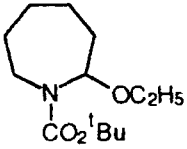
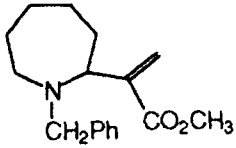
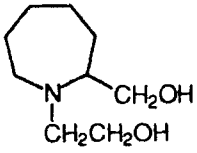
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	96–98/7	CH_3I 180–181	n_D^{22} 1.4670	33
	119–122/7	HCl 114–115	n_D^{22} 1.4809	33
	Chromatography			41
	83/2 90–92/3		IR, MS, ^{1}H NMR	41 44
	78/2			41
	Chromatography		IR, MS, ^{1}H NMR	74
	140–160/1.0–1.5		IR	34

Table 5 (continued)

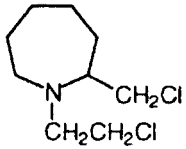
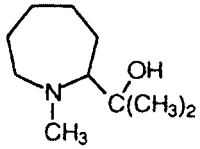
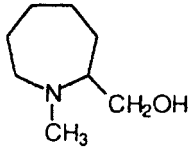
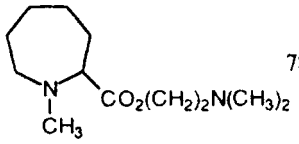
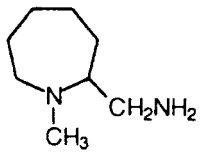
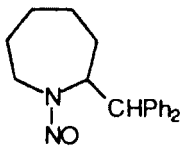
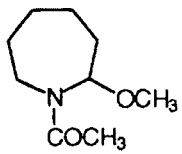
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	132-133			34
	104-106/14			183
	52–53/2		n_D^{20} 1.4557	8
	78-79/1		n_D^{20} 1.4681	8
	68–69/6		n_D^{20} 1.4834	8
	158.5	HCl 271 (d)	^{1}H NMR	120
	53/0.07		n_D^{25} 1.4775, ^{1}H NMR	127

Table 5 (continued)

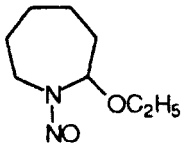
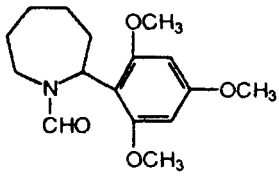
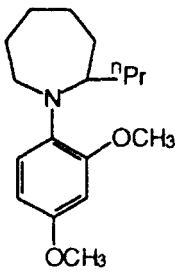
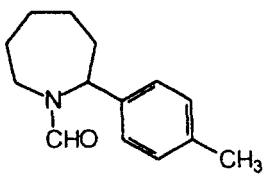
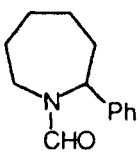
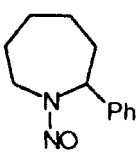
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	60/0.1		^{1}H NMR, IR, MS	180
	99–105		MS, ^{1}H NMR	129
	128–130/0.01			118
	146–150/0.5		MS, ^{1}H NMR	130
	134/1.2 143–148/0.8		^{1}H NMR	128, 130
	138/0.02		n_D^{20} 1.5602, IR, MS, ^{1}H NMR	141

Table 5 (continued)

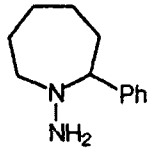
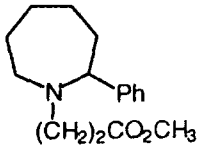
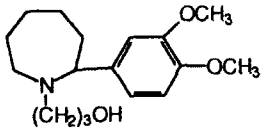
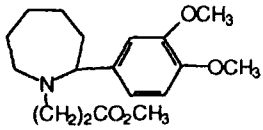
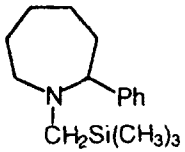
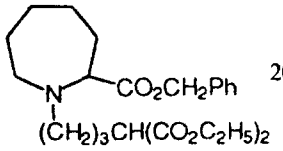
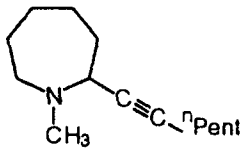
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	102–105/0.7	*N*-Acetyl 81.5–83 CH_3I 165–167	n_D^{20} 1.5474, IR, MS, ^{1}H NMR	141
	130–132/0.25			61
	165–170/0.1			61
	171–175/0.3			61
	150/6		^{1}H NMR	139
	205–210/0.1			136
	68–70/0.5		IR, ^{1}H NMR	195

Table 5 (continued)

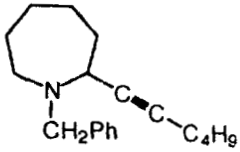
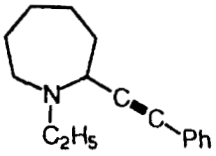
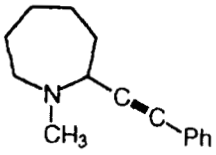
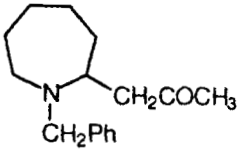
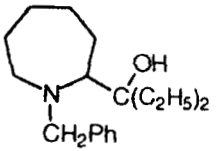
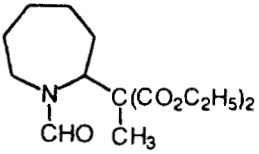
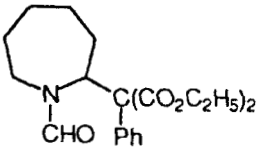
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
				84
			^{1}H NMR, IR, MS	196
	90–95/0.5		IR, ^{1}H NMR	195
	Chromatography		^{1}H, ^{13}C NMR, MS	71
			Supplement	125
	163–170/0.7–0.9		MS, ^{1}H NMR	131
	72–76		MS, ^{1}H NMR	131

Table 5 (continued)

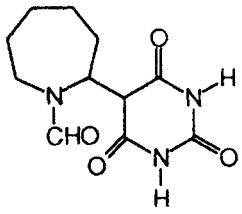
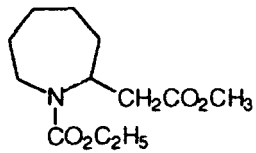
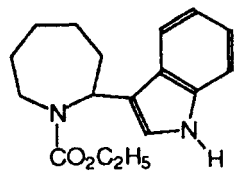
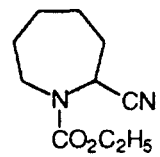
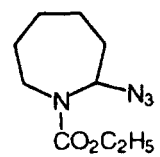
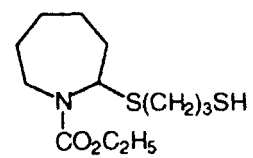
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	124–127		^{1}H NMR, MS (no M^+)	131
	125/3		IR, MS, ^{1}H NMR	44
	Chromato-graphy		IR, MS, ^{1}H NMR	44
	100–102/2		IR, MS, ^{1}H NMR	44
	Chromato-graphy		IR, MS, ^{1}H NMR	44
	Chromato-graphy		IR, MS, ^{1}H NMR	44

Table 5 (continued)

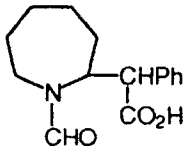
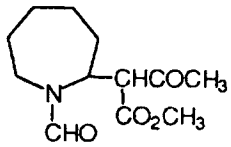
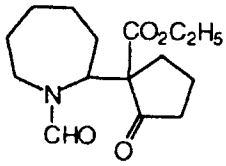
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	214–215		MS, ^{1}H NMR	131
	87–91		MS, ^{1}H NMR	131
	187–191/1.3 119–122		MS, ^{1}H NMR	131

Table 6. 1,3-Disubstituted azepanes

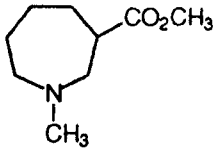
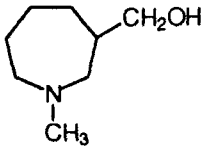
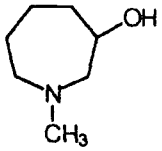
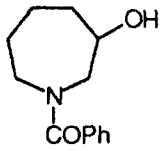
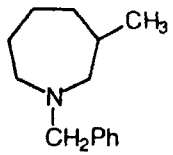
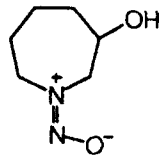
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			IR, ^{1}H NMR	37
			IR, ^{1}H NMR	37
	78–79/15	*O*-Acetyl 81–82/10 *O*-Benzoyl 125/2–3 CH_3I 141–142	IR	197
	Chromatography		IR, ^{1}H, ^{13}C NMR	143
			^{1}H NMR, MS, IR	36
	Wax		^{13}C NMR, MS, IR	198

Table 6 (continued)

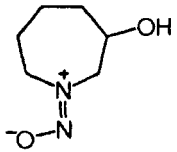
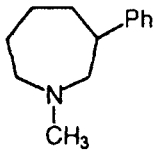
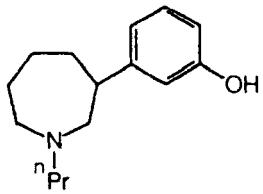
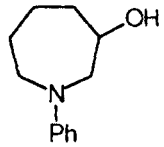
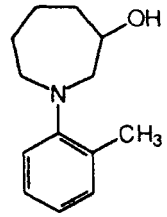
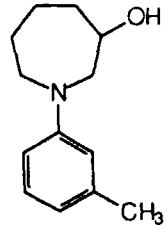
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	51.5–52.5		^{13}C NMR, MS, IR	198
			^{1}H NMR, MS	80
		HCl 148–150		199
			^{1}H, ^{13}C NMR, MS, IR	12
			^{1}H, ^{13}C NMR, MS, IR	12
			^{1}H, ^{13}C NMR, MS, IR	12

Table 6 (continued)

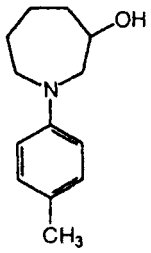
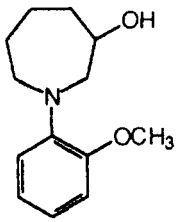
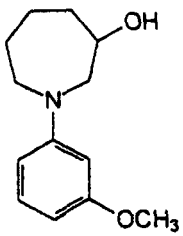
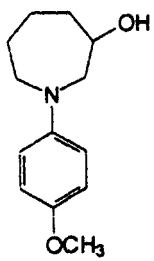
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			^1H, ^{13}C NMR, MS, IR	12
			^1H, ^{13}C NMR, MS, IR	12
			^1H, ^{13}C NMR, MS, IR	12
			^1H, ^{13}C NMR, MS, IR	12

Table 6 (continued)

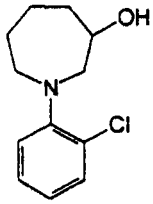
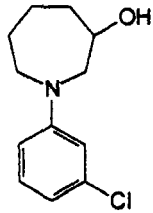
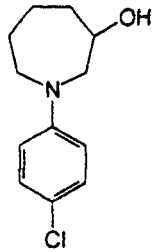
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			^{1}H, ^{13}C NMR, MS, IR	12
			^{1}H, ^{13}C NMR, MS, IR	12
			^{1}H, ^{13}C NMR, MS, IR	12

Table 7. 1,4-Disubstituted azepanes

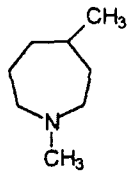
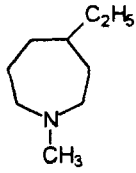
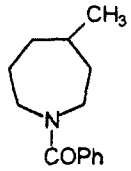
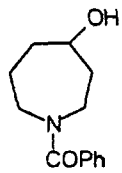
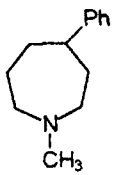
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		Picrate 188–191		77
		Picrate 146–147		76
	120–128/ 0.08–0.09		IR, ^{1}H NMR	200
			IR IR, ^{1}H NMR	201 143
	88–90/0.25	Picrate 149–150 HCl 78–79 CH_3I 146–147 $CH_3CH_2CH_2I$ 166–169		28 52

Table 7 (continued)

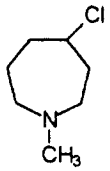
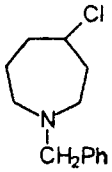
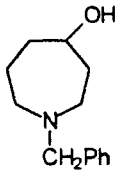
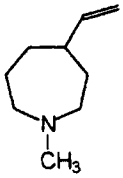
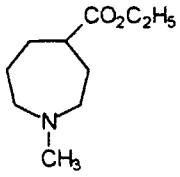
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	30–35/2	HCl 125–126 Picrate 173–174 Picrate 138–139		81 232
	104–105/0.3			189
	129/0.5	Picrate 136–138	IR, ^{1}H NMR, MS	189 82, 232
	173–176	Picrate 113–115		76
	102–104/10	Picrate 128–130		76

Table 7 (continued)

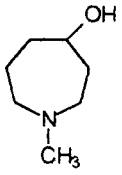
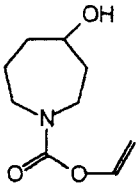
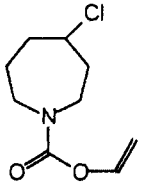
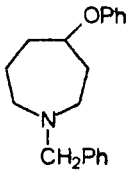
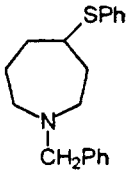
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	95–98/12 96/11 105–107/2	Picrate 180–181 Benzoate 104–105/0.07 Picrate 141–143	n_D^{23} 1.4863 IR	81 232
			^{1}H NMR, IR, MS	82
	Chromatography		^{1}H NMR, IR, MS	82
	Chromatography		^{1}H NMR, IR, MS	82
	Chromatography		^{1}H NMR, MS	82

Table 7 (continued)

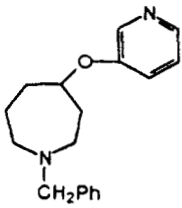
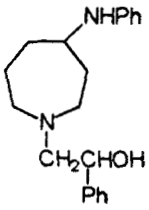
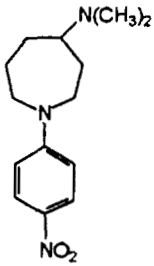
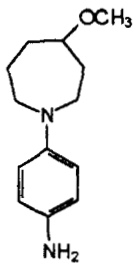
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Chromato-graphy		^{1}H NMR, MS	82
			^{1}H NMR, MS	202
	242–244			188
		HCl 184–187		188

Table 7 (continued)

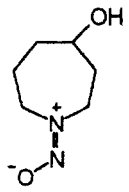
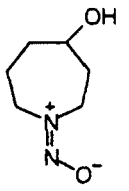
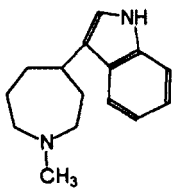
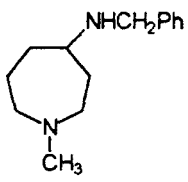
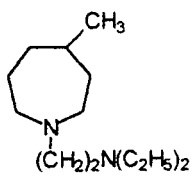
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	43–45		^{13}C NMR, MS, IR	198
	80.5–81.5		^{13}C NMR, IR	198
				203
	96–98/0.02	Dipicrate 177–179		81
	136–141/15	2HCl 201–203		114

Table 7 (continued)

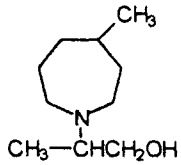
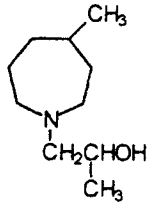
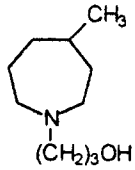
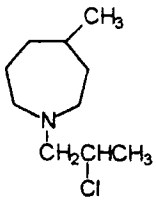
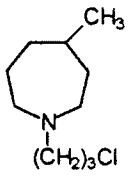
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	111–113/11	CH_3I 77–78	n_D^{22} 1.4705	33
	101–104/12	HCl 105–106	n_D^{22} 1.4643	33
	123–127/12	HCl 115–116	n_D^{22} 1.4780	33
		HCl 198–199 Picrate 127–128		33
		HCl 158–159		33

Table 7 (continued)

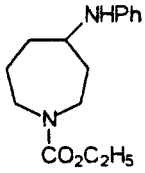
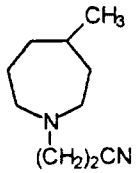
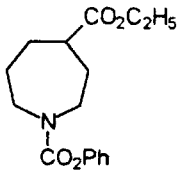
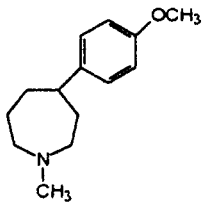
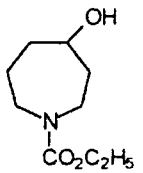
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	170–175/0.75		^{1}H NMR	191
	129–130/15		n_D^{30} 1.4692	115
			IR, ^{1}H NMR, MS	68
		CH_3I 142- 143.5		62
	143–144/0.5	$OCO_2C_2H_5$ 155–7/0.5	IR, ^{1}H NMR, MS	232

Table 8. Miscellaneous disubstituted azepanes

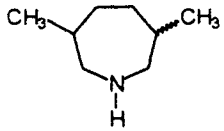
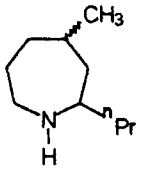
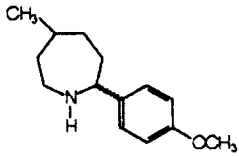
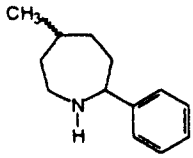
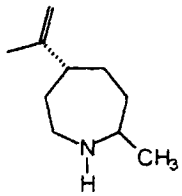
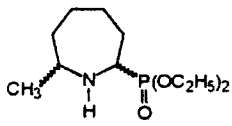
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	169- 170.5/760			188
	53–55/4	*N*-Benzoyl 200–202/13 HCl 197–200 Chloroplat. 195	n_D^{20} 1.4550, d_4^{20} 0.8461	21
	125–140/0.01		IR, ^{1}H NMR, MS	22
	130–150/0.01		IR, ^{1}H NMR, MS	22
	2 isomers		IR, ^{1}H NMR	85
	81–83		IR, ^{1}H NMR	58

Table 8 (continued)

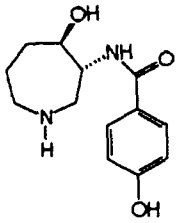
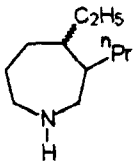
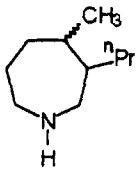
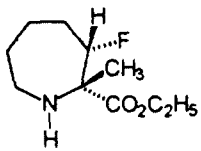
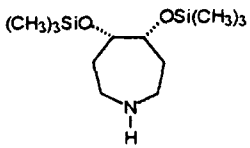
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			X-ray	204
	95/10		n_D^{20} 1.4600, d^{20} 0.8585	184
	71/8		n_D^{20} 1.4590, d^{20} 0.8518	184
			^{13}C, ^{1}H, ^{19}F NMR, MS, IR	205
	107–118/2		^{1}H NMR, IR, MS	206

Table 8 (continued)

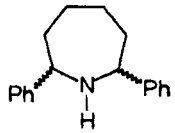
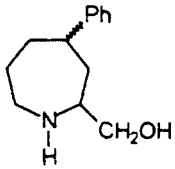
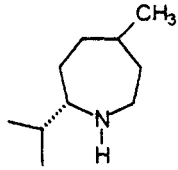
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	96–98	Picrate 175–180		207
	120–133/0.08	*N*-Benzoyl 170–172.5	IR	35
	170–176/760 84/18	HCl 149, $[\alpha]_D^{23}$ − 0.8 (c = 4, CH_3OH)	IR, ^{1}H NMR $[\alpha]_D^{22}$ + 7.4 (c = 0.55, C_2H_5OH)	40

Table 9. Miscellaneous trisubstituted azepanes

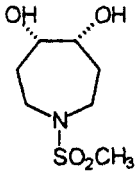
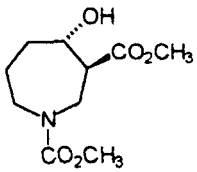
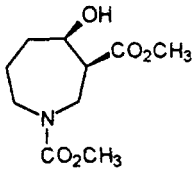
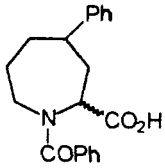
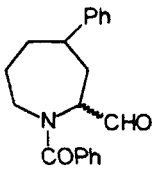
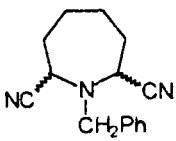
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	170–173	Bis-*O*-methylsulphonyl 137–138	^{1}H NMR, IR	206
(±) 	180/60		IR	185
(±) 	55.5–57.5		IR	185
	Impure		IR	35
	Impure		IR	35
	*R*R** oil *R*S** 75–76		IR, MS, ^{1}H NMR IR, MS, ^{1}H NMR	208

Table 9 (continued)

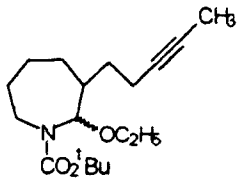
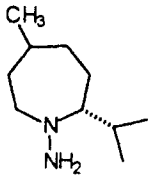
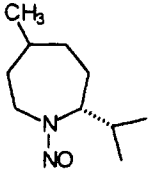
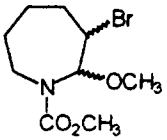
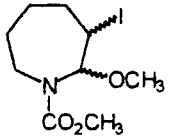
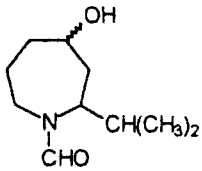
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Oil		IR, MS, ^{1}H NMR	135
	106/0.9	HBF_4 138	$[\alpha]_D^{23}$ + 21.4 (c = 5.7, C_6H_6) IR, MS, ^{1}H NMR	40
	100/0.7		$[\alpha]_D^{23}$ − 120 (c = 0.5, C_2H_5OH) IR, MS, ^{1}H NMR	40
			IR, MS, ^{1}H NMR	209
			IR, MS, ^{1}H NMR	209
			IR, MS, ^{1}H NMR	25

Table 9 (continued)

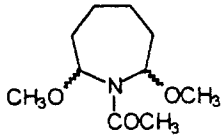
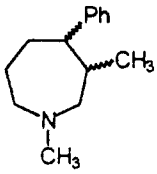
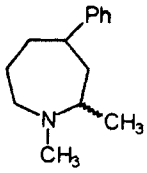
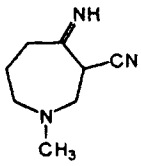
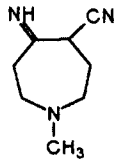
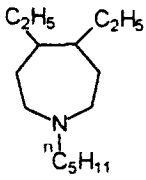
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	74–75/0.9		n_D^{25} 1.4673, ^{1}H NMR	127
	98–100/0.25	CH_3I 184 190	n_D^{31} 1.5251	210
	106–108/0.2	Picrate 128–130	n_D^{27} 1.5255	52
	140–142 or 108–109			211
	108–109 or 140–142			211
	98–100/2		n_D^{25} 1.4570	5

Table 9 (continued)

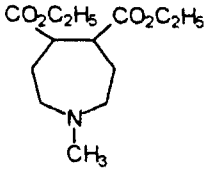
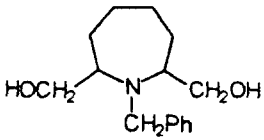
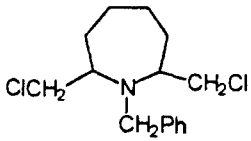
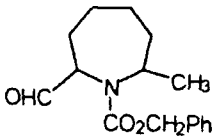
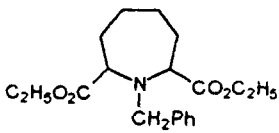
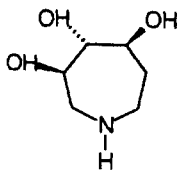
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			No data	212 69
	196–199/0.4			7
	145–150/0.5 83–85			7
	85–89		^{13}C NMR *cis* and *trans*	123
	135–150/0.05 'impure'			7
		Tetraacetate 112–114	$[\alpha]_D^{20}$ + 4.8 (c = 1, CH_3OH) IR, MS	20

Table 9 (continued)

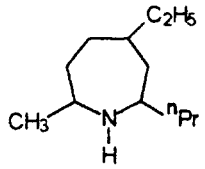
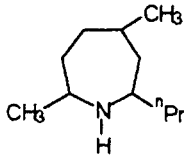
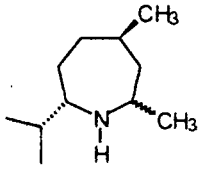
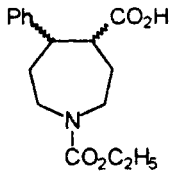
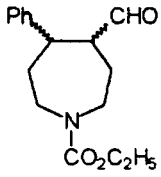
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	85–88/5	*N*-Benzoyl 205–8/14 HCl 198–200 Chloroplat. 185	d_4^{20} 0.8463, n_D^{20} 1.4570	21
	61–63/2	*N*-Benzoyl 192–5/14 HCl 168 Chloroplat. 190	d_4^{20} 0.8398, n_D^{20} 1.4550	21
 *cis* and *trans*	170–176		IR, ^{1}H NMR	46
	146–147		IR, ^{1}H NMR	226
	180–183/0.1		IR, ^{1}H NMR	226

Table 10. Miscellaneous tetra- and higher substituted azepanes

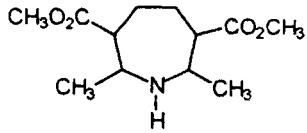
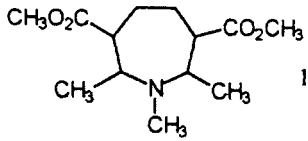
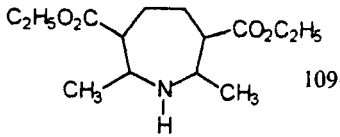
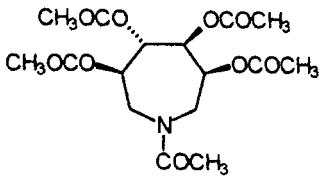
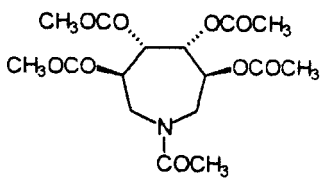
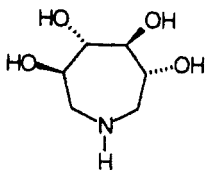
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	92–94/0.05		$n_D^{21.5}$ 1.4792, n_D^{25} 1.4698, IR	56
	130/0.05		n_D^{25} 1.4596, ^{1}H NMR	57
	109–110/0.3		n_D^{25} 1.4716, ^{1}H NMR, IR	56
	Syrup		$[\alpha]_D^{20}$ − 7.3 (c = 1, CH_3OH) IR, MS	20
	149.5–152		IR, MS	20
	Yellow syrup		$[\alpha]_D^{23}$ + 19.9 (c = 2, H_2O)	20

Table 10 (continued)

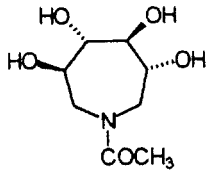
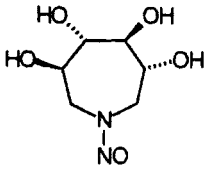
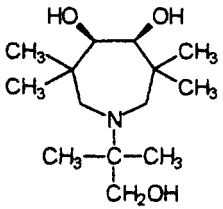
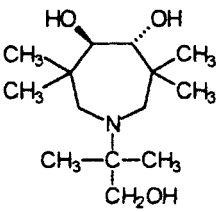
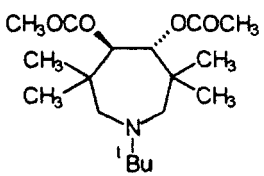
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	113–114.5		$[\alpha]_D^{20}$ + 44.5 (c = 1, H_2O)	20
	162–163.5		$[\alpha]_D^{23}$ + 9.7 (c = 1, H_2O)	20
	136–137		IR, MS, ^1H, ^{13}C NMR	213
	161–162 (subl.)		MS, ^1H, ^{13}C NMR	213
	65–66			140

Table 10 (continued)

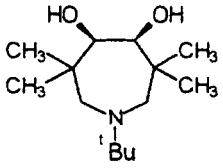
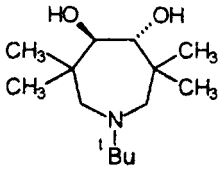
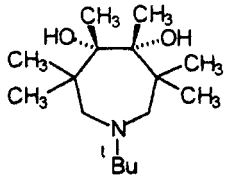
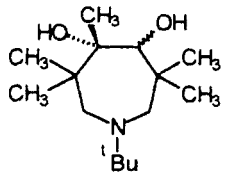
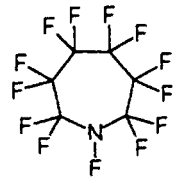
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	140–141	Di-*O*-acetate 91.5–92.5	IR, ^{1}H NMR, MS	214
	140–142 (subl.)	Di-*O*-acetate 79–82	IR, ^{1}H NMR, MS	214
	91–94		IR, ^{1}H NMR, MS	214
	122–123		IR, ^{1}H NMR, MS	214
	81/760		IR, NMR, MS	215

Table 10 (continued)

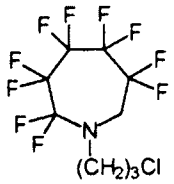
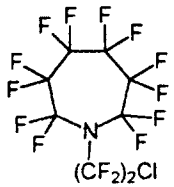
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	150–151.5/760		n_D^{20} 1.3178	216
	124–125.5/760		n_D^{20} 1.3156	216

Table 11. 2,2-Disubstituted azepanes

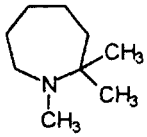
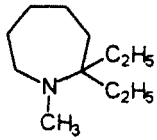
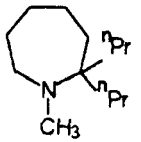
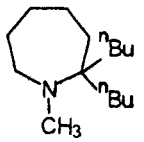
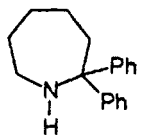
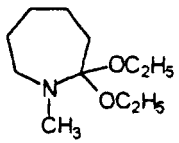
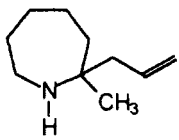
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	163–165/760 171/~760	Picrate 248–249 CH_3I 211	d^{20} 0.8564, n_D^{20} 1.4566	32b 217
	99/17 95.5/15	Picrate 173–174 CH_3I 131	d^{20} 0.8785, n_D^{20} 1.4705	32b 217
	108–109/9	Picrate 149.5–150		32b
	135.5–135.5/10	HCl 107–110 Picrate 93.5–94	n_D^{20} 1.473	32b
	Details in supplement		Spectra in supplement	218
	88/22		n_D^{20} 1.4758	219
	Chromato-graphy		^{1}H NMR	46

Table 11 (continued)

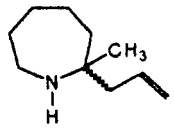
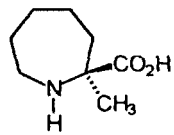
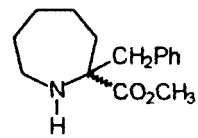
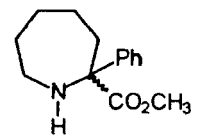
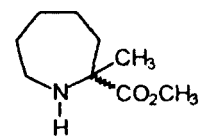
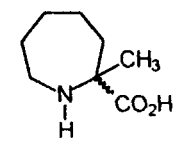
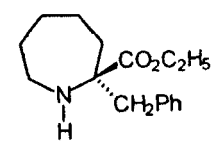
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Chromato-graphy			50
	>255 (d)		^{1}H NMR, IR, α_D − 17 (c = 1, H_2O)	18
		HCl >280	IR, ^{1}H NMR	15
		HCl 190–192	IR, ^{1}H NMR	15
	151–152		IR, ^{1}H NMR	15
	>280	HCl 253–255	IR, ^{1}H NMR	15
			^{1}H NMR, α_D − 7.6 (c = 1, $CHCl_3$), ee > 95%	45

Table 11 (continued)

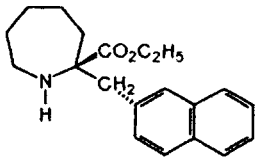
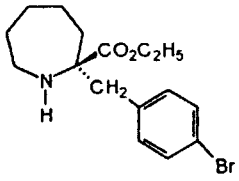
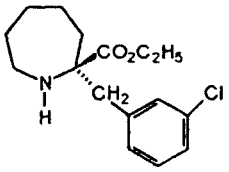
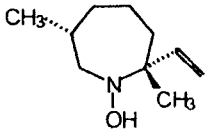
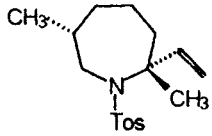
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			^{1}H NMR, α_D − 10.2 (c = 1, $CHCl_3$), ee > 95%	45
			^{1}H NMR, α_D − 3 (c = 1, $CHCl_3$), ee > 95%	45
			^{1}H NMR, α_D − 10.5 (c = 1, $CHCl_3$), ee > 95%	45
 2R*6S*	44–46		IR, MS, ^{1}H, ^{13}C NMR	235
 2R*6S*	59–60		IR, MS ^{1}H, ^{13}C NMR, X-ray	235

Table 12. 3,3-Disubstituted azepanes

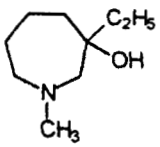
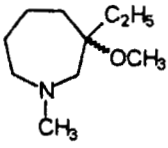
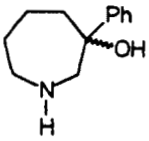
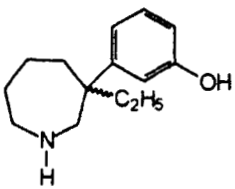
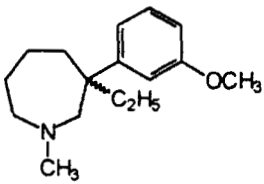
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
		$HClO_4$ 85.5–86.5	IR, ^1H NMR	83
		$HClO_4$ 111–111.5	^1H NMR, IR	83
	203–204		IR	38
	116–118	HBr 187–188		220
	108–112/0.1	HBr 140–142		220

Table 12 (continued)

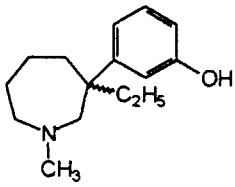
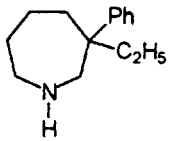
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	127.5–133	HCl 184–186		220
	110–112/0.5	Picrate 118–120 *N*-Propionyl 145–150/0.2		230

Table 13. 4,4-Disubstituted azepanes

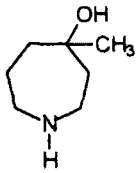
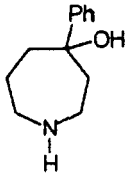
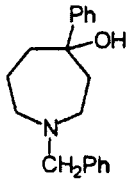
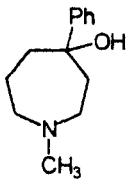
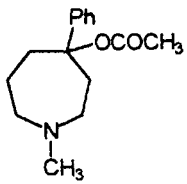
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HCl 134–136		77
		HCl 98		190
	53	HCl 204		190
	120–122/0.3		n_D^{26} 1.5515	211
	120–125/0.3 147–152/0.3	CH_3I 215–217 (d) CH_3I 218–219 Picrate 183–183.5	n_D^{29} 1.5375	211 52

Table 13 (continued)

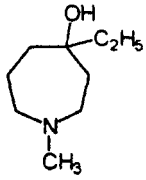
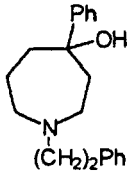
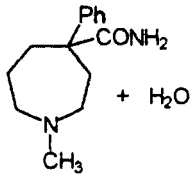
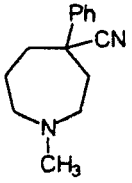
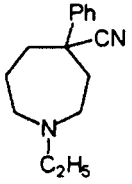
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	102–105/20			76
		HCl 163		190
	95–96			28
	119–121/0.25 130–132/0.35 133–135/1	CH_3Cl 270 Picrate 173–175 CH_3Br 248–249 HCl 150–151 CH_3Br 241–241.5 CH_3Cl 245–246	n_D^{22} 1.5341, d^{22} 1.030	28, 52 26
	136–139/1	HCl 182–183		26

Table 13 (continued)

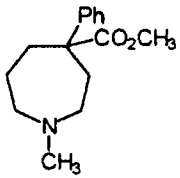
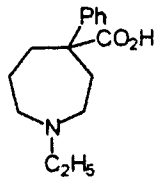
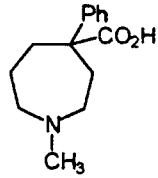
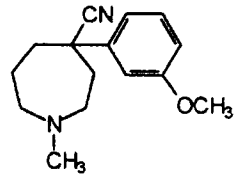
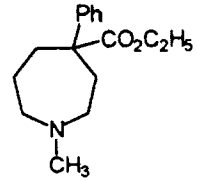
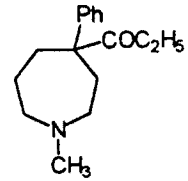
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	124–125/0.3	HCl 174–176	n_D^{28} 1.5278, d_4^{28} 1.062	28
	171–173	Ethyl ester HCl 178–179		26
	222–223	Sulphate 250–251 (d)		28
	150–154/0.3	CH_3Cl 212–213	n_D^{22} 1.5332, d^{22} 1.062	30
	128–130/0.3	HCl 151–153 Picrate 169–170 CH_3Br 215–217	n_D^{28} 1.5220, d_4^{26} 1.038	28
	132–136/0.3	CH_3I 217–219 HCl 122–125	n_D^{26} 1.5302	30

Table 13 (continued)

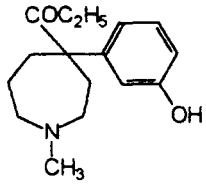
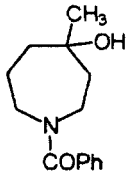
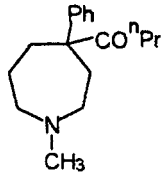
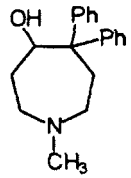
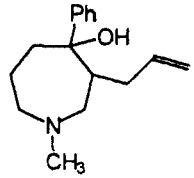
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	135–136			30
	94–96		α_D – 4 (c = 0.747, $CHCl_3$) IR, ^1H NMR	200
	132–133/0.3	Picrate 138–140	n_D^{26} 1.5300	30, 221
	128.2–129.8			222
	76–77	HCl 172–173 *O*-Propionyl HCl 142–143		223

Table 13 (continued)

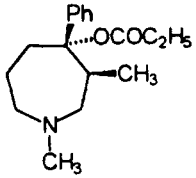
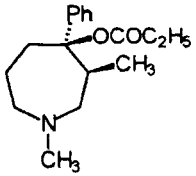
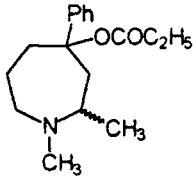
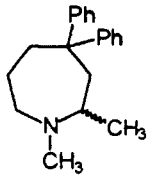
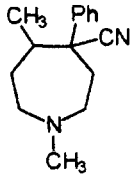
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	124–128/0.3	HCl 201–202 Picrate 114–115	n_D^{25} 1.5142	224 231
	126/0.3	HCl 207 HBr 201–202 Picrate 162–163	n_D^{28} 1.5182, n_D^{21} 1.5215 ^{1}H NMR	52, 224 231
	138–148/0.3	CH_3I 60–65		52
		CH_3Cl 265–267 CH_3I 234–236		27
	128–130/0.4	CH_3Cl 253–256	n_D^{29} 1.5332	29

Table 13 (continued)

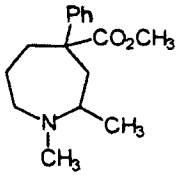
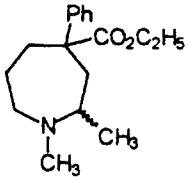
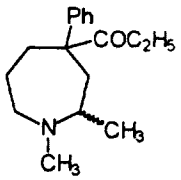
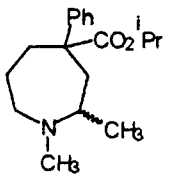
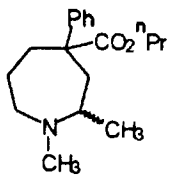
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	120–122/0.25	Picrate 159–161 HCl 206–207	n_D^{32} 1.5250, d^{32} 1.060	210
	122–124/0.25	Picrate 177–178 HCl 145–146.5		210
	135–142/0.3	CH_3I 183–185	$n_D^{27.5}$ 1.5350, d^{26} 1.035	30
	118–120/0.25	Picrate 193–194 (d)	n_D^{27} 1.5160, d^{27} 0.999	210
	128–130/0.25	Picrate 169–171	$n_D^{27.5}$ 1.5160, $d^{27.5}$ 1.012	210

Table 13 (continued)

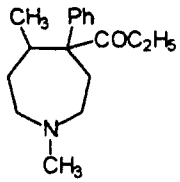
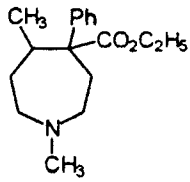
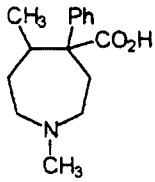
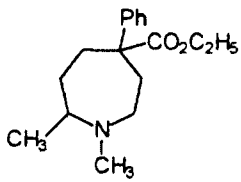
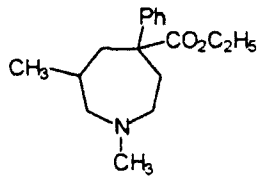
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	130–145/0.3			29
	126–128/0.3	CH_3I 165–170	$n_D^{28.5}$ 1.5235	29
	182–184			29
	134–140/0.3 126–130/0.2	CH_3I 222–223	n_D^{23} 1.5232, d^{23} 1.044	29
	122–124/0.3		n_D^{24} 1.5278	29

Table 13 (continued)

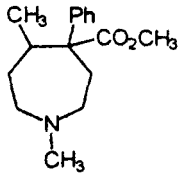
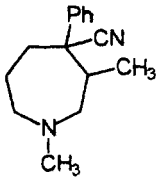
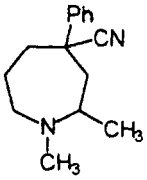
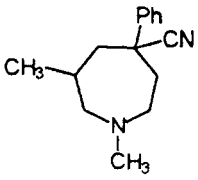
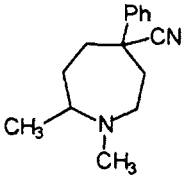
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	122–126/0.3	HCl 179–181	n_D^{23} 1.5301	29
	117–120/0.2	Picrate 195–197 (d) HCl 258–259 CH_3I 259–261	n_D^{26} 1.5330, d^{26} 1.016	210
	123–126/0.2	Picrate 199–202 CH_3I 254–255 CH_3Cl 259	n_D^{27} 1.5341, d^{27} 1.019	210
	120–140/0.3		n_D^{26} 1.5351	29
	125 130/0.3		n_D^{25} 1.5249, d^{25} 0.907	29

Table 13 (continued)

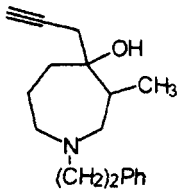
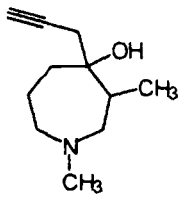
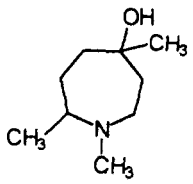
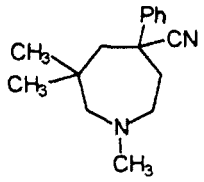
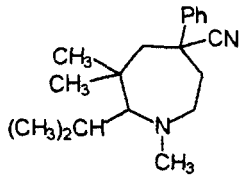
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	140–150/0.1	HCl 147–149	$n_D^{22.6}$ 1.5392	225
	130–135/25	HCl 148–150	$n_D^{22.6}$ 1.4665	225
	95–100/8	CH_3I 225–232		64
	160–162.5			29
	172/0.5			29

Table 13 (continued)

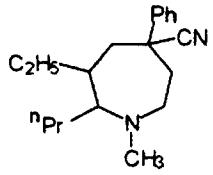
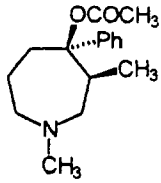
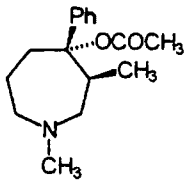
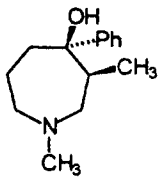
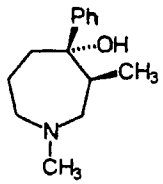
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	170–174/0.8–0.9	Ethyl ester 174–8/0.7	n_D^{30} 1.5048	29
	142–152/0.3	HCl 216 CH_3I 95–97	$n_D^{27.5}$ 1.5242, ^1H NMR	224, 231
	142–152/0.3	HCl 196	^1H NMR	224, 231
	91–92	Picrate 157	^1H NMR	231
		HCl 250–251	^1H NMR	231

Table 13 (continued)

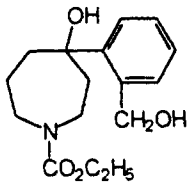
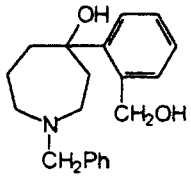
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Chromato-graphy		IR, ^{1}H NMR	226
	Chromato-graphy		IR, ^{1}H NMR	226

Table 14. Alkenyl-substituted azepanes

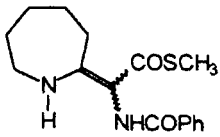
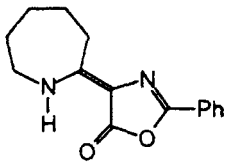
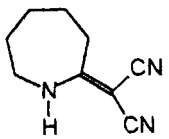
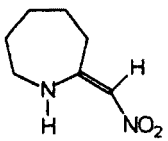
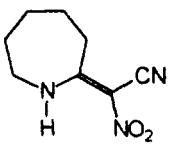
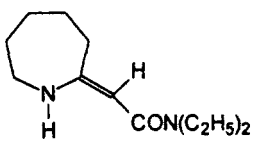
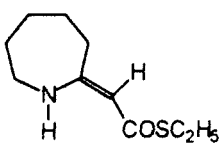
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	200–203 (d)		IR	102
	132–134		IR	102
	108	*N*-Acetyl 247–248.5 *N*-Methyl 81 *N*-Heptyl 200	IR	103
	89–91			92
	137–139		IR	151
	145/0.05			147
	134/0.05			147

Table 14 (continued)

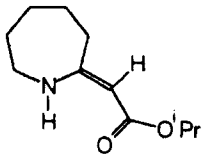
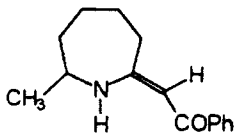
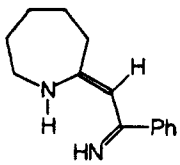
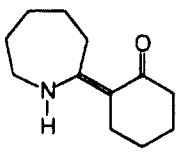
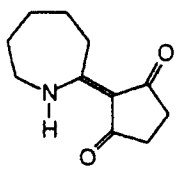
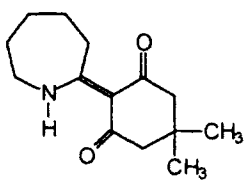
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	104/0.07			147
			^{1}H NMR, IR (not detailed)	107
			Data not given but compound used	106
	58 129–132/0.01		UV, IR	152
	164–165			89
	142–143 146			89 101

Table 14 (continued)

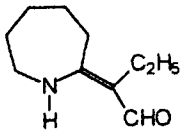
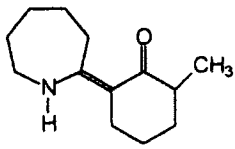
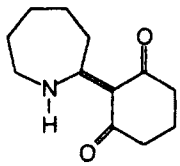
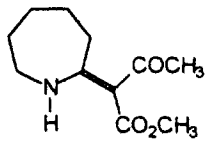
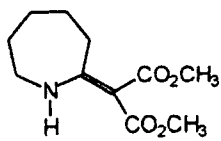
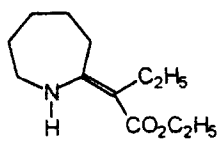
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			^{1}H NMR, IR	107
			^{1}H NMR, IR	107
	84			101
	150/0.05			101
	150/0.05			101
	100/0.01		IR, ^{1}H NMR	148

Table 14 (continued)

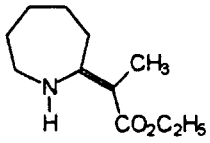
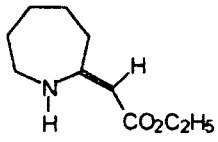
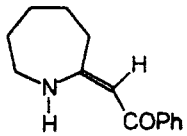
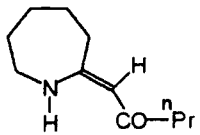
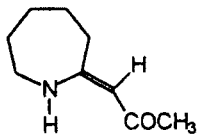
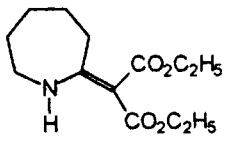
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	93/0.07		IR, ^{1}H NMR	148
 (Z)	55–56		^{1}H NMR	100
	76		IR, ^{1}H, ^{13}C NMR	99
	Chromato-graphy		IR, ^{1}H, ^{13}C NMR	99
	110/0.05		IR, ^{1}H, ^{13}C NMR	99
	128/0.05		IR, ^{1}H NMR	149

Table 14 (continued)

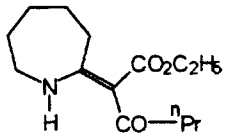
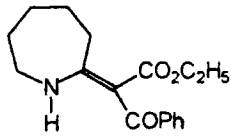
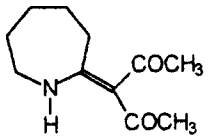
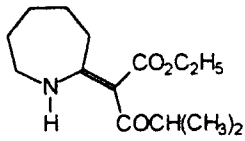
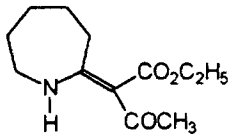
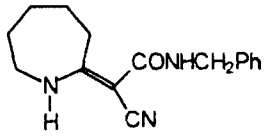
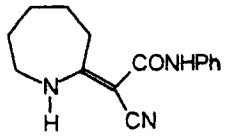
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	124/0.01		IR, ^{1}H NMR	149
	44		IR, ^{1}H NMR	149
	55		IR, ^{1}H NMR	149
	126/0.01		IR, ^{1}H NMR	149
	115/0.01		IR, ^{1}H NMR	149
	138–140		MS	145
	162–164		MS	145

Table 14 (continued)

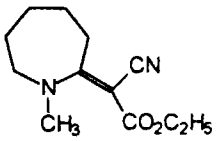
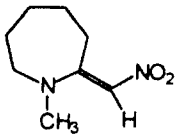
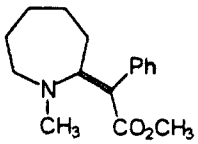
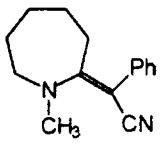
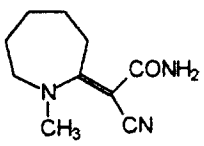
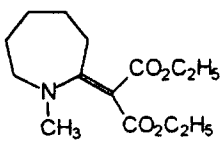
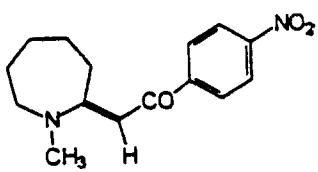
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	73–76		IR, UV, ^{1}H NMR	92
	84–85		IR, UV, ^{1}H NMR	92
	76–79		IR, UV, ^{1}H NMR	92
	79–83		IR, UV, ^{1}H NMR	92
	189–190		IR, UV, ^{1}H NMR	92
	61–63		IR, UV, ^{1}H NMR	92, 227
	126–127		^{1}H NMR	93

Table 14 (continued)

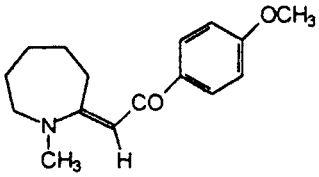
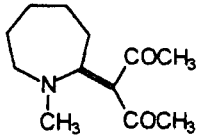
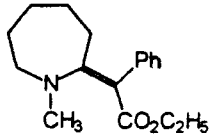
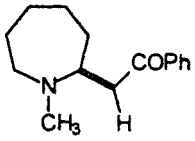
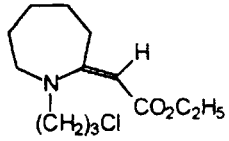
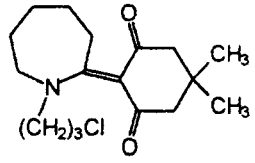
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	92–93 80		^{1}H NMR	93 90
	152–155/2		^{1}H NMR	93
	182–183/2		IR, UV, ^{1}H NMR	92, 93
	85–87 65		IR, UV, ^{1}H NMR	92, 93 90
	51–52		IR, ^{1}H NMR	146
	169		IR, ^{1}H NMR	146

Table 14 (continued)

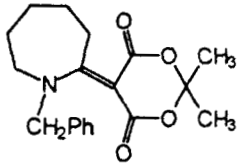
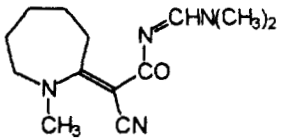
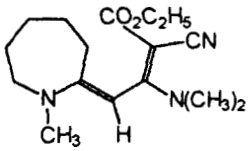
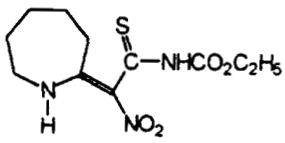
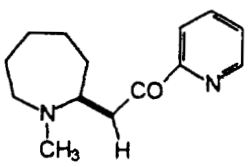
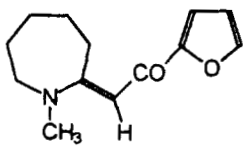
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	198		IR, ^{1}H NMR, MS	105
	132–135		^{1}H NMR	94
	100–102		^{1}H NMR, IR, UV	95
	210–214			150
	103			90
	100			90

Table 14 (continued)

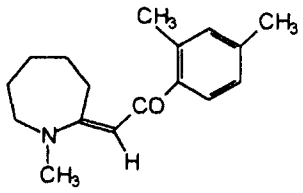
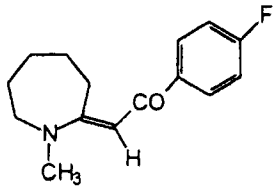
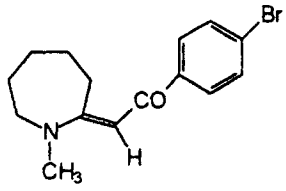
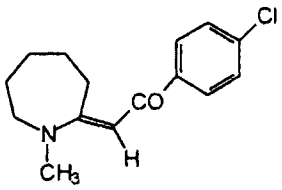
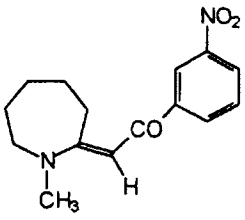
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	90			90
	50			90
	94			90
	75			90
	90			90

Table 14 (continued)

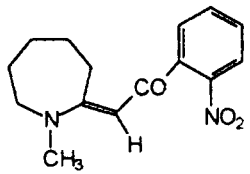
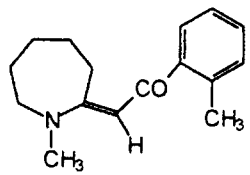
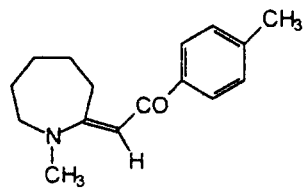
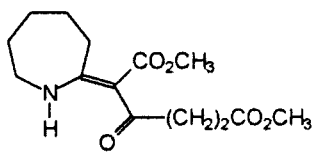
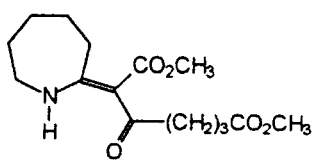
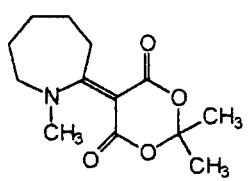
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	65			90
	90			90
	8			90
	Chromatography		IR, ^{1}H, ^{13}C NMR	99
	Chromatography		IR, ^{1}H, ^{13}C NMR	99
	131		IR, ^{1}H NMR	105

Table 14 (continued)

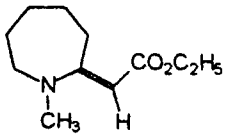
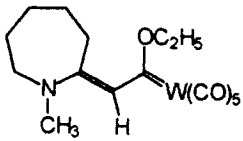
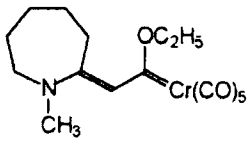
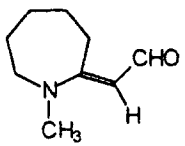
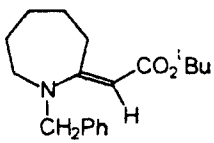
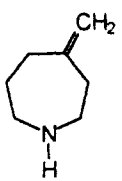
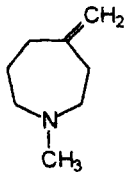
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	106–108/0.05		IR, ^{1}H NMR	104
	107		IR, MS, ^{1}H, ^{13}C NMR	228
	90		IR, MS, ^{1}H, ^{13}C NMR	228
	Oil		IR, MS, ^{1}H, ^{13}C NMR	109
	104–105		IR, ^{1}H NMR, MS	229
		HCl 165		77

Table 14 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HCl 119–121 Picrate 176–177 CH_3I 206–209		77

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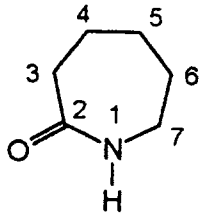
CHAPTER 3

Azepanones

I. AZEPAN-2-ONES (CAPROLACTAMS)



The literature contains an enormous number of papers pertaining to this subject area. This state of affairs is largely due to the fact that caprolactam (above) polymerises to nylon-6, one of the more popular polyamides used in fibre production.[1] The availability of caprolactam has stimulated much organic chemistry research in the last 40 years. It is not our intention to deal with the industrial aspects of caprolactam production which is generally based on the Beckmann rearrangement of cyclohexanone oxime or related variations.[1]

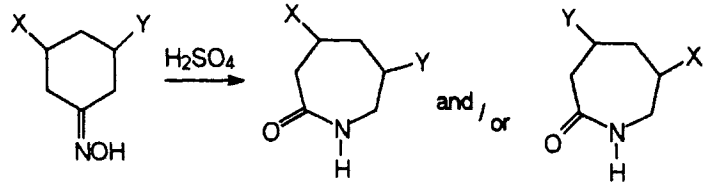
However, it is appropriate to mention here the connection with L-lysine, which arises by hydrolytic ring opening of 3-aminocaprolactam. This has been utilised for the production of both chiral and racemic lysine on a commercial scale.[2,3]

Considering the wealth of papers published in the area, it is surprising that the organic chemistry of caprolactam and its derivatives has not been reviewed previously. However, casual references do appear in a recent text devoted to lactam chemistry.[210]

PREPARATION

1. Beckmann Rearrangements

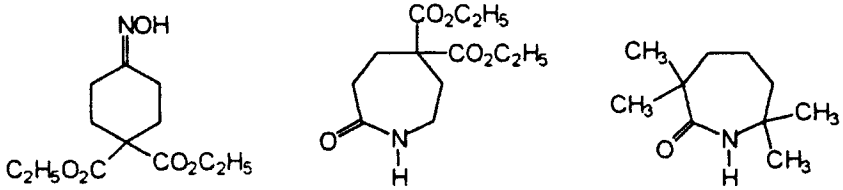
From the earliest days,[4–6] the Beckmann rearrangement has been the most popular method for construction of the caprolactam skeleton. Sulphuric acid has very frequently been the reagent of choice for this transformation.[7–12]



(1) (2) (3)

Many other reagents have been used, e.g. benzenesulphonyl chloride in alkaline solution,[13,31] toluene-*p*-sulphonyl chloride in alkaline solution,[14,15,20] PCl_5,[16,17,21] $POCl_3$,[18,19,22] toluene-*p*-sulphonyl chloride in pyridine,[23,24] polyphosphoric acid[25–30] and hydroxylamine-*O*-sulphonic acid.[32] Further modifications have included the use of trimethylsilyl polyphosphate, which was considered superior to polyphosphate ester (PPE) on the grounds of ease of formation,[33] although yields of lactams were similar. More recently, the combined use of tetrabutylammonium perrhenate(VII) and trifluoromethanesulphonic acid has been suggested for inducing the Beckmann rearrangement of oximes,[34] as has montmorillonite clay/KSF in refluxing toluene.[35] Further work may confirm the generality of these new devices.

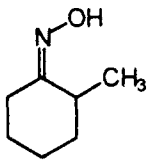
There is a report that attempted hydrogenation of the oxime **4** over Raney nickel yielded lactam **5**, although the yield was poor.[36] The lactam **6** may be obtained by photolysing the appropriate oxime in methanol using radiation which is 90% 253.7 nm.[37]



(4) (5) (6)

The well known dependence of the Beckmann rearrangement upon the stereoselectivity of the oximes used leads to the conclusion that, unless the oximes are purified, mixtures of lactams (e.g. **1** → **2** + **3**) may be expected.

Indeed, in early days, it was very difficult to identify and purify products (e.g. from **1** → **2** + **3**) and this probably explains the discrepancies found in the literature melting points (see tables). The advent of chromatography has largely solved these problems. In some cases, special efforts have been made to pre-purify oximes so that the Beckmann rearrangement gave regiospecific results. Thus, regiospecific methylation of the dilithio salt of cyclohexanone oxime gave the *Z*-isomer **7**, which underwent rearrangement (85% H_2SO_4/0 °C) giving predominantly the 3-methylcaprolactam isomer **8**, while the *E*-isomer **9** (oximation of 2-methylcyclohexanone) gave 7-methylcaprolactam (**10**).[38] The separated 2-methylcyclohexanone oximation products were later shown to behave similarly even using sulphuric acid at 110 °C.[39]



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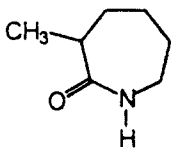

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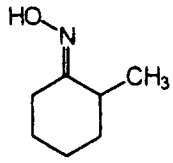

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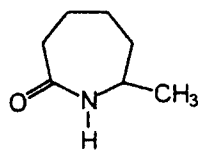
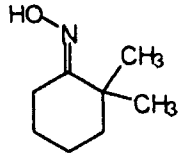
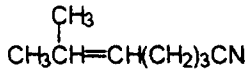


(10)

It has been recognised that in some cases the Beckmann fragmentation reaction intervenes depending on the reagent used. Thus, 2,2-dimethylcyclohexanone oxime (**11**) reacted with PCl_5 in diethyl ether (0 °C) giving 6-methyl-5-heptenenitrile (**12**) in 94% yield, whereas 7,7-dimethylcaprolactam



(11)



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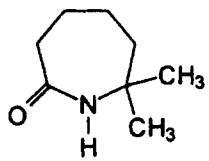
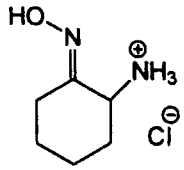


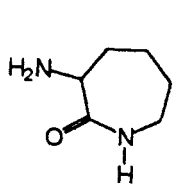
(13)



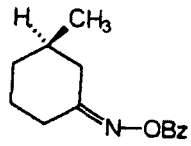
(14)

(**13**) was obtained in poor yield using thionyl chloride.[17] Other examples are seen when the 2-substituent stabilised a carbocation at C-2 of the oxime[21,23,40] leading to fragmentation products.

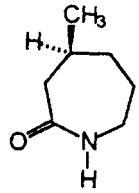
Apart from bulky substituents at C-2, Beckmann rearrangement of cyclohexanone oximes tolerates the presence of several substituent groups in various positions round the ring. 2-Aminocyclohexanone oxime hydrochloride (**14**) underwent rearrangement to 3-aminocaprolactam (**15**) in 96% H_2SO_4; apparently a pre-isomerisation of (*E*)- to (*Z*)-oxime took place.[41] The same rearrangement has been reported using a medium of SO_3 in liquid SO_2.[42] Other



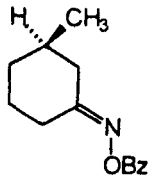
(**15**)



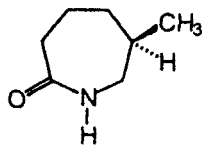
(**16**)



(**17**)

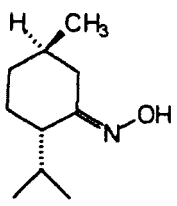


(**18**)

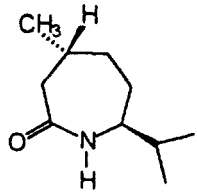


(**19**)

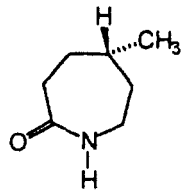
groups compatible with the rearrangement are $-CH_2SiMe_3$ and $-SiMe_3$,[43] $-NF_2$,[44] $-CH_2OCOPh$, $-CH_2O^tBu$ and $-CO_2{}^tBu$,[45] $Ph_2P(O)CH_2-$[46] and $-CN$.[47,48] Several examples involving chiral substrates have been reported: it is possible, with care, to avoid racemisation. Thus, **16** gave **17** and **18** gave **19**[42] and (−)-menthone oxime (**20**) gave **21** with $POCl_3$,[14,19] or benzenesulphonyl chloride/NaOH.[49] A Beckmann rearrangement of an optically active (+)-4-methylcyclohexanone oxime in a chiral host [(−)-1,6-bis(*o*-chorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol] yielded (*S*)-(−)-5-methylcaprolactam (**22**) in 80% ee.[50]



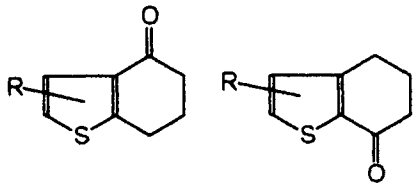
(**20**)



(**21**)

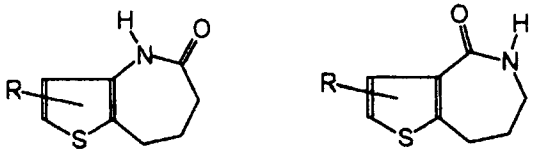


(**22**)



(23) (24)

Caprolactams have been obtained by an ingenious protocol involving Beckmann rearrangements of oximes of thiophenocyclohexanones (**23**, **24**) followed by desulphurisation of the thiophenocaprolactams thus obtained. Since the rearrangement gives, in general, a separable mixture of regioisomers (e.g. **25** and **26** from **23**), and thiophenes can carry a variety of substituents (R in

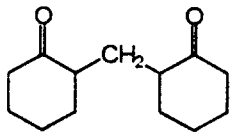


(25) (26)

23, **24**), this is a versatile approach. The following caprolactams are exemplary: 7-ethyl;[51] 3-ethyl, 7- and 3-propyl;[52] 4-ethyl;[53] various 3- and 7-aminoalkyl;[54] 3- and 7-cycloalkyl[55] and 7-ω-carboxyalkyl.[56]

2. Schmidt Reaction

2-Methylcyclohexanone has long been known[57] to react with hydrazoic and sulphuric acids giving 7-methylcaprolactam (**10**). A more detailed study of the Schmidt reaction applied to 2-alkyl-, 2-cyano-, 2-chloro- and 2-ethoxycarbonylcyclohexanones revealed that exclusive formation of 7-substituted caprolactams took place.[58] In this work hydrazoic acid in $CHCl_3$ was used. 7-Cyanocaprolactam was similarly obtained with sulphuric acid/$CHCl_3$/NaN_3 mixture.[59] Introduction of polyphosphoric acid (PPA) as both reagent and solvent with sodium azide[60] was shown to be a superior way of conducting Schmidt reactions and most, but not all,[61] subsequent applications for caprolactams have followed this lead:[62] in the case of methylene-2,2-bicyclohexanone (**27**), the polyphosphoric acid medium was much superior;[63] the products were a pair of diastereomers of 7,7′-methylenebiscaprolactam (**28**). The 4,4′-isopropylidene compound **29** similarly gave two diastereomers of 5,5′-isopropylidenebiscaprolactam (**30**).[64] When 2-arylmethylcyclohexanones were treated with sodium



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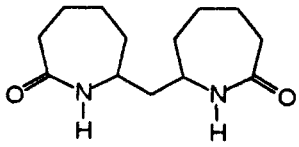

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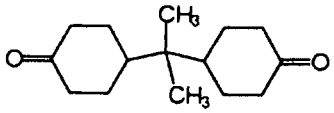

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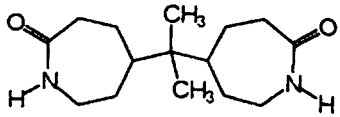
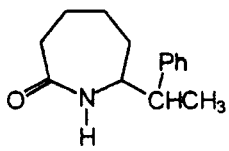


(30)

azide in PPA, 7-arylmethylcaprolactams were obtained in modest yield,[65] compound **31** again proving to be a diastereomeric mixture. 2-Arylcyclohexanones give either 3- or 7-arylcaprolactams depending upon the conditions used for the Schmidt reaction: low temperatures in PPA favour the formation of the 3-aryl isomers.[65,66]



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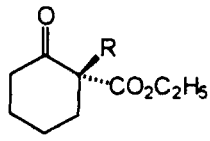

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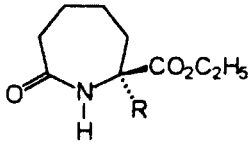

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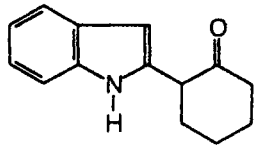

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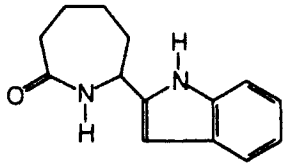
Fairly recent work[67,68] has revealed that when chiral substituted β-keto esters (e.g. **32**) were reacted with sodium azide and methanesulphonic acid in chloroform at reflux, the products (**33**, R = $PhCH_2$, 2-naphthyl-CH_2, p-$BrC_6H_4CH_2$, and m-$ClC_6H_4CH_2$) were formed with good retention of configuration and in good yield.

In several cases, Schmidt reactions have yielded different products from those obtained by the Beckmann rearrangement.[63,64] An interesting case involved

2-indolyl-2-cyclohexanone (**34**).[69] Here Beckmann rearrangement of the oxime yielded the 7-isomer **35** whereas the Schmidt reaction gave the 3-isomer **36**.



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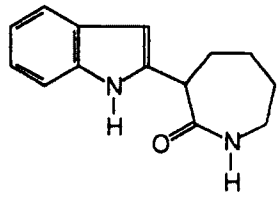

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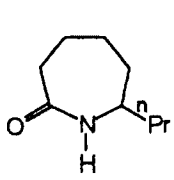
3. Cyclising Reactions

Since lactams are reversibly related to the appropriate amino acids, it is not surprising that caprolactams have frequently been obtained by cyclisation of 6-aminohexanoic acid or its derivatives. Indeed, this method has served to establish beyond doubt the structure of some substituted caprolactams when Beckmann or Schmidt reactions gave ambiguous mixtures.[70,71] Heating 6-amino-6,6-dimethylhexanoic acid at 280 °C for 30 min gave 7,7-dimethyl-caprolactam (**13**);[72] however, heating amino acids over Al_2O_3 is more highly recommended.[73] Amino esters can more easily be thermally cyclised: several caprolactams have been thus obtained; lactams **37** and **38** (R = CH_3, C_2H_5),[74] **39**,[75] **40**,[76] **41**[77] and **42**[91] are examples. The amino acid **43** cyclised to



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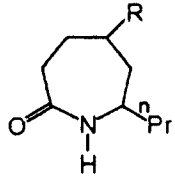

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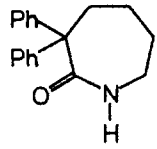

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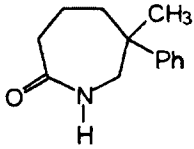

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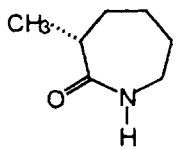

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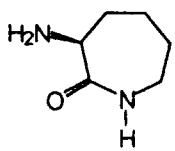

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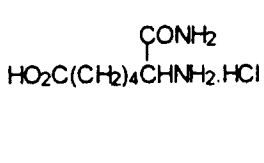

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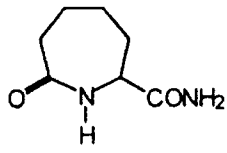

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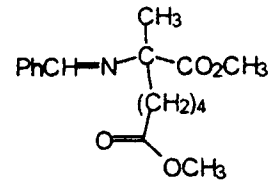

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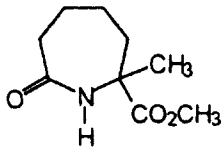

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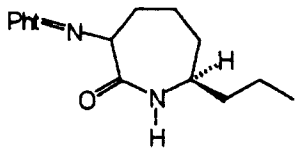

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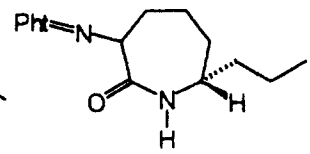
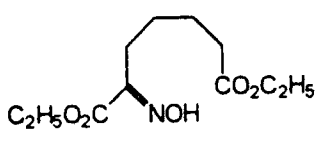


(48)

44 under the influence of diethyl phosphite.[79] More unusual was the thermolysis of **45**, which yielded the lactam **46**.[80]

A popular procedure has been reduction of nitrile esters and subsequent cyclisation either with or without isolation of the intermediate amino esters. These reactions appear to result in good yields of caprolactams.[70,71,81] Reductive cyclisations of various azido-sugar derivatives have been reported;[82–85] this approach makes available polyhydroxycaprolactams of known stereochemistry (see tables for examples). Catalytic reductive cyclisation of a protected chiral amino ester has been shown to give an excellent yield of the chiral aminocaprolactam L-Boc-**15**.[87] Acyclic azido esters may also be reductively cyclised without loss of chirality: **47** and **48** were thus obtained[88] and easily separated chromatographically. Similarly, reduction of ω-oximino esters gives caprolactams,[89] but in the special case of the oximino diester **49**, reduction with reduced iron powder gave the desired hydroxamic acid **50** in only 1.5% yield.[90] 6-Ketohexanoic esters were reduced with hydrogen and ammonia over nickel–aluminium catalyst to provide the caprolactams **38** (R = H, CH_3, C_2H_5).[74] Sodium methoxide was shown to cause cyclisation of methyl lysinate hydrochloride to aminocaprolactam (**15**) in either chiral or racemic form.[91] There is one example of a palladium-catalysed carbonylation of an iodoalkenylamine (**51**) leading to an interesting methylene caprolactam structure



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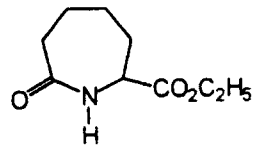

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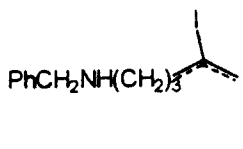

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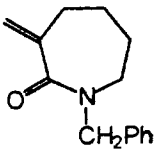
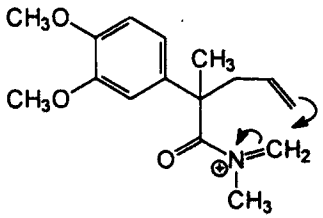


(52)

(52).[92] Likewise, there is a single example of an iminium ion cyclisation (53 → 54) leading to a substituted caprolactam;[93] there seems no reason why other examples of this type should not be uncovered.



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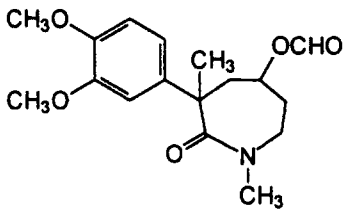

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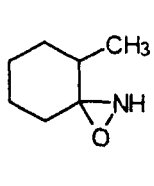
4. Miscellaneous Preparations

Spirooxaziridines have proved to be a useful source of caprolactams. Originally these were deduced to lie on the pathway to *N*-ethylcaprolactam, for example when nitroethane was irradiated in cyclohexane.[94] Later work showed that irradiation of oximes gave caprolactams presumably via oxaziridines (e.g. **55**)[95] and subsequently the oxaziridines were isolated (oxidation of imines) and photolysed.[95,96] This led to the first example of a chiral oxaziridine → caprolactam synthesis[96] giving (*S*)-(−)-5-*tert*-butylcaprolactam (**56**), the structure of which was confirmed by X-ray analysis. The methodology was extended by other workers to several further examples of 5-substituted caprolactams[97] and 3-, 4-, 6- and 7-substituted caprolactams.[98] It was recently disclosed that the ring opening of spirooxaziridines can be catalysed by manganese(III) tetraphenylporphyrin in a regio- and stereospecific manner.[99]

Claisen rearrangement of alkyl imidates (**57**, R = H, Ph) at 210–212 °C gave both 3-allyl and *N*-allyl products (**58** and **59**, respectively). The proportion of the latter increased with increasing temperature.[100,101] A related, but milder, reaction involves reaction of the imidate **60** with lithium salts of allyl alkoxides **61** (R^2, R^3 = H, CH_3, Ph, etc.). The diastereomeric products generally favoured one isomer (e.g. **62**) over the other.[102]



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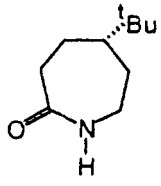

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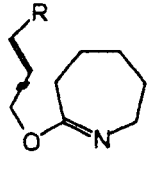

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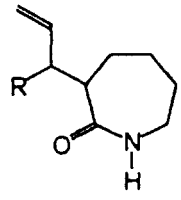

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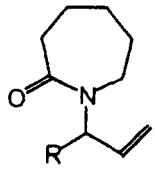

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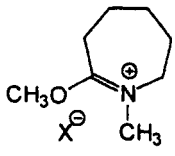

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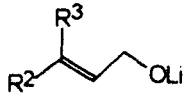

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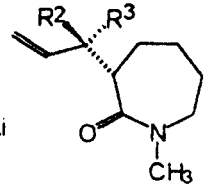
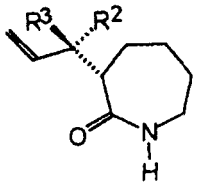


(62)

Allylic peroxidation of the endocyclic imine **64** gave **65** with R = either H or OH, depending on the conditions used.[103] Ozonolysis of a dimethoxybenzazepinone (**66**) gave the muconate **67** in fair yield[104] in a fast (20 min) reaction regulated by addition of boron trifluoride etherate.



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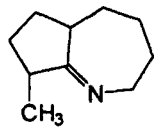

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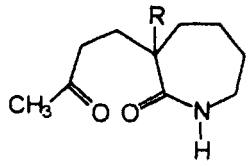

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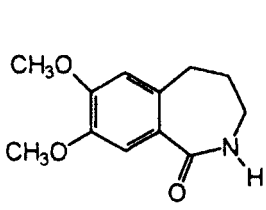
Several ring expansion protocols leading to caprolactams have been published. For example, 1-chloro-1-nitrosocyclohexane (**68**, R = H) reacted



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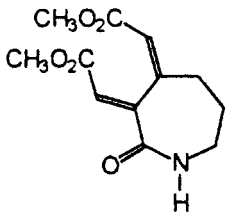

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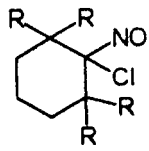
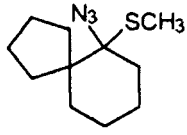


(68)

with triphenylphosphine[105] to give caprolactam in reasonable yield and triphenylaluminium caused the conversion of the tetramethyl analogue (**68**, R = CH_3) into 3,3,7,7-tetramethylcaprolactam **6**.[106]



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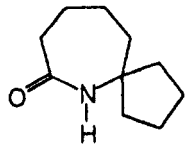

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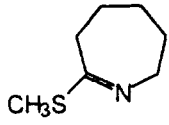

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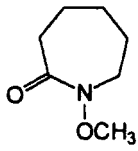

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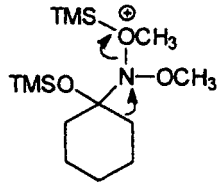
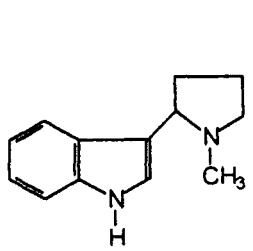


(73)

1,1-Azidosulphides (e.g. **69**) reacted with a four molar proportion of trifluoroacetic acid in chloroform to give the spiro derivative **70**.[107] On the other hand, tin(IV) chloride led to the formation of imino thioether structures such as **71**, which can be converted into caprolactams or used as activated lactams in reactions with nucleophiles. Ring expansion of cyclohexanone was brought about by the combined action of dimethoxyamine [$HN(OCH_3)_2$] and trimethylsilyl triflate which gave the *N*-methoxycaprolactam **72**,[108] presumably via intermediate **73**. More unusual and specialised was the conversion (in 13% yield) of the 3-pyrrolidinylindole **74** into the substituted caprolactam **75** by refluxing with diethyl malonate and powdered sodium hydroxide in xylene for 2 days.[109]



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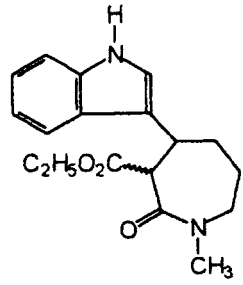

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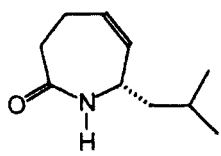

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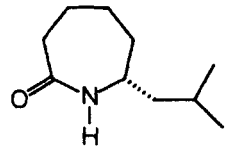
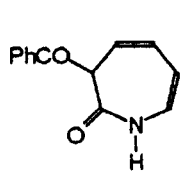


(77)

Not surprisingly, reduction of double bonds in unsaturated lactams leads to caprolactams (hexahydroazepin-2-ones). For example, hydrogen over palladium converted **76** into **77** without loss of chirality.[110] Various tetrahydroazepin-2-ones have been hydrogenated over palladised carbon[111] and dihydroazepinone **78** was likewise reduced to the hexahydro state.[112] Sodium borohydride reduced the α,β-unsaturated ketone **79** to the caprolactam **80**[113] and the imine **81** to the



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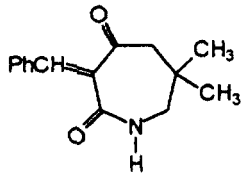

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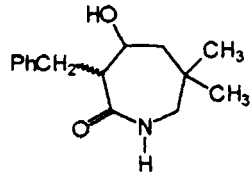

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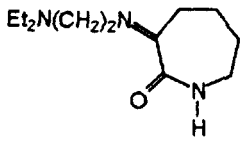

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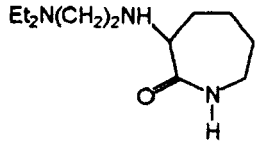
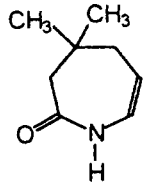


(82)

aminocaprolactam **82**.[114] Addition of methanol across the double bond in **84** was achieved using mercury(II) acetate in methanol and gave **85**.[115]



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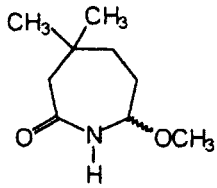
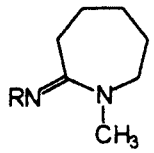


(85)

5. Caprolactam Imines

These structures are of interest, partly because as cyclic amidines they may show some biological activities. Reaction of chlorosulphonyl isocyanate with *N*-methylcaprolactam gives the chlorosulphonyl derivative **86** (R = SO_2Cl), from which the simple imine **86** (R = H) was obtained using aqueous sodium hydroxide.[116]



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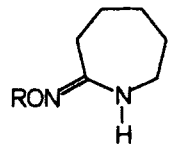

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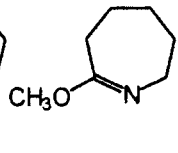

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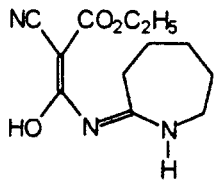

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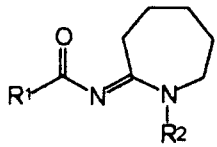
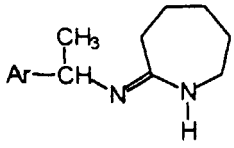


(90)

Oximinocaprolactam (**87**, R = H) arises when caprolactam is treated with hydroxylamine hydrochloride and sodium hydrogencarbonate in methanol at reflux[117] or by using phosgene, then methanol (to give the lactim ether **88**) followed by hydroxylamine.[118] Other derivatives (**87**, R = CH_3SO_2-, $-CO_2CH_3$) were made from **87** (R = H) using the relevant reactive acid halides.[118] The tosyl analogue **86** (R = tosyl) arose from treatment of *N*-methylcaprolactam with tosyl isocyanate.[119] Several methyl-substituted caprolactams were oximated after conversion into the corresponding thiolactams.[120] More

complex cyclic amidines have been made from lactim ether **88** by treatment with various nitrogen nucleophiles: examples include **89**,[121] **90** (R^1 = various aryl, R^2 = H, CH_3),[122] **90** (R^1 = various aryl-NH, R^2 = H, CH_3)[123] and **91** (various aryl).[124] Aryl sulphimides **92** were made from **86** (R = SO_2Cl) in Friedel–Crafts-type reactions with arenes and $AlCl_3$.[125] Lactam acetal **93**[126] has



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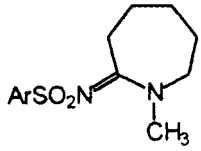

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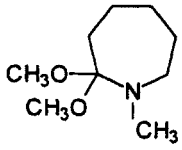

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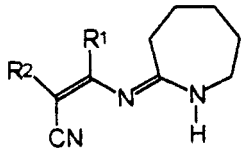
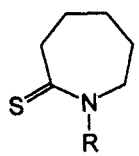


(94)

proved a very popular substrate for making caprolactam imines: it reacts with many different kinds of nitrogen nucleophiles. The following selection gives an idea of the scope. Arylamines yielded products such as **86** (R = various aryl),[127–129] **94** (R^1 = aryl, R^2 = CN, *p*-$NO_2C_6H_4$),[130] **94** (R^1 = H, R^2 = CO_2CH_3),[131] **86** (R = $CONH_2$, $CO_2C_2H_5$),[132] **92**[133] and **86** (R = *o*-$CO_2C_2H_5C_6H_4$).[134]

6. Caprolactam Thiones (Thiocaprolactams)

An early paper[135] described how cyclohexanone oxime with benzenesulphonyl chloride in pyridine saturated with hydrogen sulphide gave the parent of this series **95** (R = H). The *N*-methyl analogue (**95**, R = CH_3) was made from the corresponding *N*-methylcaprolactam in 20% yield[136] by heating with P_4S_{10} in xylene, although a 68.5% yield had previously been reported.[120] An earlier



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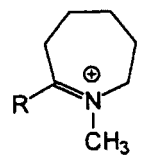

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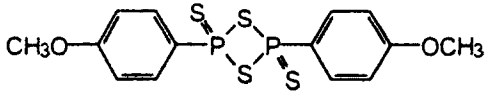

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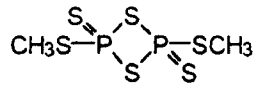


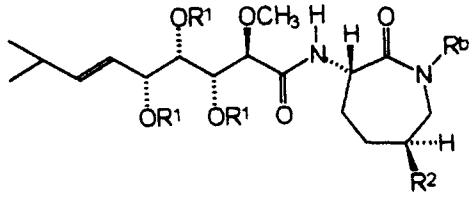
(98)

method using CS_2 does not now appear attractive.[137] The use of hydrogen sulphide was recommended when activated iminium species such as **96** (R = Cl or OSO_2Ph) were the substrates.[138,139] Owing to the developing interest in thiolactams, several improved reagents have more recently been introduced for the conversion of caprolactams into their thio analogues. Lawesson's reagent[140] (**97**) and an 'improved' version (**98**) have been published. Other devices include treatment of the caprolactam with bis(tricyclohexyltin) sulphide/boron trichloride, which generates B_2S_3 *in situ*,[142] and treatment of the lactam with P_4S_{10} and organolithiums (^nBuLi, CH_3Li or PhLi) under mild conditions.[143] Alternatively, the fluoroborate salt **96** (R = OEt) could be reacted with NaSH[144] or the lactam with bis(1,5-cyclooctanediylboryl) sulphide [$(9BBN)_2S$], which gave an 88% yield of **95** ($R = CH_3$).[145] Nowadays, it appears that the choice of reagent for this conversion is a matter of personal preference.

7. Natural Products

Until recent times, the caprolactam nucleus was not a feature of many natural product structures. Mycobactins[146] were exceptional. The appearance of the reduced azepine ring in natural products is due to the connection of 3-aminocaprolactam with lysine; it is indeed 'cyclolysine,' so lysine and δ-hydroxylysine are implicated in the biosynthetic pathways involved.

The bengamides (**99**), isolated from a Fijian sponge show a variety of biological actions, including anthelmintic and bacteriostatic.[147] Some bengamides

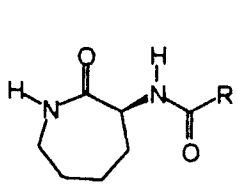


(99)

contain a 6-hydroxy-3-aminocaprolactam moiety, e.g. bengamide B [**99**, $R^1 = H$, $R^2 = CH_3(CH_2)_{12}CO_2-$, $R^b = CH_3$), whereas others are merely 3-aminocaprolactams such as bengamide E (**99**, $R^1 = R^2 = R^b = H$).[148] Several

total syntheses of bengamide E have been reported,[149–151] including an enantioselective example.[152] Bengamides A[153] and B[152] have also been synthesised. Sponges have yielded other examples.[359,360]

Caprolactins A and B [**100**, R = $-(CH_2)_5CH(CH_3)_2$ and $-(CH_2)_4CH(CH_3)(C_2H_5)$] were isolated from a bacterium in a deep ocean sediment and have been synthesised.[154] The pathogenic fungus *Periconia circinata* has yielded a non-toxic metabolite called circinatin **101**[155] and the cobactins have continued to receive attention;[156] benzyl-cobactin T (**102**, R = CH_2Ph) was synthesised from the corresponding Boc-protected 3-aminocaprolactam and catalytically debenzylated to cobactin T (**102**, R = H).



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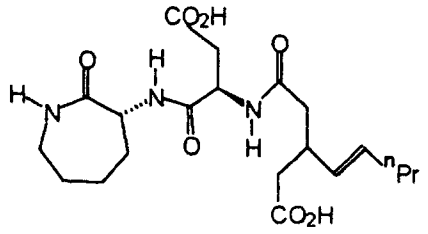

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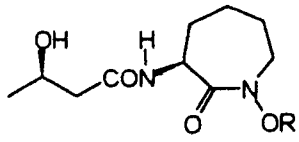


(102)

Mycobactin S2 has been synthesised.[157] Since the bulk of synthetic problems in this area are concerned with the side chain rather than the heterocyclic nucleus, detailed discussion of the relevant chemistry is outside the scope of this volume.

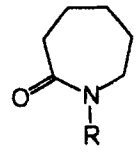
PROPERTIES AND REACTIONS

Caprolactams are, on the whole, thermally stable solids or distillable oils. They are generally neutral, typical lactams which may be hydrolysed to the corresponding amino acids (see below). In early work the only physical measurements recorded were refractive indices, but gradually infrared and, later, nuclear magnetic resonance spectra have been reported. Accordingly, most authors during the last 30 years have provided useful reference data to which we allude in the tables. The preferred conformations to be found in the ring system have attracted passing interest[158,159,207] and it seems that the conformational preferences of caprolactams are similar to those of cyclohexanes.[159]

Caprolactams undergo a variety of chemical transformations, many of which are predictable but a few are not.

1. Substitution on Nitrogen

As expected, *N*-substitution with alkyl halides and bases is facile: sodium hydride is a very satisfactory reagent for the deprotonation of caprolactams;[160] many other examples are given in the tables. *N*-Acylation does not necessarily require any base to be present; for example, *N*-acetylation[161] and *N*-benzoylation[162] have been thus carried out. However, it seems more expedient to use a base such as triethylamine or *N*,*N*-dimethylaniline.[163] A two-stage haloalkylation has been carried out by heating caprolactam with trimethyl silyl chloride and paraformaldehyde; in this way **103** (R = CH_2Cl) was obtained.[164]



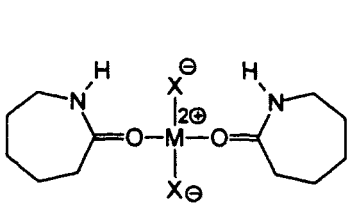
(103)

Michael additions are frequently encountered; thus acrylonitrile reacted with caprolactam in the presence of Triton B, giving **103** (R = CH_2CH_2CN),[165] and phenylacetylene reacts in the presence of sodium to yield *N*-styrylcaprolactam **103** (R = $PhCH{=}CH_2$).[166] Styrene reacted with caprolactam in hexamethylphosphoramide to give **103** (R = CH_2CH_2Ph).[167] Carbamates (e.g. **103**, R = PhNHCO–) arise by using isocyanates.[168] Trimethylsilylation [**103**, R = $(CH_3)_3Si$] was achieved with trimethylsilyl chloride in the presence of triethylamine or better with trimethylsilyldiethylamine.[169] *N*-Nitrosocaprolactam **103** (R = NO) has been made by reaction with nitrosating gases (from $NaNO_2$ and H_2SO_4)[170] or by direct reaction with sodium nitrite and concentrated hydrochloric acid at −10 °C.[171] The chemical behaviour of *N*-nitrosocaprolactam has been studied,[170–172] particularly with respect to ring opening.

