# MONOCYCLIC AZEPINES

## The Syntheses and Chemical Properties of the Monocyclic Azepines

**GEORGE R. PROCTOR**
*University of Strathclyde*

**JAMES REDPATH**
*Organon Laboratories Ltd*

A Wiley–Interscience Publication

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*This is the Fifty-sixth Volume in the Series*

**THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS**

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A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR

*Editor*

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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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# Contents

* 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 |

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

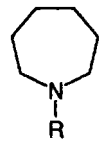
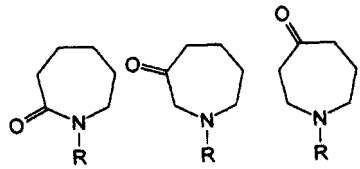
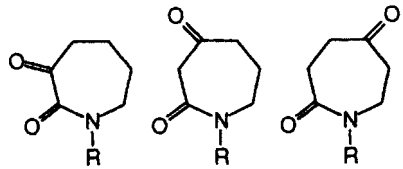
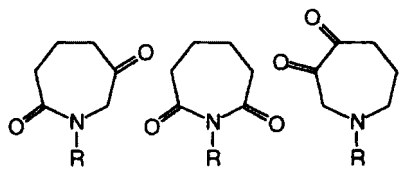
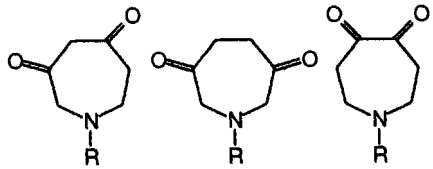
| Chapter No. | Compound name | Structure |
|---|---|---|
| 2 | **Azepanes** (hexahydroazepines) |  |
| 3 | **Azepanones** | |
| | I. Azepan-2-ones<br>II. Azepan-3-ones<br>III. Azepan-4-ones |  |
| 4 | **Azepanediones** | |
| | I. Azepane-2,3-diones<br>II. Azepane-2,4-diones<br>III. Azepane-2,5-diones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

**Table 1 (continued)**

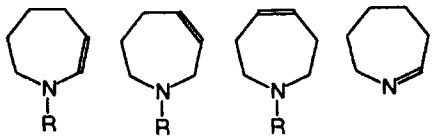
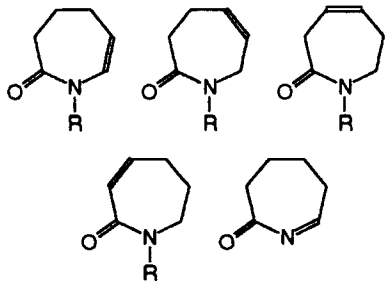
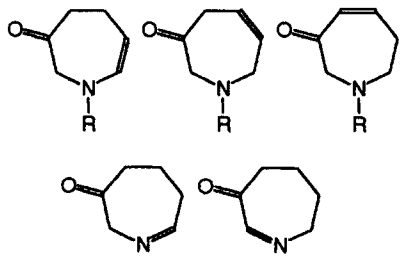
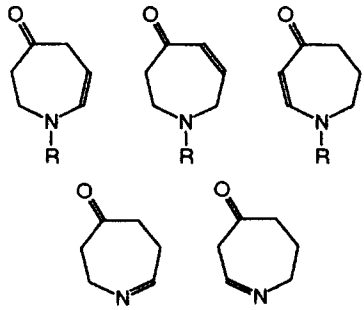
| Chapter No. | Compound name | Structure |
|---|---|---|
| 5 | **Tetrahydroazepines** | |
| | I. 2,3,4,5-Tetrahydro[1*H*]-azepines<br>II. 2,3,4,7-Tetrahydro[1*H*]-azepines<br>III. 2,3,6,7-Tetrahydro[1*H*]-azepines<br>IV. 3,4,5,6-Tetrahydro[2*H*]-azepines |  |
| 6 | **Tetrahydroazepinones** | |
| | I.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