2. Metal Complexes

Copper(II) complexes are known in which both two (**104**, M = Cu, X = Br, Cl)[173] and three (**105**, M = Cu, X = Cl)[174] molecules of caprolactam are incorporated. Manganese(II) forms complexes of type **105** (M = Mn, X = Cl),[173] while zinc(II) is also found as in **104** (M = Zn, X = Br) and **105**

(M = Zn, X = I).[175] Platinum(II) behaves as in **104** (M = Pt, X = Cl)[176] but rhodium(III) appeared as a three-caprolactam assembly (**106**).[176]



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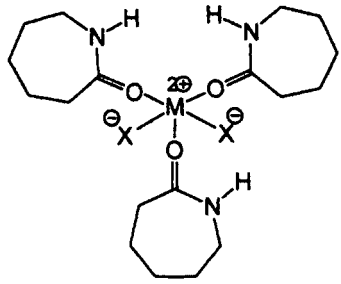

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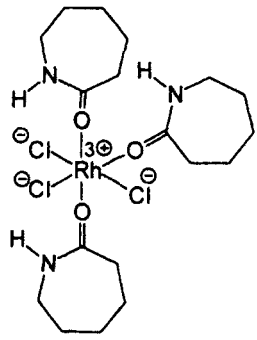

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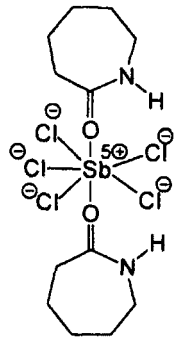
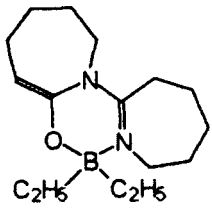


(107)

$VOCl_2$ complexes two caprolactams (**104**, M = VO, X = Cl)[177] and antimony pentachloride gave the complex **107**.[178] Boron compounds associate with caprolactam in different ways depending on the attached ligands. BF_3 forms a [BF_3 + 2-caprolactam] complex[178–180] but the reaction with triethylboron leads to a more fundamental change (**108** and **109** isolated).[181] Triisopropylboron gave the four-membered ring compound **110**.[181] The



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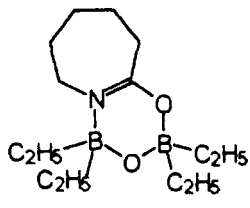

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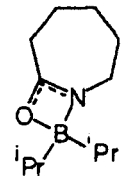
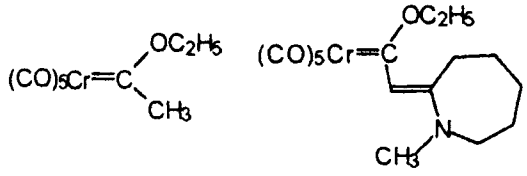


(110)

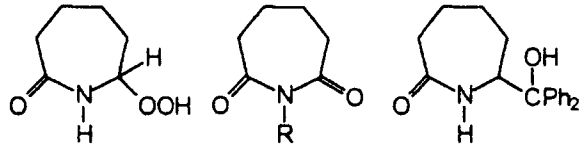
chromium carbonyl carbene compound **111** reacted with *N*-methylcaprolactam to give the product **112**.[182]



(111) (112)

3. Oxidation and Reduction

Oxygenation of caprolactam under the influence of UV irradiation gave a hydroperoxide (**113**);[183] zinc chloride was shown[184] to accelerate this reaction. Cobalt salts induced the conversion of **113** into the dione **114** (R = H) (adipimide). The peracid-, cobalt- or manganese-catalysed oxidation of caprolactam led directly to an adipimide (**114**, R = H).[185] The initially formed radical in this photo process was trapped with benzophenone yielding the tertiary alcohol **115**.[186]



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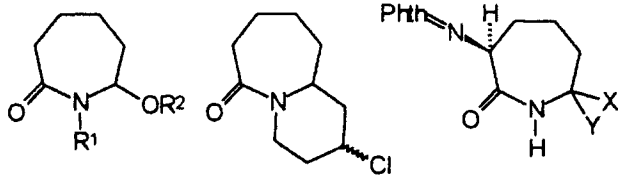
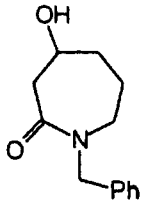


(116) (117) (118)

Anodic oxidation of caprolactam in the presence of alcohols gives the 7-alkoxylactams **116** (R^1 = H, R^2 = CH_3, C_2H_5);[187] conversion of the latter into the bisalkoxy compound **116** (R^1 = CH_2OH, R^2 = CH_3) followed by $TiCl_4$-induced reaction with allyltrimethylsilane gave the annulated product **117**.[188] However, anodic oxidation of *N*-alkylcaprolactams takes another course; thus *N*-methylcaprolactam gave a mixture of **103** (R = H, CH_2OH, CHO).[189] Similarly, RuO_4 oxidations gave mixtures involving *exo*- and

endo-carbon atoms: *N*-Methylcaprolactam (**103**, R = CH_3) yielded caprolactam (24%), *N*-formyl caprolactam (**103**, R = CHO) (35%) and *N*-methyladipimide (**114**, R = CH_3) (38%).[190] The (*S*)-3-*N*-phthaloylcaprolactam **118** (X = Y = H) could be oxidised to the (*S*)-3-*N*-phthalimidoadipimide **118** (X + Y = O) using benzene seleninic anhydride[191] or $KMnO_4$ in $CH_3CO_2H/H_2O/H_2SO_4$.[192] The *R*-isomer behaved similarly.[191] Biological oxidation of *N*-benzylcaprolactam (**103**, R = $PhCH_2$) with *Beauveria sulfurescens* gave a mixture of 4- and 5-hydroxy products (**119** and **120**).[193]



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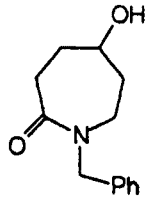

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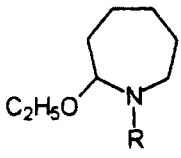
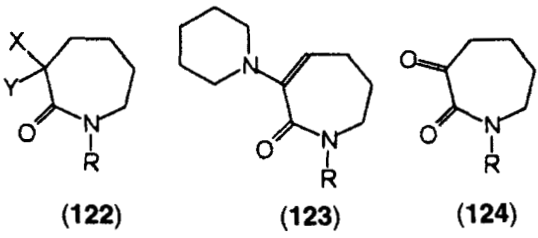


(121)

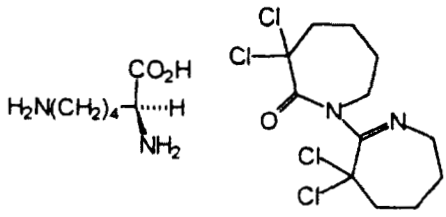
There are really only two useful modes of reduction for caprolactams. First, $LiAlH_4$ has been widely used to convert the lactams into azepanes (Chapter 2).[194–197] On the other hand, sodium borohydride treatment of *N*-substituted caprolactams (**103**, R = $CO_2C_2H_5$, CO_2CH_2Ph or $CO_2{}^tBu$) gave the very useful ethoxyazepanes **121** (R = $CO_2C_2H_5$, CO_2CH_2Ph or $CO_2{}^tBu$) (Chapter 2).[198,199]

4. Halogenation

Invariably caprolactams undergo halogenation at C-3. Monochlorination is difficult to achieve, the 3,3-dichlorolactam **122** (R = H, X = Y = Cl) usually being the principal product.[57,200–203] The reagents used have generally been PCl_5 alone or in admixture with $POCl_3$; it is advisable to carry out these reactions at low temperatures.[200,205] The dibromo-compound **122** (R = H, X = Y = Br) was similarly (Br + PCl_5) obtained[203,204] and used to obtain enamine **123** (R = H) from which dione **124** (R = H) and other derivatives were made.[204] A related series of reactions from the dichloro analogue **122** (R = CH_3, X = Y = Cl) gave the 2,3-dione **124** (R = CH_3).[205] By contrast, monochlorination of *N*-benzoylcaprolactam is straightforward using sulphuryl chloride;[163] the technical process has been improved by transamidation of the product (**122**, R = PhCO, X = H, Y = Cl) with caprolactam which gave a better and more convenient overall conversion into 3-chlorocaprolactam (**122**, R = X = H, Y = Cl).[206] The latter has been efficiently obtained by catalytic hydrogenolysis of the dihalide **122** (R = H, X = Y = Cl).[201,203] Replacement of halogen atoms with the amino group has been much studied[2,201–203,208] since the



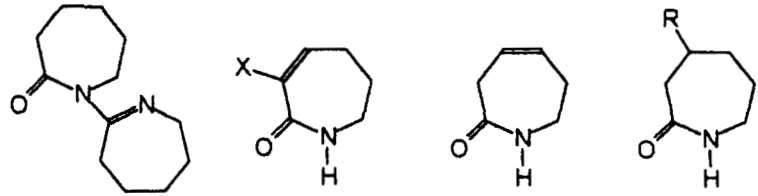
(122) (123) (124)



(125) (126)

3-aminocaprolactam so obtained can be converted into lysine by hydrolysis. 3-Chlorocaprolactam may either be aminated directly with ammonia[202,203] or first displaced with azide ion (to **122**, R = X = H, Y = N_3) and subsequently reduced catalytically.[201,207,211] Production of L-lysine is an important industrial process: in one case (Toray), racemic 3-aminocaprolactam is hydrolysed enzymatically to L-(*S*)-lysine (**125**) using L-caprolactam hydrolase (*Candida humicola*) and simultaneously the unwanted (*R*)-aminocaprolactam is racemised by D-aminocaprolactam racemase (*Alcaligenes faecalis*). Thus all material is converted into L-lysine.[209] 3-Iodocaprolactam was obtained from the 3-bromo analogue by reaction with sodium iodide.[202]

Not all halogenations proceed uneventfully; it was demonstrated that sulphuryl chloride in CCl_4 first converted caprolactam into an intermolecular condensation product (**126**) which gave **122** (R = H, X = Y = Cl) on treatment with methanol and HCl.[212] $POCl_3$ alone converted caprolactam into **127**, which also gave **126** by treatment with sulphuryl chloride.[212]



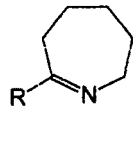
(127) (128) (129) (130)

Direct displacement of bromine from **122** (R = H, X = Y = Br) with sodium diethylmalonate gave the substitution product **122** [R = X = H,

Y = $CH(CO_2Et)_2$],[213] which was converted into several other substances (e.g. **122**, R = X = H, Y = CH_2CO_2H).

Elimination of halides, on the other hand, is known. The dichlorocaprolactam **122** (R = H, X = Y = Cl), made from caprolactam with $COCl_2$ and Cl_2, underwent conversion to the cyclic acrylamide **128** (X = Cl) when heated with $AlCl_3$ in CCl_4.[214] Dehydrobromination of 3-bromocaprolactam (**122**, R = X = H, Y = Br) by lutidine gave two products (**128**, X = H, and **129**), both of which reacted with sodium diethylmalonate yielding the 4-substituted ester **130** [R = $CH(CO_2Et)_2$].[215,216] The latter reaction is of Michael type, it being considered that the two alkenyl substrates involved were in equilibrium via an enol during the reaction. In similar fashion, 3-bromocaprolactam and sodium methoxide gave **130** (R = OCH_3),[217] although earlier workers[162] had mistakenly thought that this treatment comprised a direct displacement of bromide by methoxide leading to **122** (R = X = H, Y = OCH_3).

Chlorination of caprolactam with *tert*-butyl hypochlorite gave the *N*-chlorocaprolactam **103** (R = Cl), which underwent photolytic dehydrohalogenation and solvent capture in methanol which led to the methoxy lactam **116** (R^1 = H, R^2 = CH_3).[219] If caprolactam is allowed to react with phosgene ($COCl_2$) alone, the imidoyl chloride **131** (R = Cl) is obtained and reacted with Meldrum's acid



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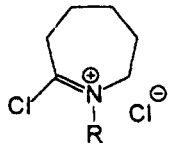


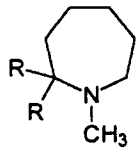
(132)

leading to 2-alkenylazepanes (Chapter 2).[220] On the other hand, *N*-alkylcaprolactams gave chloroiminium salts (**132**), which also reacted with Meldrum's acid yielding useful 2-alkenyl-*N*-alkyl azepanes[221,222] (Chapter 2).

5. Substitution at C-2

In addition to the cases above, which arise by preliminary halogenation of caprolactams, several other methods are known for achieving substitution at C-2. It has long been known[223] that Grignard reagents add to *N*-methylcaprolactam in bis-fashion (**133**, R = CH_3, C_2H_5, C_3H_7, C_4H_9). More recently, it was shown that alkynyl boranes add to *N*-alkyllactams and that after $LiAlH_4$ reduction, alkynylamines were obtained.[244] In this way compound **134** was made.

The behaviour of caprolactam with dimethyl sulphate is interesting: mild treatment brought about conversion to the lactim ether (**131**, R = OCH_3),[225] which reacts as previously with Meldrum's acid.[226] However, if more vigorous



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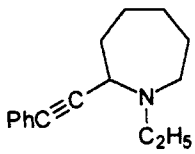

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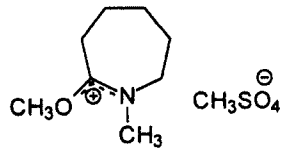
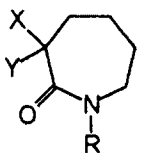


(135)

conditions are employed, alkyl O to N migrations take place and *N*-alkylcaprolactams (**103**, R = CH_3, C_2H_5, etc.) are obtained.[225] On the other hand, *N*-methylcaprolactam forms a salt (**135**) with dimethyl sulphate; application of sodium methoxide then leads to the acetal (**133**, R = OCH_3).[126a] The latter reacts easily with various activated methylene compounds (e.g. CH_3NO_2, malonates); the products are 2-alkenylazepanes (Chapter 2).[228] As stated above (Section 5), lactam acetals are useful starting materials for preparation of lactam imines (**86**).

6. Substitution at C-3

It was to be expected that deprotonation of *N*-substituted caprolactams would be possible and that the resulting anions would react with electrophiles. LDA is a suitable base to achieve this objective; introduction of the diethyl carbonate or carbon dioxide led to isolation of the substituted products (**122**, R = CH_3, X = H, Y = $CO_2C_2H_5$ or CO_2H, respectively).[229,230] Examples of C-3 alkylation have been reported.[244] The *N*-acyl caprolactam **103** (R = CH_3CO) could be



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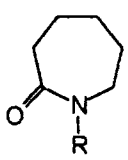

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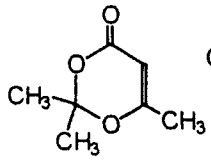

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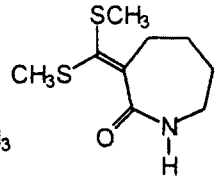
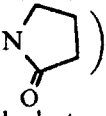
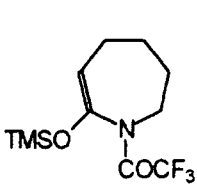


(137)

deprotonated using NaH in THF and was then hydroxylated with veratraldehyde giving **122** $\left(R = CH_3CO, X = H, Y = CH(OH)\text{-}C_6H_3(OCH_3)_2\right)$.[231]

Caprolactam itself has been C-3 acylated using the combination of BuLi/TMEDA with the heterocycle **136** followed by treatment with HCl,[232] the product being **122** (R = X = H, Y = $COCH_2COCH_3$). *N*-Trimethylsilylcaprolactam [**103**, R = $(CH_3)_3Si$] was reacted with $LiNEt_2$/HMPT and benzophenone to yield **122** (R = X = H, Y = $-C(OH)Ph_2$);[233] other ketones could probably be introduced.[233] *N*-Methylcaprolactam (**103**, R = CH_3)

underwent Vilsmeier reaction to give **122** [R = CH_3, X + Y = $CHN(CH_3)_2$] and the formyl derivative **122** (R = CH_3, X = H, Y = CHO).[234] Nitration of caprolactam[235,236] with fuming nitric acid gave 3-nitrocaprolactam (**122**, R = X = H, Y = NO_2), catalytic reduction of which gave 3-aminocaprolactam (**122**, R = X = H, Y = NH_2) with poor enantioselectivity using either ruthenium or palladium catalysts.[236,237] CS_2 reacted with *N*-benzoylcaprolactam and $^tC_5H_{11}ONa$ followed by methyl iodide to give the C-3 substitution product **137**;[238] sodium hydride has also been used in this reaction in place of $^tC_5H_{11}ONa$.[239] Conversion of the *N*-trifluoroacylcaprolactam **103** (R = CF_3CO) into the *O*-trimethylsilyl derivative **138** permitted alkylation in the presence of trimethylsilyl triflate and isolation of the C-3-substituted product (**122**, R = X = H, Y = ).[240] Lactam acetals (**122**, R = CH_3, X = Y = Et) have reacted with electrophiles such as benzoyl chloride giving, for example, 3-alkenyl structures (**139**) as a mixture of isomers from which 3-benzoylcaprolactam (**122**, R = CH_3, X = H, Y = COPh) could be



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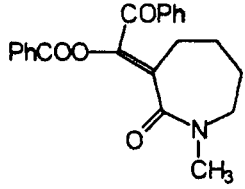

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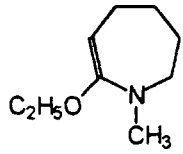
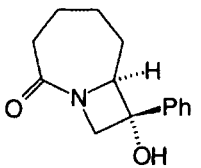


(140)

obtained by heating with HCl.[241] The success of such a reaction is considered to be due to the fact that the original acetal comes into equilibrium with the enol ether **140**, which then reacts at C-3 with an electrophilic reagent.[241]

7. Annulations or Cyclisations Involving the Caprolactam Nucleus

There are several modes of cyclisation elaborating from the caprolactam ring system. 1,7-Photocyclisation of *N*-phenacylcaprolactam (**103**, R = $PhCOCH_2$–) gave diastereomers **141** and **142** in 26% and 17% yield, respectively.[242] The action of sodium on ester **143** in the presence of ethyl acrylate caused *N*-alkylation (Michael reaction) followed by Dieckmann



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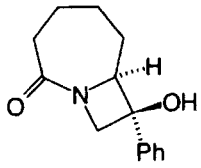

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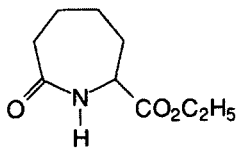

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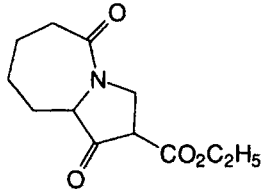
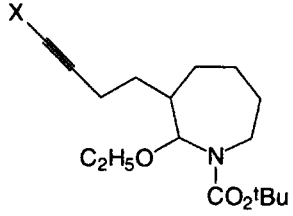
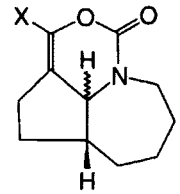


(144)

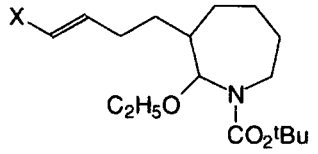
cyclisation to **144**.[243] A very interesting series of 2,3-cyclisations via iminium ions has been reported;[244] both alkynes and alkenes have participated in these reactions. Exemplary is the conversion of **145** [X = CH_3, $(CH_3)_3Si$, $(CH_3)_3SiCH_2$, Ph] to mixtures of diastereomers **146** and the alkene analogue **147**, which, when treated with $SnCl_4$ at −23 °C, was converted in good yield exclusively into one diastereomer (**148**, X = Ph, CH_3). Several other examples



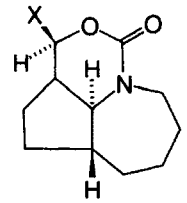
(145)



(146)

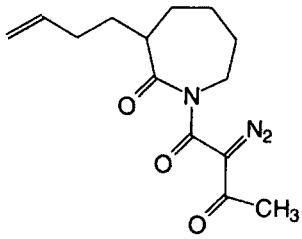


(147)

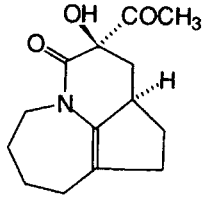


(148)

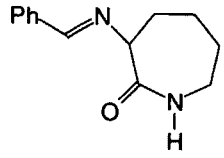
were presented.[244] A 1,3-cyclisation has been contrived by the rhodium acetate-induced conversion of the diazoalkene **149** into an intermediate which on silica was changed into the tricyclic product **150**.[245]



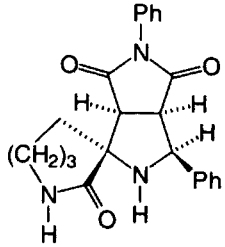
(149)



(150)

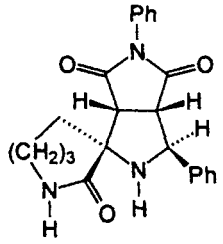


(151)



(152)

Spiro cyclisation takes place when the imine **151**, generated *in situ*, reacts with a dipolarophile such as *N*-phenylmaleimide to yield **152** and **153**.[246] It is



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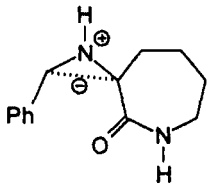


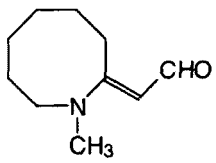
(154)

considered that the 1,3-dipolar species involved can be regarded as in **154**, arising from **151** by prototropic shift.

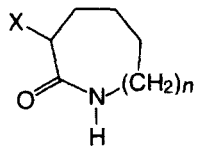
The Russian literature contains examples of annulations via the α-cyanolactam (**122**, R = CH_3, X = H, Y = CN) leading to pyrimido[4,5-*b*]azepine derivatives.[351,358] The lactam acetal **133** (R = OC_2H_5) has also been used to elaborate the pyrimido[4,5-*b*]azepine ring system[132] and the quinolo[2,3-*b*]azepine system.[134]

8. Ring Expansion and Contraction

As far as we are aware there is only one recorded example of a ring expansion involving the caprolactam nucleus. Lithium triphenylsilylacetylide reacted with *N*-methylcaprolactam (**103**, R = CH_3) to yield an α,β-unsaturated aldehyde containing the octahydroazocine ring (**155**).[247] Unfortunately, the structure of the above product was incorrectly formulated in the original report.[248]



(155)



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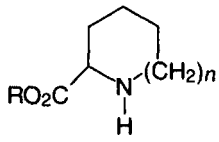
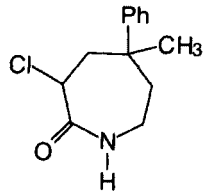
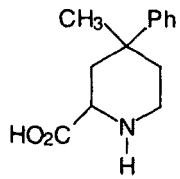


(157)



(158)

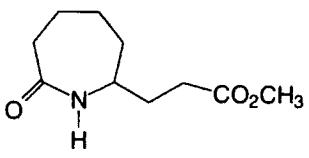


(159)

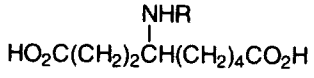
Ring contraction by the Favorskii rearrangement has been known for some time.[249,250] Thus, a series of lactams **156** (n = 1–6; X = Cl, Br) gave the amino acids or esters (depending on work-up conditions) (**157**, n = 1–6: R = H or CH_3) by refluxing with NaOH in dioxane. Although details for conversion of the halocaprolactams **156** (n = 1, X = Cl, Br) are sketchy (the main interest was in larger rings), this does seem to be a method applicable to seven-membered ring halolactams. This view is confirmed by the report[251] that $KO^tBu/^tBuOH$ converted the halolactam **158** into the substituted pipecolic acid **159**. It is surprising that more use has not been made of this conversion; overall it represents a possible method for conversion of substituted cyclohexanones (via Beckmann or Schmidt reactions) into substituted pipecolic acids.

9. Hydrolysis of Caprolactams

It is clear that lactams and the corresponding amino acids are interrelated by hydrolysis and dehydrations. Caprolactam on hydrolysis yields 6-aminocaproic acid (6-aminohexanoic acid).[252] By substitution of the caprolactam nucleus followed by hydrolysis, one has a useful method for synthesising some unusual amino acids. *N*-Alkylcaprolactams such as *N*-hexadecylcaprolactam were hydrolysed by 48% HBr to give hexadecylaminocaproic acid hydrobromide in good yield.[254] 6-Aminostearic acid was made similarly.[254] Amino diacids can be obtained by hydrolysis of 7-carboxyalkylcaprolactams (**160**); in this way, amino acid derivatives (**161**, R = H or CO_2CH_2Ph) were made.[255] Since the 7-substituent on the caprolactam ring was introduced by a combination of alkylation of cyclohexanone enamine + Schmidt reaction chemistry, this approach is obviously open to further expansion.



(160)



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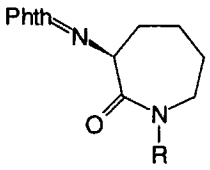
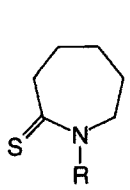


(162)

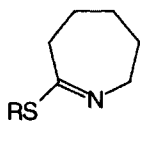
Hydrolysis of 3-aminocaprolactam to lysine was mentioned at the beginning of this chapter. *N*-Methyl-L-lysine has also been obtained by *N*-hydroxyalkylation (**162**, R = H → **162**, R = CH_2OH) followed by reduction ($Et_3SiH/CF_3CO_2H/CHCl_3$) to **162** (R = CH_3) and hydrolysis.[256] The conversion of 3-aminocaprolactam into L-lysine by microbial enzymes was reviewed in 1974.[257]

10. Thiocaprolactams

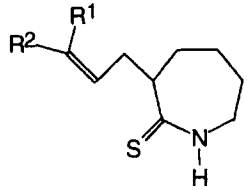
Thiocaprolactam is less basic than caprolactam[258] and has a greater dipole moment and lower infrared stretching frequency which confirms that C-2 is more positive in the thiolactam.[259] Hydrogen peroxide oxidation of thiocaprolactam in neutral solution led to the formation of the corresponding *S*-oxide.[260] Trimethylsilylthiolactam [**95**, R = $(CH_3)_3Si$] reacts with alkyl halides yielding compounds **163** (R = CH_3, C_2H_5, C_3H_7, etc.), which on further treatment give *N*-alkylthiolactams (**95**, R = CH_3, C_2H_5, C_3H_7, etc.).[261] Alkylation and acylation of thiocaprolactams is a facile process:



(95)



(163)



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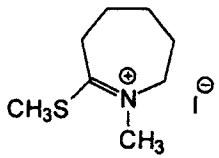
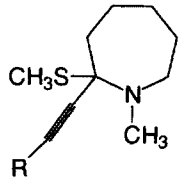


(165)

the *N*-benzyl analogue **95** (R = CH_2Ph) was C-3 formylated with $^tBuOCH(NMe_2)_2$ and acylated with $^iPr_2NMgBr/(MeO)_2C{=}O$ in good yield. The *N*-unsubstituted thiolactam **95** (R = H) may be alkylated using 2 equivalents of ^nBuLi yielding products **164** ($R^1 = R^2 = H$; $R^1 = H$, $R^2 = CH_3$; $R^1 = R^2 = CH_3$).[264]



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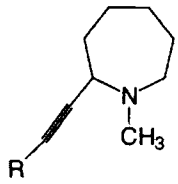

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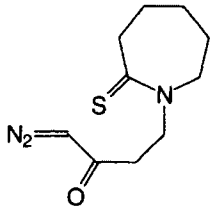

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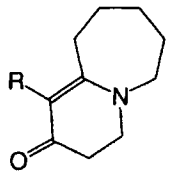


(169)

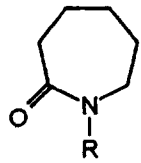
N-Methylthiocaprolactam (**95**, R = CH_3) reacted with methyl iodide yielding the iminium salt **165**, which gave intermediates **166** (R = Ph, C_5H_{11}, CH_3 or TMS) on treatment with the appropriate alkynes; $LiAlH_4$ converted these into the 2-alkynylazepanes **167**.[265] Rhodium acetate served to convert the diazothiolactam **168** into the thiol **169** (R = SH) and thence to the enone **169** (R = H) with Raney nickel.[266] *S*-Allylthioimidates (**163**, R = $CH_2CX{=}CH_2$, X = $HNCO_2Et$) undergo rearrangements to *N*-allylthiolactams **95** (R = $CH_2CX{=}CH_2$, X = $HNCO_2Et$) either on treatment with $^iPr_2NEt$[267] or by palladium(II) catalysis.[268,269]

CAPROLACTAM TABLES

The literature contains a very large number of structures involving the caprolactam ring; we have had to be selective, omitting those examples in which the seven-membered ring comprised a minor part of the total structure. The tables present details of more than 450 substances whose structures appear authentic.

In most cases we present the structures as the authors have published them. The usual conventions of stereochemical representation (wedge and dashed bonds) are retained where appropriate. If any doubt exists as to stereochemistry, bonds of average thickness are employed. Absolute (*R* and *S*) stereochemical representations are shown where claimed by authors and these may be assumed to be relative configurations unless supported by rotation measurements indicating relationship to chiral material of known absolute configuration. In only a few cases has the optical purity been established; these are shown in the tables where available.

Table 1. *N*-Substituted caprolactams



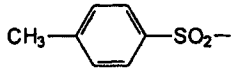
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
H	127–133/7			7
	65–68			
CH_3CO	134–136/26–27		n_D^{25} 1.4885, d_4^{25} 1.094	225
	134–135/26		IR	15
	130–131/13			161
	126/0.14		n_D^{25} 1.4868, d^{25} 1.1335	270
	85/0.05		IR, ^{1}H NMR	231
C_2H_5CO	85/0.1			270
n-C_3H_7CO	100/0.1		n_D^{25} 1.4818, d^{25} 1.0845	270
n-$C_9H_{19}CO$	175/0.1		n_D^{25} 1.4740	270
	123–124.5		IR	160
$(CH_3)_3Si$	111–111.5/16		n_D^{20} 1.4700, d_4^{20} 0.9573	169

Table 1 (continued)

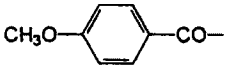
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
CO_2Et	90/0.2	Amide 101	IR, ^{1}H NMR	113
	118/5		IR, ^{1}H NMR	199
CHO	148/16		IR, ^{1}H NMR	190
PhCO	67–69.5			163, 271
	68–69			162
	76			270
ON	12.8–14			170
	11.0			171
HO	80–81			272
	82–83		IR, MS	90
CH_3	120/19		n_D^{25} 1.4818	273
	128/32		n_D^{25} 1.4812, d_4^{25} 1.0154	225
	100–102/18			113
C_2H_5	97/5.5		n_D^{25} 1.4777, d_4^{25} 0.9850	225, 274
	110–113/8			113
	140–142/55		IR, ^{1}H NMR, MS	94
n-C_3H_7	122/14			356
i-C_3H_7	87–89/0.7			94
n-C_4H_9	137–140/17		n_D^{20} 1.4782, IR	160
	145/14			276, 356
	80–82/0.6			113
	110–112/6	Dimethyl acetal 105–115/11		275
$(CH_3)_2CHCH_2$	148–150/25			113
	141/14			356
$CH_3CH_2CH_2CH(CH_3)$–	82–83/0.01			94

Table 1 (continued)

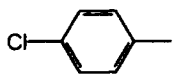
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
$(CH_3)_2CHCH_2CH_2$	148–150/18			113
n-C_6H_{13}	190–197/30 167–174/20		n_D^{20} 1.4754, IR	160
cyclo-C_6H_{11}	50–51			94
n-C_8H_{17}	152–154/2.5 164–167/7 150–160/5	 Diethyl acetal 155–170/12		113 275 253
$CH_3(CH_2)_5CH(CH_3)-$	130–132/0.05			94
n-$C_{16}H_{33}$	215–223/2–3			253
$PhCH_2$	56–57 110/0.01 145–149/1 55–57		 IR, MS, ^{1}H NMR 	277 221 278 94
$PhCH_2CH_2$	152–154/0.01			94, 167
$CH_2=CHCH_2$	76–78/0.4		IR, MS, ^{1}H NMR n_D^{20} 1.4960	101 279
Ph	75 75–76.5		^{1}H NMR	113 280, 281
	67			113
$ClCH_2$	140–143/13 132–134/8 118–120/3.5–4		n_D^{20} 1.5085 n_D^{20} 1.5098	164 322
$Cl(CH_2)_3$	99/0.01		IR, ^{1}H NMR	222
$PhCHCH_2-$ OH	88–89			166

Table 1 (continued)

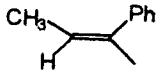
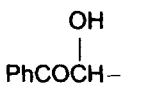
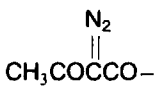
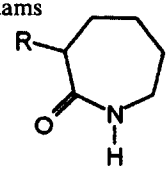
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
$C_2H_5SCH_2-$	138–141/5–6		n_D^{25} 1.5189, d_4^{25} 1.0689	225
PhCH=CH–	*cis* 47–48 *trans* 117–118			166
	Oil		IR, ^{1}H NMR, MS	101
$CH_2=CH(CH_2)_9-$	160–165/0.8 165 168/1		IR	160
PhNHCO–	67–69			168
$CH_2=CHCO-$	95/0.25			282
$NCCH_2$	Chromatography, oil		IR, ^{1}H NMR, MS	283
$H_2NCH_2CH_2$		HCl 130–131 *N*-$COCH_3$ 140/0.001	IR, MS IR, ^{1}H NMR, MS	283
$NCCH_2CH_2$	150–156/2 153–158/1.5–1.8 32–34		n_D^{25} 1.4903, d_4^{25} 1.074	225
$(CH_3)_2NCH_2$	Chromatography, oil		IR, ^{1}H NMR, MS	283
	110–111	*O*-$COCH_3$ 89–90	IR, ^{1}H, ^{13}C NMR	242
	Oil		IR, ^{1}H NMR	245

Table 2. 3-Substituted caprolactams



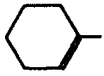
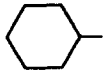
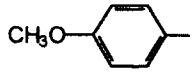
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
CH_3	97–98			39
	92–93			113
	95.5–96.5		^{1}H NMR, IR	38
	96–97			70
CH_3 (*S*)	89–92		$[\alpha]_D$ +31.6° (c = 0.5, $CHCl_3$) ^{1}H, ^{13}C NMR, 84% ee	98
CH_3 (*R*)	89–92		$[\alpha]_D$ − 26.2° (c = 0.5, $CHCl_3$) ^{1}H NMR, 74% ee	98
	86–90		$[\alpha]_D^{25}$ − 26.77° (c = 4.4, $CHCl_3$)	77
C_2H_5	99–100			52
	98–99			113
n-C_3H_7	80–81			52
	79–80			113
t-C_4H_9	154.3–154.8		MS, ^{13}C NMR	159
	146–148		IR	284
	107.5–108.5			55
Ph	183–185		IR, ^{1}H NMR	113, 66
	198–200		^{1}H NMR	66
CH_3O_2C	79–80	*N*-Phenyl 104–105	^{1}H NMR, MS	285
Cl	97.2–98			58
	91–93			201
	92–93			162

Table 2 (continued)

Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
Br	111–112			162
	113–115			203
	109–113			202
I	127–128			202
NO_2	163–164		IR, ^{1}H NMR	236
N_3	107		IR, ^{1}H NMR	211
	105–108			201
CH_3O (*S*)	54–55		IR, ^{1}H NMR	98
NC	159–160/0.5			286
	105.5		IR, UV	48
	92–96		^{1}H, ^{13}C NMR, MS,	285
	98–99		IR	358
	94–98			
PhCO	203		IR, ^{1}H NMR	232
	186–188			112
CH_3COCH_2CO	133–134		IR	232
H_2N	167/12	HCl 294–296		78, 202
	68–71	Picrate 223 N^3COCH_3 162		201
	61–65			73
	68–70	HCl 291–295		287
	75–79.5			91, 288
PhCONH	208–210			289
PhCH=N	125–126		^{1}H NMR, IR	246
	Oil	Fumarate 215	^{1}H NMR, MS	290
H_2N (*S*)	71–72	HCl 300–305(d) $[\alpha]_D^{25}$ − 26.4	$[\alpha]_D^{25}$ − 34.0° (*c* = 4, 1 M HCl) ee 100%	91
			$[\alpha]_D^{25}$ − 24.5 ± 1.2° (*c* = 4, 1 M HCl)	201
		BzOCO^{3}NH 145–148	^{1}H NMR	291

Table 2 (continued)

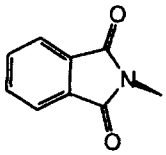
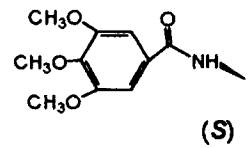
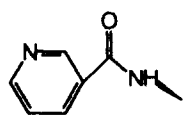
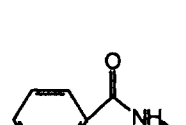
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
 (*S*)	250–255 (d), no melt		^{1}H NMR $[\alpha]_D^{20}$ + 64.5° (c = 1, $CHCl_3$), ^{1}H NMR	191 256
(*S*)	187		$[\alpha]_D^{20}$ + 28° (c = 1, $CHCl_3$), ^{1}H NMR	256
(*S*)				
(*S*)	152–153	N^1CH_2COMe oil $[\alpha]_D^{25}$ +25.3	$[\alpha]_D^{25}$ + 39° (c = 1, $CHCl_3$), MS, ^{1}H NMR	292
 (*S*)	176		$[\alpha]_D^{25}$ + 83° (c = 1, $CHCl_3$), ^{1}H NMR	293
		$N^1CH_2CO_2Me$ 60–62	$[\alpha]_D^{25}$ + 1.2° (c = 1, MeOH)	
		$N^1CH_2CONH_2$ 208–210	$[\alpha]_D^{25}$ + 12.4° (c = 1, MeOH)	
		$N^1CH_2CH_2OH$ 89–92	$[\alpha]_D^{25}$ + 6.5° (c = 1, MeOH)	
 (*S*)	95–97		$[\alpha]_D^{25}$ + 35.7° (c = 1, MeOH), ^{1}H NMR	293
 (*S*)	177		$[\alpha]_D^{25}$ + 88° (c = 1, MeOH), ^{1}H NMR	293
(*S*)	218–219		$[\alpha]_D^{25}$ + 26.9° (c = 1, MeOH), ^{1}H NMR	293

Table 2 (continued)

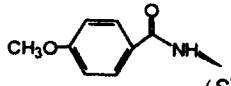
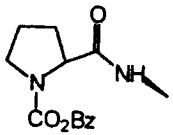
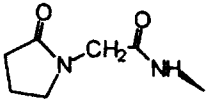
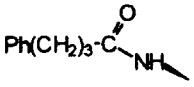
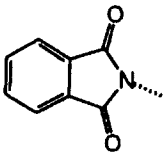
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
 (*S*)	170–172		$[\alpha]_D^{25}$ + 42.2° (*c* = 1, MeOH), ^{1}H NMR	293
(*S*)	147–149		$[\alpha]_D^{25}$ + 13.7° (*c* = 1, MeOH), ^{1}H NMR	293 148
 (*S*)	156–158		$[\alpha]_D^{25}$ -69.7° (*c* = 1, MeOH), ^{1}H NMR	293
 (*S*)	245–247		$[\alpha]_D^{25}$ + 7.1° (*c* = 1, MeOH), ^{1}H NMR	293
 (*S*)	106–108		$[\alpha]_D^{25}$ + 10.2° (*c* = 1, MeOH), ^{1}H NMR	293
		$N^1CH_2CO_2Me$ oil	$[\alpha]_D^{25}$ − 9.7° (*c* = 1, MeOH)	
		$N^1CH_2CONH_2$ 153–155	$[\alpha]_D^{25}$ + 8.2° (*c* = 1, MeOH)	
		$N^1CH_2CH_2OH$ oil	$[\alpha]_D^{25}$ − 1° (*c* = 2.2, MeOH)	
(*R*)	Not quoted		$[\alpha]_D^{25}$ + 26.4° (*c* = 4, 1 M HCl), ee > 99%	91
 (*R*)	248–253			191

Table 2 (continued)

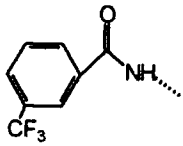
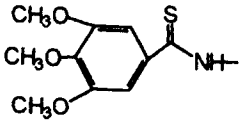
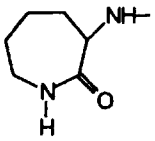
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
^{t}BuOCONH..... (*R*)	150–151		$[\alpha]_D^{25}$ – 39.2° (c = 1.2, $CHCl_3$), MS	292
		N-CH_2CO_2Me oil	$[\alpha]_D^{25}$ – 22.8° (c = 0.143, $CHCl_3$) MS, ^{1}H NMR	
 (*R*)	218–219		$[\alpha]_D^{25}$ – 26.3° (c = 1, MeOH), ^{1}H NMR	293
$Et_2N(CH_2)_2NH$–	149–156/1–2 57–60	Tartrate 128–129	IR	114
	206–207		IR	294
$(HO_2CCH_2)_2N$–			^{13}C NMR	295
$CH_3CH(OH)$- CH_2CONH–	183–185		IR, ^{1}H NMR	146
	220/0.25		IR, ^{1}H NMR	296
$(HO_2C)_2CH$–	160	Monoethyl ester 76–77 Diethyl ester 94–96		213
HO_2CCH_2	176–177	Ethyl ester 76.5–77.5 Amide 202		213
$HOCH_2CH_2$	89–91			297

Table 2 (continued)

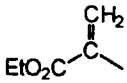
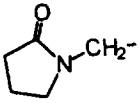
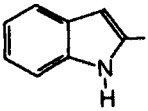
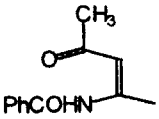
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
$CH_2=CHCH_2-$	87		IR, ^1H NMR, MS	101
$CH_2=CHCH(Ph)-$ 2 diastereomers	116–117		UV, ^1H NMR	101
	87–88			213
	Oil		^1H NMR, IR, MS	244
$CH_3COCH_2CH_2$	91–93		IR, MS, ^1H, ^{13}C NMR	103
$CH_3C\equiv C(CH_2)_2$	78–79		IR, MS, ^1H NMR	244
	173–175		IR, ^1H, ^{13}C NMR	240
$Ph_2C(OH)-$	260		IR, ^1H NMR	233
	176		IR	69
	204–206		MS, IR, ^1H NMR	232
CH_3SSC-	144–145		IR, MS	239
$HSSC-$	103–105		IR, ^1H NMR	239
$Ph_2P(=O)CH_2$	Crystalline no m.p. given		IR, ^1H NMR	46
$(CH_3)_3SiCH_2$	VPC pure		IR, ^1H NMR, MS	43

Table 2 (continued)

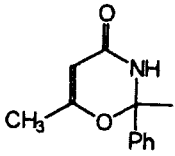
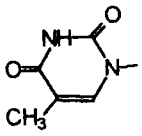
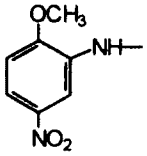
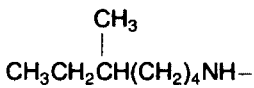
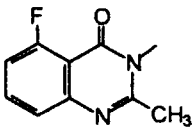
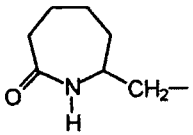
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	178–179		IR, ^{1}H NMR	232
	>300		^{1}H NMR	298
$CH_2{=}CHCH_2CH_2$	66–67		IR, ^{1}H NMR	245
	194–195		IR, ^{1}H, ^{13}C NMR	299
	white powder, no m.p. given		IR, ^{1}H, ^{13}C NMR, MS	154
$(CH_3)_2CH(CH_2)_5NH-$	white powder, no m.p. given		IR, ^{1}H, ^{13}C NMR, MS	154
	193–194		^{1}H NMR, IR	300
	174–182		IR	63

Table 2 (continued)

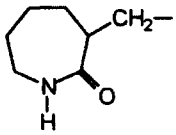
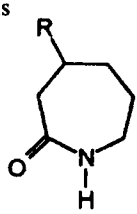
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	247		IR	63
$H_2NCH_2CH_2$	82–84	Maleate 99–100 Oxalate 158–161		54

Table 3. 4-Substituted caprolactams



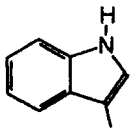
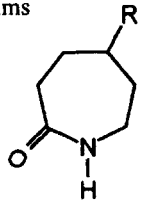
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
CH_3	78 100–101 97.7–98 104–106		IR, ^{1}H NMR	111 6 71 49, 218
(*R*) CH_3	98–103		$[\alpha]_D$ − 34.0° (c = 0.7, H_2O) ^{1}H, ^{13}C NMR, IR	98
		N-(*R*)-$CH(CH_3)$Ph oil	^{1}H, ^{13}C NMR, IR, MS	49
$CH_3(CH_2)_3$	118–119/0.8		IR, ^{1}H NMR, MS	65
CH_3O	62		IR, ^{1}H NMR	217
$(HO_2C)_2CH$	162 (d)	Diethyl ester 49–50		216 215
HO_2CCH_2-	193–194	Ethyl ester 78.5–80 Amide 206–208		216 215
$(CH_3)_3Si$	Chromatography		IR, ^{1}H NMR, MS	43
	149–150.5		UV, IR	109
C_2H_5O	54.5–56			53

Table 4. 5-Substituted caprolactams



Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
CH_3	41–42			9, 301
	46–47		IR, ^1H NMR	45
CH_3 (*R*)	Oil		$[\alpha]_D + 18.0°$ ($c = 1.4$, MeOH) IR, ^1H, ^{13}C NMR, MS	9, 97
	44–46		$[\alpha]_D^{25} + 29.44°$ ($c = 2.4$, $CHCl_3$)	77
CH_3 (*S*)	45–46		$[\alpha]_D^{25} - 28.9°$ ($c = 2.4$, $CHCl_3$)	45
	44–46		$[\alpha]_D^{25} - 20.8°$ ($c = 2.1$, MeOH) IR, UV	302
C_2H_5	56–57			303
	124–130/0.5			304
C_2H_5 (*R*)	61–62		$[\alpha]_D + 14.3°$ ($c = 0.46$, MeOH) IR, ^1H, ^{13}C NMR, MS	65, 97
$CH_3CH_2CH_2$	82			305
	81–82			304
	145–149/0.75			
^tBu (*R*)	151–152		$[\alpha]_D + 14.7°$ ($c = 0.5$, MeOH) IR, ^1H, ^{13}C NMR, MS	97
^iPr	82.5–83.5			304
^tBu	155–156			304

Table 4 (continued)

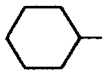
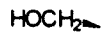
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	156–157			304
$^{n}C_7H_{15}$	71.5–72			304
Ph	129–134 199–200		IR	281 28
(*S*)	194–196		$[\alpha]_D$ – 45.3° (c = 0.73, MeOH) ^1H, ^{13}C NMR	97
CF_3	101–102.5			306
$HOCH_2$	127–129	*O*-Tosyl 109–110 *O*-^{t}Bu 77–78 OBzOCO– 116	IR, ^1H NMR	45 307
 (*R*)	73		$[\alpha]_D^{25}$ + 16.0°, IR, ^1H NMR	45
		O-^{t}Bu 73	$[\alpha]_D^{25}$ + 15.9° (c = 2.7, MeOH)	
(*S*)	73		$[\alpha]_D^{25}$ – 16.2°	45
		O-^{t}Bu 73	$[\alpha]_D^{25}$ – 16.1° (c = 2.1, MeOH)	
		O-Tosyl 109–111	$[\alpha]_D^{25}$ – 13.25 (c = 1.2, MeOH)	
ICH_2	127–128		IR, ^1H NMR	45
(*S*)	121–122		$[\alpha]_D^{23}$ – 16.7° (c = 2.3, MeOH) IR, ^1H NMR	45
HO	138–141	*O*-$COCH_3$ 62		309, 310
PhCOO	133.5–135		IR, ^1H NMR	30
(*R*)	130–132		$[\alpha]_D$ + 18.9° (c = 0.46, MeOH) IR, ^1H, ^{13}C NMR, MS	30, 97

Table 4 (continued)

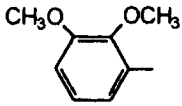
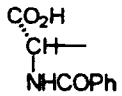
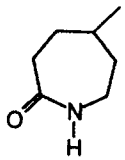
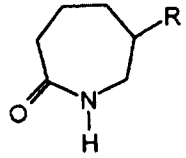
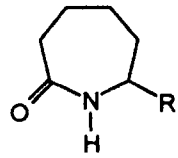
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
HO_2C	129–130	HCl 157 Methyl ester 76 ^{t}But ester 92–93 (HCl 109)	IR, ^{1}H NMR	45
HO_2C (*R*)	168–169	Methyl ester 93	$[\alpha]_D^{25}$ + 31.9, IR, ^{1}H NMR	45
HO_2C (*S*)	168–169	Methyl ester 93–94	$[\alpha]_D^{25}$ − 31.9° (c = 3.0, MeOH)	45
	181–183		IR	26
	268–272		IR, ^{1}H NMR	31
2 diastereomers				
	288.5–289.5		IR	64

Table 5. 6-Substituted caprolactams



Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
CH_3	60			6
	64–65		IR, ^{1}H NMR	111
	69–70			49
	140–142/10			71
	70–72			
CH_3 (*R*)	99–100		$[\alpha]_D - 21.2°$ ($c = 0.69$, EtOH) IR, MS, ^{1}H, ^{13}C NMR	98
	68–69		$[\alpha]_D - 22.2°$	308
Ph	150		IR, ^{1}H NMR	207
BzOCO	128–131		IR, ^{1}H NMR	65
EtO_2C	160–165/0.6		IR, ^{1}H NMR	65
Me_3Si	91–92		IR, ^{1}H NMR, MS	43

Table 6. 7-Substituted caprolactams



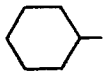
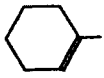
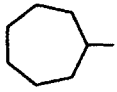
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
CH_3	90–91		IR, ^{1}H NMR	8, 39, 60
	91–92		MS, IR, ^{1}H NMR	12, 190
	90.5–91.5			58
	89.5–90.5			9, 305
C_2H_5	91.5–92			51, 58
$CH_3CH_2CH_2$	100.5–101.5			10
	98.6–99.2			58
	97–98			60
	101–102			74
	180–185/14			
$CH_3CH_2CH_2CH_2$	73–73.5			65
	70			311
$(CH_3)_2CHCH_2$	80–81		^{1}H, ^{13}C NMR, IR, MS	110a
$(CH_3)_2CH_2CH_2$ (*R*)	Oil: Chromatography		$[\alpha]_D^{20} - 9.3°$ ($c = 0.53$, MeOH)	110, 110a
			IR, ^{1}H NMR	
^{t}Bu	127.3		^{13}C NMR, MS	159
	134–135		IR, MS	21
	139		^{1}H NMR	65
	146–147			55
	111		IR, MS	21
	116–118		IR	284
	118–119		^{1}H NMR, IR	312
	128–130			55

Table 6 (continued)

Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
$nC_{12}H_{25}$	59–60		IR	254
CH_3O	69–70		^{1}H NMR, IR	219
	106–108/0.18		^{1}H NMR	187
CH_3O (*R*)			IR, ^{1}H NMR	98
C_2H_5O	106/0.18		^{1}H NMR	187
$C_2H_5O_2C$	97.2–98			58
	96.5–98			60
	48–49.5		IR, ^{1}H NMR, MS	90
	150–160/1–2		IR	227
H_2NOC	239–241			60
	217			79
NC	126.6–127.4			58
	126–127			60
	127–128			59
$C_2H_5O_2CCH_2$	113–114		^{1}H NMR	313
$HO_2CCH_2CH_2$	152–153	Methyl ester 79–80 Amide 182–183		255
	154			314
$HO_2CCH_2CH_2CH_2$	103	Ethyl ester 96.5		314
$C_2H_5O_2CCH{=}CHCH_2$	102			314
$CH_3O_2C(CH_2)_4$	55–56			56
$CH_3O_2C(CH_2)_5$	64–65			56
$CH_3O_2C(CH_2)_6$	55–57			56
$CH_3O_2C(CH_2)_7$	65–66			56
$(CH_3)_3SiCH_2$	75–76		IR, MS, ^{1}H NMR	43
CH_3CO	104–105		IR, MS, ^{1}H NMR	62

Table 6 (continued)

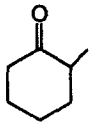
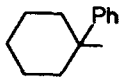
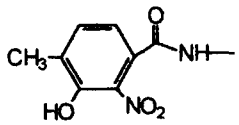
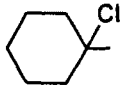
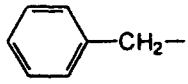
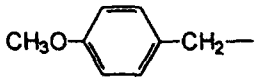
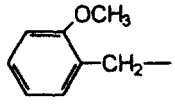
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	161–163			315
	118–120			20
$BrCH_2CH_2$	121–122		IR, MS, ^1H NMR	313
$HOCH_2CH_2$	138		MS, ^1H NMR, IR	313
	220–222			316
	260		IR, ^1H NMR	186
	185–187 (d)		IR, MS	21
	157–160			65
	153–155			65
	120–122			65

Table 6 (continued)

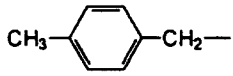
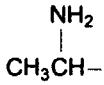
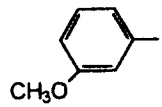
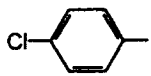
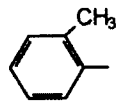
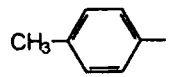
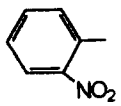
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	174–175			65
H_2N	156–158/10 23			51
$H_2N(CH_2)_2$	181–186/8 98–99	Oxalate 180–181(d) Maleate 129.5–131		54
	70–73			56
$H_2N(CH_2)_4$		HCl salt 198–200	IR, MS (base)	310
Ph	135–136 138–139		^{1}H NMR, IR	207 66, 317
	99–100			81
	172–174		IR	23
	109–115		IR	23
	153–154 150–151		MS, IR UV, ^{1}H NMR	23 66
	182–183		^{1}H NMR	66

Table 6 (continued)

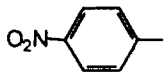
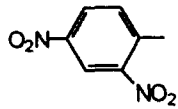
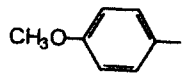
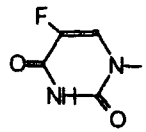
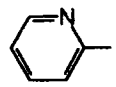
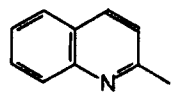
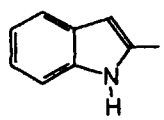
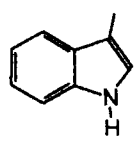
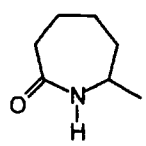
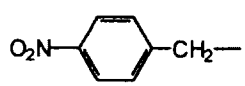
Structure (R)	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	141–142		^{1}H NMR	66
	~210 (d)		^{1}H NMR, UV	66
	152–153		^{1}H NMR	66
	183		^{1}H NMR	318
	96–96.5			40
	190–192			40
	196		IR	69
	235		IR	319
	235–236 Diastereo-isomers 195–197		IR	63
	153–154		IR, ^{1}H NMR	65

Table 7. 1,3-Disubstituted caprolactams

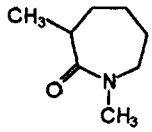
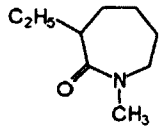
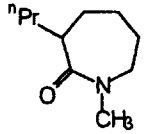
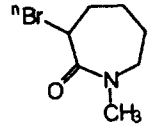
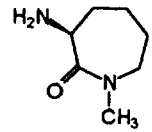
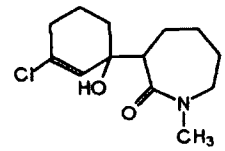
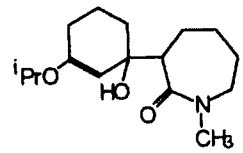
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	96–97/13		IR, ^{1}H NMR, MS	113 95
	64/0.5 110–111/28			320 81 113
	116–118/23			113
	124/23			113
		*N*-Phthalimido (d) *N*-Trityl 89	$[\alpha]_D^{20}$ + 69.0° (c = 1, $CHCl_3$) ^{1}H NMR $[\alpha]_D^{20}$ + 17.5° (c = 1, $CHCl_3$) ^{1}H NMR	256
	126–127			81
	119–121			81

Table 7 (continued)

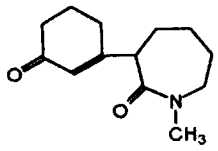
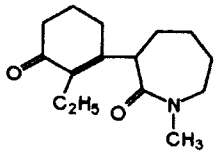
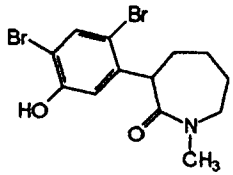
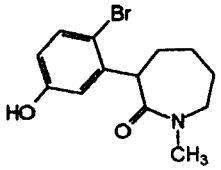
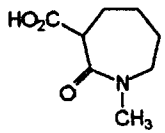
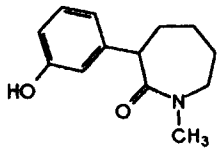
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	109–110			81
	114–116			81
	205–207			81
	160–163			81
	118–119		IR, ^{1}H NMR	229
	192–193	OMe 74–75		81

Table 7 (continued)

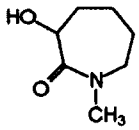
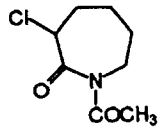
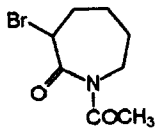
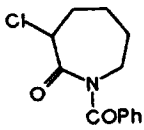
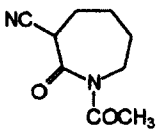
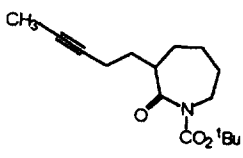
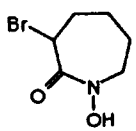
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	94–94.5/2–3		IR	205
	94.5–96/0.5		n_D^{25} 1.5104	203
	109.5–110.5/0.8		n_D^{25} 1.5321	203
	118 120–122 121 122–123		IR, ^{1}H NMR	162 163 206 203
	150–151/0.7		n_D^{20} 1.5101	286
	64–65		^{1}H NMR, IR, MS	244
	Chromato-graphy		MS, ^{1}H NMR	90

Table 7 (continued)

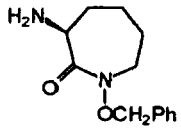
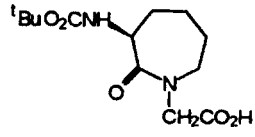
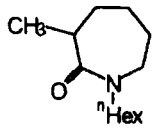
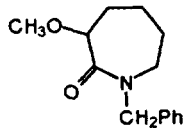
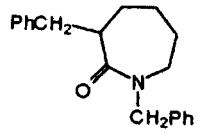
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Oil	*N*-BOC 102.5–103.5 *N*-$COCH_2$-$CH(OH)CH_3$ 130.5–131.5	$[\alpha]_D^{23}$ – 11.3° (c = 2.2, MeOH) ^{1}H NMR $[\alpha]_D^{23}$ – 16.35° (c = 5.5, MeOH)	157
	Foam		$[\alpha]_D^{24}$ – 3.06° (c = 0.98, MeOH) IR, ^{1}H NMR	321
	Chromatography		IR, ^{1}H NMR	95
	Chromatography		IR, ^{1}H NMR	95
	Chromatography		IR, ^{1}H NMR	95

Table 8. 1,*n*-Disubstituted caprolactams

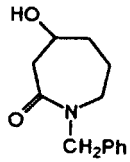
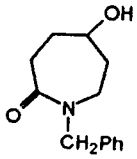
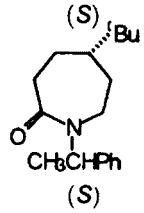
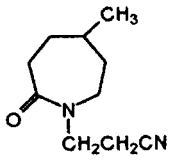
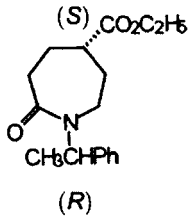
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	98–99		IR, ^{1}H, ^{13}C NMR, MS	193
	83–84		IR, ^{1}H, ^{13}C NMR, MS	193
 (*S*)	90–95		$[\alpha]_D^{20}$ − 143° (c = 0.32, MeOH) $[\alpha]_{578}^{20}$ − 153° (c = 0.32, MeOH) ^{1}H NMR, IR, X-ray	96
	136–139/1		n_D^{20} 1.4786	165
 (*R*)	Chromato-graphy		$[\alpha]_D$ +98.0° (c = 1.0, MeOH) ^{1}H, ^{13}C NMR	97

Table 8 (continued)

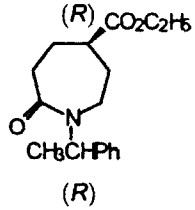
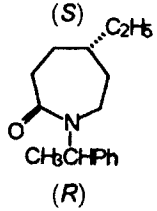
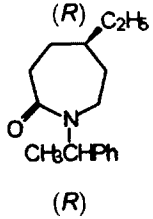
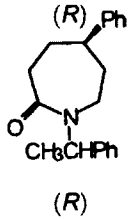
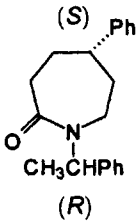
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Chromatography		$[\alpha]_D$ +81.3° (c = 1.3, MeOH) ^1H, ^{13}C NMR, MS, IR	97
	Chromatography		$[\alpha]_D$ +126.9° (c = 1.3, MeOH) IR, ^1H, ^{13}C NMR	97
	Chromatography		$[\alpha]_D$ +111.5° (c = 1.8, MeOH) IR, ^1H, ^{13}C NMR	97
	Chromatography		$[\alpha]_D$ +133.5° (c = 0.93, MeOH) IR, ^1H, ^{13}C NMR	97
	Chromatography		$[\alpha]_D$ −63.1° (c = 1.12, MeOH) IR, ^1H, ^{13}C NMR	97

Table 8 (continued)

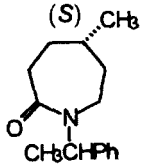
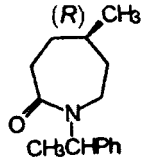
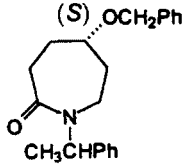
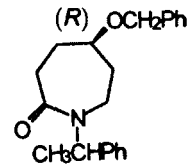
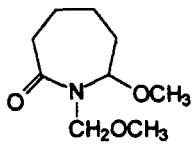
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
 (*R*)	Chromatography		$[\alpha]_D$ +140.9° (*c* = 0.97, MeOH) IR, ^1H, ^{13}C NMR	97
 (*R*)	Chromatography		$[\alpha]_D$ +125.9° (*c* = 1.3, MeOH) IR, ^1H, ^{13}C NMR	97
 (*R*)	Chromatography		$[\alpha]_D$ +86.8° (*c* = 1.1, MeOH) ^1H, ^{13}C NMR	97
 (*R*)	Chromatography		$[\alpha]_D$ +73.4° (*c* = 1.0, MeOH) IR, ^1H, ^{13}C NMR	97
				188

Table 8 (continued)

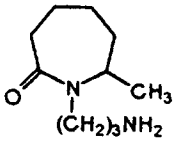
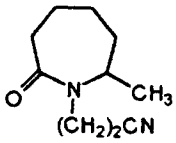
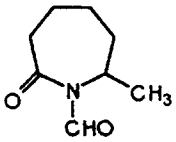
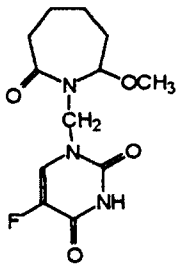
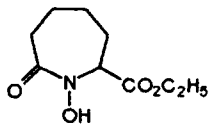
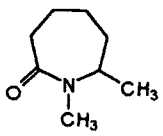
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	125–126/3		^{1}H NMR	39
	150–151/3		^{1}H NMR	39
	135/13		IR, ^{1}H NMR	190
	156–157		IR, ^{1}H NMR, UV	318
	187		IR, MS	90
	Chromato-graphy		^{1}H NMR	95

Table 8 (continued)

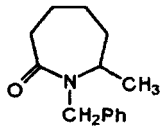
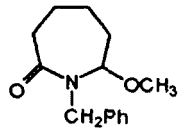
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Chromato-graphy		^{1}H NMR	95
	Chromato-graphy		^{1}H NMR	95

Table 9. Ring-disubstituted caprolactams

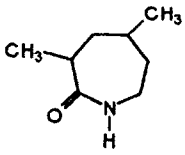
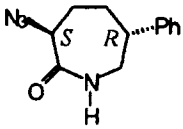
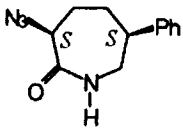
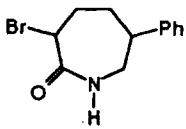
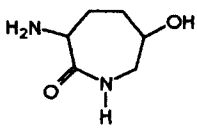
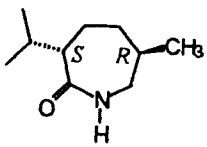
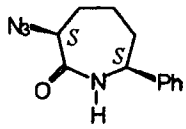
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
 (*cis*)	122–123			9
	149	*N*-$CH_2CO_2{}^tBu$ 115–116	^1H NMR, IR	207
	124.5		^1H NMR, IR	207
	229		^1H NMR, IR	207
	226–228	HCl + H_2O 222 Picrate 223	IR	323 324
	100–100.5		$[\alpha]_D^{17}$ +6.37° (c = 0.92, EtOH) IR, MS	29
	117–118	*N*-$CH_2CO_2{}^tBu$ 131–133	^1H NMR, IR	207

Table 9 (continued)

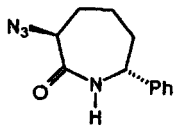
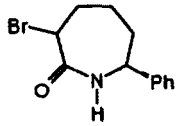
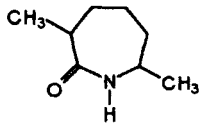
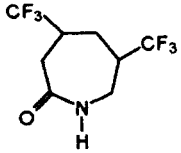
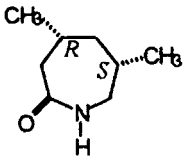
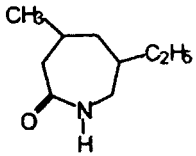
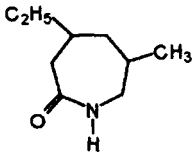
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Syrup		^{1}H NMR, IR	207
	80–100		^{1}H NMR, IR	207
	No data			335
	128–130			306
	134–136		$[\alpha]_D$ – 15.1° (c = 0.57, MeOH) IR, ^{1}H, ^{13}C NMR, MS	98 65
	100–101			11
	105.5–106			11

Table 9 (continued)

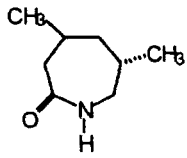
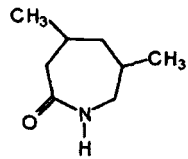
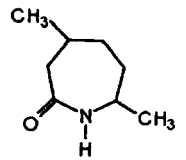
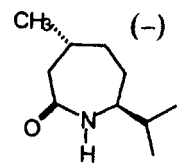
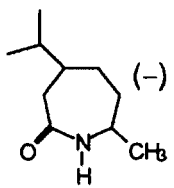
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
 (*trans*)	73–73.5		IR, MS	111
 (*cis*)	130			281
	124–126			111
	122–123			9
	125–126			9
 (–)	118.7–119.9		$[\alpha]_D^{27}$ – 56.22° (c = 4.61, EtOH), IR, MS, ^{1}H NMR	29
	120–122		$[\alpha]_D$ – 51.0°	49
	119–121		$[\alpha]_D^{23}$ – 56.5° (c = 1, EtOH), ^{1}H NMR, MS, IR	19
	119–121.5		$[\alpha]_D^{20}$ – 51.9° (c = 2.25, MeOH)	14
	118–120		$[\alpha]_D^{20}$ – 56.7° (c = 5.5, MeOH)	158
			IR	61, 65, 281
				4, 5
 (–)	101		$[\alpha]_D^{20}$ – 58.8° (c = 5.5, MeOH), IR	158

Table 9 (continued)

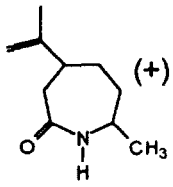
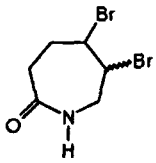
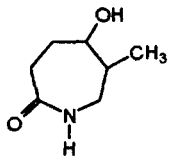
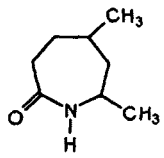
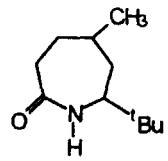
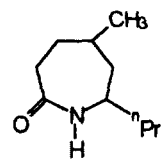
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	88		$[\alpha]_D^{20}$ +85.0° (c = 5.9, MeOH), IR	158
	147.5–148.5			325
	115–118/0.05 75–78 Diastereo-isomers 98–101		IR, ^{1}H NMR	326
	133.5–134.5			9
	105–106			9
	184–189/8 6–8			74

Table 9 (continued)

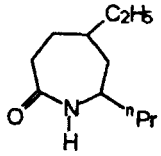
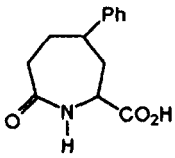
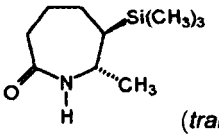
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	175–180/8			74
	237–240	Ethyl ester 94–96	^{1}H NMR, IR	195
 (*trans*)	71–72		IR, ^{1}H NMR, MS	43

Table 10. *gem*-Disubstituted caprolactams

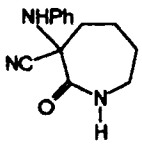
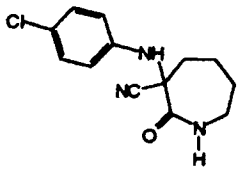
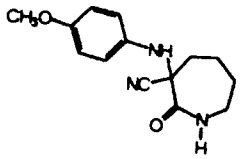
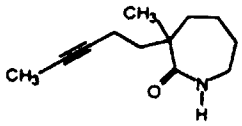
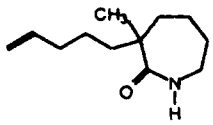
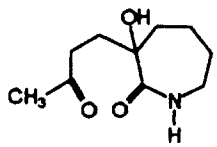
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	185–186		IR	327
	130–132		IR	327
	142–144		IR	327
	88.5–90.5		IR, ^{1}H, ^{13}C NMR, MS	244
			IR, ^{1}H, ^{13}C NMR, MS	444
	100/0.001		MS, ^{1}H NMR, IR	103

Table 10 (continued)

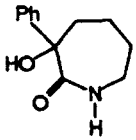
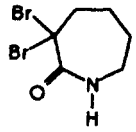
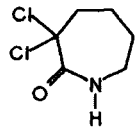
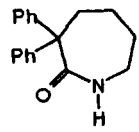
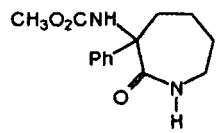
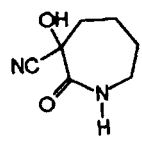
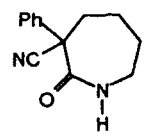
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	139–140 141–142	*N*-CO_2Et 72–74	^{13}C NMR, IR	114 204
	162–163.5 160–162		^{13}C NMR, IR	203 204
	124.5–126.5 124–126 123.5–125.5 126		IR IR, ^{1}H NMR, MS	201 202 212 214
	214			75
	149–150		^{1}H NMR, IR, MS	285
	132–134		IR	327
	136–137		^{1}H, ^{13}C NMR, MS	285

Table 10 (continued)

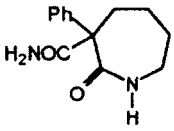
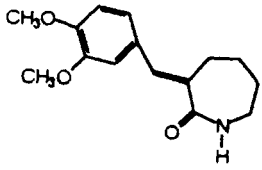
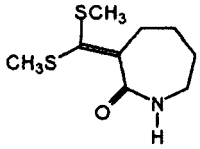
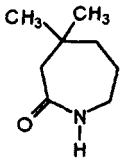
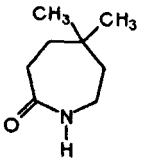
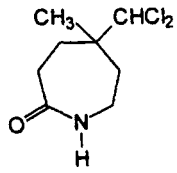
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	192–193		^1H, ^{13}C NMR, IR, MS	285
	166–168		IR, ^1H NMR	231
	145–147 152–153		^1H NMR IR, ^1H NMR	238 239
	140–141 (subl.) 103–104		^1H NMR ^1H NMR, IR	27 65
	90.5–92.5 88		^1H, ^{13}C NMR	328 65
	152–154		IR, ^1H NMR	16

Table 10 (continued)

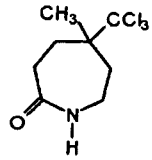
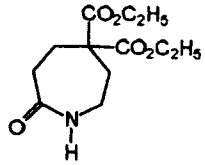
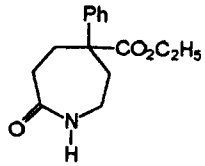
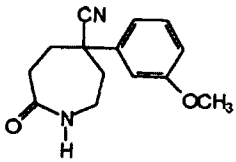
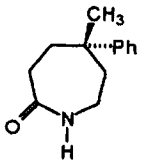
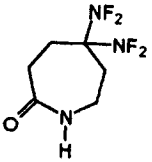
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	160–161		IR, ^{1}H NMR	16
	84–85		IR, ^{1}H NMR	36
	107–108	HCl salt 128–131		329
	146–147	*N*-CH_3 106–108	IR	47
	134–135		$[\alpha]_D$ + 24.6° (c = 0.79, MeOH) IR, ^{1}H, ^{13}C NMR, MS	97
	100–102			44

Table 10 (continued)

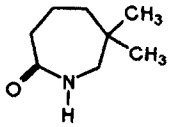
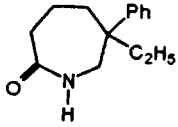
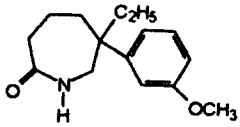
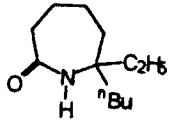
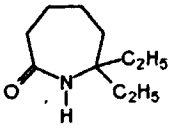
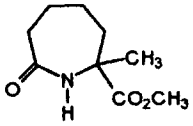
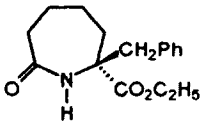
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	81–82 100–101		^{1}H NMR ^{1}H NMR, IR	27 65
	172/0.3 96–97			76
	87–88			81
	115–117/0.1		IR	25
	101–104/0.05			255
	128		^{1}H NMR, MS	80
			$[\alpha]_D$ + 4.6° (c = 1, $CHCl_3$) (ee > 95%)	67

Table 10 (continued)

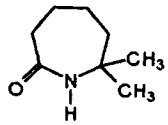
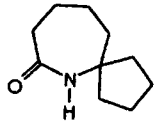
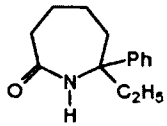
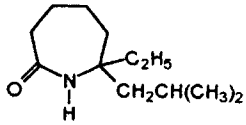
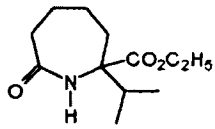
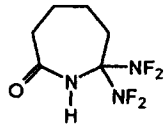
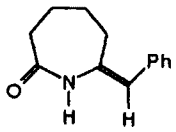
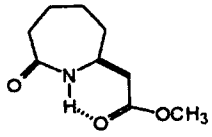
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	90.5–91 135/13 102–103			17 72
	108–110			107 331
	150–160/0.01		IR	25
	120–132/0.01		IR	25
	109–110		IR, MS	332
	70–71		^{19}F NMR	333
	124		IR, ^{1}H NMR	24
	Oil		IR	330

Table 11. Trisubstituted caprolactams

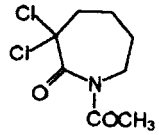
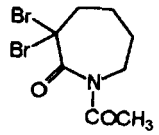
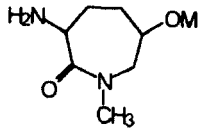
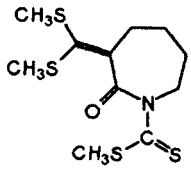
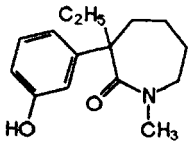
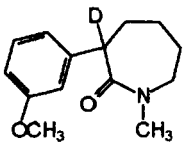
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	100.5–102/0.5		n_D^{25} 1.5177	203
	126–127/0.5		n_D^{25} 1.5640	203
 (M = myristoyl)			IR, ^{1}H, ^{13}C NMR, MS	152
	54–56		^{1}H NMR	238
	172–180	OMe 68–69 140/0.1	IR, ^{1}H NMR	81
	82–83		MS, ^{1}H NMR, IR	81

Table 11 (continued)

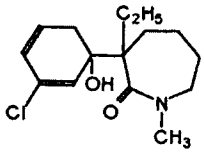
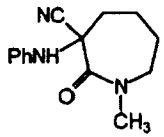
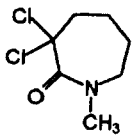
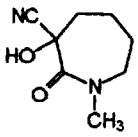
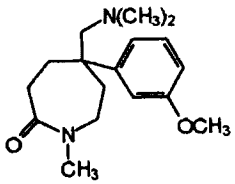
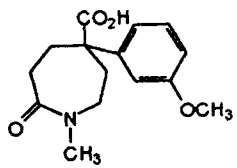
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	138–139			81
	160–162		IR, UV	205
	128–129/1–2		n_D^{20} 1.5172, IR	205
	95–95.5		IR	205
	Oil	Picrate 248–249	IR, ^{1}H NMR	47
	113–114		IR	47

Table 11 (continued)

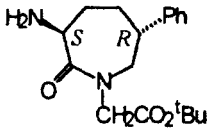
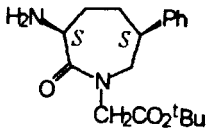
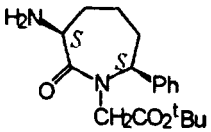
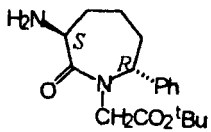
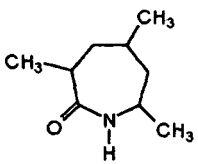
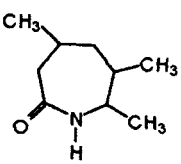
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	112		^{1}H NMR, IR	207
	Syrup	Maleate 138–140	^{1}H NMR, IR	207
	Syrup	Maleate 160–161	^{1}H NMR, IR	207
	Syrup	Maleate 149–150.5	^{1}H NMR, IR	207
	73.5–75 73–75		IR	9 334
	137–138			9

Table 11 (continued)

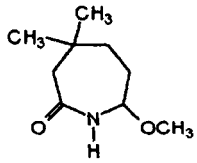
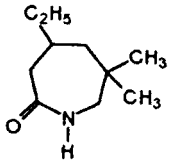
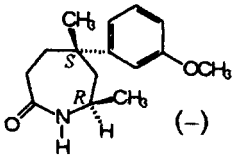
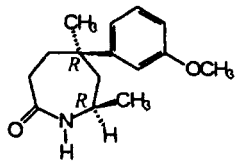
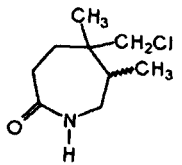
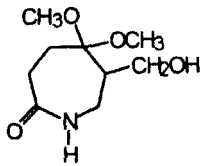
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	109–110		^{1}H NMR, MS, IR	115
	72–78		IR, MS	111
	133–134		$[\alpha]_D^{18}$ − 29.6° (c = 1.2, $CHCl_3$) (ee > 80%), IR, ^{1}H, ^{13}C NMR, MS	22
	113–114		$[\alpha]_D^{18}$ + 1.1° (c = 1.2, $CHCl_3$) IR, ^{1}H, ^{13}C NMR, MS	22
	172–174		IR, ^{1}H NMR	16
	123.5–124.5	*O*-acetate 153–4		338

Table 11 (continued)

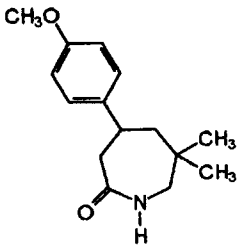
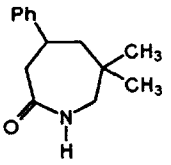
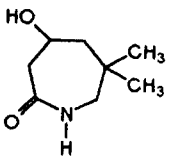
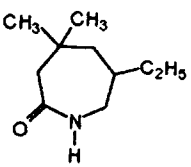
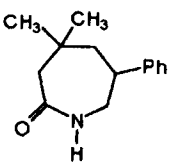
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	134–136		IR, MS	111
	189–193		IR, MS	111
	184–185		IR, ^{1}H NMR, MS	115
	100–106 (subl.)		IR, MS	111
	169–173		IR, MS	111

Table 11 (continued)

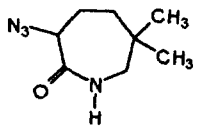
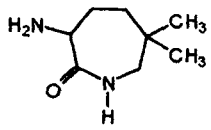
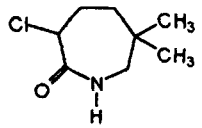
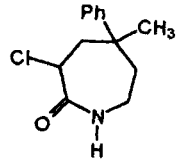
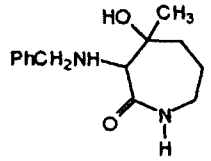
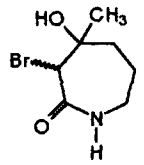
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	100–101		IR	331
	116–118		IR	331
	101.5–103		^{1}H NMR	331
	179–180		MS, IR, ^{1}H NMR	251
	141–153 135/0.001		IR, ^{1}H NMR	337
	181.5–184 (d) (subl.) 155		IR, ^{1}H NMR, MS	337

Table 11 (continued)

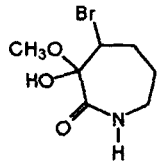
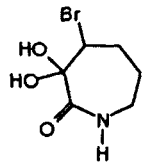
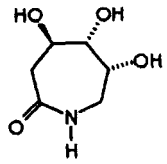
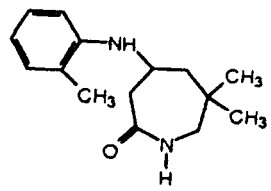
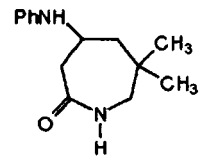
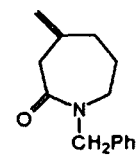
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	124–126		IR, UV	336
	120–121		IR, UV	336
	202 203		$[\alpha]_D^{20}$ – 41.0° ($c = 0.8$, H_2O) ^{13}C NMR	85
	174–175		IR	65
	214–215		IR	65
			IR, ^1H NMR, MS	92

Table 11 (continued)

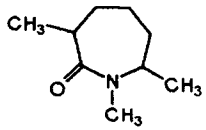
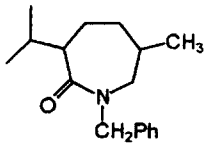
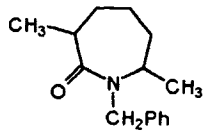
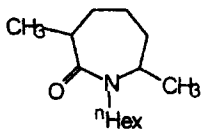
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Chromato-graphy		IR, ^{1}H NMR	95
	Chromato-graphy		IR, ^{1}H NMR	95
	Chromato-graphy		IR, ^{1}H NMR	95
	Chromato-graphy		IR, ^{1}H NMR	95

Table 12. Tetrasubstituted caprolactams

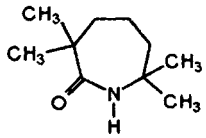
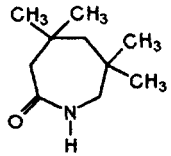
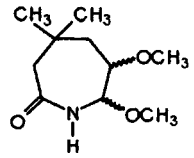
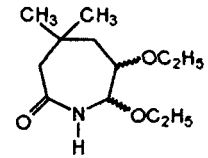
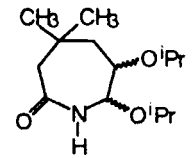
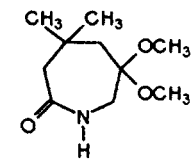
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	108 113.5–114.5		^{1}H NMR, IR, MS	106 37
	145–151		^{1}H NMR, IR, MS	111
	79–80		^{1}H NMR, IR, MS	115
	36–38		^{1}H NMR, IR, MS	115
	Oil		^{1}H NMR	115
	70		IR, ^{1}H NMR	65

Table 12 (continued)

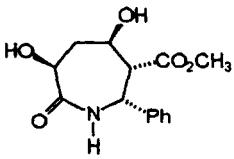
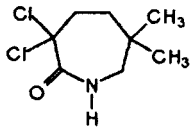
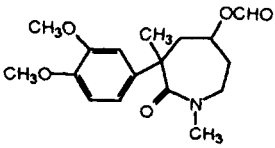
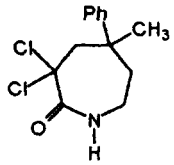
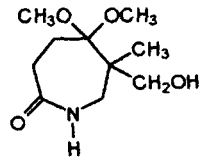
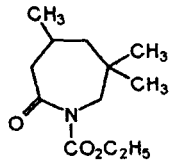
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	212–214		^{1}H NMR, IR, MS	339
	129–129.5		IR	27
	109–110		IR, ^{1}H NMR	93
	144–145		^{1}H NMR, IR, MS	251
	160–161	*O*-acetate 124–126	IR, ^{1}H NMR	338
	125/0.05		^{1}H NMR, MS	111

Table 12 (continued)

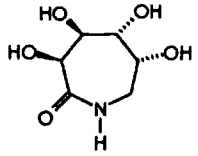
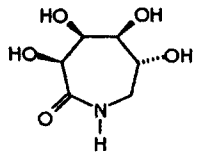
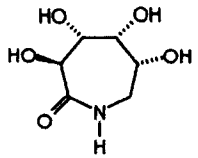
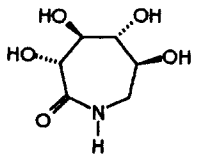
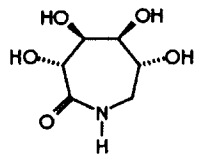
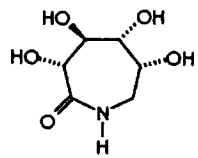
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	178–180	Tetraacetate 195.5–196.5	$[\alpha]_D^{22}$ + 24.0° (c = 1.06, H_2O) $[\alpha]_D^{20}$ + 18.1° (c = 1.8, $CHCl_3$)	83b
	235	Tetraacetate 207	$[\alpha]_D^{20}$ 0°, IR, $[\alpha]_{365}^{20}$ − 17.4° (c = 1.1, H_2O) $[\alpha]_D^{22}$ − 9.4° (c = 1.1, $CHCl_3$)	83b
	Syrup	Tetraacetate 204	$[\alpha]_D^{20}$ +36.81 ± 1° (c = 1.1, $CHCl_3$), IR	84
	179–180	Tetraacetate 181 and 190.5 (d)	$[\alpha]_D^{20}$ + 2.3° $[\alpha]_{436}^{20}$ − 4.0° (c = 3.55, H_2O) $[\alpha]_D^{25}$ − 21.8° (c = 1.1, $CHCl_3$)	83b
	175–177		$[\alpha]_D$ − 22° (c = 0.13, H_2O), IR	86
	212–214 (d) 214		$[\alpha]_D$ − 71° (c = 0.4, H_2O), IR	86 82 83a

Table 12 (continued)

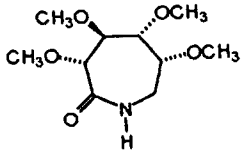
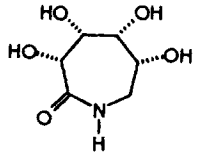
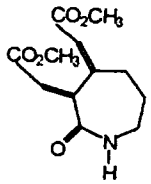
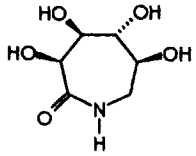
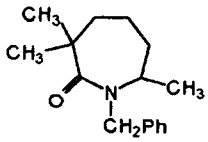
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	69–71		$[\alpha]_{365}^{20}$ −22.2° ($CHCl_3$) $[\alpha]_D^{20}$ 0°, IR, ^{1}H NMR	83a
	167–170		$[\alpha]_D$ −91.4° (H_2O), IR	82
	150–152		^{1}H NMR, IR, MS	104
	195 (d)	Tetraacetate 214–5	$[\alpha]_D^{20}$ +49° (c = 1, H_2O) $[\alpha]_D^{20}$ +75° (c = 1, H_2O)	340
	Chromato-graphy		IR, ^{1}H NMR	95

Table 13. Thiocaprolactams

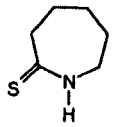
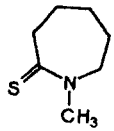
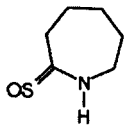
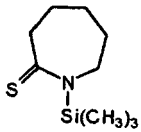
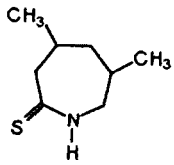
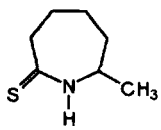
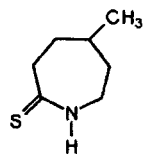
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	105–106 106 101–104	IR, MS, ^{1}H, ^{13}C NMR	139 140, 141 142, 181
	49–51 148–151/12 159–163/13 48–50	IR, MS, ^{1}H, ^{13}C NMR	139 136 138 144 145
	106–108		260
	97/1	n_D^{20} 1.5414, ^{1}H, ^{13}C NMR	261
	130		281
	83 87–88		120 65
	76–78 76–77		120, 281

Table 13 (continued)

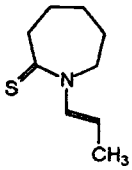
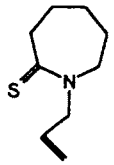
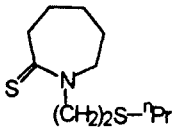
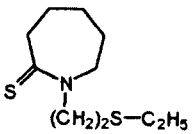
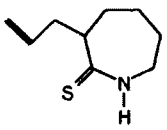
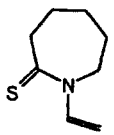
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	103.5–105/1.0 41–42		341
	83/0.3	IR, ^{1}H NMR	268, 269, 343b
	134–135/1	n_D^{20} 1.5630	342
	36.5–37	n_D^{20} 1.5730	342
	58–60 60–60.5 127–129/0.1	IR, ^{1}H NMR	264 343a
	67.5–68.5 150–155/0.6	IR, ^{1}H NMR	101
			342, 347

Table 13 (continued)

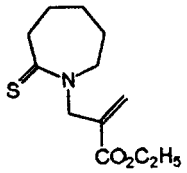
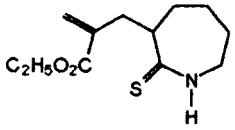
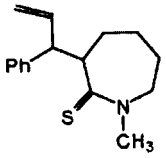
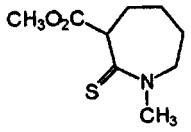
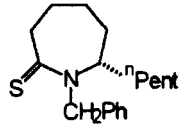
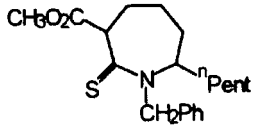
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	150–153/0.23	^{1}H NMR	267, 269
	107–109	^{1}H NMR	269
			344
	128/0.05	IR, ^{1}H NMR	230
	59–61	$[\alpha]_D^{25}$ +123.0° (c = 5, MeOH)	345
 2 diastereomers	Oil Chromatography	IR, ^{1}H NMR	263

Table 13 (continued)

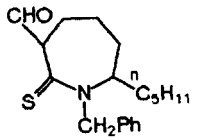
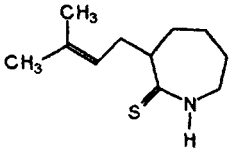
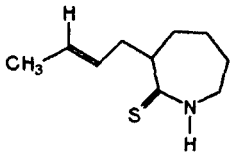
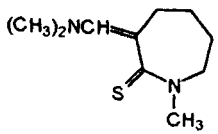
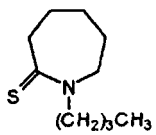
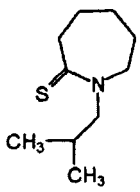
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
 2 diastereomers	Oil Chromatography	IR, ^{1}H NMR	263
	91 -94	IR, ^{1}H NMR	264
	97–104	IR, ^{1}H NMR	264
	Unstable oil	^{1}H NMR, UV	346
	110/0.01		65
	118- 120/0.01		65

Table 13 (continued)

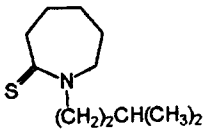
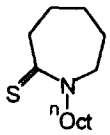
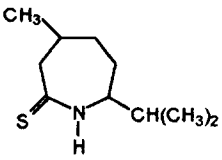
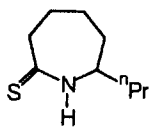
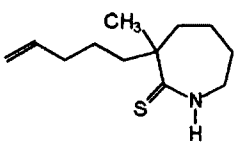
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	120/0.01		65
	110–112/0.01		65
	106–107		65
	83–83.5		65
		^{1}H, ^{13}C NMR	444

Table 14. Caprolactam imines

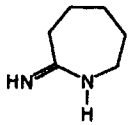
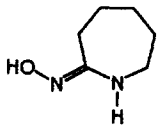
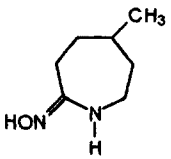
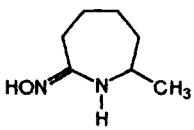
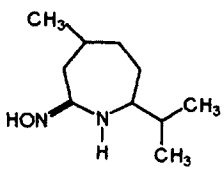
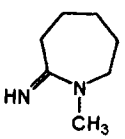
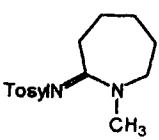
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HCl 159–160.5 HCl 161–163 HCl 165–167 Benzene-sulphonate 133		225 123 348, 349 13
	165–165.5 169–170	 *O*-Tosyl 128 *O*-Mesyl 89–90 *O*-CO_2Me. HCl 158–160	IR	117 350 118
	154			120
	128			120
	85			120
	143–145		^{1}H NMR, IR	123
	109–111		^{1}H NMR	119

Table 14 (continued)

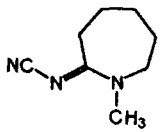
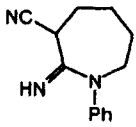
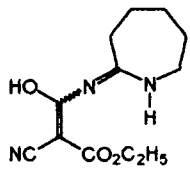
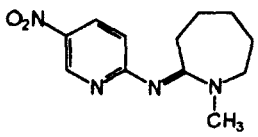
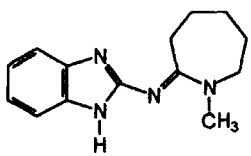
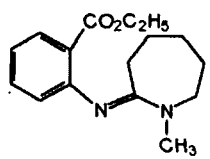
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
				351
	65–66			352
	215–216		IR, UV, ^{1}H NMR	121
	91			128
	210			128
	197 198/3	Acid 144		134 357

Table 14 (continued)

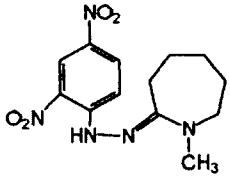
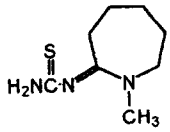
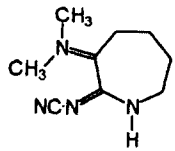
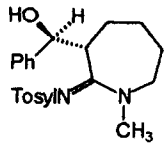
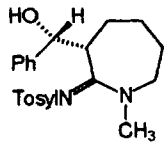
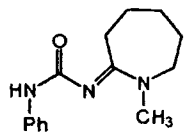
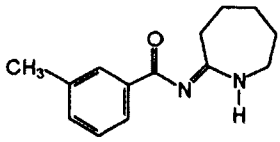
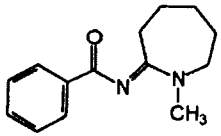
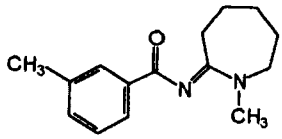
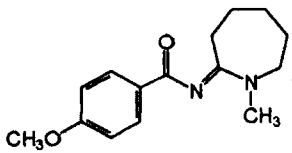
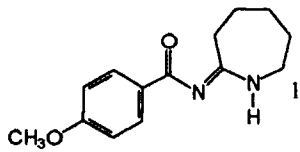
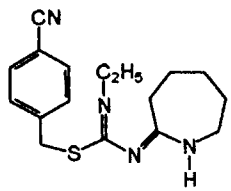
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	174–175			357
	130		IR, ^{1}H NMR	128
	156/9		IR, UV	351
	170–171		^{1}H NMR	119
	156–157		^{1}H NMR	119
	132–134 136–137		MS, IR IR, ^{1}H NMR	122 123

Table 14 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	64–66		MS, IR, ^{1}H NMR	122
	66–68		MS, IR, ^{1}H NMR	122
	52–53		MS, IR, ^{1}H NMR	122
	100–102		MS, IR, ^{1}H NMR	122
	135–137		MS, IR, ^{1}H NMR	122
	109–111		MS, IR, ^{1}H NMR	353

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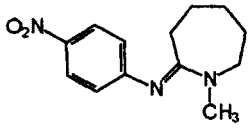
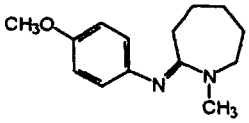
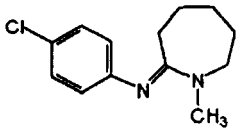
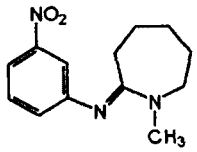
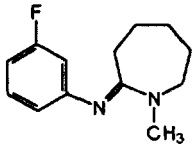
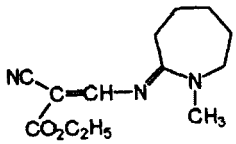
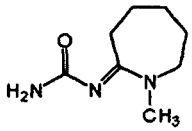
		HCl 244–245		127
		HCl 162–163		127
		HCl 228–229		127
	194–196/1	HCl 203–205		127
		HCl 177.0–177.5	pK_a 7.89, ^{1}H NMR, IR	127 129
	82–83		^{1}H NMR	131
	83–86			132

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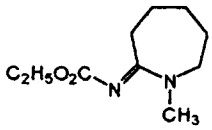
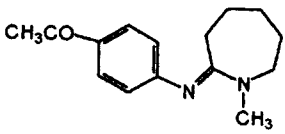
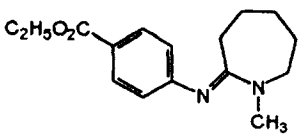
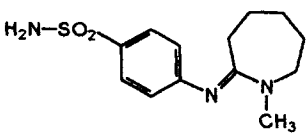
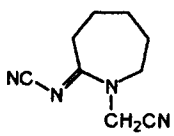
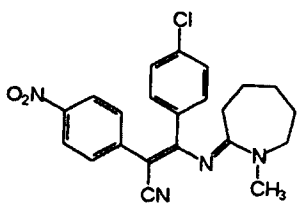
	151–152			132
	190–192/3 101–102		IR, ^{1}H NMR, pK_a 7.21	129
	198–200/3		pK_a 7.44, IR, ^{1}H NMR	129
	239–240			129
	145–147		IR, ^{1}H NMR, MS	354
	153–154		^{1}H NMR	130

Table 14 (continued)

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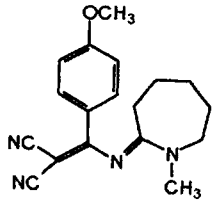
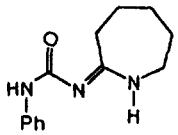
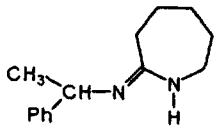
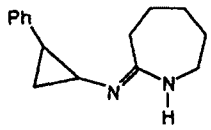
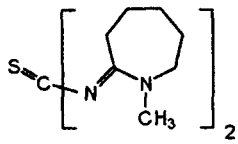
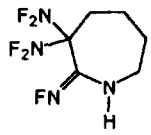
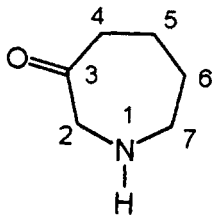
	131–132		^{1}H, ^{13}C NMR	130
	132–134		IR, ^{1}H NMR	123
		HCl 245–247		124
		HCl 232–233		355
	135–138		IR, ^{1}H NMR	133
	75 77		^{19}F NMR	333

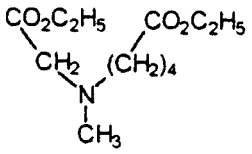
II. AZEPAN-3-ONES



This group is sparsely represented in the chemical literature.

PREPARATION

The first reference to an azepan-3-one[361] described the Dieckmann (NaOEt/xylene) cyclisation of diester **170** to give a β-keto ester which hydrolysed to **171** (R = H). This approach was later used to obtain the amino ketones **171**



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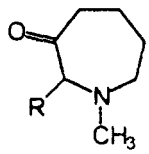

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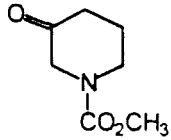

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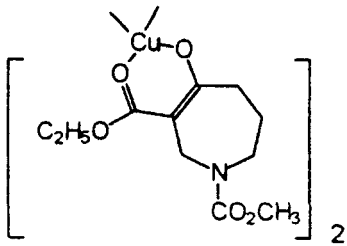

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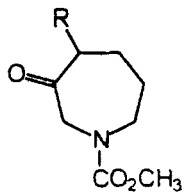
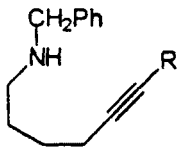


(174)

(R = CH_3, C_2H_5).[362,363] Diazoacetate ring expansion applied to *N*-methoxycarbonyl-3-piperidone (**172**) yielded a mixture of azepane-3-keto and -4-keto esters from which the latter was removed as a copper chelate (**173**). The 3-keto ester **174** (R = $CO_2C_2H_5$) was then hydrolysed to the amino ketone and *N*-reprotected to give **174** (R = H).[364]

It has been reported that iminium ion vs. alkyne cyclisations are possible if mediated by external nucleophile intervention (e.g. I^-). Thus aminoalkynes **175** (R = H, CH_3, C_2H_5, Ph) reacted with formaldehyde and Bu_4NI to cyclise in moderately good yield to 3-alkylideneazepanes (**176**, R = H, CH_3, C_2H_5,



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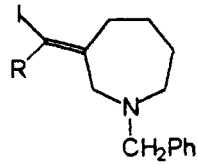

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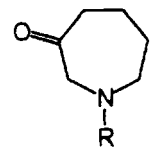

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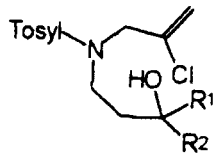

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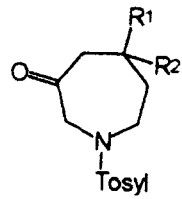
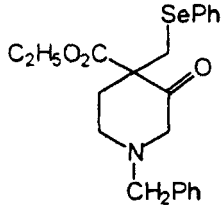


(179)

Ph).[365] Ozonolysis of **176** (R = CH_3), after iodine/hydrogen exchange, gave the amino ketone **177** (R = CH_2Ph). Intramolecular Friedel–Crafts cyclisation of *N*-tosylchloroalkenols **178** ($R^1 = R^2 = CH_3$ and R^1 = Ph, R^2 = H) was effected in 90% H_2SO_4 at −15 to 0 °C providing ketones **179** ($R^1 = R^2 = CH_3$ and R^1 = Ph, R^2 = H) (30% and 71% yields, respectively).[366] Ring expansion of the phenyl selenide **180** was achieved using $^nBu_3SnH$; in this way the keto ester **181** was obtained in 71% yield.[367]



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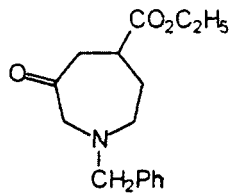

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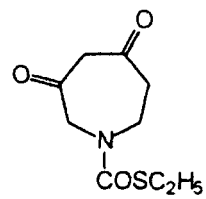
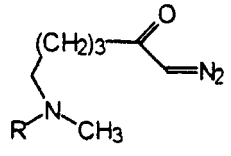


(182)

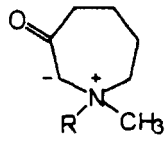
Microorganisms have, in a few cases, been shown to oxygenate *N*-substituted azepines; mixtures of products have included azepan-3-ones. The earliest examples demonstrated that *Sporotrichum sulfurescens* converted *N*-benzoylazepane into several products including **177** (R = PhCO), the 4-keto isomer and the corresponding alcohols.[368] The overall conversion to ketones was improved by treating the crude bioconversion mixture with Jones reagent.[369] *N*-Nitrosoazepan-3-one (**177**, R = NO) has been detected in the urine of rats given *N*-nitrosoazepane.[370] 3-Ketomolinate **177** (R = $COSC_2H_5$) was detected when molinate (a herbicide) came in contact with microorganisms of a *Fusarium* species[371] and a more highly oxygenated product (**182**) appeared in Kazakhstan

rice paddies when ordram (≡ molinate) was metabolised by organisms present.[372]

Some further activity in the azepan-3-one area was seen in 1994. First, electrochemical oxidation of *N*-carbomethoxyazepane followed by *m*-chloroperbenzoic acid oxidation yielded 50% of the ketone **174** (R = H)[441] and second, two separate groups of workers disclosed that generation and rearrangement of certain ammonium ylides could give β-amino ketones.[442,443] Thus α-diazo ketones **182A** (R = $PhCH_2$ or $CH_2CH{=}CH_2$) with $Cu(acac)_2$



(182A)

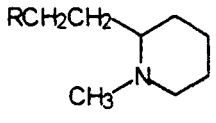


(182B)

gave the azepan-3-ones **171** (R = $PhCH_2$ or $CH_2CH{=}CH_2$) in acceptable yields by a process thought to involve intramolecular formation of ammonium ylides (**182B**; R = $PhCH_2$ or $CH_2CH{=}CH_2$) followed by [2,3]-sigmatropic rearrangement.

REACTIONS

Because of their rarity, not much work has been done on azepan-3-ones. Reduction of the carbonyl group with $NaBH_4/C_2H_5OH$ appears to proceed normally to give a 3-hydroxyazepane; for example, **177** (R = NO) gave the corresponding alcohol (Chapter 2).[373] It has long been known[362,363] that Clemmensen reduction of bases such as **171** (R = CH_3, C_2H_5) gave rearranged products



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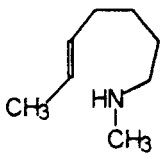

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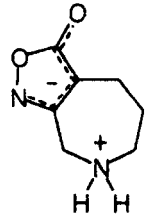


(185)

(**183**, R = H, CH_3 respectively) but Wolff–Kishner reduction was thought to proceed more or less as expected to give azepanes. However, it was later disclosed[374] that such reactions also produced alkenes. For example, 2-methyl-*N*-methylazepan-3-one (**171**, R = CH_3) gave, in addition to 2-methyl-*N*-methylazepane, 36.5% of unsaturated material considered to be **184**. All of

the *N*-alkylazepan-3-ones reported, being α-amino ketones, are of dubious stability but form salts without apparent difficulty.

Notwithstanding their instability, azepan-3-ones have been successfully employed to annulate further rings to the structure. Thus the keto ester **174** (R = $CO_2C_2H_5$) reacted with hydroxylamine followed by hydrogen chloride to provide the zwitterionic compound **185**.[326,375] Other examples can be found in the patent literature.[377,378]

Table 15. Azepan-3-ones

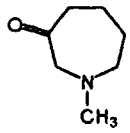
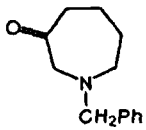
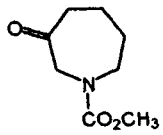
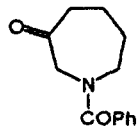
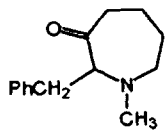
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HCl 195–196		361
			IR	365
	140/40		IR, ^{1}H NMR MS	364 441
	113–114		IR	368
	Supplement		Supplement	443

Table 15 (continued)

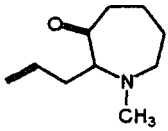
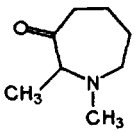
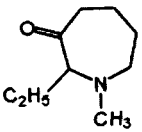
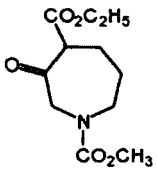
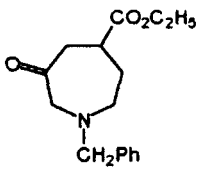
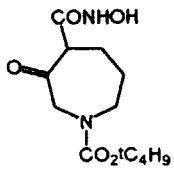
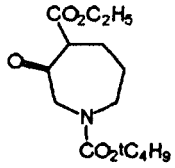
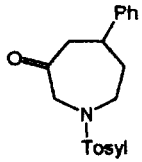
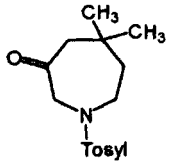
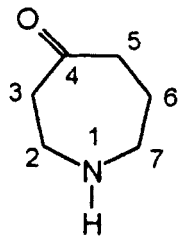
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
				442
	72–73/11	Picrate 174	n_D^{20} 1.4700	363, 374
	91–92/13	HCl 162.5–163 Picrate 169–169.5 Picrolonate 164.5–165.5	n_D^{20} 1.4696	362
	160/55		IR, ^{1}H NMR	364, 376
	Colourless oil		^{1}H ^{13}C NMR, IR, MS	367
	145 (d)		IR, ^{1}H NMR	375

Table 15 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	147–148/60			375
	115–117		IR, MS, ^{1}H NMR	366
	100–102		IR, MS, ^{1}H NMR	366

III. AZEPAN-4-ONES

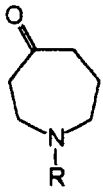


The members of this series have been thoroughly researched.

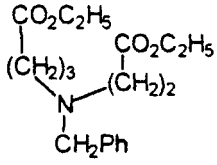
PREPARATION

The hydrochloride of the parent amino ketone (**186**, R = H) was first reported by Yokoo and Morosawa in 1956:[379] the *N*-benzyl ester **187** was subjected to the Dieckmann cyclisation ($NaOC_2H_5$/xylene), the intermediate cyclic β-keto esters

were hydrolysed yielding a modest 21.7% yield of the hydrochloride of **186** (R = CH_2Ph). The latter on hydrogenolysis (H_2/PdO) gave **186** (R = H), isolated as the hydrochloride. The corresponding *N*-benzoyl compound **186** (R = COPh) was not obtainable by Dieckmann cyclisation.[379] It was later revealed[380,383] that difficulties with the production of the diester **187** made this



(186)



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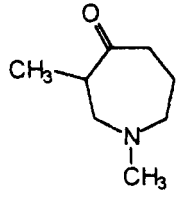

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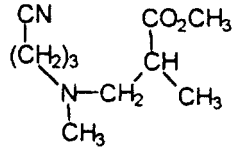


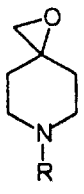
(189)

synthesis less attractive than that involving diazomethane ring expansion of *N*-benzylpiperid-4-one (see below). Later work on the Dieckmann reaction favoured use of potassium ethoxide[381] or sodium hydride[382] as reagent, but the yields were not much improved. In contrast, the Thorpe–Ziegler cyclisation of dinitriles has been recommended for the preparation of both **186** (R = CH_2Ph)[384] and **186** (R = CH_3)[385] on the grounds that starting materials were more easily obtained; the yields, however, were not improved. The 3-methyl analogue (**188**) was obtained by a mixed Thorpe–Dieckmann cyclisation of the cyano ester **189** in 33% yield ($NaOCH_3$/xylene).[386]

As inferred above, ring expansion of 4-piperidones has become a popular methodology for the production of azepan-4-ones. Originally,[350] diazomethane (from *N*-nitrosomethylurethane) reacted with *N*-benzylpiperid-4-one at −15 °C giving a 43.6% yield of the ketone (as hydrochloride) (**186**, R = CH_2Ph). However, it was possible to obtain better yields (not precisely recorded) using preformed ethereal diazomethane.[387] In the case of the *N*-benzenesulphonyl derivative (**186**, R = $PhSO_2$), *in situ* generation of diazomethane (from *N*-nitrosomethylurethane) gave a very poor yield,[388] so one has to conclude that preformed diazomethane is preferable.[390] In most cases the expanded products (**186**) are accompanied by variable amounts of epoxide (**190**);[388,389] it appears that the precise experimental conditions employed are crucial.

Diazo ester ring expansions have become popular: this protocol has the advantage of generating cyclic β-keto esters (**191**) in one step from piperid-4-ones. In the earlier work,[391] keto esters **191** (R = $PhCH_2$, $CO_2C_2H_5$; R^1 = C_2H_5) were obtained directly in around 30–34% yields. Later work[392] revealed that, using the same technique ($N_2CH_2CO_2C_2H_5/BF_3$/−25 °C), hydrolysis of the unisolated β-keto ester and reprotection of the nitrogen atom led to a 50% yield of the ketone **186** (R = $CO_2C_2H_5$). This work has been confirmed.[364,393] The 5-phenyl analogue **192** was likewise obtained from

N-benzylpiperid-4-one using ethyl *N*-nitrosobenzyl carbamate and potassium carbonate in methanol at <25 °C, the yield being 21%.[395] Diazoacetic ester ring expansion was particularly successful for the *N*-*tert*-butoxycarbonyl case (**191**, R = $CO_2{}^tBu$, $R^1 = C_2H_5$),[396] which, after hydrolysis, provided a 67% overall yield of **186** (R = H, as hydrochloride). Again there are reported cases (e.g. **191**, R = $PhCH_2$, $CO_2C_2H_5$; $R^1 = C_2H_5$) where greatly improved yields arose from process modifications.[397] The *N*-nitroso diester **193** was shown to react with *N*-benzylpiperid-4-one providing a 51% yield of **194**.[398]



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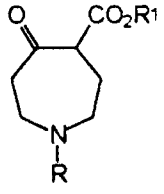

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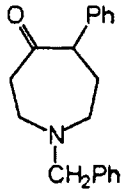

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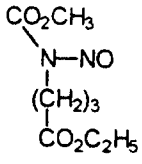

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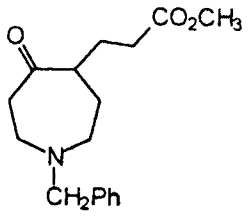
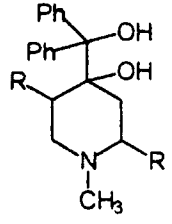


(194)

Other types of ring expansion are known. Thus, a Wagner–Meerwein type of rearrangement ensued when the tertiary dialcohol **195** (R = H) was treated with concentrated H_2SO_4 at 0 °C: the product **196** (R = H) was obtained in 79% yield.[399] Similarly, the diol **195** ($R = CH_3$) gave **196** ($R = CH_3$) and



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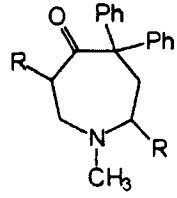

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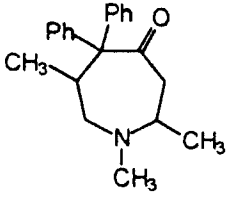

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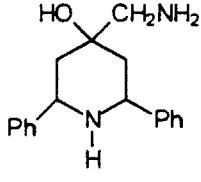
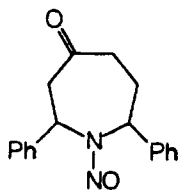


(198)

197.[400] Mechanistically similar was treatment of the amine **198** with nitrous acid at 0 °C which gave the *N*-nitroso ketone **199** in 20% yield.[401] A free-radical ring expansion (e.g. **200** → **201**) has been reported.[367] A yield of 66% was achieved

($^nBu_3SnH$/AIBN/benzene/reflux) in the case of **200** (R = Ph_3C); a poorer yield in the case of **200** (R = CH_2Ph) is attributable to transannular hydrogen atom abstraction from the benzyl group (CH_2Ph). This protocol has the advantage of employing readily accessible piperidones to give azepan-4-ones carrying functionality (CO_2CH_3) at a normally inaccessible (C-6) position.



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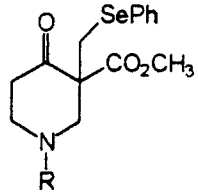

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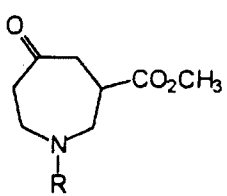
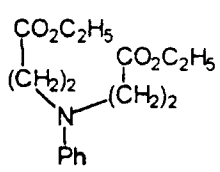


(201)

The acyloin reaction was first applied to azepan-4-one synthesis in 1954:[402] conversion of diester **202** into hydroxy ketone **203** (R = Ph) proceeded in only



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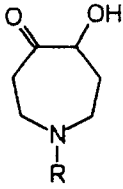

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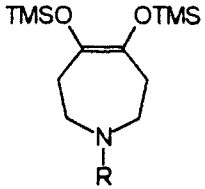
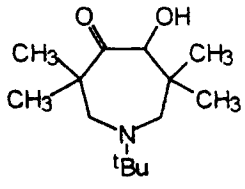


(204)

10% yield (Na/xylene). The *N*-ethyl diester corresponding to **202** failed to give an acyloin although all of the higher homologues studied gave larger ring acyloins in satisfactory yields.[402] On the other hand, when the acyloin reaction was conducted in the presence of trimethylsilyl chloride as trapping agent, the protected product (**204**, R = $PhCH_2$) related to acyloin **203** (R = CH_2Ph) was isolated in good yield.[403] It is now standard procedure to include trimethylsilyl chloride in acyloin reactions[404,405] designed to provide 5-hydroxyazepan-4-ones. It should be noted that where alkyl groups replace hydrogen atoms α- to ester functionality (e.g. in **202**), the acyloin reaction proceeds well under classical conditions, for example hydroxy ketone **205** was obtained in 80% yield[406] from the corresponding diester using sodium in toluene and without trimethylsilyl chloride. This outcome is attributable to the suppression of Dieckmann reactions which require hydrogen atoms α- to ester groups.

An intramolecular Friedel–Crafts type of electrophilic cyclisation has been uncovered in the case of the chloroalkenyl-protected amino acid chloride **206**, which cyclised in alcohol-free dichloromethane at ambient temperature yielding the dichloro ketone **207** in 56% yield.[366] This procedure also has the merit of providing access to an azepan-4-one substituted at C-6; moreover, **207** was

easily converted into the tetrahydroazepinones **208** (R = Cl and OCH_3)[366] (Chapter 5). Flash vacuum thermolysis of the spirooxazolidine **209** gave the



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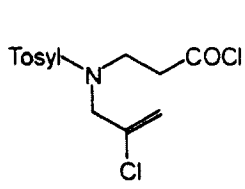

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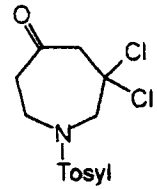

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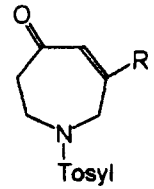
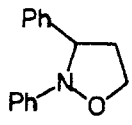


(208)

2-phenylazepan-4-one **210** in 42% yield, accompanied by other identified products.[408,409]



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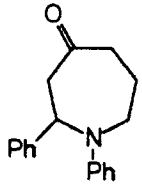

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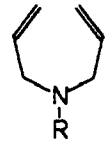

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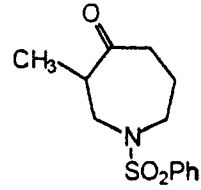
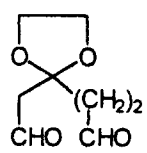


(212)

Various *N*-protected bisallylamines (**211**) have been shown to undergo hydroboration/carbon monoxide insertion using chloroborane/dimethyl sulphide.[410] Generally two or more products were isolated; the most successful in the present context involved the diene **211** (R = $PhSO_2$), which gave ketone **212** in 40% yield along with the corresponding perhydroazocin-5-one. Other *N*-protecting groups (**211**, R = CO_2CH_3, CO_2CH_2Ph) were much less efficient.[410] This is an interesting approach worthy of further study, perhaps utilising chloroallyl groups as in **206**.

A logical adaptation of standard cyclisations for azepanes (Chapter 2) involved ketone protection (as acetal), which allowed the reductive amination of dialdehyde **213** with various amines (CH_3NH_2, $PhNH_2$, cyclohexyl-NH_2)



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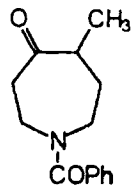

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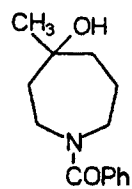


(215)

using $NaCNBH_3$.[411] The products were the acetal-protected azepan-4-ones **186** (R = CH_3, Ph and c-C_6H_{11}); after deprotection (10% HCl) the yields overall of

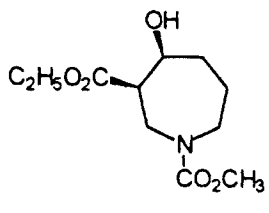
azepan-4-ones from cyclohex-2-enone were fairly poor; however, this has the merit of novelty.

Microbiological oxygenation of both *N*-benzoyl and *N*-tosylazepane using *Sporotrichum sulfurescens* led to mixtures of azepan-3-ones (Section II) and azepan-4-ones along with the corresponding alcohols.[368] After CrO_3 oxidation of the mixtures, azepan-4-ones (**186**, R = PhCO, tosyl) were isolated and identified (yields ~50%). *N*-Benzoyl-4-methylazepane, on the other hand, gave only 11% of the 5-methylazepan-4-one **214**; the major product involved oxidation to the tertiary alcohol **215**.[412] Several other microorganisms have the ability to oxygenate azepanes.[371] The herbicide molinate has been extensively studied. 4-Ketomolinate (**186**, R = $COSC_2H_5$) has been detected in various soils,[371,372,413] rivers[414] and fish,[415,416] while *N*-nitrosoazepan-4-one (**186**, R = NO) has been found in rats urine[370] after administration of *N*-nitrosoazepane. However, none of these studies has yet been developed into the status of a synthesis.

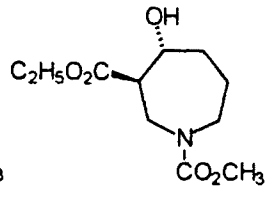
REACTIONS

Most reactions reported for azepan-4-ones are predictable. It was demonstrated more than 40 years ago that transannular electron donation from nitrogen to carbonyl in a seven-membered acyloin (**203**, R = Ph) was unlikely since the infrared stretching frequency of the carbonyl group (1701 cm^{-1}) was, unlike those of nine-membered analogues (1666, 1671 cm^{-1}), normal.[402,417] *N*-Benzylazepan-4-one (**186**, R = CH_2Ph) forms an ethylene ketal whose ^{13}C NMR spectrum has been recorded and compared with those of similar structures.[418] Simple azepan-4-ones (**186**, R = H, CH_3, C_2H_5) are fairly unstable bases, usually best handled as salts; the *N*-acyl derivatives do not appear to involve significant problems.

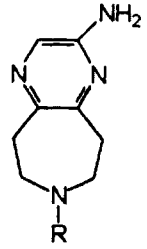
Not surprisingly, reduction of the carbonyl group in this series can be brought about using $NaBH_4$; in the case of the β-keto ester **191** (R = CO_2CH_3, R^1 = C_2H_5), the two stereoisomers (**216**, **217**) were isolated.[419] Similar molecules have been reduced catalytically (H_2/Ni)[420] to the corresponding alcohols. The vinyl-oxycarbonyl group in **186** (R = CH_2=CHOCO–) survived



[(±)**216**]



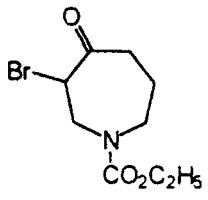
[(±)**217**]



(**218**)

$NaBH_4$ reduction of the carbonyl group to an hydroxy group.[421] $LiAlH_4$ served to reduce the carbonyl group in **186** (R = $PhCH_2$).[421] The expected addition of organometal reagents to azepan-4-ones has been reported; for example, the 3-methyl analogue **188** underwent addition with phenyllithium.[422] Oxidation of *N*-substituted azepan-4-ones with selenium dioxide has been claimed to yield mixtures of 3,4- and 4,5-diones.[423] Although the latter were not isolated, subsequent reactions with 2-aminoacetamidine led to *N*-substituted 2-amino-6,7,8,9-tetrahydro-5*H*-pyrazino[2,3-*d*]azepines (**218**); accordingly, the structures of 4,5-diones are thus confirmed. It has to be inferred that the above-mentioned 3,4-diones were minor products.[423]

Bromination of **186** (R = $CO_2C_2H_5$) with *N*-bromosuccinimide was originally thought to give 3-bromoazepan-4-one (**219**),[424] while bromine in acetic acid gave a mixture of 3- and 5-bromo (**220**) isomers and the 3,5-dibromo



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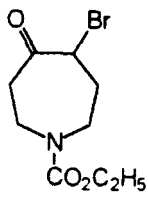

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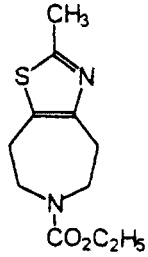

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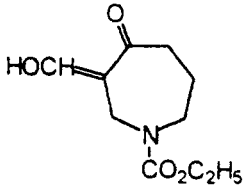
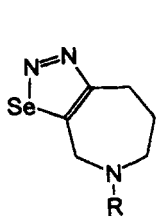


(222)

compound.[424] However, later work[425] suggested that bromination generally gave the 5-bromo isomer as the major product, since reaction with thioacetamide gave thiazoloazepine (**221**), contrary to the original conclusion.[426] On the other hand, reaction of **186** (R = $CO_2C_2H_5$) with ethyl formate gave a hydroxymethylene compound,[427] subsequently proved by NMR spectroscopy to have structure **222**.[425]

A number of heterocycles have been fused to the azepane ring using azepan-4-one derivatives as starting materials. The 5-bromo derivative **220** has been used to obtain a number of thiazolo- and oxazoloazepines,[428] while the hydroxymethylene derivative **222** served to generate a pyrazoloazepine structure.[427] β-Keto esters (**191**) are useful precursors for pyrimido[4,5-*d*]azepines[429] by reaction with thiourea, acetamidine, guanidine or cyanoguanidine. Isoxazolo[3,4-*d*]azepine derivatives[430] and the corresponding isothiazolo[5,4-*c*]azepines[431] were made as potential GABA-mimetic compounds also commencing with β-keto esters. 1,2,3-Selenadiazole rings can be annulated to the azepane nucleus by reaction of semicarbazones of ketones (**186**, R = CH_2Ph or $CO_2C_2H_5$) with SeO_2 or by selenoyl dichloride ($SeOCl_2$) treatment of the corresponding ketone tosylhydrazones.[432] The selenadiazole isomer **223** was generally the preferred product, although the ratio of **223** to **224** was drastically affected by changes in solvent. In this work ^{77}Se NMR was usefully deployed.[432] The

ketone **186** (R = CH_2Ph), when subjected to Schmidt reaction conditions, gave 7% of a tetrazolodiazocine (**225**), but the major product was the diazocinone **226** (64%).[61]



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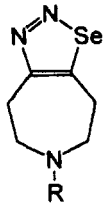

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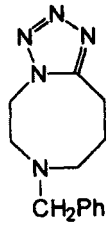

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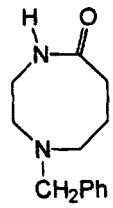

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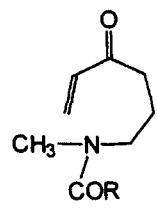
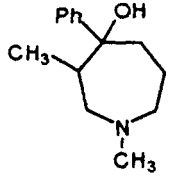


(227)

The relative position of carbonyl group and heterocyclic nitrogen atom in azepan-4-ones (i.e. β-amino ketones) makes Hofmann elimination reactions likely; these have been demonstrated for the *N*-acylium salts of **186** (R = CH_3) which gave enones **227** (R = CH_3 and $-CH{=}CH_2$) when refluxed with Hünig's base ($^iPr_2EtN$) in toluene.[433]

Ring contraction reactions are known in this series. Thus the alcohol **228** gave the pyrrolidine derivatives **229** on being refluxed with propionic anhydride;[422] a transannular electron donation (N → C-4) was postulated to explain this phenomenon. A similar behaviour was seen[421] when ketone **186** (R = CH_2Ph)



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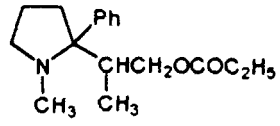
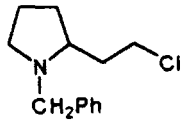
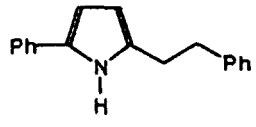


(229)



(230)



(231)

was reduced to the corresponding alcohol and the latter reacted with triphenylphosphine/carbon tetrachloride giving **230** (see Chapter 2). Attempted Wolff–Kishner reaction on the hydrazine of ketone **199** (H for NO) led to the pyrrole **231**.[401]

Table 16. Monosubstituted azepan-4-ones

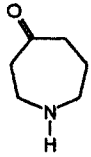
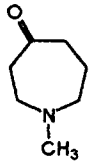
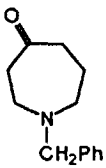
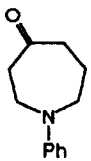
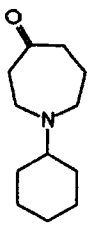
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	105–108/0.25		MS, IR	393
		HCl 161–163	^{1}H NMR	396
		HCl 171		379, 380, 427
	115–120/45	Picrate 171–172	n_D^{23} 1.4893, d_4^{23} 0.963	385, 434
	97–100/18	Picrate 151–152		435
		HCl 166.5–167		390
		HCl 160 (d)		381
	115–118/0.01	HCl 186–187		379, 427
		2,4-DNPH.HCl 206		
	129/0.05	HCl 192–194		380 381
	120/0.3	HCl 188–191	n_D^{20} 1.5539	384
	98–100/0.1		IR	428
			^{13}C NMR, IR, MS	411
		HCl 144		428, 436
	114		IR, ^{1}H, ^{13}C NMR, MS	411

Table 16 (continued)

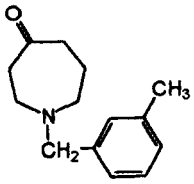
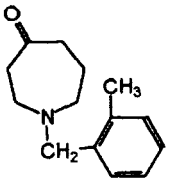
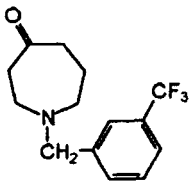
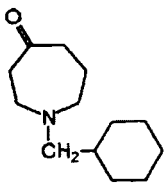
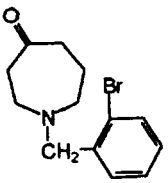
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HCl 169		428
		HCl 165		428
		HCl 176–178		428
		HCl 180		428
		HCl 179		428

Table 16 (continued)

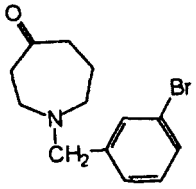
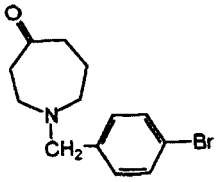
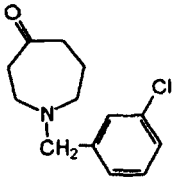
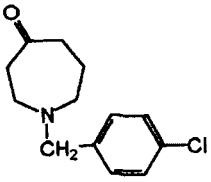
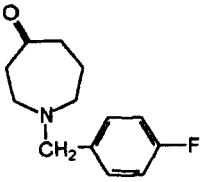
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HCl 192		428
		HCl 215		428
		HCl 212		428
		HCl 210		428
		HCl 208		428

Table 16 (continued)

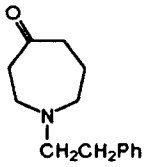
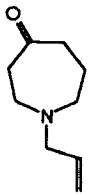
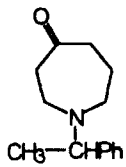
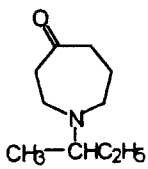
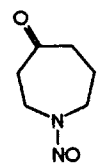
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	130–134/0.4	HCl 195		387 428
	52–54/0.2			428
	105/0.1			428
	58–60/0.1			428
	160/0.05		IR, MS, ^{1}H NMR	389

Table 16 (continued)

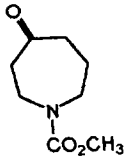
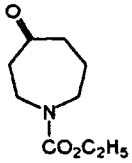
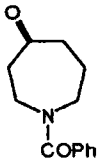
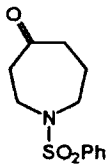
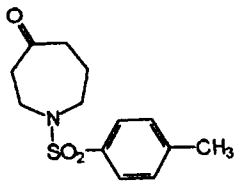
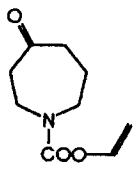
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	140/40		IR, ^{1}H NMR	364
	117/1	Semicarbazone 184.5–186	^{1}H NMR	393, 427 432
	170/0.25 173/0.3		IR	373 368
	121–122	Oxime 172–173 2,4-DNPH 197		388
	89–90		IR	368
	Oil		IR, ^{1}H NMR, MS	421

Table 16 (continued)

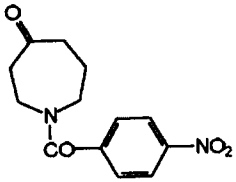
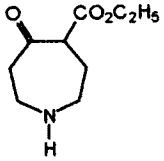
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	118.5–119	2,4-DNPH 123–125 Oxime 203.5–204		388
	112–114/0.6	HCl 133–134		391, 397

Table 17. Disubstituted azepan-4-ones

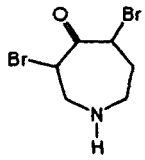
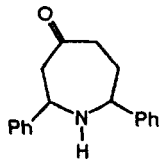
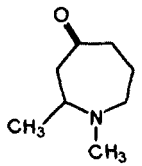
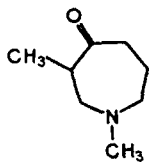
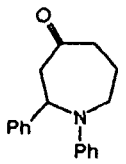
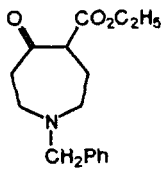
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		HBr 186 (d)		424
	110–111			401
	100–120/27			382
	110/35	Picrate 192–193 HCl 158–160	n_D^{29} 1.4656	434 385 386
	93–94		^1H, ^{13}C NMR, MS, IR	408
			IR, ^1H NMR, MS	367

Table 17 (continued)

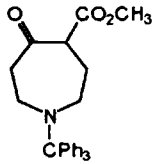
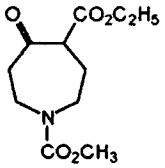
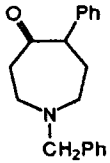
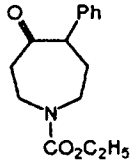
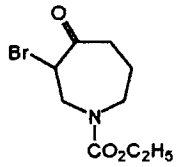
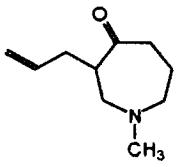
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			^1H, ^{13}C NMR, MS, IR	367
	210/0.3		IR, ^1H NMR	420
		HCl 225	IR, ^1H NMR, X-ray	395, 407
	171/0.15		IR, ^1H NMR	395
	140–145/1	2,4-DNPH 149–152(d)		424
	123–124/35	Picrate 138–139		394

Table 17 (continued)

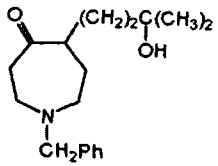
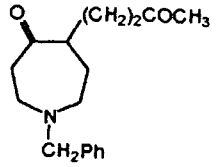
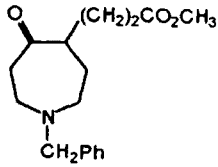
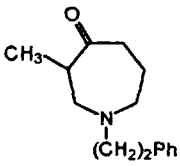
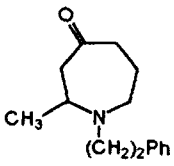
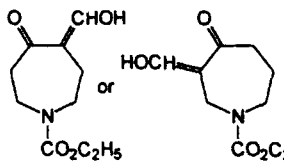
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Oil		^{1}H, ^{13}C NMR, MS	398
	Oil		^{1}H, ^{13}C NMR, MS, IR	398
	Oil		^{1}H, ^{13}C NMR, IR	398
		Picrate 124–130		382
				382
	127–130/0.7	2,4-DNPH 172		427

Table 17 (continued)

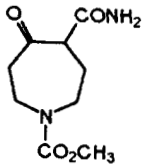
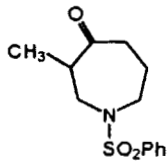
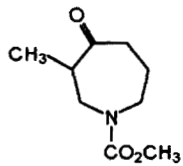
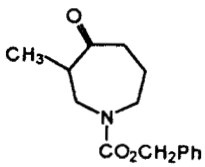
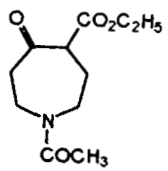
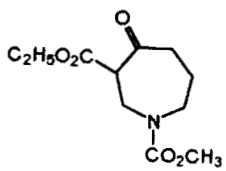
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	130.5–132			431
			^{1}H NMR, MS, IR	410
	Chromato-graphy		^{1}H NMR, MS, IR	410
	Chromato-graphy			410
	154/0.28		IR	391, 429, 430
	160/55		^{1}H NMR, IR	364, 419

Table 17 (continued)

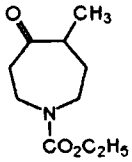
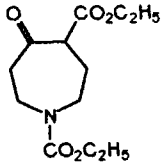
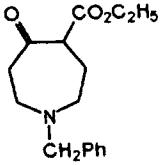
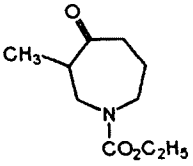
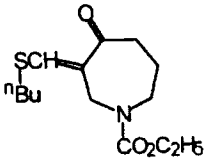
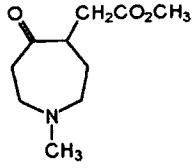
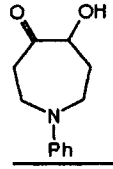
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	93–95/0.1	2,4-DNPH 145–146		391
	133–135/0.15	2,4-DNPH 119.5		391–393, 397, 430, 437
	160–162/0.4	HCl 164.5 2,4-DNPH.HCl 179		391, 397, 438 430
	132–134/0.7	2,4-DNPH 177–179		425
	85–86	2,4-DNPH 117–119		425
				439
	112–113	*p*-Nitro-benzoate 146–147		402, 439

Table 18. Tri- and polysubstituted azepan-4-ones

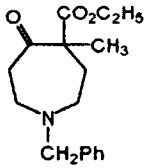
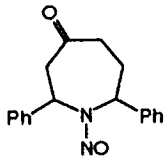
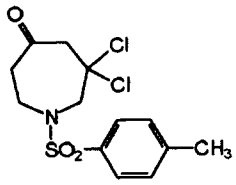
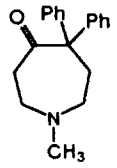
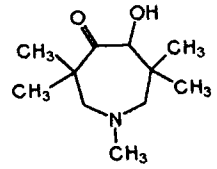
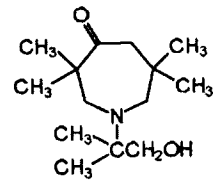
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	171–173/0.2			391
	138–142	2,4-DNPH 224–226		401
	109–111		IR, ^{1}H NMR, MS	366
	91–92	HCl 244–246 MeI 201–203		399
			^{1}H NMR	440
	78–80 (subl.)		IR, ^{1}H, ^{13}C NMR, MS	405

Table 18 (continued)

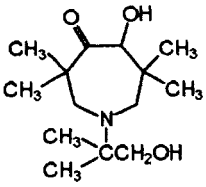
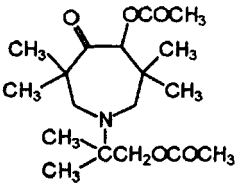
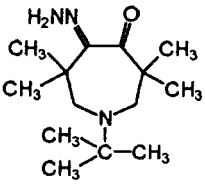
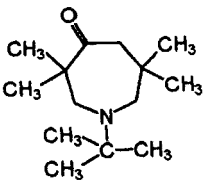
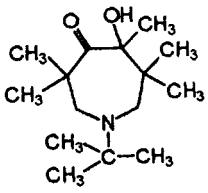
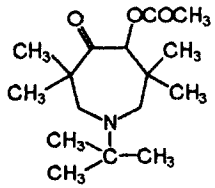
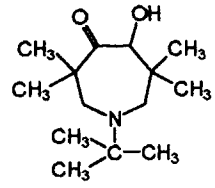
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	67–69 (subl.)		IR, ^{1}H, ^{13}C NMR, MS	405
	76–79 (subl.)		IR, ^{1}H NMR, MS	405
	78–80		IR	406
	37–38 (subl.)		IR, ^{1}H NMR, MS	406
	57–60 (subl.)		IR, ^{1}H NMR, MS	406

Table 18 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	86–88 (subl.)		IR, ^{1}H NMR, MS	406
	55–56 (subl.)		IR, ^{1}H NMR, UV, MS	406, 440

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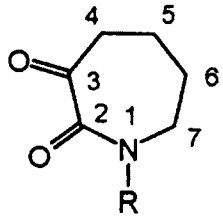
CHAPTER 4

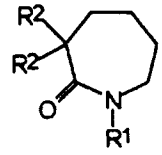
Azepanediones

Of the nine possible combinations in this group, only azepane-3,6-diones are not mentioned in the literature. However, azepane-2,6-diones, azepane-3,4-diones and azepane-3,5-diones are not properly authenticated. The other five members are well known.

I. AZEPANE-2,3-DIONES



These diones are generally obtained from caprolactams. When 3,3-dihalocaprolactams (e.g. **1**, $R^1 = H$, $R^2 = Cl$) react with secondary amines such as piperidine or morpholine, enamines (**2**, R = H, X = CH_2, O) are obtained.[1]



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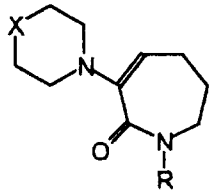

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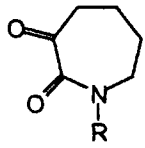
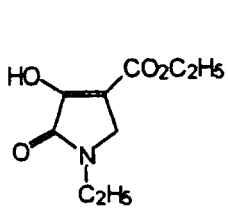
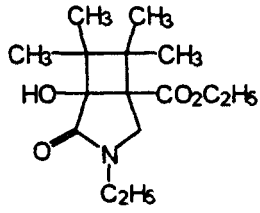


(3)

Hydrolysis of the latter with dilute acid provides the required 2,3-diones (**3**; R = H[2] and CH_3).[3] In the case of enamine **2** (R = H, X = CH_2), it was



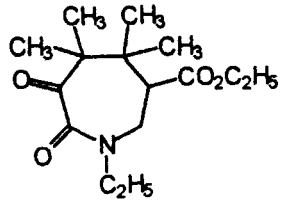
(**4**)



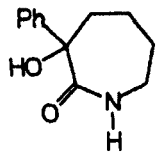
(**5**)

discovered[4] that passage through a column of silica converted the enamine into the diones **3** (R = H).

The only other method for obtaining azepane-2,3-diones involves a 5 + 2 ring expansion scheme in which the enolic dioxopyrrolidine **4** underwent photochemical [2 + 2] cycloaddition with 2,3-dimethylbut-2-ene yielding adduct **5**. The latter was converted into the azepanedione **6** by heating with sodium hydrogencarbonate in ethanol.[5]



(**6**)



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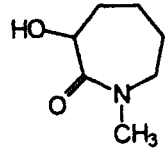
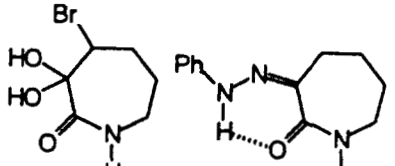


(**8**)

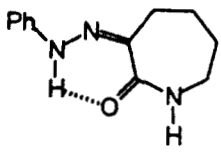
The azepane-2,3-diones behave in a predictable manner. Infrared spectroscopy revealed carbonyl stretching frequencies at 1630 and 1720 cm^{-1} for the amide carbonyl group and the 3-keto group, respectively[2] in **3** (R = H). In the case of **3** (R = CH_3), the corresponding frequencies were 1650 and 1715 cm^{-1}.[3] Addition of arylmagnesium bromide to **3** (R = H) took place at C-3 giving **7**,[4] while sodium borohydride as expected gave **8** from **3** (R = CH_3),[3] whereas $LiAlH_4$ caused conversion into 3-hydroxy-*N*-methylazepane.[3] Hydrogen cyanide also added at C-3.[2] The dione **3** (R = H) reacted with bromine in water to yield a 4-bromo hydrate (**9**).[6] As expected, hydrazines reacted with the ketone carbonyl group (C-3);[7–10] the phenyl hydrazone of dione **3** (R = H) was isolated in both *syn* (**10**) and *anti* (**11**) forms,[8] as were the corresponding isomers from *N*-methyldione **3** (R = CH_3).[8] *N*-Arylimines **12** (R = H, Cl, OCH_3, OH) are also known.[11]

The main impetus for work in this area has come from the desire to obtain polycyclic ring systems involving azepane nuclei, principally carried out by Glushkov and co-workers in the former USSR. In some cases diones[7] were used, in others[1,6–8] the enamines[2] were the starting materials. Thus a variety

of multi-ring heterocyclic compounds were constructed. These include indoloazepines (**13**, R = H, OCH_3),[1] azepinopyrrolopyrimidines (**14**, R = CH_3, CH_2Ph),[7] pyridopyrroloazepines (**15**, **16**),[10] pyridoazepines (e.g. **17**)[12] and benzofuroazepines (**18**).[13] In some cases,[13] the azepine ring is contracted during reaction. For example, treatment of the *O*-phenyloxime of dione **3**



(9)



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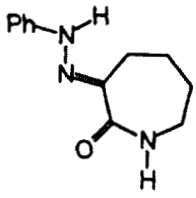

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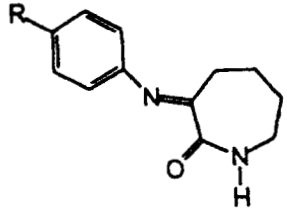

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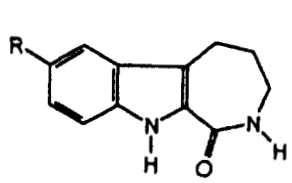

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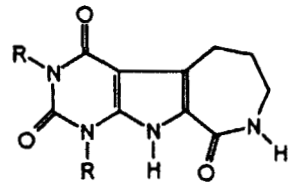

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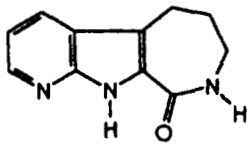
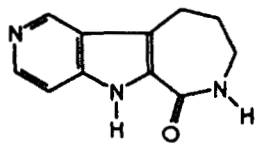


(15)



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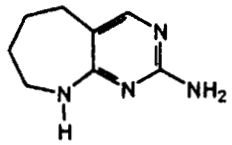

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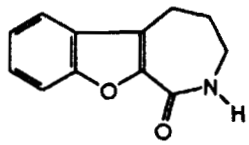
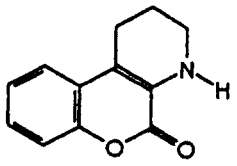


(18)

(R = H) with gaseous HCl in propan-2-ol at 0 °C gave the pyridocoumarin **19** in good yield along with **18** as a minor product.[13] The furoazepine **20**, the thiazoloazepine **21** and the benzothiazinoazepine **22** have also been reported.[6]

The reactivity at C-4 of azepan-2,3-diones has been exploited. Enamines (**2**) react with aryldiazonium chloride to give arylhydrazones (**23**, R = H, OMe), which are formally derivatives of azepane-2,3,4-triones.[1] By further reaction with various hydrazines, **23** (R = H) was converted into indoloazepines (**24**,



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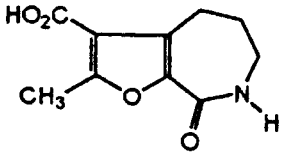

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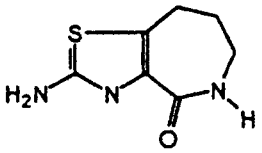

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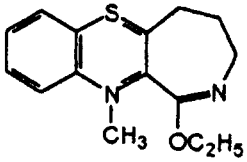

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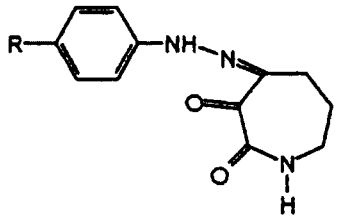
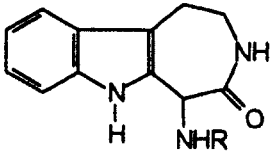


(23)

R = $COCH_3$, 2,4-di-$NO_2C_6H_3$)[14] and a triazoloazepinone (**25**).[15] Reaction of azepane-2,3-dione (**3**, R = H) with dimethylformamide acetal gave the aminomethylene compound **26**,[16] which, as is usual in such cases, underwent displacement reactions involving the $-N(CH_3)_2$ group. This led to the synthesis



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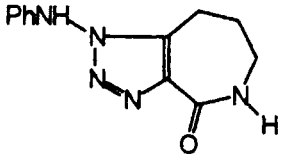

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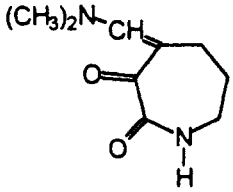

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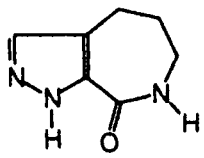

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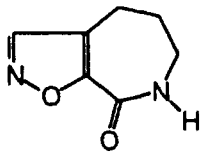


(28)

of pyrazoloazepines (e.g. **27**)[17] using hydrazines and to an isoxazoloazepine (**28**) with hydroxylamine.[18]

Table 1. Azepane-2,3-diones and related imines

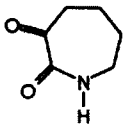
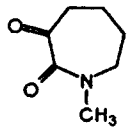
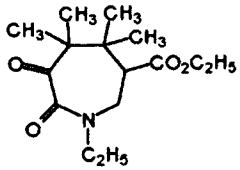
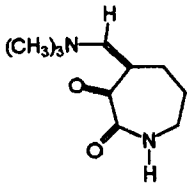
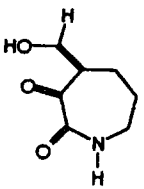
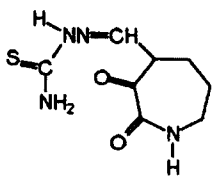
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	71–72		^{13}C NMR, IR	2, 4
	126–127/2		IR	3
	55–57		IR, ^{1}H NMR	5
	175–176			16
	144.5–145			16
	169–170		IR, UV, ^{1}H NMR	17

Table 1 (continued)

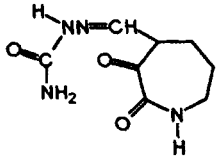
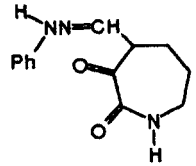
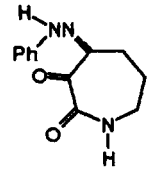
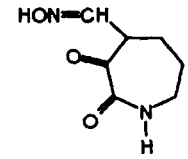
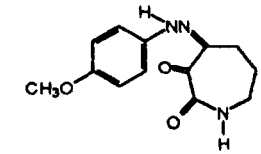
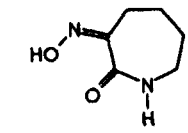
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	215–217		IR, UV, ^{1}H NMR	17
	144–147		IR, UV, ^{1}H NMR	17
	205–207			1
	185–186		IR, UV, ^{1}H NMR	18
	198–200			1
	201–202 206–208			8 71

Table 1 (continued)

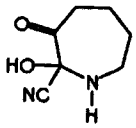
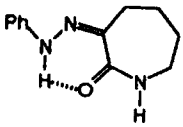
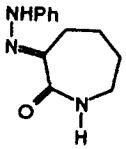
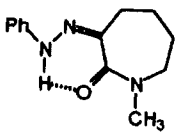
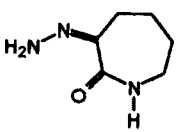
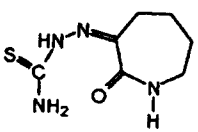
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	132–134	*N,O*-di-OAc 132–134		2
	137–138		IR, UV	8
	213		IR, UV	8
	96–96.5		IR, UV	8
	214–214.5		IR, UV	8
	214		IR	8
	239–241		IR, UV	8

Table 1 (continued)

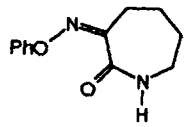
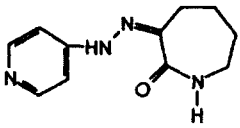
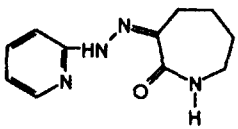
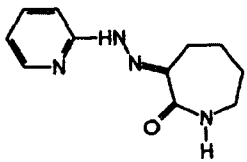
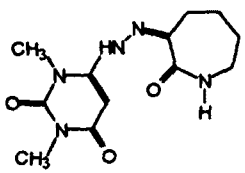
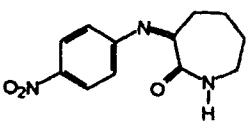
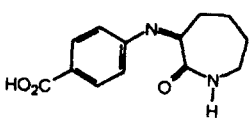
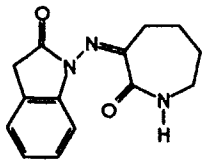
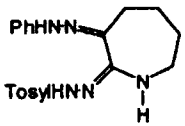
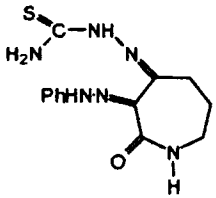
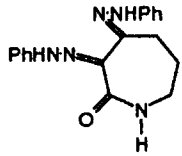
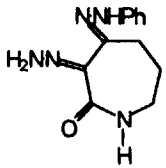
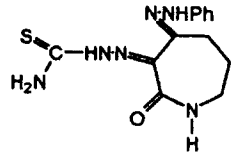
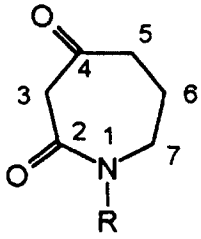
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	125		IR, MS, UV	13
	190–190.5			10
	129–131			10
	181–182			10
	233		IR, UV	7
	168–170			2
	190–190.5			2

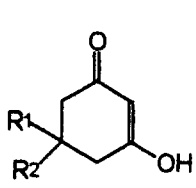
Table 1 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	184–186		IR, ^{1}H NMR	9
	137–138		IR	15
	225–226		IR, UV	14
	205–207		IR, UV	14
	177–178		IR, UV	14
	228 (d)		IR, UV	14

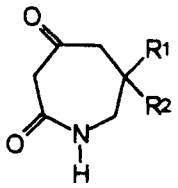
II. AZEPANE-2,4-DIONES



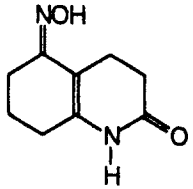
Ring expansion of cyclohexane-1,3-diones has been the most popular method for obtaining azepane-2,4-diones. Thus the enolic diones **29** ($R^1 = R^2 = H$ or CH_3 and $R^1 = CH_3$, $R^2 = H$) or their enol ethers were oximated and subjected to Beckmann rearrangements in PPA to give the azepanediones **30**



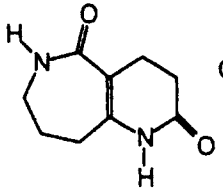
(29)



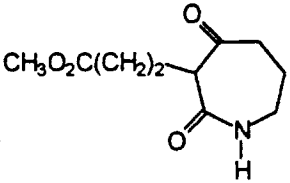
(30)



(31)

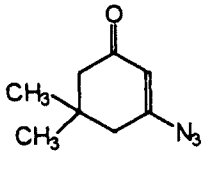


(32)

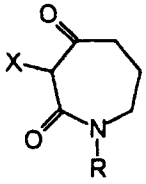


(33)

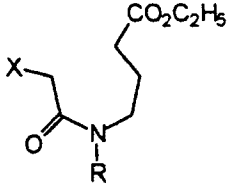
($R^1 = R^2 = H$ or CH_3 and $R^1 = CH_3$, $R^2 = H$).[19] A more subtle example involved Beckmann reaction on the bicyclic oxime **31** which, after hydrolysis of **32**, gave the dione **33**.[20] Photolysis of azido ketone **34** also gave dione **30** ($R^1 = R^2 = CH_3$),[21] but thermal versions of this approach appear preferable.[22]



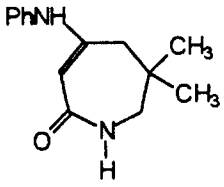
(34)



(35)



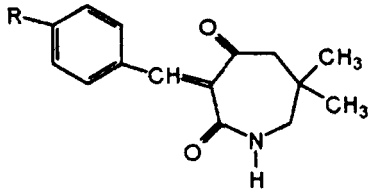
(36)



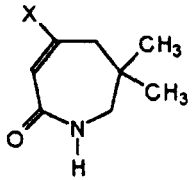
(37)

Azepane-2,4-diones have also been made by intramolecular cyclisation of amido esters (**36**, R = Ph, CH_2Ph, X = H, Cl). Deprotonation and cyclisation of **36** only proceeds in the presence of the appropriate crown ether. In this way the parent (**35**, R = Ph, CH_2Ph, X = H)[23] and chloro-substituted systems (**35**, R = Ph, CH_2Ph, X = Cl)[24] have been obtained.

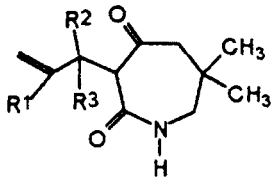
The chemistry of azepane-2,4-dione is unexceptional. Infrared stretching frequencies in the region of 1720 and 1670 cm^{-1} appear typical for the C-4 and C-2 carbonyl groups, respectively.[20,22,24] . The C-4 carbonyl group, as expected, is more easily reduced ($NaBH_4$) than the C-2 carbonyl[25] and is involved in enamine formation (e.g. **37**).[26] Condensations with aldehydes takes place at C-3 (e.g. **38**, R = H, Cl, NO_2),[25] while enol ethers (**39**, X = OR) are easily obtained from the chloro compound (**39**, X = Cl).[27] Allyl enol ethers undergo Claisen rearrangement giving a range (**40**, R^1, R^2, R^3 = H and CH_3) of C-3 substituted products.[27]



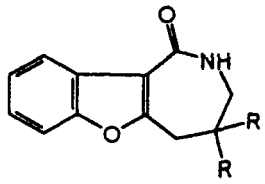
(38)



(39)

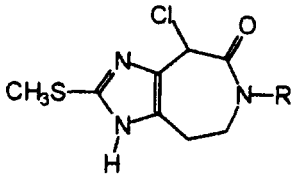


(40)



(41)

Azepane-2,4-diones have been employed in conversions to fused systems such as benzofuroazepinones (**41**, R = H, CH_3) by reaction with *O*-phenylhydroxylamine.[28] It has been claimed[24] that bromination of chloro diones (**35**, R = Ph, CH_2Ph, X = Cl) followed by reaction with *S*-methylisothiourea gave halo-substituted imidazoazepines (**42**, R = Ph, CH_2Ph).



(42)

Table 2. Azepane-2,4-diones

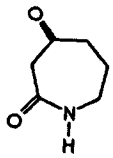
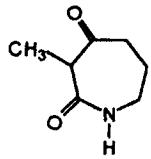
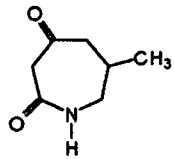
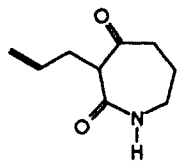
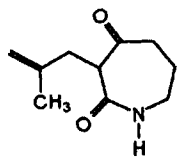
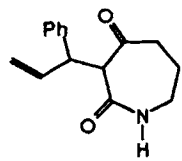
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	94.5		^{1}H NMR	19
	150–153		IR, ^{1}H NMR, MS	20
	98.5–99		^{1}H NMR	19
	98–100		IR, ^{1}H NMR	27
	115–120		IR, ^{1}H NMR	27
	155–165		IR, ^{1}H NMR	27

Table 2 (continued)

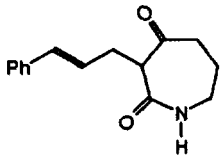
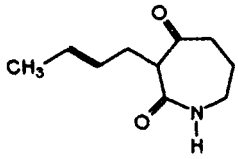
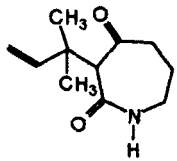
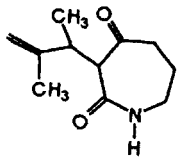
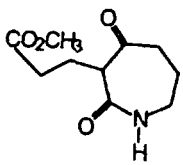
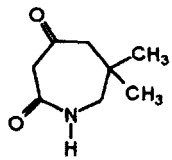
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	128–132		IR, ^{1}H NMR	27
	97–107		IR, ^{1}H NMR	27
	130–132		IR, ^{1}H NMR	27
	153–155		IR, ^{1}H NMR	27
	121–124 150–200/0.1		IR, ^{1}H NMR, MS	20
	146–147 144–144.5 145.5–146.5		^{1}H NMR	26 21, 22 19

Table 2 (continued)

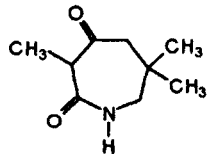
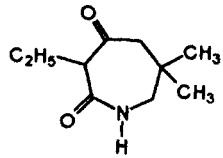
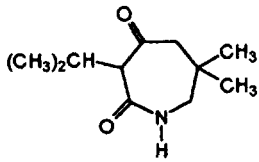
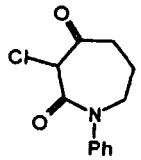
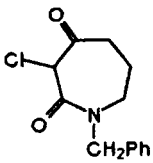
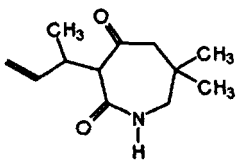
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	124–125		IR, ^{1}H NMR	25
	132–133		IR, ^{1}H NMR	25
	150–151		IR, ^{1}H NMR	25
	130/0.05	5-Bromo 50	IR, ^{1}H NMR	24
	120/0.05	5-Bromo 140/0.05	IR, ^{1}H NMR	24
	118–120		IR, ^{1}H NMR	27

Table 2 (continued)

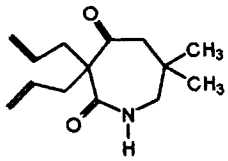
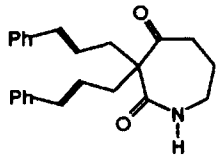
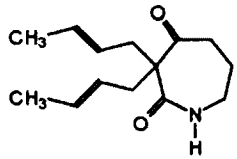
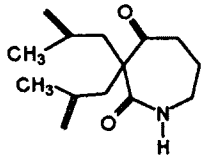
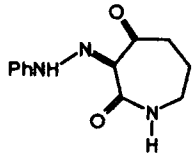
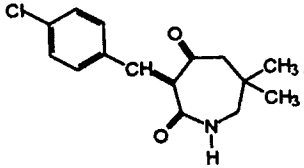
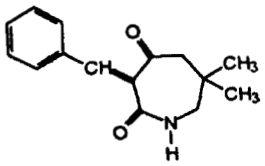
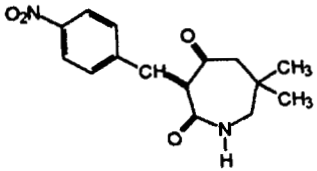
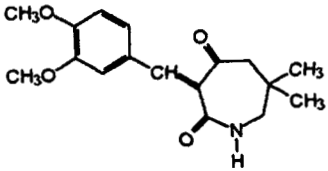
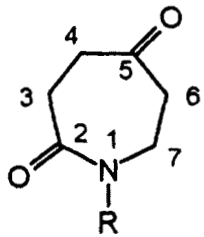
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	115–116		IR, ^{1}H NMR	27
	155–157		IR, ^{1}H NMR	27
	68.5–70		IR, ^{1}H NMR	27
	77–80		IR, ^{1}H NMR	27
	185–188		IR, UV	14
	189–190			25

Table 2 (continued)

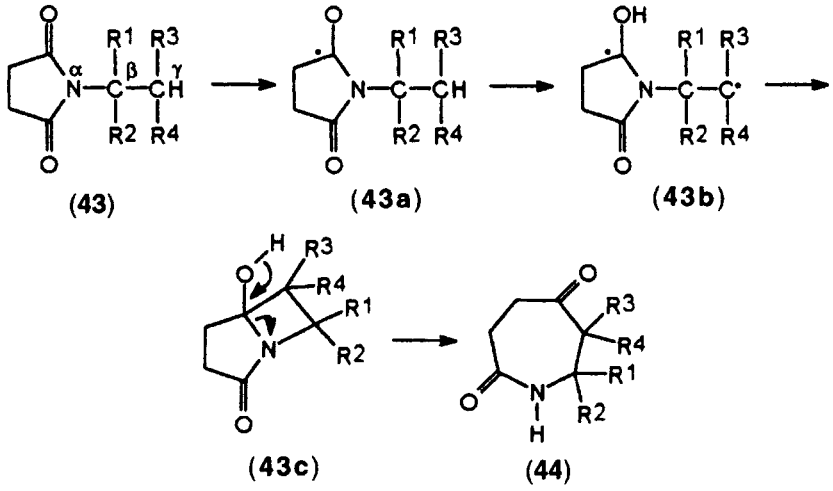
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	217–218			25
	193–194			25
	187–188			25

III. AZEPANE-2,5-DIONES



Several methods are recorded for production of azepane-2,5-diones. However, the most popular, developed by Kanaoka and co-workers,[29–35] involves photolysis of *N*-substituted succinimides. Others have contributed to our knowledge of this useful methodology.[36–40]

It is widely accepted that when succinimides are irradiated (~240 nm), hydrogen atom transfer takes place (**43a** → **43b**) so that the reaction proceeds via an azetidine (**43c**), leading to azepane-2,5-diones substituted as indicated in **44**.

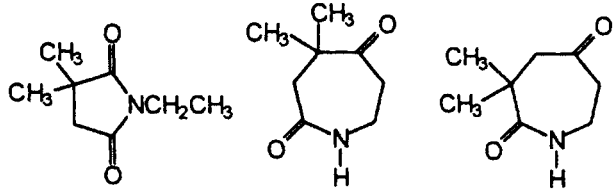


(43) (43a) (43b)

(43c) (44)

Various alkyl-substituted succinimides were initially used,[29] later extended to alkenyl-substituted succinimides[34] and also those carrying oxygen or sulphur atoms in the side-chain[32] and nitrogen protected by acyl groups[33,35] (see Table 3). It is unfortunate that some products were wrongly formulated[33] and later republished[35] correctly without further comment. In the case of **44** ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$) obtained from **43** ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$), an X-ray analysis[37] has settled beyond doubt the regiochemistry of the photolysis. Unsymmetrically ring-substituted succinimides (e.g. **45**) gave mixtures of regioisomeric products **46** and **47**[31] as one would expect, given the above mechanism of reaction.

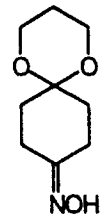
The photochemical conversion of *N*-substituted succinimides is tolerant of a variety (e.g. Ph, OH, CN, $CO_2C_2H_5$) of attachments on Cγ in **43**,[38] but absence of a hydrogen atom at Cγ (**43**) causes the reaction to proceed in other directions, leading to useful syntheses of bi- and tricyclic systems.[32,33,35,39,40]



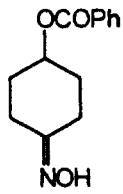
(45) (46) (47)

Beckmann rearrangment has played a part in obtaining certain azepane-2,5-diones. Thus the oximes **48** and **49** have been expanded to azepane-2,5-dione[41]

and 5-hydroxycaprolactam,[42,43] respectively. In the latter case (Chapter 3), oxidation gave the dione **44** ($R^1 = R^2 = R^3 = R^4 = H$).

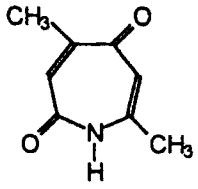


(48)

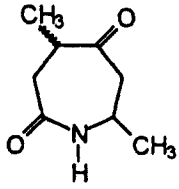


(49)

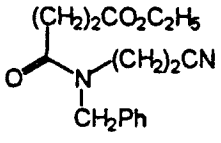
Schmidt reaction on benzoquinones gives 2,5-dihydro[1*H*]azepine-2,5-diones (Chapter 10), which can be hydrogenated catalytically (5% Pd/C) to yield azepane-2,5-diones,[44] e.g. **50** → **51**.



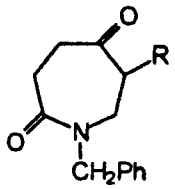
(50)



(51)



(52)



(53)

Intramolecular Dieckmann-type cyclisation of the cyano ester **52** is said to take place using KO^tBu in toluene; the product (**53**, R = CN) appears to be enolic (^1H NMR), but on vigorous acid hydrolysis was claimed to yield an *N*-benzyldione (**53**, R = H).[24] This matter seems worthy of further examination.

Azepane-2,5-diones have not been much further studied.

Table 3. Azepane-2,5-diones

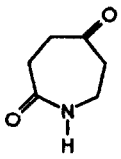
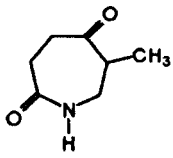
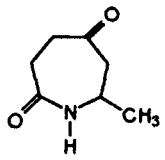
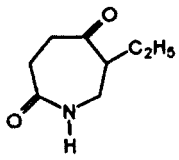
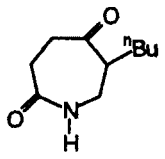
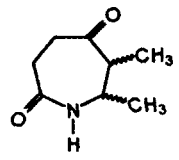
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Oil	2,4-DNPH 234	IR	41
	139–140		IR, UV, ^{1}H NMR	29, 30
	140–141			42
	137–140			38
	138–138.5	4,4-Ethylene-dithiane 165–166	IR, ^{1}H NMR	43
	120–121		IR, UV, ^{1}H NMR	29
	117–120			38
	139.5–140.5		IR, UV, ^{1}H NMR	29
	84–86			38
	85–87		IR, UV, ^{1}H NMR	29
	57–60		IR, ^{1}H NMR	38
	109–110		IR, UV, ^{1}H NMR	29

Table 3 (continued)

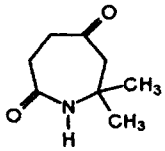
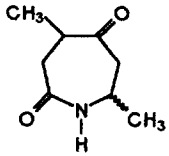
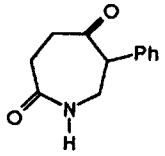
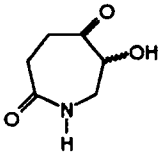
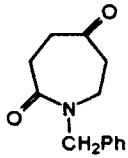
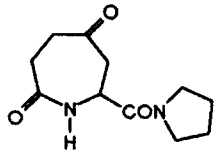
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	175–176		IR, UV, ^{1}H NMR X-ray	29 37
	166–168		IR, ^{1}H NMR	44
	154–156		IR, MS, ^{1}H NMR	38
	159–163		IR, MS, ^{1}H NMR	38
	57		IR, ^{1}H NMR	24
	136–140		IR, MS, ^{1}H, ^{13}C NMR	35

Table 3 (continued)

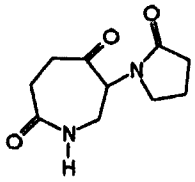
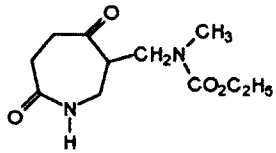
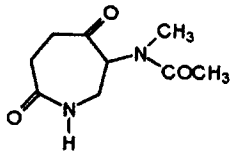
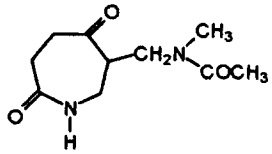
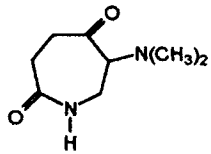
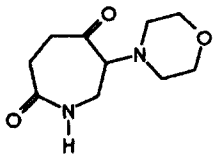
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	154–156		IR, MS, ^{1}H, ^{13}C NMR	33, 35
	78–81		IR, MS, ^{1}H, ^{13}C NMR	33, 35
	115.5–117.5		IR, MS, ^{1}H, ^{13}C NMR	33, 35
	115.5–117		IR, MS, ^{1}H, ^{13}C NMR	33, 35
			IR, MS, ^{1}H, ^{13}C NMR	40
	176–178		^{1}H, ^{13}C NMR	39

Table 3 (continued)

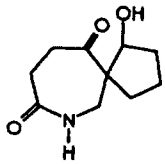
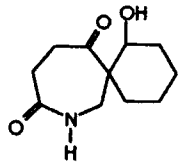
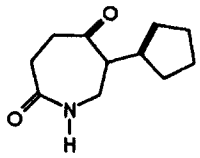
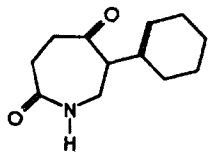
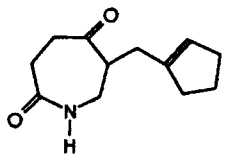
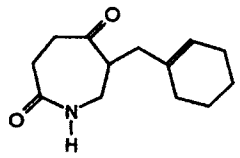
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	121–124		IR, MS, ^{1}H NMR	34
	118–120		IR, MS, ^{1}H NMR	34
	158–161		IR, MS, ^{1}H NMR	34
	169–171		IR, MS, ^{1}H NMR	34
	145–150		IR, MS, ^{1}H NMR	34
	142–144		IR, MS, ^{1}H NMR	34

Table 3 (continued)

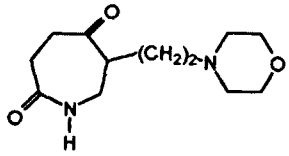
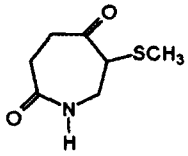
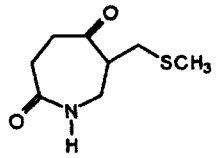
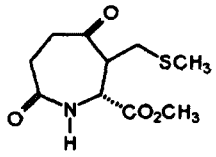
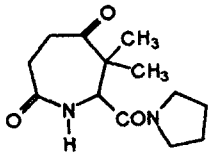
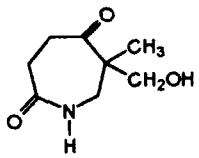
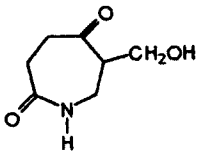
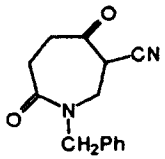
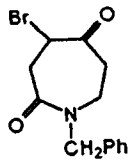
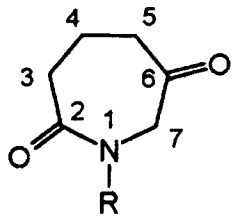
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			IR, MS, ^{1}H, ^{13}C NMR	40
	122–123			32
	99–100			32
	156–157			32
	203–204.5		IR, MS, ^{1}H, ^{13}C NMR	35
	Oil	*O*-Acetate 111–112.5 Di-Me acetal 153–154	IR, ^{1}H NMR	36

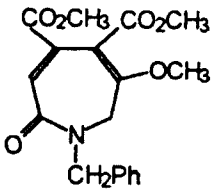
Table 3 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
		Di-Et acetal 132.5–133.5 Di-Me acetal 153–154		36
	99		IR, ^{1}H NMR	24
	70		IR, ^{1}H NMR,	24

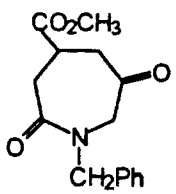
IV. AZEPANE-2,6-DIONES



Surprisingly, there is only one reference to a member of this series in the literature.[45] It was reported[45] that refluxing the diester **54** with trimethylsilyl iodide in



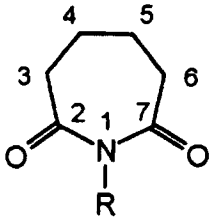
(54)



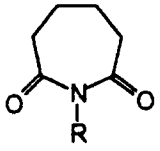
(55)

chloroform for 2.5 days gave a 25% yield of the dione **55**, the structure of which seemed reasonably well supported by spectroscopic, analytical and other data. Unfortunately, this reaction could not be repeated and, in any case, it is not entirely clear how reduction could have occurred. One has to conclude that azepane-2,6-diones remain an interesting synthetic challenge.

V. AZEPANE-2,7-DIONES

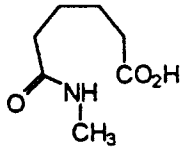


Azepane-2,7-diones (**56**), otherwise known as adipimides, have been well studied. The most useful methods for their preparation involve either cyclisation of adipic acid derivatives or oxidation of caprolactams (Chapter 3, Section I).

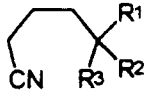


(56)

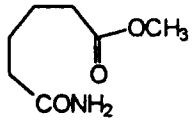
Adipimide (**56**, R = H) was obtained by heating adipamide at 250–260 °C,[46] whilst *N*-methyladipimide (*N*-methylazepane-2,7-dione) (**56**, R = CH_3) arose from *N*-methyladipamic acid (**57**) either by heating at 250–260 °C[47] or by treatment with thionyl chloride at 0–4 °C.[48] 3,3-Disubstituted azepane-2,7-diones



(57)



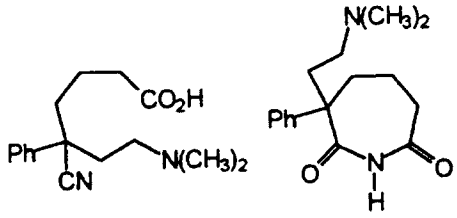
(58)



(59)

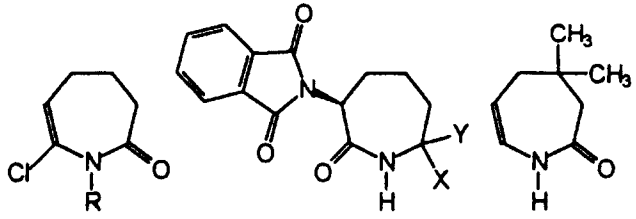
have been made by cyclisation of the appropriate nitrile esters or dinitriles (**58**, R^3 = $CO_2C_2H_5$ or CN) by heating with acetic and sulphuric acids[49] (see Table 4). The parent system (**56**, R = H) was obtained from the amido ester **59** by heating with potassium methoxide in toluene, but the yield was only 35%.[50] This tendency of adipic acid derivatives was unexpectedly noted in the case of the cyano acid **60**, which gave the imide **61** when heated with polyphosphoric

acid at 90 °C instead of cyclising to a benzosuberone.[51] Adipic anhydrides have been claimed as precursors for *N*-substituted azepane-2,7-diones by heating

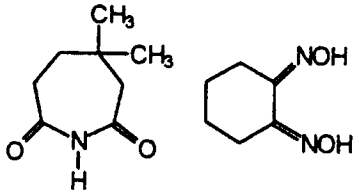


(60) (61)

with aliphatic primary amines.[52] Adipoyl chloride has also been a source of azepane-2,7-diones by reaction with an aliphatic amine in the presence of triethylamine[53] or with the iminophosphorane $PhCH_2N{=}PPh_3$. In the latter case,[54] the yield was a mere 2% of **56** (R = CH_2Ph), but the principal product



(62) (63) (64)



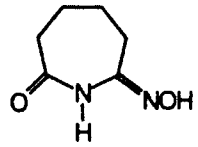
(65) (66)

(31%) was the chloro compound **62** (R = CH_2Ph), from which, presumably, more of the azepanedione **56** (R = CH_2Ph) could be obtained. Other analogues of **62** (R = Ph and $CH_2CO_2C_2H_5$) were obtained similarly in acceptable yields[54] (Chapter 6), so it seems possible that this approach could be developed into a method for obtaining *N*-substituted azepane-2,7-diones.

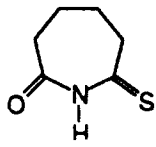
Turning to the oxidation of caprolactams, several oxidant systems have been used. First, peracetic acid at −10 °C (in the presence of manganic acetylacetonate) was shown to give an 84% yield of adipimide;[55] more recently,[56] the combination of ruthenium tetraoxide and sodium periodate was demonstrated to be useful in some cases. For example, *N*-isopropylcaprolactam gave 89% of

N-isopropylazepane-2,7-dione (**56**, R = ^{i}Pr).[56] It should be noted that the otherwise promising anodic oxidation of cyclic amides (Chapter 3, Section I), when applied to *N*-substituted caprolactams, gave several products none of which was an azepane-2,7-dione.[57] Oxidation of 3-*N*-phthaloylcaprolactam **63** (X = Y = H) to **63** (X + Y = O) has been brought about by potassium permanganate in aqueous acetic acid (anhydrous acetic acid was not effective)[58] and also by the agency of benzeneseleninic anhydride [$(PhSeO_2)_2O$].[59] Hydroboration of the tetrahydroazepinone **64** provided a product which, when treated with chromic oxide, led to the azepane-2,7-dione **65**.[60]

There is an interesting report[61] of a photochemically induced ring expansion which converted 2-nitrocyclohexanone into the *N*-hydroxyimide **56** (R = OH) in moderate yield. The report[62] concerning ring expansion of the dioxime **66** with bromine in liquid SO_2 is, however, open to doubt. The initial product claimed was a monooxime of adipimide (**67**) having a melting point of



(**67**)



(**68**)

155 °C; it may or may not be so. However, the product (m.p. 166.5 °C) of reacting **67** with thionyl chloride cannot be adipimide (**56**, R = H) as stated, because the latter substance has a well authenticated melting point of 98 °C (see Table 4).

A recipe for converting azepane-2,7-diones into the monothio derivative **68** has been published.[63] The dione was first converted into the *O*-ethyl lactim ether (via silver salt and ethyl iodide), which was then treated with dry H_2S; a yield of 51% was thus obtained.

Table 4. Azepane-2,7-diones

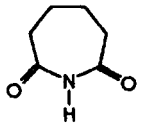
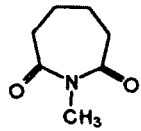
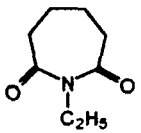
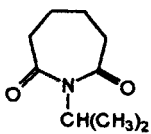
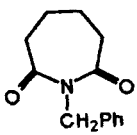
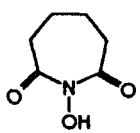
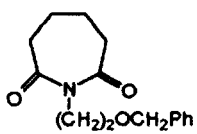
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	98 166.5 (?) 93–94	Oxime 155	IR	46, 72 62 50, 55, 73
	119/18 96–100/6		UV, IR, ^{1}H NMR, MS	47 48
	103/3		IR, ^{1}H NMR	56
	84/2		IR, MS, ^{1}H NMR	56
	76		IR, MS, ^{1}H NMR	54
	169–171		IR	61
			IR	53

Table 4 (continued)

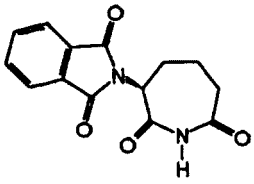
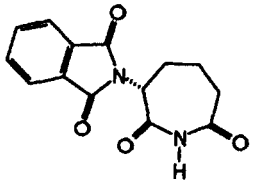
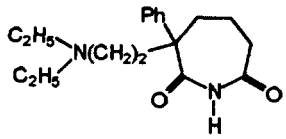
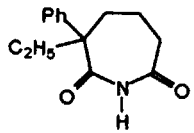
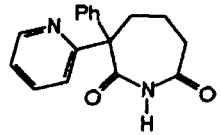
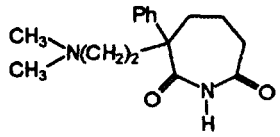
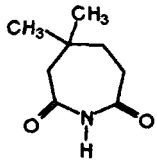
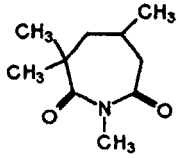
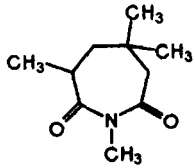
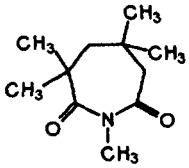
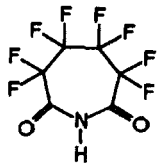
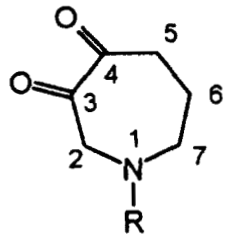
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	265–270 (d)		$[\alpha]_D^{21}$ −31.3	59
	265–268		$[\alpha]_D^{21}$ +30.2	59
	109–110			49
	198–204/0.05			49
	146–147			49
	180/0.05		IR, MS, ^{1}H NMR	51

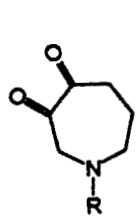
Table 4 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	106–107		IR, MS, ^{1}H NMR	60
	84/0.05		n_D^{20} 1.4779	52
	91/0.05		n_D^{20} 1.4795	52
	55/0.025		n_D^{20} 1.4789	52
	167/760		n_D^{20} 1.3620, d_4^{20} 1.8047	74

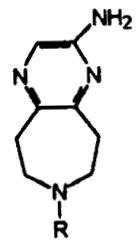
VI. AZEPANE-3,4-DIONES



The only mention of azepane-3,4-diones (**69**) in the literature indicated that they were inferred constituents of mixtures obtained when azepan-4-ones were



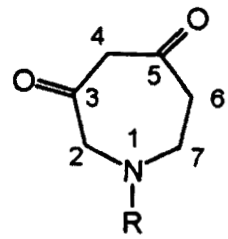
(**69**)



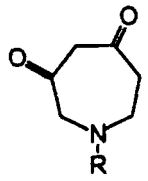
(**70**)

reacted with selenium dioxide (Chapter 3, Section III).[64,65] The principal products were azepan-3,4-diones (not isolated; Section VIII), which reacted with aminoacetamidine to give 2-amino-6,7,8,9-tetrahydro-5*H*-pyrazino[2,3-*d*]azepines (**70**). The latter were adequately authenticated and were accompanied by isomeric by-products which in one case (**69**, R = $CO_2C_2H_5$) appeared to arise from the 3,4-dione.[66]

VII. AZEPANE-3,5-DIONES



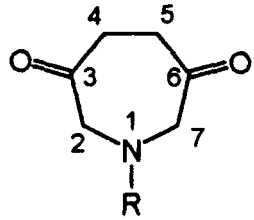
It has been claimed that the dione **71** (R = $COSC_2H_5$) could be detected when certain microorganisms transformed the 4-ketoazepane Ordram after application to rice paddies.[67] No data in support of this contention was offered



(71)

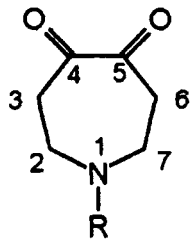
and, perhaps surprisingly, no other references to this ring system have been found.

VIII. AZEPANE-3,6-DIONES

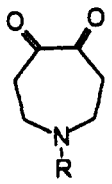


There have been no compounds based on the azepane-3,6-dione structure reported in the literature.

IX. AZEPANE-4,5-DIONES

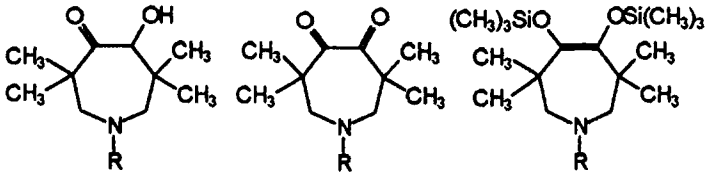


As recounted in Section VI, oxidation of a series of azepan-4-ones with SeO_2 in aqueous dioxane gave *N*-substituted azepan-4,5-diones (e.g. **72**, R = COC_6H_4Cl,

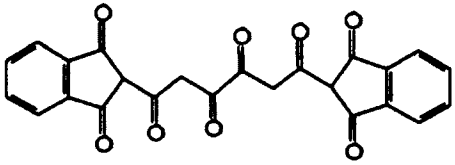


(72)

CH_3CO, $CO_2C_2H_5$), although they were not purified and contained some quantities of the isomeric 3,4-diones.[64,65] It is now established that the addition of water to the dioxane was unnecessary.[66] Authentic diones (**74**) in this series were isolated from acyloins (**73**, R = ^{t}Bu, CH_3) by oxidation with lead tetra acetate;[68,69] 74 (R = ^{t}Bu)[68] was fully characterised, but **74** (R = CH_3) was less



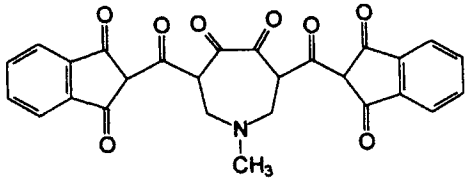
(73) (74) (75)



(76)

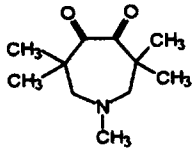
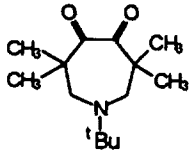
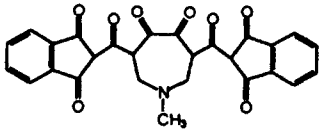
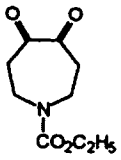
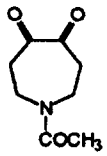
well described. It was pointed out that the corresponding protected acyloins (**75**) also gave diones after treatment with bromine in carbon tetrachloride.[69] There seems no reason why other azaacyloins (Chapter 3, Section III) should not be suitable precursors for azepane-4,5-diones, but this area has not been of interest.

Finally, there has been a report[70] that a polyketone (**76**) underwent a Mannich reaction yielding the hydrochloride of the azepane-4,5-dione (**77**). It is possible that this claim is correct but it is based on scanty information and is worthy of more detailed study.



(77)

Table 5. Azepane-4,5-diones

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			^{1}H NMR	68, 69
	73–74/0.1		IR, ^{1}H NMR, UV	68
		HCl >300	IR	70
	Not purified			65
	Not purified			65

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George R. Proctor, James Redpath
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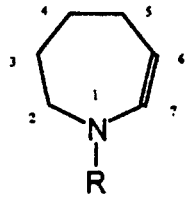
CHAPTER 5

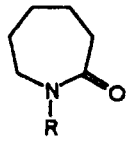
Tetrahydroazepines

I. 2,3,4,5-TETRAHYDRO[1*H*]AZEPINES

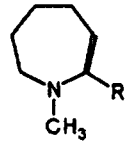


PREPARATION

Given the ready availability of caprolactam (**1**, R = H), it is perhaps not surprising that many synthetic approaches in the literature to 2,3,4,5-tetrahydro[1*H*]azepines have been based on either the lactam itself (**1**, R = H), or one of its *N*-substituted derivatives (**1**, R = alkyl or acyl). For example, **1** (R = CH_3) has been converted using an appropriate Grignard reagent into the corresponding alkyl (**2**, R = C_5H_{11}, C_6H_{13}, C_7H_{15}, $C_{10}H_{21}$)[1] and aryl (**2**, R = Ph, 1-naphthyl)[2,3] derivatives. A useful modification of this approach



(**1**)



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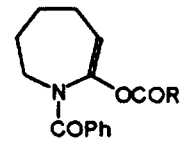
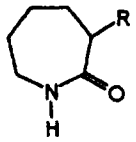


(**3**)

involved treatment of the lithio derivative of **1** (R = COPh) with an acyl chloride to give **3** (R = Ph, Et).[4]

Treatment of caprolactams (**4**, R = H, Cl, CH_3) with $COCl_2$ also proved a useful method of achieving substituted 2,3,4,5-tetrahydro[1*H*]azepines, giving chloro derivatives (**5**, R = H, Cl, CH_3).[5–9] The product **5** (R = H), could be further derivatised on the N atom to give the amides **6** (R = NH_2, NHPh)[6] or the ester **6** (R = OEt);[10] alternatively brominated on the double bond, **5** (R = H) gave **7** (R = Cl),[6] which could be further converted into the amide **7** (R = NH_2) or the ester **7** (R = OEt).[6]



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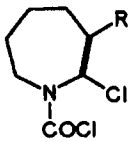

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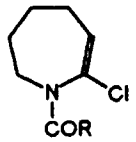

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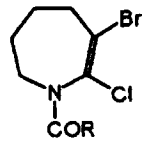
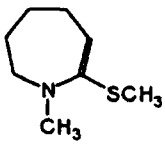


(7)

The action of P_2S_5 on *N*-methylcaprolactam **1** (R = CH_3), followed by treatment with methyl iodide and then base, has been reported to give the methylthio derivative of 2,3,4,5-tetrahydro[1*H*]azepine **8**,[11] whereas the same sequence of reactions with caprolactam (**1**, R = H) gave the 3,4,5,6-tetrahydro[2*H*]azepine (**9**).[12] Reaction of **8** with aryl isocyanates occurred exclusively at the double bond giving products such as **10** (R = H, CH_3, Cl, Br),[13,14] whereas **9** reacted to give the *N*-substituted 2,3,4,5-tetrahydro[1*H*]azepine **11** (R = NHPh).[15] *N*-Substitution also occurred on acylation of **9**, giving **11** (R = CH_3, Ph),[16] and on treatment with ethyl chloroformate, giving **11** (R = OCH_3).[17]



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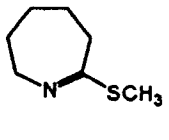

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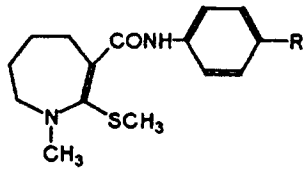

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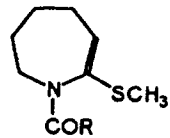
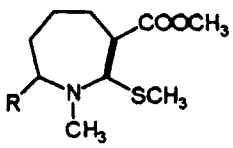


(11)

Removal of the methylthio group in the analogous derivatives **12** (R = H, *n*-C_5H_{11}), **13** (R = H, *n*-C_5H_{11}) and **14** was achieved smoothly with Raney nickel to give **15** (R = H, *n*-C_5H_{11}),[18] **16** (R = H, *n*-C_5H_{11})[19] and **17**,[19a] respectively.



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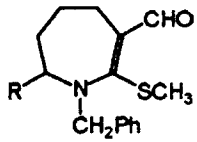

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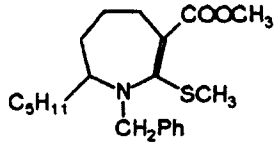
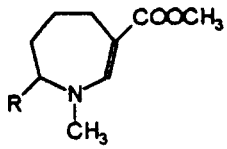


(14)

In contrast to the well documented use of the thioenol ethers **8**–**14**[11–19] for the preparation of the 2,3,4,5-tetrahydro[1*H*]azepine ring system, little use has been



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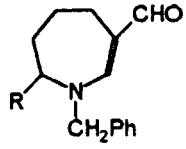

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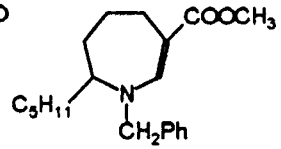
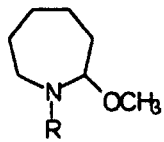


(17)

made of the corresponding enol ethers **2** (R = $OSiMe_3$, and its 1-trifluoroacetyl derivative),[20,21] mainly because they readily re-form the lactam system (**1**) on acid treatment. The saturated ethers **18** (R = CO_2Et, CHO), however, have been utilised, yielding the 2,3,4,5-tetrahydro[1*H*]azepines **19** (R = CO_2Et, CHO)[22,23] on demethoxylation with NH_4Br. In a similar fashion, treatment of the phenyl selenide **20** with hydrogen carbonate introduced a double bond into the ring to give **19** (R = $CH{=}NCMe_3$).[24]



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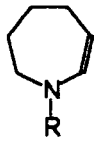

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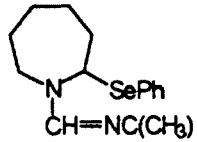
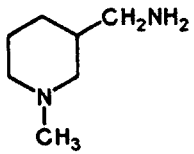


(20)

Ring expansion reactions for the preparation of 2,3,4,5-tetrahydro[1*H*]azepines have been reported, but in general they cannot be considered important methods of preparation because the yields are poor and often a wide range of by products is formed. For example, a Demjanov reaction of 1-methyl-3-aminomethylpiperidine (**21**) gave nine products, including 1-methyl-2,3,4,5-tetrahydro[1*H*]azepine (**2**, R = H),[25a] and a photolytic rearrangement of the bicyclic system **22** produced three products including **23**, isolated in 9% yield.[26]



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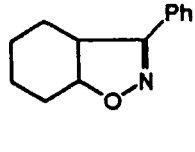

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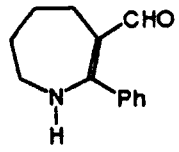
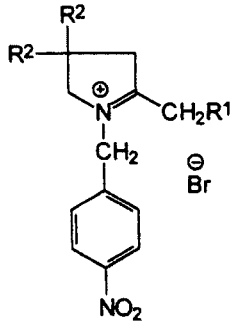


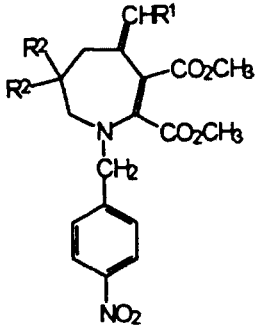
(23)

An interesting ring expansion reaction involving the insertion of a two-carbon chain into 2-alkyl-Δ^1-pyrrolinium salts such as **24** (R^1 = H, R^2 = CH_3 and R^1 = Ph, R^2 = H) using dimethyl acetylenedicarboxylate (DMAD) in the presence of triethylamine gave a mixture of the tetrahydro[1*H*]azepines (**25**, R^1 = H, R^2 = CH_3 and R^1 = Ph, R^2 = H) along with the corresponding

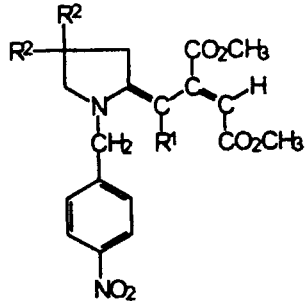
pyrrolidines (**26**, R^1 = H, R^2 = CH_3 and R^1 = Ph, R^2 = H). The products (**25** and **26**) could be separated by chromatography, although only modest yields (34% and 13%, respectively) of the azepines **25** were claimed.[27]



(24)

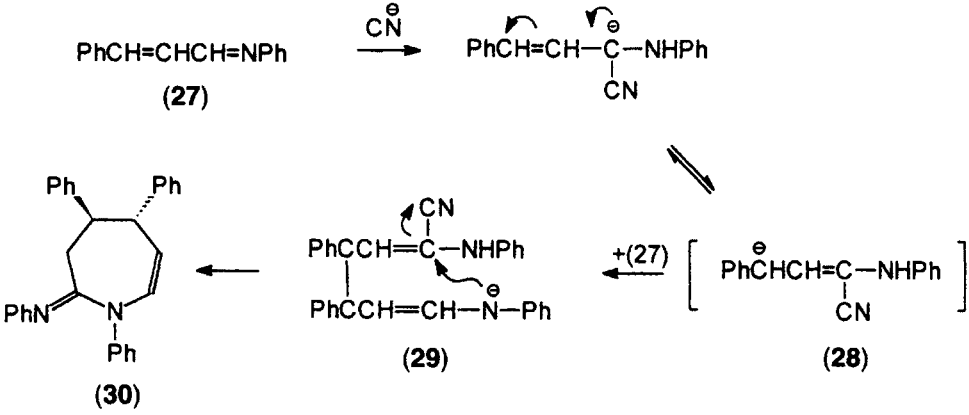


(25)



(26)

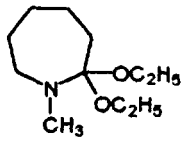
Finally, a novel approach[28] involved treatment of cinnamalaniline (**27**) with KCN in dimethyl sulphoxide or dimethylformamide, to give the intermediate ion **28**, which then underwent a 1:4 addition to a second mole of **27**, to give the dimeric product **29**, which cyclised with loss of cyanide ion to give the 4,5-*trans*-diphenyltetrahydroazepine **30**.