**Table 1 (continued)**

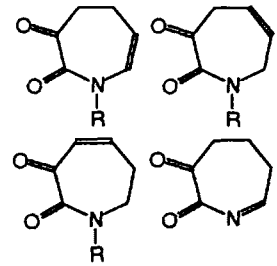
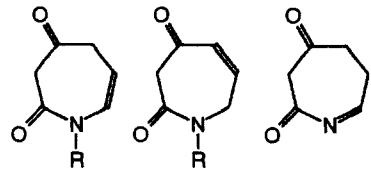
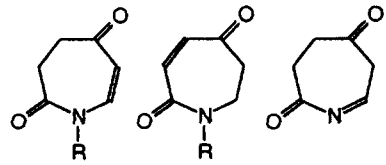
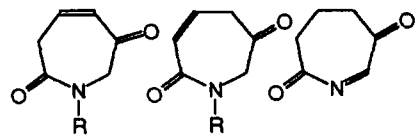
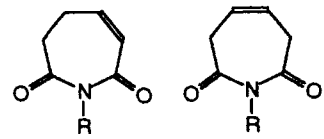
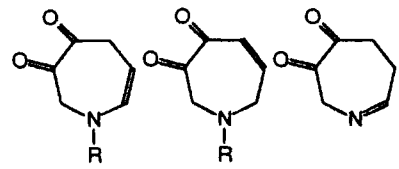
| Chapter No. | Compound name | Structure |
|---|---|---|
| 7 | **Tetrahydroazepinediones** | |
| | I. 2,3,4,5-Tetrahydro[1*H*]-azepine-2,3-diones<br>II. *2,3,4,7-Tetrahydro[1H]-azepine-2,3-diones*<br>III. *2,3,6,7-Tetrahydro[1H]-azepine-2,3-diones*<br>IV. *3,4,5,6-Tetrahydro[2H]-azepine-2,3-diones*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

**Table 1 (continued)**

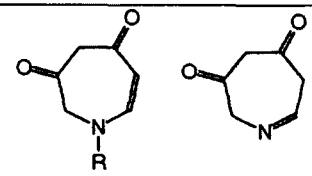
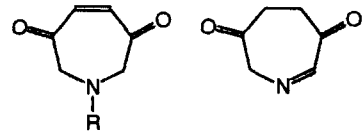
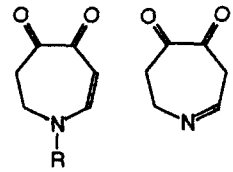
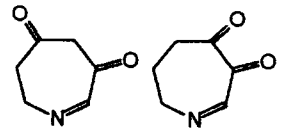
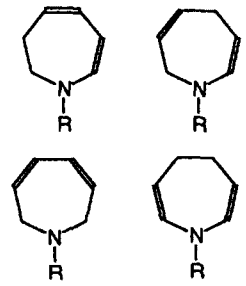
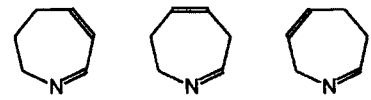
| Chapter No. | Compound name | Structure |
|---|---|---|
| | XIX. *2,3,4,5-Tetrahydro[1H]-azepine-3,5-diones*<br>XX. *3,4,5,6-Tetrahydro[2H]-azepine-3,5-diones* |  |
| | XXI. *2,3,6,7-Tetrahydro[1H]-azepine-3,6-diones*<br>XXII. *3,4,5,6-Tetrahydro[2H]-azepine-3,6-diones* |  |
| | XXIII. 2,3,4,5-Tetrahydro[1*H*]-azepine-4,5-diones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

**Table 1 (continued)**

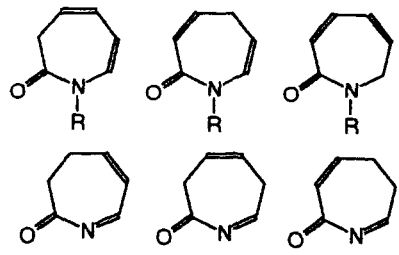
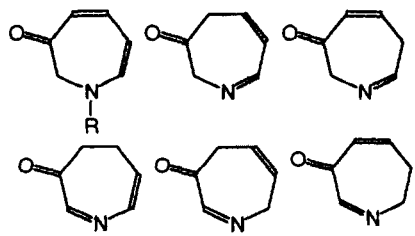
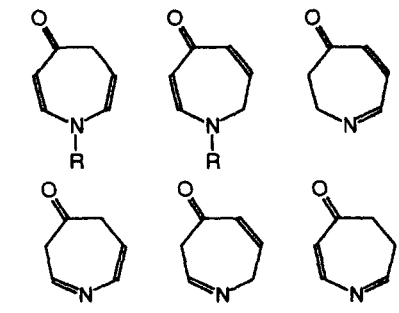
| Chapter No. | Compound name | Structure |
|---|---|---|
| | VIII. 4,5-Dihydro[3*H*]-azepines |  |
| 9 | **Dihydroazepinones** | |
| | I. 1,3-Dihydro[2*H*]-azepin-2-ones<br>II. 1,5-Dihydro[2*H*]-azepin-2-ones<br>III. 1,7-Dihydro[2*H*]-azepin-2-ones<br>IV. 3,4-Dihydro[2*H*]-azepin-2-ones<br>V. 3,6-Dihydro[2*H*]-azepin-2-ones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