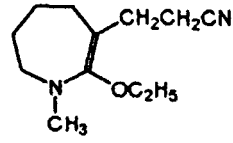
PROPERTIES

The 2,3,4,5-tetrahydro[1*H*]azepines are low-melting solids or oils. Being enamines, they are fairly reactive compounds, particularly the members of the series which are unsubstituted on the N atom. Alkylation or acylation on the N atom produces more stable compounds, which nevertheless still undergo typical enamine reactions. Substitution on the double bond, at position 6, has already been mentioned, producing derivatives such as **10**.[13] Many 6-substituted derivatives can react further at position 7 to form fused systems. For example,

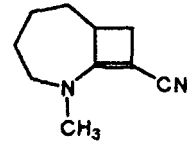
the lactam acetal **31** on treatment with acrylonitrile in benzene gave three products (**1**; R = CH_3, **32** and **33**)[29] in a ratio of 1:5:4. It is probable that



(31)



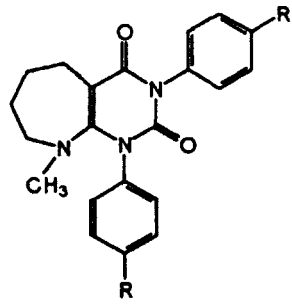
(32)



(33)

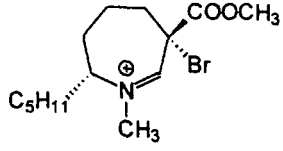
the fused-ring product **33** was formed from **32** as an intermediate, since it was also formed from **32** directly on heating in ethylene glycol.

A fused-ring system was also obtained when the amides **10** (R = H, CH_3, Cl, Br), formed as described above from **8** with aryl isocyanates in diethyl ether at room temperature, underwent further reaction at reflux temperature in toluene to give the bicyclic compounds **34** (R = H, CH_3, Cl, Br).[13,14]

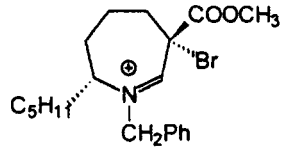


(34)

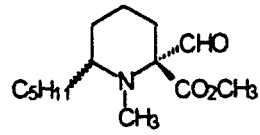
2,3,4,5-Tetrahydro[1*H*]azepines have also been reported to undergo ring-contraction reactions. For example, the enaminium bromides **35** and **36** derived from the alkyl derivatives **15** (R = *n*-C_5H_{11}),[18b] and **17**,[19a] on treatment with aqueous triethylamine, gave the corresponding piperidines **37** and **38**.



(35)

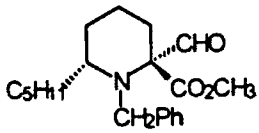


(36)

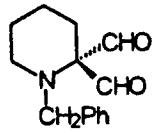


(37)

In the case of the *N*-methyl derivative (**37**), the authors were uncertain of the relative configuration of the *n*-C_5H_{11} group and the ester,[18b] but in the case of the *N*-benzyl derivative (**38**) they presented strong evidence in favour of a *trans*



(38)



(39)

relationship.[19a] A similar sequence of reactions resulting in a ring contraction had previously been reported from the aldehyde **16** (R = H)[19b] giving the piperidine **39** as the product.

Table 1 lists those 2,3,4,5-tetrahydro[1*H*]azepines whose identities are generally supported by chemical analyses and, in most cases, by spectroscopic measurements. Blanks in the table indicate that the compound has been claimed but not characterised.

Table 1. 2,3,4,5-Tetrahydro[1*H*]azepines

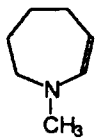
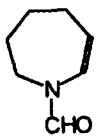
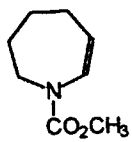
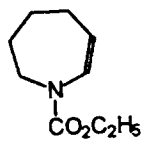
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
		^{1}H NMR	25
	108–111/15	MS, ^{1}H NMR	22a
	94–95/25	IR, ^{1}H NMR	149
	No data given		23

Table 1 (continued)

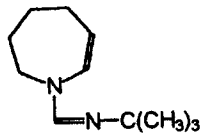
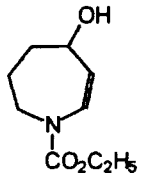
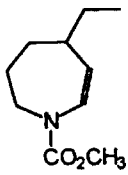
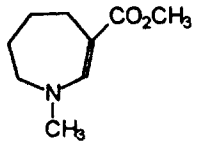
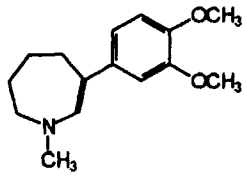
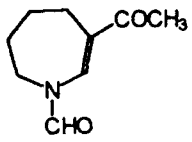
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	45/115	IR, ^{1}H NMR	24
	75–77/2.5	IR, ^{1}H NMR	23
			32
	Oil	IR, ^{1}H NMR	18a
	47–49	IR, MS, ^{1}H NMR	148
	134–137/1	MS, ^{1}H NMR	22b

Table 1 (continued)

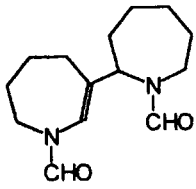
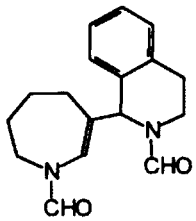
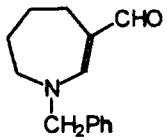
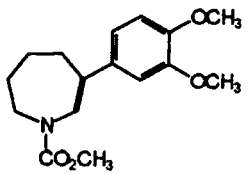
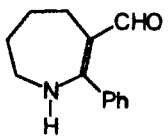
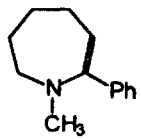
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	160–210/0.2	MS, ^{1}H NMR	22b
	200–250/0.2	MS, ^{1}H NMR	22b
	69–70	IR, ^{1}H, ^{13}C NMR	19b
	71–73	IR, MS, ^{1}H NMR	148
	129–129.5	IR, ^{1}H NMR, UV, MS	26a, 26b
	152–155/18 150–160/20	IR	2b, 3

Table 1 (continued)

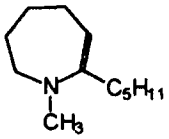
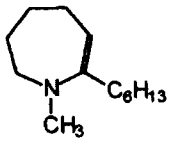
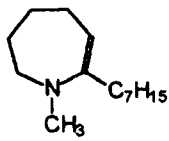
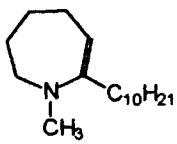
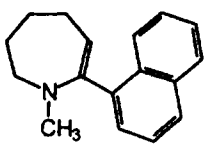
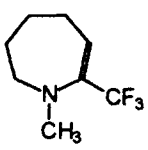
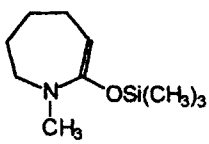
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	106-112/12		1
	118–120.5/6		1
	138–140/7		1
	162–165/11		1
	62-63 145–155/0.5	IR, UV	2a, 2b
	152.1/760	IR, MS, ^{1}H NMR	151
	62–65/2	IR, ^{1}H NMR	20

Table 1 (continued)

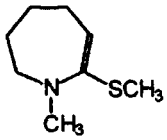
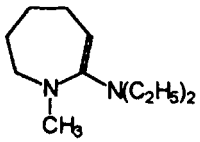
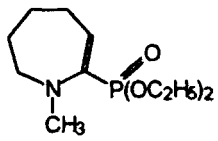
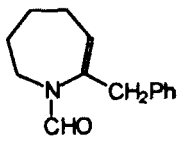
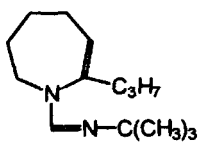
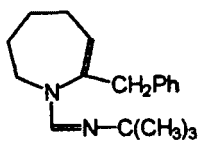
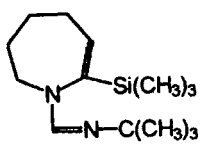
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	86–87.5/10		11
	91/11	IR, UV	30
	88/0.2	IR, ^{1}H NMR	31
	100/0.05	^{1}H NMR	24
	Oil	IR, ^{1}H NMR	24
	Oil	IR, ^{1}H NMR	24
	Oil	IR, ^{1}H NMR	24

Table 1 (continued)

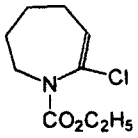
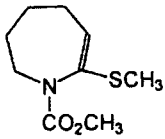
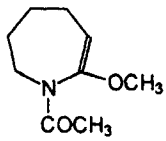
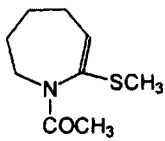
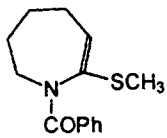
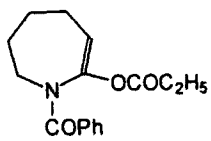
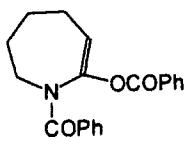
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	69/0.1	IR	10
	143–146/0.1	MS, ^{1}H NMR	17
	79–82/0.4	IR, ^{1}H NMR	37
	103–104/0.4	IR, MS, ^{1}H NMR	16
	135/0.0004	IR, MS, ^{1}H NMR	16
	98–99	IR, ^{1}H NMR	4
	85–86	IR, MS, ^{1}H NMR	4

Table 1 (continued)

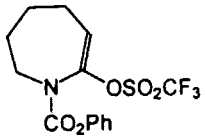
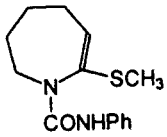
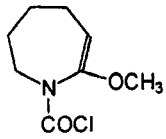
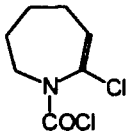
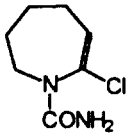
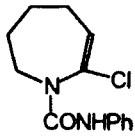
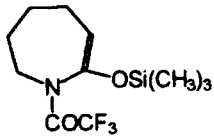
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
		IR, ^1H, ^{13}C NMR	150
	Oil	IR, MS, ^1H NMR	15
	76–78/0.1	IR, ^1H NMR	37
	112–114/10, 125/12	IR	5–7
	89	IR	6
	88–89		6
	117–118/7	IR, ^1H NMR	21

Table 1 (continued)

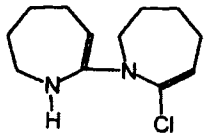
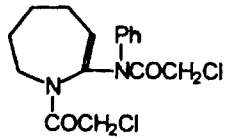
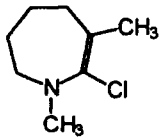
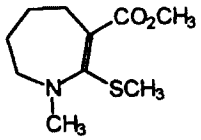
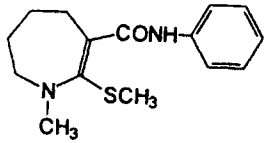
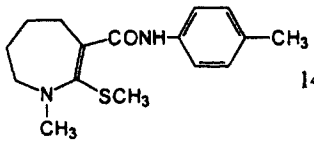
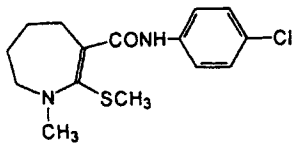
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	125/2		36
	138–139	^{1}H NMR	33
			9
	Oil	IR, ^{1}H NMR	18a
	147–149	IR, MS, ^{1}H NMR	13, 14
	144–146	IR, MS, ^{1}H NMR	13, 14
	152–154	IR, MS, ^{1}H NMR	13, 14

Table 1 (continued)

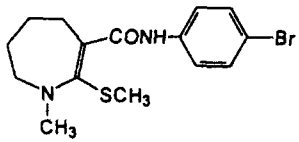
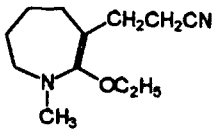
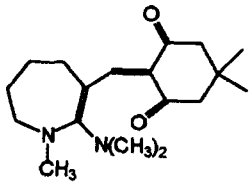
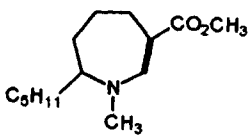
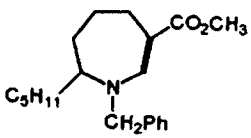
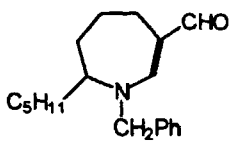
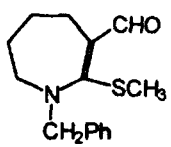
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	157–159	IR, MS, ^{1}H NMR	13, 14
	129–130/1	IR, UV	29
	159–162	MS, ^{1}H NMR	34
	175–179/11	IR, MS, ^{1}H NMR	18b
	Oil	IR, ^{1}H NMR	19a
	Oil	IR, ^{1}H, ^{13}C NMR	19a
	88–89	IR, ^{1}H, ^{13}C NMR	19b

Table 1 (continued)

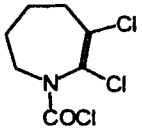
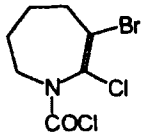
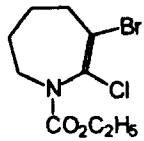
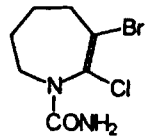
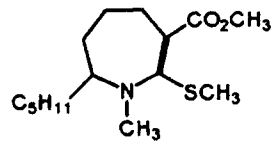
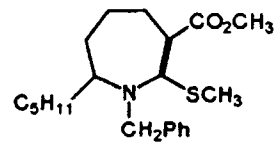
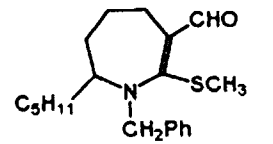
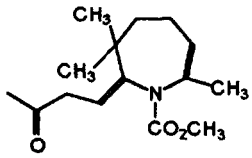
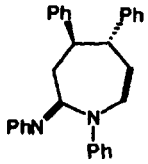
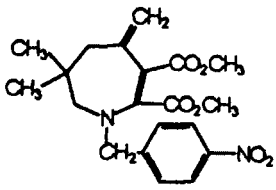
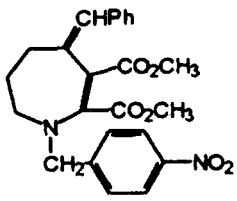
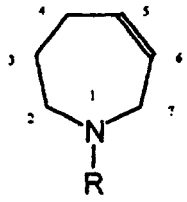
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	42 110–112/2		8
	38–40 130/5	IR	6
	120–125/3	IR	6
	131	IR	6
	Oil	IR, MS, ^{1}H NMR	18b
	Oil	IR, ^{1}H NMR	19a
	Oil	IR, ^{1}H NMR	19a

Table 1 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	145/0.03	IR, MS, ^{1}H, ^{13}C NMR	35
	172	IR, MS, ^{1}H NMR	28
	134–135	IR, UV, ^{1}H, ^{13}C NMR, MS	27
	164	IR, UV, ^{1}H NMR, MS	27

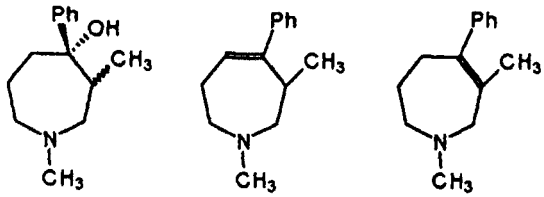
II. 2,3,4,7-TETRAHYDRO[1*H*]AZEPINES



PREPARATION

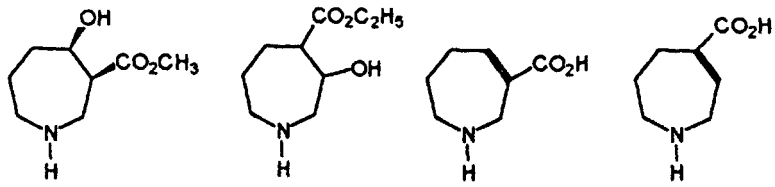
Substituted 2,3,4,7-tetrahydro[1*H*]azepines are fairly well represented in the literature, although the parent compound itself does not appear to have been reported. A frequently used method of preparation involves dehydration of an appropriate alcohol, itself usually prepared from the corresponding ketone. The disadvantage of this approach is that the product is often a mixture of double bond isomers which can be difficult to separate.

For example, the alcohol **40** on dehydration with aqueous HCl gave a mixture of the isomers **41** and **42** in a ratio of 2.7:1 after 24 h, reversing to a 1:3 ratio after 48 h.[38] Formation of a single isomer could only be guaranteed when the



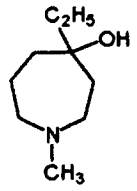
(40) **(41)** **(42)**

dehydration resulted in a conjugated system, as in the acids **45** and **46**, formed from the alcohols **43** and **44**, respectively, on treatment with aqueous mineral acid.[39,40]

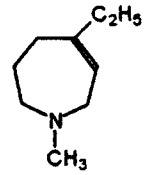


(43) **(44)** **(45)** **(46)**

A claim[41] that the 2,3,4,7-tetrahydro[1*H*]azepine **48** was the sole product of dehydration of the alcohol **47** was not fully supported by the evidence presented.

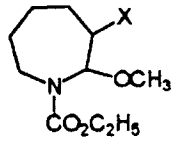


(47)

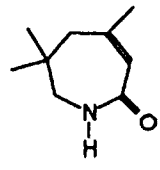


(48)

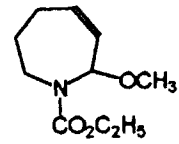
Dehydrohalogenation of azepane halides (**49**, X = Cl, Br, I)[23] and reduction of the amide **50**[42,43] appear to offer more reliable means of synthesising 2,3,4,7-tetrahydro[1*H*]azepines specifically, giving **51** and **52**, respectively, free from double-bond isomers.



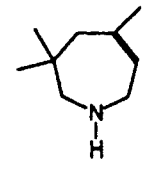
(49)



(50)

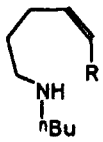


(51)

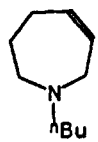


(52)

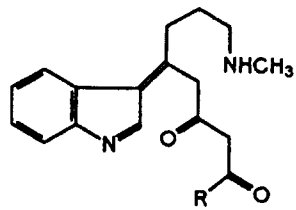
An alternative strategy which proved useful was ring formation from an appropriately substituted non-cyclic amine. This has been utilised both for fairly simple systems such as the formation of **54** from **53** [R = H, $Si(CH_3)_3$] in the presence of HCHO[44] and for more highly substituted products such as



(53)



(54)



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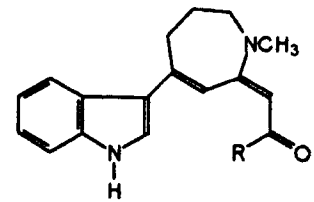
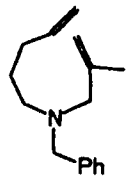


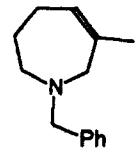
(56)

56 (R = CH_3, Ph) from **55** (R = CH_3, Ph).[45,46] An interesting, novel variation on this theme[47] is the cyclisation of the tertiary amine **57** with loss of ethylene, to give **58**, using a complexed molybdenum catalyst to effect the ring closure.

Ring expansion reactions for the preparation of 2,3,4,7-tetrahydro[1*H*]azepines have also been reported. For example, the 1-methyl derivative **59** was also reported as a minor product from the Demjanov rearrangement of the aminomethylpiperidine **21**[25] as described above, but again, because of the



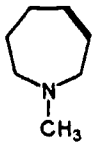
(57)



(58)

low yields and the complexity of the mixture formed, this cannot be considered as an important synthetic procedure.

A more satisfactory ring-expansion method utilised 2-phenyl-2-vinylaziridine (**60**) which could be shown to undergo thermal cycloaddition with electron-poor olefins, either via a concerted 4 + 2 addition, or a dipolar intermediate. With these reagents (**61**, R = CN, CO_2CH_3, SO_2Ph), the 6-phenyl-2,3,4,7-tetrahydro[1*H*]azepines (**62**, R = CN, CO_2CH_3, SO_2Ph) were formed in good yields.[48]



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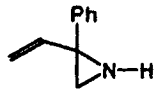
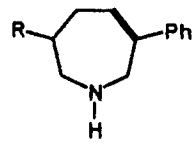


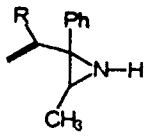
(60)

(61)

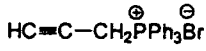


(62)

The more highly substituted aziridine **63** (R = H, CH_3) had previously been shown to react with acetylenes such as 2-propynyltriphenylphosphonium bromide (**64**) to give phosphonium bromide salts of 2,3,4,7-tetrahydro[1*H*]azepines (**65**, R = H, CH_3).[49]



(63)



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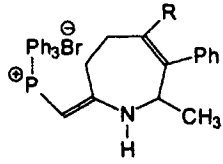
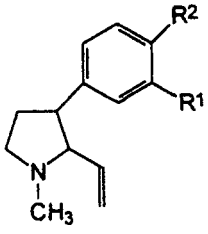
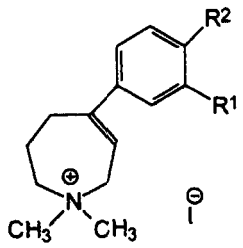


(65)

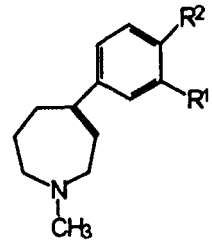
A further possibility involving ring expansion for synthesising 2,3,4,7-tetrahydro[1*H*]azepines was the reported isomerisation of the 2-vinylpyrrolidines **66a–c**[50] using methyl iodide, which gave the corresponding quaternised tetrahydroazepines **67a–c**. Thermal dealkylation of one of the derivatives (**67b**) gave the corresponding tetrahydroazepine (**68b**), which was unstable in air, but could be readily re-quaternised with methyl iodide.



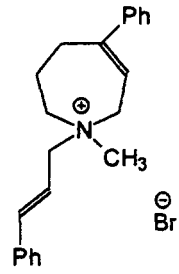
(66)



(67)



(68)



(69)

(**a**) $R^1 = R^2 = H$
(**b**) $R^1 = H, R^2 = OCH_3$
(**c**) $R^1 = R^2 = OCH_3$

A similar sequence of reactions using cinnamyl bromide with the 2-vinylpyrrolidine **66a** gave the corresponding quaternary salt (**69**), which was readily dealkylated with Na/Hg to give **68a**. Direct thermal ring expansion, without forming the intermediate quaternary salts, of the vinylpyrrolidines **66** in the presence of a variety of Lewis acids proved unsuccessful.[50]

PROPERTIES

The 2,3,4,7-tetrahydro[1*H*]azepines are low-melting solids or oils, frequently characterised as crystalline salts such as picrates or hydrochlorides. They are fairly stable compounds and demonstrate the expected chemical properties of secondary or tertiary amines depending on whether or not they are substituted on the N atom. The more commonly reported reactions, alkylation or acylation on the N atom, occur readily using traditional methods such as Eschweiler Clark alkylation[42] or acyl halides.[43]

Table 2 lists those 2,3,4,7-tetrahydro[1*H*]azepines whose identities are supported in most cases by chemical analyses and by spectroscopic measurements. Blanks in the table indicate that the compound has been claimed but not characterised.

Table 2. 2,3,4,7-Tetrahydro[1*H*]azepines

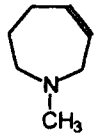
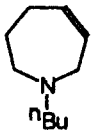
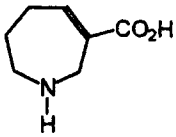
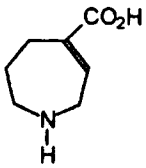
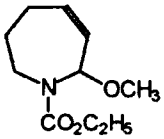
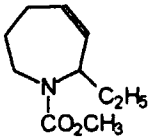
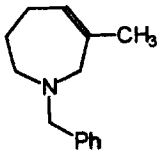
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
				25
	100/1		MS, IR, ^{1}H, ^{13}C NMR	44
		HBr, 224.5–225.5	IR, UV, ^{1}H NMR	39
		HBr, 183–184.5	UV, ^{1}H NMR	40
	68–71/1.5		IR, ^{1}H NMR	23
				32
	Oil		MS, IR, ^{1}H, ^{13}C NMR	47

Table 2 (continued)

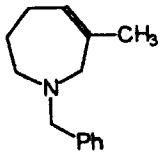
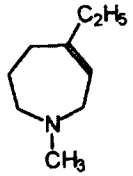
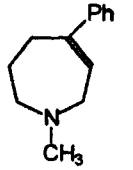
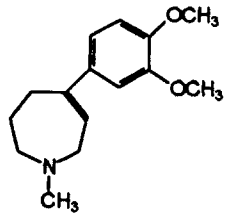
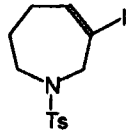
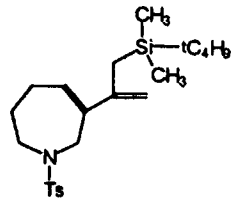
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Oil		MS, IR, ^{1}H, ^{13}C NMR	47
	112–115/25	Picrate 117–119		41
	Oil		UV	50
	70–75/0.03			50
	Colourless oil		IR, MS, ^{1}H NMR	152
	No data given			153

Table 2 (continued)

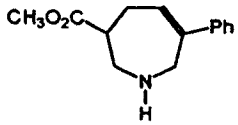
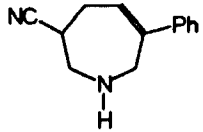
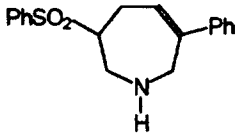
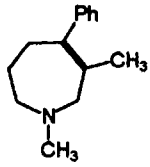
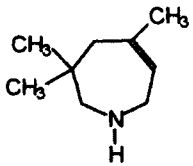
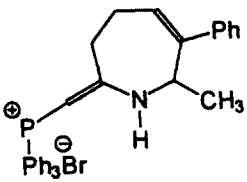
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	56–57			48
	70–71			48
	105–106			48
	73–75/0.05	HCl, 172–174	^{1}H NMR	38
	32–35/0.5	HBr, 149–151	MS, ^{1}H NMR	43
	229–234		MS, IR, ^{1}H, ^{13}C NMR	49

Table 2 (continued)

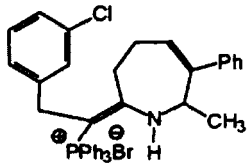
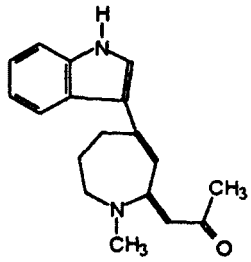
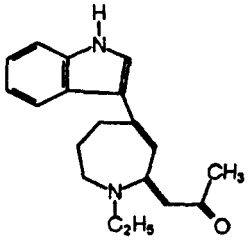
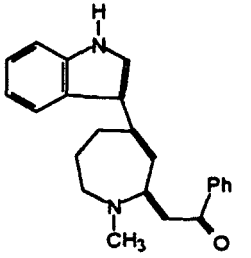
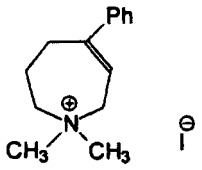
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	140–155		MS, IR, ^{1}H, ^{13}C NMR	49
	184–185		MS, IR, UV, ^{1}H NMR	45
	199–201		MS, IR, UV, ^{1}H NMR	45
	259–267		MS, IR, UV, ^{1}H NMR	46
	213–214		UV, ^{1}H NMR	50

Table 2 (continued)

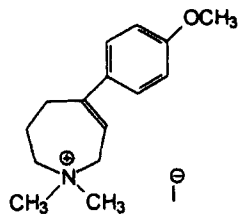
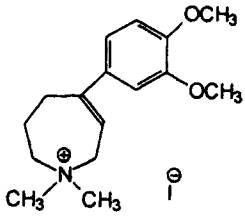
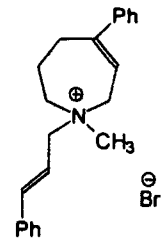
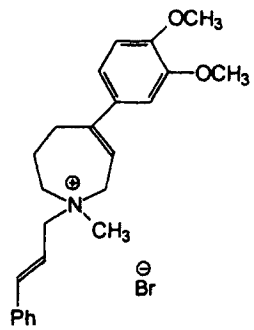
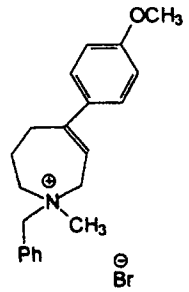
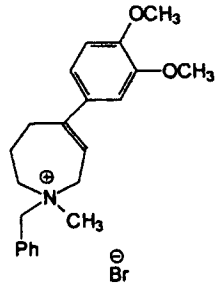
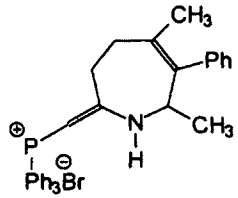
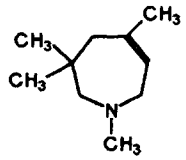
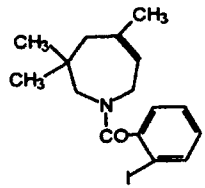
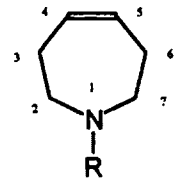
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	186–188		UV, ^{1}H NMR	50
	196–197		UV,^{1}H NMR	50
	Oil			50
	164–167		UV,^{1}H NMR	50

Table 2 (continued)

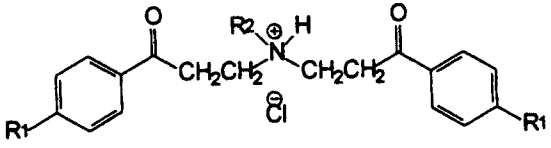
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	167–170		UV, ^{1}H NMR	50
	154–159		UV	50
	232–234		MS, IR, ^{1}H, ^{13}C NMR	49
	No data presented			42
	Oil		MS, IR, ^{1}H NMR	43

III. 2,3,6,7-TETRAHYDRO[1*H*]AZEPINES

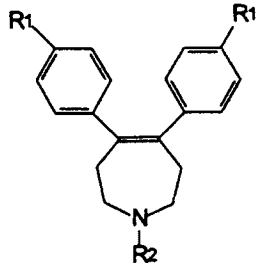


PREPARATION

2,3,6,7-Tetrahydro[1*H*]azepines are fairly well documented and have been synthesised by a number of approaches. A synthetic method which was particularly useful for preparing symmetrically substituted derivatives utilised intramolecular reductive coupling of Mannich base hydrochlorides in the presence of low-valency titanium, prepared *in situ* from $TiCl_4$ and zinc powder.[51] In this way the amines **70** (R^1 = H, R^2 = CH_3, C_2H_5, ^nBu; and R^1 = R^2 = CH_3) were converted into the corresponding 2,3,6,7-tetrahydro[1*H*]azepines **71** (R^1 = H, R^2 = CH_3, C_2H_5, ^nBu; and R^1 = R^2 = CH_3) in yields around 60%.[51]

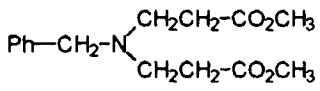


(70)

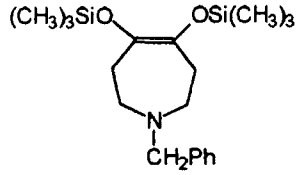


(71)

A symmetrically substituted 2,3,6,7-tetrahydro[1*H*]azepine (**73**) was also formed from the diester **72** with trimethylsilyl chloride and sodium in toluene.[52]



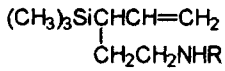
(72)



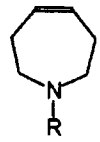
(73)

Intramolecular aminomethylation–desilylation of ω-monoalkylaminoallyltrimethylsilanes such as **74** (R = ^iPr, ^nBu, CH_2Ph) in the presence of formaldehyde and trifluoroacetic acid readily gave the corresponding

2,3,6,7-tetrahydro[1*H*]azepines (**75**, R = ^{i}Pr, ^{n}Bu, CH_2Ph) in yields of 60–96%.[53] Reaction of **74** (R = ^{n}Bu) with ^{n}PrCHO in place of formaldehyde gave the corresponding 4-*n*-propyl analogue (**76**) and using the disilylated derivative **77** with formaldehyde gave the 4-trimethylsilyl derivative **78**,[53] although in both of these cases the yields were substantially lower (18 and 40%, respectively).

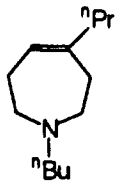


(74)

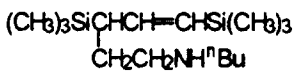


(75)

Traditional chemical methods, such as reduction or Grignard alkylation of a carbonyl group followed by dehydration of the alcohol formed, as discussed in the previous section, have also been used for the preparation of 2,3,6,7-tetrahydro[1*H*]azepines. This approach has been applied to the preparation of the acid **79**[40] and the 4-phenyl derivative **80**,[38,54] although formation of isomeric mixtures of products sometimes occurs.[38] Simultaneous direct reduction of the amide carbonyl group and the imine double bond of **81** gave the tetramethyl derivative **82**.[55]



(76)



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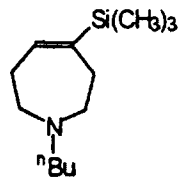
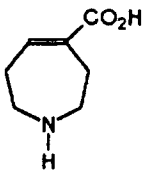


(78)

Formation of an enamine system from a carbonyl group has also been used to give products which are formally 2,3,6,7-tetrahydro[1*H*]azepines, as in the preparation of the amines **84** (R = $COCH_3$, CO_2Et, CH_2Ph) and **85**



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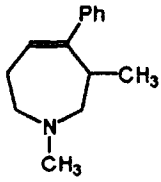

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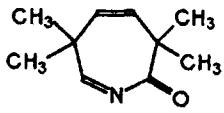

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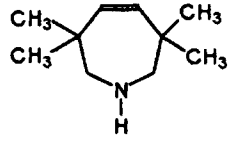
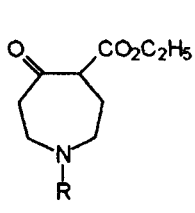
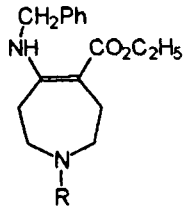


(82)

(R = CH_2Ph, CO_2Et) from the corresponding ketones (**83**, R = $COCH_3$, CO_2Et, CH_2Ph[56] and R = CH_2Ph, CO_2Et).[57] As might be expected, the enamines **84** and **85** are not particularly stable and **85** (R = CH_2Ph) has not been isolated in a pure form.



(83)



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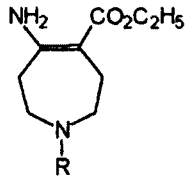
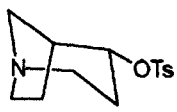


(85)

An interesting rearrangement of the bicyclic tosylate **86** using water was claimed to give the parent 2,3,6,7-tetrahydro[1*H*]azepine **87** (R = H) along with 3-vinylpyrrolidine (**88**) as a 91:9 mixture.[58] It was proposed that the



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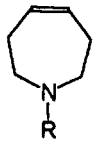

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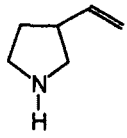
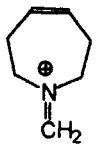


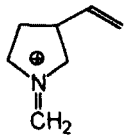
(88)

reaction proceeded via the initially formed immonium salt **89**, which in turn underwent hydrolysis with loss of formaldehyde. The minor amounts of 3-vinylpyrrolidine formed resulted from a sigmatropic [3,3] rearrangement of the immonium salt **89** to its isomer **90** before hydrolysis. The unsubstituted azepine **87** (R = H) was not isolated, but was converted *in situ* into the *N*-tosyl derivative **87** (R = $CH_3C_6H_4SO_2$).

An alternative procedure involving reaction of the bicyclic tosylate **86** with aqueous sodium hydroxide in the presence of tosyl chloride was claimed to give the tosylate **87** (R = $CH_3C_6H_4SO_2$) as the sole product. Unfortunately, no supporting physical-chemical evidence was quoted to support the assigned structures **87** (R = H, $CH_3C_6H_4SO_2$).



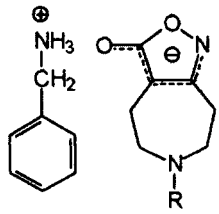
(89)



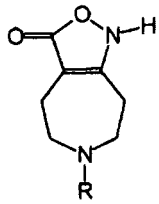
(90)

PROPERTIES

In general, the 2,3,6,7-tetrahydro[1*H*]azepines are low-melting solids or oils, frequently characterised by conversion into the crystalline picrates or hydrochlorides. As an exception to this general rule, the 4,5-diphenyl derivatives such as **71** are readily crystallisable, high-melting solids. Stability is rarely a problem with the exception of the 4-amino derivatives **84** and **85**, which, being enamines, readily underwent hydrolytic decomposition.[57] These are also the most reactive derivatives. For example, the benzylamino derivatives **84** (R = $COCH_3$, CO_2Et, CH_2Ph) readily underwent condensation reactions with hydroxylamine to give the corresponding benzylammonium salts **91** (R = $COCH_3$, CO_2Et, CH_2Ph), which in turn afforded the isoxazolin-5-ones **92** (R = $COCH_3$, CO_2Et, CH_2Ph) with methanolic hydrogen chloride.[56] Similarly, the amine **85** (R = CO_2Et) condensed with diethyl malonate in the presence of sodium ethoxide to give the 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*d*]azepin-2-one **93** (R = CO_2Et). Treatment of this latter compound with hydrochloric acid removed the 3-carbethoxy group and gave the pyridoazepinone **93** (R = H).[57]



(91)



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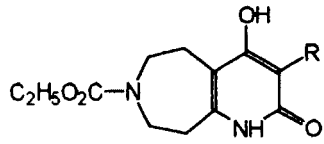


(93)

Table 3 lists those 2,3,6,7-tetrahydro[1*H*]azepines whose identities are supported by chemical analyses and by spectroscopic measurements.

Table 3. 2,3,6,7-Tetrahydro[1*H*]azepines

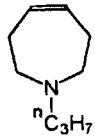
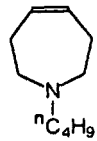
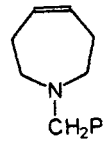
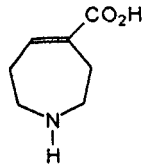
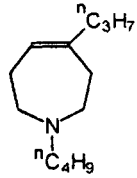
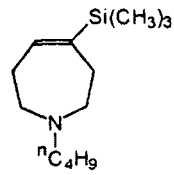
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Oil		IR, ^{1}H NMR	53
	Oil		IR, ^{1}H NMR	53
	Oil		IR, MS, ^{1}H NMR	53
		HBr, 174.5–176.5	IR, ^{1}H NMR	40
	Oil		IR, ^{1}H NMR	53
	Oil		IR, ^{1}H NMR	53

Table 3 (continued)

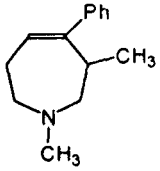
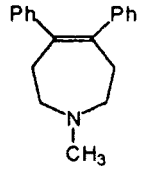
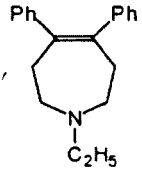
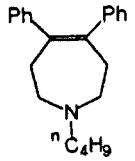
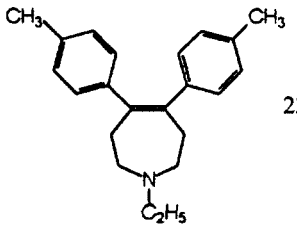
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	99–100/0.3 73–75/0.05	Picrate 126–127 HCl 96–98	^{1}H NMR ^{1}H NMR	54 38
	103–104		IR, MS, ^{1}H NMR	51
	60–61		IR, MS, ^{1}H NMR	51
	55–56		IR, MS, ^{1}H NMR	51
	222–224		IR, MS, ^{1}H NMR	51

Table 3 (continued)

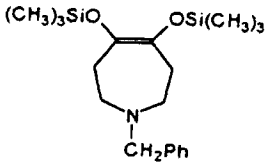
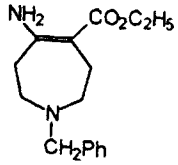
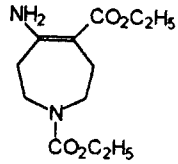
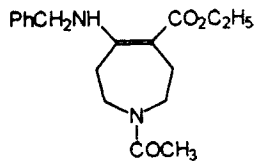
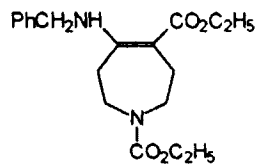
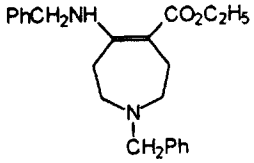
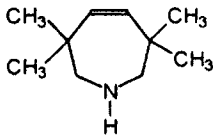
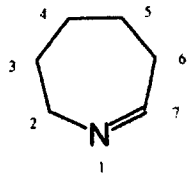
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	151–153/0.2		IR, MS, ^{1}H NMR	52
	Unstable		IR, ^{1}H NMR	57
	75–76		IR, ^{1}H NMR	57
	106–108.5		IR, UV, ^{1}H NMR	56
	36.5–39		IR, UV, ^{1}H NMR	56

Table 3 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Oil		IR, UV, ^{1}H NMR	56
	Oil	Picrate 142–143	IR, ^{1}H NMR	55

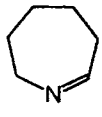
IV. 3,4,5,6-TETRAHYDRO[2*H*]AZEPINES



This series of compounds is the best represented of the tetrahydroazepines with over 500 references in the literature, dating back to 1930. A selection had therefore to be made to include the most useful methods of preparation of the different types of derivatives. Table 4 is fairly comprehensive and includes a large number of the structures published, but in order to keep it to a reasonable length, references to polymers have been excluded, and patent references have been kept to a minimum.

PREPARATION

The parent 3,4,5,6-tetrahydro[2*H*]azepine (**94**) has been mentioned in the literature as a likely intermediate in the catalytic hydrogenation of 7-amino-3,4,5,6-tetrahydro[2*H*]azepine (**95**),[59] but the main product isolated was the completely reduced material (**96**). Consequently, the existence of a stable parent (**94**) cannot be considered as definitely established.



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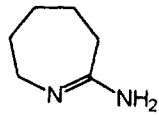

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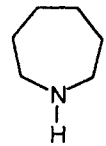
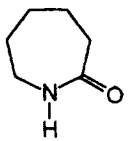
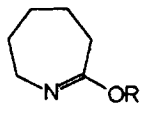


(96)

Much of the chemistry associated with the preparation of substituted 3,4,5,6-tetrahydro[2*H*]azepines is based on caprolactam (**1**, R = H) or one of its enol ethers (**97**, R = alkyl). Details of a procedure for the preparation of the simple enol ethers **97** (R = CH_3, C_2H_5) first appeared in 1948,[60] although the compounds were used as starting materials for other derivatives as early as 1930,[61] but no details of preparation were given in the earlier paper. Treatment of caprolactam (**1**) with dimethyl or diethyl sulphate[60] was used in a number of preparations,[62–69] and various boiling points were quoted for the product (see Table 4). An improved procedure from caprolactam (**1**, R = H) using diazomethane and a silica catalyst was claimed in 1979.[70] The 7-chloro derivative **98**, prepared by the action of phosgene on caprolactam was also used as an intermediate, followed by treatment with the corresponding alcohol[71] and this procedure was extended[72] to give a range of ethers [**97**, R = CH_3, $CH(CH_3)_2$, cyclohexyl, $PhCH_2$, Ph]. Although the method was successful, the use of phosgene as a reagent did not gain wide acceptance,



(1)



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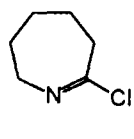

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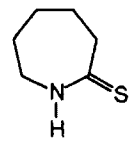


(99)

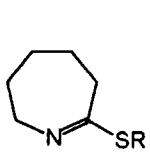
(100)

and a later improvement[73] from the thiolactam **99** and the half-ester half-acid chloride **100** extended the range of ethers available [**97**, R = C_2H_5, $CH_2CH(CH_3)_2$, $CH_2C(CH_3)_3$.

The 7-thio ethers **101** (R = alkyl) have been prepared by routes similar to those used for the preparation of the 7-ethers (**97**, R = alkyl), using the thiolactam **99** as starting material. For example, thiolactam **99** with methanesulphonic acid,[62,66] diazomethane,[70] or methyl iodide,[74,75] gave the 7-methyl thio ether **101** (R = CH_3), and other analogues (**101**, R = $PhCH_2$, $CH{=}CHCH_2$, $CH_2{=}CH$, NH_2COCH_2), have been prepared[73,76–79] using a variety of reagents.

Ring expansion of the oximes **102** and **103** with methanesulphonyl chloride followed by treatment with ^{i}BuAlSMe has been used[80] to give the 2-methyl- and 6-methyl-7-thio ethers **104** and **105**, respectively, and a ring expansion

reaction[81] of the thioacetals **106** (R = H, CH_3) with sodium azide or trimethylsilyl azide, followed by treatment of the unisolated intermediate azides **107**



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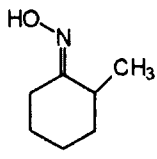

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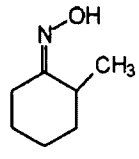

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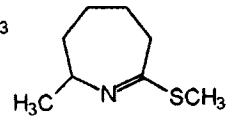

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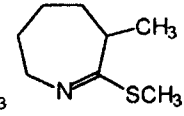

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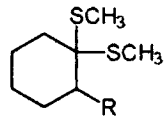

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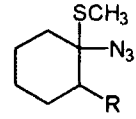
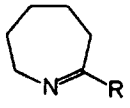


(107)

(R = H, CH_3) with $NaOH/Na_2S_2O_3$ gave the corresponding thio ethers **101** (R = CH_3) and **105**.

The preparation of 7-alkyl-3,4,5,6-tetrahydro[2*H*]azepines has been reported. Direct reaction of Grignard reagent on caprolactam (**1**) gave the 7-*n*-butyl derivative **108** (R = ^{n}Bu),[82] but required heating to 150°C to effect the reaction. Milder methods have been reported subsequently using the enol ether **97** (R = CH_3) rather than caprolactam to give a range of alkyl derivatives [**108**, R = CH_2=$CH(CH_2)_3$ and R = CH_3, C_2H_5, ^{n}Pr, ^{n}Bu, Ph, $PhCH_2$].[83,84]



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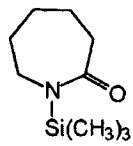

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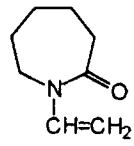

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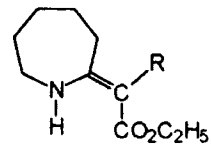
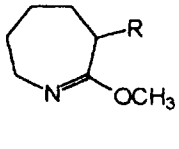


(111)

Preparation of 7-alkyl derivatives (**108**, R = alkyl) by direct alkylation of caprolactam using alkyllithium reagents does not seem to be possible, but successful reactions have been reported when the nitrogen atom has been protected. For example, the trimethylsilyl derivative **109** and the 1-vinyl derivative **110** with methyllithium both gave the 7-methyl derivative **108** (R = CH_3).[85,86] In contrast, no pure product could be isolated from **110** using phenyllithium.[86] More recently, several 7-alkyl derivatives (**108**, R = CH_3, ^{n}Pr, ^{n}Bu, ^{t}Bu, Ph) have been prepared under fairly mild conditions from the enol ether **97** (R = CH_3) and the corresponding alkyllithium in diethyl ether.[87] The 7-alkyl derivatives **108** (R = CH_3, C_2H_5, ^{n}Pr, CH_2CH_2Ph) have also been prepared by

decarboxylation by boric acid of the esters **111** (R = H, CH_3, C_2H_5, CH_2Ph).[88,89]



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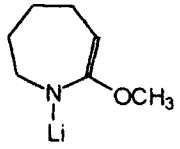

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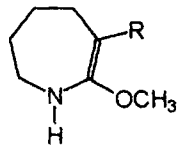

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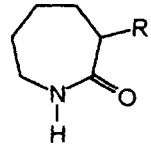
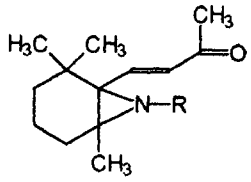


(115)

Direct alkylation of the enol ether **97** (R = CH_3) to give the 6-alkyl enol ethers **112** (R = CH_3, C_2H_5, ^nPr) has been achieved[67] using $^iPr_2NLi$ to give the lithio derivative **113**, followed by treatment with the appropriate alkyl halide. The reaction is presumed to go via an intermediate, probably the isomers **114** (R = CH_3, C_2H_5, ^nPr) which were not isolated, but were converted into **112** by acidification with the weak acid ammonium chloride. Attempted acid hydrolysis[67] of the enol ethers **112** (R = CH_3, C_2H_5, ^nPr) was unsuccessful, whereas the use of mineral acid instead of ammonium chloride on the intermediates **114** (R = CH_3, C_2H_5, ^nPr) gave the lactams **115** (R = CH_3, C_2H_5, ^nPr), albeit in poor yields.

As is the case with the isomeric tetrahydroazepines already described, ring-expansion reactions have also proved useful for the preparation of alkyl-substituted 3,4,5,6-tetrahydro[2*H*]azepines. In some instances ring expansion from a six-membered ring has been used to obtain derivatives with unusual substitution patterns which are not readily available by direct substitution of the azepine itself. For example, heating the aziridine **116** (R = H) gave the 3,3,7-trimethyl derivative **117** (R = H),[35] although the isomeric product **118** (see Table 1) resulted on similar treatment of the ester **116** (R = CO_2CH_3).[35]



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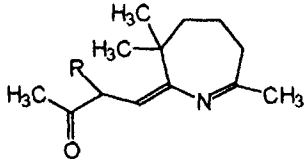

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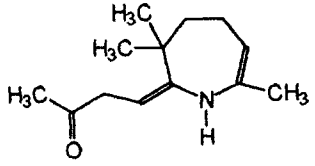
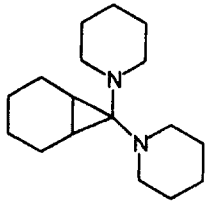


(118)

In contrast, ultraviolet irradiation at room temperature of the aziridines **116** (R = H, CO_2CH_3) gave mixtures,[90] and although the products **117** (R = H) and a rearranged product **117** (R = CO_2CH_3) originating from **118** were detected, no pure materials could be isolated because of further rearrangement during the reaction.

In other instances, pyrolytic processes have been used to prepare derivatives with relatively simple substitution patterns and since the products formed are probably more readily available from caprolactam (**1**, R = H) or its enol ether

(**97**, R = CH_3), it is possible that the primary aim of these efforts was to study the reaction mechanisms. Nevertheless, some useful synthetic methods resulted. For example, pyrolysis of the diamine **119** gave a mixture of cyclohexene and the enamine **120**,[91] isolated as the picrate, the structure of which was confirmed by a separate synthesis from the 7-chloro derivative **98** treated with piperidine.[91]



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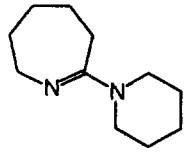
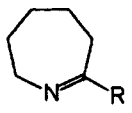


(120)

Ring expansion of hydroxylamines via the amine sulphonate esters has also been investigated as a route to alkyl-substituted 3,4,5,6-tetrahydro[2*H*]-azepines. The sulphonates **121** (R^1 = CH_3, R^2 = NO_2, CF_3) were shown to rearrange to the 7-methyl product **108** (R = CH_3),[92,93] and the reaction was extended to other analogues (**121**, R^1 = CH_3, ^{n}Bu, CH_2Ph, R^2 = NO_2)[94] to give the corresponding 7-alkyl derivatives **108** (R = CH_3, ^{n}Bu, CH_2Ph). The 2,7-dialkyl product **123** has also been prepared from the corresponding hydroxylamine (**122**).[94]



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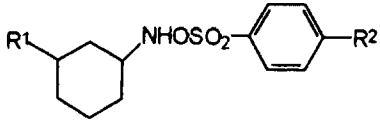

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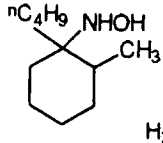

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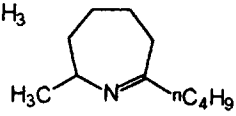
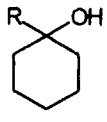


(123)

Acid treatment of the azides **125** (R = CH_3, C_2H_5, cyclohexyl), prepared from the corresponding tertiary alcohols (**124**, R = CH_3, C_2H_5, cyclohexyl), yielded the 7-alkyl derivatives (**108**, R = CH_3, C_2H_5, cyclohexyl)[95] with loss of nitrogen, and similar treatment of the azides **127** and **129** from the secondary



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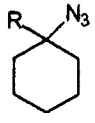

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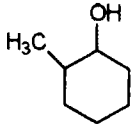

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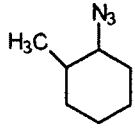
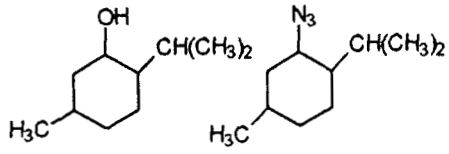


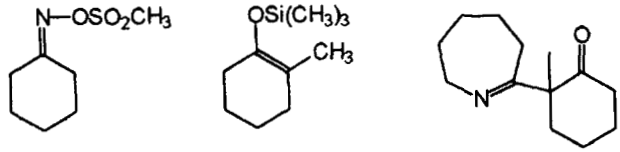
(127)

alcohols **126** and **128** gave the 7-methyl and 4,7-dialkyl derivatives (**108**, R = CH_3 and **130**), respectively.[96]



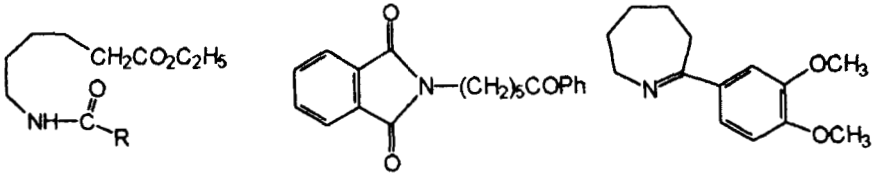
(128) **(129)** **(130)**

The final variation on this theme is the Beckmann rearrangement of the methane sulphonate (**131**) in the presence of the trimethyl silyl ether (**132**), which gave the cyclohexanone derivative (**133**)[97] on treatment with diethylaluminium chloride.



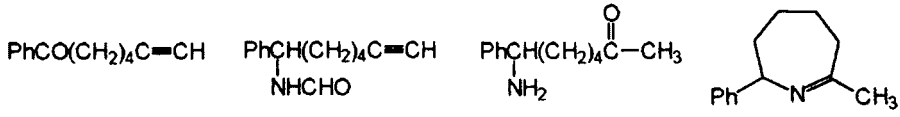
(131) **(132)** **(133)**

Several procedures involving ring closure of esters,[98] ketones,[99,100] acetylenes[101,102] and azides[103–106] have been utilised successfully to form the 3,4,5,6-tetrahydro[2*H*]azepine ring system. The amide esters **134** (R = CH_3, Ph), derived from ϵ-aminocaproic acid, on treatment with $NaOH/Ca(OH)_2$, cyclised and decarbethoxylated to give the corresponding 7-methyl- and 7-phenyl-3,4,5,6-tetrahydro[2*H*]azepines (**108**, R = CH_3, Ph),[98] and the latter compound (**108**, R = Ph) was also formed from the phthalimido derivative **135**, which on hydrolysis[99] or hydrazinolysis[100] released the free amine which cyclised. The corresponding 3,4-dimethoxyphenyl derivative (**136**) was prepared in a similar manner.[99]



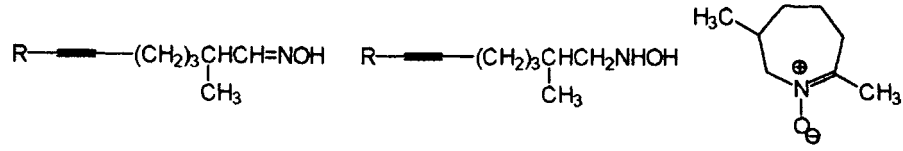
(134) **(135)** **(136)**

In an alternative cyclisation procedure, the acetylene **137** on treatment under Leuckart conditions with ammonium formate gave the formamido derivative **138**, which in turn was treated with acid to give an unisolated intermediate (**139**) which cyclised to 2-phenyl-7-methyl-3,4,5,6-tetrahydro[2*H*]azepine **140**.[101]



(137) (138) (139) (140)

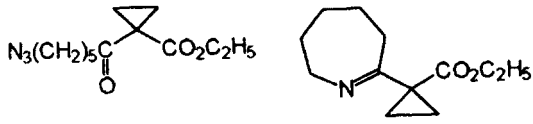
The acetylenes **141** [R = H, $(CH_3)_3Si$] have also been cyclised, after reduction with $NaCNBH_3$ to the unisolated heptynylhydroxylamines **142** [R = H, $(CH_3)_3Si$] and refluxing in toluene. In each case the product was the nitrone **143** with the terminal alkyne **142** (R = H) cyclising more efficiently than the silyl derivative **142** [R = $(CH_3)_3Si$].[102]



(141) (142) (143)

The cyclisation of terminal azides was described in a series of papers by Vaultier and co-workers.[103–106] The keto azide **144** (R = CH_3) on treatment with triphenylphosphine underwent an intramolecular aza-Wittig reaction via the transient phosphinimine **145** to give the 7-methyl-3,4,5,6-tetrahydro[2*H*]azepine **108** (R = CH_3).[103] The reaction was subsequently extended to the cyclopropyl ester **146**, which under the same reaction conditions cyclised to give the 7-cyclopropyl derivative **147**,[104] and the generality of the reaction was demonstrated further by cyclising the azides **144** (R = CH_3, Ph, cyclohexyl[105] and R = CH_3)[106] to give the corresponding 7-substituted analogues **108** (R = CH_3, Ph, cyclohexyl).

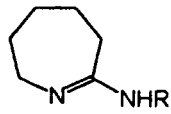
(144) (145)



(146) (147)

The parent 7-amino-3,4,5,6-tetrahydro[2*H*]azepine **148** (R = H) has been described[59] as the product formed by cyclisation of the dinitrile **149**. Its

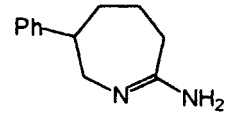
3-phenyl analogue **150** was prepared by the action of ammonia or ammonium chloride on the 7-ethyl ether **151** in an autoclave at elevated temperature.[107]



(148)

$NC(CH_2)_4CN$

(149)



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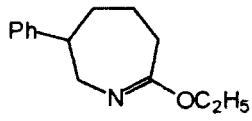

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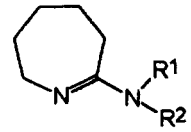
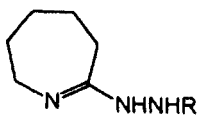


(152)

The 7-substituted-amino-3,4,5,6-tetrahydro[2*H*]azepines **148** have been prepared in abundance, by the action of an amine on either the 7-methyl ether **97** (R = CH_3) or the 7-chloro derivative **98**. These routes have been used to prepare a range of 7-alkylamino- (**148**, R = CH_3, *n*-C_6H_{13}, *n*-C_8H_{17}, *n*-$C_{12}H_{25}$, *n*-$C_{14}H_{29}$),[108–111] 7-arylamino (**148**, R = Ph, 2-, 3-, 4- and 5-substituted phenyl, 2-thiazolyl)[110–114] and 7-aralkylamino derivatives [**148**, R = CH_2Ph, $(CH_2)_2Ph$].[108] In addition, a further range of secondary amines **148** with a variety of substituted alkyl or acyl groups have been described,[5,69,111,115–121] as well as a number of tertiary amines (**152**, R^1 = alkyl, R^2 = phenyl, acyl).[32,122,123] Full details of these structures, and a further range of related 7-amino derivatives,[124–129] are given in Table 4.

7-Hydrazino-3,4,5,6-tetrahydro[2*H*]azepine (**153**, R = H) was first described in 1930,[61] at which time there was some doubt whether the compound existed as structure **153** (R = H) or as its tautomer **154** (R = H). Subsequent investigation has done little to clarify the situation, and while later papers formulate the unsubstituted 7-hydrazino derivative as **153** (R = H),[65,130,131] there is some evidence for the existence of the tautomeric form **154** with the acyl-substituted hydrazino analogues (**154**, R = PhCO, 4-$CH_3OC_6H_4CO$, 4-ClC_6H_4CO and 4-pyridyl-CO)[132] and the thioacyl derivatives (**154**, R = CH_3SCS, C_2H_5NHCS, PhNHCS),[133] particularly when the material is in solution.[133] Most authors, however, favour the tautomeric form **153**.



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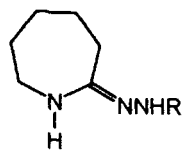

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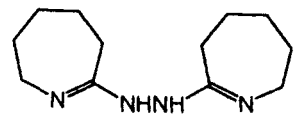
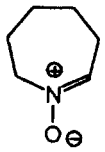


(155)

The favoured method of preparation of both unsubstituted (**153**, R = H),[65,130] and substituted derivatives (**153**, R = alkyl, acyl)[108,132,134] is by treatment of the enol ether **97** (R = CH_3) or the thioether **101** (R = CH_3) with the appropriate hydrazine. For example, the alkyl hydrazines **153** (R = *n*-C_4H_9, *n*-C_6H_{13}, *n*-C_8H_{17}, *n*-$C_{10}H_{21}$, *n*-$C_{12}H_{25}$) have been prepared from both starting materials[108] and the acyl hydrazines **153** (R = CH_3CO, C_2H_5CO, 4-$NO_2C_6H_4CO$, 3- and 4-pyridyl-CO)[134] and (**153**, R = PhCO, 4-$CH_3OC_6H_4CO$, 4-ClC_6H_4CO and 4-pyridyl-CO)[132] were prepared from the enol ether. The reaction of hydrazine and phenylhydrazine with the thioether **101** (R = CH_3) has proved useful for the preparation of the dimer **155** and the phenyl analogue **153** (R = Ph),[135] respectively. A full list of related 7-substituted hydrazino analogues is included in Table 4.

PROPERTIES

Apart from the parent 3,4,5,6-tetrahydro[2*H*]azepine (**94**)[59] and the nitrone **156**,[136] the compounds in this class exhibit remarkable stability, even withstanding distillation at temperatures as high as 200 °C in some cases, and often forming stable, high-melting salts. Remarkably also, with a few rare exceptions, including the two compounds mentioned above (**94** and **156**), most derivatives have a substituent at position 7, emphasising again their common origin from caprolactam (**1**, R = H).



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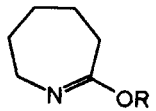

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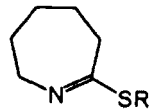

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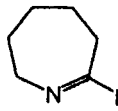
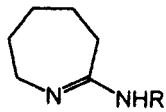


(108)



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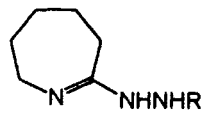
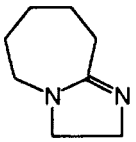


(153)

The chemistry of the enol ethers **97** and the thioether **101** is unremarkable, the compounds finding their main use as synthetic intermediates for other 7-substituted derivatives such as the 7-alkyl (**108**), 7-amino (**148**) and 7-hydrazino (**153**) derivatives. Chemically the two latter series of compounds (**148** and **153**) have proved to be extremely useful starting materials for the preparation of fused bicyclic systems. For example, the fused diazoles **157** and **158** have been prepared by cyclisation of the bromoethylamine **159** and the acetal **160**, respectively,[116,117] and the more highly substituted derivative **161** was prepared from the corresponding ketone **162**.[107]



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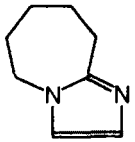

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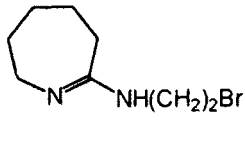

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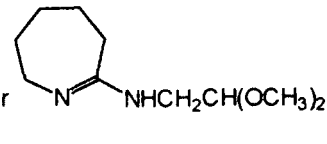

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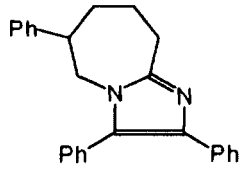

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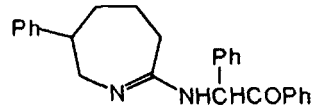
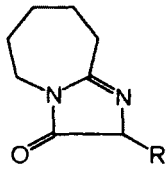
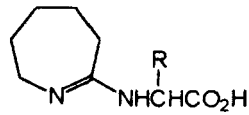


(162)

The 3-keto analogues **163** (R = H, and R = ^{i}Pr, CH_2Ph, H) have been prepared also from the corresponding acids **164** (R = H, and R = ^{i}Pr, CH_2Ph, H).[115,120]

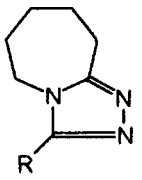


(163)



(164)

Following similar procedures, the fused 1,2,4-triazoles **165** (R = H, CH_3) were prepared from 7-hydrazino-3,4,5,6-tetrahydro[2*H*]azepine (**153**, R = H) on treatment with formic acid or acetic acid,[130] and the pyridino derivative **166** was formed by cyclisation of the corresponding isonicotinoyl hydrazide (**167**).[130] The fused tetrazole 'corazole' (**168**) has been prepared by cyclisation of the hydrazine **153** (R = H) using sodium nitrite and 20% sulphuric acid.[65]



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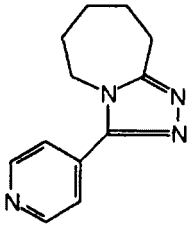

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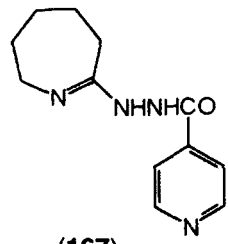

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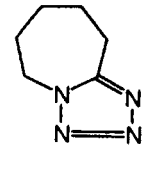
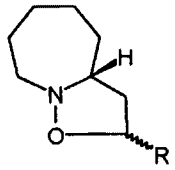


(168)

A 1,3-dipolar cycloaddition has been reported to give epimeric mixtures of the fused products **169** (R = Ph, OC_2H_5, CH_2OH, CN, CO_2CH_3, CHO) when

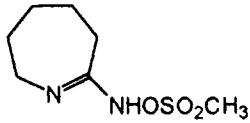
the nitrone **156** was reacted with the alkenes **170** (R = Ph, OC_2H_5, CH_2OH, CN, CO_2CH_3, CHO). Separation of the main products from the co-formed stereoisomers, however, was not achieved.[136]



(169)

CH_2=CHR

(170)



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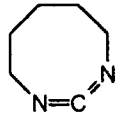


(172)

Finally, ring expansion of the methane sulphonate of 7-hydroxylamino-3,4,5,6-tetrahydro[2*H*]azepine (**171**) has been reported, giving the eight-membered ring **172** on treatment with base.[124] A full list of 3,4,5,6-tetrahydro[2*H*]azepines is given in Table 4.

Table 4. 3,4,5,6-Tetrahydro[2*H*]azepines

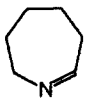
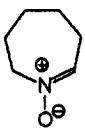
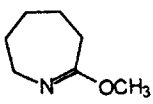
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Oil			59
				136
	65–67/24			60
	82.5/11			62
	64–66/20		IR	63
	66–67/24			
	71.5–72/24			66
	164.5–165.5/760			
	100–102/75			67
	50–52/0.4			69
	60–62/20			71
	48–50/16		^{1}H NMR, IR, MS	72a
				64, 65, 70

Table 4 (continued)

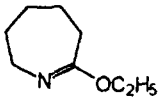
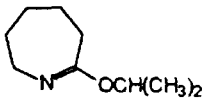
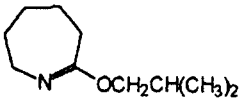
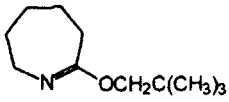
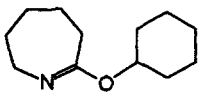
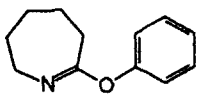
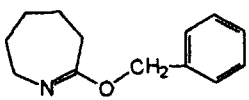
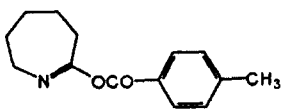
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	30–31/0.7 81–82/26 88–89/28	 HCl 92–95	 IR 	10 60 61 68 73
	32–33/0.4		^{1}H NMR, IR, MS	72a
	115–116/20	HCl 103–106		73
	98–100/15	HCl 165–166		73
	73–74/0.2		^{1}H NMR, IR, MS	72a
	87–90/0.2		^{1}H NMR, IR, MS	72a
	115–119/0.4		^{1}H NMR, IR, MS	72a
	85/6.5	IR		63

Table 4 (continued)

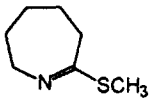
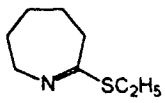
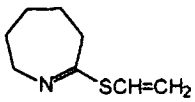
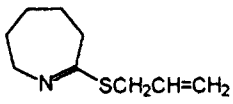
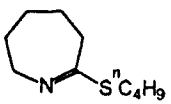
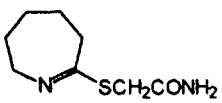
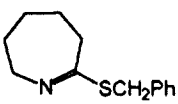
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	82.5/12			62
	100.5–101.5/21			66
	87–88/15–20	HI 175–177		74
		Methiodide 122–124		74
		HI		75
	Oil		^{1}H NMR, IR	80
			^{1}H, ^{13}C NMR, IR	81
				70
	Oil		^{1}H NMR, IR	80
				78
		HBr		75
				77
	95/1			146
		HCl 158–159		79
	140–145/7	HCl 163–165		73
		HBr 151–153		76
	150–152.5/4	HCl 102		75

Table 4 (continued)

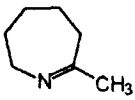
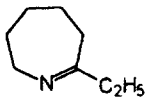
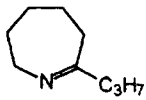
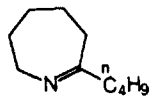
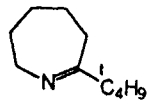
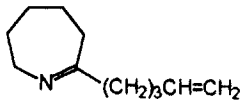
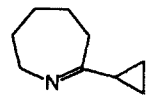
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	43–47/8			84
	Oil		^{1}H NMR, IR, MS	86
	Oil		MS	87
	110/760			88, 89
			IR, ^{1}H NMR	92, 93
	Oil		^{1}H NMR, IR	94
	140–149/760			96
	110–160/21	Picrate 189–190		98
	70–80/18		IR, ^{13}C NMR	103
	44–45/18	Picrate 194–195	^{1}H, ^{13}C NMR, IR, MS	105
				85, 95, 106
	60–63/15			84
	60/20			88, 89
				95
	73–75/11			84
	Oil		MS, ^{1}H NMR	87
	78/20			88, 89
	99–100/16			84
		Picrolonate 173		82
	Oil			87
			MS, ^{1}H NMR	94
	Oil		MS, ^{1}H NMR	87
	110–113/14.5			83
	70–80/5	Picrate 141	^{1}H, ^{13}C NMR, IR, MS	105

Table 4 (continued)

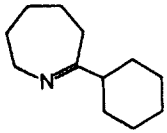
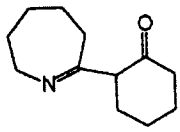
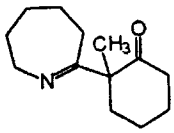
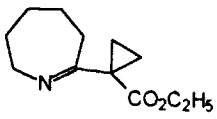
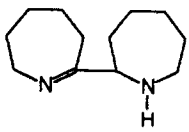
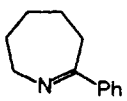
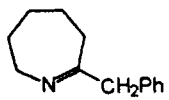
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
				95
				139
	Oil		IR, ^{1}H NMR	97
	110–115/0.05		^{1}H, ^{13}C NMR, IR, MS	104
	Oil		^{1}H NMR, IR, MS	138
	139–141/9	Methiodide 176–179		84
	Oil		MS, ^{1}H NMR	87
	103–108/4	Picrate 175–176		98
	142–245/15			99
	108/0.6		^{1}H NMR	100
	85–95/1		^{1}H, ^{13}C NMR, IR, MS	105
		$MeClO_4$ salt		142
	143.5–146/11			84
	Oil		^{1}H, ^{13}C NMR, IR, MS	94

Table 4 (continued)

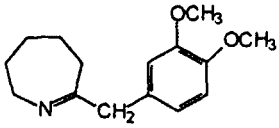
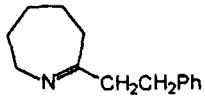
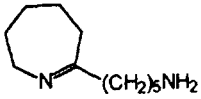
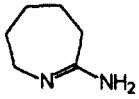
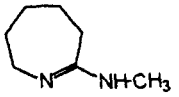
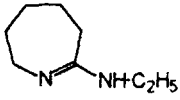
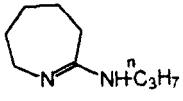
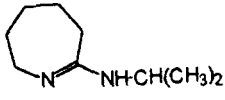
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	195–200/0.2 64.5–66			99
	105/0.05			88, 89
	134/0.6 142–146/9			137a 137b 137c
	93–94/1.5	HCl 159.5–160.5 Phenyl hydrogen methyl phosphonate 110–111.5		59 60 147
	106–107 100–102	HCl 215–216	 ^{1}H NMR	33 110 109
			^{1}H, ^{13}C NMR	111
	109–110	2HCl 252–255	^{1}H NMR	118 144
	110–111/10 57–60			144
	74–77/0.07 65–67			144
	128–131/22 86–87			144

Table 4 (continued)

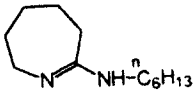
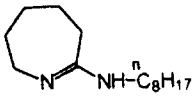
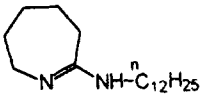
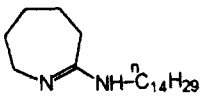
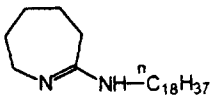
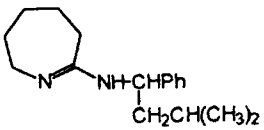
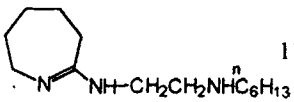
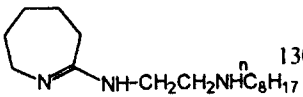
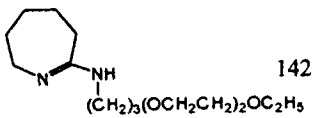
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	105–109/0.002	HCl 146–147		108
	110–117/0.001	HCl 152–154		108
	53–54	HCl 148–149		108
	56–58			108
	73–74	Oxalate 105.5–107		60
	106–107			108
	113–115/0.002			108
	130–131/0.003			108
	142–147/0.01			108

Table 4 (continued)

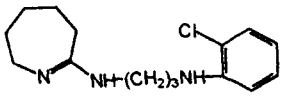
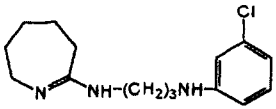
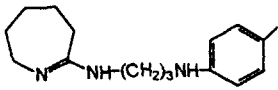
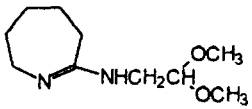
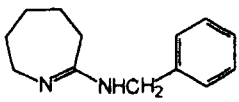
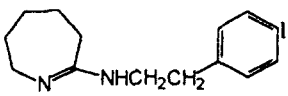
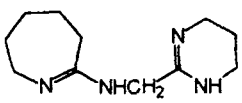
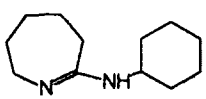
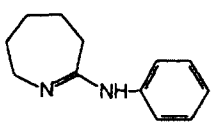
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	150/0.0001			108
	160/0.0001			108
	150/0.0001	HCl 218–220		108
		HCl 172–173		117
	76–77 75–76.5			108 144
	120–121/0.01			108
		2HCl 210–212		118
	129–130 129.5–131			60 144
	126–128/1–2 105 105.6–106 102–104		 ^{1}H NMR, MS, IR, UV	33 112 110 113

Table 4 (continued)

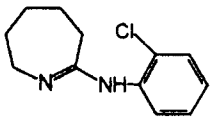
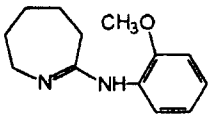
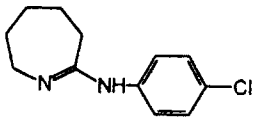
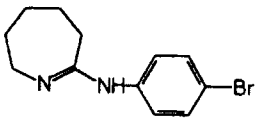
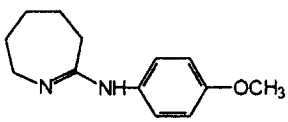
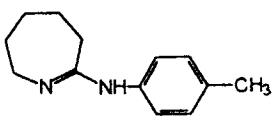
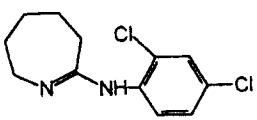
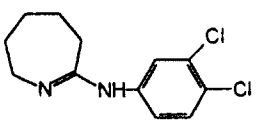
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	92–94 126–128		^{1}H NMR, MS, IR, UV	113 60
	86–88			60
	128–130		^{1}H NMR, MS, IR, UV	113
	127–128		^{1}H NMR, MS, IR, UV	113
	83–85		^{1}H NMR, MS, IR, UV	113
			^{1}H, ^{13}C NMR	111
	104–105		^{1}H NMR, MS, IR, UV	113
	109–110		^{1}H NMR, MS, IR, UV	113

Table 4 (continued)

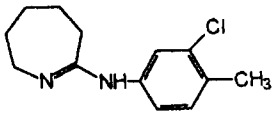
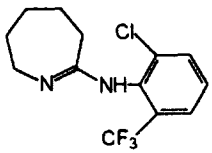
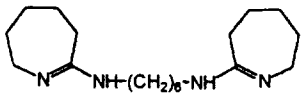
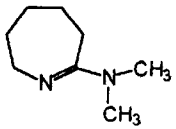
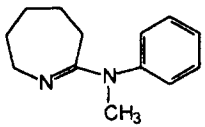
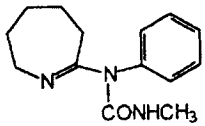
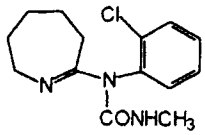
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	110–113		^{1}H NMR, MS, IR, UV	113
	113–115		^{1}H NMR, MS, IR, UV	113
	160–160.5			60
	95–96/14	HCl 185–187		145
	82/0.05	*p,p'*-Dichloro-diphenyldi-sulphimide 222		122
	108–110		^{1}H NMR, MS, IR, UV	113
	Glassy solid		^{1}H NMR, MS, IR, UV	113

Table 4 (continued)

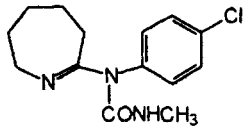
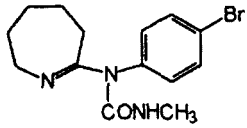
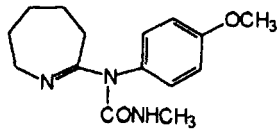
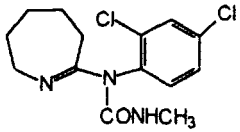
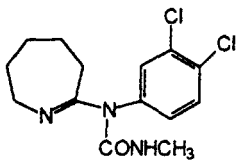
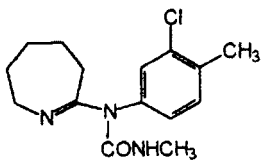
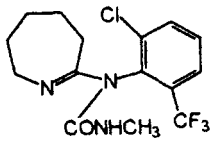
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	95–97		^{1}H NMR, MS, IR, UV	113
	121–123		^{1}H NMR, MS, IR, UV	113
	06–108		^{1}H NMR, MS, IR, UV	113
	76–79		^{1}H NMR, MS, IR, UV	113
	103–105		^{1}H NMR, MS, IR, UV	113
	Glassy solid		^{1}H NMR, MS, IR, UV	113
	Glassy solid		^{1}H NMR, MS, IR, UV	113

Table 4 (continued)

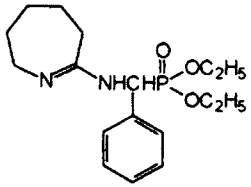
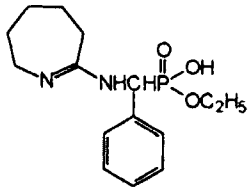
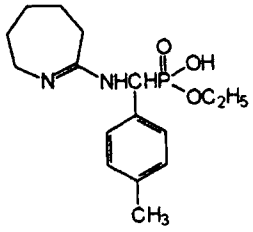
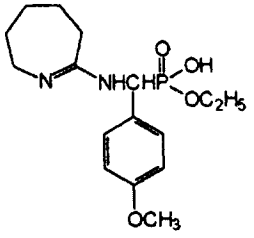
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Oil		^{1}H, ^{31}P NMR	111
	233		^{1}H, ^{31}P NMR	111
	256–258		^{1}H, ^{13}C, ^{31}P NMR MS	111
	268–269		^{1}H, ^{31}P NMR, MS	111

Table 4 (continued)

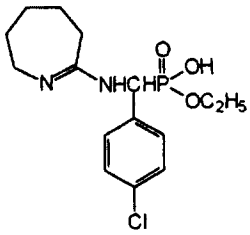
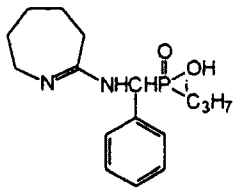
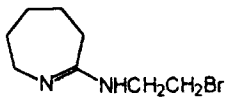
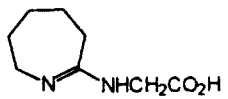
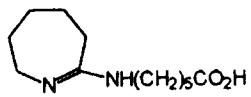
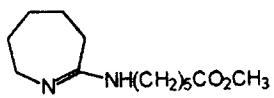
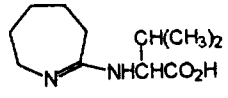
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	282–283		^1H, ^{31}P NMR, MS	111
	247–248		^1H, ^{31}P NMR, MS	111
		HBr 182		116
	173–174 176–177	HCl 152–153	 MS	115 120
		HCl 152–154 *p*-Toluene-sulphonate 124 HCl 148, 150 Benzene-sulphonate 99	 IR (salt) IR, ^1H NMR (salt) IR (salt)	5 119 119 119
	80			144
	154/0.005			5
	173–175		^1H NMR, IR, MS	120

Table 4 (continued)

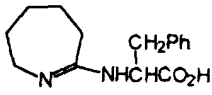
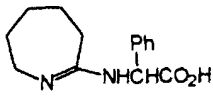
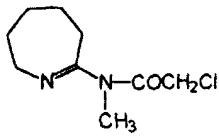
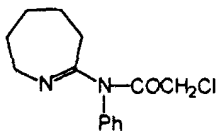
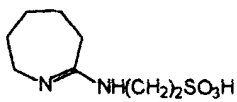
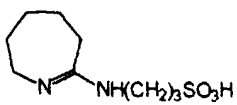
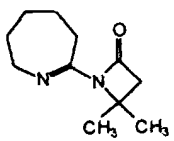
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	139–141		^{1}H NMR, IR, MS	120
	167–168		^{1}H NMR, IR, MS	120
			^{1}H NMR	33
			^{1}H NMR	33
	279–280		IR, ^{1}H NMR	154
	307–308		IR, ^{1}H NMR	154
	82–85/0.1 87–88			125

Table 4 (continued)

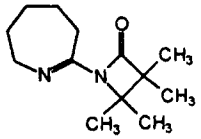
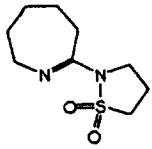
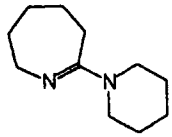
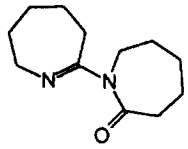
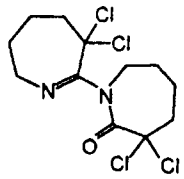
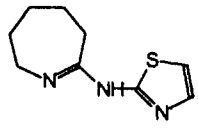
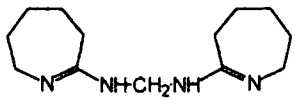
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	92/0.4, 73–74			125
	129–131		IR, ^{1}H NMR	154
	56–58/0.01 133–134/760	Picrate 118	IR, ^{1}H NMR	91 114
	30.5–32 31–32 113/0.04 30–32		IR, ^{1}H NMR ^{1}H NMR, MS	140b 140a 126
	84.5–85		IR, ^{1}H NMR	126
				114
	120–121			110

Table 4 (continued)

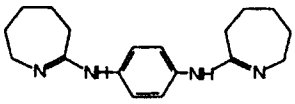
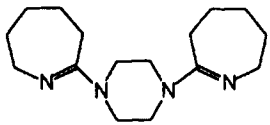
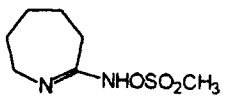
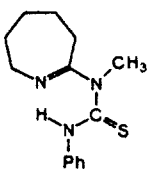
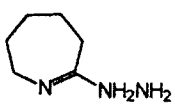
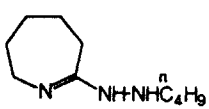
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	213–214			110
				114
	89–90			124
	190		IR, ^{1}H NMR	121
	172		IR, ^{1}H NMR	121
	189		IR, ^{1}H NMR	121
	106		IR, ^{1}H NMR	123
	103.5–104.5 112	Picrate 136		60 61 65, 130, 132
	144–145/12	HCl 153–157		108

Table 4 (continued)

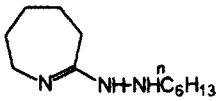
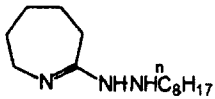
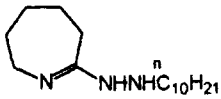
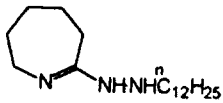
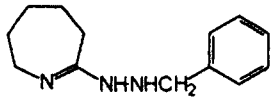
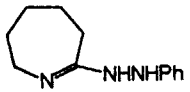
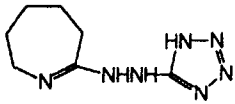
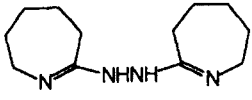
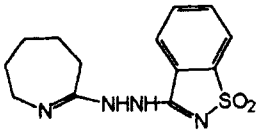
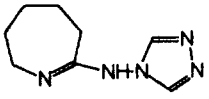
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	105–109/0.01	HCl 155–158		108
	128–131/0.03	HCl 146–150		108
	145–149/0.01			108
	159–163/0.01			108
	140–145/0.01	Oxalate 156–157		108
	109–111 113–115 108		 IR	110 130 135
	225			134
	125.5–126.5 125.5		 IR	60 135
	197–198			134
	242			134

Table 4 (continued)

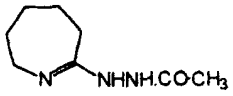
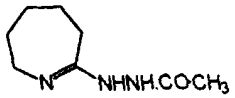
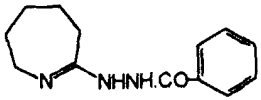
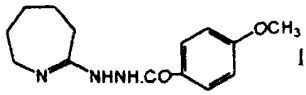
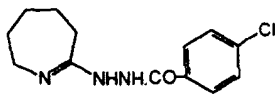
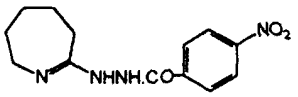
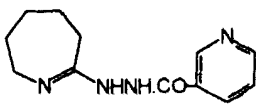
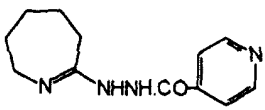
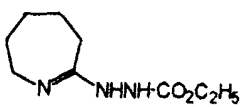
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	176–177	HCl 181		134
	169			134
	173–179			132
	179–185			132
		HCl 199–201		132
	188			134
	108			134
	208–210 210			130 134 132
	122			134

Table 4 (continued)

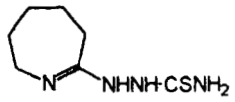
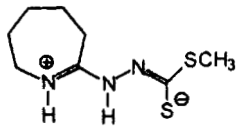
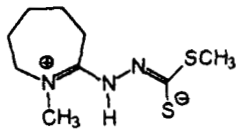
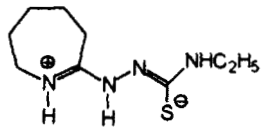
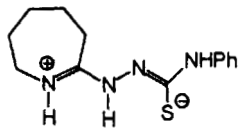
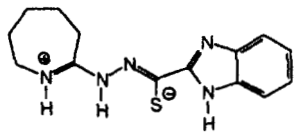
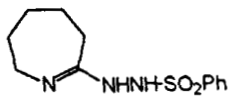
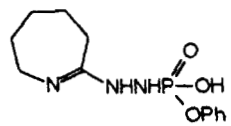
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	240–250			134
	174–176		^1H, ^{13}C NMR, MS, UV	133
	158–160		^1H, ^{13}C NMR, MS, UV	133
	125		^1H NMR, MS	133
	166–167		^1H NMR, MS	133
	241–243		^1H NMR, MS	133
	190–191			134
			IR, ^1H NMR	131

Table 4 (continued)

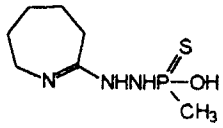
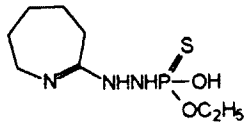
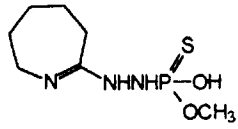
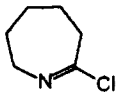
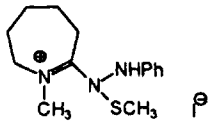
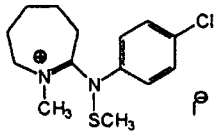
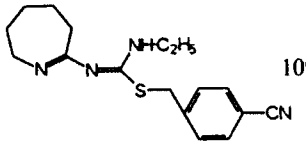
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			IR, ^{1}H NMR	131
			IR, ^{1}H NMR	131
			IR, ^{1}H NMR	131
		HCl 66–70		71, 72a,b 112
	192–193			128
	168–170			128
	109–111		^{1}H NMR, MS	127

Table 4 (continued)

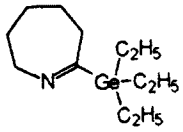
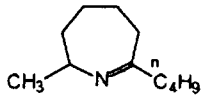
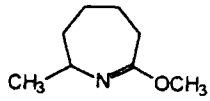
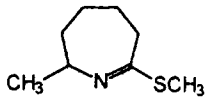
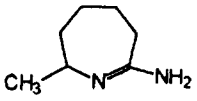
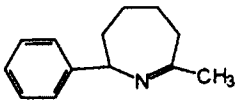
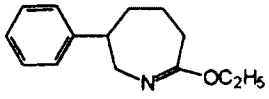
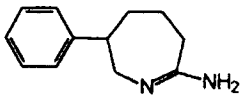
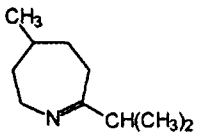
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			^1H, ^{13}C NMR, MS	141
	Oil		^1H NMR, IR, MS	94
	110/25 70–73/8			67 129
	45/0.1 90–92/20 130–135/5	HI 120–125	^1H NMR, IR	67 74 80
		HCl 94–97		129
	105–106/0.5		^1H, ^{13}C NMR, IR	101
	107–110/0.2			107
		HCl 258		107
	198–201/766		IR	96

Table 4 (continued)

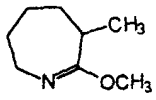
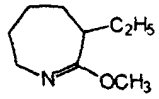
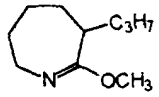
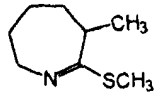
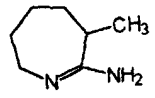
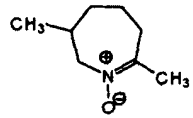
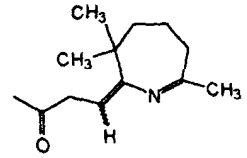
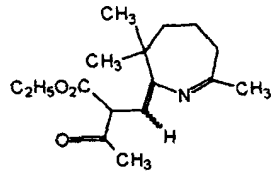
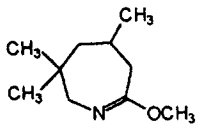
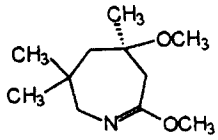
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	60–62/12 70–73/8			67 129
	70–72/11			67
	89–90/10			67
	Oil		^{1}H NMR, IR ^{1}H, ^{13}C NMR, IR	80 81
		HCl 94–97		129
	Oil		IR, MS, ^{1}H NMR	102a 102b
			^{1}H, ^{13}C NMR	35 90
			^{1}H, ^{13}C NMR	90

Table 4 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	40/0.1			67
	Oil		^{1}H NMR, IR, MS	143

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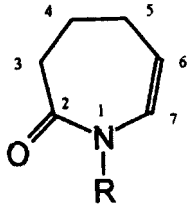
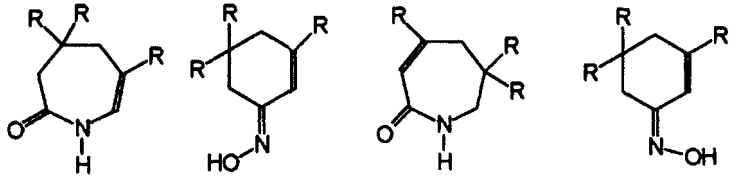
CHAPTER 6

Tetrahydroazepinones

I. 1,3,4,5-TETRAHYDRO[2*H*]AZEPIN-2-ONES



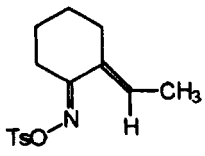
The parent 1,3,4,5-tetrahydro[2*H*]azepin-2-one **1** (R = H) has been prepared by a Beckmann rearrangement of *anti* cyclohexen-2-one oxime (**2**, R = H), using oleum at 140 °C.[1] In a similar fashion, but using phosphorus pentachloride[2] or polyphosphoric acid,[3] the *anti*-oxime of isophorone (**2**, R = CH_3) gave the trimethyl analogue (**1**, R = CH_3).[2,3] The corresponding *syn*-oximes (**4**, R = H, CH_3) were shown to give the isomeric 1,5,6,7-tetrahydro[2*H*]azepin-2-ones (**3**, R = H, CH_3)[2,3] (see Section IV).



(1) **(2)** **(3)** **(4)**

The Beckmann rearrangement has also been used under milder conditions with similar results. For example, heating the *anti*-oxime tosylate **5** in methanol under reflux gave the rearranged product **6**.[4] Under these mild conditions,

however, the *anti*-oxime tosylates **7** (R = H, CH_3) failed to rearrange, although the analogous isomeric 1,5,6,7-tetrahydro products **9** (R = H, CH_3) were obtained from the *syn*-oxime tosylates **8** (R = H, CH_3).[4]



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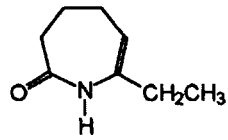

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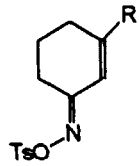

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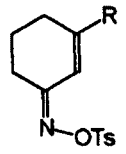

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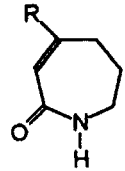
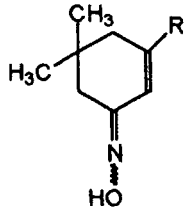


(9)

The Beckmann procedure has also been applied to a number of oximes (**10**, R = CH_3, C_2H_5, ^iPr, ^nBu, Ph, 4-nitrophenyl),[5] without prior separation of the *syn*/*anti* mixture. As might be expected, the products also consisted of mixtures of the 1,3,4,5-tetrahydro- and the 1,5,6,7-tetrahydro[2*H*]azepin-2-ones (**11** and **12**, R = CH_3, C_2H_5, ^iPr, ^nBu, Ph, 4-nitrophenyl),[5] respectively.



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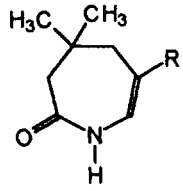

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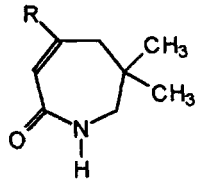
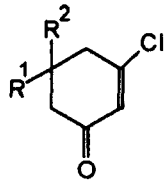


(12)

The Schmidt rearrangement has also been used to produce 1,3,4,5-tetrahydro[2*H*]azepin-2-ones; however, the products are mixtures of the 1,3,4,5- and the 1,5,6,7-products, as illustrated by the formation of both isomers **14** (R^1 = H, R^2 = CH_3 and R^1 = R^2 = H, CH_3) and **15** (R^1 = H, R^2 = CH_3 and R^1 = R^2 = H, CH_3) on treatment of the 3-chlorocyclohexenones **13** (R^1 = H, R^2 = CH_3 and R^1 = R^2 = H, CH_3) with sodium azide.[5,6]

In marked contrast to the above observations, ring expansion of the inseparable *syn*/*anti*-*N*-methylnitrones **16** and **17** gave exclusively the 1-methyl-1,3,4,5-tetrahydro[2*H*]azepin-2-ones **18** and **19**, using either *p*-toluenesulphonyl chloride[7] or chlorosulphonyl isocyanate.[8] In the latter case the authors[8] claimed



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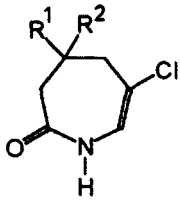

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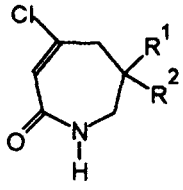
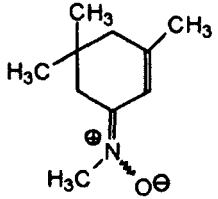


(15)

that the nature of the products was determined by the migratory aptitude of the substituents rather than the initial configuration of the *N*-methylnitrones.