**Table 1 (continued)**

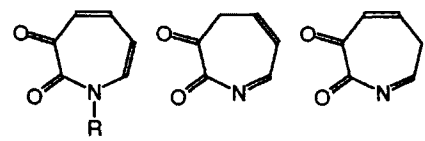
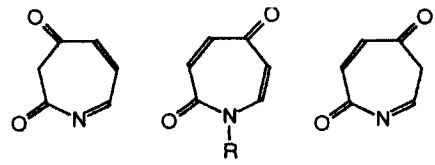
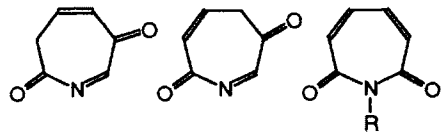
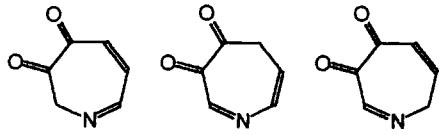
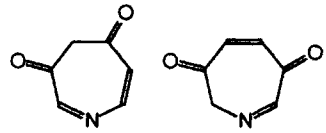
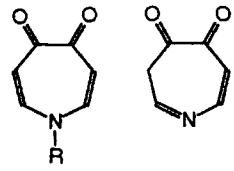
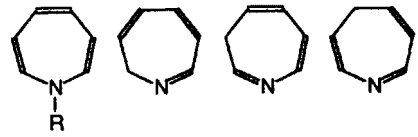
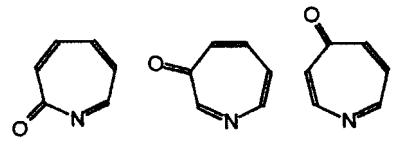
| Chapter No. | Compound name | Structure |
|---|---|---|
| 10 | **Dihydroazepinediones** | |
| | I. 2,3-Dihydro[1*H*]-azepine-2,3-diones<br>II. *3,4-Dihydro[2H]-azepine-2,3-diones*<br>III. *3,6-Dihydro[2H]-azepine-2,3-diones* |  |
| | IV. *3,4-Dihydro[2H]-azepine-2,4-diones*<br>V. 2,5-Dihydro[1*H*]-azepine-2,5-diones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

**Table 1 (continued)**

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

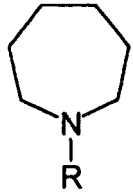
In Table 1, structures which are theoretically possible but which have not been found in the literature are shown in *italics*. For the sake of completeness, these structures are shown in the above diagrams, but they are not referred to further in the text. The authors hope that by highlighting the missing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

## REFERENCES

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.

CHAPTER 2

# Azepanes (Hexahydroazepines)

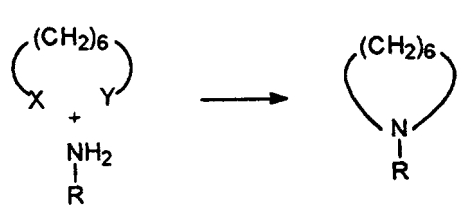


Originally the parent (R = H) of this series was referred to as 'hexamethyleneimine.' Later, and more correctly, these substances were seen as hexahydroazepines, but recently the name azepane has been preferred. The literature contains several thousand references to azepanes since it has been popular, 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.

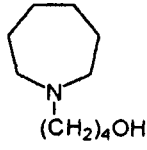
## PREPARATION

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

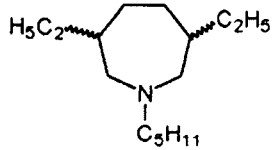
### 1. Reaction of 1,6-Difunctional Hexanes with Ammonia or Amines



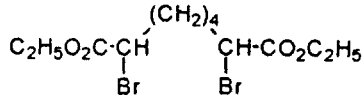
This approach, introduced in 1928,[2] has continued to be employed from time to time with some variations.[3] In the latter case, 1,6-diaminohexane reacted with butane-1,4-diol in the presence of Raney nickel giving **1**, although Adkins and co-workers had developed high-pressure treatment of various 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.



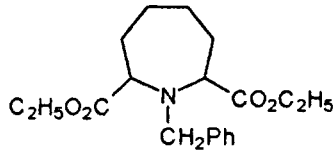
**(1)**



**(2)**

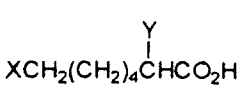


**(3)**



**(4)**

However, the presence of electron-withdrawing groups $\alpha$- 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, $\alpha,\omega$-dihalo-monocarboxylic acids **5** reacted with a variety of amines yielding the $\alpha$-amino acid derivatives **6**.[8]



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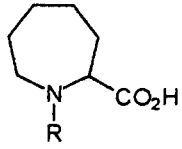
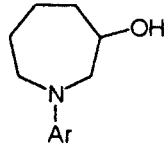


**(6)**



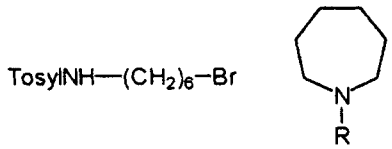
**(7)**

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

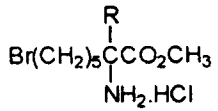
yields of 3-hydroxy-*N*-arylazepanes **7**, but unfortunately failed for benzylamine and furfurylamine.[12]

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

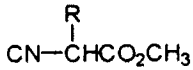
This has been a popular and successful approach which could be regarded as a stepwise variation of the previously discussed direct reaction of 1,6-dihalohexanes with amines. The first and relatively inefficient preparation of azepane,[13] later improved,[1] involved treating 1,6-haloamines with aqueous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



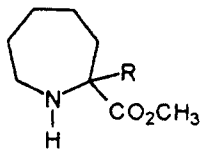

(**8**) (**9**)



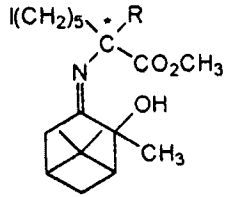

(**10**)



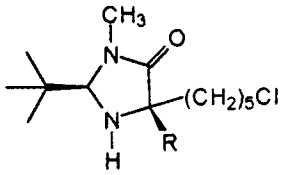

(**11**)




(**12**)




(**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]

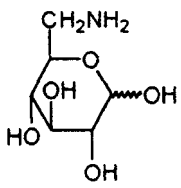
The amino acids **6** (R = H, $CH_3$, $C_2H_5$) have been obtained by cyclising the acyclic haloamino acids **5** (X = Cl, Y = $NH_2$, $NHCH_3$, $NHC_2H_5$ etc.) by boiling aqueous solutions of their alkali metal salts for 10 h along with some potassium iodide (~10%).[16] However, this approach did not 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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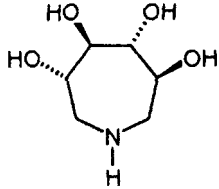
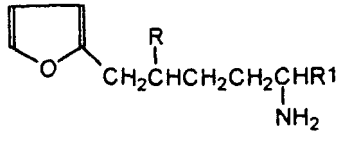
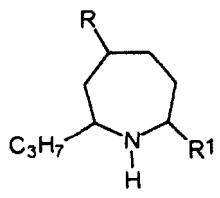


**(17)**

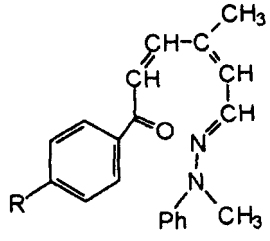


**(18)**

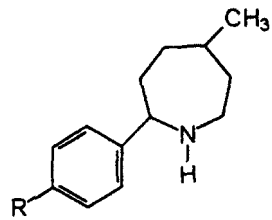
generated *in situ* from a carbonyl component. For example, catalytic hydrogenation of 6-amino-6-desoxy-D-glucose (**16**) yielded the tetrahydroxyazepane (**17**).[20] The equivalence of furans to 1,4-diones has been exploited by catalytic ($H_2$/Pt–C/220 °C) reduction of some furan amines (**18**,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



**(19)**



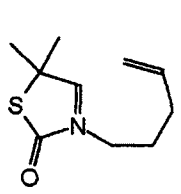
**(20)**



**(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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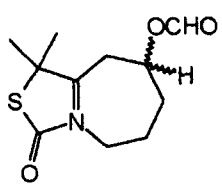