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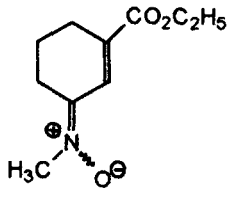

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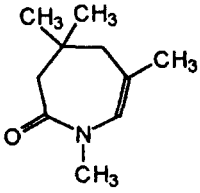

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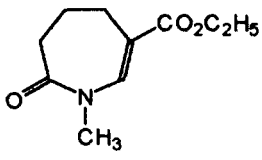
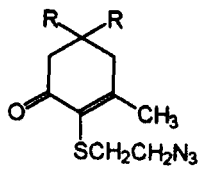


(19)

An interesting ring expansion procedure has been reported in which the 2-azidoethylthiocyclohexenones **20** (R = H, CH_3), on heating in xylene, rearranged to form the fused thiazolidines **21** (R = H, CH_3). Subsequently the trimethyl derivative **21** (R = CH_3) was desulphurated with nickel boride to produce the corresponding 1-ethyl-1,3,4,5-tetrahydro[2*H*]azepin-2-one **22**.[9]



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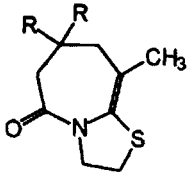

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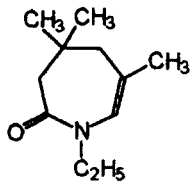
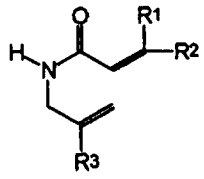


(22)

Two ring-closure procedures have been reported for the preparation of substituted 1,3,4,5-tetrahydro[2*H*]azepin-2-ones, both of which are potentially of wide application. In the first of these, cyclisation of substituted *N*-allyl-2-propenoic acid amides **23** (R^1 = R^2 = CH_3; R^3 = H, CH_3) with one equivalent

of sodium hydride in xylene gave the tetrahydro[2*H*]azepinones **24** ($R^1 = R^2 = CH_3$; $R^3 = H$, CH_3) in high yields.[10] In the presence of methyl iodide and two equivalents of sodium hydride, *N*-alkylated products (**25**,



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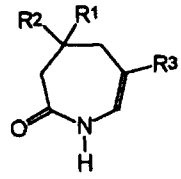

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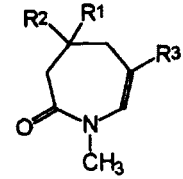
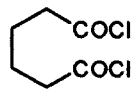


(25)

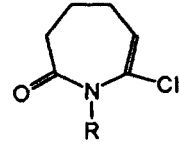
$R^1 = R^2 = CH_3$; $R^3 = H$, CH_3) were obtained and under these latter conditions the amides **23** ($R^1 = CH_3$, Ph, $R^2 = Ph$, $R^3 = H$) were converted directly into the *N*-alkylated azepinones **25** ($R^1 = CH_3$, Ph, $R^2 = Ph$, $R^3 = H$).[10] In these latter examples, no products corresponding to **24** were isolated.

The second ring closure involved the cyclisation of adipoyl chloride (**26**) with an appropriately substituted iminophosphorane (**27**, R = Ph, CH_2Ph, $CH_2CO_2C_2H_5$). In this case the product was a 1-substituted-7-chloro-1,3,4,5-tetrahydro[2*H*]azepin-2-one (**28**, R = Ph, CH_2Ph, $CH_2CO_2C_2H_5$).[11]



(26)

(27)



(28)

A list of substituted-1,3,4,5-tetrahydro[2*H*]azepin-2-ones is given in Table 1.

Table 1. 1,3,4,5-Tetrahydro[2*H*]azepin-2-ones

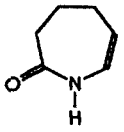
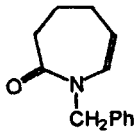
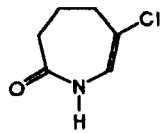
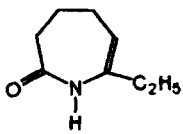
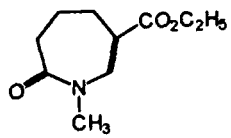
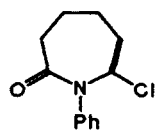
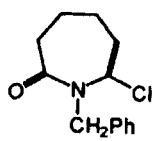
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	133–135/2	IR, UV	1 14
	110/0.1	IR, MS, ^{1}H NMR	15
	80–84	IR, UV	6
	Oil	IR, MS, ^{1}H NMR	4
	90/0.05	IR, MS, ^{1}H NMR	7
	80–82	IR, MS, ^{1}H NMR	11
	35	IR, MS, ^{1}H NMR	11

Table 1 (continued)

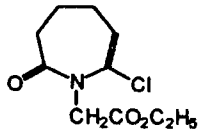
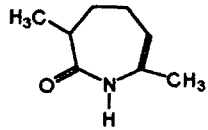
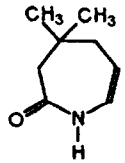
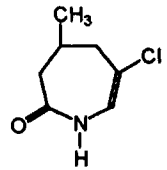
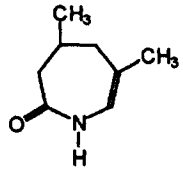
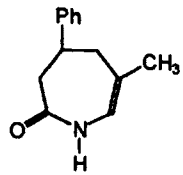
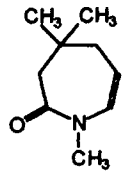
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	32	IR, MS, ^{1}H NMR	11
		IR, ^{1}H NMR	13
	78–80/0.01 64–65	IR, ^{1}H NMR IR, MS, ^{1}H, ^{13}C NMR	10 15
	94–96	IR, ^{1}H NMR	5
	71.5–72.5	IR, MS, ^{1}H NMR	5
	118.3–118.7	UV	2
		IR, ^{1}H NMR IR, MS, ^{1}H, ^{13}C NMR	10 15

Table 1 (continued)

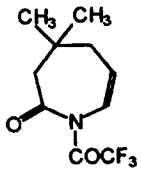
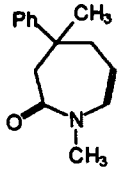
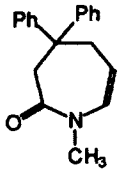
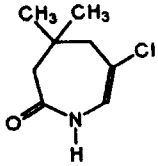
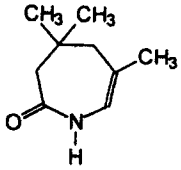
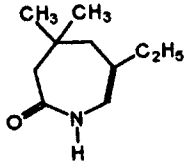
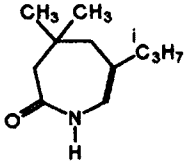
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	Oil	IR, ^{1}H NMR	15
	Liquid	IR, ^{1}H NMR	10
	122	IR, ^{1}H NMR	10
	95–96	IR, UV	6
	90.1–90.7 92–93 82	UV UV	2 3 10 5
	72.5–73.5	IR, MS, ^{1}H NMR	5
	102–104	IR, MS, ^{1}H NMR	5

Table 1 (continued)

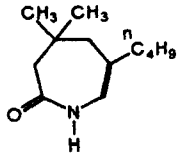
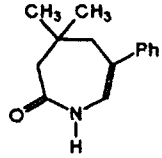
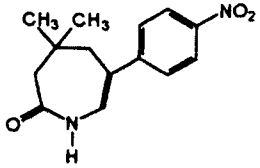
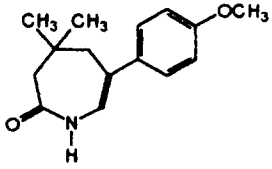
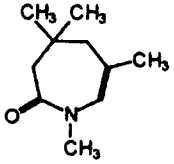
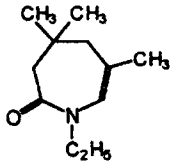
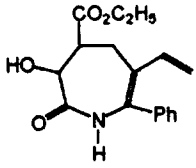
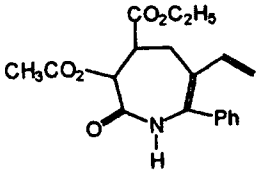
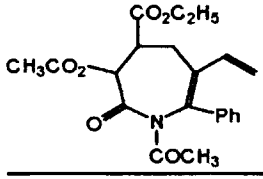
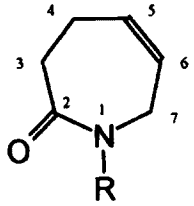
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	45–46	IR, MS, ^{1}H NMR	5
	149–151	IR, MS, ^{1}H NMR	5
	209–220	IR, MS, ^{1}H NMR	5
	167–170	IR, MS, ^{1}H NMR	5
	50/0.05 49–50/0.05 56–57/0.02	IR, MS, ^{1}H NMR IR, ^{1}H NMR	7 8 10
		^{1}H NMR	9
	Amorphous solid	IR, UV, MS, ^{1}H NMR	12

Table 1 (continued)

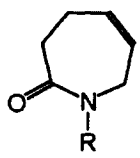
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	145–150	IR, UV, MS, ^{1}H NMR	12
	123–128	IR, UV, MS, ^{1}H NMR	12

II. 1,3,4,7-TETRAHYDRO[2*H*]AZEPIN-2-ONES

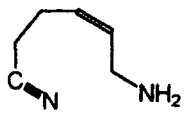


There are relatively few examples in the literature of 1,3,4,7-tetrahydro[2*H*]azepin-2-ones, and although no methods of synthesis of a general nature have been published, a variety of specific ring-expansion and ring-closure reactions have been utilised, some of which potentially are capable of broader application.

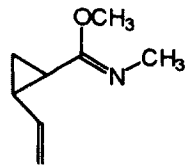
The parent compound in the series (**29**, R = H) has been prepared by allowing a refluxing hydrochloric acid solution of the unsaturated aminonitrile **30** to pass through an alumina column at 300 °C. The reaction proceeds via hydrolysis of the nitrile followed by direct lactam formation from the intermediate unsaturated acid.[16]



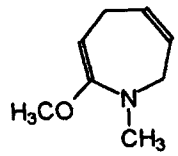
(29)



(30)



(31)

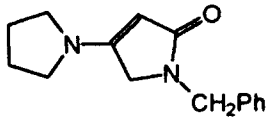


(32)

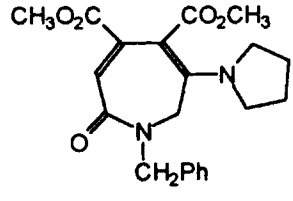
(33)

The simplest substituted analogue, the 1-methyl derivative (**29**, R = CH_3), has been prepared by a Cope rearrangement of the cyclopropyl imidate **31**, followed by hydrolysis of the moisture-sensitive intermediate enol ether **32**.[17] This study was carried out to compare the kinetics of the reaction with those of the corresponding isoconjugate olefinic counterparts (e.g. **33**) and it was concluded that the imidates, as represented by **31**, are slower to react and require more forcing conditions.[17]

Ring expansion of the enamine lactam **34** with dimethyl acetylenecarboxylate has been used to give the enaminocaprolactam **35**, which on hydrolysis gave the corresponding 6-hydroxy-1,7-dihydro[2*H*]azepinone **36** (for full details see Chapter 9, Section III). Reduction of **36** with trimethylsilyl iodide gave the 1-benzyl-1,3,4,7-tetrahydro[2*H*]azepin-2-one **37**.[18]



(34)



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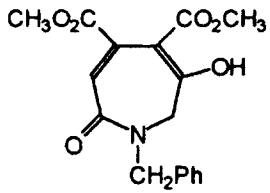
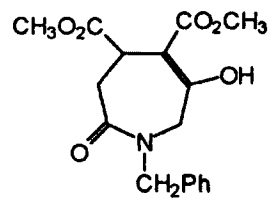


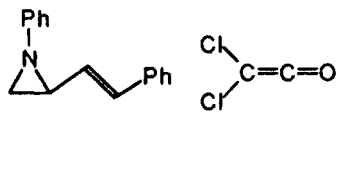
(36)



(37)

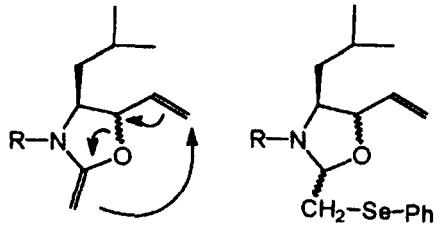
Ring expansion of the vinylaziridine **38** with dichloroketene (**39**), generated *in situ* by dehydrochlorination of dichloroacetyl chloride, led to the formation of the 1,4-diphenyl-3,3-dichloro-1,3,4,7-tetrahydro[2*H*]azepin-2-one **40** in 40% yield, but the reaction does not appear to have been exploited further by using other substituted vinylaziridines.[19]

Claisen rearrangement of the vinyl-substituted oxazolidine **41** (R = *p*-$CH_3C_6H_4SO_2$, $PhCH_2OCO$), prepared *in situ* from the precursor phenyl selenides **42** (R = *p*-$CH_3C_6H_4SO_2$, $PhCH_2OCO$) by oxidative removal of

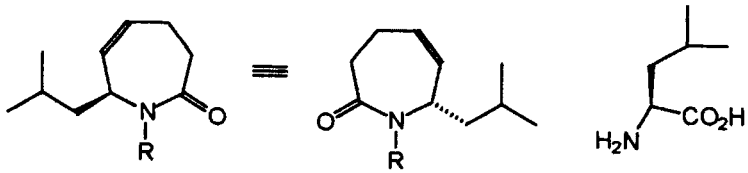


(38) (39) (40)

selenium in the presence of DBU, gave the protected 7-substituted [2*H*]azepin-2-ones **43** (R = *p*-$CH_3C_6H_4SO_2$, $PhCH_2OCO$).[20] Removal of the protecting groups by appropriate means gave the 7-isobutyl-1,3,4,7-tetrahydro[2*H*]-azepin-2-one **43** (R = H) with retention of stereochemistry throughout the complete sequence of reactions (eight steps) from (*S*)-leucine (**44**), which was used as the starting material.[20]

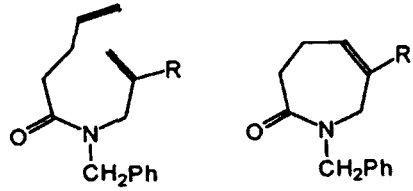


(41) (42)



(43) (44)

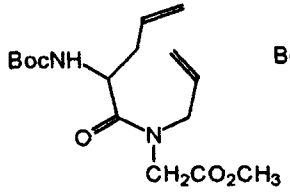
Another ring-closure reaction reported for 1,3,4,7-tetrahydro[2*H*]azepin-2-ones is a modification of the previously quoted (see Chapter 5, Section II) molybdenum-catalysed procedure. In this case the dienamides **45** (R = H,



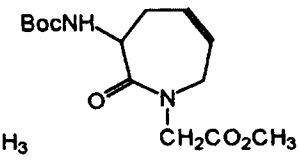
(45) (46)

CH_3), on treatment with the catalyst system, gave the corresponding 1-benzyl-1,3,4,7-tetrahydro[2*H*]azepin-2-ones **46** (R = H, CH_3) with loss of ethylene.[21a]

The alternative use of a ruthenium catalyst has also been reported to effect the ring closure **45** (R = H) → **46** (R = H)[21b] and because of the greater tolerance



(45A)



(46A)

of this catalyst, the reaction has been extended to the cyclisation of the amino acid derivative **45A** which was cyclised to **46A** in 50% yield.[21c]

A list of the reported 1,3,4,7-tetrahydro[2*H*]azepine-2-ones is given in Table 2.

Table 2. 1,3,4,7-Tetrahydro[2*H*]azepin-2-ones

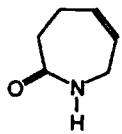
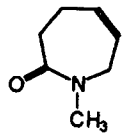
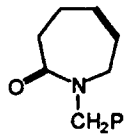
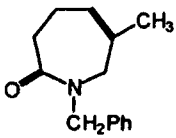
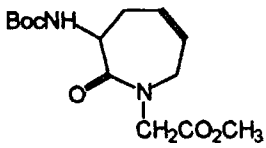
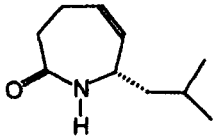
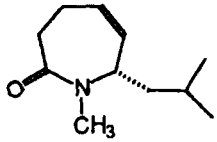
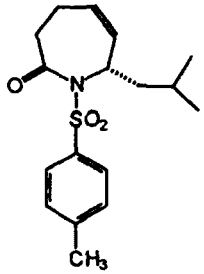
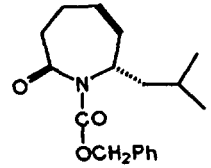
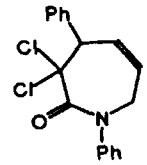
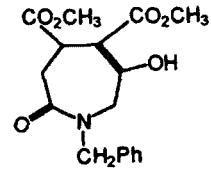
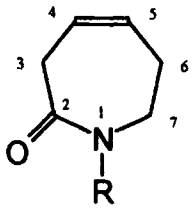
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
			16
			17
		IR, MS, ^{1}H, ^{13}C NMR	21a 21b
		IR, MS, ^{1}H, ^{13}C NMR	21a
		IR, MS, ^{1}H, ^{13}C NMR (supplementary material)	21c

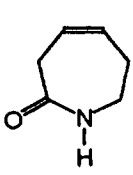
Table 2 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	88–90	α_D α_D, IR, MS, ^1H, ^{13}C NMR	20a 20b
	Oil	α_D α_D, IR, MS, ^1H, ^{13}C NMR	20a 20b
	115–117	α_D α_D, IR, MS, ^1H, ^{13}C NMR	20a 20b
	Oil	α_D α_D, IR, MS, ^1H, ^{13}C NMR	20a 20b
	173–177	IR, MS, ^1H, ^{13}C NMR	19
	Oil	IR, MS, ^1H NMR	18

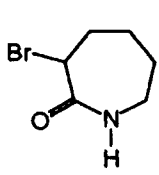
III. 1,3,6,7-TETRAHYDRO[2*H*]AZEPIN-2-ONES



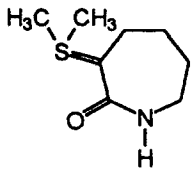
The parent, unsubstituted 1,3,6,7-tetrahydro[2*H*]azepin-2-one (**47**) has been prepared from 3-substituted caprolactams. Unexpectedly, 3-bromocaprolactam (**48**) in the presence of lutidine[22] or the 3-sulphur ylide **49**, on treatment with sodium hydride followed by triethylborane and alkaline hydrogen peroxide,[23] both gave the β,γ-unsaturated ketone **47** as the major product along with a smaller amount of the expected α,β-unsaturated ketone **50**. A mechanistic scheme involving the dienol **51** has been proposed[22] to account for these results.



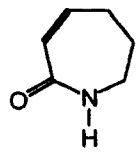
(**47**)



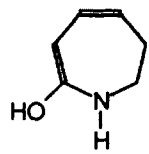
(**48**)



(**49**)

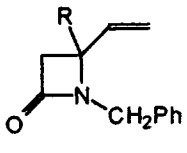


(**50**)

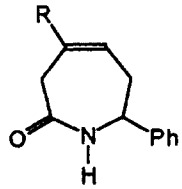


(**51**)

Various ring-expansion procedures have been used to prepare substituted 1,3,6,7-tetrahydro[2*H*]azepin-2-ones. For example, the 1-benzyl-4-vinylazetidinones **52** (R = H, CH_3) were shown to undergo a base-catalysed [2,3] sigmatropic shift in the presence of lithium diisopropylamine to give the 1,3,6,7-tetrahydro[2*H*]azepin-2-ones **53** (R = H, CH_3) in high yield.[24] Relief of ring strain in going from a four-membered ring to a seven-membered ring was postulated as the reason for the ease of the reaction.



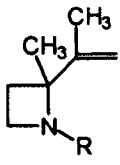
(**52**)



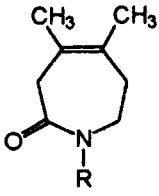
(**53**)

Vinylazetidines have also proved to be useful starting materials in studying the cobalt-catalysed carbonylation/ring-expansion reaction. At elevated temperature (90 °C) and 3.4 atm pressure of carbon monoxide, the vinylazetidines **54** (R = H, $CH_2CH_2COCH_3$, $CH_2CH_2CO_2CH_3$,, CH_2CH_2CN) rearranged with

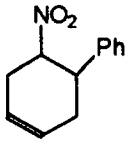
insertion of –CO– to yield the corresponding 1,3,6,7-tetrahydro[2*H*]azepin-2-ones **55** (R = H, $CH_2CH_2COCH_3$, $CH_2CH_2CO_2CH_3$, CH_2CH_2CN), in sharp contrast to azetidines containing a saturated substituent at position 4, which gave pyrrolidines as the main products.[25]



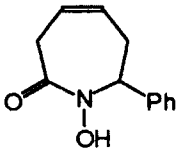
(54)



(55)



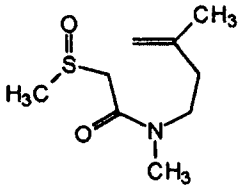
(56)



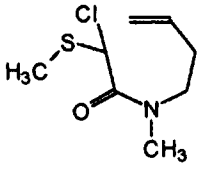
(57)

As part of a study on the photochemistry of nitroalkanes, 4-phenyl-5-nitrocyclohexene (**56**) was irradiated, undergoing ring expansion to give the *N*-hydroxyazepine **57** in 46% yield.[26]

Ring-closure techniques have also featured in the literature for the preparation of 1,3,6,7-tetrahydro[2*H*]azepin-2-ones. Cationic alkene cyclisation of the sulphoxide **58** with trifluoroacetic anhydride gave a mixture of saturated azepinones as well as the 1,3,6,7-tetrahydro product **60** (R = CH_3), which was isolated by chromatography.[27] Similarly, the chlorinated methylthio derivative **59** on treatment with $SnCl_4$ gave the lactam **60** (R = H).[27] A mechanism for the ring closure of the Pummerer intermediates **61** (R = H, CH_3) was discussed.



(58)



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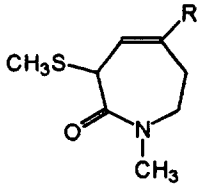

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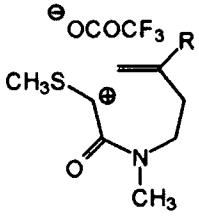
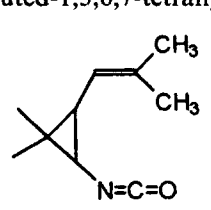
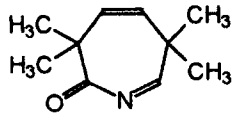


(61)

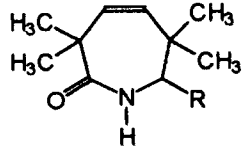
The Cope rearrangement of *cis*-2,2-dimethyl-3-isobutenylcyclopentyl isocyanate (**62**) under forcing conditions (at 144 °C) gave the 3,6-dihydro-3,3,6,6-tetramethyl[2*H*]azepin-2-one **63**, which in turn was converted with water, methanol and thiophenol, respectively, to give the corresponding 7-substituted-1,3,6,7-tetrahydro-3,3,6,6-tetramethyl[2*H*]azepin-2-ones **64** (R = OH,



(62)



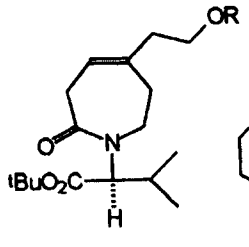
(63)



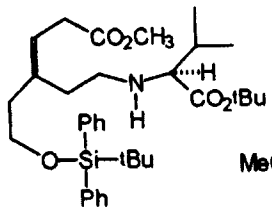
(64)

OCH_3, SPh).[28,29] Catalytic hydrogenation of **63** with Adam's catalyst reduced the 1,7-double bond, yielding 1,3,6,7-tetrahydro-3,3,6,6-tetramethyl[2*H*]azepin-2-one **64** (R = H).[28,29]

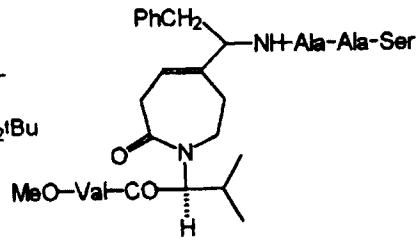
More recently, as part of a study into inhibitors of HIV-1 protease, the 1,3,6,7-tetrahydro[2*H*]azepin-2-one **64A** (R = $SiPh_2{}^tBu$) was prepared by hydrolysis of the ester **64B** followed by ring closure using DPPA. Further elaboration of the deprotected azepine **64A** (R = H) led to the peptidomimetic azepine **64C**.[30a] In a similar manner, ring closure of the ester **64D** led to the 1,3,6,7-tetrahydro-tetramethyl[2*H*]azepin-2-one **64E**, which was also elaborated to several peptidomimetic azepines for testing as potential inhibitors of HIV-1 protease.[30a]



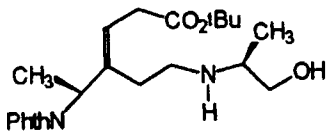
(64A)



(64B)



(64C)



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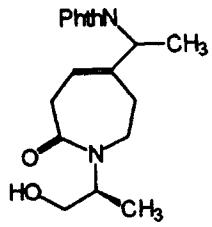


(64E)

A full listing of the published 1,3,6,7-tetrahydro-tetramethyl[2*H*]azepin-2-ones is given in Table 3.

Table 3. 1,3,6,7-Tetrahydro[2*H*]azepin-2-ones

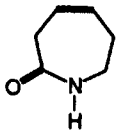
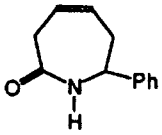
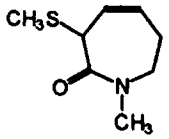
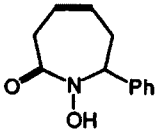
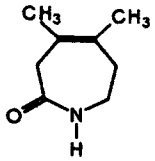
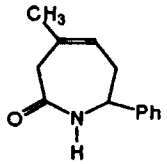
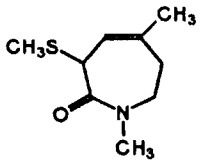
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	79	IR, ^{1}H NMR ^{1}H NMR	22 23
		IR, ^{1}H NMR	24
	Oil	IR, MS, ^{1}H NMR	27
		IR, MS, ^{1}H NMR	26
	109–111	IR, MS, ^{1}H, ^{13}C NMR	25
		IR, ^{1}H NMR	24
		IR, ^{1}H NMR	27

Table 3 (continued)

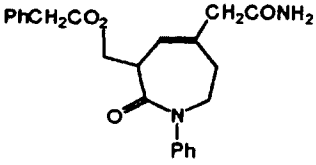
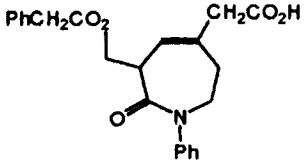
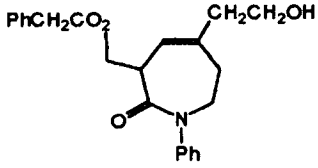
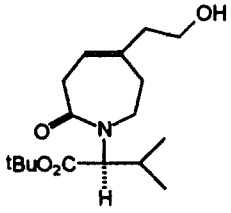
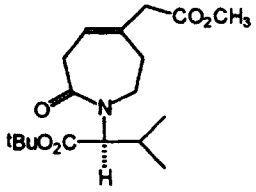
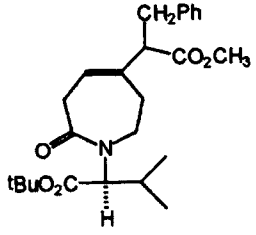
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
			30b
			30b
			30b
		^{1}H NMR	30a
		^{1}H NMR	30a
		^{1}H NMR	30a

Table 3 (continued)

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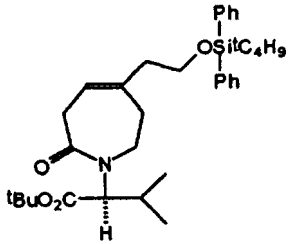
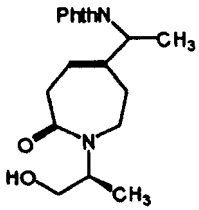
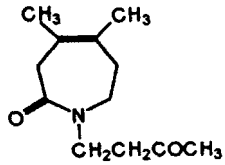
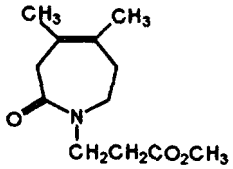
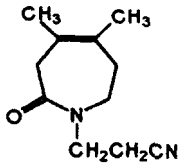
		^{1}H NMR	30a
		^{1}H NMR	30a
	14–115	IR, MS, ^{1}H, ^{13}C NMR	25
		IR, MS, ^{1}H, ^{13}C NMR	25
		IR, MS, ^{1}H, ^{13}C NMR	25

Table 3 (continued)

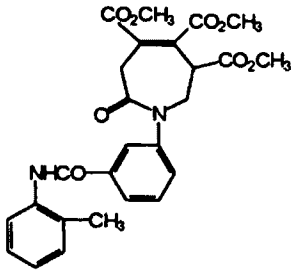
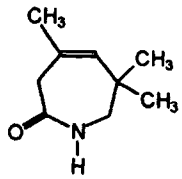
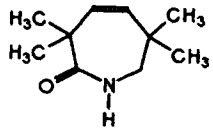
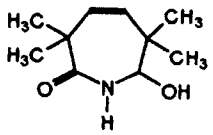
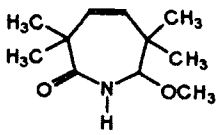
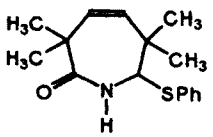
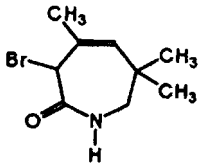
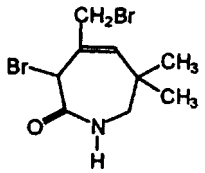
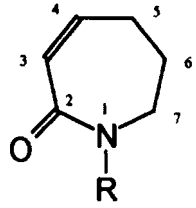
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	239–242	IR, MS, ^{1}H NMR	32
	147–148	IR, MS, ^{1}H NMR	31
	113–114	IR, UV, ^{1}H NMR	28, 29
	144	IR, UV, ^{1}H NMR	28, 29
	Oil	IR, ^{1}H NMR	28, 29
	102–103	IR, ^{1}H NMR	28, 29

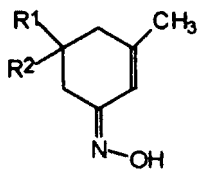
Table 3 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
		^{1}H NMR	31
		^{1}H NMR	31

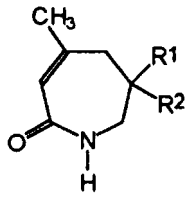
IV. 1,5,6,7-TETRAHYDRO[2*H*]AZEPIN-2-ONES



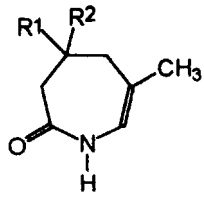
As early as 1952 it was recognised that Beckmann rearrangement of *syn*-oximes, such as **65** ($R^1 = H$, $R^2 = CH_3$)[33] and **65** ($R^1 = H$, $R^2 = Ph$ and $R^1 = R^2 = CH_3$)[2] led to 1,5,6,7-tetrahydro[2*H*]azepin-2-ones (**66**, $R^1 = H$, $R^2 = CH_3$, Ph and $R^1 = R^2 = CH_3$), whereas the corresponding *anti*-oximes gave the 1,3,4,5-tetrahydro[2*H*]azepin-2-ones **67** ($R^1 = H$, $R^2 = Ph$ and $R^1 = R^2 = CH_3$)[2] (see Section I for details). Later many other workers exploited this reaction to give the monomethyl derivative **66** ($R^1 = R^2 = H$),[4] the trimethyl derivative **66** ($R^1 = R^2 = CH_3$)[3,5,34–36] and the unsubstituted parent compound **68**.[1,37]



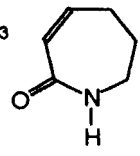
(65)



(66)



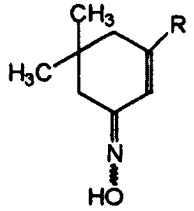
(67)



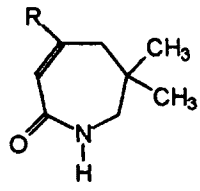
(68)

As discussed earlier (Section I) the mixed *syn*- and *anti*-oximes **10** (R = CH_3, C_2H_5, ^iPr, ^nBu, Ph, 4-nitrophenyl) gave both 1,5,6,7-tetrahydro and 1,3,4,5-tetrahydro isomers (**12** and **11**, respectively, where R = CH_3, C_2H_5, ^iPr, ^nBu, Ph, 4-nitrophenyl).[5]

Other derivatives prepared by this procedure included the 4-chloro derivatives **15** (R^1 = R^2 = H, CH_3 and R^1 = H, R^2 = CH_3)[38,5] and the acid **69**.[39]



(10)



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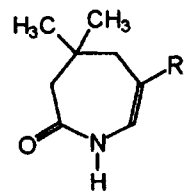

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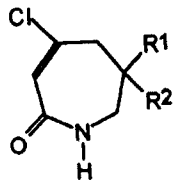

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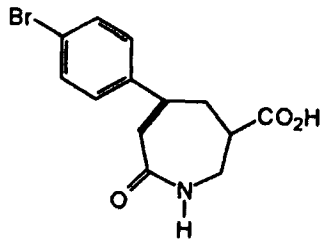
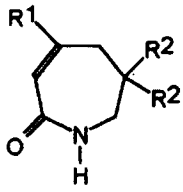
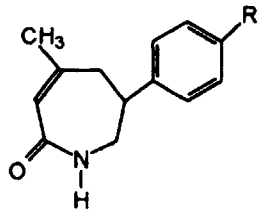


(69)

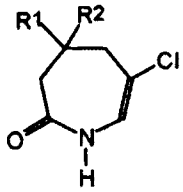
Ring expansion of appropriately substituted cyclohexenones using the Schmidt rearrangement has been used to give the 1,5,6,7-tetrahydro[2*H*]azepin-2-ones **15** (R^1 = R^2 = H, CH_3) and **70** (R^1 = H, CH_3, R^2 = H)[6,40] and the 6-aryl derivatives **71** (R = H, OCH_3, NO_2).[41] In the preparation of the 4-chloro derivatives **15** (R^1 = R^2 = H, CH_3), the isomeric 1,3,4,5-tetrahydro compounds **14** (R^1 = R^2 = H, CH_3) are also formed[6] (see also Section I).



(70)

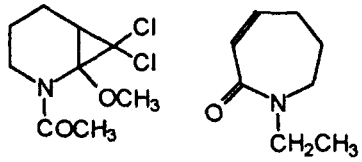


(71)



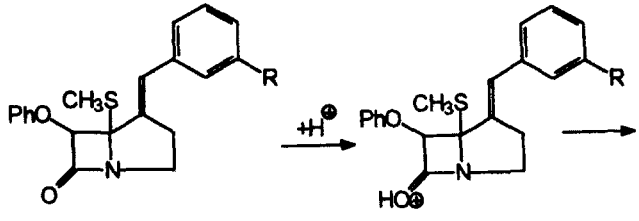
(14)

Treatment of the dichlorocarbene adduct **72** from piperidone with $LiAlH_4$ and base gave the expected ring expansion product **73**; however, the yield was poor (9%) and the method produced a number of substituted piperidone by-products, making isolation difficult.[42]

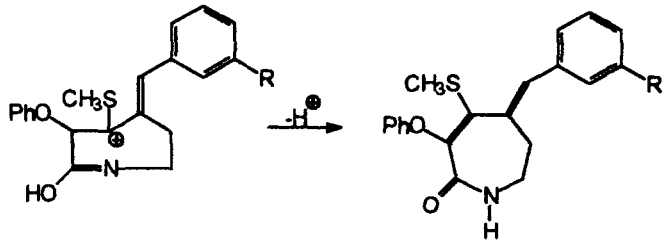


(72) **(73)**

The 5-methylthioazabicycloheptanes **74** (R = H, NO_2) underwent a rapid exothermic rearrangement on treatment with trifluoroacetic acid to give the corresponding 1,5,6,7-tetrahydro[2*H*]azepin-2-ones **77** (R = H, NO_2) in yields of over 90%,[43] illustrating how successful this approach can be. The proposed mechanism is protonation of the β-lactam carbonyl group to give the intermediate **75** (R = H, NO_2), followed by rearrangement to a carbocation **76** (R = H, NO_2) which loses a proton.[43]

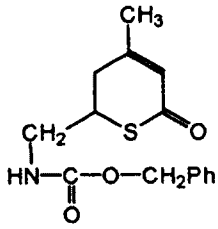


(74) **(75)**

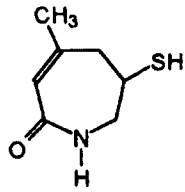


(76) **(77)**

The thiolactone **78**, on treatment with trimethylsilyl iodide, underwent an acyl transfer process from the S atom to the N atom, generating a new C–N bond as it lost the *N*-Boc protecting group and giving the tetrahydroazepinone **79**. The driving force was claimed to be the electrophilic character α to the sulphur atom.[44]

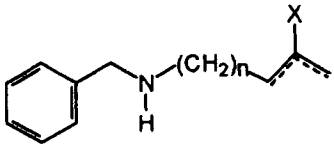


(78)

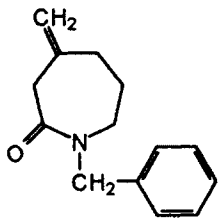


(79)

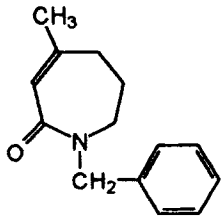
Palladium-catalysed carbonylation, using $Pd(OCOCH_3)_2$ and PPh_3 as catalyst, has been used as a general means of cyclising iodoalkylamines (**80**, $n = 1$–3; X = I, Br).[45] In the presence of $^nBu_3N$ and carbon monoxide, the products are five-, six- or seven-membered lactams, depending on the length of the alkyl chain. In the specific case of the alkylamine **80** ($n = 3$; X = I) the product consisted of a mixture of the two lactams **81** and **82**, from which the 1,5,6,7-tetrahydro[2*H*]azepin-2-one **82** was separated by chromatography in 23% yield.[45]



(80)

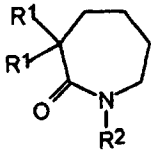


(81)

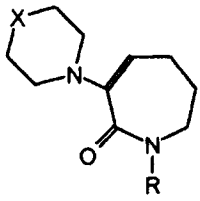


(82)

Elimination of halogen substituents from 3,3-dibromo- or 3,3-dichlorocaprolactams has been shown to be a useful method for the preparation of 3-substituted-1,5,6,7-tetrahydro[2*H*]azepin-2-ones. For example, treatment of 3,3-dichlorocaprolactam (**83**, R^1 = Cl, R^2 = H) with piperidine or morpholine gave the 3-piperidino and 3-morpholino derivatives **84** (R = H; X = CH_2, O).[46] Similar results were obtained on treatment of the *N*-methyl analogue **83** (R^1 = Cl, R^2 = CH_3) and the dibromo derivative **83** (R^1 = Br, R^2 = H) with piperidine, giving the corresponding products (**84**, R = CH_3, H; X = CH_2).[47,48]



(83)



(84)

A variety of elimination reactions has also been used to produce 3-substituted-1,5,6,7-tetrahydro[2*H*]azepin-2-ones;[22,49–51] full details of the products from these reactions, along with a number of other derivatives described in the literature,[52–57] are given in Table 4.

Table 4. 1,5,6,7-Tetrahydro[2*H*]azepin-2-ones

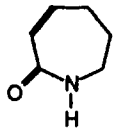
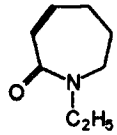
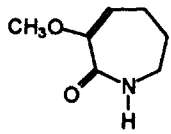
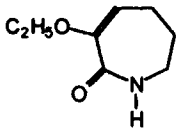
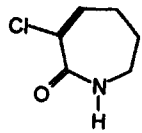
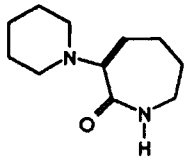
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	58; 138–140/2 Oil 60–65/0.5	IR, ^{1}H NMR	1 22 37 6, 23
	Oil	^{1}H NMR	42
	96–98; 133–140/0.1		49
	67–69; 112–113/0.04		49
	83	IR, MS, ^{1}H NMR	50
	156–158 158–160	IR, ^{13}C NMR	46 48

Table 4 (continued)

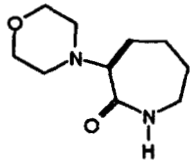
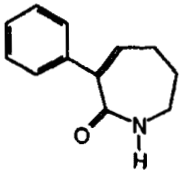
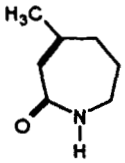
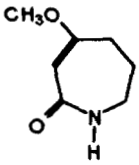
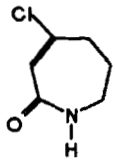
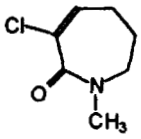
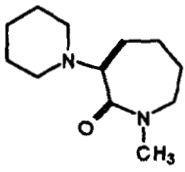
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	140–141		46
	138–139	IR, MS, ^{1}H, ^{13}C NMR	51
	81–82 Tosylate 142–143	IR, UV Tosylate IR, ^{1}H NMR	40 4
	70–72; 119–125/0.012	IR, UV, ^{1}H NMR	38
	128–129.5 128.5–129	 IR, ^{1}H NMR	6 38
	98/0.03	IR, ^{1}H NMR	50
	137–140/1–2	IR, UV	47

Table 4 (continued)

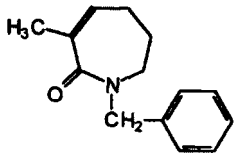
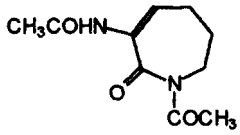
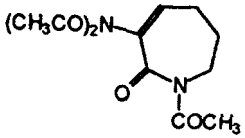
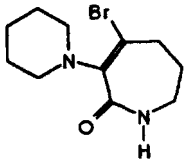
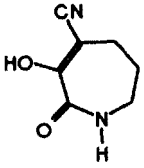
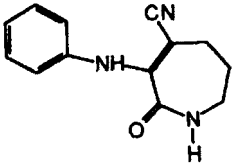
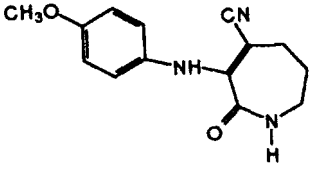
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	Oil	IR, MS, ^{1}H NMR	45
	128–131	^{1}H NMR	53
	106	^{1}H NMR	53
	120–121		56
	200–203	IR, UV, ^{1}H NMR	54
	240–243	IR, UV, ^{1}H NMR	54
	173–177	IR, UV, ^{1}H NMR	54

Table 4 (continued)

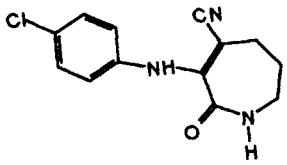
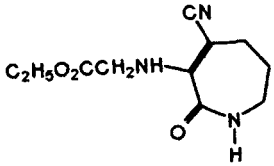
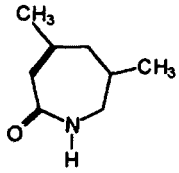
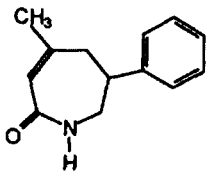
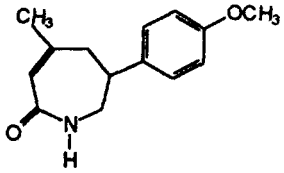
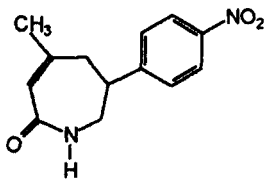
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	189–194	IR, UV, ^{1}H NMR	54
	102–104	IR, UV, ^{1}H NMR	57
	71–72.5 72.5–74.5	UV, IR	33 5
	146–146.6 142–146	UV IR, MS, ^{1}H NMR	2 41
	189–192	IR, MS, ^{1}H NMR	41
	200–202	IR, MS, ^{1}H NMR	41

Table 4 (continued)

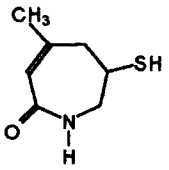
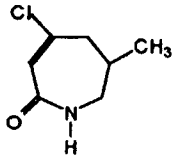
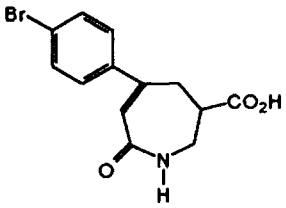
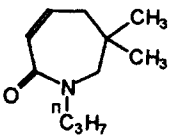
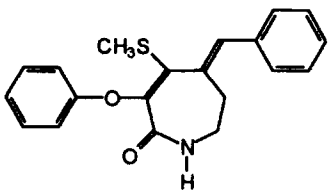
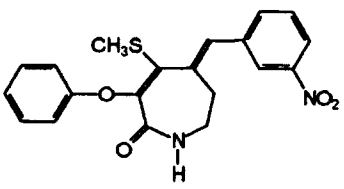
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	Oil	IR, ^{1}H NMR	44
	91–92	IR, ^{1}H NMR	5
	232	IR	39
			52
	193–195	IR, MS, ^{1}H NMR	43
	225–230	IR, ^{1}H NMR	43

Table 4 (continued)

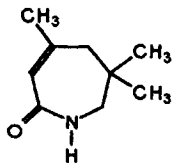
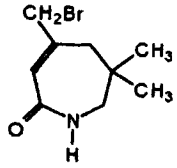
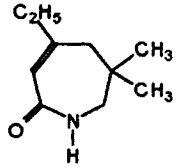
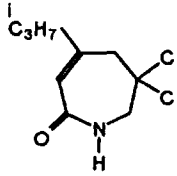
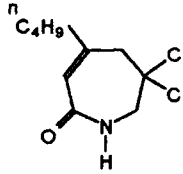
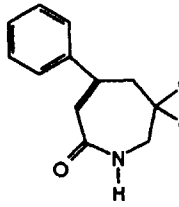
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	108.8–109.1 112–113 112–113	UV UV IR, ^{1}H NMR	2 3 34 5, 35, 36
		MS, ^{1}H NMR	31
	66.5	IR, MS, ^{1}H NMR	5
	108–110	IR, MS, ^{1}H NMR	5
	110/0.5	IR, MS, ^{1}H NMR	5
	163.5–164.5	IR, MS, ^{1}H NMR	5

Table 4 (continued)

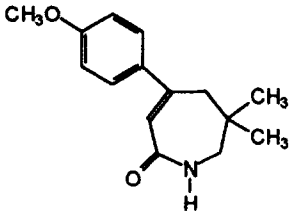
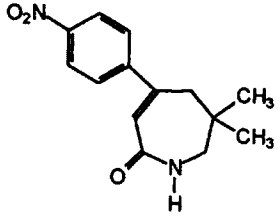
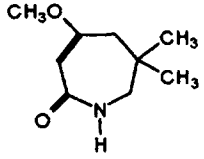
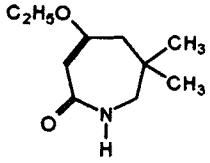
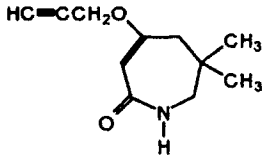
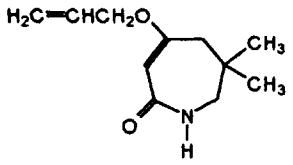
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	153–154	IR, MS, ^{1}H NMR	5
	191–202	IR, MS, ^{1}H NMR	5
	148–149	IR, ^{1}H NMR	41
	112–113 112–113	IR, ^{1}H NMR	41 23
	133.5–134	MS, IR, ^{1}H NMR	55
	83–84.5	IR, ^{1}H NMR	55

Table 4 (continued)

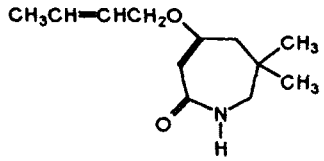
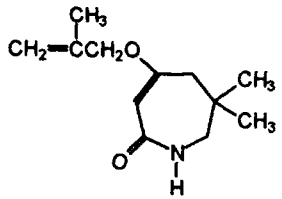
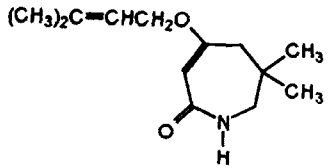
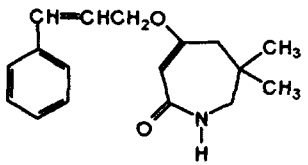
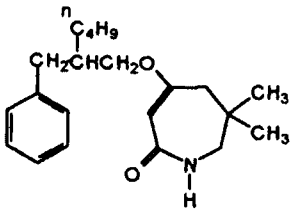
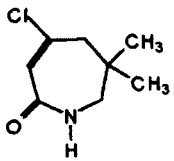
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	128–130	IR, ^{1}H NMR	55
	78–84	IR, ^{1}H NMR	55
	88–91	IR, ^{1}H NMR	55
	163–165	IR, ^{1}H NMR	55
	Oil	IR, MS, ^{1}H NMR	55
	84.5–85.5 84.5–85.5	IR, ^{1}H NMR	6 38 41, 55

Table 4 (continued)

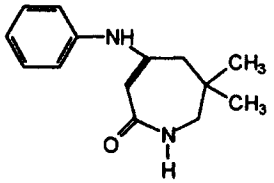
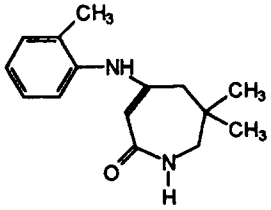
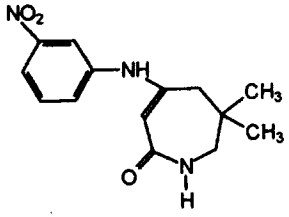
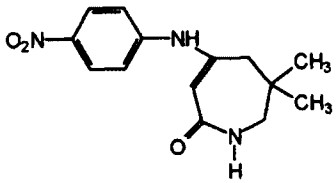
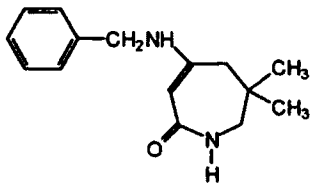
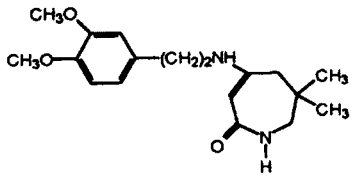
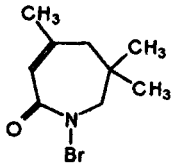
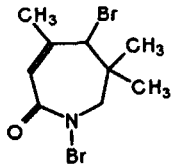
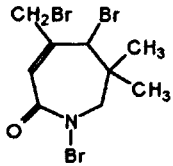
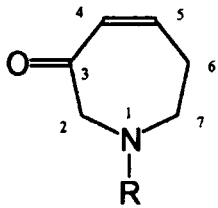
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	232		41
	227–228		41
	228–230		41
	42–243		41
	:06–297		41

Table 4 (continued)

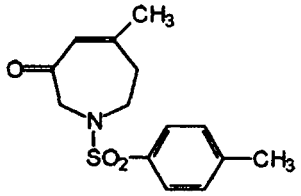
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	174–175		41
	Liquid	IR, ^{1}H NMR	31
	113	MS, ^{1}H NMR	31
	171- 173	MS, ^{1}H NMR	31

VIII. 1,2,6,7-TETRAHYDRO[3*H*]AZEPIN-3-ONES

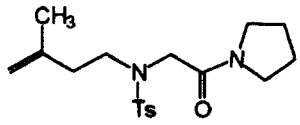


The single representative of this series to appear in the literature (**85**) was isolated as a by-product from the intramolecular [2 + 2] cycloaddition of the ketiminium salt **87** generated *in situ* from the α-*N*-tosylaminoamide **86**.[58] In general, this reaction leads to azabicyclic ketones, but in this specific case

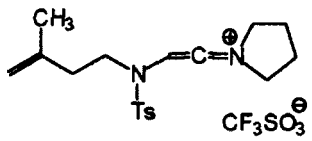
treatment of **87** with trifluoroacetic anhydride gave the azabicyclic ketone **88** in 71% yield, along with 7% of 1-tosyl-5-methyl-1,2,6,7-tetrahydro[3*H*]azepin-3-one (**85**). Characterisation of the by-product **85** was claimed by IR, ^{1}H, ^{13}C NMR, MS, and elemental analysis, but unfortunately no physical data were quoted in the publication.[58]



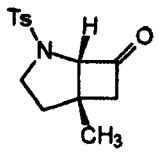
(85)



(86)

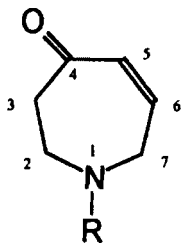


(87)



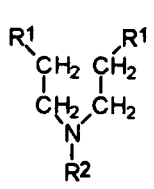
(88)

XII. 1,2,3,7-TETRAHYDRO[4*H*]AZEPIN-4-ONES

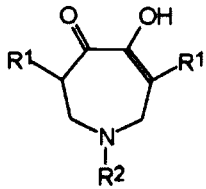


The preparation of the 1,2,3,7-tetrahydro[4*H*]azepin-4-one **90** (R^1 = CN; R^2 = H) was claimed in 1961 from the reaction of the β,β'-iminodipropionic acid dinitrile **89** (R^1 = CN, R^2 = H) with ethyl oxalate in the presence of sodium ethoxide,[59] but the structural assignment of the product was erroneous and was subsequently shown to be the corresponding pyrroline (**91**).[60] The other tetrahydro[4*H*]azepin-4-one derivatives **90** (R^1 = CO_2CH_3, R^2 = H; R^1 = CN, R^2 = $COCH_3$) claimed in the earlier paper,[59] therefore, by analogy are all wrongly assigned and consequently will not be discussed further.

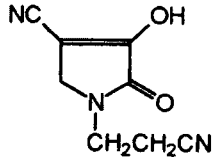
The only genuine preparation of a 1,2,3,7-tetrahydro[4*H*]azepin-4-one was achieved by an intramolecular Friedel–Crafts cyclisation, at room temperature, of the readily accessible 3-[*N*-(2-chloroprop-2-enyl)propanoic acid **92**



(89)

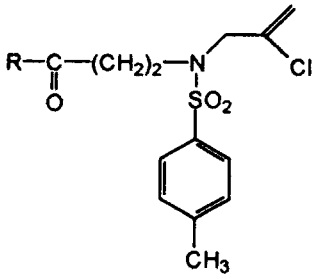


(90)

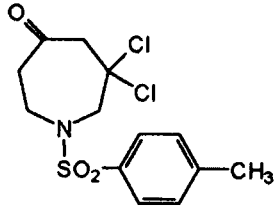


(91)

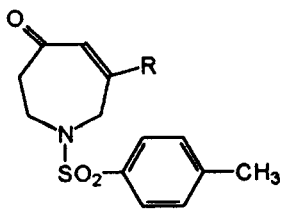
(R = OH) via the acid chloride **92** (R = Cl) to give 6,6-dichloro-*N*-tosylazepan-4-one **93**.[61] Compound **93** was converted into the 6-chloro- and 6-methoxy-1,2,3,7-tetrahydro[4*H*]azepin-4-ones **94** (R = Cl, OCH_3) on treatment with sodium carbonate in aqueous tetrahydrofuran and in methanol, respectively.[61]



(92)



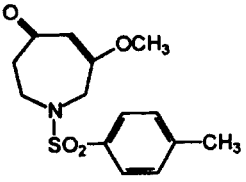
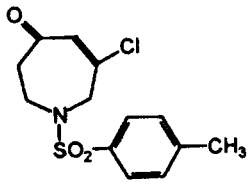
(93)



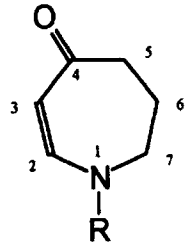
(94)

The two derivatives characterised[61] are given in Table 5.

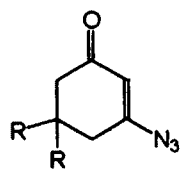
Table 5. 1,2,3,7-Tetrahydro[4*H*]azepin-4-ones

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	122–123	MS, IR, ^{1}H NMR	61
	98	IR, ^{1}H NMR	61

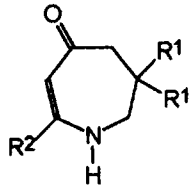
XIII. 1,5,6,7-TETRAHYDRO[4*H*]AZEPIN-4-ONES



Methods for the preparation of 1,5,6,7-tetrahydro[4*H*]azepin-4-ones are based on ring-expansion procedures. For example, Curtius rearrangement of the azides **95** (R = H, CH_3) in the presence of methanol[62] or ethanol[62,63] led to the corresponding 2-substituted-1,5,6,7-tetrahydro[4*H*]azepin-4-ones **96** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5), whereas with benzene as the solvent, rearrangement resulted in the formation of the diones **97** (R = H, CH_3). In the presence of aniline, the Curtius reaction on the azide **95** (R = CH_3) led to the amine **96** (R^1 = CH_3; R^2 = NHPh).[63] The ketones **96** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5) existed in solution in equilibrium with the tautomeric 3,5,6,7-tetrahydro[4*H*]azepin-4-ones **98** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5)[62,63] (see Section XV).



(95)



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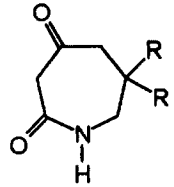

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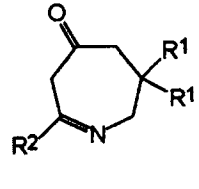
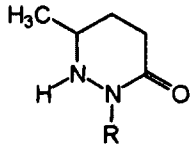


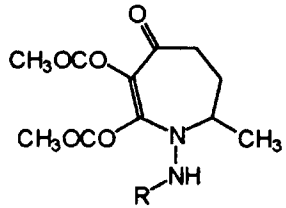
(98)

A possible mechanism for the conversion of vinyl azides such as **95** (R = H) into the corresponding tetrahydroazepines **96** (R^1 = H, R^2 = OCH_3) and **98** (R^1 = H, R^2 = OCH_3) has been proposed.[64]

In an unusual ring-expansion/rearrangement reaction, the 6-methyltetrahydropyridazin-3-ones **99** (R = Ph, cyclohexyl), on treatment with dimethyl



(99)

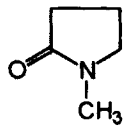


(100)

acetylenedicarboxylate, yielded the corresponding 1-anilino- and 1-cyclohexylamino-1,5,6,7-tetrahydro[4*H*]azepin-4-ones **100** (R = Ph, cyclohexyl).[65]

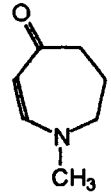
It was postulated that the reaction might have occurred through a Michael addition of the secondary amine group of the pyridazinone to the dimethyl acetylenedicarboxylate, followed by attack of a carbanion on the carbonyl group to give a bicyclic intermediate which in turn underwent ring opening to give the product. No simple Michael addition products were observed, however.[65]

A two-carbon homologation of *N*-methylpyrrolidone (**101**) using lithium triphenylsilylacetylide (**102**) led to 1-methyl-1,5,6,7-tetrahydro[4*H*]azepin-4-one (**103**) in a yield of 70%.[66] The method is of broad application and has been used for the preparation of eight- and nine-membered rings and for the azepine ring system.[66]



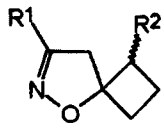
(101)

(102)



(103)

Flash vacuum thermolysis of 4,5-dihydroisoxazole-5-spirocyclobutanes (**104**, $R^1 = CH_3$, Ph; $R^2 = H$) induced rearrangement to produce 2-substituted-1,5,6,7-tetrahydro[4*H*]azepin-4-ones (**105**, R = CH_3, Ph) as the main products.[67,68] The reaction has the disadvantage that it also produces 1-alkenylpyrrolidin-2-ones (**106**, R = CH_3, Ph) as by-products, and requires severe conditions (700 °C) to obtain the best results. Under the same conditions the benzyl-substituted isoxazole **104** ($R^1 = CH_3$, $R^2 = CH_2Ph$) gave a mixture of the 7- and 5-benzyl-1-methyl-1,5,6,7-tetrahydro[4*H*]azepin-4-ones **107** ($R^1 = CH_2Ph$, $R^2 = H$ and $R^1 = H$, $R^2 = CH_2Ph$) in poor yields.[68]



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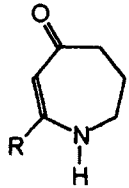

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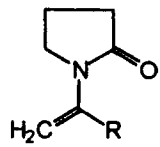
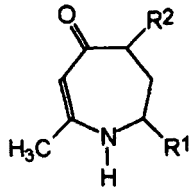
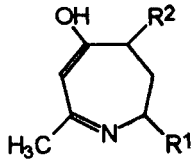


(106)

On prolonged standing at room temperature, the 2-methyl derivatives **105** (R = CH_3) and **107** ($R^1 = CH_2Ph$, $R^2 = H$ and $R^1 = H$, $R^2 = CH_2Ph$) rearranged to the corresponding azadienols **108** ($R^1 = R^2 = H$; $R^1 = CH_2Ph$, $R^2 = H$; $R^1 = H$, $R^2 = CH_2Ph$).[68]



(107)



(108)

A list of 1,5,6,7-tetrahydro[4*H*]azepin-4-ones reported in the literature is given in Table 6.

Table 6. 1,5,6,7-Tetrahydro[4*H*]azepin-4-ones

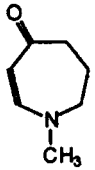
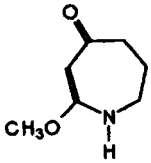
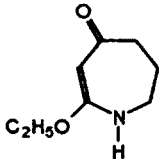
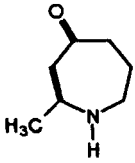
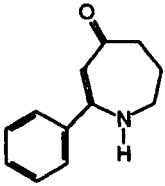
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	81.5–82	IR, MS, ^{1}H, ^{13}C NMR	66
	90–91	IR, UV, ^{1}H NMR	63 62, 64
	78–78.5	IR, UV, ^{1}H NMR	63
	87–88	^{1}H, ^{13}C NMR IR, MS, ^{1}H, ^{13}C NMR	67 68
	144–146	^{1}H, ^{13}C NMR IR, MS, ^{1}H, ^{13}C NMR	67 68

Table 6 (continued)

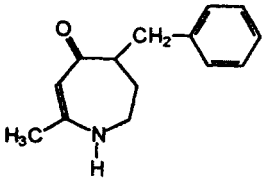
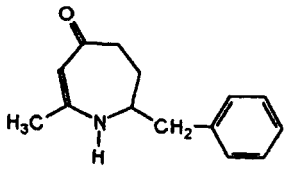
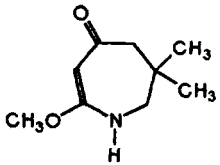
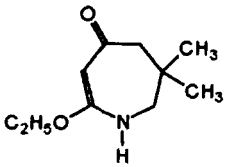
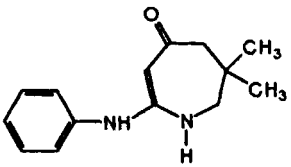
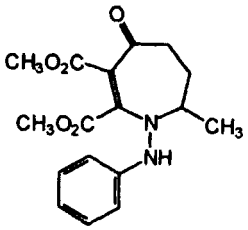
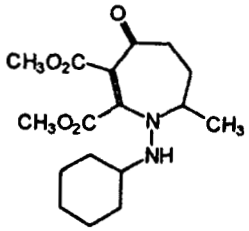
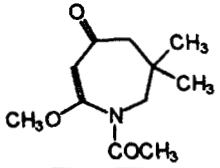
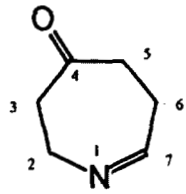
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
		IR, MS, ^{1}H, ^{13}C NMR	68
		IR, MS, ^{1}H, ^{13}C NMR	68
	146–146.5	IR, UV, MS, ^{1}H NMR	63 62
	127.5- 128.5	IR, UV, ^{1}H NMR	63
	214–214.5	IR, UV, ^{1}H NMR	63
	177–178	IR, MS, ^{1}H NMR	65

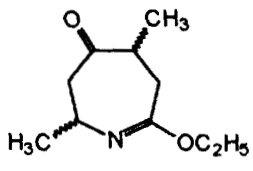
Table 6 (continued)

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	126–127	IR, MS, ^{1}H NMR	65
	82.5–83	IR, UV, ^{1}H NMR	63

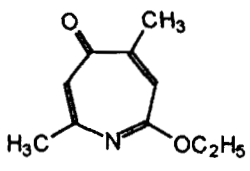
XIV. 2,3,5,6-TETRAHYDRO[4*H*]AZEPIN-4-ONES



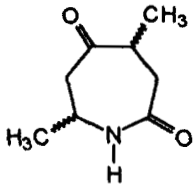
There is only one reference[69] in the literature to 2,3,5,6-tetrahydro[4*H*]azepin-4-ones and only the 2,5-dimethyl-7-ethoxy derivative (**109**) is described. The compound was prepared as an epimeric mixture at C-2 and C-5, either by hydrogenation of the azatropone **110** or by alkylation of the azepane-2,5-dione **111** with triethyloxonium fluoborate. Compound **109** is an oil (b.p. 42/0.2 mmHg), the structure of which was confirmed by IR and ^{1}H NMR spectra and elemental analysis.[69]



(109)

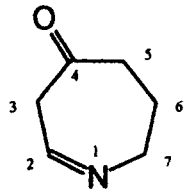


(110)

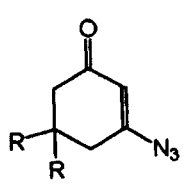


(111)

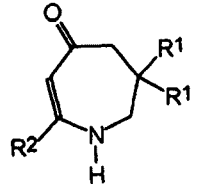
XV. 3,5,6,7-TETRAHYDRO[4*H*]AZEPIN-4-ONES



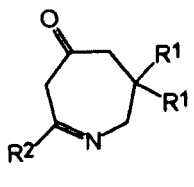
The only reference to the preparation of derivatives of 3,5,6,7-tetrahydro[4*H*]azepin-4-one is to the enol ethers **98** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5),[62] which were formed by a Curtius reaction in methanol or ethanol on the azides **95** (R = H, CH_3). The 3,5,6,7-tetrahydro[4*H*]azepin-4-ones **98** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5) exist as the minor tautomers in solution along with the major tautomeric 1,5,6,7-tetrahydro[4*H*]azepin-4-ones **96** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5) (see Section XIII). The existence of the compounds **98** (R^1 = H, CH_3; R^2 = OCH_3, OC_2H_5) was demonstrated by



(95)



(96)



(98)

examination of their ^{1}H NMR spectra, but they have not been isolated in a pure state.[62]

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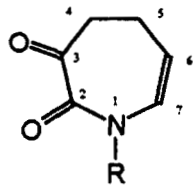
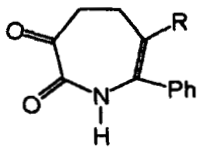
CHAPTER 7

Tetrahydroazepinediones

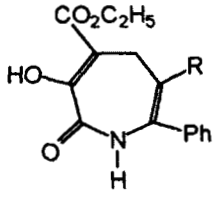
I. 2,3,4,5-TETRAHYDRO[1*H*]AZEPINE-2,3-DIONES



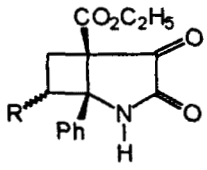
The preparation of the 7-phenyl derivatives **1** (R = Ph, OC_2H_5, $OCOCH_3$, H), the sole representatives of the 2,3,4,5-tetrahydro[1*H*]azepine-2,3-diones, was achieved by de-ethoxycarbonylation of the dihydroazatropolones **2** (R = Ph, OC_2H_5, $OCOCH_3$, H), which in turn were prepared by base-catalysed ring expansion of the photoadducts **3** (R = β-Ph, α-OC_2H_5, α-$OCOCH_3$, H) formed from the olefins **4** (R = Ph, OC_2H_5, $OCOCH_3$, H) and the dioxopyrroline **5**.[1] The products were obtained in yields of 63–65% from **2**. Direct de-ethoxycarbonylation of the diphenyl adduct **3** (R = β-Ph) also produced the



(1)

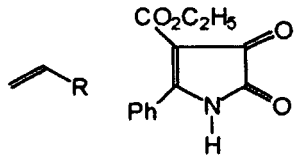


(2)



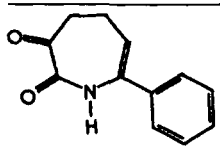
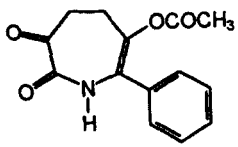
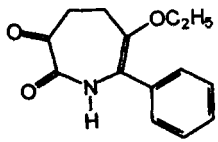
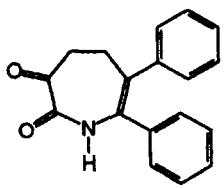
(3)

6,7-diphenyl-2,3,4,5-tetrahydro[1*H*]azepine-dione **1** (R = Ph) in a yield of 31% from **3**. Details of the compounds are listed in Table 1.

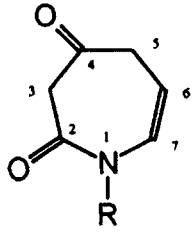


(4) **(5)**

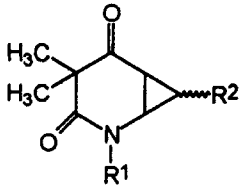
Table 1. 2,3,4,5-Tetrahydro[1*H*]azepine-2,3-diones

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	162–164	IR, UV, MS, ^{1}H NMR	1
	101–103	IR, UV, MS, ^{1}H NMR	1
	121–126	IR, UV, MS, ^{1}H NMR	1
	204–208	IR, UV, MS, ^{1}H NMR	1

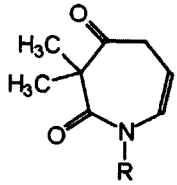
V. 2,3,4,5-TETRAHYDRO[1*H*]AZEPINE-2,4-DIONES



Irradiation of the azabicycloheptane-3,5-diones **6** ($R^1 = CH_3$, CH_2Ph; $R^2 = H$) using a high-pressure mercury lamp gave the corresponding 2,3,4,5-tetrahydro[1*H*]azepine-2,4-diones **7** ($R = CH_3$, CH_2Ph) by a cyclopropane ring-opening mechanism in yields of 47% and 34%, respectively.[2] The reaction, however, is limited in that the corresponding 7-phenylazabicycloheptane-3,5-diones **6** ($R^1 = CH_3$, CH_2Ph; $R^2 = Ph$), on irradiation, led to complex mixtures from which no ring expansion products could be isolated.[2]



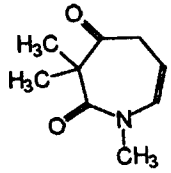
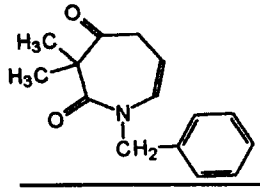
(6)



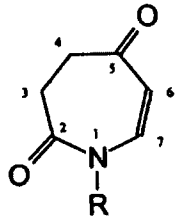
(7)

The physical data for the two products (**7**, $R = CH_3$, CH_2Ph), the only representatives of the 2,3,4,5-tetrahydro[1*H*]azepine-2,4-diones in the literature, are listed in Table 2.

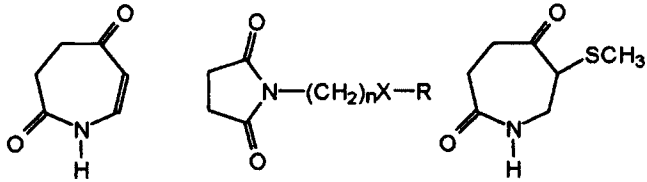
Table 2. 2,3,4,5-Tetrahydro[1*H*]azepine-2,4-diones

Structure	B.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	140/13	IR, MS, ^{1}H NMR	2
	170/0.3	IR, MS, ^{1}H NMR	2

VIII. 2,3,4,5-TETRAHYDRO[1*H*]AZEPINE-2,5-DIONES

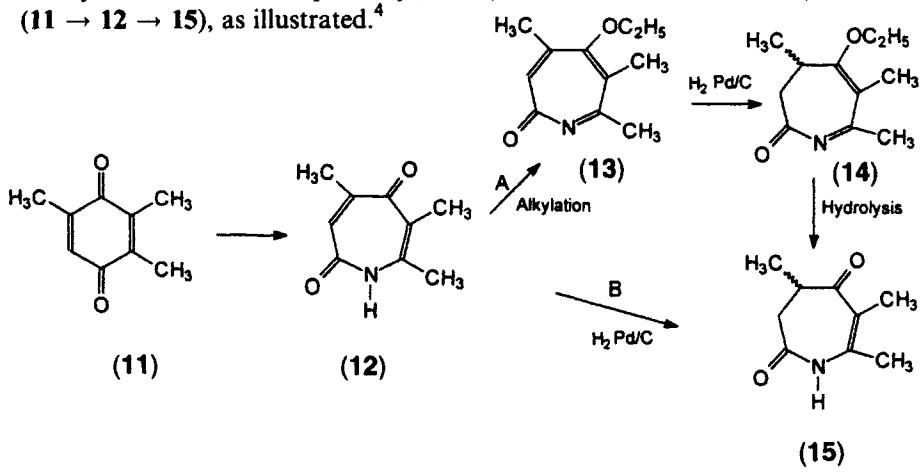


The unsubstituted parent compound (**8**) in this series was isolated in the course of a study on the photolysis of *N*-alkylthioalkyl- and *N*-alkoxyalkylsuccinimides (**9**, $n = 1$–3, X = S, R = CH_3; $n = 1$, X = O, R = alkyl).[3] Whereas the ethers **9** ($n = 1$, X = O, R = alkyl) gave bicyclic products on irradiation, the thioether **9** ($n = 1$, X = S, R = CH_3) failed to react and the thioethers **9** ($n = 2$–3, X = S, R = CH_3) gave ring-expanded products. The 2,3,4,5-tetrahydro[1*H*]azepine-2,5-dione **8** was formed from the thioether **9** ($n = 2$, X = S, R = CH_3) but was only isolated in a 3% yield. A similar yield of the saturated azepanedione **10** was also isolated from the same reaction.[3]



(**8**) (**9**) (**10**)

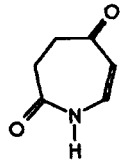
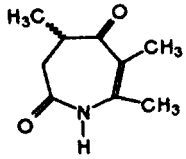
The only other representative of this series, 4,6,7-trimethyl-2,3,4,5-tetrahydro[1*H*]azepine-2,5-dione (**15**), has been prepared from the benzoquinone **11** by two alternative pathways, A (**11** → **12** → **13** → **14** → **15**) and B (**11** → **12** → **15**), as illustrated.[4]



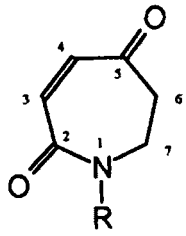
(**11**) (**12**) (**13**) (**14**) (**15**)

The ring expansion of the benzoquinone **11** was achieved by a Schmidt reaction, and the alkylation reaction was performed using triethyloxonium fluoborate. Pathway B represents the most efficient route to **15**, but pathway A was investigated in order to examine spectroscopically the intermediates (**13** and **14**) which differed from their corresponding 4,7-dimethyl analogues in that the 2-ketone in the 4,7-dimethyl analogue of **12** formed an enol ether rather than the 5-ketone as in **13**.[4] Table 3 gives the data on the two known 2,3,4,5-tetrahydro[1*H*]azepine-2,5-diones.

Table 3. 2,3,4,5-Tetrahydro[1*H*]azepine-2,5-diones

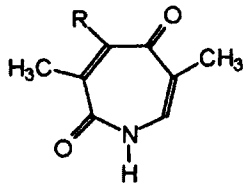
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	155–157	IR, UV, MS, ^{1}H NMR	3
	101–102	IR, UV, ^{1}H NMR	4

IX. 2,5,6,7-Tetrahydro[1*H*]azepine-2,5-diones

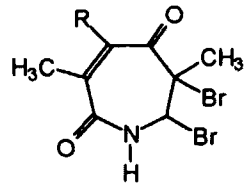


Misiti *et al.*[5] claimed that treatment of the 2,5-dihydro[1*H*]azepine-2,5-diones **16** (R = H, CH_3) with bromine gave the bromo-2,5,6,7-tetrahydro[1*H*]azepine-2,5-dione derivatives **17** (R = Br, CH_3, CH_2Br). A subsequent publication by Rickards and Smith,[6] however, demonstrated that Misiti *et al.*'s 2,5-dihydro[1*H*]azepine-2,5-diones **16** (R = H, CH_3) had been assigned the wrong structures, and were the 2,5-dihydro[1*H*]azepine-2,5-diones **18** (R = H, CH_3) (see also Chapter 10, Section V). This correction invalidates the originally

proposed structures for the two bromo compounds (**17**, R = Br, CH_3) and, in the absence of further evidence, the existence of 2,5,6,7-tetrahydro[1*H*]azepine-2,5-diones must be considered doubtful since no other analogues have been reported.



(16)



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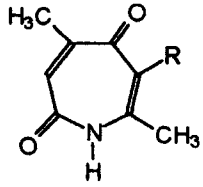
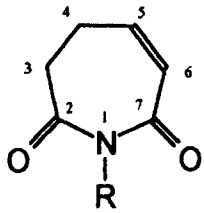
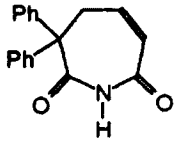


(18)

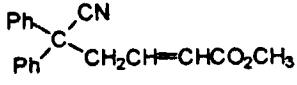
XIV. 2,3,4,7-TETRAHYDRO[1*H*]AZEPINE-2,7-DIONES



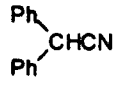
The 3,3-diphenyl-2,3,4,7-tetrahydro[1*H*]azepine-2,7-dione **19** was prepared by cyclisation of the nitrile ester **20**, which in turn was synthesised from diphenylacetonitrile (**21**) and the methyl ester of γ-bromocrotonic acid (**22**) in the presence of sodamide. The ring-closure reaction to **19** was carried out by hydrolysing the nitrile ester **20** with aqueous methanol and completing the cyclisation of the nitrile acid with sulphuric acid. The product (**19**) was prepared for comparison with the corresponding tetrahydropyridine and no other azepine derivatives were synthesised by this procedure.[7]



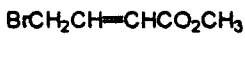
(19)



(20)



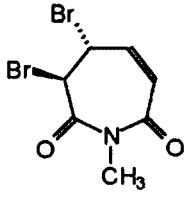
(21)



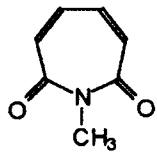
(22)

The *trans*-3,4-dibromo-2,3,4,7-tetrahydro[1*H*]azepine-2,7-dione **23** was prepared by the action of bromine on 1-methylazepine-2,7-dione (**24**). ^{1}H NMR

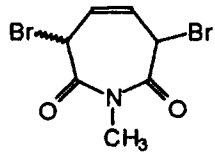
and IR spectroscopy demonstrated that the dibromo compound was the 1,2-addition product (**23**) rather than the 1,4-addition product (**25**).[8] The physical data are presented in Table 4.



(**23**)

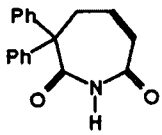
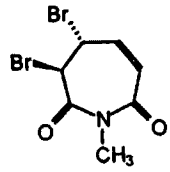


(**24**)

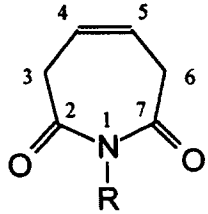


(**25**)

Table 4. 2,3,4,7-Tetrahydro[1*H*]azepine-2,7-diones

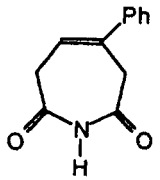
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	173		7
	78–79	IR, UV, ^{1}H NMR	8

XV. 2,3,6,7-TETRAHYDRO[1*H*]AZEPINE-2,7-DIONES

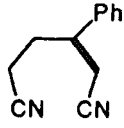


The only compound reported in this series is 4-phenyl-2,3,6,7-tetrahydro[1*H*]azepine-2,7-dione (**26**), which was prepared by cyclisation of the dinitrile **27** to 2-amino-7-bromo-5-phenyl[3*H*]azepine hydrobromide (**28**) using anhydrous hydrogen bromide, followed by hydrolysis using aqueous

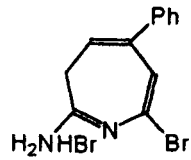
dimethylformamide.[9] The product (**26**) melted at 157–158 °C and had IR and ^{1}H NMR spectra consistent with the structure proposed.



(**26**)

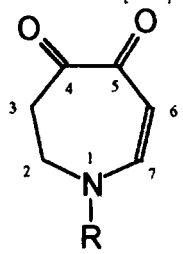


(**27**)

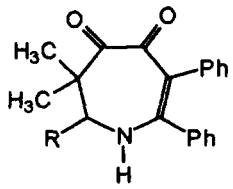


(**28**)

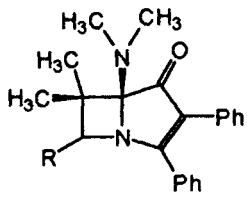
XXIII. 2,3,4,5-TETRAHYDRO[1*H*]AZEPINE-4,5-DIONES



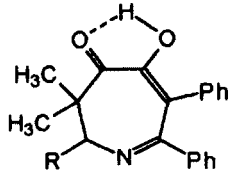
There are only two representatives of the 2,3,4,5-tetrahydro[1*H*]azepine-4,5-diones in the literature, the 6,7-diphenyl-3,3-dimethyl-substituted derivative **29** (R = H) and the 2,6,7-triphenyl-3,3-dimethyl analogue **29** (R = Ph).[10]



(**29**)



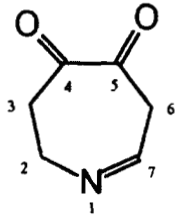
(**30**)



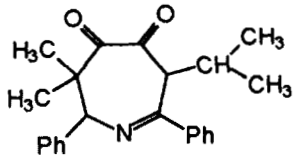
(**31**)

The diphenyl compound **29** (R = H) was prepared along with its enol tautomer **31** (R = H) by hydrolysis of the azeto[1,2a]pyrrole **30** (R = H). A yield of 30% was achieved using 2M HCl in ethanol at room temperature. By contrast, the 2,6,7-triphenyl-*endo*-azeto[1,2a]pyrrole **30** (R = Ph) produced only the enol tautomer **31** (R = Ph) under the same conditions, but gave a 10% yield of the 2,5-dione tautomer **29** (R = Ph) under milder hydrolysis conditions using silica.[10] The structure of the 2,6,7-triphenyl compound **29** (R = Ph), m.p. 214 °C, was confirmed by its IR, ^{1}H, and ^{13}C NMR spectra, but no data were quoted in the publication for the 6,7-diphenyl analogue **29** (R = H).[10]

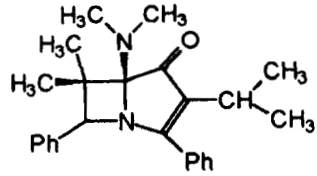
XXIV. 3,4,5,6-TETRAHYDRO[2*H*]AZEPINE-4,5-DIONES



The 2,7-diphenyl-6-isopropyl-3,3-dimethyl-substituted derivative **32** is the only representative of this series. It was prepared from the azeto[1,2a]pyrrole **33** in the same manner as the related derivatives **29** described above.[10] In this case a yield of 95% was achieved and no other tautomers were formed. The product (**32**) melted at 165–166 °C and was characterised by its IR, ^{1}H and ^{13}C NMR spectra.



(**32**)



(**33**)

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George R. Proctor, James Redpath
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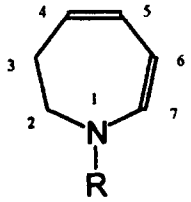
CHAPTER 8

Dihydroazepines

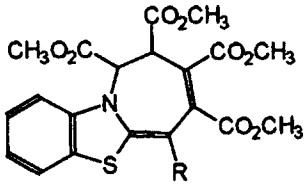
I. 2,3-DIHYDRO[1*H*]AZEPINES



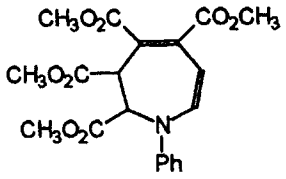
PREPARATION

This group of compounds is fairly well represented in the literature, their apparent stability presumably being attributable to the conjugated dienamine structure therein. Many of the syntheses reported for 2,3-dihydro[1*H*]azepines involve ring expansions of either five- or six-membered ring compounds.

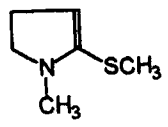
One of the earliest and most ingenious approaches involved the double cycloaddition of dimethyl acetylenedicarboxylate (DMAD) with 2-alkylbenzothiazoles. Thus the initial adduct **1** (R = H) was desulphurised by Raney nickel



(1)



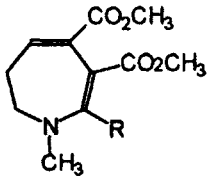
(2)



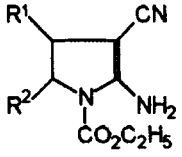
(3)

yielding the *N*-phenyldihydroazepine **2**. Although desulphurisation of the adduct **1** (R = CH_3) was not reported, there seems little doubt that this could be successfully achieved.[1]

Ring expansion of various pyrrole derivatives has been a popular strategy. 2-Methylthio-1-methyl-2-pyrroline (**3**), but not the corresponding dimethylacetal, reacted easily with DMAD yielding the dihydroazepine **4** (R = SMe), along with other products.[2] This work has been repeated and extended[3] by desulphurisation to give **4** (R = H), and it was inferred that if *N*-acylpyrrolines were employed, reduced enamine activity caused the reaction to stop at the [2 + 2] cycloaddition stage; such intermediates were isolated from the higher homologues of **3**.[3]



(4)



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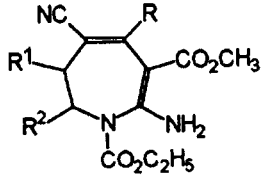

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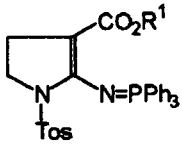
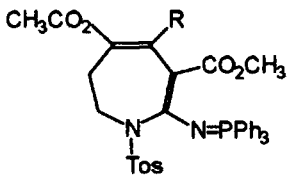


(7)

In similar fashion, *N*-acylpyrrolines (**5**) carrying an amino group underwent cycloaddition/ring expansion with DMAD and, less efficiently, with methyl propiolate.[4] Better yields of products **6** (R = H, CO_2Me) were obtained after relatively short reaction times in DMSO rather than xylene. The iminophosphoranes **7** also underwent acetylenic ester ring expansions in good yields, giving **8** (R = H, CO_2Me, CO_2Et).[5] The latter were shown to react with DMAD yielding ultimately indole derivatives by ring expansion to azonine



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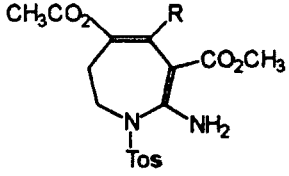
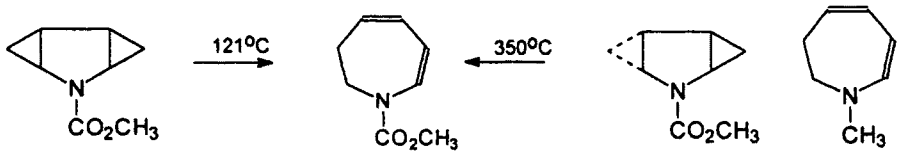


(9)

compounds, followed by ring collapse.[6] Acid treatment of **8** gives the free amino compounds **9**; detailed spectroscopic details for all dihydroazepines were provided.[5,6] It has been shown that the iminophosphoranes **8** react with isocyanates to produce pyrimido[4,5-*b*] azepines;[7] this usefully complements the already available methods.[8]

It was demonstrated in 1973[9] that 2,3-dihydro[1*H*]azepines arise from thermal rearrangements of biscyclopropapyrrolidines. Thus **10** was obtained from both *syn*- (**11**) and *anti*- (**12**) isomers. The large difference in activation energies for these processes were convincingly explained by the more favourable

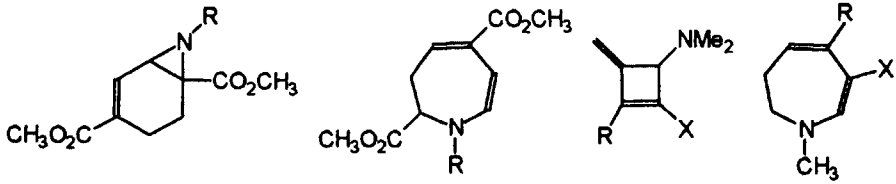
interaction of the two cyclopropyl groups in the *syn* isomer (**11**) compared with the *anti* isomer (**12**) in which the relevant p orbitals lie at a mutual angle of 60°.



(**11**) (**10**) (**12**) (**13**)

The electron-withdrawing tendency of the CO_2CH_3 group must also contribute to the energy barrier since the *N*-methyl *anti* isomer gave **13** at a substantially lower temperature (280 °C).

Ring expansion of cyclic vinylaziridines (**14**) is a thermal process leading to 2,3-dihydroazepines (**15**);[10] the nitrogen atom could be substituted by phenyl or benzyl but analogues lacking ester substituents behaved differently. These materials undergo solvent-dependent reactions with DMAD leading either to substitution or to ring expansion.

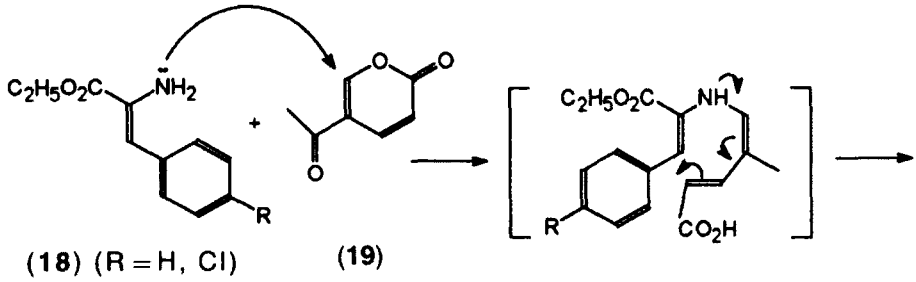


(**14**) (**15**) (**16**) (**17**)

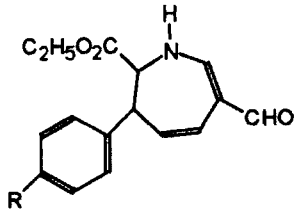
During studies on allenic amines, it was discovered that the initial [2 + 2] cycloaddition products (**16**) from acetylenic esters and ketones were converted easily into **17** (X = $COCH_3$, CO^nPr, CO_2Me; R = H or CH_3).[11] Full details have not been published.

A very interesting, novel approach[12] involves a one-step conversion by reaction of 1-aminoacryl derivatives with certain 2-pyranone compounds. Thus **18** and **19** in methanol at 25 °C gave dihydroazepines (**20**), presumably via Michael addition, decarboxylation, electrocyclisation and proton transfer as shown. This seems to be the only example of its kind.

Other approaches to 2,3-dihydro[1*H*]azepines involve manipulations of dihydroazepinones, their derivatives or [1*H*]azepines. For example, among the products obtained when palladium acetate in acetic acid reacted with *N*-ethoxycarbonyl[1*H*]azepine (**21**) was the 2,3-diacetoxydihydroazepine **22**, of undetermined stereochemistry.[13] The unstable [3*H*]azepine **23** yielded the dihydroazepine **24** on catalytic hydrogenation; this served to establish the constitution of **23**, itself the product of dihydropyridine ring expansion[14] (see Chapter 11).

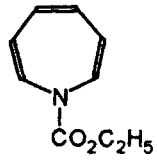


(18) (R = H, Cl) (19)



(20) (R = H, Cl)

There are several examples of $LiAlH_4$ reduction of 1,3-dihydro[2*H*]azepin-2-ones (e.g. **25**, R,R = O) yielding the corresponding dihydroazepines (**25**, R = R = H)[15] (see Chapter 9).



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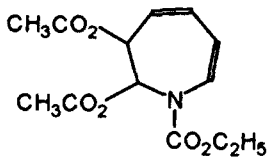

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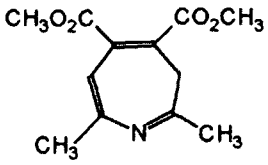

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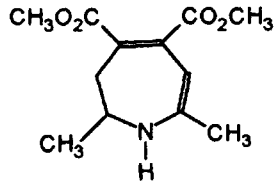
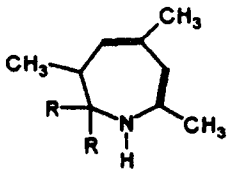


(24)

The naturally occurring yellow pigment muscaflavin (**26**) from fly agaric has been synthesised from a pyridylalanine; the key step in this biomimetic procedure involves closure of N to C-7.[18]



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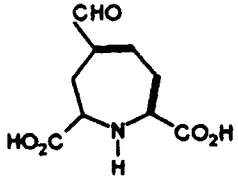

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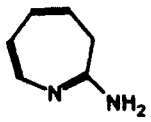

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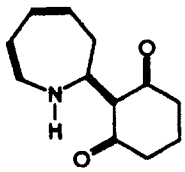

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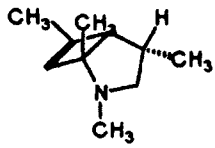


(29)

For completeness, we mention here the fact that aminoazepines (e.g. **27**) (Chapter 11) condense with certain reactive methylene compounds such as dimedone to give products (e.g. **28**) which are effectively dihydroazepines.[16]

PROPERTIES

Most 2,3-dihydro[1*H*]azepines are oils or low-melting solids. Although relatively stable, particularly below 0 °C, witness the production of **10** at 350 °C,[9] nevertheless they do tend to decompose on standing and from early work they have been shown to form stable crystalline salts (see Table 1). The site of protonation was shown to be C-4.[15b] Irradiation (UV) converts the bases by valence-bond isomerisation into 2-azabicyclo[3.2.0]hept-6-enes. For example, the *N*-methyl derivative of **25** gave **29** as the major isomer.[15] Diels–Alder reactions take place readily[10b,15] even with DMAD, which ordinarily reacts with enamines by [2 + 2] cycloadditions followed by ring expansion.[17] However, **8** reacts with dienophiles in [2 + 2] fashion at the C-4–C-5 double bond.[6] Dehydrogenation attempts (DDQ) on compounds **6** were unsuccessful; only in one case did a ring contraction take place which could be explained by assuming that dehydrogenation to the corresponding azepine was followed by an azanorcaradiene rearrangement.[4] Not surprisingly, catalytic hydrogenation of the 2,3-dihydro[1*H*]azepine ring can lead to an azepane.[9,19]

Table 1 lists those 2,3-dihydro[1*H*]azepines whose identities are fully supported by chemical analyses and, in most cases, by spectroscopic measurements.