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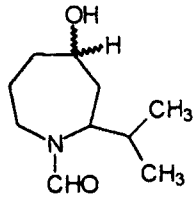
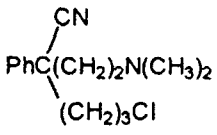


(24)

Cyclisation of $\omega$-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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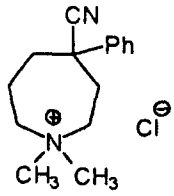

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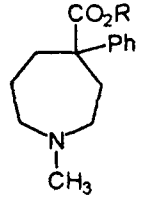
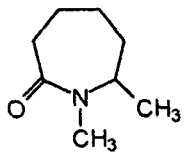


(27)

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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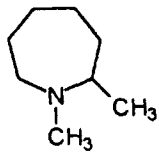

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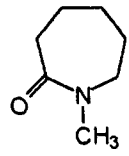
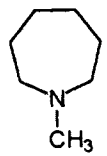
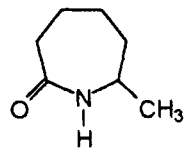


(30)



(31)



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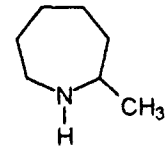
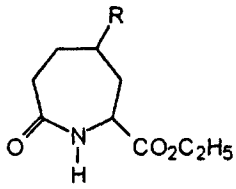


(33)

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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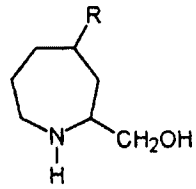

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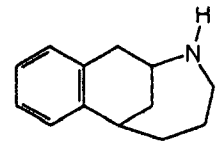

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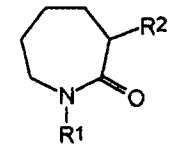
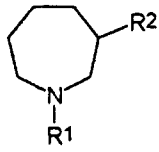


(37)

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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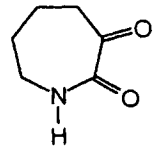

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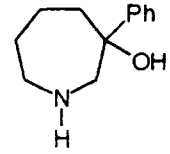
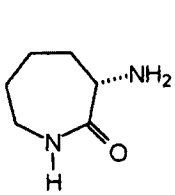


(40)

$LiAlH_4$ 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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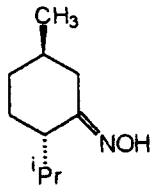
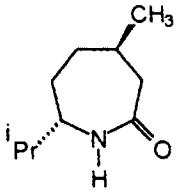


(42)



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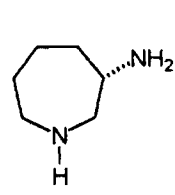

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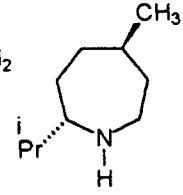
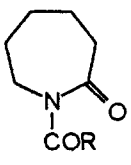


(45)

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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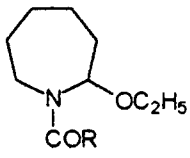

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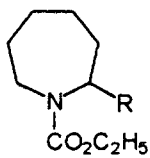

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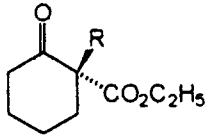

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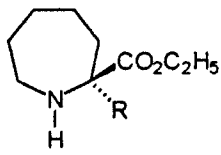
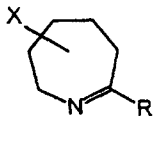


(50)

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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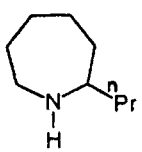

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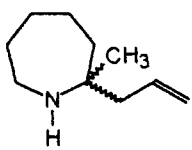

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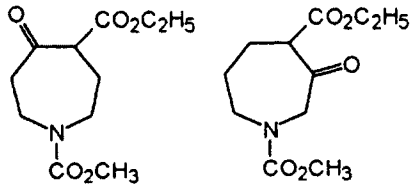
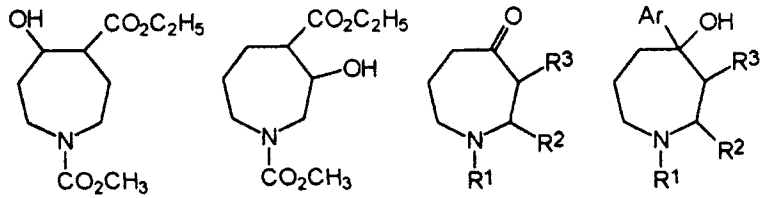


(54) (55)

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 $\beta$-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.