Table 1. 2,3-Dihydro[1*H*]azepines

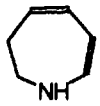
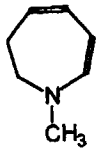
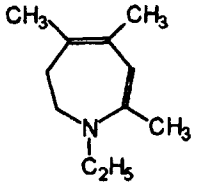
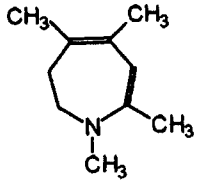
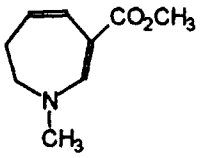
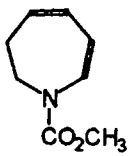
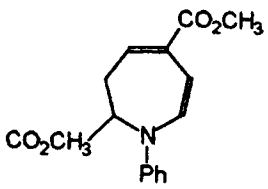
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	62/11		IR, UV	19
			IR, ^{1}H NMR	9, 19
	61–64/1	$HClO_4$ 99–101 *N*-Phenyl-maleimide 149–150	^{1}H NMR	15b
	50–54/1	$HClO_4$ 106–106.5 *N*-Phenyl-maleimide 98–98.5	^{1}H NMR	15b
			IR, ^{1}H,^{13}C NMR	11
		*N*-Phenyl-maleimide 177.5–178	UV, IR, ^{1}H NMR	9
	123		UV, IR, ^{1}H NMR	10a

Table 1 (continued)

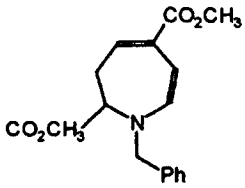
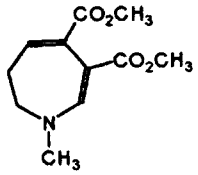
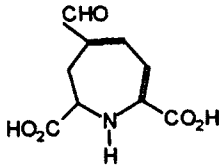
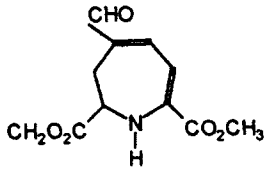
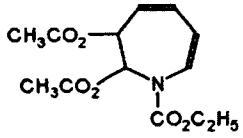
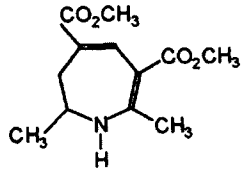
Structure	M.p. (°C)/b.p. (°C/mmHg)		Spectroscopic evidence	Ref.
	110	*N*-Phenyl-maleimide 248	^1H, ^{13}C NMR	10a, 10b
			IR, ^1H NMR	3
	120		MS, ^1H NMR	18
	104–105.5	Semicarb. 189–191	UV, MS, IR	18
	Oil		MS, ^1H NMR	13
	98–99		IR, UV	14

Table 1 (continued)

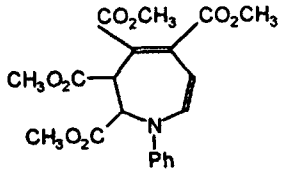
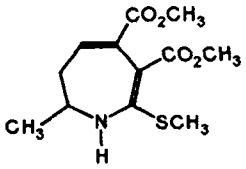
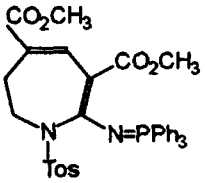
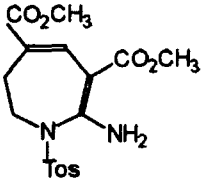
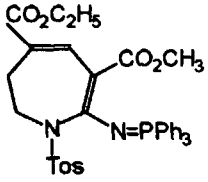
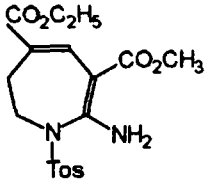
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	127	IR	1
	163–164	MS, ^{1}H NMR, UV	2, 3
	209	UV, IR, ^{1}H, ^{13}C NMR	5, 6
	135	UV, IR, ^{1}H, ^{13}C NMR	5, 6
	178–179	UV, IR, ^{1}H, ^{13}C NMR	5
	121	UV, IR, ^{1}H, ^{13}C NMR	5

Table 1 (continued)

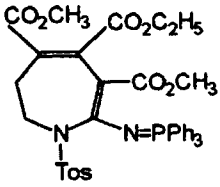
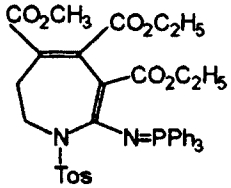
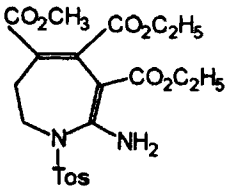
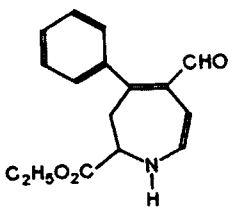
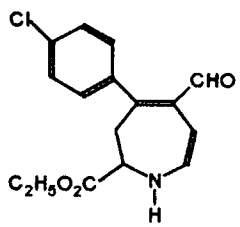
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	254	UV, IR, ^{1}H, ^{13}C NMR	5
	254	UV, IR, ^{1}H, ^{13}C NMR	5
	234	UV, IR, ^{1}H, ^{13}C NMR	5
	118–120	^{1}H, ^{13}C NMR	12
	155–157	^{1}H, ^{13}C NMR	12

Table 1 (continued)

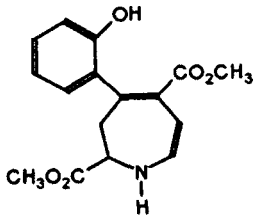
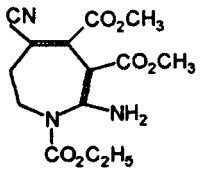
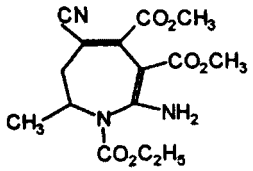
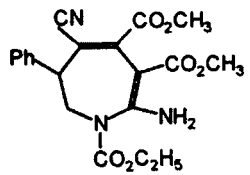
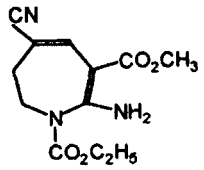
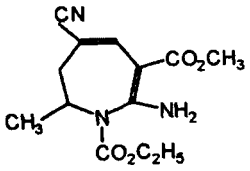
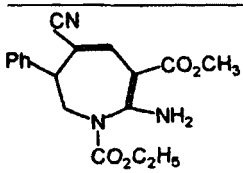
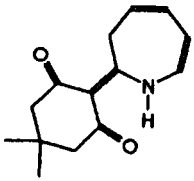
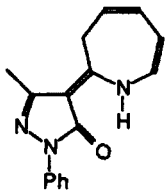
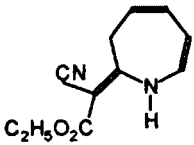
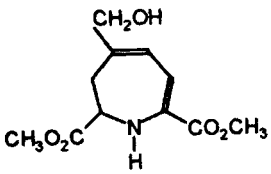
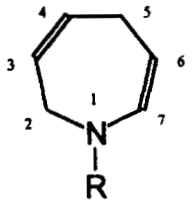
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	'Schaum'	^1H, ^{13}C NMR	12
	150–151	^1H, ^{13}C NMR, MS, IR	4
	166–168	^1H, ^{13}C NMR, MS, IR	4
	198–199	^1H, ^{13}C NMR, MS, IR	4
	123	^1H, ^{13}C NMR, MS, IR	4
	137	^1H, ^{13}C NMR, MS, IR	4

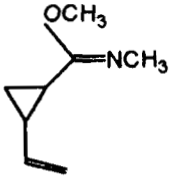
Table 1 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)		Spectroscopic evidence	Ref.
	159		^1H, ^{13}C NMR, MS, IR	4
	113–116		IR, ^1H, ^{13}C NMR UV	16
	140–141	HBF_4 128–129	IR, ^1H, ^{13}C NMR UV	16
	74–75		IR, ^1H, ^{13}C NMR UV	16
	Oil			18

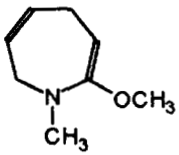
II. 2,5-DIHYDRO[1*H*]AZEPINES



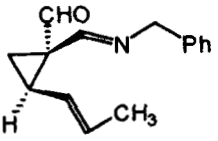
Several groups of workers have made contributions to this area within the last 20 years. Cope rearrangements of *cis*-iminovinylcyclopropanes (e.g. **30**) would



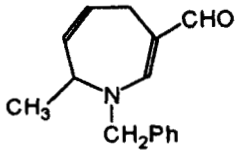
(30)



(31)

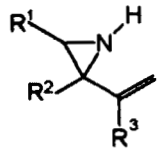


(32)



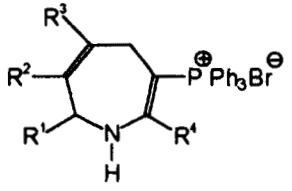
(33)

be expected to yield 2,5-dihydro[1*H*]azepines. In this case **30** did give **31** which was air- and moisture-sensitive,[20] but a more favourable equilibrium in the rearrangement involves having a π-stabilising group attached to the cyclopropane.[21] Thus the cyclopropyl compound **32**, prepared *in situ*, rearranged in 95% yield to **33**. Vinylaziridines have been employed in two ways undergoing cycloadditions with alkynes. First, vinylaziridines (e.g. **34**, $R^1 = R^3 = CH_3$, $R^2 =$ Ph) react with alkynylphosphonium salts (e.g. **35**, $R^4 = CH_3$ or Ph) to

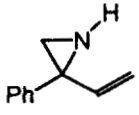


(34)

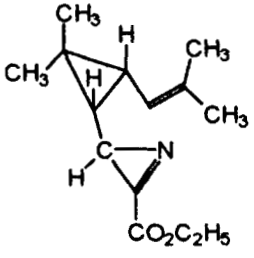
(35)



(36)

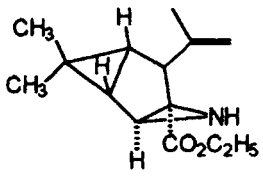


(37)

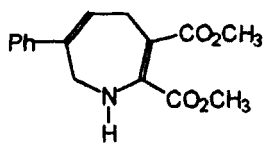


(37A)

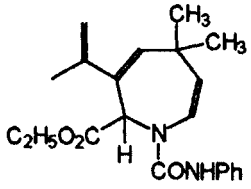
give dihydroazepines (**36**) (see Table 2).[22] This is to be seen as a hetero-Cope rearrangement. Second, vinylaziridines **37** react even at −20 °C with DMAD giving **38**.[23,24] It is thought that initially **37** adds to DMAD in Michael fashion, but thereafter it is not possible to distinguish between the options.[24] Recently the cyclopropylazirine **37A** was thermolysed to the tricyclic amine **37B**, which reacted with phenyl isocyanate to yield the dihydroazepine **38A**.[77]



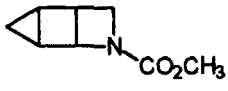
(37B)



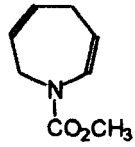
(38)



(38A)



(39)



(40)

Finally in this section, one of the simplest examples of a 2,5-dihydro[1*H*]-azepine (**40**) was reported[25,26] to arise by thermolysis of the tricyclic system **39** in refluxing xylene (see Table 2).

Table 2. 2,5-Dihydro[1*H*]azepines

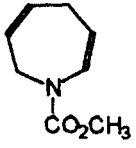
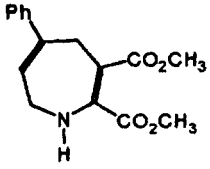
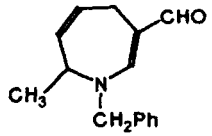
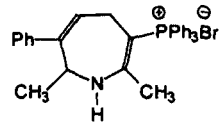
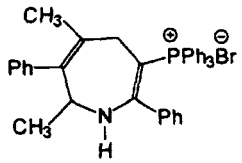
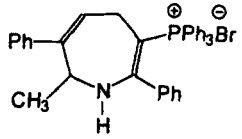
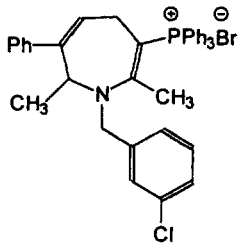
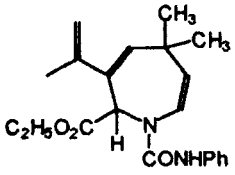
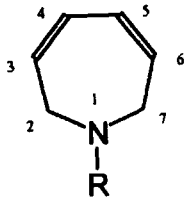
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	Oil	IR, MS, ^{1}H NMR	26
	122–123	IR, ^{1}H NMR	24

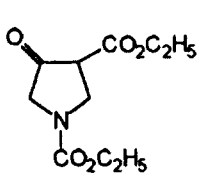
Table 2 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
			21
	242–246	IR, ^{1}H, ^{13}C, ^{31}P NMR, MS	22
	214–222	IR, ^{1}H, ^{13}C, ^{31}P NMR, MS	22
	130–135	IR, ^{1}H, ^{13}C, ^{31}P NMR, MS	22
	140–160	IR, ^{1}H, ^{13}C, ^{31}P NMR	22
	209–211	^{1}H NMR	77

III. 2,7-DIHYDRO[1*H*]AZEPINES



There are, surprisingly, only two examples.[27] The anion derived from **41** reacted with DMAD to provide the enolic product **42**. Such ring expansions generally



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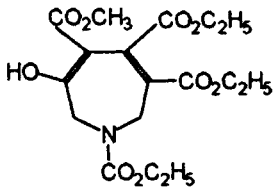
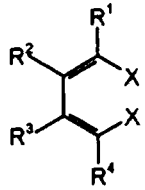


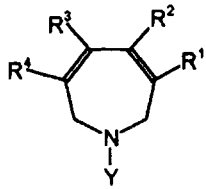
(42)

yield enolic products,[28–30] although decarboxylation of the ester group at C-4 generally reveals a ketone carbonyl group at C-3; in this case, hydrolysis gave unstable products.[31]

Recently it has been shown[79] that the *cis,cis* dienes **42A** (X = CH_2Br) react with various nitrogen nucleophiles to give 2,7-dihydro[1*H*]azepines **42B** (Y = CH_2Ph, ^nBu, tosyl; $R^1 = R^3 = {}^tBu$; $R^2 = R^4 = H$). This synthesis has the advantage of versatility since the key dienes were obtained by catechol



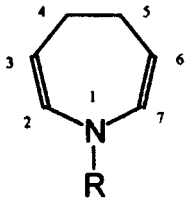
(42A)



(42B)

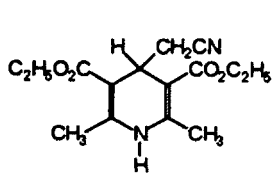
oxidation [$Pb(OAc)_4$] and subsequent mild manipulations (**42A**; X = $CO_2CH_3 \rightarrow CH_2OH \rightarrow CH_2Br$).

IV. 4,5-DIHYDRO[1*H*]AZEPINES



PREPARATION

This is a thoroughly explored area. Treatment of 4-chloromethyl-1,4-dihydropyridines with potassium cyanide gave cyanodihydroazepines (e.g. **43** → **44**) as far back as 1920,[32] but it was only in 1962 that it was shown that the product was **44** and that the reaction was best conducted at room temperature[33] or



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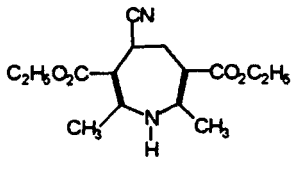

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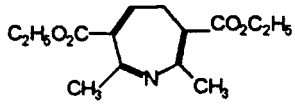

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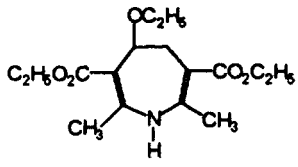
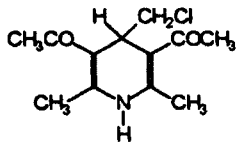


(46)

below.[34] A study of the kinetics[35] of this ring expansion, taken with the isolation of the [4*H*]azepine **45**,[36] implicated **45** in the process since cyanide ion rapidly converted **45** into **44**. Sodium ethoxide also solvolyses **43** giving the ethoxydihydroazepine **46**.[37] The diacetyl analogue **47** was also shown to react with



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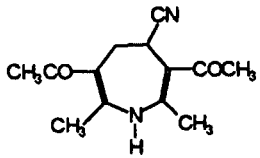

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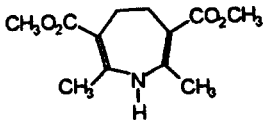
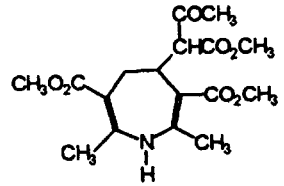


(49)

aqueous alcoholic KCN to give the expected dihydroazepine **48**.[38] The dimethyl ester corresponding to **43** reacted with $NaBH_4$ in acetonitrile giving **49**,[39] whereas in liquid ammonia over 7 days it yielded **50** and methyl 2-methylpyrrole-3-carboxylate.[40] Later it was demonstrated that the dihydropyridine methyl and ethyl esters **51** reacted with sodium cyanide in DMSO or with



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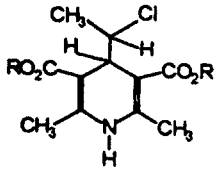

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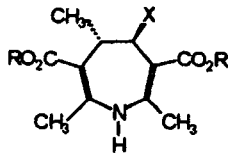

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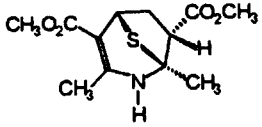

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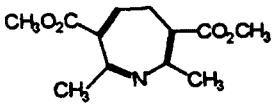


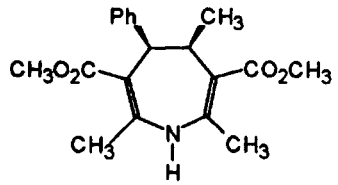
(54)

methanol containing triethylamine to give the dihydroazepines **52** (X = CN and OMe, respectively).[41] Furthermore, the carbon nucleophile from acetonylacetone could also[42] participate in the ring expansion reaction, producing for example **52** [X = $CH(COCH_3)_2$].

To summarise, dihydropyridines such as **43** and **51**, under controlled conditions, react with a variety of basic nucleophiles yielding 4,5-dihydro[1*H*]azepines; SH^- is an exception where a sulphur-bridged product (**53**) has been established.[39] It is accepted that the ring expansion proceeds initially by abstraction of the proton from the >NH group, followed by its conversion into the [4*H*]azepine structure (e.g. **54**).[43,44] The latter was shown to react with cyanide ion yielding **44** (methyl esters), as pointed out earlier.[35]

Aryl-substituted 4,5-dihydro[1*H*]azepines were obtained from the appropriate dihydropyridines (**43**, **51**) by reaction with aryl Grignard reagents; the products (**55**) contain the *cis* isomers as major products but alkyl Grignards

gave predominantly the *trans* isomers,[45] as seen above.[41] Solvolysis of the tosylate **56** gave the exomethylene derivative **57**.[46]



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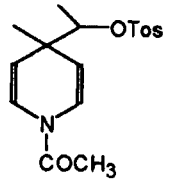

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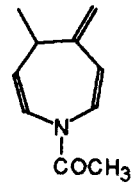

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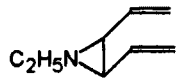

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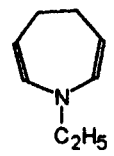
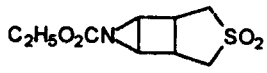


(59)

Apart from routes involving dihydropyridines, there have been several other approaches to the 4,5-dihydro[1*H*]azepine ring system. One of the earliest of these[47] involved Cope rearrangement of *cis*-divinylaziridine (**58**) to **59**. A later similar study on the *N*-methyl analogue of **58** and the dipropenylaziridines also states that 4,5-dihydro[1*H*]azepines were identified on scanty evidence.[48,49] Flash vacuum pyrolysis of the aziridine **60** gave in poor yield the dihydroazepine



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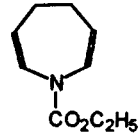

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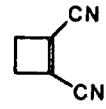

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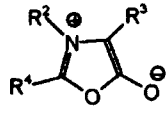

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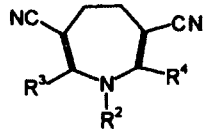
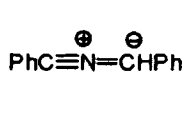


(64)

61, which was stable enough to be isolated.[50] Dicycanocyclobutene (**62**) undergoes 1,3-dipolar cycloadditions with mesoionic oxazolones (e.g. **63**, $R^2 = CH_3$ or H, R^3,$R^4 = CH_3$, Ph or $PhCH_2$)[51,52] giving dihydroazepines (**64**). The nitrile ylid **65** has also been reacted with **62** to give **64** ($R^3 = R^4 = Ph$, $R^2 = H$).[53] In one case, an intermediate bicyclic carboxylic acid (**66**) was isolated from an oxazolone reaction; its structure was confirmed by X-ray analysis and it was then converted thermally into the expected dihydroazepine.[54a] This reaction has been rationalised using MO calculations.[54b]



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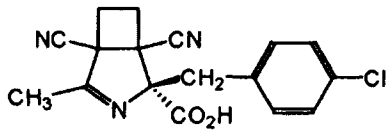

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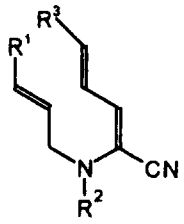

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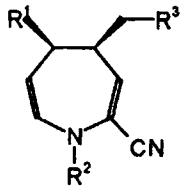
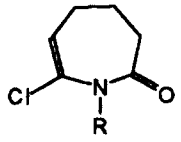


(68)

There is only one synthetic method for 4,5-dihydro[1*H*]azepines which depends on direct cyclisation of acyclic precursors; the (2*Z*,4*E*)-α-allyldienenitriles **67** in refluxing xylene were converted into the dihydroazepines (**68**).[55] It was considered that the first step is a [1, 6] hydrogen shift which leads to a helical 8π transition state suitable for cyclisation.

Conversions of already formed azepine rings are known. Thus, the tetrahydroazepinones **69** reacted with Vilsmeier reagent ($POCl_3$/DMF) to give **70**.[56] On the other hand, the [1*H*]azepine **71** adds iodine azide (IN_3) yielding



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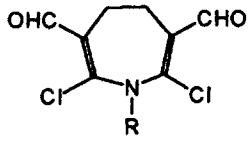

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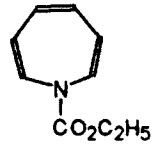

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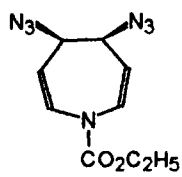

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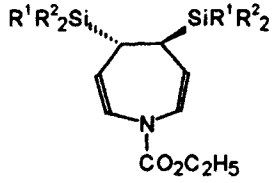


(73)

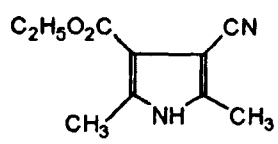
72,[57] whilst **71** undergoes reductive silylation with chlorosilanes and magnesium in HMPA producing **73**.[58–60] Both regio- and stereochemistry were deduced from ^1H NMR spectra. The chlorosilanes used were CH_3SiCl, Ph_2SiCl_2 and $(CH_3)_2SiCl_2$ and yields were moderate.[59] Temperature-dependent ^1H and

^{13}C NMR spectra were used[60] to infer restricted rotation between the nitrogen atom and the carbonyl group.

PROPERTIES

The least substituted *N*-alkyl members of this series appear to be rather reactive,[47,49] not entirely surprising given that they are doubly enaminic. On the other hand, *N*-acyl compounds (e.g. **61**) are more easily handled, are fully characterised and have been utilised by several groups.[50,57,59] Attachment of substituents, particularly electron-withdrawing groups, at C-2, C-3, C-6 and C-7, have a beneficial effect on stability, as one might expect.

4,5-Dihydro[1*H*]azepines are sensitive to many reagents. Thus the early studies[32] on conversions **43** → **44** failed at temperatures above ambient since it was later found that the dihydroazepine could be converted into a pyrrole (**74**)[34] and ethyl acrylate. Similarly, the tricyano compound **75** gave the dicyanopyrrole **76**.[34] Heating[41] 4-substituted 4,5-dihydro[1*H*]azepines (**44**, **46**) gave



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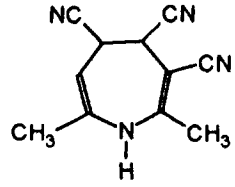

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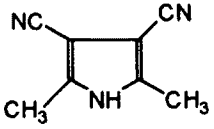
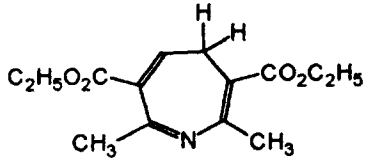
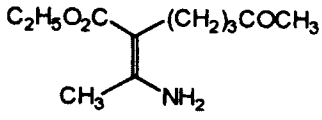


(76)

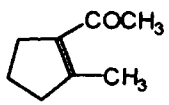


(77)

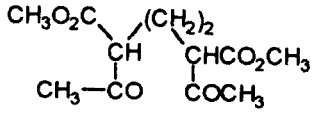
[4*H*]azepines (e.g. **77**) at around 265 °C; these then isomerised at 320 °C to [3*H*]azepines, which are thermodynamically more stable (see Chapter 11).[36] A 4-unsubstituted compound (**49**) reacted differently with KOH in ethanol or water; it gave first an amino diester (**78**) and then 1-acetyl-2-methylcyclopentene



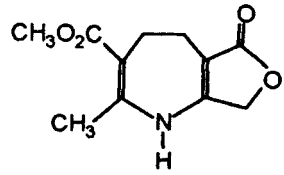
(78)



(79)



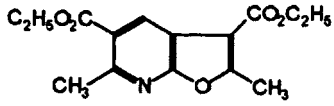
(80)



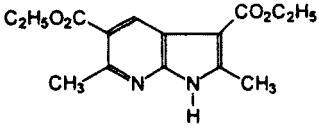
(81)

(79),[37] whilst in aqueous acid, **80** was isolated. A lactone (**81**) was obtained by treatment of **49** with NBS.[43]

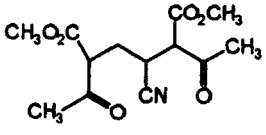
Amongst the original experiments[63] aimed at dehydrogenation of 4,5-dihydro[1*H*]azepines, sodium nitrite in acetic acid was employed. The final product was eventually shown to be the furo[2,3-*b*]pyridine **82**,[62] hot aqueous ethanolic silver nitrite proving to be a superior medium for production of the furopyridine; it was accompanied by a minor product formulated as a pyrrolo[2,3-*b*]pyridine (**83**). This problem was addressed later[64] and by treating



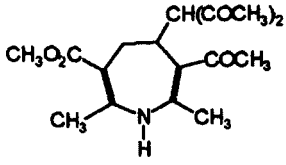
(82)



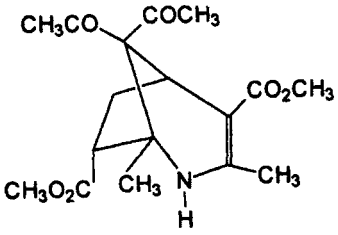
(83)



(84)



(85)



(86)

44 with an acidic ion-exchange resin, the previously suspected[62] cyano octanedione diester (**84**) intermediate was isolated. There are cases where ring contraction back to 1,4-dihydropyridine derivatives has been seen,[41] particularly with hydrogen halides. An interesting transannular cyclisation, **85** → **86**,[42] gives useful access to 2-azabicyclo[3.2.1]oct-3-enes. Not surprisingly, catalytic hydrogenation of 4,5-dihydro[1*H*]azepines yielded azepanes; for syntheses of the latter carrying particular substituents, this has to be an attractive method.[36,37] Table 3 displays most of the 4,5-dihydro[1*H*]azepines reported in the literature to date.

Table 3. 4,5-Dihydro[1*H*]azepines

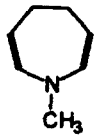
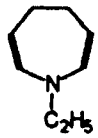
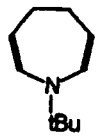
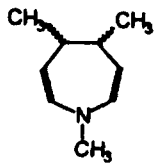
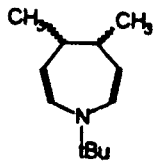
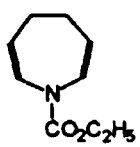
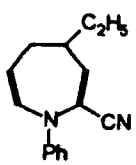
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
		^{1}H NMR	49
	69–70/20	IR	47
		^{1}H NMR	49
		^{1}H NMR	49
		^{1}H NMR	49
	Oil	^{1}H NMR	50
	Oil	IR, ^{1}H, ^{13}C NMR, MS	55

Table 3 (continued)

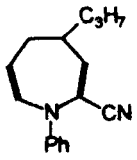
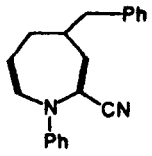
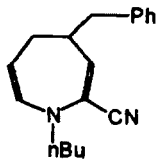
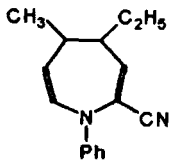
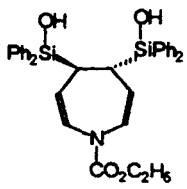
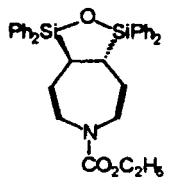
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	Oil	IR, ^{1}H, ^{13}C NMR, MS	55
	Oil	IR, ^{1}H, ^{13}C NMR, MS	55
	Oil	IR, ^{1}H, ^{13}C NMR	55
	Oil	IR, ^{1}H, ^{13}C NMR, MS	55
	Oil	UV, IR, ^{1}H NMR, MS	59
	174–175	UV, IR, ^{1}H NMR, MS	59

Table 3 (continued)

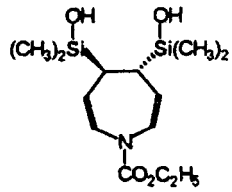
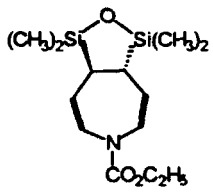
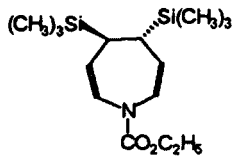
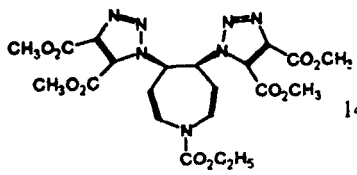
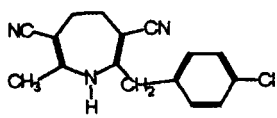
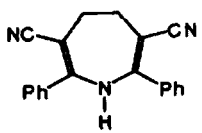
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	99–100	UV, IR, ^{1}H NMR, MS	59
	Oil	UV, IR, ^{1}H NMR, MS	59
	Oil	UV, IR, ^{1}H NMR, MS	59
	149–151	IR, ^{1}H NMR	57
	102–103.5	IR, ^{1}H NMR, MS	54
	216	UV	53

Table 3 (continued)

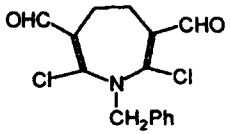
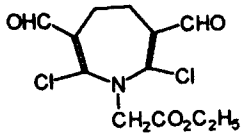
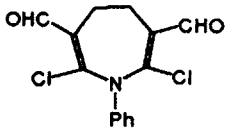
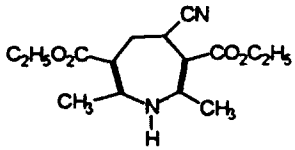
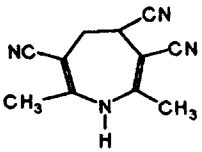
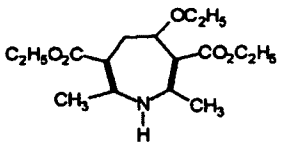
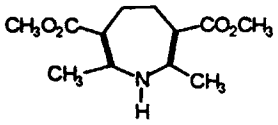
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	147–148	IR, ^{1}H NMR, MS	56
	Unstable oil	IR, ^{1}H NMR	56
	111	IR, ^{1}H NMR, MS	56
	106–107	UV, IR	34
	153–153.5	UV, IR	34
		UV	36
	91–92	UV, IR, ^{1}H NMR	36, 37

Table 3 (continued)

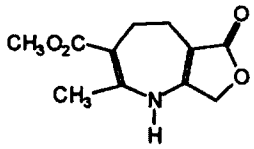
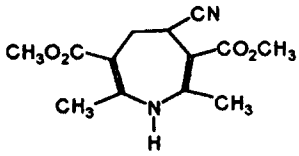
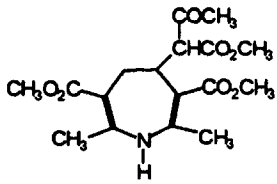
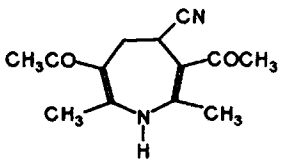
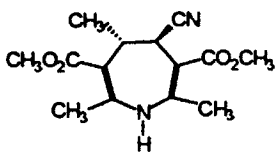
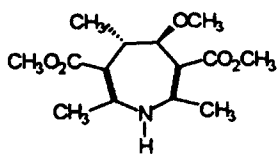
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	222–223	UV, IR, ^{1}H NMR	43
	187–188	UV, IR, ^{1}H NMR	37
	138–139	UV, IR, MS, ^{1}H NMR	40
	151	UV, IR, ^{1}H NMR	61
	147–148.5	IR, MS, ^{1}H NMR	41
	157–159	IR, MS, ^{1}H NMR	41

Table 3 (continued)

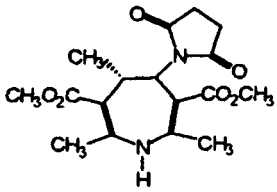
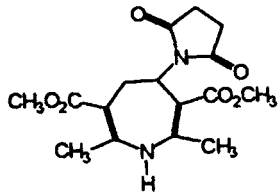
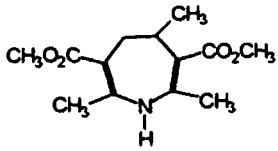
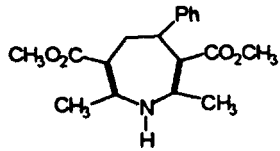
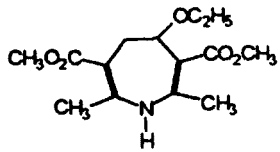
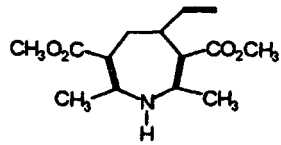
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	180–181	IR, MS, ^{1}H NMR	41
	192.5–193.5	UV, IR, MS, ^{1}H NMR	41
	Oil	^{1}H NMR	45
	135–137	^{1}H NMR	45
	86–88	UV	37
	82–84	^{1}H NMR	45

Table 3 (continued)

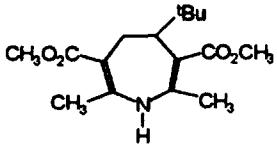
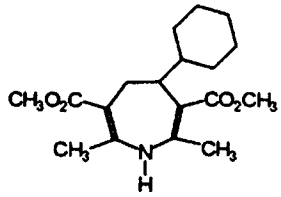
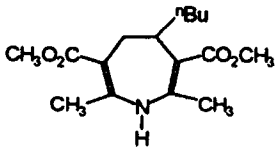
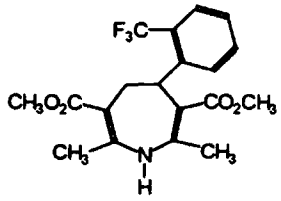
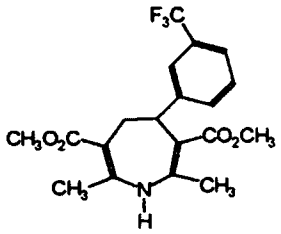
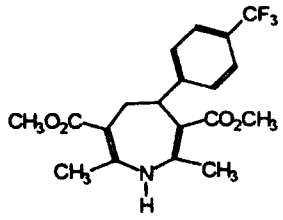
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	125–126	^{1}H NMR	45
	112.5–113.5	^{1}H NMR	45
	Oil	^{1}H NMR	45
	157–158.5	^{1}H NMR	45
	93–94	^{1}H NMR	5
	105.5–106.5	^{1}H NMR	45

Table 3 (continued)

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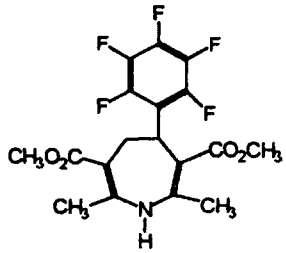
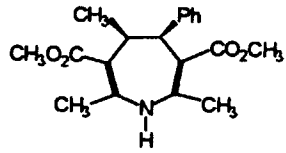
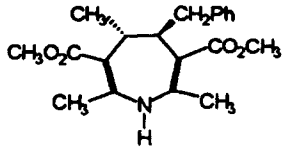
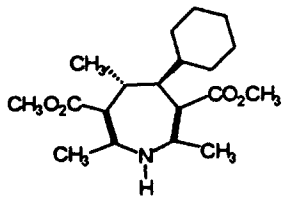
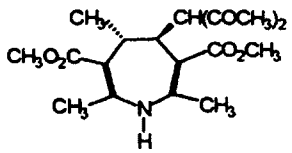
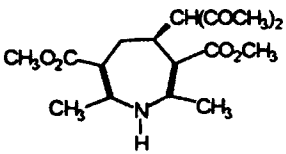
	117–118	^{1}H NMR	45
	122–122.5	^{1}H NMR	45
	107–108	^{1}H NMR	45
	58–60	^{1}H NMR	45
	104–106	UV, IR, ^{1}H NMR, MS	42
	147–148.5	UV, IR, ^{1}H NMR, MS	42

Table 3 (continued)

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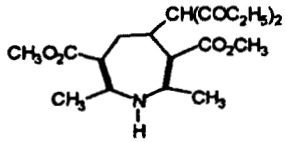
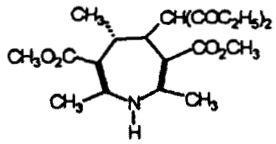
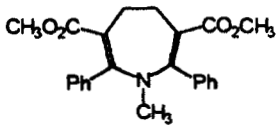
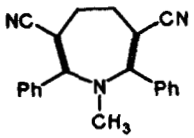
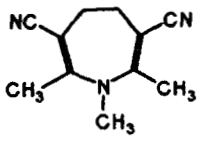
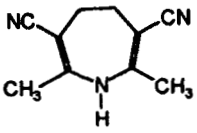
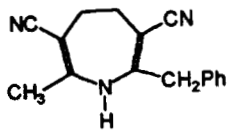
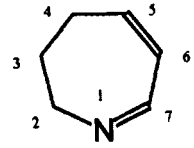
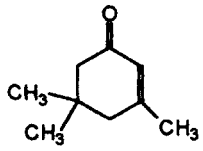
	99–100.5	UV, IR, ^{1}H NMR, MS	42
	125.5–127	UV, IR, ^{1}H NMR, MS	42
		UV, ^{1}H NMR	51
	243–245	IR, ^{1}H NMR	52
	93–94	IR, ^{1}H NMR	52
		IR, MS, ^{1}H NMR	52
	115–116	IR, MS, ^{1}H NMR	52

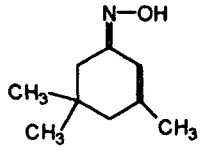
V. 3,4-DIHYDRO[2*H*]AZEPINES



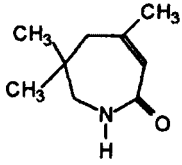
The only bona fide synthesis of the 3,4-dihydro[2*H*]azepine ring system involved isophorone (**87**), either by Schmidt rearrangement in methanol or by Beckmann rearrangement of the *syn*-oxime (**88** → **89**) followed by treatment with trimethyloxonium fluoroborate.[65]



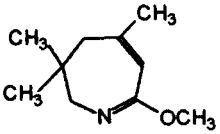
(87)



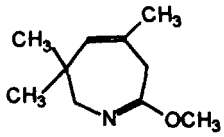
(88)



(89)

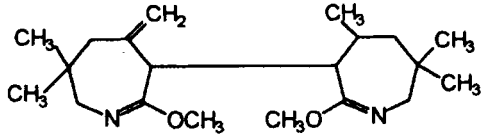


(90)

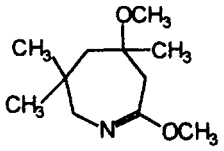


(91)

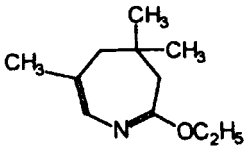
The product (**90**) was accompanied by a small percentage of the isomer **91**, which was laboriously separated (see Section VI). Pyrolysis of **90** was only fruitful using sensitisers; with acetophenone as sensitiser, a dimeric structure



(92)



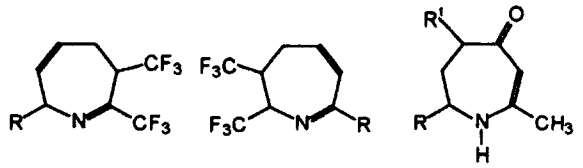
(93)



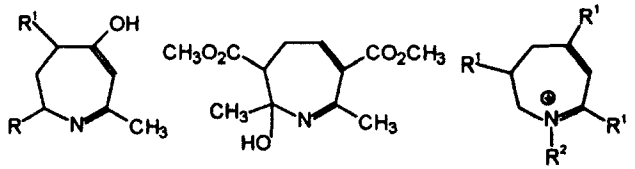
(94)

(**92**) was seen, but in the presence of methanol, the latter added to the 3,4-bond giving **93**. There was no evidence for valence isomerisation such as was seen in the case of **94**;[66] see Section VIII.

Slow isomerism (**95** → **96**; R = H or vinyl) was reported,[67] in the case of 1,2-divinylaziridines facile thermal valence isomerisation to 5,6-dihydro[2*H*]-azepines (**95**), but 3,4-dihydro[2*H*]azepines (**96**) were not isolated; see Section VII. Similarly, certain tetrahydroazepinones (**97**) are said to tautomerise to **98**



(**95**) (**96**) (**97**)

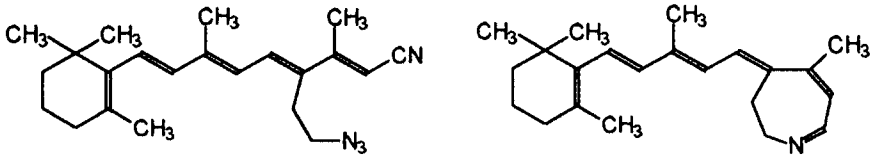


(**98**) (**99**) (**100**)

on standing neat or, more rapidly, in solution. However, although the ^{1}H NMR evidence is fairly convincing, structures such as **98** were not isolated.[68]

There is one example (**99**) of a 3,4-dihydro[2*H*]azepine which arose from acid-catalysed hydration of a [3*H*]azepine.[43] Hot acidic methanol caused ring contraction to a 1,4-dihydropyridine (**47**; OCH_3 for Cl); it was presumed that dehydration of **99** preceded the ring contraction which is typical of [3*H*]- and [4*H*]azepines in this series (Chapter 11). It was shown[15] that when some 2,3-dihydro[1*H*]azepines were protonated, this took place at C-4 leading to perchlorates of cations such as **100**. Many other examples are mentioned in the patent literature.[74–76]

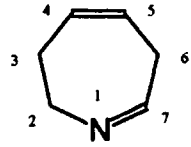
There is one report[78] of a direct cyclisation leading to a 3,4-dihydro[2*H*]-azepine. Thus the one-pot reduction (dibal) of **100A** to the corresponding



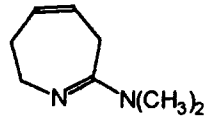
(**100A**) (**100B**)

amino aldehyde followed by hydrolysis (pH 5.5–6.5) gave the dihydroazepine **100B**.

VI. 3,6-DIHYDRO[2*H*]AZEPINES



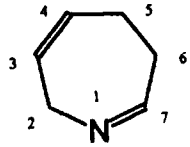
This is a little known subject. As stated above, **91**, which arose as a by-product during the preparation of **90**,[65] was not characterised adequately, being estimated as only 80% pure. On the other hand, a cyclic amidine (**101**) does seem to



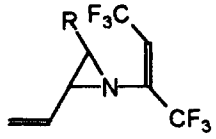
(101)

have been isolated by reaction of the appropriate lactam[70] with *N,N*-dimethylcarbamoyl chloride.[69] Such amidines were shown to react with diphenylcyclopropenone giving cyclopentyl annulations across the N–C-2 bond.[69]

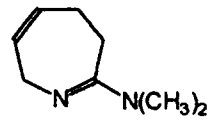
VII. 5,6-DIHYDRO[2*H*]AZEPINES



As mentioned in Section V, a rapid thermal valency isomerisation (**102** → **95**) has been reported.[67] The products (**95**, R = H and vinyl) were adequately



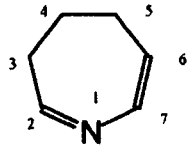
(102)



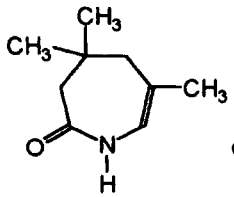
(103)

identified by elemental analysis (one case), IR, ^{19}F NMR and ^{1}H NMR spectroscopy. However, they did isomerise fairly rapidly to **96**, which are obviously thermodynamically more stable. The work cited in the previous section on the cyclic amidines[69] also led to formation of a 5,6-dihydro[2*H*]azepine (**103**) by treatment of the appropriate lactam[71] with *N*,*N*-dimethylcarbamoyl chloride.

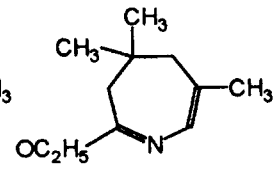
VIII. 4,5-DIHYDRO[3*H*]AZEPINES



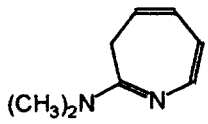
Several distinct methods have been employed to approach this ring system. First the *anti*-oxime of isophorone (**87**) underwent Beckmann rearrangement to **104**, which gave **105** when reacted with triethyloxonium tetrafluoroborate.[66] Second,



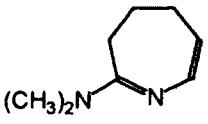
(**104**)



(**105**)

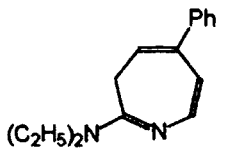


(**106**)

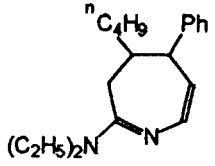


(**107**)

selective catalytic hydrogenation over 5% palladium on charcoal of the 2-dimethylamino[3*H*]azepine **106** gave **107**. Another example of the second approach is to be found in the work carried out on the 8π anion obtained from another [3*H*]azepine (**108**) by treatment with various bases.[72,73] Whilst



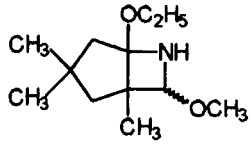
(**108**)



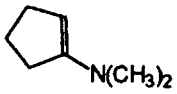
(**109**)

in several cases, the anion from **108** reacted usefully with several electrophiles giving C-3 substitution, low-temperature treatment of **108** with *n*-butyllithium in the presence of potassium *tert*-butoxide led to addition of the reagent across the C-4–C-5 bond giving **109**.

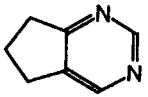
Photochemical irradiation of the available 3,6-dihydro[2*H*]azepines revealed a difference in behaviour. Whereas **105** on sensitised irradiation was converted through isolable 7-azabicyclo[3.2.0]hept-6-ene derivatives (e.g. **110**),[66] **107** gave



(110)



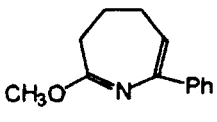
(111)



(112)

111 and **112** but no azabicycloheptene, although one might argue that it could have been an intermediate.

Photochemical reaction of benzonitrile with 1-methoxycyclopentene yielded the 4,5-dihydro[3*H*]azepine **113** in around 40% yield.[80]



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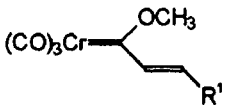

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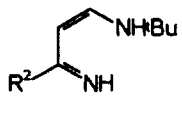

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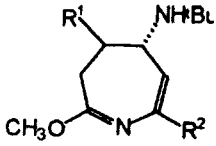

(116)

Lastly, chromium complexes (**114**; R^1 = Ph, 2-furyl) have recently been shown to react with azadienes (**115**; R^2 = C_2H_5, Ph, *p*-tolyl, cyclopropyl, *p*-ClC_6H_4) providing dihydroazepines (**116**) in acceptable yields (52–90%).[81] Several examples were quoted.

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George R. Proctor, James Redpath
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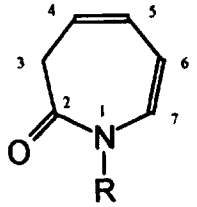
CHAPTER 9

Dihydroazepinones

I. 1,3-DIHYDRO[2*H*]AZEPIN-2-ONES

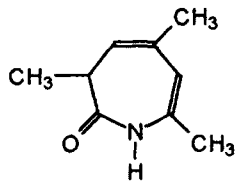


A great deal is known on this subject. This is due partly to the ease of preparation of 1,3-dihydro[2*H*]azepin-2-ones, and partly because of their stability.

PREPARATION

At about the same time (1962–63) in Germany and the USA, a novel entry to 1,3-dihydro[2*H*]azepin-2-ones was disclosed.[1–3] In this unusual procedure, a cold ethereal solution of chloramine is added to vigorously stirred sodium salts of 2,6-dialkylphenols held at 125–150 °C.[1] Full experimental details have been provided;[4] for example, 2,4,6-trimethylphenol gives 3,5,7-trimethyl-1,3-dihydro[2*H*]azepin-2-one (**1**).

Many other 3,7-dialkyl-1,3-dihydro[2*H*]azepin-2-ones were claimed,[5–10] but phenols lacking 2,6-disubstitution did not participate. Details of the mechanism have been addressed[11] and it was shown that in the case of unsymmetrically disubstituted 2-methylphenols, increasing the size of the 6-substituent increased the degree to which amination proceeded at the methyl-bearing carbon atom C-2. It is generally accepted that chloramine provides an electrophilic nitrogen-containing species to react at the nucleophilic carbon centres (C-2,



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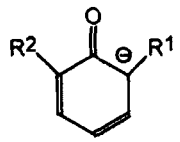

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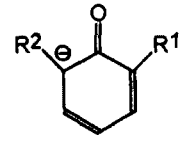
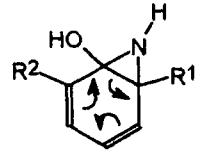
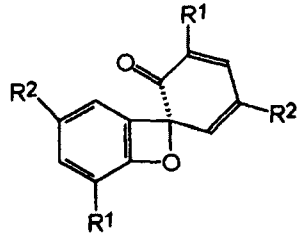


(2′)



(3)

C-6) of the phenol (**2**, **2′**). Along the reaction pathway one can visualise an azanorcaradiene structure (**3**) plausibly leading to the observed products (e.g. **1**). 7-Aryl-1,3-dihydro[2*H*]azepin-2-ones were also obtained from phenolic precursors.[12,13] Thus the spiroquinol ethers **4** obtained by oxidative coupling of phenols (**5**) reacted with some primary amines to give good yields of the



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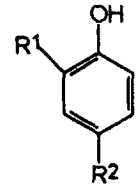

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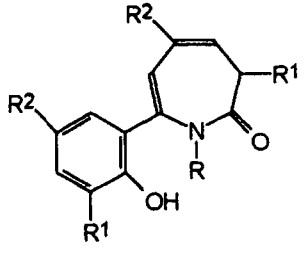

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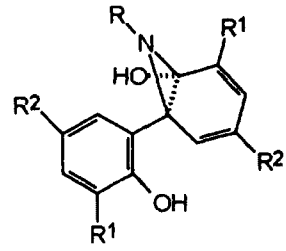
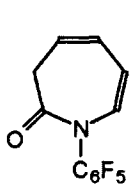


(7)

7-aryl derivatives (**6**). Formation of the latter were rationalised[13] as proceeding via an azanorcaradiene intermediate (**7**), so there is a similarity between this procedure and the phenoxide and chloramine approach, even though the amino components are differently charged in the two cases.

Phenylnitrene has been a fruitful source of azepines (Chapter 11). In certain circumstances, generation of phenylnitrenes can lead to the formation of 1,3-dihydro[2*H*]azepine-2-ones. Thus reductive treatment of pentafluoronitrosobenzene with triethyl phosphite in anisole gave **8**[14] in poor yield along with other products.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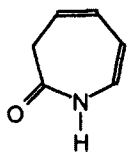
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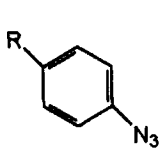
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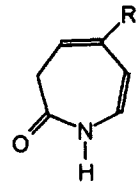
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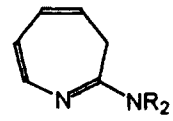
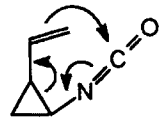

(12)

Photolysis and thermolysis of phenyl azide in acetic acid was also shown to yield the dihydroazepinone ring product **9** amongst several other materials.[15] The Salford group have improved on this approach; based on earlier work,[16] it has been shown that photolysis of phenyl azides carrying electron-withdrawing groups in aqueous THF is a very useful method for making 1,3-dihydro[2*H*]azepin-2-ones.[17,18] Thus **10** gave **11** (R = electron-withdrawing groups; see Table 1) in generally acceptable yields. Intramolecular nitrene insertion was invoked to explain the formation of acetyl-substituted 1,3-dihydro[2*H*]azepinones when 2-alkylindazoles were irradiated in dilute acid solution.[36]

It is known that hydrolysis of 2-amino[3*H*]azepines **12** gives 1,3-dihydro[2*H*]azepin-2-ones. Thus **12** (R = H) gave **11** (R = H);[19] treatment of **12** (R = H) with H_2S gave the thia analogue (**15**). Diethylaminoazepines (**12**, R = C_2H_5, various substituents; see Table 1) were quaternised on the ring nitrogen and hydrolysed in good yield to 1,3-dihydro[2*H*]azepin-2-ones[20] whilst 2-acetoxy[3*H*]azepines were also shown[21] to undergo hydrolysis to give **11** (R = H) in excellent yields.

Finally on the preparative side, Curtius rearrangement, performed on *cis*-2-vinylcyclopropyl carbonylazide (**13**), led to **11** (R = H), presumably via

(13)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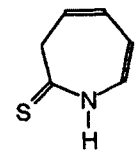
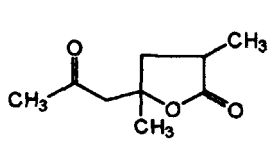

(15)

the *cis*-vinyl isocyanate (**14**) as shown. This reaction proceeds at 80 °C to completion and can be thought of as an aza-Cope rearrangement (**14** → **11**). The *trans*-vinylcyclopropyl isocyanate was isolated (b.p. 85–86 °C/165 mmHg) and proved to be stable up to 200 °C.[22,23]

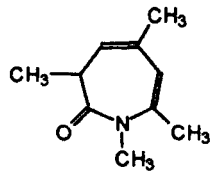
PROPERTIES

Reduction of 1,3-dihydro[2*H*]azepin-2-ones is fairly predictable. Catalytic hydrogenation gave the appropriate caprolactam,[1,19,22] whilst $LiAlH_4$ reduction

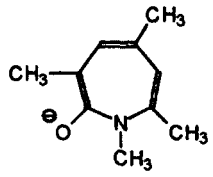
gave 2,3-dihydro[1*H*]azepines[24,25] (Chapter 8). Where the substitution pattern allows, both of these represent an efficient two-step synthesis from a phenol. Treatment of **1** with hydrochloric acid yielded a lactone (**16**);[2] *N*-alkylation was



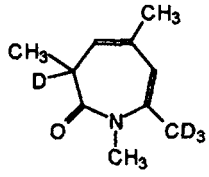
(16)



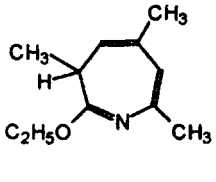
(17)



(18)



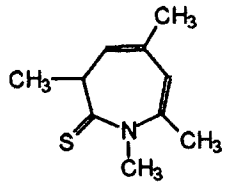
(19)



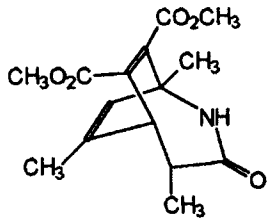
(20)

brought about using sodium hydride in DMF to obtain **17**, for example,[2] which could also be reacted by direct reaction of 2,4,6-trimethylphenol with chloromethylamine.[2] Although **17** appeared to deprotonate uniquely using the methylsulphinyl carbanion (Na^+ $^-CH_2SOCH_3$) in DMSO producing a highly coloured red solution,[18] electrophilic addition by methyl iodide failed.[26] However, when deprotonation was achieved using $CD_3SOCD_2^-$ Na^+/CD_3SOCD_3 followed by quenching with D_2O, convincing ^1H NMR evidence was obtained for the exchange (almost complete) of four hydrogen atoms as shown (**19**). This striking result illuminating the acidity of the 7-CH_3 hydrogen atoms was rationalised as being due to the proximity of the nitrogen atom. The other methyl hydrogens at C-3 and C-5 did not exchange at all. Eventually, *O*-alkylation of **1** was achieved using triethyloxonium tetrafluoroborate.[23,27] The 2-ethoxy product **20** hydrolysed in dilute acid giving the lactone **16** and prolonged treatment of **20** with piperidine led to the 2-amino[3*H*]azepine **12** [$R_2 = -(CH_2)_5-$]. P_2S_5 was used to convert **1** into the thia analogue **21**, which also reacted with triethyloxonium tetrafluoroborate giving the thia analogue of **20**.[27]

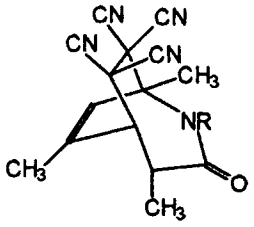
Although **1** failed to undergo Diels–Alder reaction with either maleic anhydride or *N*-phenylmaleimide, it gave a poor yield (19.6%) of **22** with DMAD and a quantitative yield of the adduct **23** (R = H) with TCE. The *N*-methyl compound **17** also reacted satisfactorily with TCE giving **23** ($R = CH_3$); the corresponding *N*-ethyl analogue was obtained in 91% yield.[28] On the other hand, hexafluoro-2-butyne and **1** reacted differently; a low yield of a



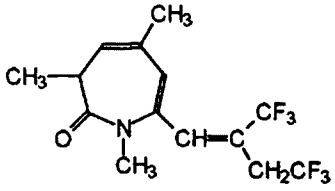
(21)



(22)



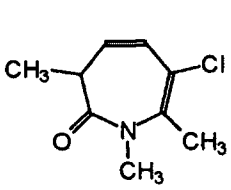
(23)



(24)

7-methyl-substituted compound (**24**) was isolated, a further testimony to the acidity of the hydrogen atoms in the 7-methyl group of compounds such as **1** and **17**.

A study of chlorinations involving 1,3-dihydro[3*H*]azepin-2-ones using *N*-chlorosuccinimide in refluxing methylene chloride[29] revealed that in molecules lacking a 5-substituent, the monochlorinated product proved to be the 6-chloro isomer (e.g. **25**), whereas in the structure including a 5-substituent, the major product was the 4-chloro compound **26**. This was explained in terms of the principle of least motion.[29]



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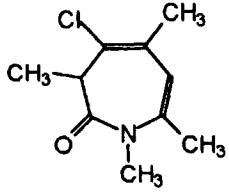

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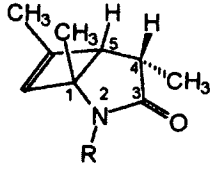
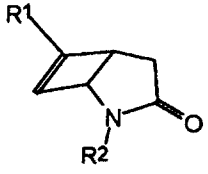


(27)



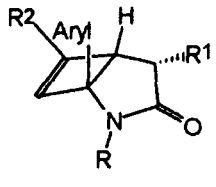
(28)

Photochemistry of 1,3-dihydro[2*H*]azepin-2-ones has been a popular area of study. Similarities in structure compared with cycloheptadienes and cycloheptatrienes encouraged the expectation that the azepinones might yield 2-azabicyclo[3.2.0]heptenones on irradiation, and this proved to be correct.

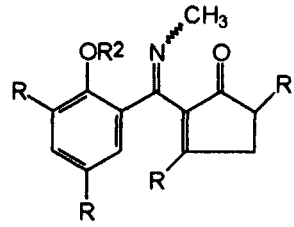
Compound **1**, for example, gave **27** (R = H) in THF or methanol and the *N*-methyl variant (**17**) gave **27** (R = CH_3).[24,30] Assignment of the stereochemistry as in **27** arises through the observation that the coupling between the 5H and neighbouring 4H in the ^{1}H NMR spectrum was 10 Hz. The dihedral angle between the relevant C–H bonds must therefore be low (Karplus equation). Overall this is a very suitable two-step synthesis of 2-azabicyclo[3.2.0] heptenes from phenols.

It was confirmed[31] that irradiation of **1** and of **17** in diethyl ether gave the same products (**27**, R = H and CH_3), but a later re-examination detected minor unstable by-products thought to arise from decarbonylation.[32] In this work small amounts of isomers epimeric at C-4[27] were isolated by GLC; as expected, the coupling constant between H-5 and H-4 was below 3 Hz, consonant with these protons being mutually *trans*. Thus the methyl group at C-4 is on the convex (*exo*) face of the bicyclic structure. Photolysis of **9**[23] and **11** (R = Ph)[20] provided the typical products **28** (R^1 = R^2 = H and R^1 = Ph, R^2 = CH_3, respectively).

7-Aryl-1,3-dihydro[2*H*]azepin-2-ones (**6**) on irradiation gave different products[33] depending upon the solvent. Thus the expected product (**29**) was



(29)



(30)

obtained in benzene, but in chloroform, imines (**30**, R = ^{t}Bu, R^2 = CH_3 or H) were isolated. In methanol mixtures of two enol forms of **30** were seen.

Table 1. 1,3-Dihydro[2*H*]azepin-2-ones

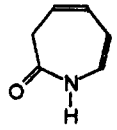
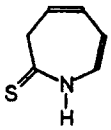
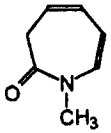
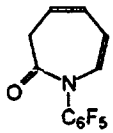
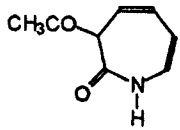
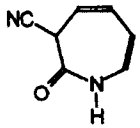
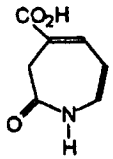
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	47–49	^{1}H NMR, IR	18a, 19, 21, 23
	106–107.5		19
	50–54/0.6 94–95/12	IR, UV	20, 23
	128–130/0.4	IR	14
	135–136	IR, ^{1}H NMR, MS	36
	148–149	IR, ^{1}H NMR, MS	18b
	144–145	IR, ^{1}H NMR	18a

Table 1 (continued)

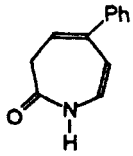
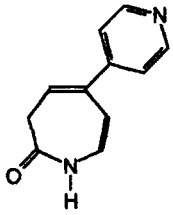
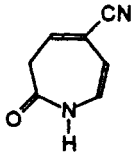
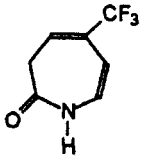
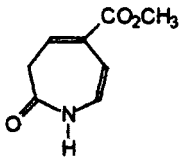
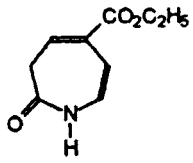
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	141–142	UV	20
	163–165	IR, UV	20
	115	^{1}H NMR	18a
	50	^{1}H NMR	18a
	112	^{1}H NMR	18a
	82	^{1}H NMR	18a

Table 1 (continued)

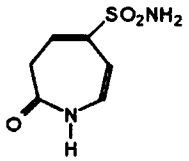
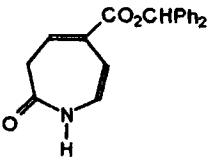
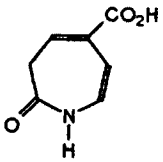
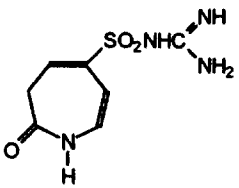
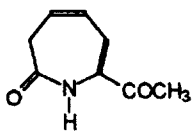
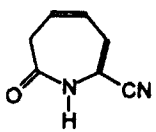
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	171	^{1}H NMR, X-ray, MS	18a, 35
	154	^{1}H NMR	18a
	180	^{1}H NMR	18a
	190–192	IR, ^{1}H NMR, MS	35
	100–105/0.001	R, ^{1}H NMR, MS	36
	143	IR, ^{1}H NMR, MS, X-ray	18b

Table 1 (continued)

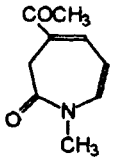
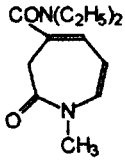
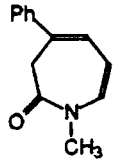
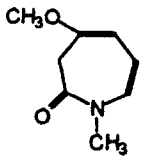
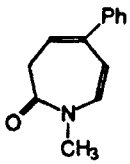
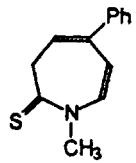
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	54–56	UV, ^{1}H NMR	20
	71–73	UV, ^{1}H NMR	20
	42–44	UV, ^{1}H NMR	20
	82.3/0.3	UV, ^{1}H NMR	20
	92–93	UV, ^{1}H NMR	20
	115	UV, ^{1}H NMR	20

Table 1 (continued)

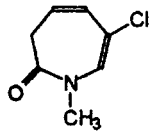
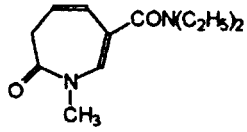
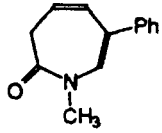
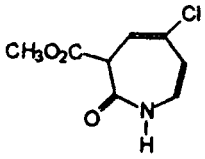
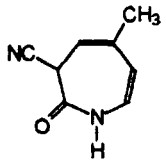
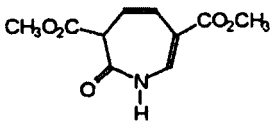
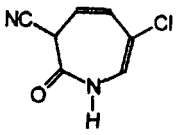
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	68–72/0.2	UV, ^{1}H NMR	20
	87–89	UV, ^{1}H NMR	20
	75–76	UV, ^{1}H NMR	20
	153	^{1}H NMR	18a
	105	IR, ^{1}H NMR, MS,	18b
	138	^{1}H NMR	18a
	156	IR, ^{1}H NMR, MS,	18b

Table 1 (continued)

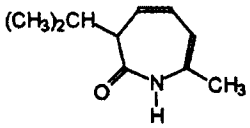
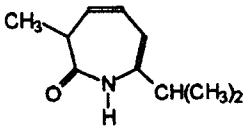
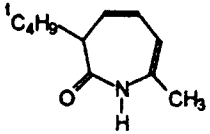
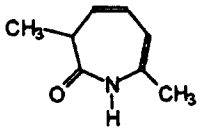
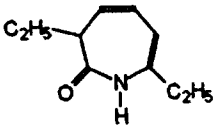
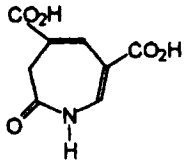
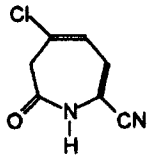
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	90–91	IR, UV, ^{1}H NMR	11
	113.5–114	IR, UV, ^{1}H NMR	11
	131–131.5	IR, UV, ^{1}H NMR	11
	121–122	IR, UV	1, 2
	88.5–89	IR, UV	2
	225	^{1}H NMR	18a
	189–190	IR, ^{1}H NMR, MS, X-ray	18b

Table 1 (continued)

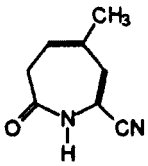
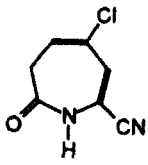
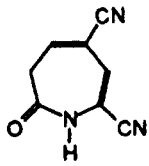
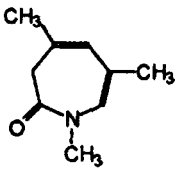
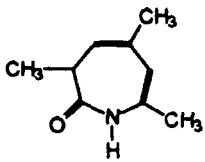
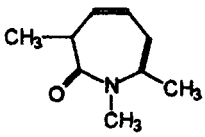
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	136–137	IR, ^{1}H NMR, MS	18b
	170	IR, ^{1}H NMR, MS	18b
	155–157	IR, ^{1}H NMR, MS	18b
	69–71/1.1	UV, ^{1}H NMR	20
	132	IR, UV	2, 4
	109–115/13		2

Table 1 (continued)

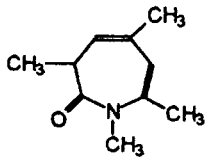
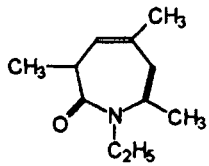
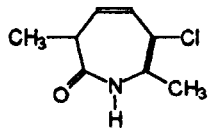
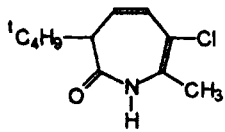
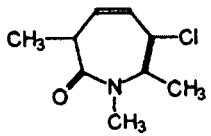
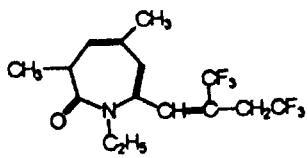
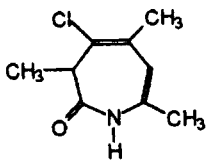
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	121–122/12		2
	116–120/12	IR, UV	28
	158–158.5	IR, ^{1}H NMR	29
	183.5–184	IR, ^{1}H NMR	29
	–	UV, IR, ^{1}H NMR	29
	132–133	IR, UV	28
	174.5–175	IR,UV, ^{1}H NMR	29

Table 1 (continued)

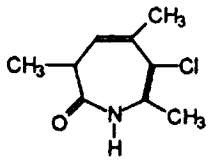
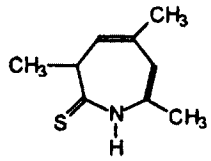
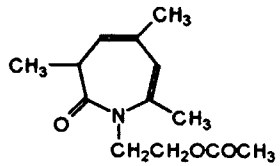
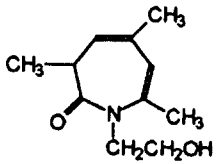
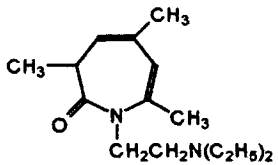
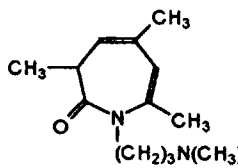
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	141–143	IR, ^{1}H NMR	29
	136.5–137	UV, ^{1}H NMR	27
	116–120/0.4	UV, IR	34
	134/0.35	IR	34
	123/0.3 HCl 159–160		34
	121–127/0.3 HCl 169–169.5		34

Table 1 (continued)

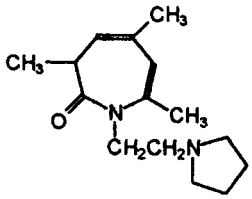
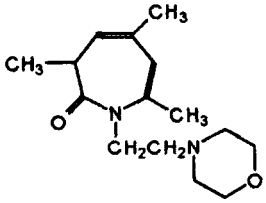
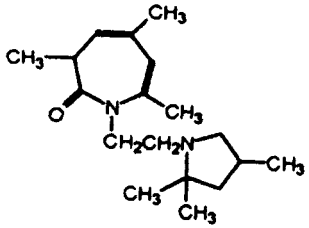
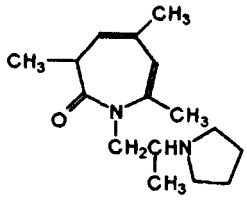
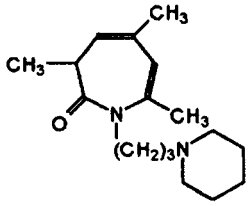
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	126–138/0.13 HCl 197–198		34
	150–158/0.15 HCl 222–224 MeI 218–219		34
	136–147/0.2 MeI 197–198		34
	129–150/0.3 HCl 247–249 MeI 180–182		34
	146–151/0.15 HCl 171–173		34

Table 1 (continued)

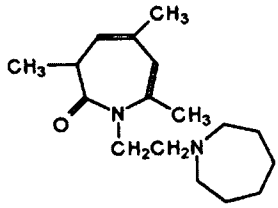
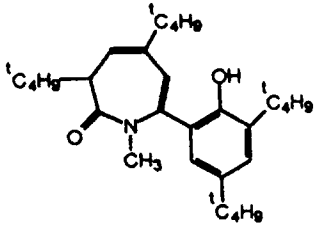
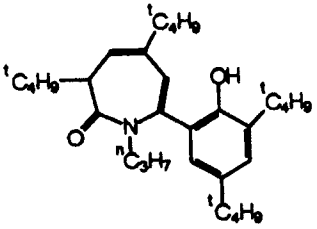
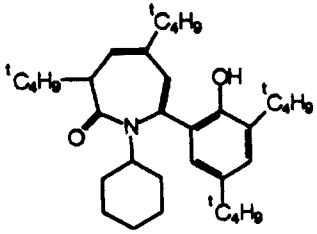
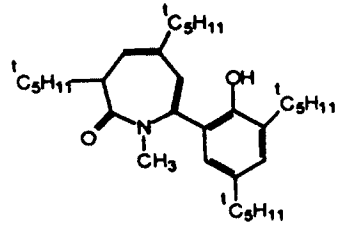
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	136–164/0.2 HCl 172–173		34
	153–155	IR, ^{1}H,^{13}C NMR, MS, UV	13
	162–164	IR, UV, ^{1}H NMR	13
	209–211	IR, UV, ^{1}H NMR, MS	13
	144–146	IR, UV, ^{1}H NMR	13

Table 1 (continued)

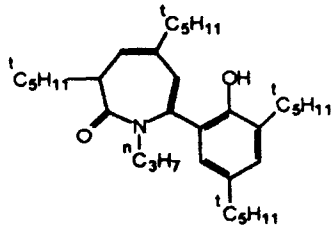
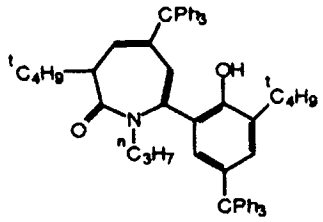
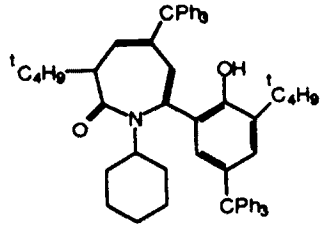
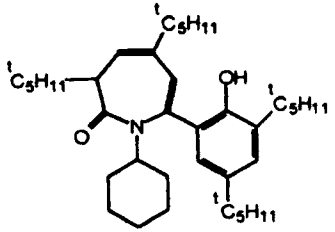
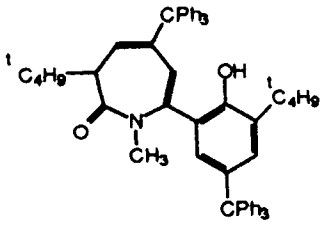
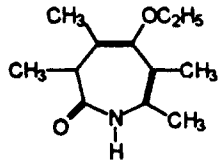
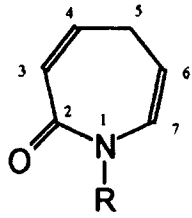
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	180–182	IR, UV, ^{1}H NMR	13
	211–214	IR, UV, ^{1}H NMR	13
	188–191	IR, UV, ^{1}H NMR	13
	153–156	IR, UV, ^{1}H NMR	13
	143–145	IR, UV, ^{1}H NMR	13

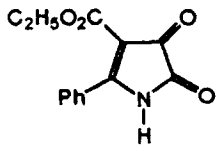
Table 1 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence	Ref.
	143–145	IR, UV, ^{1}H NMR	37

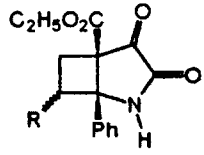
II. 1,5-DIHYDRO[2*H*]AZEPIN-2-ONES



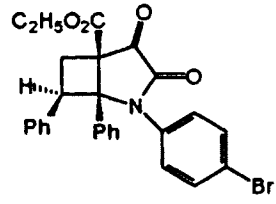
All of the work in this section is due to Sano and his co-workers. Basically the photochemically induced [2 + 2]cycloaddition of alkenes with 2-aryl pyrroline-4,5-diones (**31**) gives rise to the 2-azabicyclo[3.2.0]heptane-3,4-dione ring system (**32**).[38] The regiochemistry and, where appropriate, stereochemistry of this reaction were supported by X-ray analysis of the analogue **33**.[39] Pyridones



(**31**)

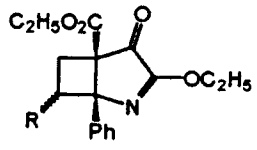


(**32**)

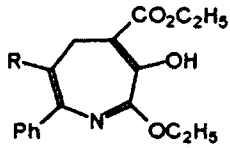


(**33**)

were also formed amongst the products[40] in variable yields. All of the 1,5-dihydro[2*H*]azepin-2-ones reported were obtained from these 2-azabicyclo[3.2.0]heptane-3,4-diones either via imidic esters (**34**)[41] when treated with $SnCl_4$, then hydrolysed (5% HCl), or more commonly from the bicycles using DBU.[42–45] Imidic esters (**34**) were obtained from diones (**32**) by treatment with triethyloxonium fluoroborate [$(C_2H_5)_3O^+$ BF_4^-] (Meerwein's reagent) and the initial $SnCl_4$ induced products were [4*H*]azepines (**35**)[41] (see Chapter 11).

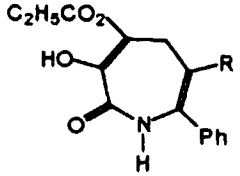


(34)

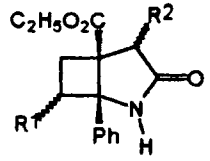


(35)

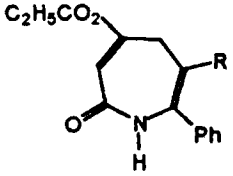
1,5-Dihydro[2*H*]azepin-2-ones (**36**) obtained thus carry a hydroxy group at C-3 and, on dehydrogenation with DDQ yield 'azatropolones' (Chapter 12):



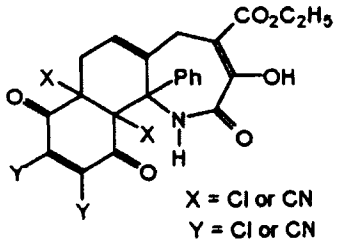
(36)



(37)



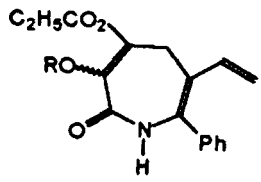
(38)



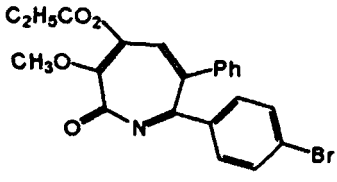
(39)

The hydroxy group may be methylated with diazomethane.[42] In some cases[45] dehydrogenation (e.g. **36**, R = C_2H_5 or OAc) did not proceed cleanly since the products underwent ring contraction to 2-pyridones via a benzilic acid type of rearrangement. Further study of the chemistry of the 2-azabicyclo[3.2.0]heptane-3,4-diones revealed that thermal reactions could lead directly to pyridine derivatives[46,47] and that borohydride reduction gave 4-hydroxy compounds (**37**, R^2 = OH) whose acetates (**37**, R^2 = OAc) underwent eliminative ring expansion to 1,5-dihydro[2*H*]azepin-2-ones lacking the 3-hydroxy group (**38**, R = Ph, OEt, vinyl).[44] The vinyl compound **36** (R = vinyl) not surprisingly underwent Diels–Alder reaction with DDQ[45] to give **39**. An alternative method for obtaining analogues without 3-hydroxy substituents was reported as follows:[44] $^nBu_4NBH_4$ reduction of **36** (R = vinyl) gave **40** (R = H), whose monoacetate (**40**, R = Ac) reacted with DBU giving **38** (R = vinyl).

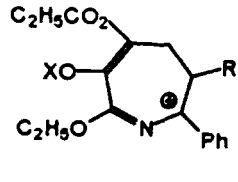
The main interest in 1,5-dihydro[2*H*]azepin-2-ones lies in their relationship with the so-called azatropolones and azatropones by dehydrogenation



(40)



(41)



(42)

referred to above.[45] Treatment with Meerwein's reagent converts them into [4*H*]azepines (e.g. **36** → **35**).

All of the reported 1,5-dihydro[2*H*]azepin-2-ones are relatively stable solid materials, thoroughly analysed and authenticated spectroscopically (UV, IR,^{1}H NMR) and, since a dehydrogenation product (**41**) has been confirmed by X-ray analysis,[48] this area can be said to have been fairly thoroughly explored. It is interesting to speculate whether the ring expansion of 2-azabicyclo[3.2.0]heptanes would be so facile in cases lacking a phenyl group at C-1 because an intermediate cation (**42**) seems likely especially in Lewis acid-promoted examples[41] and solvolyses (e.g. **37**).

Table 2. 1,5-Dihydro[2*H*]azepin-2-ones

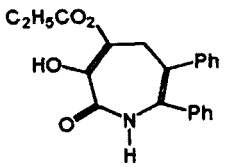
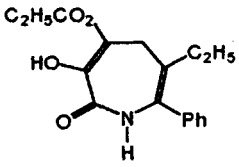
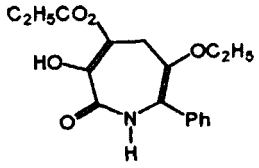
Structure	M.p. (°C)	UV: λ (nm) (ε ($l\,mol^{-1}\,cm^{-1}$))	IR (cm^{-1})	Ref.
	226–236	226 (19 200), 269 (17 600)	3200, 1670, 1600	42, 45
	140–145	227 (13 000), 263 (13 500)	3200, 1665, 1600	42, 45
	173–178	220 (13 600), 262 (17 400)	3200, 1620	42, 45

Table 2 (continued)

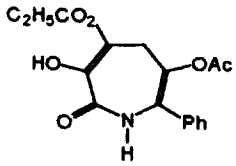
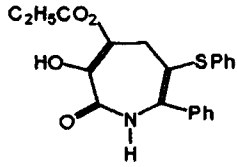
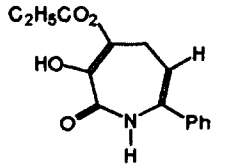
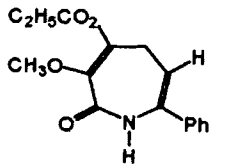
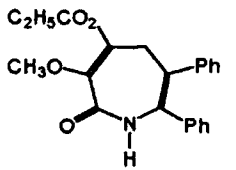
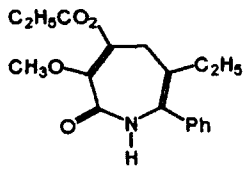
Structure	M.p. (°C)	UV: λ (nm) (ε (l mol^{-1} cm^{-1}))	IR (cm^{-1})	Ref.
	192–194	220 (14 000), 258 (15 400)	3200, 1765, 1680, 1660	42, 45
	178–180	220 (20 300), 263 (18 200)	3200, 3050, 1670, 1660	42, 45
	194–197	220 (14 000), 257 (14 600)	3200, 1680, 1660, 1600	42, 45
	130–131	222 (14 000), 249 (12 800)	1690, 1660sh, 1640, 1620	45
	178–179	228 (18 800), 300sh (10 000)	1700, 1660, 1620	45
	116–118	222 (13 300), 252 (12 200)	3160, 3050, 1700, 1660, 1620	45

Table 2 (continued)

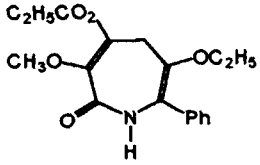
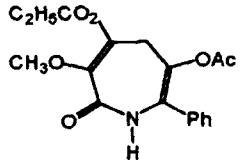
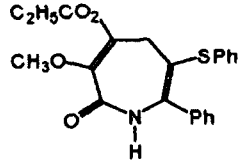
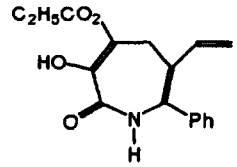
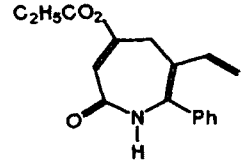
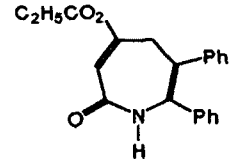
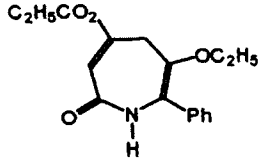
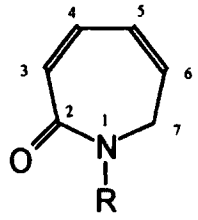
Structure	M.p. (°C)	UV: λ (nm) (ε (l mol^{-1} cm^{-1}))	IR (cm^{-1})	Ref.
	97–99	222 (13 300), 252 (12 200)	1690, 1645, 1605	45
	136–138	220 (14 000), 253 (13 400)	1765, 1700, 1660, 1625	45
	136–141	220 (21 600), 260 (15 400), 315sh (7500)	1710, 1660, 1630, 1605	45
	162–167	233 (19 900), 263 (19 600)	3200, 1680, 1660, 1610	44, 45
	154–155.5	238 (20 900), 279 (8300), 324 (9600)	1705, 1670	44
	163.5–165	238 (22 700), 330 (10 400)	3270, 1695, 1680	44

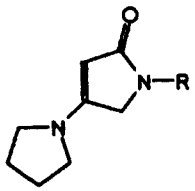
Table 2 (continued)

Structure	M.p. (°C)	UV: λ (nm) (ε (l mol^{-1} cm^{-1}))	IR (cm^{-1})	Ref.
	100–102	340 (11 500)	3180, 1720, 1695, 1690	44

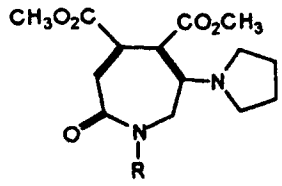
III. 1,7-DIHYDRO[2*H*]AZEPIN-2-ONES



The only reference to this group involves ring expansion of enaminopyrrolidones with dimethyl acetylenedicarboxylate.[49] Thus the enamine **43** (R = H, $PhCH_2$) gave **44** (R = H, $PhCH_2$) in 65% and 58% yield, respectively. None of the other activated alkynes investigated gave any products. Dilute acid hydrolysis of **44** gave **45** (R = H, $PhCH_2$), which were comparatively stable



(43)



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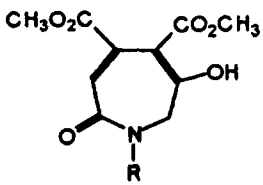
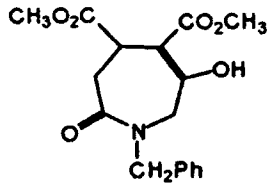


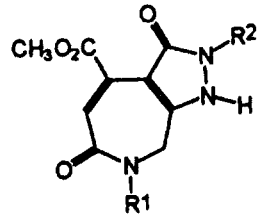
(45)



(46)

to mild hydrolysis. Compound **45** (R = $PhCH_2$) was *O*-methylated with diazomethane as one would expect; however, unexpectedly, one of the products obtained when **45** (R = $PhCH_2$) reacted with trimethylsilyl iodide proved to be the reduced compound **46**.

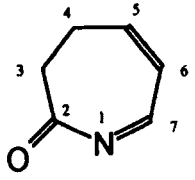
Reaction of the enols **45** (R = H, $PhCH_2$) with hydrazines gave pyrazolo[3,4-*c*] azepines (**47**, R^1 = H, $PhCH_2$; R^2 = H, Ph): these structures are tentative in so



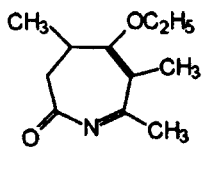
(47)

far as one cannot be sure of the position of the phenyl group in the pyrazole ring. Hydroxylamine failed to react with **45** (R = H, $PhCH_2$).[49]

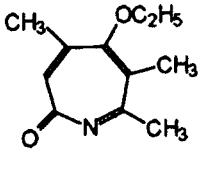
IV. 3,4-DIHYDRO[2*H*]AZEPIN-2-ONES



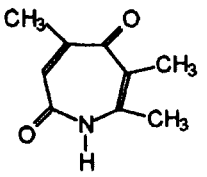
Uniquely,[37] compound **48** was obtained in 90% yield during catalytic hydrogenation of the azepin-2-one **49**. The latter was obtained by reaction of



(48)



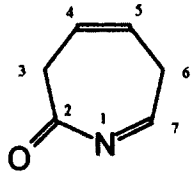
(49)



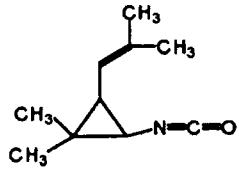
(50)

triethyloxonium fluoroborate (Chapter 12) with the dione **50**, itself the product of the reaction of the appropriate benzoquinone with sodium azide in concentrated sulphuric acid (Chapter 10).

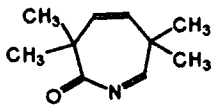
V. 3,6-DIHYDRO[2*H*]AZEPIN-2-ONES



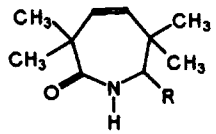
Again, there is only one example. Cope rearrangement[50] of the isocyanate **51** gave **52** in 60% yield. It was hygroscopic and was characterised by spectroscopy



(51)



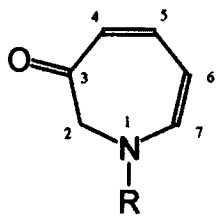
(52)



(53)

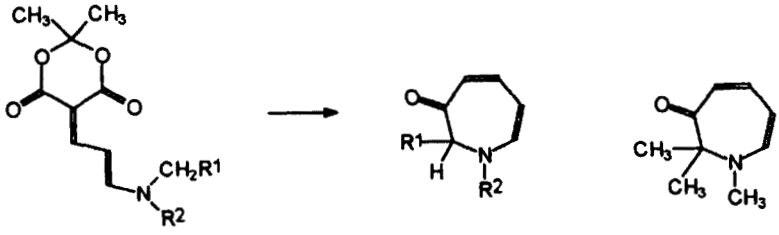
and chemical conversions to a variety of reduced structures (e.g. **53**, R = OH, OCH_3, SPh and H).

VII. 1,2-DIHYDRO[3*H*]AZEPIN-3-ONES



PREPARATION

The almost exclusive and very satisfactory method for these compounds depends upon the flash vacuum pyrolysis of certain dienamine derivatives of Meldrum's acid (**54a–d**)[51,52] at about 500 °C. In the case of **54** (R^1 = H, R^2 = ^{i}Pr), the products included both **55** (R^1 = H, R^2 = ^{i}Pr) and the fragmentation product **56**. All 1,2-dihydro[3*H*]azepin-3-ones (**55**, **56**) are yellow solids and X-ray data[52] indicated that although the seven-membered ring was

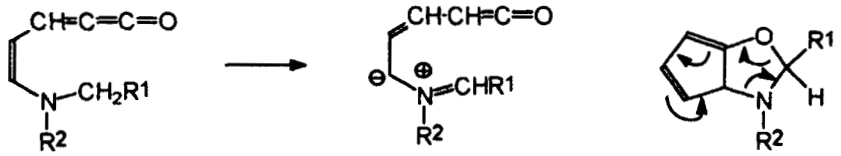


(54) (55) (56)

a; R1 = H, R2 = CH_3
b; R1 = H, R2 = Ph
c; R1 = CH_3, R2 = C_2H_5
d; R1 = R2 = Ph

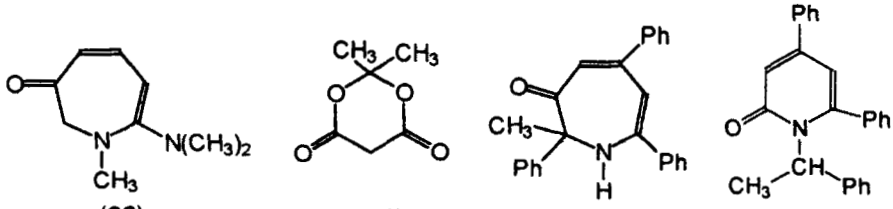
distinctly non-planar, nevertheless the dienaminone portion of the molecule was nearly planar as is found in acyclic and other cyclic examples.

A plausible mechanism[51] for the production of these compounds involved hydrogen transfer from the methylene ketene **57** to an intermediate (**58**) capable



(57) (58) (59)

of undergoing either electrocyclisation to **55** or cycloaddition to **59**, which can fragment to cyclopentadienone and an imine. This is supported by the fact that the dimer of cyclopentadienone is generally isolated along with the imine; in the case of **54** ($R^1 = R^2 =$ Ph) benzylidineaniline was identified. Recently, the synthesis was extended[53] to the 7-dimethylamino derivative **60**.



(60) (61) (62) (63)

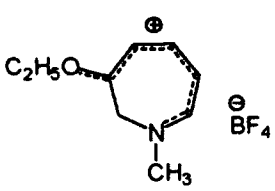
The Meldrum's acid derivatives (e.g. **54**) required for this protocol are in general fairly easily obtainable from Meldrum's acid (**61**) and the pyrolysis products are easily separated by chromatography on alumina.

There is only one other access to a 1,2-dihydro[3*H*]azepin-3-one, namely treatment of the pyridone **63** with LDA in THF, which gave the divinylogous amide **62**.[54]

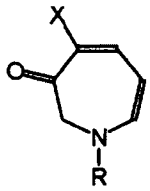
PROPERTIES

The behaviour of 1,2-dihydro[3*H*]azepin-3-ones has been examined in admirable detail by McNab and co-workers. ^{1}H and ^{13}C NMR spectra of 1-substituted, 1,2-disubstituted and 1,2,2-trisubstituted examples were obtained[55] and analysed thoroughly. All parameters were assigned and discussed; this made it possible to state with some certainty the position of attack of reagents and structures of products obtained in later work.[56–59]

It was demonstrated[57] that *O*-protonation took place in trifluoroacetic acid since there were striking similarities between ^{1}H and ^{13}C NMR spectra of the protonated *N*-methyl compound (**55**; $R^1 = H$, $R^2 = CH_3$) and the undoubted *O*-ethyl compound (**64**) obtained by reaction with Meerwein's reagent. Deuterium exchange took place in [^{2}H]trifluoroacetic acid; the rates of exchange at indicated positions were 4 > 6 ≫ 2. Reaction of the *N*-methyl (**55**, $R^1 = H$, $R^2 = CH_3$) and *N*-phenyl (**55**, $R^1 = H$, $R^2 = Ph$) derivatives with one



(64)



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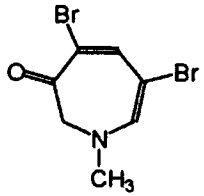

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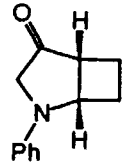
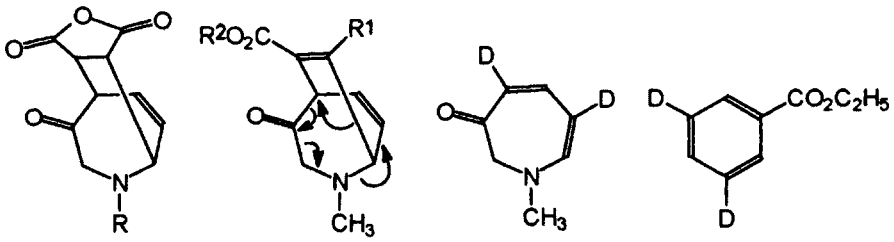


(67)

equivalent of *N*-chlorosuccinimide in methanol at 0 °C gave the 4-chloro compounds (**65**; X = Cl, R = CH_3 and Ph) in tolerable yields. They proved to be stable in the solid state but not in solution, especially when heated. Further chlorination led to 4,6-dichloro compounds. *N*-Bromosuccinimide reacted with **55** ($R^1 = H$, $R^2 = CH_3$) giving the 4,6-dibromo compound **66** as the only clearly identified product irrespective of the proportions of reagent used; with one equivalent of NBS there appeared to be unreacted starting material, possibly contaminated with **65** (R = CH_3, X = Br). The structure of **65** (X = Cl, R = CH_3) was confirmed by X-ray analysis.[57]

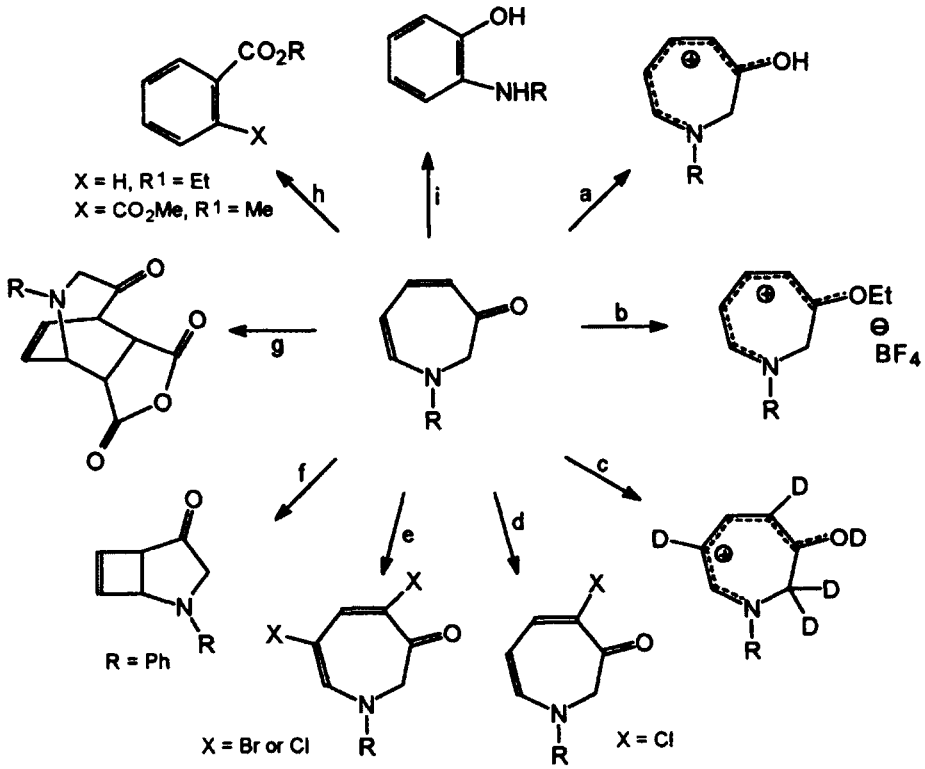
Photolysis of **55** ($R^1 = H$, $R^2 = Ph$) gave the expected electrocyclisation product **67**; this reaction was thermally reversible.[58] Cycloadditions of 1,2-dihydro[3*H*]azepin-3-ones proceeded best with maleic anhydride to give **68** (R = CH_3 and Ph). Cycloaddition with DMAD and ethyl propiolate yielded benzenoid products, presumably by loss of fragments (CO + imine) as shown (**69**). Regiochemistry of addition was elucidated by reacting the dideuterio compound **70** with ethyl propiolate, in which case the product was the *m*-dideuterioethyl benzoate **71**.[58] Treatment of the compounds **55** ($R^1 = H$, $R^2 = CH_3$ or Ph) with sodium methoxide in methanol produced



(68) (69) (70) (71)

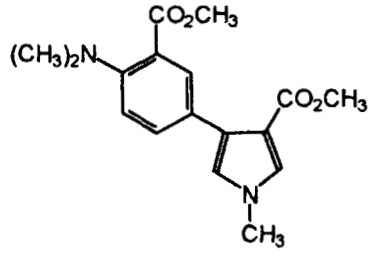
2-aminophenol derivatives; a plausible mechanism was proposed which involved an azanorcaradiene intermediate.[59]

A summary of the reactions undergone by 1,2-dihydro[3*H*]azepin-3-ones is shown in the scheme.[56]



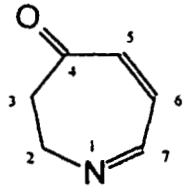
Reagents: a, CF_3CO_2H; b, $Et_3O^+ BF_4^-$; c, CF_3CO_2D; d, *N*-chlorosuccinimide; e, *N*-bromo- or *N*-chlorosuccinimide (2 equiv.); f, *hν*; g, maleic anhydride; h, $HC{\equiv}CCO_2Et$ or $MeO_2CC{\equiv}CCO_2Me$; i, NaOMe/MeOH, then H^+.

The 7-dimethylamino representative **60**, activated by the electron-donating substituent, behaved differently from those above.[53] Protonation of **60** gave a stable mixture of 22% *O*- and 78% 4*C*-protonated materials and cycloaddition with methyl propiolate yielded the 1:2 adduct (minus H_2O) (**72**).

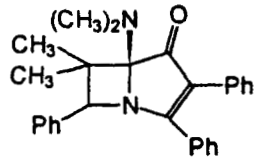


(72)

XV. 2,3-DIHYDRO[4*H*]AZEPIN-4-ONES



There appears to be only one reference[60] in the literature to these derivatives. Thus, when 2-amino-1-azetines reacted in acetonitrile with 2,3-diphenylcyclopropenones, the products were azeto[1,2-*a*]pyrroles (e.g. **73**); the latter, on



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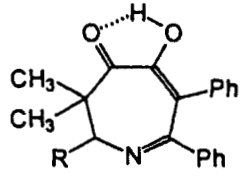

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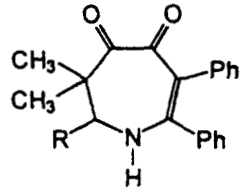
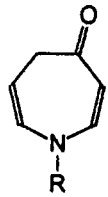


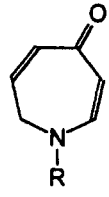
(75)

hydrolysis with 2 M HCl in ethanol at room temperature, gave the enolic tautomers (**74**) of the tetrahydrodiones (**75**). In the case of **74** (R = Ph), hydrolysis yields of about 90% were seen, but with **74** (R = H), the yield was about 7%, along with **75** (R = H) in 30% yield.[60]

There are, therefore, representatives of only seven of the eighteen possible structures that can be drawn for dihydroazepinones. It seems surprising that 1,5-dihydro[4*H*]azepin-4-ones (**76**) and 1,7-dihydro[4*H*]azepin-4-ones (**77**) have not been reported since they contain some generally conjugative stabilising features.



(76)



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George R. Proctor, James Redpath
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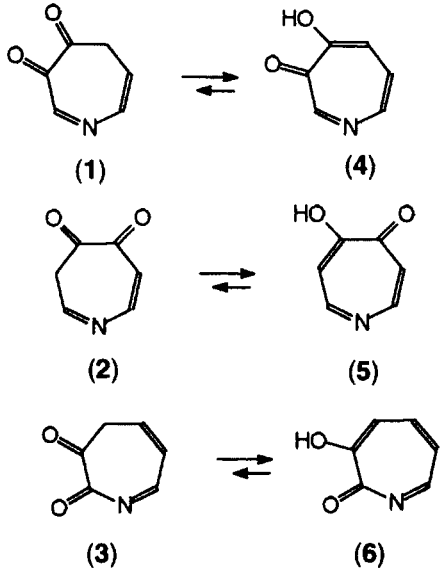
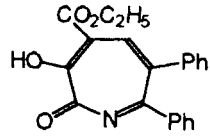
CHAPTER 10

Dihydroazepinediones

Of sixteen possible structures in this category, only three are known with certainty. It should be pointed out, however, that three of the apparently unknown dione (**1–3**) structures would be expected to exist in the corresponding enolic forms (**4–6**) which would be regarded as 'azatropolones' (Chapter 12).

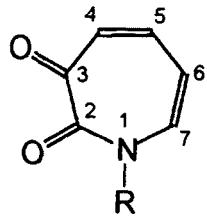


In fact, structures related to **5** were claimed more than 30 years ago,[1] but later shown to be in error.[2] Furthermore, the tautomeric form (**6**) was indeed found to be the stable assembly in several examples (e.g. **7**; Chapter 12).[3]

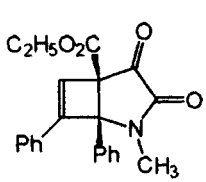


(7)

I. 2,3-DIHYDRO[1*H*]AZEPINE-2,3-DIONES



The thermal ring opening of **8** was shown to lead to the dione **9**,[6] which was obtained as yellow needles, m.p. 130–131 °C. The IR spectrum of the latter



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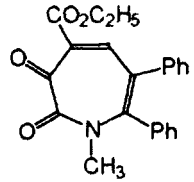
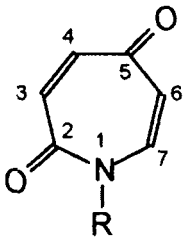


(9)

exhibited three distinct carbonyl stretching frequencies at 1730, 1685 and 1625 cm^{-1} as one might have expected. Both the ^{1}H and ^{13}C NMR spectra were consonant with structure **9**.

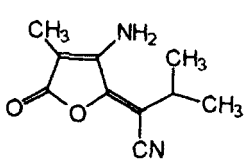
V. 2,5-DIHYDRO[1*H*]AZEPINE-2,5-DIONES



These have been obtained exclusively by application of the Schmidt reaction to 1,4-benzoquinones. The experimental conditions are crucial: the quinones were

stirred at 0 °C in concentrated sulphuric acid while sodium azide was added slowly in portions.[7–10] Some structural errors[7,8] were later corrected,[9,10] partly by re-interpretation of ^{1}H NMR spectra and partly by hydrolysis of the diones and careful isolation and identification of steam-volatile ketones and accompanying acids. In particular, aldehydes were not formed after hydrolysis; this demanded that the carbon atom next to nitrogen in the heterocycle must carry an alkyl (methyl) substituent. Corrected structures are shown in Table 1.

Not all Schmidt reactions on 1,4-benzoquinones gave 2,5-dihydro[1*H*]-azepine-2,5-diones. Thus thymoquinone under slightly different conditions gave the amino lactone **10**[12] and hydroxynaphthoquinones also gave ring-contracted products[11] (e.g. **11**, R = H, X = NH, and R = CH_3, X = O). It has been shown that aqueous sodium hydroxide at reflux converted **12** into **13**;[13] seemingly the behaviour of the diones upon hydrolysis depends very much on the substituents present.



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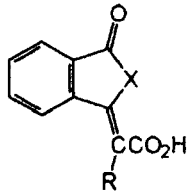

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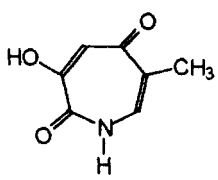

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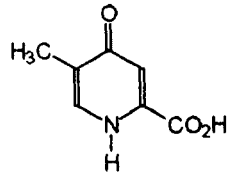


(13)

Table 1. 2,5-Dihydro[1*H*]azepine-2,5-diones

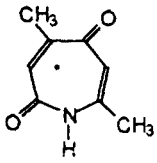
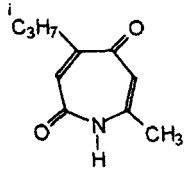
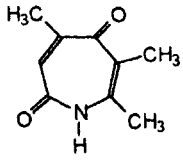
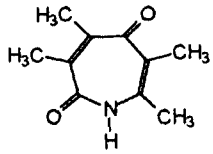
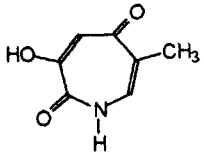
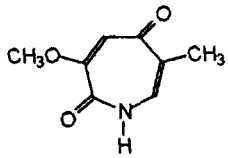
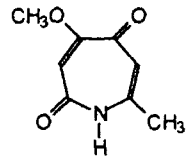
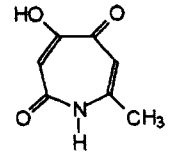
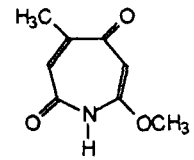
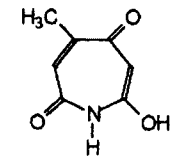
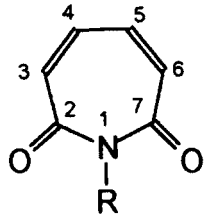
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	216–217	^{1}H NMR, UV, IR	8, 9
	169–170	^{1}H NMR, UV, IR	8–10
	199–200	^{1}H NMR, UV, IR	8, 9

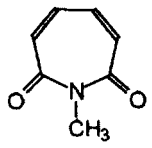
Table 1 (continued)

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	201–202 214–215	^{1}H NMR, UV, IR	9 8
	253–255	IR, MS, ^{1}H NMR	13
	285–287	IR, MS, ^{1}H NMR	13
	226–226.5	IR, MS, ^{1}H NMR	13
	250–251	IR, MS, ^{1}H NMR	13
	111–112	IR, MS, ^{1}H NMR	13
	197.5–199	IR, MS, ^{1}H NMR	13

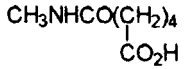
IX. 2,7-DIHYDRO[1*H*]AZEPINE-2,7-DIONES



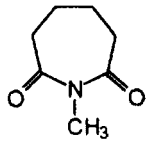
Two examples of the 2,7-dihydro[1*H*]azepine-2,7-dione system have been reported in the literature. The 1-methyl derivative (**14**) was synthesised[14] as



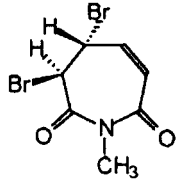
(**14**)



(**15**)



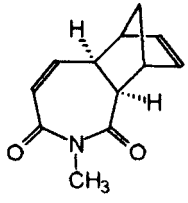
(**16**)



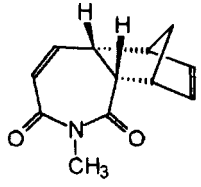
(**17**)

follows: thionyl chloride treatment of *N*-methyladipamic acid (**15**) gave the imide **16**, which could be brominated ($CuBr_2$) and dehydrobrominated (Et_3N) to **14**. The mass spectrum of the latter was discussed in some detail; it is interesting that all the major peaks are identical with those of 1-methyl-2-pyridone.

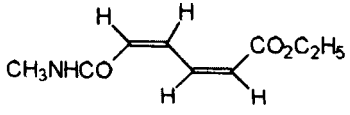
On bromination (ice-cold hexane) **14** yielded *trans*-3,4-dihydro-3,4-dibromo-1-methylazepine-2,7-dione (**17**) and the cycloaddition reaction with cyclopentadiene gave the *exo* and *endo* products (**18** and **19**) wherein the heterocycle had reacted as a dienophile. It did not react with maleic anhydride or with TCE, that



(**18**)



(**19**)

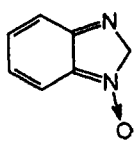


(**20**)

is, it lacks diene properties in the Diels–Alder sense. Ethanolysis of **14** gave ethyl *N*-methyl-*cis*,*cis*-muconamate (**20**).[14]

The parent compound (**22**) has recently been prepared in poor yield by the UV irradiation of the benzofuroxan **21**; a mechanism for the reaction was

postulated involving ring opening to the unstable di(nitrile oxide) **23** followed by rearrangement to the azepinedione **22**.[15]



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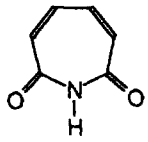

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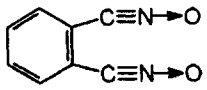
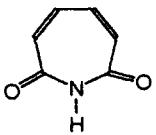
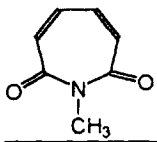


(23)

The physical data reported for the two 2,7-dihydro[1*H*]azepine-2,7-diones **14** and **22** are given in Table 2.

Table 2. 2,7-Dihydro[1*H*]azepine-2,7-diones

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	76–77.8	UV, IR, MS, ^{1}H NMR	15
	167–168	UV, IR, MS, ^{1}H, ^{13}C NMR	14

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4. T. Sano, Y. Horiguchi and Y. Tsuda, *Heterocycles*, 1979, **12**, 1427.
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6. T. Sano, Y. Horiguchi and Y. Tsuda, *Chem. Pharm. Bull.*, 1990, **38**, 3283.
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Chemistry of Heterocyclic Compounds, Volume 56
George R. Proctor, James Redpath
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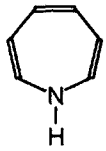
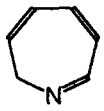
CHAPTER 11

Azepines

The fully unsaturated azepine system can exist in four isomeric forms, [1*H*]-, [2*H*]-, [3*H*]- and [4*H*]azepines (**1**, **2**, **3** and **4**, respectively), and stable derivatives of each isomer have been reported in the literature.



(1)



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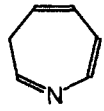

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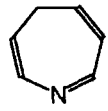
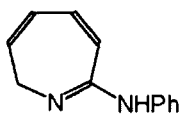


(4)

In early reports there was apparently some confusion in identifying the correct structures and many of the erroneous assignments were only corrected with the introduction of ^{1}H NMR spectroscopy as a routine analytical technique. For example, dibenzamil, isolated by Wolff in 1912,[1] was not recognised as an azepine until 1958 when Huisgen and co-workers[2,3] identified the seven-membered ring system, but preferred the [2*H*] or [4*H*] structures **5** or **6** on the basis of the UV and IR spectra. The correct identification was finally achieved by Doering and Odum,[4] who proposed the [3*H*] structure **7** on the basis of the ^{1}H NMR spectrum. A later review,[5] in which the alicyclic cycloheptatriene **8** was compared with the heterocyclic analogues confirmed the assignment and clarified the situation.



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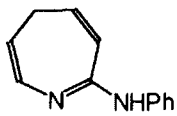

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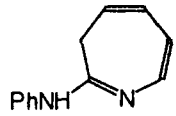

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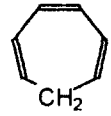
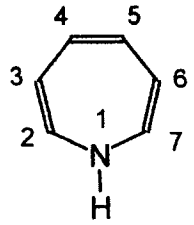


(8)

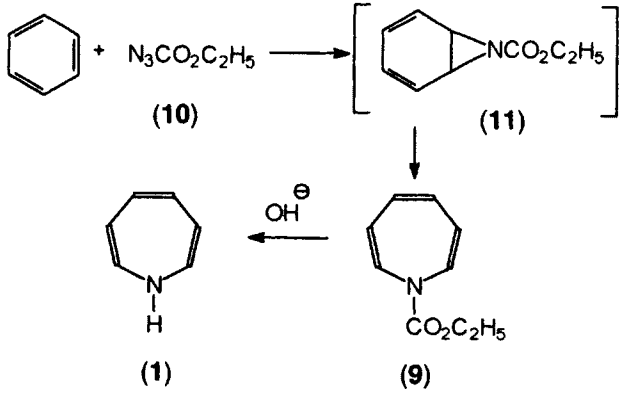
I. [1*H*]AZEPINES



PREPARATION

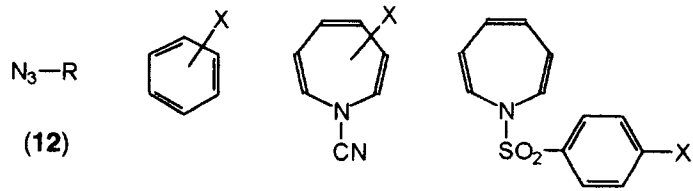
The parent [1*H*]azepine **1** was first generated by Hafner in 1963[6] by hydrolysis of ethyl [1*H*]azepine-*N*-carboxylate (**9**).[6–13] Owing to its high reactivity, however (tautomerism to the [3*H*]azepine **3** and polymerisation), it was not characterised until 1980 when Vogel and his co-workers[8] obtained the ^{1}H and ^{13}C NMR spectra of the pure compound in solution before it decomposed. At −78 °C the compound is stable for only a few hours in solution and it has not been isolated.

[1*H*]Azepines substituted on the N atom, such as the 1-carbethoxy derivative **9**, have been prepared by the method of Hafner and König[7] by insertion of a nitrene into a six-membered ring. The nitrene was generated by UV irradiation of the corresponding azide (**10**). The presumed bicyclic [4.1.0]azaheptene **11** has not been isolated, but was proposed to explain the mechanism of the insertion[7,8,10] (Scheme 1) (see, however, section III for an alternative explanation for the mechanism of the reaction).



Scheme 1

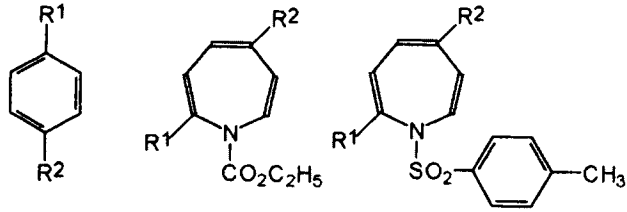
This method is of general application and has been used with various azides, e.g. the azidonitrile **12** (R = CN) and substituted benzenes **13** (X = H, alkyl, halogen, etc.) to give a range of 1-cyano[1*H*]azepines (**14**, X = H, alkyl, halogen, etc.)[14,15] (see Table 1 for details).



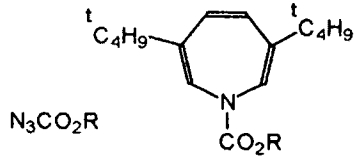
(12) **(13)** **(14)** **(15)**

A range of substituted benzenesulphonyl analogues (**15**, X = H, Cl, Br, NO_2, CH_3, OCH_3) has been made from the corresponding benzenesulphonyl azides (**12**, R = $SO_2C_6H_4X$, X = H, Cl, Br, NO_2, CH_3, OCH_3) with benzene or substituted benzenes, thus illustrating further the generality of the method.[16–18] The use of a phase-transfer catalyst has resulted in improved yields and shorter reaction times,[19] and increasing the reaction pressure has been shown to have a similar effect.[20]

The reaction of a disubstituted benzene such as **16** (R^1 = CH_3, R^2 = Cl, Br) with the azido ester **12** (R = $CO_2C_2H_5$)[21] or treatment of **16** (R^1 = R^2 = CO_2CH_3) with *p*-toluenesulphonyl azide (**12**, R = $SO_2C_6H_4$-*p*-CH_3)[22] resulted in the formation of 2,5-disubstituted azepines (**17**, R^1 = CH_3, R^2 = Cl, Br and **18**, R^1 = R^2 = CO_2CH_3, respectively).



(16) **(17)** **(18)**

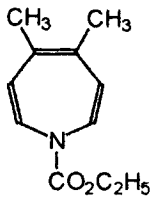


(19) **(20)**

In an exceptional case, di-*tert*-butylbenzene (**16**, R^1 = R^2 = ^{t}Bu) when reacted with a range of azido esters (**19**, R = C_2H_5, $CH_2{}^cC_3H_5$, ^{t}Bu,

C_6H_4-*p*-OCH_3) gave the 3,6-disubstituted [1*H*]azepines **20** (R = C_2H_5, $CH_2{}^cC_3H_5$, ^{t}Bu, C_6H_4-*p*-OCH_3) as the main products.[23]

A systematic study of the reactions of *o*-, *m*- and *p*-xylene (**16**, $R^1 = R^2 = CH_3$) with the azido ester **19** (R = C_2H_5) gave mixtures of isomers of dimethyl[1*H*]azepines. Of the four possible products from *o*-xylene, only the 4,5- and the 3,4-dimethyl[1*H*]azepines (**21** and **22**) were formed. Similarly, *m*-xylene gave the 3,5- and 2,4-dimethyl[1*H*]azepines (**23** and **24**) and *p*-xylene (**16**, $R^1 = R^2 = CH_3$) gave both the 2,5- and the 3,6-dimethyl[1*H*]azepines (**17**, $R^1 = R^2 = CH_3$, and **25**), although only the former compound could be isolated from the 66:34 mixture.[24]



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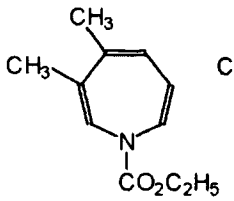

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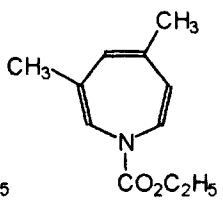

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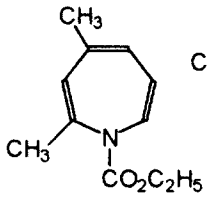

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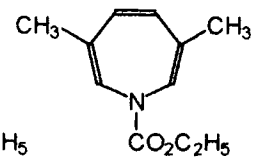
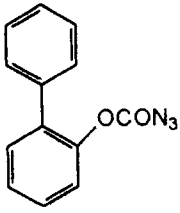


(25)

A variety of other substituted [1*H*]azepines have been prepared in an analogous manner from appropriately substituted benzenes and azides.[22,25,26a,27–33,71] In one case the nitrene from the azide **26** has been induced to insert intramolecularly to give the intermediate **27**, which yielded the [1*H*]]azepine **28** on treatment with ethylamine. By contrast, acid hydrolysis of the intermediate **27** gave the [3*H*]azepine **29**.[34]



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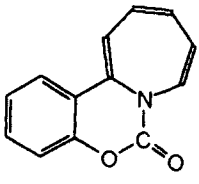

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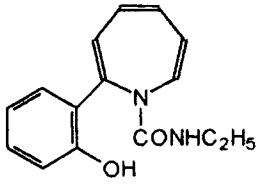

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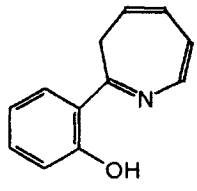
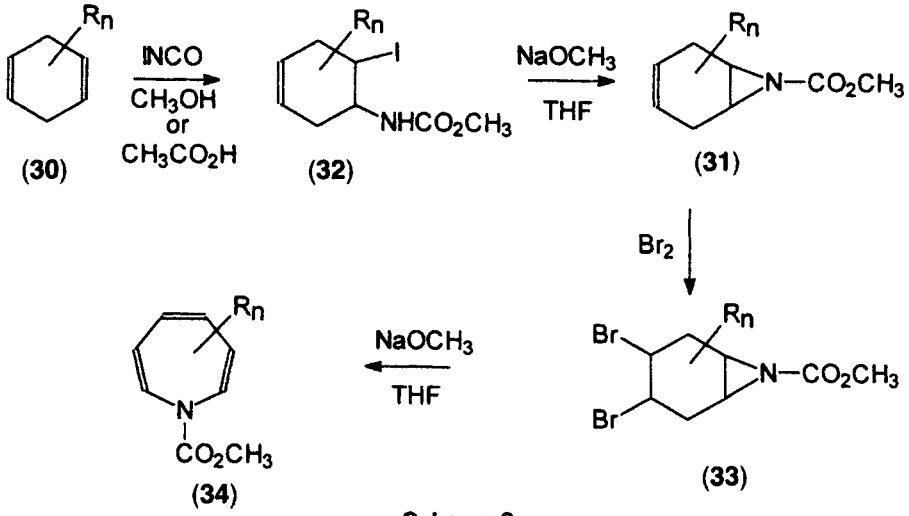


(29)

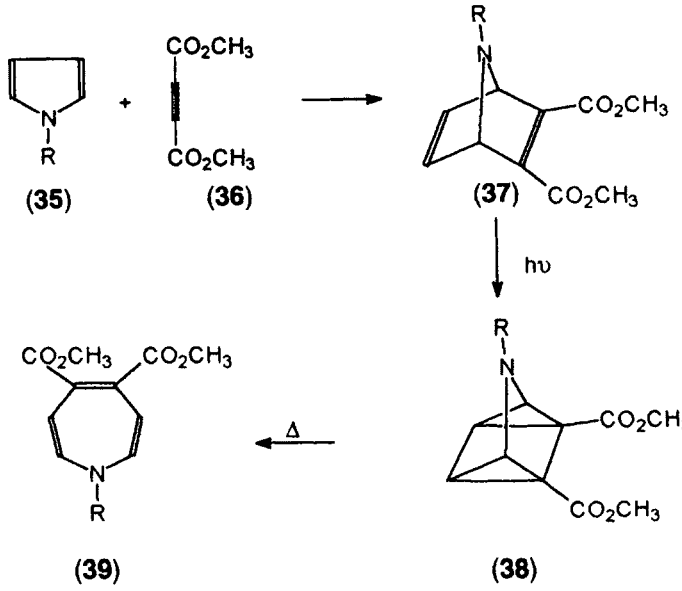
Although the bicyclic structure **11** does not appear to have been isolated,[7,8,10] Paquette and his co-workers have isolated a series of analogues (**31**, R = H, or R = CH_3, n = 1, 2) which they prepared from the corresponding 1,4-cyclohexadienes (**30**, R = H or CH_3, n = 1, 2) using iodine isocyanate in acetic acid or methanol, and reacting the intermediate iodoamide (**32**, R = H or CH_3, n = 1, 2) with $NaOCH_3$ in THF. Bromination of **31** to the dibromo compound **33** and dehydrobromination/ring opening with $NaOCH_3$ in THF gave the corresponding [1*H*]azepines **34** (R = H or CH_3, n = 1, 2) as shown in Scheme 2.[35,36]



Scheme 2

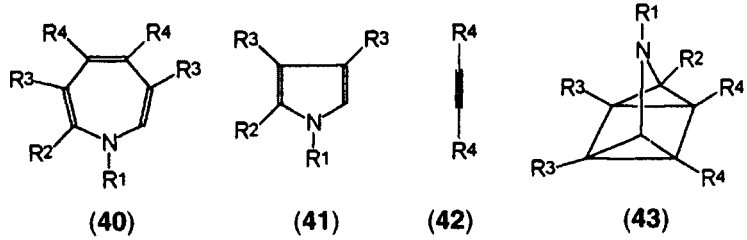
N-Substituted pyrroles, on treatment with acetylenes under Diels–Alder conditions, form [2.2.1]bicyclic systems which rearrange on UV irradiation to azaquadricyclanes. Thermal rearrangement of these azaquadricyclanes generates *N*-substituted [1*H*]azepines. This sequence of events has been used by Bansal *et al.*[37] and Prinzbach *et al.*[38] to produce [1*H*]azepines (**39**, R = CO_2CH_3 and R = $COCH_3$, $SO_2C_6H_4$-*p*-CH_3) from the pyrroles **35** (R = CO_2CH_3 and R = $COCH_3$, $SO_2C_6H_4$-*p*-CH_3, respectively) on treatment with dimethyl acetylenedicarboxylate (**36**) according to Scheme 3.[37,38]

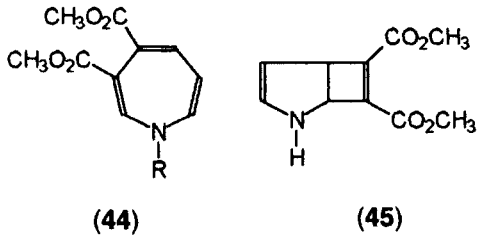
This reaction sequence has been extensively studied and exploited by Prinzbach and co-workers in the period 1968–86,[38–43] during which time they produced a wide range of azepines (**40**, R^1 = $COCH_3$, CO_2CH_3, $CONH_2$, SO_2CH_3, $SO_2C_6H_4$-*p*-CH_3, C_6H_4-*p*-NO_2, R^2 = H, $CH{=}CH_2$, R^3 = H, Cl, Ph, R^4 = H, CF_3, CO_2CH_3) from the corresponding pyrroles (**41**, R^1 = $COCH_3$, CO_2CH_3, $CONH_2$, SO_2CH_3, $SO_2C_6H_4$-*p*-CH_3, C_6H_4-*p*-NO_2, R^2 = H, $CH{=}CH_2$, R^3 = H, Cl, Ph) and appropriately substituted acetylenes (**42**, R^4 = H, CF_3, CO_2CH_3) via the corresponding azaquadricyclane intermediates



Scheme 3

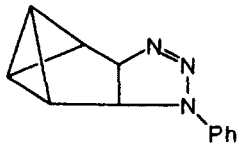
(**43**, R^1 = $COCH_3$, CO_2CH_3, $CONH_2$, SO_2CH_3, $SO_2C_6H_4$-*p*-CH_3, C_6H_4-*p*-NO_2, R^2 = H, $CH{=}CH_2$, R^3 = H, Cl, Ph, R^4 = H, CF_3, CO_2CH_3)[38–43] (see Table 1 for details).





In contrast to these results,[37–40] it has also been reported that UV irradiation of the unsubstituted pyrrole **35** (R = H) led to the 3,4-dicarbomethoxy-[1*H*]azepine **44** rather than the 4,5-analogue **39** (R = H) as might be expected. In this case, the alternative product **39** (R = H) was excluded on the basis of the proton NMR spectrum, and the intermediate proposed to explain the results was the bicyclo[3.2.1]azaheptadiene **45** rather than the azaquadricyclane **38** (R = H).[44]

Other ring expansion reactions have also been used to prepare [1*H*]azepines. For example, the *N*-phenylaziridine **47**, prepared from the triazoline **46**, on heating to 150 °C, gave 1-phenyl[1*H*]azepine (**48**), but unfortunately with substituents on the N atom other than phenyl, thermolysis does not result in the corresponding azepines.[45]



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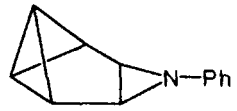

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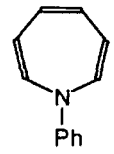
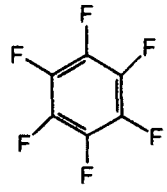


(48)

A similar sequence of reactions from hexafluorobenzene (**49**) and either phenyl azide (**12**, R = Ph) or ethyl azidoformate (**10**) gave the corresponding triazolines **50** (R = Ph, $CO_2C_2H_5$), which in turn were pyrolysed to the hexafluoro[1*H*]azepines **51** (R = Ph, $CO_2C_2H_5$).[46]



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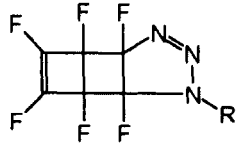

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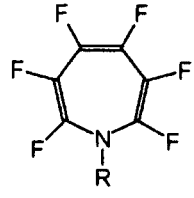
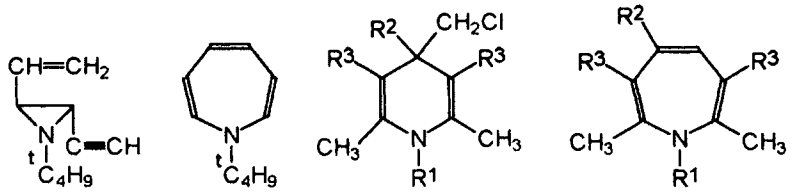


(51)

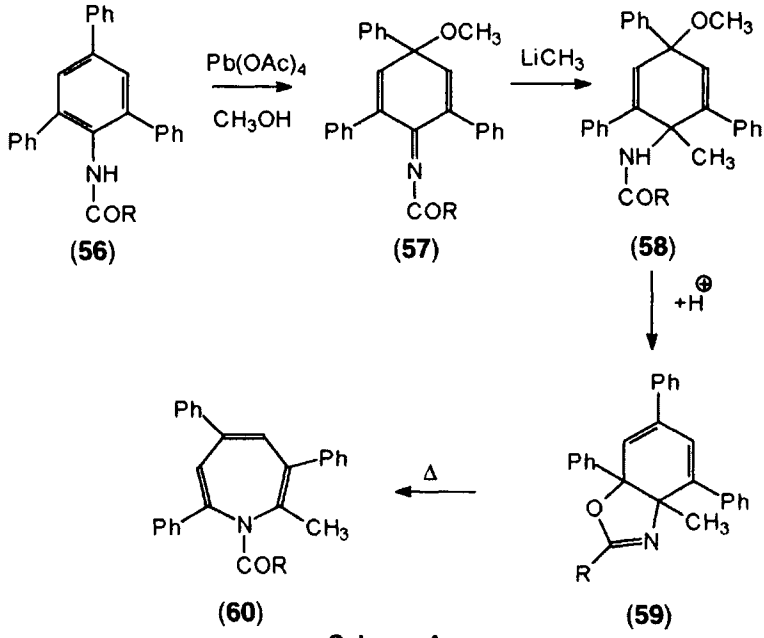
The thermally induced ring expansion of the *trans*-aziridine **52** has been reported to proceed at 100 °C to give the 1-*tert*-butylazepine **53**, albeit in low yield,[47] and the 4-chloromethyldihydropyridines **54** ($R^1 = CH_3$, $R^2 = H$, $R^3 = CO_2CH_3$, and $R^1 = CH_3$, Ph, *p*-$CH_3C_4H_6$, $R^2 = CH_3$, $R^3 = CN$) have been converted into the corresponding azepines **55** ($R^1 = CH_3$, $R^2 = H$, $R^3 = CO_2CH_3$, and $R^1 = CH_3$, Ph, *p*-$CH_3C_4H_6$, $R^2 = CH_3$, $R^3 = CN$) by treatment with KO^tBu or KOH, respectively, at room temperature.[48,49]

In a novel sequence of reactions (see Scheme 4), the 2,4,6-triphenylanilides **56** (R = CH_3, Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4) were oxidised with



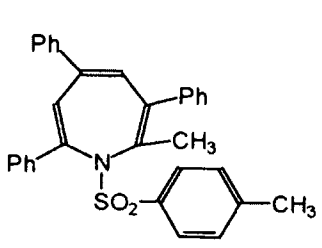
(52) (53) (54) (55)

lead tetraacetate in methanol to give the corresponding cyclohexa-2,5-diene-1-ylidenecarboxamides **57** (R = CH_3, Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4), which in turn were alkylated using methyllithium to produce the cyclohexa-2,5-dienamides **58** (R = CH_3, Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4). The latter compounds on subsequent treatment with acid gave the bicyclic oxazoline derivatives **59** (R = CH_3, Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4), which on heating to 180 °C were converted smoothly into the corresponding *N*-acyl[1*H*]azepines **60** (R = CH_3, Ph, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-BrC_6H_4).[50]



Scheme 4

The *N*-tosyl analogue **61** was prepared in a similar manner from the corresponding *p*-toluenesulphonamide **62**, but in this case the reaction proceeded without isolation of an analogous oxathiazoline intermediate.[50]



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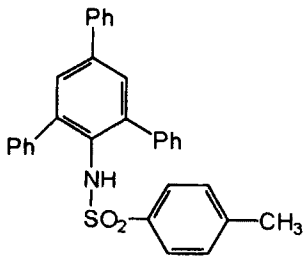

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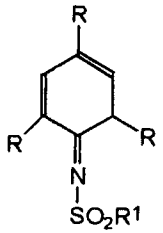

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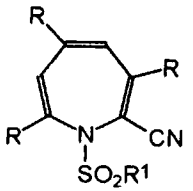
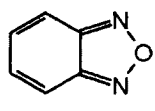


(64)

A similar ring-expansion reaction was subsequently reported, resulting from the action of potassium cyanide on the cyclohexa-2,4-diene-1-ylidene-sulphonamides **63** (R = CH_3, R^1=CH_3, Ph, *p*-$CH_3C_6H_4$ and R = Ph, R^1 = *p*-$CH_3C_6H_4$) to yield a series of 1-sulphonyl-2-cyano[1*H*]azepines (**64**, R = CH_3, R^1 = CH_3, Ph, *p*-$CH_3C_6H_4$ and R = Ph, R^1 = *p*-$CH_3C_6H_4$).[51]

Other heterocyclic and benzenoid rings have been successfully expanded to give the [1*H*]azepine ring system.[52–55] These include the benzofuran **65**[52] and the azirine aldehyde **66**,[53] which gave the azepines **67** and **68**, respectively on UV irradiation, the cyclopropylbenzene **69**, which was elaborated to the



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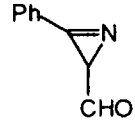

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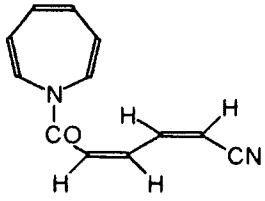

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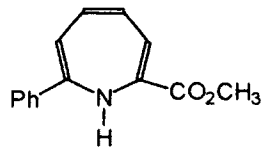
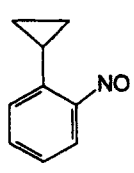


(68)

[1*H*]azepine **70** in the presence of diethylamine,[54] and the bicyclic compound **71** (R = ^{s}Bu), which on treatment with dimethyl acetylenedicarboxylate at 100 °C was converted into the tetramethyl[1*H*]azepine-3,4,5,6-tetracarboxylate **72**.[55]



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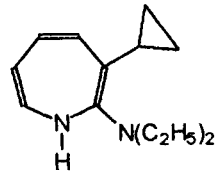

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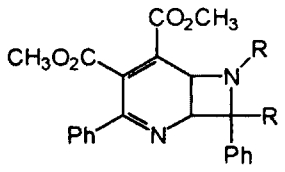

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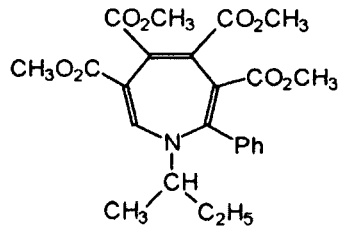


(72)

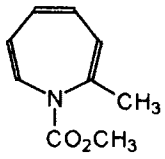
A full list of [1*H*]azepines and their physical constants is given in Table 1.

PROPERTIES

Most of the substituted [1*H*]azepines which have been studied are solids with a clearly defined melting point, although a few have only been isolated as oils. The [1*H*]azepine ring system is stable to a variety of chemical reagents, for example, withstanding acid conditions which are strong enough to hydrolyse a 1-nitrile to a 1-carboxamide,[56] or treatment with Raney nickel to remove a 1-tosylate group.[57] Even at elevated temperatures many of the compounds are stable, as witnessed by their formation under pyrolytic conditions.[37,38,45–47,50] In some cases, however, pyrolytic rearrangement or dimerisation can occur depending on the pattern of substitution on the [1*H*]azepine ring. For example, the 2-methyl derivative **73** undergoes rearrangement at 200 °C to give a bicyclic ring system (**74**),[58] whereas the unsubstituted esters [**75**, R = CH_3, C_2H_5, $C(CH_3)_3$] dimerise under the same conditions to give the bridged system **76** [R = CH_3, C_2H_5, $C(CH_3)_3$)].[59] No dimerisation takes place in the presence of a 2-, 4- or 7-methyl group.[58]

By contrast, the highly substituted [1*H*]azepine **77** rearranges in boiling toluene to give the fulvene **78**.[60]

Photochemically induced rearrangement using UV light of a series of 2-, 3- and 4-methyl[1*H*]azepines resulted in the formation of [3.2.0] bicyclic ring



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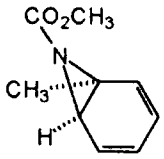

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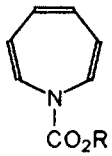

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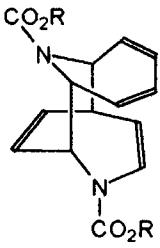
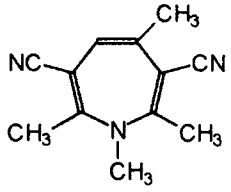
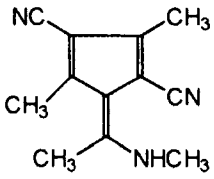


(76)

systems. For example, the 2-methyl derivative **73** gave a 14:1 isomeric mixture of **79** and **80**.[61] The products arise from the formation of a new bond from C-2

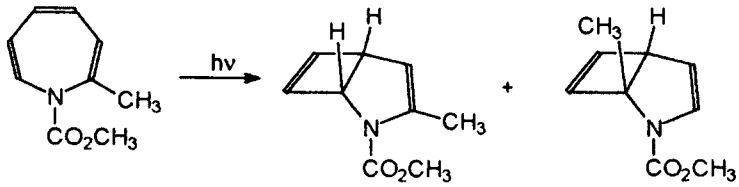


(77)

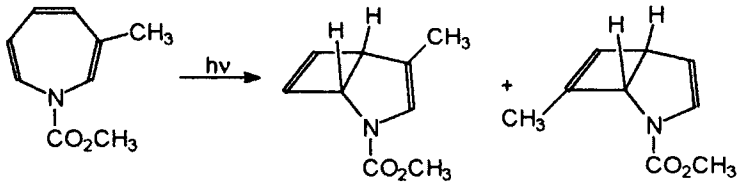


(78)

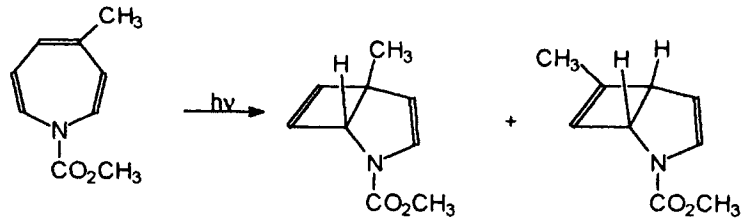
to C-5 or from C-4 to C-7 of the original [1*H*]azepine. The 3- and 4-methyl[1*H*]azepines **81** and **84** behave analogously but the products, **82**, **83** and **85**, **86**, respectively are formed in approximately 1:1 ratios.[61]



(73) (79) (80)

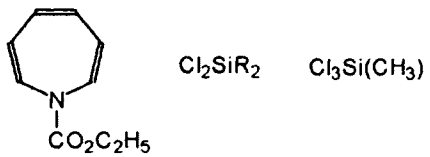


(81) (82) (83)

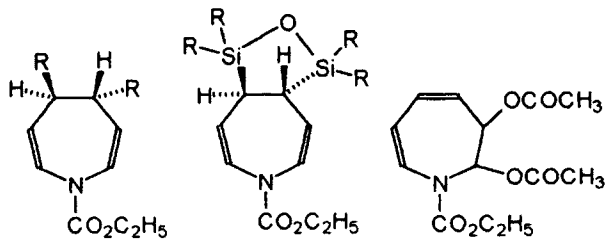


(84) (85) (86)

1,2-Addition to both the 2,3- and the 4,5-double bonds of the [1*H*]azepine system has been reported. For example, at room temperature in the presence of hexamethylphosphoric acid triamide (HMPA) and magnesium, 1-carbethoxy[1*H*]azepine (**9**) reacted with the chlorosilane derivatives (**87**, R = CH_3, Ph, and **88**) to give the corresponding 4,5-*trans*-silyl derivatives **89** [R = $Si(CH_3)_2OH$, $SiPh_2OH$, $Si(CH_3)_3$, respectively].[62,63] On heating to 120 °C, the hydroxysilyl derivatives **89** [R = $Si(CH_3)_2OH$, $SiPh_2OH$] afforded



(9) (87) (88)

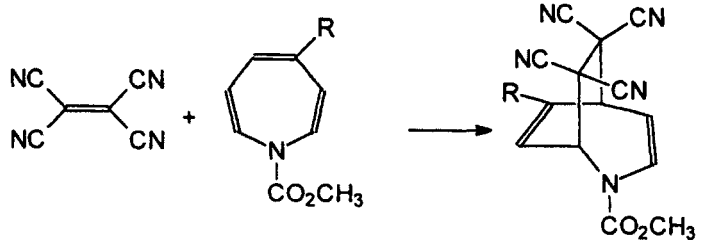


(89) (90) (91)

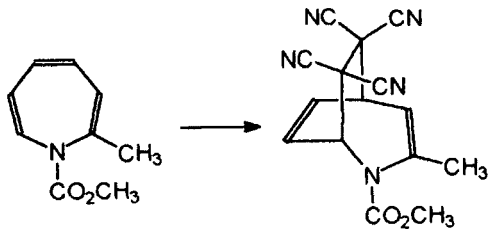
the bicyclic compounds **90** (R = CH_3, Ph) in almost quantitative yield.[63] This addition reaction only occurred on the 4,5-double bond of the [1*H*]azepine ring system. By contrast, addition of acetoxy groups to the 2,3-double bond of 1-carbethoxy[1*H*]azepine (**9**) was reported to take place using $Pd(OAc)_2$ to give the 2,3-diacetoxy derivative (**91**). The yield, however, was only 19%.[64]

Cycloaddition reactions of *N*-substituted azepines to various dienophiles and dienes have been studied.[65–70] For example, tetracyanoethylene (**92**), when reacted with a range of 4-substituted [1*H*]azepines (**84**) and **93** (R = H, Br, Cl, F, OCH_3), gave addition across the 2,5-double bond and formed the corresponding [3.2.2] bicyclic products **94** (R = H, CH_3, Br, Cl, F, OCH_3).[65]

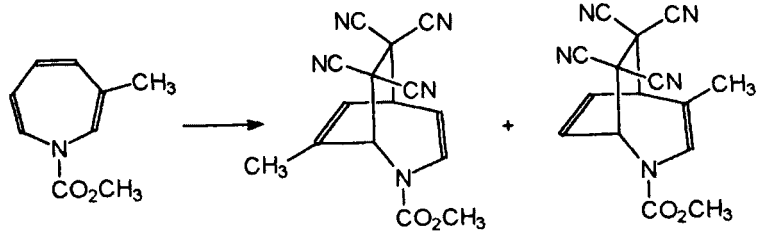
The structure of the bromo compound **94** (R = Br) has been confirmed by X-ray crystallography.[66] The reaction has also been extended to the 2-methyl- (**73**)[65,67] and 3-methyl derivatives (**81**).[67] With the 2-methyl derivative (**73**), addition occurred over the 4,7-position to give **95**, whereas with the 3-methyl derivative (**81**) a mixture of isomers (**96** and **97**) resulted from 2,5- and 4,7-addition.[67]



(92) (93) (94)

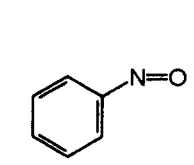


(73) (95)



(81) (96) (97)

N-Nitrosobenzene (**98**) has been reported to form cyclo-adducts with 1-carbethoxy[1*H*]azepine (**9**), to give a single adduct (**99**) in one case[68] and two isomeric adducts (**99** and **100**) in another.[69] By contrast, *N*,α-diphenyl nitrone (**101**) added across the 4,5-double bond of 1-carbomethoxy[1*H*]azepine (**93**, R = H) to give the bicyclic oxazolidine **102**[69] and, in a similar manner, tetrachlorocyclopentadiene dimethyl acetal (**103**) added to the carbethoxy analogue **9** to give the bridged ring system **104**.[70]



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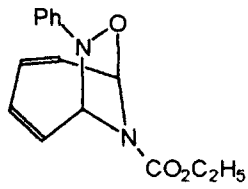

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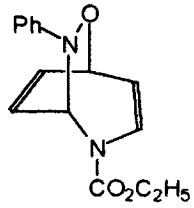
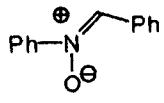
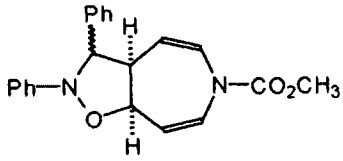


(100)



(101)



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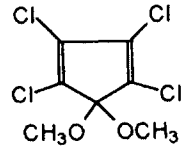
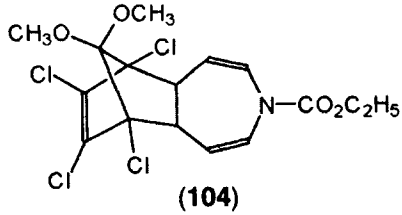


(103)



(104)

Table 1 gives details of the [1*H*]azepines described.

Table 1. [1*H*]Azepines

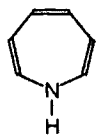
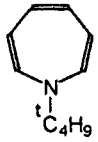
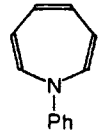
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
		^{1}H, ^{13}C NMR	6 8
		^{1}H NMR ^{1}H, ^{13}C NMR	47b 47a
	49–49.5	UV, ^{1}H NMR	28 45

Table 1 (continued)

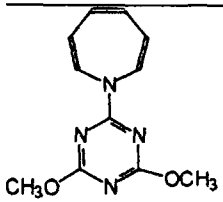
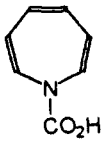
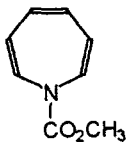
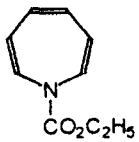
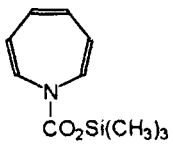
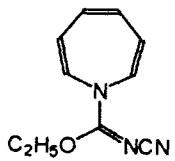
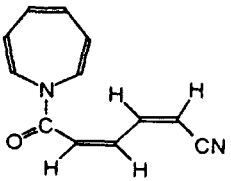
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	105–106	UV, MS, ^{1}H NMR	30
		^{1}H, ^{13}C NMR	8
	59–61/0.2 62–63/0.05	n_D^{25} 1.5379, IR, ^{1}H NMR, UV, MS ^{13}C NMR	36 11
	130/20	IR, ^{1}H NMR UV, ^{1}H NMR UV, IR ^{13}C NMR MS, ^{1}H NMR claimed	33 7 10 11 13 9, 12, 26b, 26c, 32
	63/0.02		8
		MS, ^{1}H NMR claimed	13
	121–122	UV, IR, MS, ^{1}H NMR	52

Table 1 (continued)

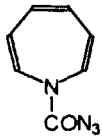
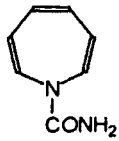
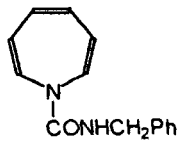
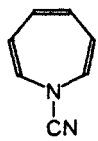
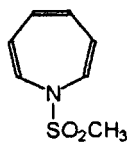
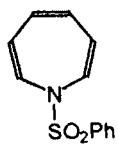
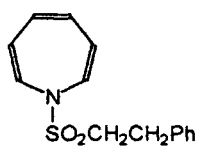
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
			12
			12
		^{1}H NMR	12
	49–50/2	IR, UV, MS, ^{1}H NMR $n_D^{25.2}$ 1.5520, IR, ^{1}H NMR	14 15
	91.5–92.5	IR, ^{1}H NMR, UV, MS ^{1}H, ^{13}C NMR	36 8
	132–133 132–133 133	 IR, ^{1}H NMR, UV, MS IR, ^{1}H NMR, MS	18 36 19
	35–36	IR, ^{1}H NMR, MS	27

Table 1 (continued)

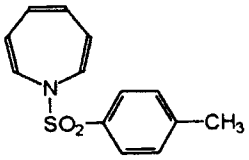
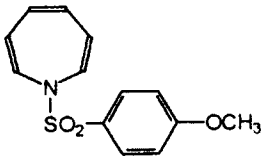
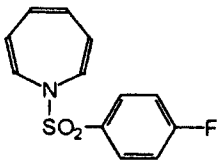
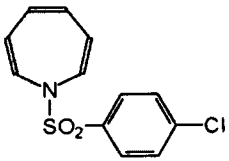
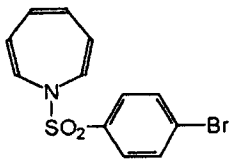
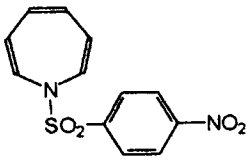
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	169 (d) 167 (d) 167 169 167	^{1}H NMR IR, ^{1}H NMR, UV, MS IR, ^{1}H NMR, MS IR, UV, ^{1}H NMR	43 20a 19 39 18, 20b
	111–112 110–111	IR, ^{1}H NMR, MS IR, UV, ^{1}H NMR, MS	19 18
	Semi-solid	IR, ^{1}H NMR, MS	19
	122–123 121–122	IR, ^{1}H NMR, MS IR, UV, ^{1}H NMR, MS	19 18
	132.5–134 132 132	IR, ^{1}H NMR, UV IR, ^{1}H NMR, MS	36 19 18
	175* 145* (*Different m.p. quoted by same authors)	IR, ^{1}H NMR, MS IR, UV, ^{1}H NMR, MS	19 18

Table 1 (continued)

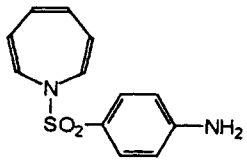
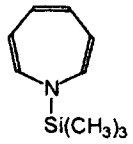
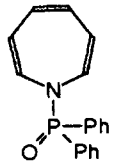
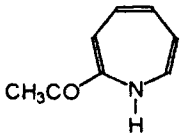
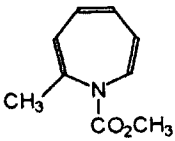
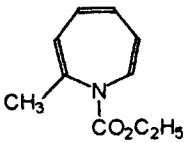
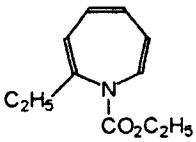
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	170–171	IR, UV, ^{1}H NMR, MS	18
		^{1}H, ^{13}C NMR	8
	151.5–153	IR, ^{1}H NMR, UV, MS	36
	144	UV, IR, ^{1}H NMR	57
	62–64/0.1	UV, ^{1}H NMR n_D^{25} 1.5264, IR, ^{1}H NMR, UV, MS	35 36
		^{1}H NMR, C,H,N analysis IR, ^{1}H NMR	21 33 32
		^{1}H NMR, C,H,N analysis	21

Table 1 (continued)

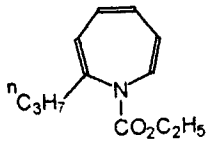
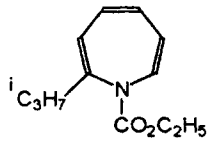
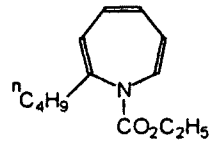
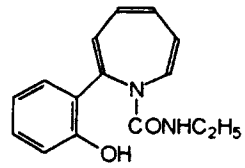
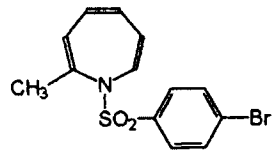
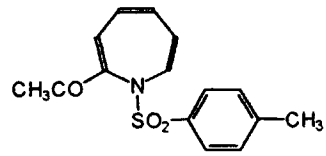
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
		^{1}H NMR, C,H,N analysis	21
		^{1}H NMR, C,H,N analysis	21
		^{1}H NMR, C,H,N analysis	21
	121–122	IR, ^{1}H NMR	34
	94.5–95.5	IR, ^{1}H NMR, UV	36
	125	IR, ^{1}H NMR, MS, UV	17

Table 1 (continued)

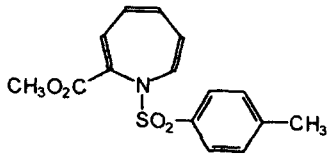
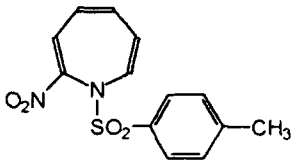
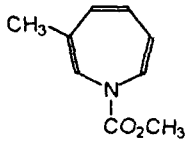
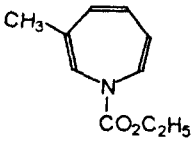
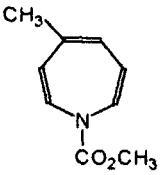
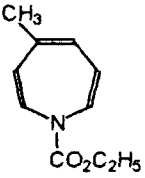
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	92	IR, UV, MS, ^{1}H NMR	16
		IR, ^{1}H NMR, MS, UV claimed	17
	62–65/0.15–0.25	UV, ^{1}H NMR IR, ^{1}H NMR, UV, MS	35 36
		IR, ^{1}H NMR	33 32
	62–65/0.2	UV, ^{1}H NMR n_D^{25} 1.5338, IR, ^{1}H NMR UV, MS	35 36
		IR, ^{1}H NMR	33 32

Table 1 (continued)

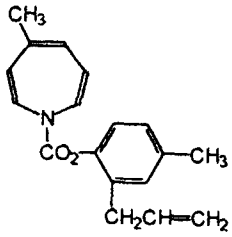
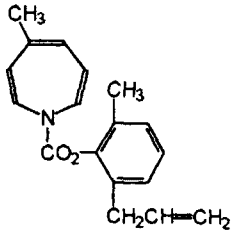
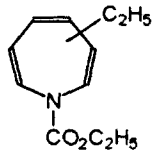
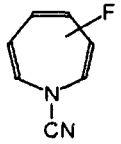
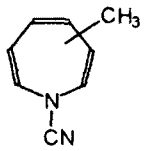
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
		^1H, ^{13}C NMR, IR, MS	29
		^1H, ^{13}C NMR, IR, MS	29
 Isomeric mixture		GC/MS	26a
 Isomeric mixture	25/0.03–0.07	IR, ^1H,^{19}F NMR	15 14
 Isomeric mixture		^1H NMR	15 14

Table 1 (continued)

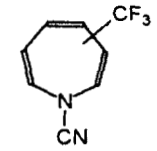
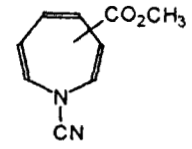
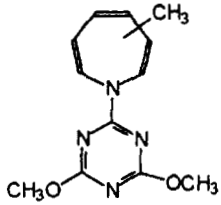
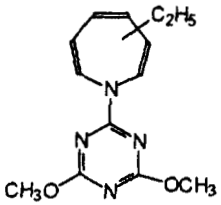
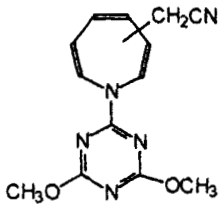
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
 Isomeric mixture	30–40/0.02	IR, MS	15 14
 Isomeric mixture	55/0.1	IR, ^{1}H NMR	15 14
 Isomeric mixture	101–102	UV, MS, ^{1}H NMR	30
 Isomeric mixture	87–88	UV, MS, ^{1}H NMR	30
 Isomeric mixture	107–108	UV, MS, ^{1}H NMR	30

Table 1 (continued)

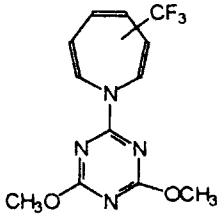
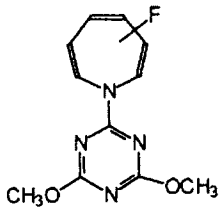
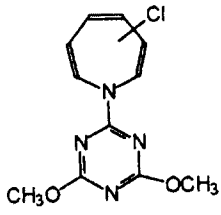
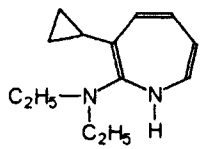
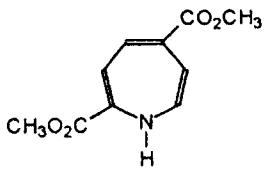
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
 Isomeric mixture	109–110	UV, MS, ^{1}H NMR	30
 Isomeric mixture	117–118	UV, MS, ^{1}H NMR	30
 Isomeric mixture	159–160	UV, MS, ^{1}H NMR	30
		n_D^{25} 1.5295, IR, ^{1}H NMR	54
	112	IR, UV, ^{1}H NMR	57

Table 1 (continued)

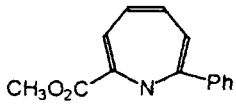
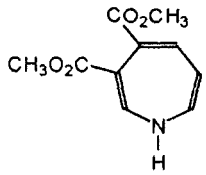
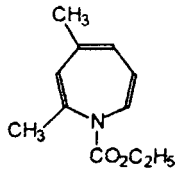
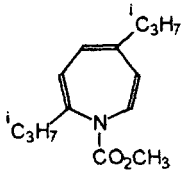
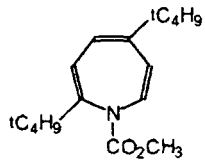
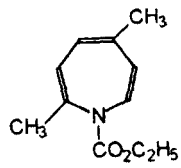
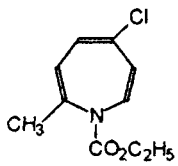
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	156–157	IR, UV, MS, ^{1}H NMR	53
	104	IR, UV, MS, ^{1}H NMR	44
		^{1}H NMR	24
	Pale yellow oil	IR, UV, ^{1}H, ^{13}C NMR, MS	71c
	56–57	IR, UV, ^{1}H, ^{13}C NMR, MS	71b
		^{1}H NMR	24
		^{1}H NMR, C,H,N,Cl analysis	21

Table 1 (continued)

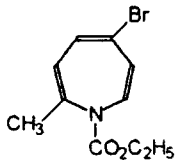
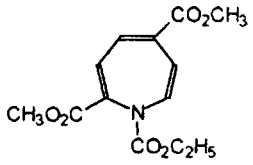
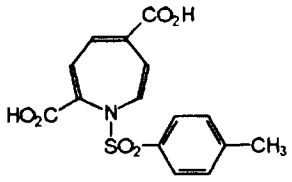
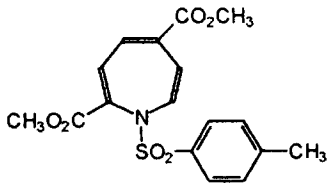
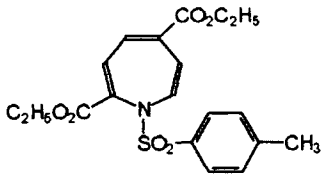
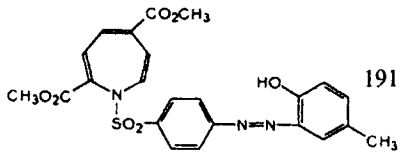
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
		^{1}H NMR, C,H,N,Br analysis	21
	94–95 93	IR, MS, ^{1}H NMR IR, UV, MS, ^{1}H NMR	22 25
	253	MS, IR	16
	127 126	IR, ^{1}H NMR IR, UV, MS, ^{1}H NMR	22 16
	69	IR, UV, MS, ^{1}H NMR	33
	191 (d)	IR, ^{1}H NMR, UV, MS	31

Table 1 (continued)

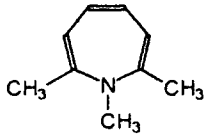
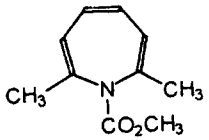
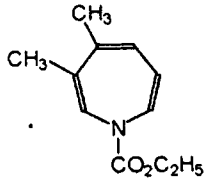
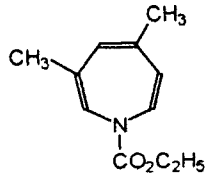
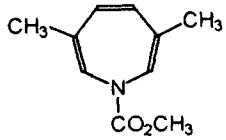
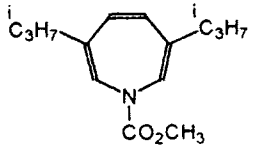
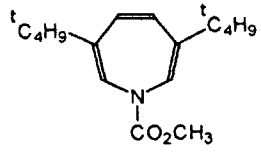
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	Decomp.	IR, ^{1}H NMR, UV	36
	53–54	IR, ^{1}H NMR, UV, MS	36
		^{1}H NMR	24
		^{1}H NMR	24
	29–31	IR, ^{1}H NMR, UV, MS ^{13}C NMR	36 11
	Pale yellow oil	^{13}C NMR IR, ^{1}H NMR, UV, MS	11 71c
	Yellow oil	^{13}C NMR IR, ^{1}H NMR, UV, MS	11 71b

Table 1 (continued)

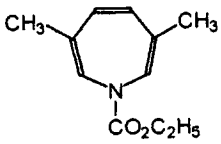
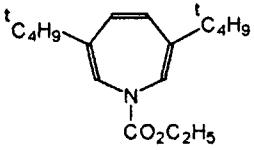
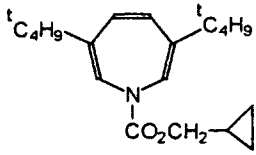
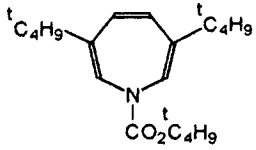
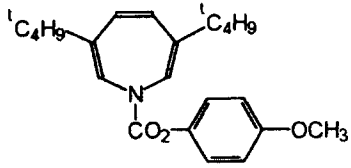
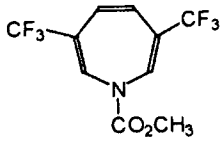
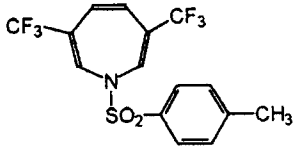
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
			24
	67–69	UV, ^{1}H NMR	23
	41–43	UV, ^{1}H NMR	23
	100–102	UV, ^{1}H NMR	23
	142–144	UV, ^{1}H NMR	23
	Yellow oil	IR, UV, ^{1}H NMR	40
	137–138	IR, UV, ^{1}H NMR	40 39

Table 1 (continued)

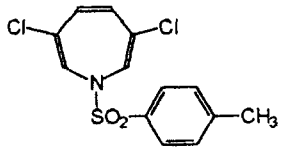
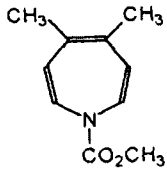
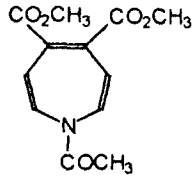
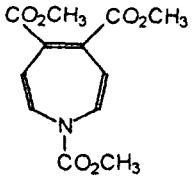
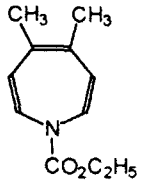
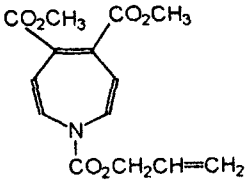
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	136	^{1}H, ^{13}C NMR ^{1}H, ^{13}C NMR, IR, UV	42 39
	60–61	IR, ^{1}H NMR, UV, MS	36
	Yellow oil	UV, ^{1}H NMR UV, IR, MS, ^{1}H NMR	38 40 39, 41
		UV, ^{1}H NMR n_D^{25} 1.5112, MS, UV, ^{1}H NMR	40 37
		^{1}H NMR	24
	Oil	IR, ^{1}H NMR	39

Table 1 (continued)

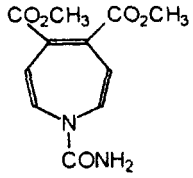
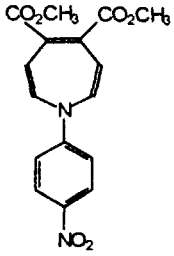
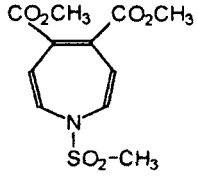
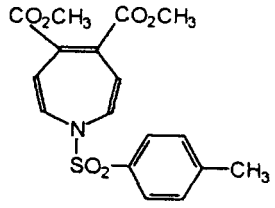
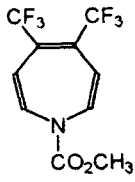
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	Yellow oil	^{1}H NMR	40
	174–175	UV, IR, ^{1}H NMR	40
	90–91	UV, IR, ^{1}H NMR	40
	111 111	UV, MS, ^{1}H NMR UV, IR, ^{1}H NMR UV, ^{1}H NMR	38 40 16 39
	Yellow oil	UV, IR, ^{1}H NMR	40

Table 1 (continued)

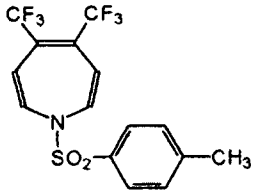
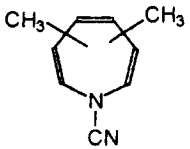
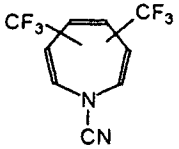
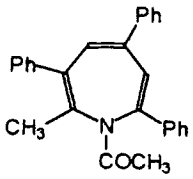
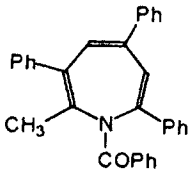
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	111.5–112.5	UV, IR, ^{1}H NMR	40
 Isomeric mixture		^{1}H NMR	15 14
 Isomeric mixture	35–40/0.02	$n_D^{25.2}$ 1.4307–1.4320, IR, ^{1}H, ^{19}F NMR	15 14
	134–135	IR, ^{1}H, ^{13}C NMR	50
	149–150	IR, ^{1}H, ^{13}C NMR	50

Table 1 (continued)

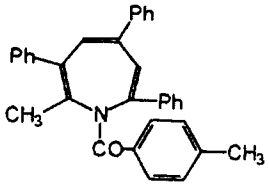
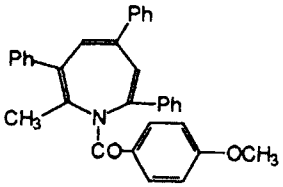
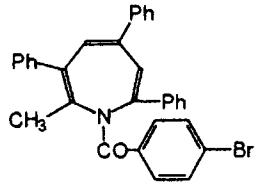
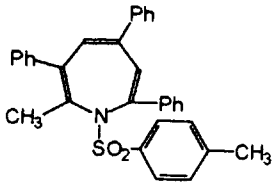
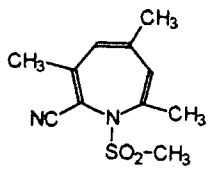
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	145–146	IR, ^{1}H, ^{13}C NMR	50
	154–155	IR, ^{1}H, ^{13}C NMR	50
	138–139	IR, ^{1}H, ^{13}C NMR, X-ray	50
	182–184	IR, ^{1}H, ^{13}C NMR	50
	200	IR, MS, ^{1}H, ^{13}C NMR	51

Table 1 (continued)

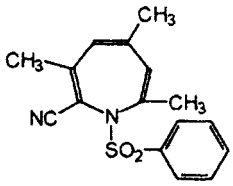
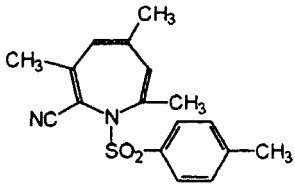
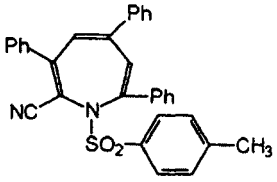
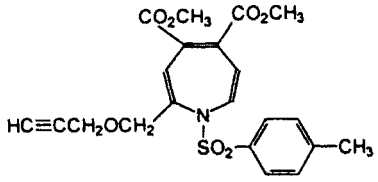
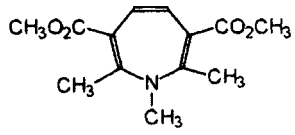
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	161	IR, MS, ^{1}H, ^{13}C NMR	51
	141	IR, MS, ^{1}H, ^{13}C NMR	51
	134	IR, MS, ^{1}H, ^{13}C NMR	51
		^{1}H NMR	39
	105–107	IR, UV, ^{1}H NMR	48b 48a

Table 1 (continued)

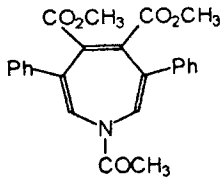
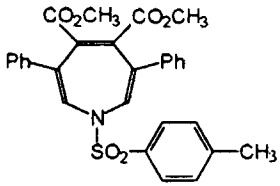
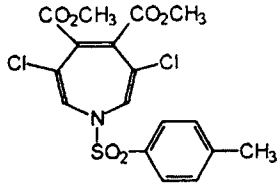
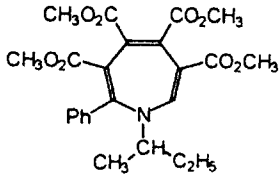
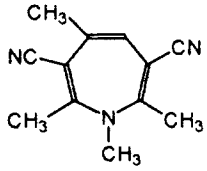
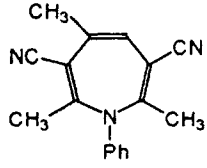
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	156–157	IR, UV, ^{1}H NMR	40
	142–143	MS, UV, ^{1}H NMR	40
		^{1}H, ^{13}C NMR ^{1}H, ^{13}C NMR, UV, IR, X-ray	42 39
	135–137	IR, MS, ^{1}H NMR	55
	97–99.5	IR, UV, ^{1}H NMR	49
	110–111	IR, UV, ^{1}H NMR	49

Table 1 (continued)

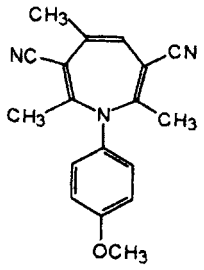
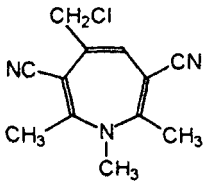
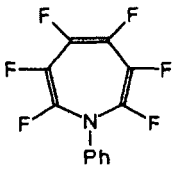
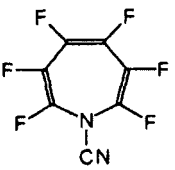
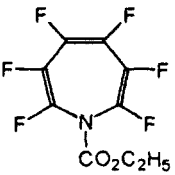
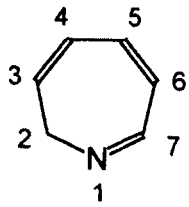
Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
		^{1}H NMR	49
		^{1}H NMR	49
	64–65	UV, ^{19}F NMR	46
	51–52 51–52	IR, UV, MS, ^{19}F NMR	15 14
	58/0.05	IR, UV, ^{1}H, ^{19}F NMR	46

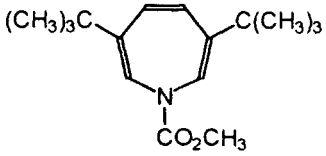
Table 1 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Spectroscopic evidence/data	Ref.
	102–103	IR, UV, MS, ^{19}F NMR	56

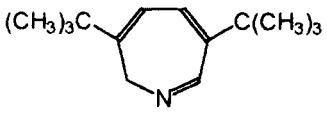
II. [2*H*]AZEPINES



The parent compound in this series has not been prepared. 3,5-Di-*tert*-butyl[2*H*]azepine (**106**) has been formed, along with the [3*H*] and [4*H*] isomers, by heating the corresponding [1*H*]azepine (**105**) with DBU in xylene. The isomers were separated and characterised by NMR.[71a,c]

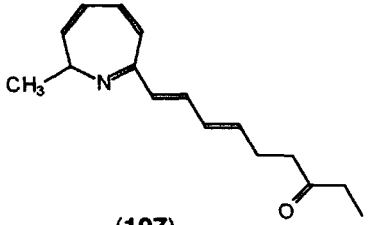


(105)

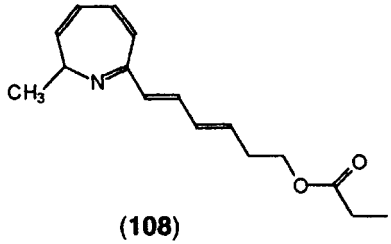


(106)

Two pungent compounds isolated from the mushroom *Chalciporus piperatus* have been identified as the substituted [2*H*]azepines chalciporone (**107**) and

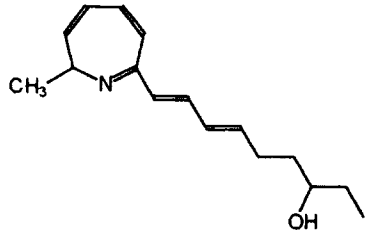


(107)



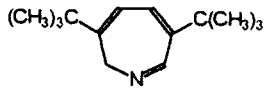
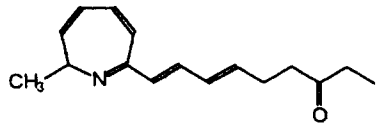
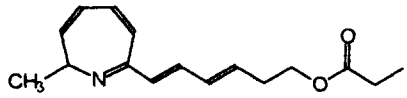
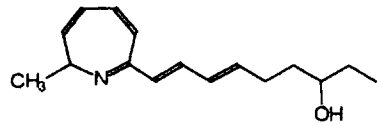
(108)

norchalciporyl propionate (**108**).[72] Physical constants of these and the reduced derivative **109** are given in Table 2. Other than the 2-keto derivatives discussed in Chapter 12, these are the only [2*H*]azepines described in the literature.

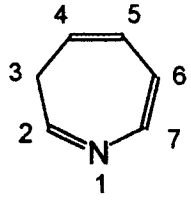


(109)

Table 2. [2*H*]Azepines

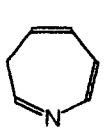
Structure	M.p. (°C)	Spectroscopic evidence/data	Ref.
	68.5–69	^{1}H, ^{13}C NMR IR, UV, ^{1}H,^{13}C NMR	71a 71c
		^{1}H, ^{13}C NMR, IR, UV, MS, $[\alpha]_D^{22}$ −452°	72
		^{1}H NMR, IR, UV, MS, $[\alpha]_D^{22}$ −290°	72
		^{1}H NMR, IR, UV, MS, $[\alpha]_D^{22}$ −351°	72

III. [3*H*]AZEPINES

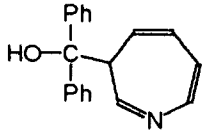


PREPARATION

Evidence for the transient existence of the parent [3*H*]azepine (**3**) has been presented by Schaden,[73–75] who demonstrated its formation from the alcohol (**110**) by pyrolysis at temperatures ranging from 150 to 900 °C. Using Curie point pyrolysis at the latter temperature, he showed the presence of [3*H*]azepine (**3**) by mass spectrometry which gave a band corresponding to $M = 93$.

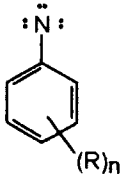


(**3**)

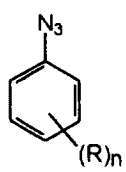


(**110**)

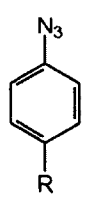
The most frequently used technique for the preparation of the [3*H*]azepine system involves the ring expansion of a nitrene (**111**) either thermally or utilising UV irradiation and trapping the intermediate with a suitable nucleophilic reagent. Various methods have been used to generate the nitrene **111**, the most popular being the decomposition of the corresponding azide **112**. The earliest reported use of this procedure by Wolff in 1912 was not recognised as producing an azepine,[1] but when it was applied by Huisgen and co-workers in 1958, the thermal decomposition of the azides **113** (R = H, CH_3) in the presence of aniline gave the 2-phenylamino[3*H*] azepines **114** (R = H, CH_3).[2] Unfortunately the authors were unable to distinguish between the different possible isomeric [2*H*]-, [3*H*]- or [4*H*]azepines and the products were only confirmed as the [3*H*] isomers using ^{1}H NMR by Doering and Odum some 8 years later.[4]



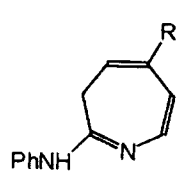
(**111**)



(**112**)

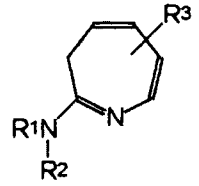


(**113**)

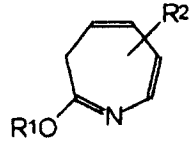


(**114**)

Further work demonstrated that treatment of phenyl azide (**113**, R = H) with 3-substituted anilines and aliphatic amines gave analogous products (**115**, R^1 = 3-$CH_3C_6H_4$, ^iPr, R^2 = R^3 = H)[76] and it was later shown that irradiation at UV wavelengths rather than thermolysis could be used as an alternative means of generating the nitrene from the azide **113** (R = H) to give the corresponding [3*H*]azepine **114** (R = H).[77]

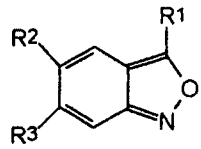


(115)



(116)

Subsequent investigators confirmed the general nature of the reaction, using a variety of phenylnitrenes (**111**, R = H, alkyl, aryl, acyl, halogen, etc.) generated from phenyl azides (**112**) or from substituted bicyclic isoxazoles (**117**), and a selection of amines such as ammonia,[4] diethylamine,[4,78–93,155] dimethylamine,[94] *n*-butylamine,[78,95] di-*n*-butylamine,[82–84,87] piperidine[96–98] and morpholine.[98] In general, it was found that if the phenyl nitrene **111** was substituted in the 4-position, then the corresponding 5-substituted [3*H*]azepine was formed,[88,90,92,94,98] the 2-substituted phenylnitrenes (**111**) gave 3-substituted [3*H*]azepines[79,84,155] and 3-substituted phenylnitrenes (**111**) gave mixtures of 4- and 6-substituted [3*H*]azepines.[89,98] With multiple substitution the pattern was less clearly defined.[91,93] Full details of the structures obtained (**115**) are given in Table 3.

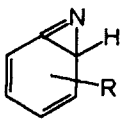


(117)

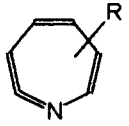
Treatment of phenylnitrenes **111** (R = H, alkyl, aryl, acyl, halogen, etc.), formed from either the corresponding azides (**112**) or from the bicyclic isoxazoles (**117**), with an alcohol in place of an amine to terminate the reaction sequence led to the corresponding 2-alkoxy- or 2-aryloxy[3*H*]azepines. For example, 2-alkoxy[3*H*]azepines (**116**, R^1 = alkyl) were obtained using methanol,[78,86,96,98–108] ethanol,[86,108] *n*-propanol[86] and cyclohexanol,[86] and 2-aryloxy[3*H*]azepines (**116**, R^1 = Ph, β-naphthyl) have been prepared using phenol[86,109] or 2-methoxynaphthalene.[154] *Ortho*-, *meta*- and *para*-substituted

phenyl azides (**112**) gave substituted 2-alkoxy[3*H*]azepines (**116**) in which the substitution patterns resembled that of the 2-amino[3*H*]azepines discussed above.[86,98,100–108] Full structural details and physical constants of these products are also listed in Table 3.

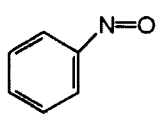
There has been considerable discussion in the literature[87] regarding the nature of the intermediate formed by thermolysis or irradiation of a nitrene (**111**). Some authors claim evidence in support of a bicyclic intermediate (**118**)[2,4,81,82,85,99,101] whereas others prefer the dehydroazepine structure (**119**).[79,88,93] Neither intermediate, however, has been isolated and arguments in support of the involvement of both structures have been made.[87]



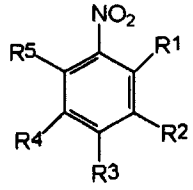
(**118**)



(**119**)

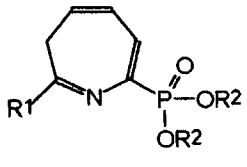


(**120**)

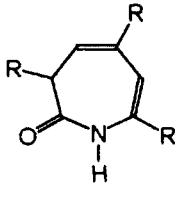


(**121**)

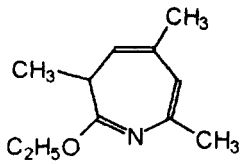
Nitrosobenzene (**120**) has been deoxygenated with triphenyl- or tri-*n*-butylphosphine as an alternative procedure for generating phenylnitrene (**111**) and in the presence of an appropriate amine has yielded the 2-substituted amino[3*H*]azepines **115** ($R^1 = CH_3$, $R^2 = H$, CH_3, $R^3 = H$; $R^1 = {}^nBu$, $R^2 = R^3 = H$; $R^1 = R^2 = C_2H_5$, $R^3 = H$).[110] Similar deoxygenation of nitrobenzene (**121**, R^1 to $R^5 = H$) with tri-*n*-butylphosphine in an alcohol has yielded a range of 2-alkoxy[3*H*]azepines (**116**, $R^1 = C_1$–C_7 alkyl, $R^2 = H$).[111] Nitrobenzenes (**121**, R^1 to $R^5 = H$;[112–114] $R^1 = CH_3$ or $R^2 = CH_3$ or $R^1 = R^3 = R^5 = CH_3$, other values of $R = H$;[112] $R^3 = CH_3$ or $R^2 = R^3 = CH_3$, other values of $R = H$;[114] and $R^1 = CH_3$ or $R^3 = CH_3$, Br, $CO_2C_2H_5$, other values of $R = H$[115,116]) on deoxygenation in a similar manner in the presence of diethylamine using $P(OC_2H_5)_3$, $CH_3P(OC_2H_5)_2$ or $P(NEt_2)_3$ yield the corresponding 2-ethylamino[3*H*]azepines **115** ($R^1 = R^2 = C_2H_5$). In the absence of an amine, deoxygenation of substituted nitrobenzenes with trimethyl or triethyl orthophosphate gave poor yields of the corresponding 7-phosphate esters (**122**, $R^1 = H$, CH_3, C_2H_5, $R^2 = CH_3$, C_2H_5).[116–118]



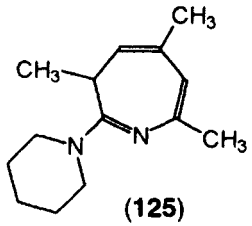
(**122**)



(**123**)



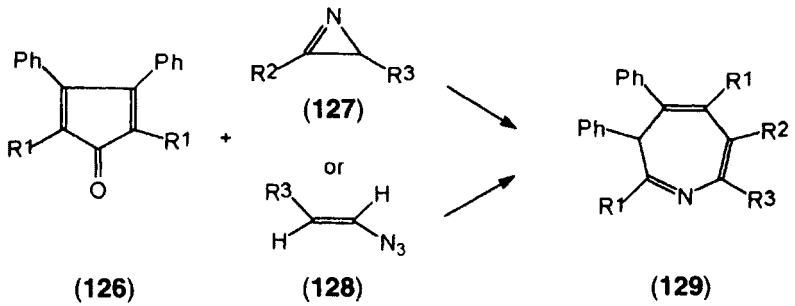
(124)



(125)

Since 2-alkoxy- and 2-amino[3*H*]azepines (**116** and **117**) are enol ethers and enamines, respectively, of 1,3-dihydro[2*H*]azepin-2-ones (**123**), this offers an alternative means of access to 2-substituted [3*H*]azepines. The unsubstituted lactam **123** (R = H) has been treated with $(CH_3)_3O^+ BF_4^-$ to give 2-methoxy-[3*H*]azepine (**116**, $R^1 = CH_3$, $R^2 = H$)[119] and 3,5,7-trimethyl-1,3-dihydro[2*H*]-azepin-2-one (**123**, $R = CH_3$) has been treated in a similar manner with $(C_2H_5)_3O^+ BF_4^-$ to give the corresponding 2-ethoxy-3,5,7-trimethyl[3*H*]-azepine (**124**).[120,121] Treatment of the 2-methoxy[3*H*]azepine **116** ($R^1 = CH_3$, $R^2 = H$) with aniline and the 2-*n*-butoxy[3*H*]azepine **116** ($R^1 = {}^nBu$, $R^2 = H$) with pyrrolidine, piperidine and morpholine led to the corresponding amines **115** ($R^1 = Ph$, $R^2 = R^3 = H$[119] and R^1 and R^2 together = $-C_4H_8-$, $-C_5H_{10}-$ and $-C_2H_4OC_2H_4-$, $R^3 = H$,[122] respectively). Similar treatment of the 3,5,7-trimethyl analogue **124** with piperidine gave the 2-piperidyl derivative **125**.[120,121]

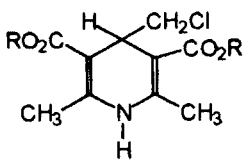
Other ring-expansion procedures have been used to produce [3*H*]azepines. For example, Nair in 1972[123] and Hassner and Anderson from 1971 to 1974[124–127] reacted a series of 3,4-diphenylcyclopentadienones (**126**, $R^1 = CH_3$, C_2H_5, Ph) with a range of substituted azirines (**127**, $R^2 = Ph$, CH_2Ph, C_2H_5; $R^3 = H$, CH_3, C_2H_5, Ph)[123,124,126,127] or with the azides **128** ($R^3 = Ph$, ^tBu)[125] to give the corresponding substituted [3*H*]azepines **129** ($R^1 = CH_3$, C_2H_5, Ph; $R^2 = Ph$, CH_2Ph, C_2H_5; $R^3 = H$, CH_3, C_2H_5, Ph, ^tBu) as shown in Scheme 5.



(126) (127) or (128) (129)

Scheme 5

Ring expansion of the 1,4-dihydropyridines **130** (R = CH_3, C_2H_5) using sodium ethoxide in ethanol gave initially the dihydro[1*H*]azepines **131** (R = CH_3, C_2H_5) and the [4*H*]azepines **132** (R = CH_3, C_2H_5), but at reflux temperature the products rearranged to give the corresponding [3*H*]azepines **133** (R = CH_3, C_2H_5).[128] In a similar manner, the 1,2-dihydropyridine **134** gave the [3*H*]azepine **135** on treatment with pyridine at 100 °C.[129] In this case the formation of a [4*H*]azepine did not appear to be involved.



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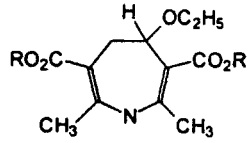

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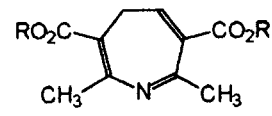

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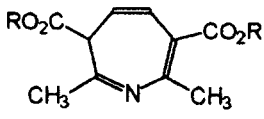

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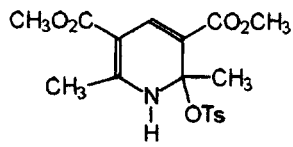

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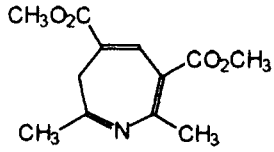
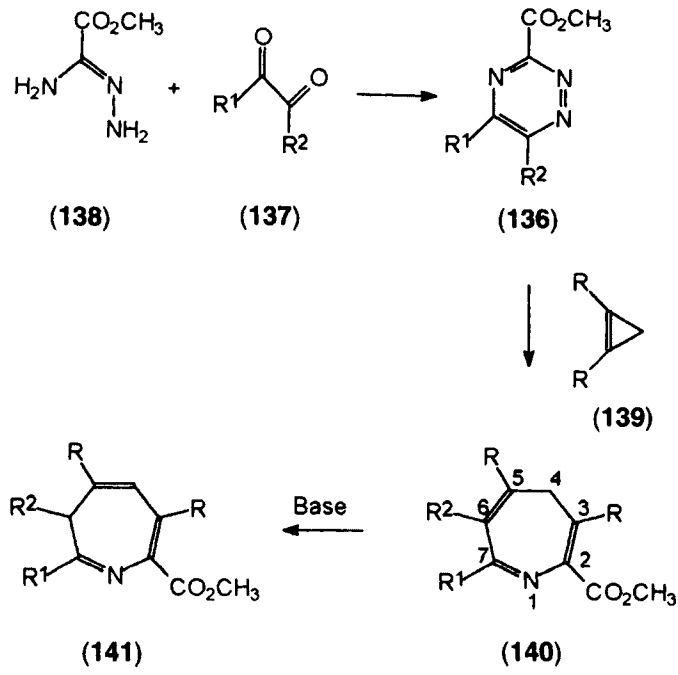


(135)

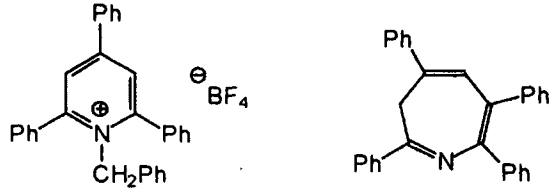
A range of 1,2,4-triazines (**138**, R^1 = CH_3, Ph, R^2 = H, CH_3, Ph), prepared by condensation of the corresponding diketones (**137**, R^1 = CH_3, Ph, R^2 = H, CH_3, Ph) with the amidrazone **136**, was used by Sauer and his co-workers[130] in a series of [4 + 2] cycloaddition reactions with the cyclopropenes **139** (R = H, Ph). The reaction sequence is shown in Scheme 6. The initial products obtained were the [4*H*]azepines **140** (R = H, Ph, R^1 = CH_3, Ph, R^2 = H, CH_3, Ph), which were converted on treatment with base into the corresponding substituted [3*H*]azepines **141** (R = H, Ph, R^1 = CH_3, Ph, R^2 = H, CH_3, Ph). The reaction was found to be of general application and was used to synthesise 22 substituted [4*H*]azepines, details of which are given in Section IV.

Other successful rearrangements which have been reported include the treatment of 2,4,6-triphenyl-*N*-benzylpyridinium tetrafluoroborate (**142**) with NaH in refluxing toluene to give 2,4,6,7-tetraphenyl[3*H*]azepine (**143**)[131] and the rearrangement of the di-*tert*-butyl[1*H*]azepines **144** [R^1 = H, R^2 = $C(CH_3)_3$ and R^1 = $C(CH_3)_3$, R^2 = H] to give the corresponding [3*H*]azepines **145** [R^1 = H, R^2 = $C(CH_3)_3$ and R^1 = $C(CH_3)_3$, R^2 = H], using UV irradiation[132] or DBU in refluxing xylene.[71] In the case of the UV-induced rearrangement,[132] the reaction proceeds via the bicyclic intermediates **146** [R^1 = H, R^2 = $C(CH_3)_3$ and R^1 = $C(CH_3)_3$, R^2 = H], which are hydrolysed and decarboxylated to **147** [R^1 = H, R^2 = $C(CH_3)_3$ and R^1 = $C(CH_3)_3$, R^2 = H]. The final rearrangement to the [3*H*]azepines **145** is achieved by heating **147** in



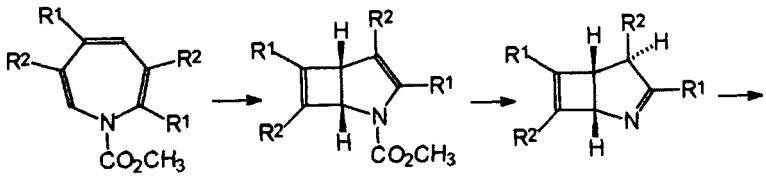
Scheme 6

benzene. The related thermal rearrangement[71] is less specific, leading to mixtures of di-*tert*-butyl-[2*H*]-, -[3*H*]- and -[4*H*]azepines. In a similar manner, the

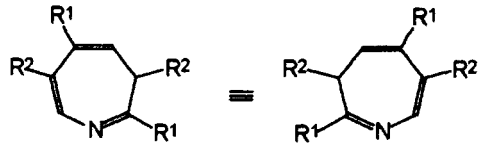


2,5- and 3,6-dimethyl[3*H*]azepines **145** (R^1 = H, R^2 = CH_3 and R^1 = CH_3, R^2 = H) and the 2,5- and 3,6-diisopropyl[3*H*]azepines **145** [R^1 = H, R^2 = $CH(CH_3)_2$ and R^1 = $CH(CH_3)_2$, R^2 = H] were formed from the corresponding dialkyl[1*H*]azepine analogues **144**;[71c] in these latter examples, however, no [2*H*]- or [4*H*]azepines were obtained.

There is only one reference in the literature to the formation of [3*H*]azepines by a ring-closure procedure. The dinitriles **148** (R^1 = H, R^2 = CH_3, Ph, C_6H_4Ph; R^1 = R^2 = Ph) have been cyclised using HBr to yield the

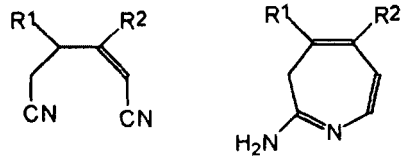


(144) (146) (147)



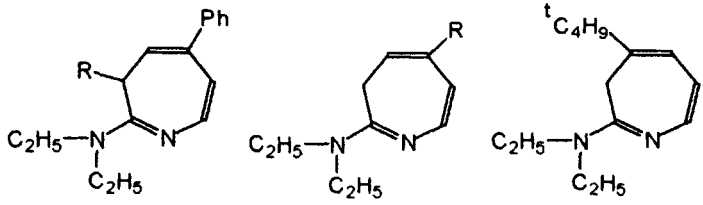
(145)

2-amino[3*H*]azepines **149** (R^1 = H, R^2 = CH_3, Ph, C_6H_4Ph; R^1 = R^2 = Ph).[133]



(148) (149)

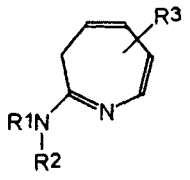
2-Diethylamino-5-phenyl[3*H*]azepine (**150**, R = H) has been alkylated successfully at the 3-position, using base and an appropriate halide, to yield a range of 3-substituted products (**150**, R = alkyl, aryl, carbethoxy, etc.). Using this technique, a series of 13 3-substituted derivatives have been prepared,[134,135] Treatment of the halides **151** (R = Cl, F) with ^{t}BuLi gives a mixture of the 4- and 5-alkylated products [**152** and **151**, R = $C(CH_3)_3$].[136] Details of these compounds and other related[3*H*]azepines are given in Table 3.[137–142]



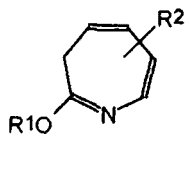
(150) (151) (152)

PROPERTIES

The [3*H*]azepines are stable oils or crystalline solids. With the obvious exception of the 2-substituted-amino and 2-alkoxy derivatives such as **115** and **116**, they are able to withstand strong acid and alkaline conditions and will undergo alkylation with base and alkyl halides as discussed above.[134,135]

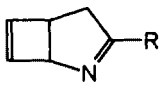


(115)

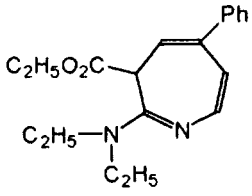


(116)

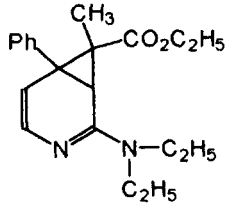
Rearrangement reactions occur occasionally either thermally or utilising UV irradiation. For example, the amines **115** ($R^1 = R^2 = H$, CH_3, $R^3 = H$) and the ether **116** ($R^1 = CH_3$, $R^2 = H$) rearranged under UV irradiation and led to the 2-azabicyclo[3.2.0]hepta-2,6-dienes **153** [R = $N(CH_3)_2$, NH_2, OC_2H_5],[143] and ring contraction of the ester **154** occurred on methylation in the presence of lithium 2,2,6,6-tetramethylpiperidide, resulting in the formation of the bicyclic compound **155**.[144]



(153)

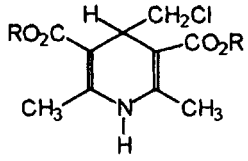


(154)

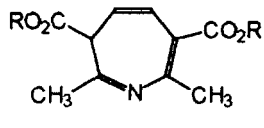


(155)

Treatment of the diester **133** (R = CH_3) with ethanolic HCl gave a mixture of three products, the main one being the pyridine ester **156** and two by-products, one of which was identified as the chloromethyldihydropyridine **130** (R = CH_3), indicating that the base-catalysed ring expansion discussed earlier[128] is reversed in the presence of acid. The second by-product of the

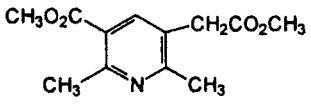


(130)

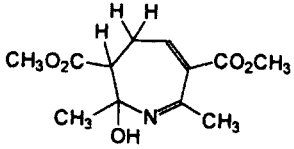


(133)

acid treatment in this reaction was formed by the 1,6-addition of the elements of water to the [3*H*]azepine ester **133** (R = CH_3), giving the 3,4-dihydro-[2*H*]azepine **157**, the structure of which was confirmed by ^{1}H NMR spectroscopy.[145]



(156)



(157)

Table 3. [3*H*]Azepines

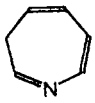
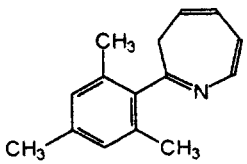
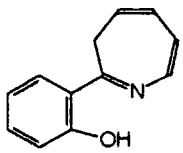
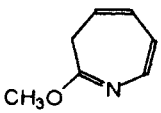
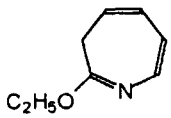
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	25/0.1		^{1}H, ^{13}C NMR	8
			MS	74, 75
			MS	73
	Oil		MS, ^{1}H NMR	138
	Yellow liquid		IR, ^{1}H NMR	34
	52/0.11		n_D^{20} 1.5203, IR, UV, ^{1}H NMR	119
	74–76/32		IR, MS, ^{1}H NMR	111
	105/78		IR, MS, ^{1}H NMR	111

Table 3 (continued)

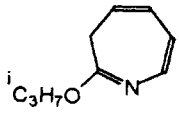
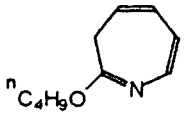
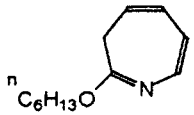
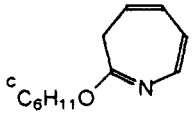
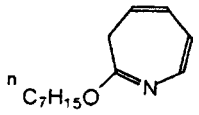
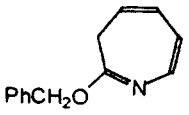
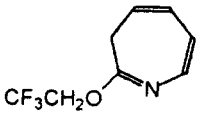
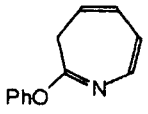
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	89/31		IR, MS, ^{1}H NMR	111
	126/49		IR, MS, ^{1}H NMR	111
	98/3.5		IR, MS, ^{1}H NMR	111
	104–106/5.5		IR, MS, ^{1}H NMR	111
	86/1		IR, ^{1}H NMR	111
	173/27		IR, MS, ^{1}H NMR	111
	69/27		IR, MS, ^{1}H NMR	111
			IR, MS, ^{1}H NMR	109

Table 3 (continued)

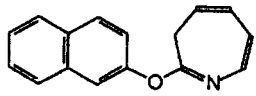
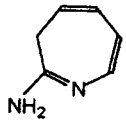
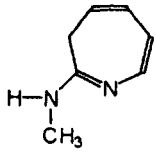
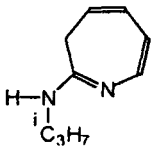
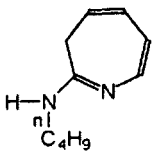
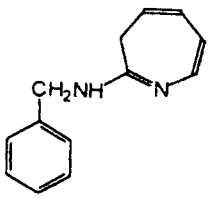
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
				154
	90.0–91.0	Picrate 200–201 (d)	^{1}H NMR	4
			IR, ^{1}H NMR	110
		Oxalate 96–97 (d)		114
			IR, ^{1}H NMR	110
	52.5–53.5		UV	2

Table 3 (continued)

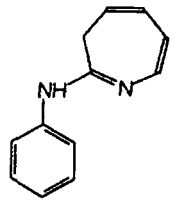
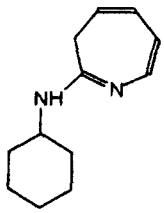
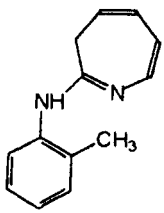
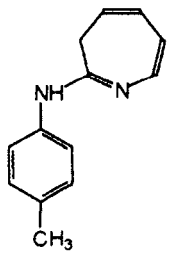
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
				3
	151			1
	151–152	HI salt 160–161	IR, UV	2
	150–151			77
	151–152.5		^{1}H NMR	4
	94–95/0.12		n_D^{20} 1.402, IR, UV, ^{1}H NMR	119
			^{1}H NMR	141
				
	123–124			2
	118–119		^{1}H NMR	83
				
	98–99		UV	76
				
	116			1
	115–115.5			2

Table 3 (continued)

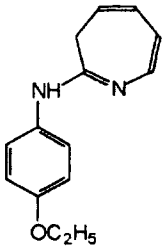
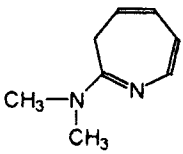
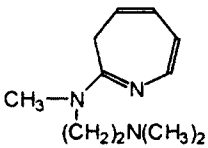
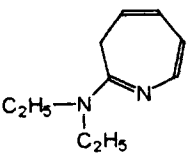
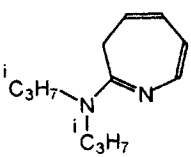
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	90–91		UV	2
			IR, ^{1}H NMR	110
			IR, MS, ^{1}H NMR	85
	85/1		IR, ^{1}H NMR	86a
			IR, MS, ^{1}H NMR	85
	59–61/0.1		IR, ^{1}H NMR	110
	65 80/2	Picrate 99- 100	$n_D^{25.5}$ 1.5513, d^{31} 0.9632, IR, UV, ^{1}H NMR	4
			^{1}H NMR	80, 116
			^{1}H NMR	83
	50–60/0.05		n_D^{25} 1.5509, ^{1}H NMR	113
			UV, ^{1}H NMR	112
			UV	82
			MS, ^{1}H NMR	90
				79, 87
	80–90/0.001	Picrate 140–142	UV	76

Table 3 (continued)

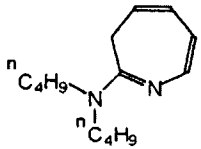
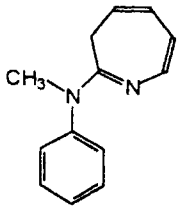
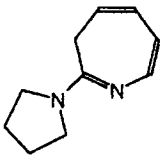
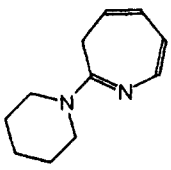
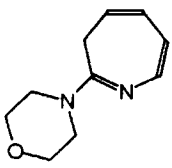
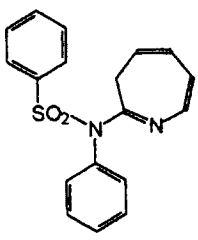
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			UV ^{1}H NMR IR, MS, ^{1}H NMR	82 83 87
	95–97/0.001	Picrate 158–159	IR	2
	90–95/0.1		IR, UV, ^{1}H NMR	122
	114–116/0.7 139–144/12	Oxalate 155	IR, UV, ^{1}H NMR	114 122 97
	127–130/0.1		IR, UV, ^{1}H NMR	122
	158–159			2

Table 3 (continued)

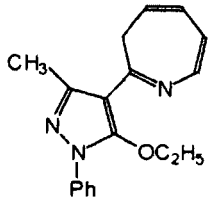
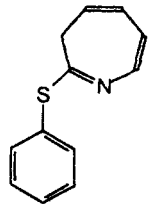
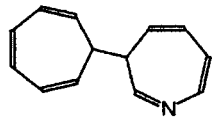
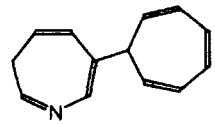
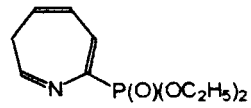
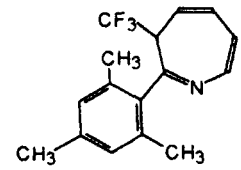
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	73.5–75	HBF_4 salt 158–159, ^1H NMR	^1H NMR	122
	117–118		UV	76
	Yellow oil		^1H, ^{13}C NMR	140
	Pale yellow oil		^1H, ^{13}C NMR	140
			^1H NMR	116
	Oil		^1H NMR	138

Table 3 (continued)

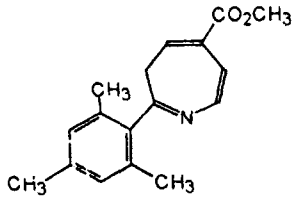
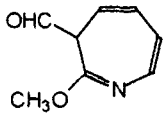
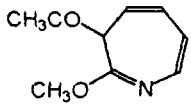
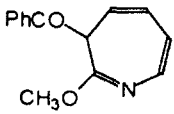
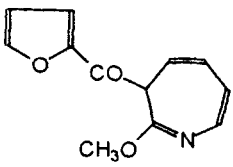
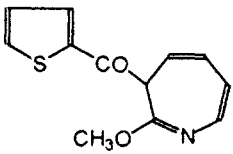
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			MS, ^{1}H NMR	138
	100/2		IR, UV, ^{1}H NMR	78
	115–116/13 117–118/11		IR, UV, ^{1}H NMR IR, UV, MS, ^{1}H NMR IR	78 99 96
	65–66		IR, UV, ^{1}H NMR	78
	73		IR, UV, ^{1}H NMR	78
	160/0.3		IR, UV, ^{1}H NMR	78

Table 3 (continued)

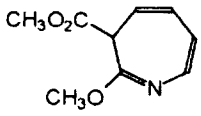
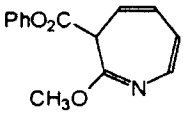
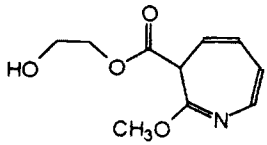
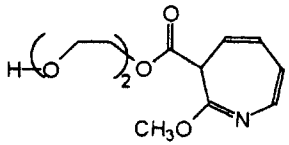
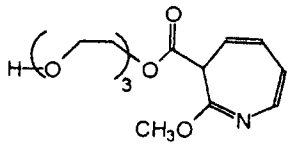
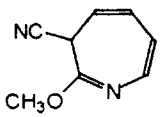
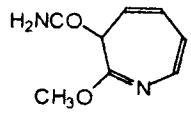
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	75/0.5		MS, UV ^{1}H NMR	86a 86b
	115/0.3 115/0.3		MS ^{1}H NMR	86a 86b
	120/0.2		^{1}H, ^{13}C NMR, MS	107
	163/0.2		^{1}H, ^{13}C NMR, MS	107
	179/0.2		^{1}H, ^{13}C NMR, MS	107
			IR, ^{1}H, ^{13}C NMR	106
	162–163		IR, UV, MS, ^{1}H NMR MS, ^{1}H NMR	101 100, 104

Table 3 (continued)

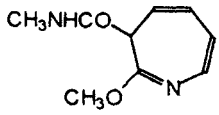
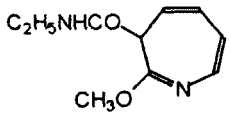
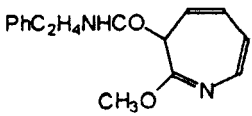
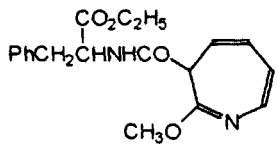
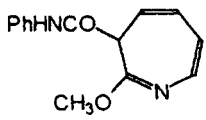
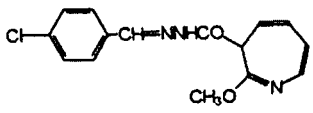
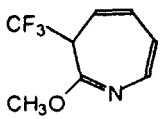
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	128–139		IR, UV, MS, ^{1}H NMR MS, ^{1}H, NMR	101 100
	111–112		UV, MS, ^{1}H NMR MS, ^{1}H, NMR	101 100
	100–101		IR, UV, MS ^{1}H NMR	101 100
	114–116		IR, UV ^{1}H NMR	101 100
	159		MS, UV, ^{1}H NMR	86a
	226			106
	80/0.6		^{1}H, ^{13}C, ^{19}F NMR	106

Table 3 (continued)

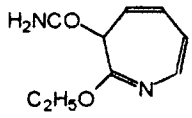
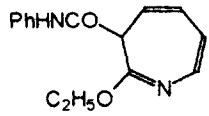
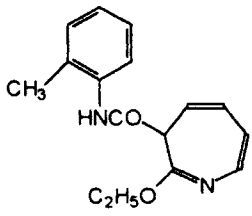
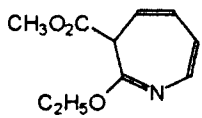
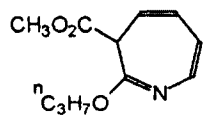
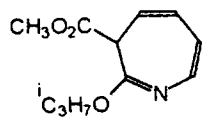
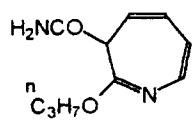
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	153–155 153		MS, ^{1}H NMR MS, UV, ^{1}H NMR	104 86a
	111		MS, ^{1}H NMR	86a
	150		MS, ^{1}H NMR	86a
	120/4		MS ^{1}H NMR	86a 86b
	130/1		^{1}H NMR	86b
	100/3		^{1}H NMR	86b
	124–125 122		MS MS, ^{1}H NMR	104 86a

Table 3 (continued)

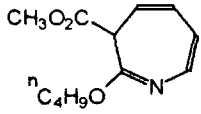
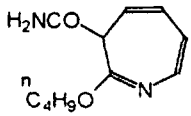
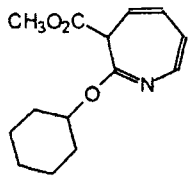
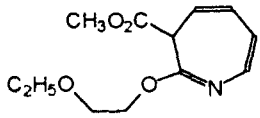
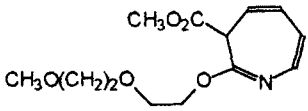
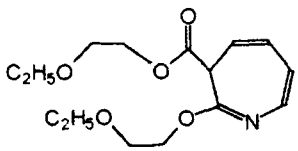
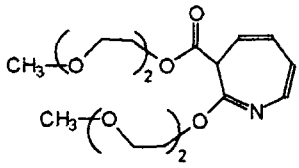
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	110/0.1		^{1}H NMR	86b
	109–110		MS	104
	127/0.1		UV, MS, ^{1}H NMR	86a
	130/0.4		^{1}H, ^{13}C NMR, MS	107
	150/0.4		^{1}H, ^{13}C NMR, MS	107
	140/0.4		^{1}H, NMR, MS	107
	170/0.4		^{1}H, ^{13}C NMR, MS	107

Table 3 (continued)

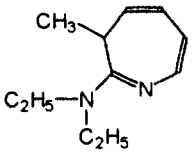
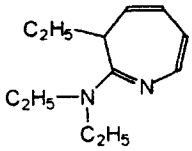
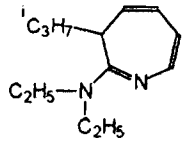
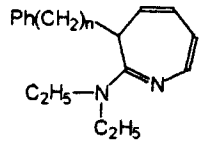
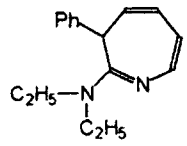
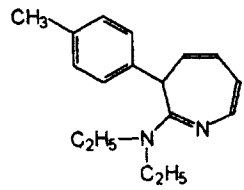
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	70–75/0.01		^{1}H NMR UV, ^{1}H NMR MS, ^{1}H NMR	80, 116 112 115
			^{1}H NMR	80
			^{1}H NMR	80
 n = 1, 2, 3 and 4	Oils		^{1}H NMR	155
	110–112/0.1		^{1}H NMR n_D^{25} 1.5904, IR, UV ^{1}H NMR, MS, UV	116 113, 81 79
			IR, ^{1}H NMR	81

Table 3 (continued)

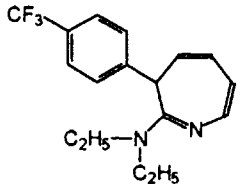
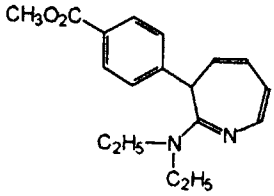
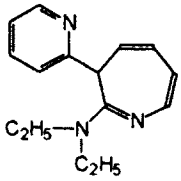
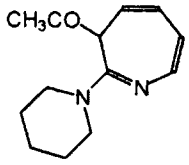
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Yellow oil		IR, ^{1}H NMR	81
	171–172		IR, ^{1}H NMR	81
	135/0.3		UV, IR, MS, ^{1}H NMR	84
	155/0.3		UV, IR, MS, ^{1}H NMR	84
	67–68		UV, IR, MS, ^{1}H NMR	96

Table 3 (continued)

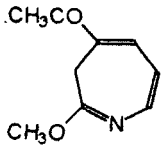
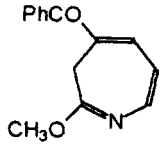
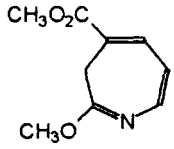
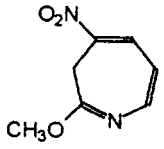
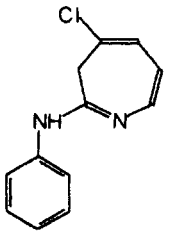
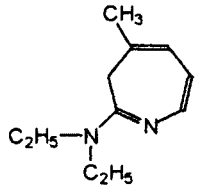
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Pale yellow oil		UV, IR, ^{1}H NMR	98, 105
	Yellow oil		UV, IR, ^{1}H NMR	98
	Yellow oil		UV, IR, ^{1}H NMR	98
			UV, IR, ^{1}H NMR	98
	165–166			77
		Oxalate 139		114

Table 3 (continued)

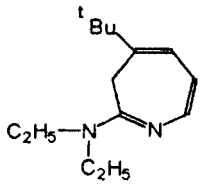
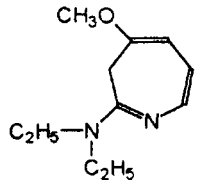
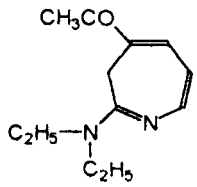
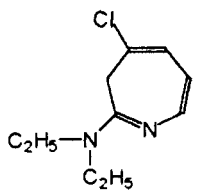
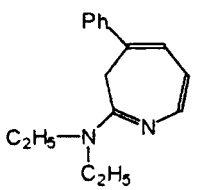
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
		Picrate 121–122	MS, ^{1}H NMR	136
		Oxalate 125–127 CH_3I 146–148	UV, IR, ^{1}H NMR	114
		Oxalate 115–117 CH_3I 154–156	UV, IR, ^{1}H NMR	114
		Oxalate 108–110	UV, IR, ^{1}H NMR	114
		Oxalate 171–172	UV, IR, ^{1}H NMR	114

Table 3 (continued)

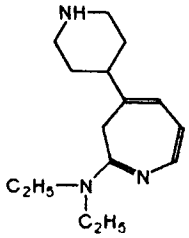
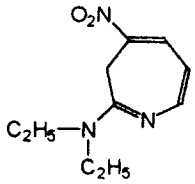
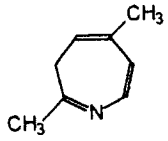
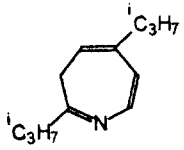
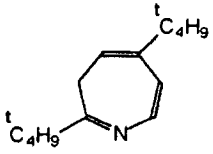
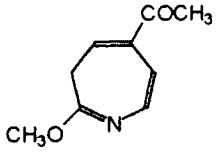
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	76–78	Oxalate 165–172	UV, IR, ^{1}H NMR	114
			IR, MS, ^{1}H NMR	89
	Pale yellow oil		IR, UV, ^{1}H, ^{13}C NMR	71c
	Pale yellow oil		IR, UV, ^{1}H, ^{13}C NMR	71c
	Yellow oil 20.5–21 20.5–21		^{1}H, ^{13}C NMR ^{1}H, ^{13}C NMR IR, UV, ^{1}H, ^{13}C NMR	71a 132 71b 71c
	Yellow oil		MS, ^{1}H NMR UV, IR, ^{1}H NMR	90 98

Table 3 (continued)

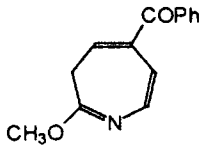
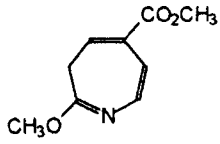
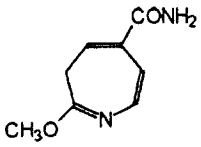
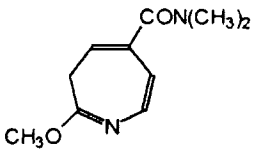
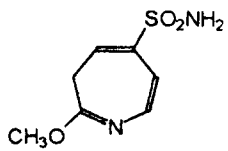
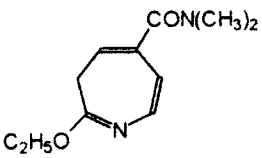
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Yellow oil		UV, IR, ^{1}H NMR	98
	77–87/0.5		IR, UV, MS, ^{1}H, ^{13}C NMR	106
	Yellow oil		UV, IR, ^{1}H NMR	98
	147–148		MS, ^{1}H NMR	104
			MS, ^{1}H NMR	108
	130–131		MS, ^{1}H NMR	104 102
			MS, ^{1}H NMR	108

Table 3 (continued)

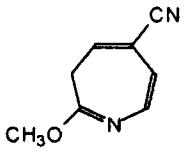
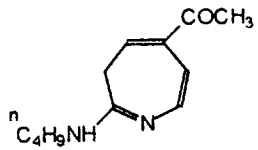
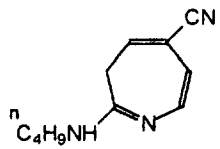
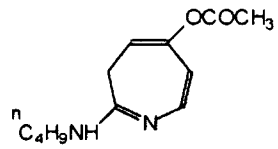
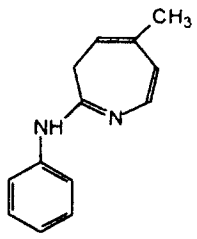
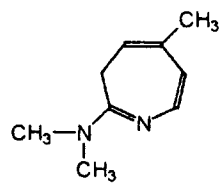
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	56		IR, UV, MS, ^{1}H, ^{13}C NMR	106
			^{1}H NMR claimed	95
			^{1}H NMR claimed	95
			^{1}H NMR claimed	95
	157–158			2
	68/0.9	Oxalate 158–160	n_D^{20} 1.5573, IR, ^{1}H NMR	114

Table 3 (continued)

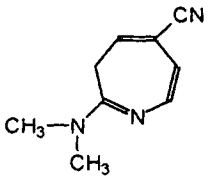
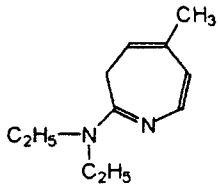
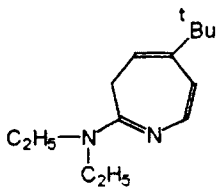
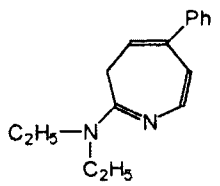
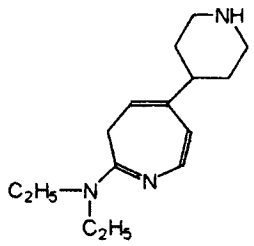
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			IR, ^{1}H NMR	94
	68–70/0.2 120/0.1		^{1}H NMR ^{1}H NMR MS, ^{1}H NMR	80 112 115
		Picrate 112–113	MS, ^{1}H NMR	136
	78–79 77–78		UV, IR, ^{1}H NMR ^{1}H, ^{13}C NMR MS, ^{1}H NMR	114 135 90
	62–63		UV, IR, ^{1}H NMR	114

Table 3 (continued)

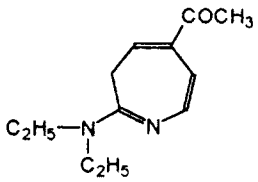
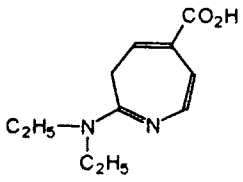
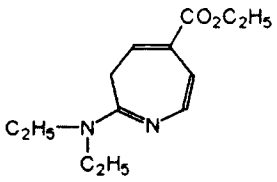
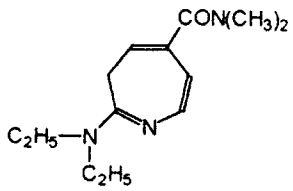
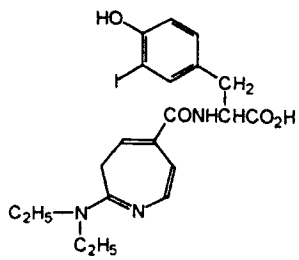
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			MS, ^{1}H NMR	90
			MS, ^{1}H NMR	90
			MS, ^{1}H NMR	115
			MS, ^{1}H NMR	88
			MS, ^{1}H NMR	92

Table 3 (continued)

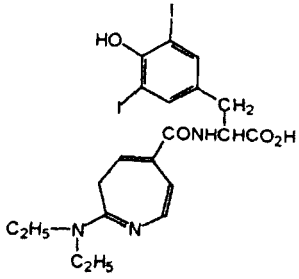
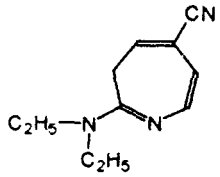
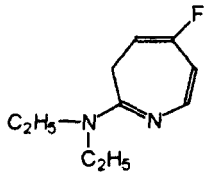
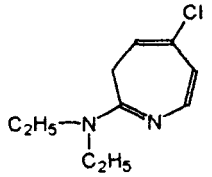
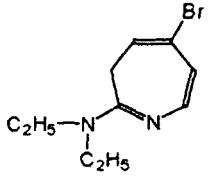
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			MS, ^{1}H NMR	92
			MS, ^{1}H NMR	90
	78–79/0.3		n_D^{20} 1.5294, MS, ^{1}H NMR	136
	126–127.5/0.7 96.5–97.5/0.2 39–40	Oxalate 107.0–109.0	MS, ^{1}H NMR n_D^{20} 1.5718, ^{1}H NMR	90 136
	80/0.15		MS, ^{1}H NMR	90, 115

Table 3 (continued)

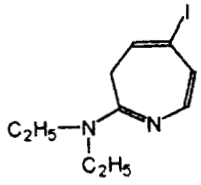
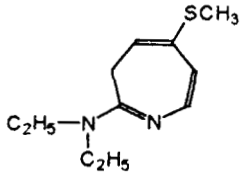
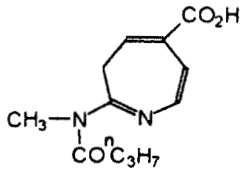
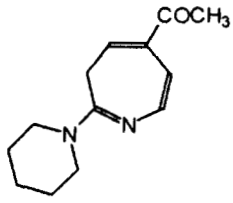
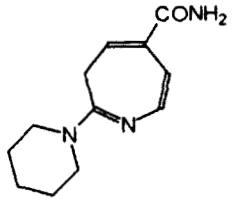
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			MS, ^{1}H NMR	90
			MS, ^{1}H NMR	90
			No data	137
	Brown oil		UV, IR, ^{1}H NMR	98
	156–157		MS	104

Table 3 (continued)

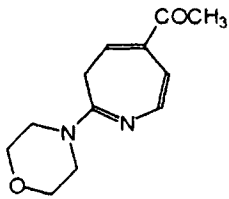
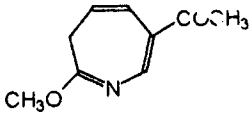
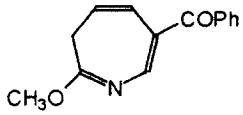
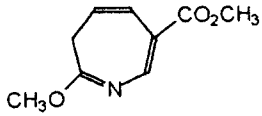
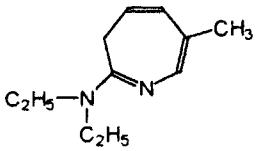
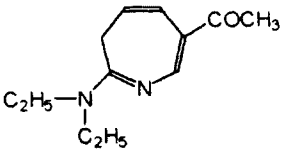
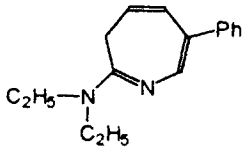
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Yellow oil		UV, IR, MS, ^{1}H NMR	98
	Yellow oil Pale yellow oil		UV, IR, ^{1}H NMR UV, IR, ^{1}H NMR	98 105
	Yellow oil		UV, IR, ^{1}H NMR	98
	Yellow oil		IR, UV, MS, ^{1}H, ^{13}C NMR UV, IR, ^{1}H NMR	106 98
		Oxalate 120–125	UV, IR, ^{1}H NMR	114
		CH_3I 134–137	UV, IR, ^{1}H NMR	114
	75–76	Oxalate 137–138	UV, IR, ^{1}H NMR	114

Table 3 (continued)

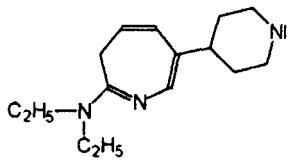
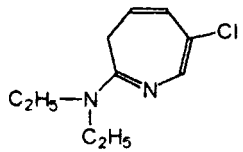
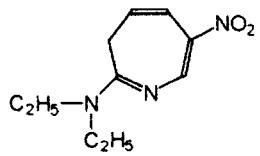
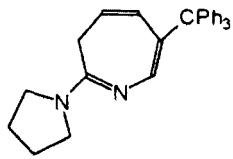
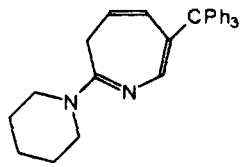
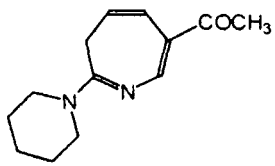
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	97–99		UV, IR, ^{1}H NMR	114
		Oxalate 119–120	UV, IR, ^{1}H NMR	114
	Yellow oil		IR, MS, ^{1}H NMR UV, IR, ^{1}H NMR	89 98
	235–236		IR, UV, ^{1}H NMR	122
	224–225		^{1}H NMR	122
	Brown oil		UV, IR, MS, ^{1}H NMR	98

Table 3 (continued)

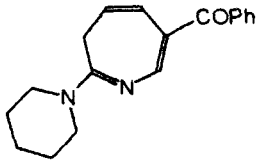
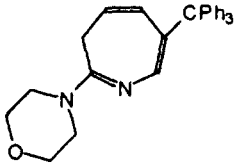
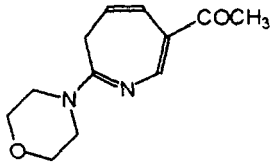
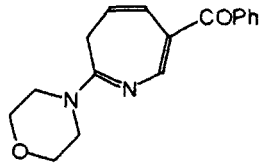
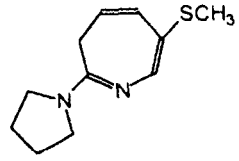
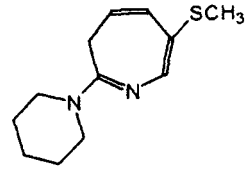
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Yellow oil		UV, IR, ^{1}H NMR	98
	227–229		^{1}H NMR	122
	Yellow oil		UV, IR, ^{1}H NMR	98
	Brown oil		UV, IR, MS, ^{1}H NMR	98
	Pale yellow oil		IR, ^{1}H NMR	122
	Pale yellow oil		^{1}H NMR	122

Table 3 (continued)

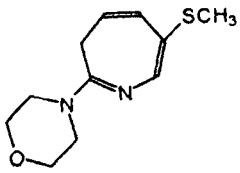
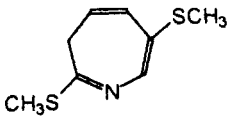
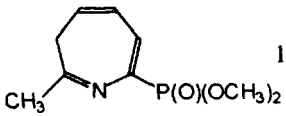
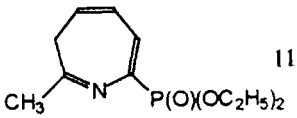
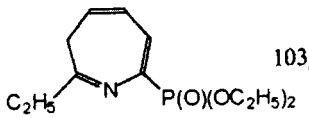
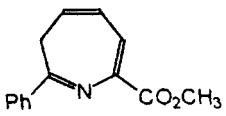
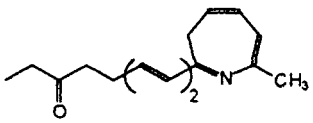
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	Pale yellow oil		^{1}H NMR	122
	Pale yellow oil, 150/0.01		IR, ^{1}H NMR	122
	105/0.04		^{1}H NMR	118 116
	115–120/0.02		n_D^{20} 1.5040 ^{1}H NMR	118 116
	103/0.02		n_D^{20} 1.5066 ^{1}H NMR	118 116
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, MS, ^{1}H, ^{13}C NMR	72

Table 3 (continued)

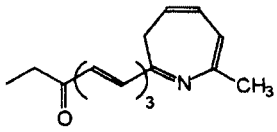
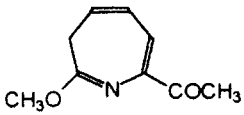
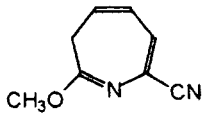
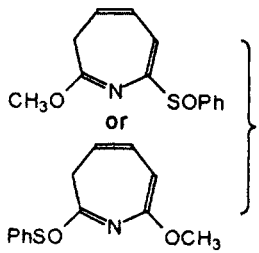
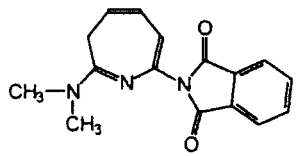
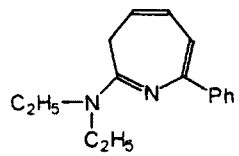
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			IR, UV, MS, ^{1}H, ^{13}C NMR	72
			^{1}H NMR IR, ^{1}H NMR	105 96
			^{1}H, ^{13}C NMR	106
	100/0.8		IR, ^{1}H, ^{13}C NMR	106
			^{1}H NMR	139
			^{1}H NMR	116

Table 3 (continued)

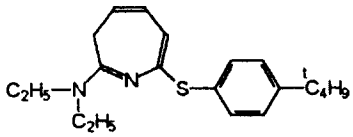
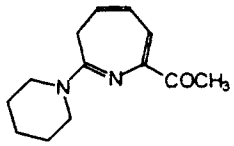
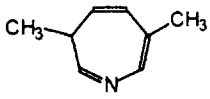
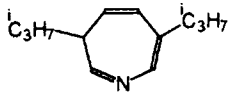
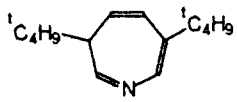
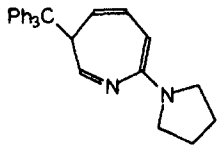
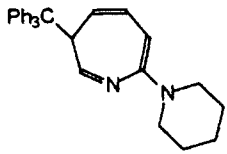
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			^{1}H NMR	116
			IR, UV, MS, ^{1}H NMR	96
	Pale yellow oil		IR, UV, ^{1}H, ^{13}C NMR	71c
	Pale yellow oil		IR, UV, ^{1}H, ^{13}C NMR	71c
	26–27 57.5–58.5 57.5–58.5		^{1}H, ^{13}C NMR ^{1}H, ^{13}C NMR IR, ^{1}H, ^{13}C NMR, MS	71a 132 71b 71c
	153–154		IR, UV, ^{1}H NMR	122
	151–152		^{1}H NMR	122

Table 3 (continued)

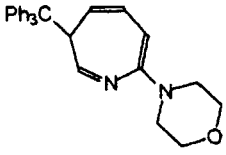
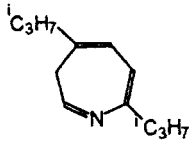
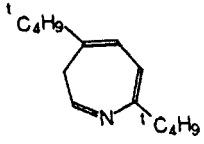
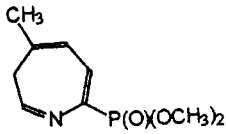
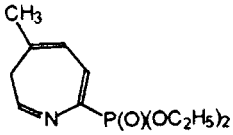
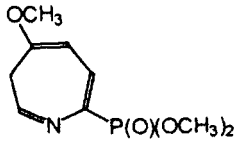
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	153–154		^{1}H NMR	122
	Pale yellow oil		IR, UV, ^{1}H, ^{13}C NMR	71c
	Pale yellow oil		^{1}H, ^{13}C NMR IR, UV, ^{1}H, ^{13}C NMR	71a 71c
	110/0.05		^{1}H NMR	118 116
			No data	117
	125–130/0.05		^{1}H NMR	118 116

Table 3 (continued)

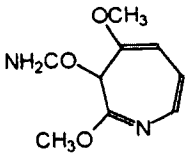
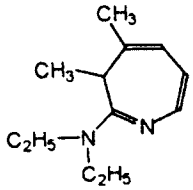
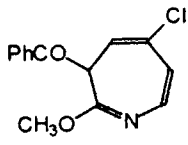
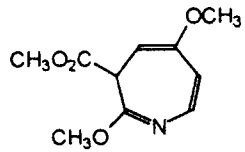
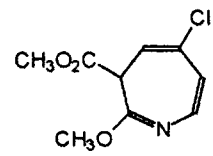
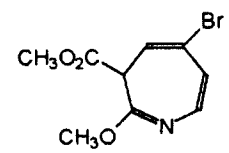
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	196		UV, MS, ^{1}H NMR	86a
			^{1}H NMR	80
	83.5–84.5		IR, UV, MS, ^{1}H NMR	78, 99
	77		UV, MS, ^{1}H NMR	86a
	44 90/0.01		UV, MS, ^{1}H NMR	86a
	42 90/0.02		UV, MS, ^{1}H NMR	86a

Table 3 (continued)

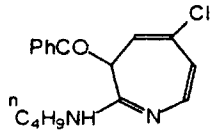
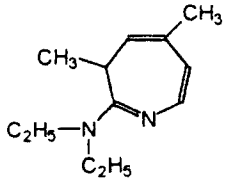
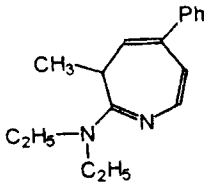
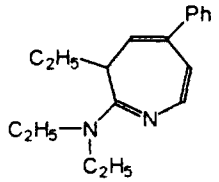
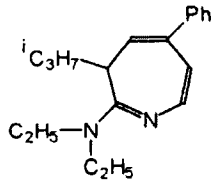
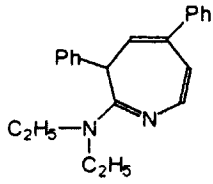
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	105–107		IR, UV, ^{1}H NMR	78
		Oxalate 85–86	UV, IR, ^{1}H NMR ^{1}H NMR	114 80
	88.5–89.5 88.5–89.5		^{1}H NMR MS, ^{1}H, ^{13}C NMR	134 135
	71.5–72.5		MS, ^{1}H, ^{13}C NMR	135
	80.5–81.5		MS, X-ray, ^{1}H, ^{13}C NMR ^{1}H NMR	135 142
	82.5–93.5		MS, ^{1}H, ^{13}C NMR	135

Table 3 (continued)

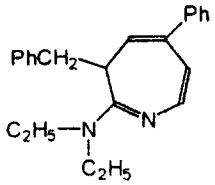
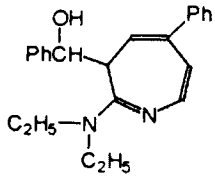
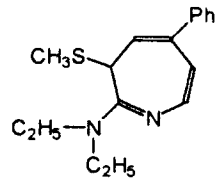
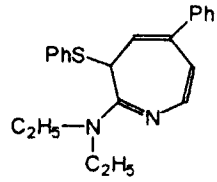
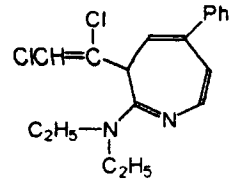
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	124–125 125–126		^{1}H NMR MS, ^{1}H, ^{13}C NMR	134 135
	172–173.5		IR, MS, ^{1}H NMR	135
	109.5–110.5 109.5–110.5		^{1}H NMR MS, ^{1}H, ^{13}C NMR	134 135
	91.5–92.5		MS, ^{1}H, ^{13}C NMR	135
	64–65		MS, ^{1}H NMR	135

Table 3 (continued)

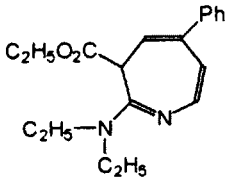
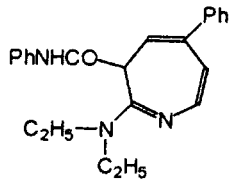
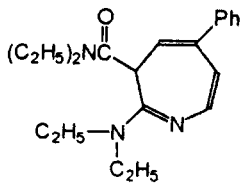
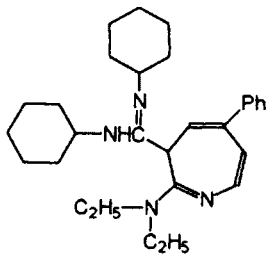
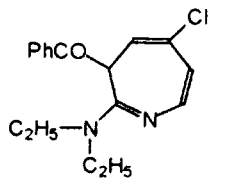
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	72.5–73.5		IR, MS, ^{1}H, ^{13}C NMR	135 144
	152.5–153.5		IR, MS, ^{1}H, ^{13}C NMR	135
	127.5–128		IR, MS, ^{1}H, ^{13}C NMR	135
	101.5–102.5		IR, MS	135
	131–132		IR, UV	78

Table 3 (continued)

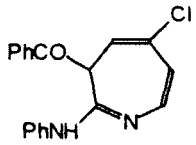
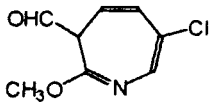
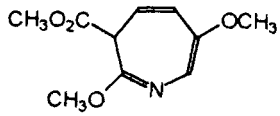
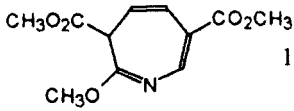
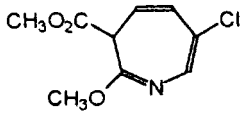
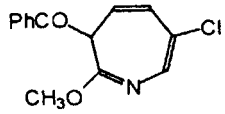
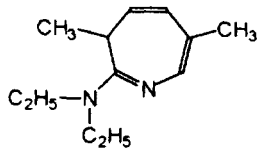
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	129–131		IR, UV, ^{1}H NMR	78
	70–80/6 78/6		IR, UV, ^{1}H NMR IR, UV, MS, ^{1}H NMR	78 99
	62		UV, MS, ^{1}H NMR	86a
	120/0.1		UV, MS, ^{1}H NMR	86a
	40 80/0.02		UV, MS, ^{1}H NMR	86a
	93.5–95.5		IR, UV, ^{1}H NMR	78
			^{1}H NMR	80

Table 3 (continued)

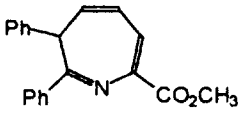
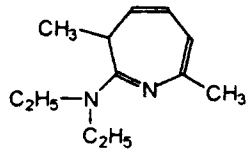
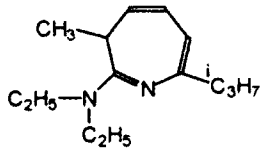
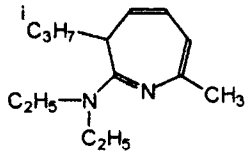
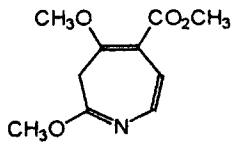
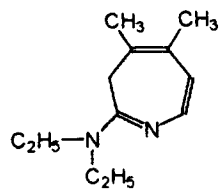
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			IR, UV, ^{1}H, ^{13}C NMR	130
			^{1}H NMR	80
			^{1}H NMR	80
			^{1}H NMR	80
			IR, UV, MS, ^{1}H NMR	103
		Oxalate 119–120	IR, ^{1}H NMR	114

Table 3 (continued)

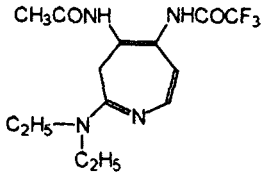
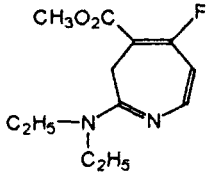
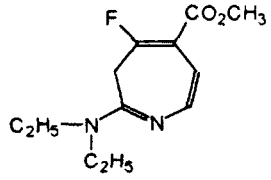
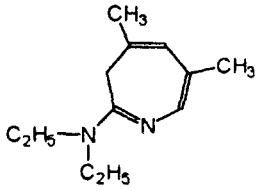
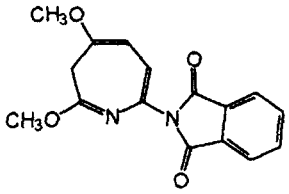
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			MS, ^{1}H, ^{13}C NMR	93
			MS, ^{1}H, ^{19}F NMR	91a
			MS, ^{1}H, ^{19}F NMR	91a
	*96–99/1.3*		UV, IR, ^{1}H NMR	114
			^{1}H NMR	139

Table 3 (continued)

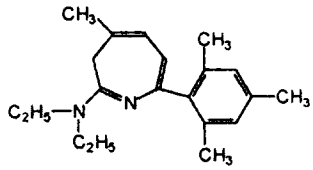
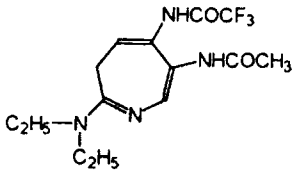
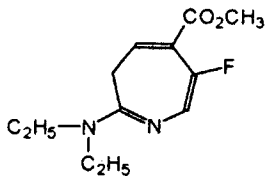
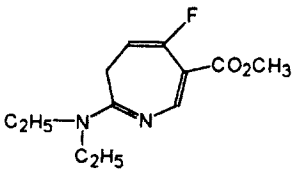
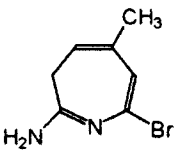
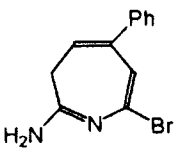
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			UV, ^{1}H NMR	80
			MS, ^{1}H, ^{13}C NMR	93
			MS, ^{1}H, ^{19}F NMR	91a
			MS, ^{1}H, ^{19}F NMR	91a
	160–165		IR, ^{1}H NMR	133
	173–175 (d)	HBr, 210–230 IR, ^{1}H NMR	IR	133

Table 3 (continued)

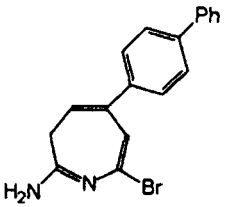
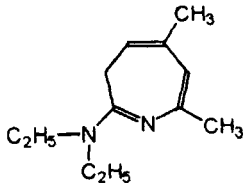
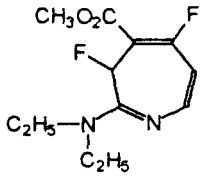
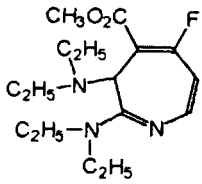
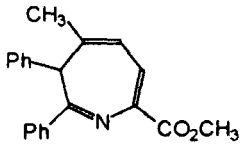
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	195–200 (d)	HBr, 245–250 IR	IR	133
		Oxalate 140–141	UV, IR, ^{1}H NMR	114
			MS, ^{1}H, ^{19}F NMR	91a
			MS, ^{1}H, ^{19}F NMR	91a
			IR, UV, ^{1}H, ^{13}C NMR	130

Table 3 (continued)

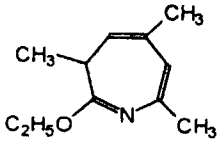
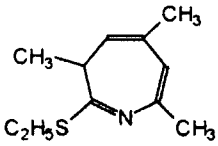
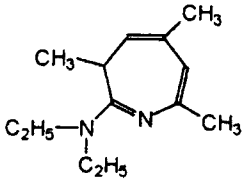
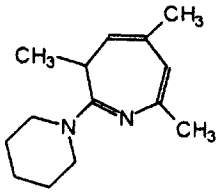
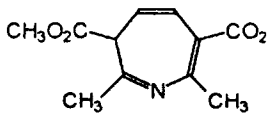
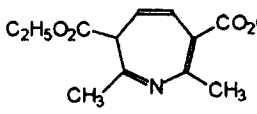
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	57/1.1		IR, UV, ^{1}H NMR n_D^{26} 1.4946, IR, UV, ^{1}H NMR	120 121
	76/0.25 76/0.25		^{1}H NMR n_D^{26} 1.4498, UV, ^{1}H NMR	120 121
	Yellow liquid		^{1}H NMR ^{1}H NMR	80 112
	105–112/1.3	$HClO_4$ salt 156–157 $HClO_4$ salt 156–157		120 121
	130–132/1.5		IR, ^{1}H NMR	128b 128a
	122–123/0.2		IR, UV, ^{1}H NMR	128b 128a

Table 3 (continued)

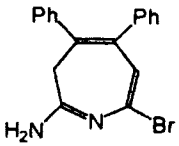
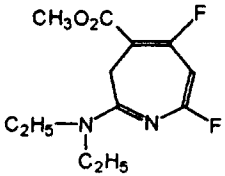
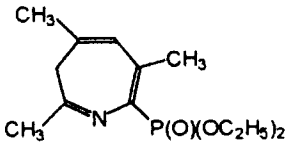
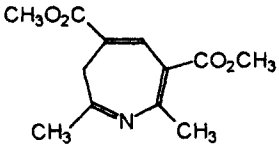
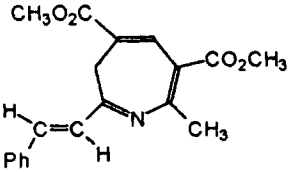
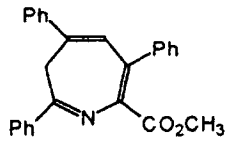
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	212–215 (d)	HBr 275 (d), IR	IR	133
			MS, ^{1}H, ^{19}F NMR	91a
			IR, UV, ^{1}H NMR	112
	Oil		IR, UV, ^{1}H NMR	129
	122–123.5		IR, UV, ^{1}H NMR	129
			IR, UV, ^{1}H, ^{13}C NMR	130

Table 3 (continued)

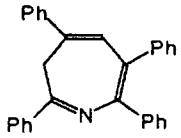
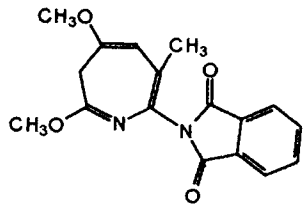
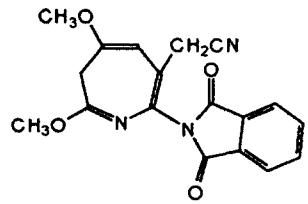
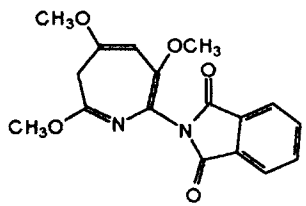
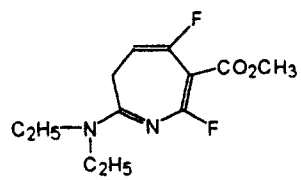
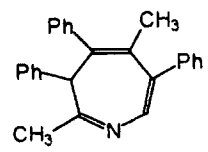
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	214–215		IR, UV, MS, ^{1}H, ^{13}C NMR X-ray	131
			^{1}H NMR	139
			^{1}H NMR	139
			^{1}H NMR	139
			MS, ^{1}H, ^{19}F NMR	91a
	123 133–134		^{1}H NMR ^{1}H NMR UV, ^{1}H NMR	126 124 123

Table 3 (continued)

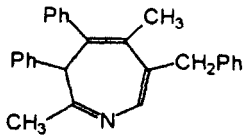
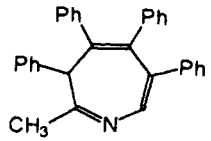
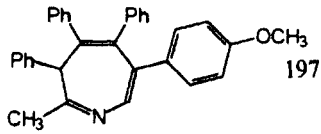
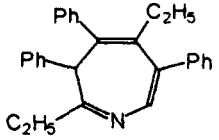
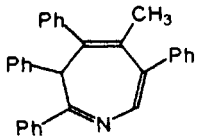
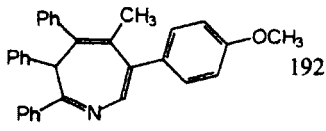
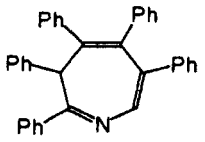
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	90		^{1}H NMR	126
	174		^{1}H NMR	126
	197		^{1}H NMR	126
	Oil Oil	Picrate 169, Picrate 169, ^{1}H NMR	^{1}H NMR	127 126
	170		^{1}H NMR	126
	192		^{1}H NMR	126
	212 217–218		^{1}H NMR ^{1}H NMR UV, ^{1}H NMR	126 124 123

Table 3 (continued)

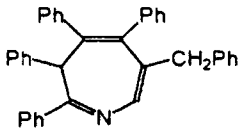
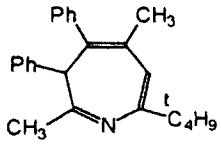
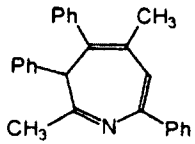
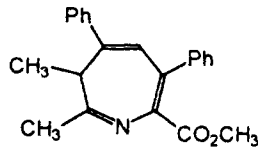
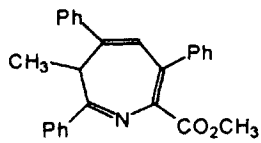
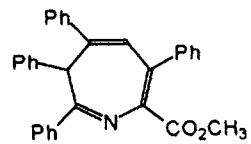
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	161		^{1}H NMR ^{1}H NMR	126 124
	97		MS, ^{1}H NMR	125
	108		MS, ^{1}H NMR	125
			^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130

Table 3 (continued)

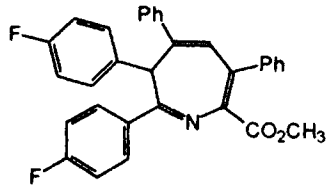
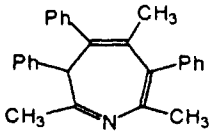
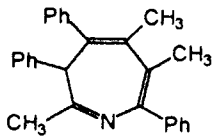
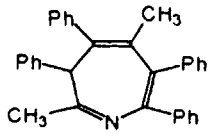
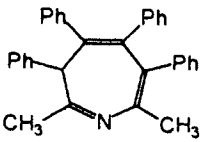
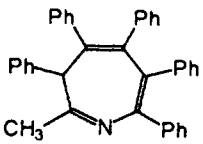
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
			IR, UV, ^{1}H, ^{13}C NMR	130
	182–183 182		UV, ^{1}H NMR ^{1}H NMR	123 126
	181		^{1}H NMR	126
	189 186–188		^{1}H NMR ^{1}H NMR UV, ^{1}H NMR	126 124 123
	164		^{1}H NMR ^{1}H NMR	126 124
	206		^{1}H NMR	126

Table 3 (continued)

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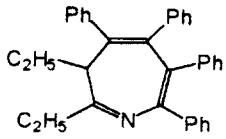
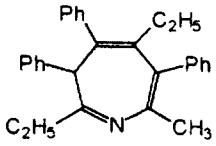
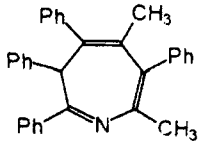
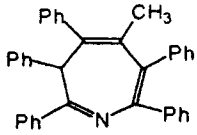
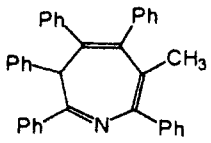
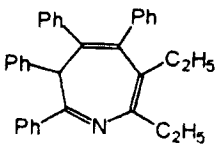
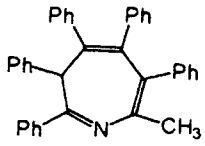
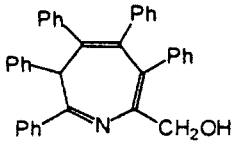
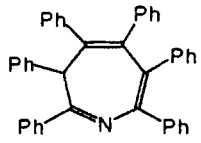
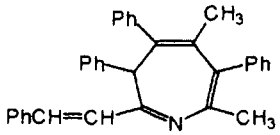
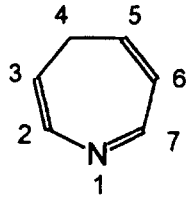
	127		^{1}H NMR	126
	128		^{1}H NMR	124
	113		^{1}H NMR	126
	165		^{1}H NMR	126
	187		^{1}H NMR	126
	177		^{1}H NMR	126
	151		^{1}H NMR	126
	151		^{1}H NMR	124
	212		^{1}H NMR	124, 126
	208		UV, ^{1}H NMR	123

Table 3 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence/data	Ref.
	213		^{1}H NMR	126
	227 227		UV, ^{1}H NMR ^{1}H NMR ^{1}H NMR	123 126 124
	161–163		UV, ^{1}H NMR	123

IV. [4*H*]AZEPINES

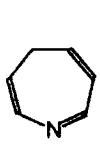


PREPARATION

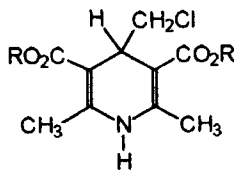
Evidence for the existence of the parent [4*H*]azepine (**4**) has not been presented. Substituted derivatives are, however, fairly widely represented in the literature.

As discussed earlier (Section III), ring-expansion procedures have been used to prepare [3*H*]azepines, and some of these methods have also been usefully applied with suitable modifications to give the [4*H*] isomers. Thus Gregory and Johnson and their co-workers treated the dihydropyridines **158** (R = CH_3, C_2H_5) with potassium cyanide[128,146–148] and with sodium ethoxide at room

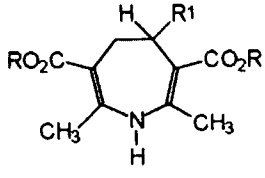
temperature[128] to achieve the 4,5-dihydro[1*H*]azepines **159** (R = CH_3, C_2H_5, R^1 = CN, OC_2H_5) (see also Chapter 8, Section IV). At elevated temperatures



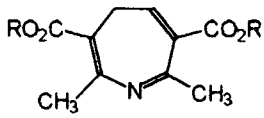
(4)



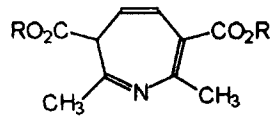
(158)



(159)

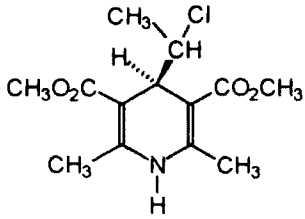


(160)

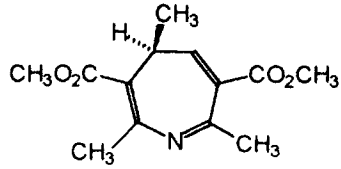


(161)

these latter compounds were converted into the corresponding [4*H*]azepines **160** (R = CH_3, C_2H_5) with loss of HCN or C_2H_5OH, respectively.[128,148] Elimination of ethanol occurred readily at temperatures up to the boiling point of ethanol, whereas eliminating HCN required fairly forcing conditions (265 °C). Even higher temperatures (320 °C) resulted in further rearrangement to the [3*H*]azepines **161** (R = CH_3, C_2H_5).[128] The [4*H*]azepine **163** was obtained directly from the dihydropyridine **162** using either potassium carbonate in dimethyl sulphoxide at room temperature or sodium ethoxide in ethanol.[148]

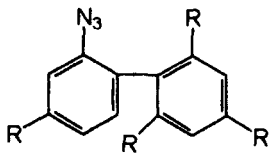


(162)

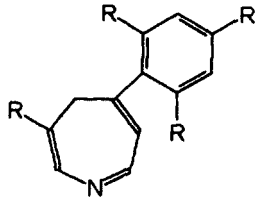


(163)

Photolysis of aromatic azides, which proved to be a successful approach to [3*H*]azepines[79,80] (Section III), has also been shown to give [4*H*]azepines although usually in poor yields as the minor products of the reaction. For example, the [4*H*]azepines **165** (R = H, CH_3) were separated as the minor components from the photolysis of the biphenyl azides **164** (R = H, CH_3) in diethylamine, the corresponding [3*H*]azepines being the other components.[79,80]



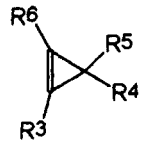
(164)



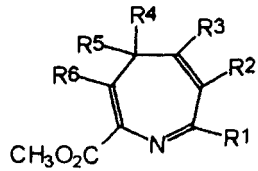
(165)

[4*H*]Azepines were also formed, in this case as the main products of the reaction, by the [4 + 2] cycloaddition of 1,2,4-triazines (**136**, R^1 = H, CH_3, Ph, *p*-anisyl, *p*-FC_6H_4, R^2 = H, CH_3, Ph, *p*-FC_6H_4 or R^1 = R^2 = H, Ph, CO_2CH_3)[130,149] and cyclopropenes (**166**, R^3 to R^6 = H, CH_3, Ph). Using this procedure, Sauer and his co-workers[130,149] produced 28 examples of substituted [4*H*]azepines (see Scheme 6, Section III); details of the products (**167**, R^1, R^2 = H, CH_3, Ph, *p*-anisyl, *p*-FC_6H_4, CO_2CH_3; R^3 to R^6 = H, CH_3, Ph) are given in Table 4.

(136)



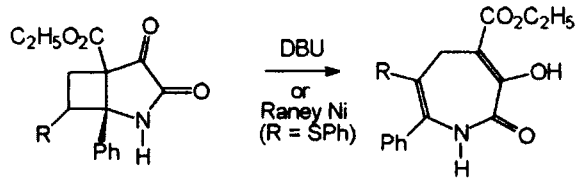
(166)



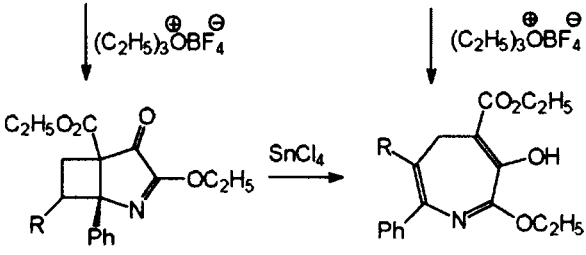
(167)

Sano and his co-workers have investigated the rearrangement of bicycloheptenes[150] and -heptanes[151,152] as a method for the preparation of a series of 'azatropolones'. In the course of their investigations they found that treatment of the azabicyclo[3.2.0]heptane-3,4-diones **168** (R = Ph, OC_2H_5, $OCOCH_3$, SPh, C_2H_5) with DBU led to the corresponding 1,5-dihydro-[2*H*]azepine-2-ones **169** (R = Ph, OC_2H_5, $OCOCH_3$), which on treatment with $(C_2H_5)_3O^+$ BF_4^- gave the 7-ethoxy[4*H*]azepines **170** (R = Ph, OC_2H_5, $OCOCH_3$).[151,152] An alternative procedure, treating the biyclic enol ethers **171** (R = Ph, OC_2H_5, $OCOCH_3$) with $SnCl_4$, led directly to the same products. Treatment of **168** (R = SPh) with Raney Ni gave the dihydro[2*H*]azepin-2-one **169** (R = H), which was similarly converted into the 7-ethoxy[4*H*]-azepine **170** (R = H) with $(C_2H_5)_3O^+$ BF_4^-.[151,152]

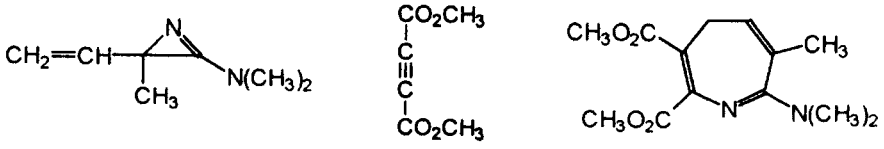
An unusual ring-expansion reaction was shown to occur on treatment of 3-methyl-3-vinyl-2-dimethylaminoazirine (**172**) with dimethyl acetylenedicarboxylate (**173**), which led to the formation of the [4*H*]azepine **174** by incorporation of both the acetylene and the vinyl substituents into the ring system. The structure of **174** was confirmed by X-ray analysis.[153]



(168) (169)

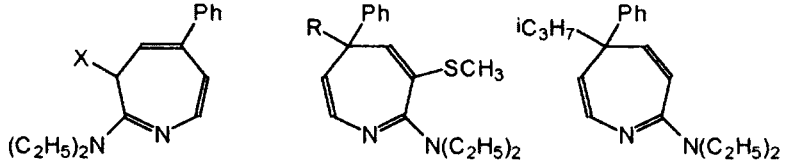


(171) (170)



(172) (173) (174)

[4*H*]Azepines (**176**, R = CH_3, CH_2Ph) were formed by alkylation of 5-phenyl[3*H*]azepine (**175**, X = SCH_3), using methyl iodide and benzyl chloride,



(175) (176) (177)

respectively, in the presence of KNH_2/liquid NH_3. Similarly, alkylation of the [3*H*]azepine **175** (X = H) with 2-bromopropane in the presence of lithium diisopropylamide gave the 4-phenyl-4-isopropyl[4*H*]azepine **177**.[142]

Physical data for the [4*H*]azepines are detailed in Table 4.

Table 4. [4*H*]Azepines

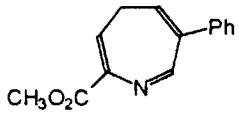
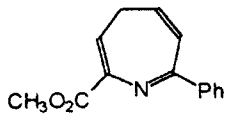
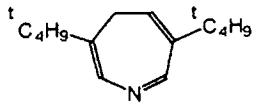
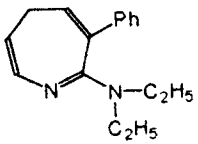
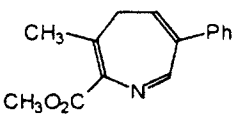
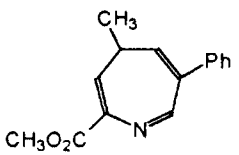
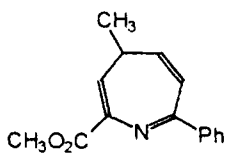
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130
			^{1}H, ^{13}C NMR	71
			UV, ^{1}H NMR	79
			^{1}H, ^{13}C NMR	130
			^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130

Table 4 (continued)

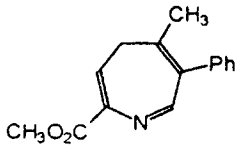
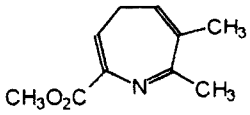
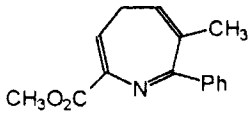
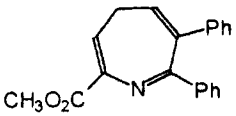
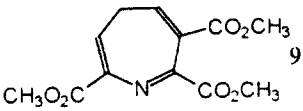
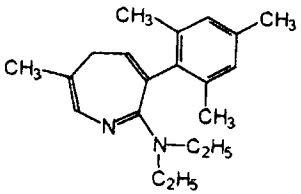
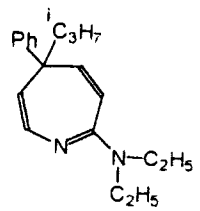
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			^1H, ^{13}C NMR	130
			^1H, ^{13}C NMR	130
			IR, UV, ^1H, ^{13}C NMR	130
			IR, UV, ^1H, ^{13}C NMR	130
	95–96		^1H NMR	149
		Picrate 179–179.5	^1H NMR	80
	48–49		MS, ^1H, ^{13}C NMR	142

Table 4 (continued)

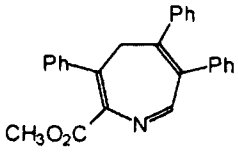
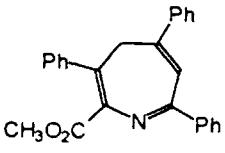
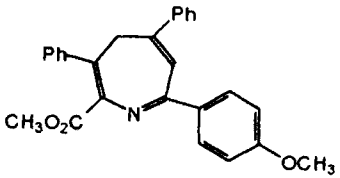
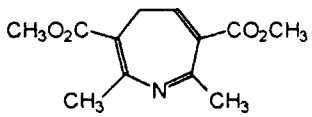
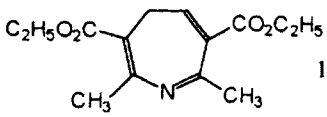
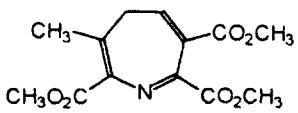
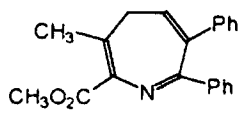
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130
	76.5–77		IR, UV, ^{1}H NMR	128b 128a
	142–145/0.1		IR, UV, ^{1}H NMR	128b 128a
	82–83		^{1}H NMR	149
	113–114		^{1}H NMR IR, UV, ^{1}H, ^{13}C NMR	149 130

Table 4 (continued)

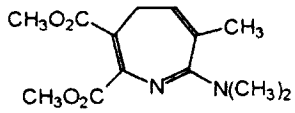
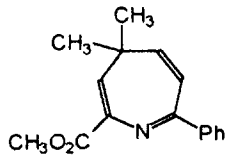
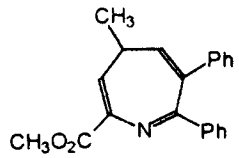
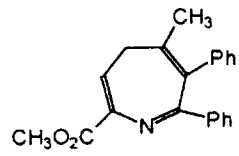
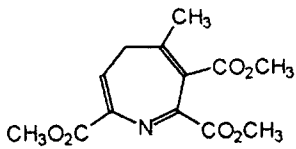
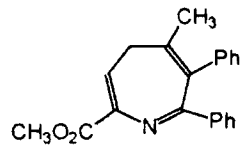
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			X-ray	153
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130
			IR, UV, ^{1}H, ^{13}C NMR	130
	139–141		^{1}H NMR	149
	144–145		^{1}H NMR	149

Table 4 (continued)

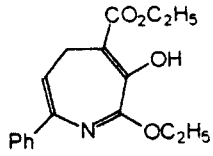
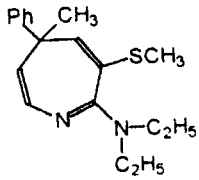
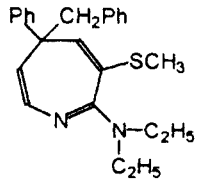
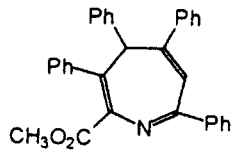
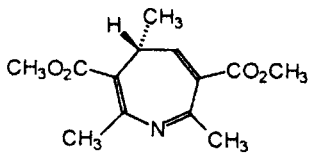
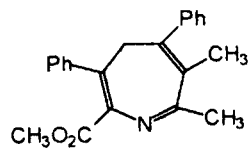
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	Gum		IR, UV, MS, ^{1}H NMR	151, 152
	36–37		MS, X-ray, ^{1}H, ^{13}C NMR	142
	Oil		MS, ^{1}H, ^{13}C NMR	142
			IR, UV, ^{1}H, ^{13}C NMR	130
	110–115/0.03		IR, UV, MS, ^{1}H NMR	148
			IR, UV, ^{1}H, ^{13}C NMR	130

Table 4 (continued)

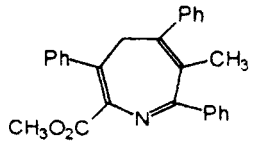
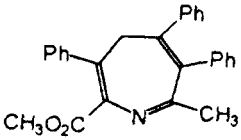
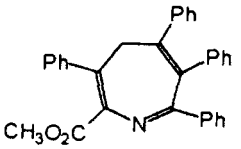
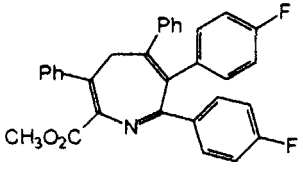
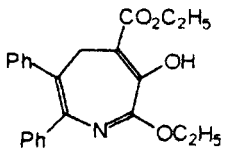
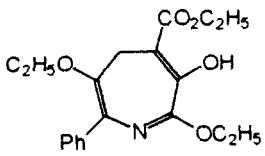
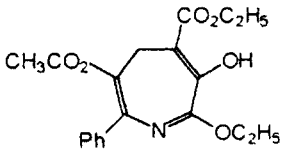
Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
			^1H, ^{13}C NMR	130
			IR, UV, ^1H, ^{13}C NMR	130
			IR, UV, ^1H, ^{13}C NMR	130
			IR, UV, ^1H, ^{13}C NMR	130
	114–115		IR, UV, MS, ^1H NMR	151, 152
	Gum		IR, UV, MS, ^1H NMR	151, 152

Table 4 (continued)

Structure	M.p. (°C)/b.p. (°C/mmHg)	Derivatives and m.p. (°C)	Spectroscopic evidence	Ref.
	73–75		IR, UV, MS, ^{1}H NMR	151, 152

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Chemistry of Heterocyclic Compounds, Volume 56
George R. Proctor, James Redpath
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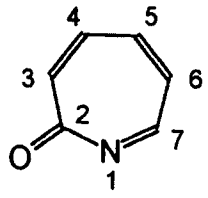
CHAPTER 12

Azepinones

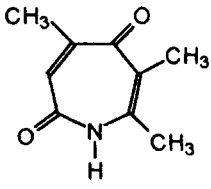
Examples of the three types of azepinones are known but the most common by far are [2*H*]azepin-2-ones. All may be regarded as azatropones and have aroused interest for that reason. Whether or not tropolones and tropones should be regarded as 'aromatic' has been much discussed.[1–3] The present view is that the word 'aromatic' should be applied with some reservation.[4–6] Just as pyridines exhibit fewer of the ideal 'aromatic' properties (both physical and chemical) of benzene, so one might expect aza analogues of tropone and tropolone to behave even less like benzene in these respects. On the whole, that prediction seems to be correct (see below).

I. [2*H*]AZEPIN-2-ONES



PREPARATION

This group has proved more accessible than the other two types. Treatment of the diones **1** and **2**, obtainable by Schmidt reaction on quinones (Chapter 10), with either trimethyl- or triethyloxonium fluoroborate gave the products **3** and **4** (R = CH_3 or C_2H_5) in fairly good yield (50–70%).[7] Azepin-2-ones have also



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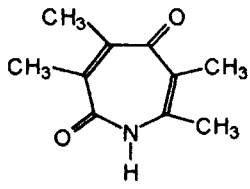

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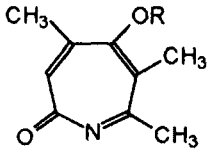

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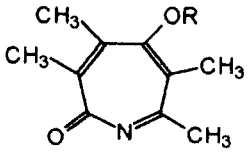
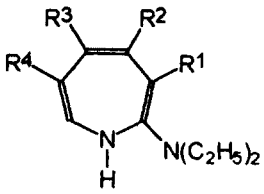


(4)

been obtained from a range of [1*H*]azepines (**5**, R^1 to R^4 = H or CH_3) by oxygenation immediately after photolytic treatment of aryl azides in diethylamine.[8] The products (**6**, R^1 to R^4 = H or CH_3) (see Table 1) were separated by chromatography and isolated in moderate yields (20–36%).



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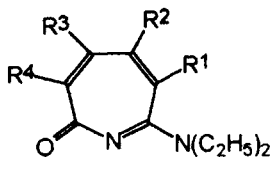

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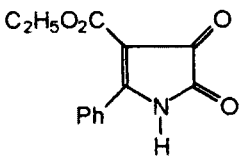

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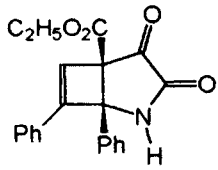
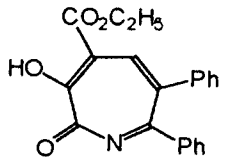


(8)

The only α-hydroxy ketones (azatropolones) known have been made by an ingenious protocol developed by Sano and co-workers.[9] Thus, irradiation of phenylacetylene and the pyrrolinedione **7** gave the cyclobutene adduct **8**, which was converted thermally into the hydroxy ketone **9** in 60% yield. On the other hand, irradiation of **8** gave the isomeric product **10** but in only 5% yield. It was plausibly proposed that the latter result was due to a photo-induced ring-opening/reclosure of **8** (via **11** and **12**) to **13**, which would provide **10** thermally.



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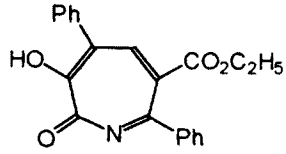
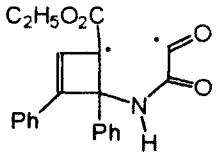


(10)



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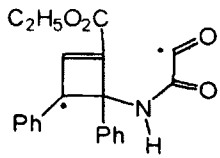
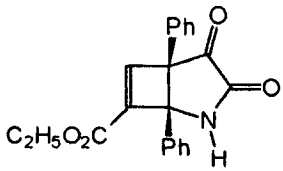


(12)

The structure of **9** was confirmed by X-ray analysis of the *O*-methyl ether of a 7-*p*-bromophenyl analogue.[10]



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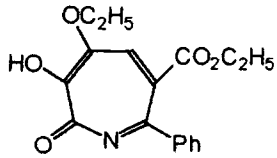

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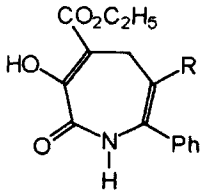

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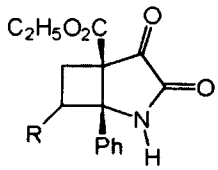
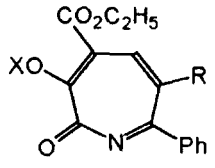


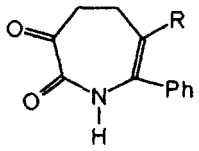
(16)

The tendency for rearrangement (e.g. to **10**) referred to above was known to intrude seriously in some cases.[11] For example, the procedure employing ethoxyacetylene yielded only 20% of the rearranged azepinone **14**.[11] Accordingly, a more robust synthesis was developed which commenced with photoaddition of the pyrrolidinedione **7** with alkenes rather than alkynes. This produced dihydroazepinones (Chapters 9 and 10)[12,13] (**15**, R = Ph, C_2H_5, OAc, OC_2H_5, SPh and H) after treatment of the cyclobutanes **16** (R = Ph, C_2H_5, OAc, OC_2H_5, SPh and H) with DBU.[11] DDQ dehydrogenation of **15** was capricious, but the *O*-methyl ethers of **15** underwent slow but moderate yielding reaction with DDQ; the products were the *O*-methyl ethers of the

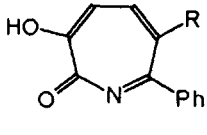
azepinones **17** (X = CH_3, R = Ph, C_2H_5, OAc, OC_2H_5, SPh, H). All except **17** (X = CH_3, R = H) were easily purified and appeared to be yellow gums; however, some were later found to be crystalline.[14]



(17)



(18)



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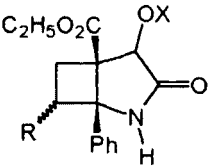
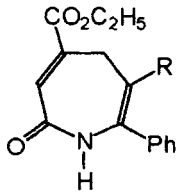


(20)

Less highly substituted azepinones were made by two modifications. Decarboxylation of **15** (R = Ph or OC_2H_5) using $CaCl_2$/DMSO yielded the diones **18** (R = Ph, OC_2H_5), which were dehydrogenated using DDQ, producing **19** (R = Ph, OC_2H_5).[15] Alternatively, eliminative ring expansion of **20**[17] (hydride reduction products from **16**) as *O*-acetates or mesylates (X = Ac or OMs) with DBU gave the dihydroazepinones **21** (R = Ph, OC_2H_5, vinyl), which DDQ



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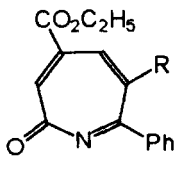

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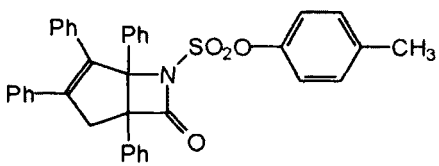

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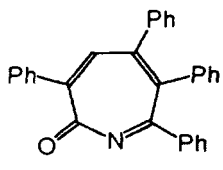


(24)

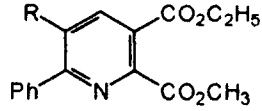
converted into the fully unsaturated products (**22**, R = Ph, OC_2H_5, vinyl) in variable but satisfactory yields.[16] Finally, there is a report[18] that the β-lactam **23** reacted with sodium hydride to give 40% of the azepinone **24**.

PROPERTIES

On the whole, azepin-2-ones are solids of reasonable stability; the 3-hydroxy and 3-methoxy derivatives are yellow. Fairly extensive physical data[7–17] are available and serve to illustrate that these compounds behave as cyclic ketones

with multiple unsaturation; there are no striking features suggesting abnormal electron delocalisation.[7] Thus peripheral hydrogen atoms resonate between about δ 6.5 and 8.0, M – CO peaks are generally seen in the mass spectra and the only X-ray analysis reported[10] reveals that the heterocyclic ring is non-planar and bond lengths are alternate. Infrared stretching frequencies attributable to carbonyl groups are seen in the region 1660–1695 cm^{-1}, usual for $\alpha\beta$-unsaturated ketones.

Since most azepin-2-ones seen so far are fairly heavily substituted, one should not be surprised at the foregoing; a final assessment of 'aromaticity' or the lack of it awaits the discovery of simple analogues. Judging by chemical reactivity, these substances do not exhibit especially stabilising features, indeed the opposite is the case. 3-Hydroxyazepin-2-ones (e.g. **17**, X = H) are extremely reactive in protic solvents,[9,14] generating pyridine esters (**25**, R = Ph, OC_2H_5, OAc, C_2H_5, SPh, H) in methanol. The *O*-ethyl analogues (**17**, X = C_2H_5) also



(25)

underwent ring contraction to pyridine esters,[14] but usually this required acid or base. The mechanism has been discussed;[14] compared with tropolones which, in general, require more forcing conditions, these azepin-2-one analogues are far less stable. The 3-hydroxy compounds **17** (X = H) give yellow-green colorations with iron(III) chloride and are sufficiently acidic to methylate with diazomethane.[9,14]

It is entirely to be expected that the azepinones **3** and **4** were hydrolytically converted back to their precursors (**1** and **2**).[7] Instability in solution prevented the measurement of pK_a values.[14] One has to conclude that the introduction of a nitrogen atom to this ring system has had a considerable perturbing effect and that these 'azotropolones' seem unlikely to exhibit the interesting features associated with their carbocyclic analogues.

Table 1. [2*H*]Azepin-2-ones

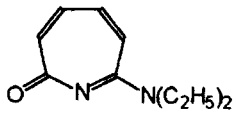
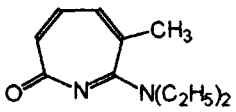
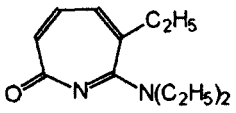
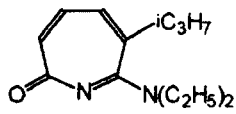
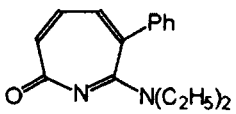
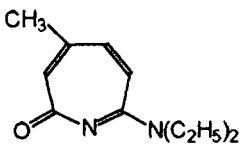
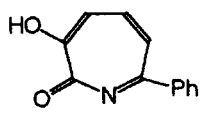
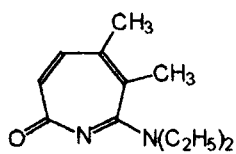
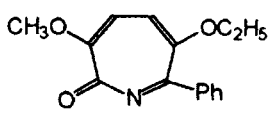
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	80–81	UV, ^{1}H NMR	8
	84–85	UV, ^{1}H NMR	8
	61–62	UV, ^{1}H NMR, MS, IR	8
	80–81	UV, ^{1}H NMR	8
	116-118	UV, ^{1}H NMR	8
	77–78	UV, ^{1}H NMR	8
	133–138	IR, UV, MS, ^{1}H NMR	15
	Liquid	^{1}H NMR	8
	130–133	IR, UV, MS, ^{1}H, ^{13}C NMR	14

Table 1 (continued)

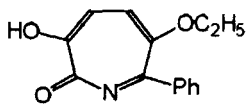
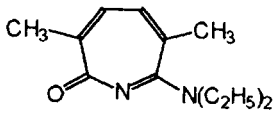
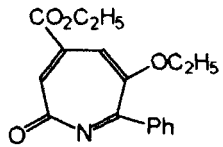
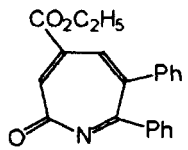
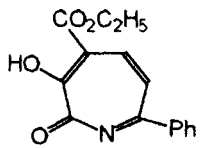
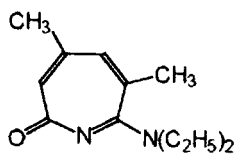
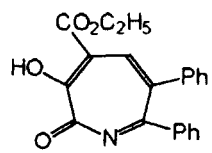
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	Yellow gum	IR, UV, MS, ^{1}H NMR	15
	115–116	^{1}H NMR	8
	109–110	IR, UV, MS, ^{1}H, ^{13}C NMR	16
	Colourless gum	IR, UV, MS, ^{1}H, ^{13}C NMR	16
	Yellow gum 187–189	UV IR, MS, ^{1}H, ^{13}C NMR	11 14
	110–112	^{1}H NMR	8
	151–154	IR, UV, MS, ^{1}H, ^{13}C NMR	9, 14

Table 1 (continued)

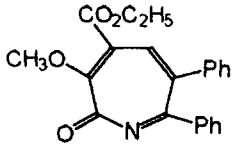
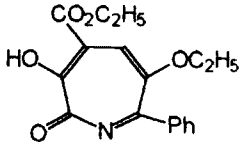
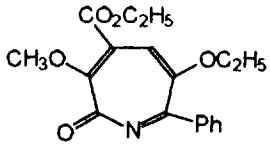
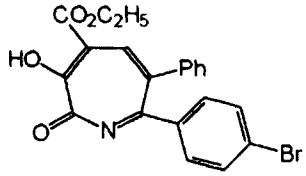
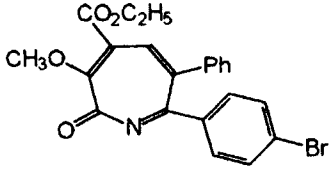
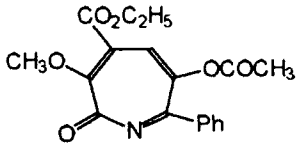
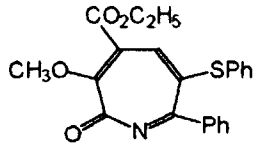
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	131–134	IR, ^{1}H, ^{13}C NMR	9, 14
	92–95	UV IR, MS, ^{1}H, ^{13}C NMR	11 14
	Yellow gum 72–73	UV IR, MS, ^{1}H, ^{13}C NMR	11 14
	153–154 155–156	IR, UV MS, ^{1}H, ^{13}C NMR	10 14
	133–136	IR, UV, X-ray MS, ^{1}H, ^{13}C NMR	10 14
	Yellow gum	UV IR, MS, ^{1}H NMR	11 14
	Yellow gum	UV IR, MS, ^{1}H NMR	11 14

Table 1 (continued)

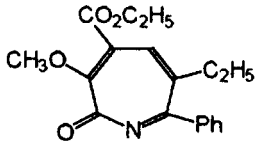
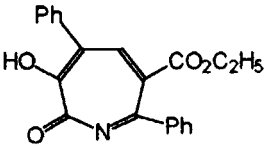
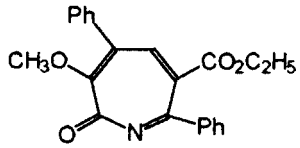
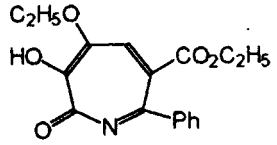
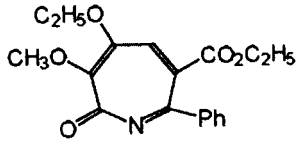
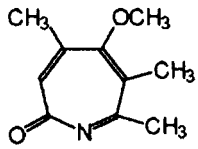
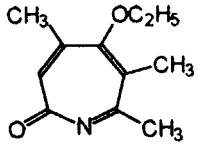
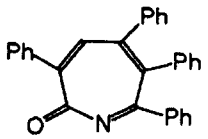
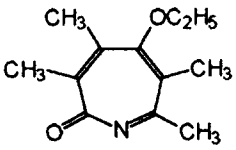
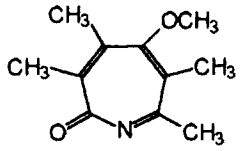
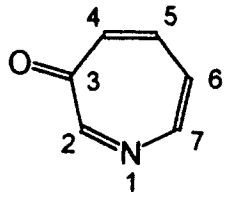
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	Yellow gum	UV IR, MS, ^{1}H NMR	11 14
	191–194	UV, IR, MS, ^{1}H NMR	9
	102–105	IR, UV, ^{1}H NMR MS	9 14
	179–181	IR, UV, MS, ^{1}H, ^{13}C NMR	14
	60–63	IR, UV, MS, ^{1}H NMR	14
	52	^{1}H NMR	7
	71–72	^{1}H NMR	7

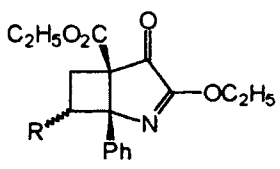
Table 1 (continued)

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	52	IR, ^{1}H NMR, MS	18
	68.5–70	^{1}H NMR	7
	84–85	^{1}H NMR	7

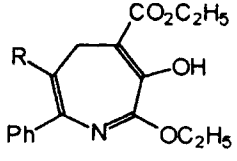
II. [3*H*]AZEPIN-3-ONES



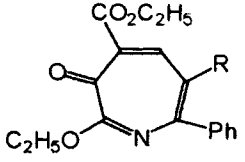
The only examples are to be found in the work of Sano and co-workers.[7,9,14] When compounds **16** (R = Ph, OC_2H_5, OAc) were converted into the lactim ethers **26** (R = Ph, OC_2H_5, OAc), the latter reacted with tin(IV) chloride giving



(26)

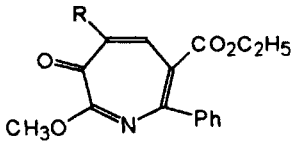


(27)

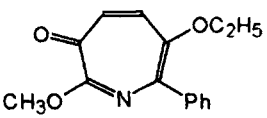


(28)

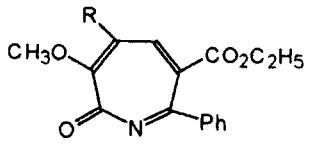
the ring-expanded products **27** (R = Ph, OC_2H_5, OAc), which DDQ dehydrogenation transformed into the [3*H*]azepin-3-ones **28** (R = Ph, OC_2H_5, OAc).[7] It was later reported[14] that **28** (R = H) could also be obtained in this way. Alternatively, diazomethane methylation of the hydroxy ketones **10**, **14** and **19** (R = OC_2H_5) gave roughly equal amounts of the azepin-3-ones **29** (R = Ph, OC_2H_5) and **30**[9,14] and the corresponding azepin-2-ones **31** (R = Ph, OC_2H_5) and **32**. Such behaviour is typical of tropolones, but **9** with diazomethane gave exclusively one product (**17**, X = CH_3, R = Ph) in 70% yield.[9] This result would appear to be attributable to hydrogen bonding involving the ester group at C-4.



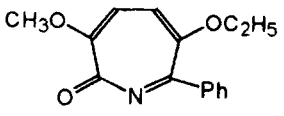
(29)



(30)



(31)



(32)

The chemistry of [3*H*]azepin-3-ones has not been studied.

Table 2. [3*H*]Azepin-3-ones

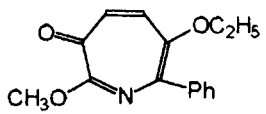
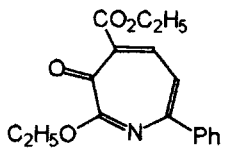
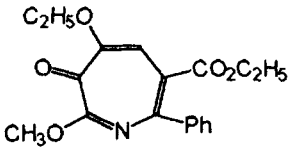
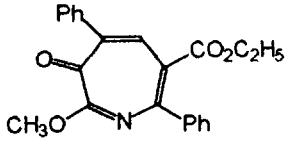
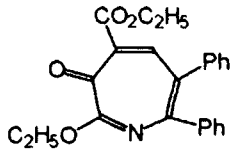
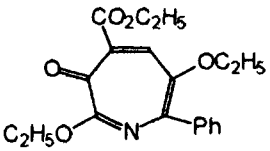
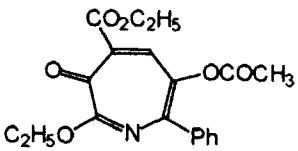
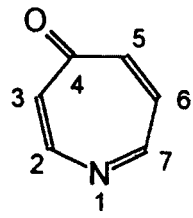
Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	79–81	IR, UV, MS, ^1H, ^{13}C NMR	14
	Yellow gum	IR, UV, ^1H NMR	22 14

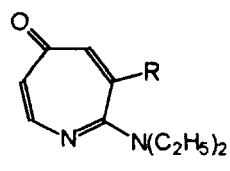
Table 2 (continued)

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	Yellow gum	IR, UV, MS, ^{1}H NMR	14
	133–135	IR, UV, ^{1}H NMR MS	9 14
	Yellow gum	IR, UV, ^{1}H NMR ^{13}C NMR, MS	22 14
	Yellow gum	IR, UV, ^{1}H NMR ^{13}C NMR, MS	22 14
	Yellow gum	IR, UV, ^{1}H NMR MS	22 14

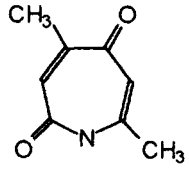
III. [4*H*]AZEPIN-4-ONES



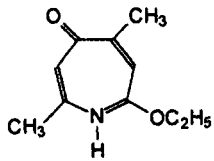
Until recently, the only references to [4*H*]azepin-4-ones appeared during 1972. First, it was disclosed that if the oxygenation of [1*H*]azepines (**5**, $R^2 = R^3 = R^4 = H$, $R^1 = H$ or ^iPr) previously mentioned (Section I) was carried out in the presence of small amounts of copper(II) ion, the products included azepin-4-ones (**33**, R = H or ^iPr).[8] Yields were low.



(33)

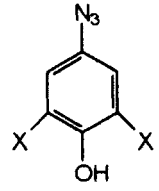


(34)

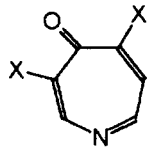


(35)

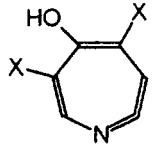
The dione **34** reacted with triethyloxonium fluoroborate giving extremely low yields (<5%) of the azepin-4-one **35**.[7,19] One has to suspect that these compounds were reactive. The latter view is supported by very recent matrix photolysis work.[20] In concentrated nitrogen matrices at 10–20 K, irradiation ($\lambda = 280 \pm 10$ nm) of both dichloro- and dibromo-4-azidophenols (**36**, X = Cl,



(36)



(37)

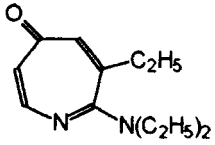
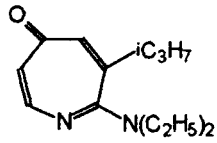
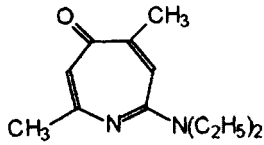


(38)

Br) showed evidence of the presence of azepin-4-ones (**37**, R = Cl, Br). Thus, IR bands at 1625 cm^{-1} (C=N) and 1679, 1672, 1669 cm^{-1} (C=O) were seen to persist up to near room temperature. In less concentrated matrices, evidence ($\nu_{C=C=N}$ 1887 cm^{-1}) for the established[20] didehydroazepine intermediates **38** (X = Cl, Br), but not for ketones, was seen. Intramolecular hydrogen transfer in concentrated matrices was adduced to explain the appearance of **37**. At

present this seems unlikely to provide a synthetic route to the [4*H*]azepin-4-ones.[21]

Table 3. [4*H*]Azepin-4-ones

Structure	M.p. (°C)	Spectroscopic evidence	Ref.
	Liquid	IR, UV, ^{1}H NMR	8
	Liquid	^{1}H NMR,UV	8
	57–58 69	IR UV, MS, ^{1}H NMR	7 19

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George R. Proctor, James Redpath
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