# THE CHEMISTRY OF 1,2-DIAZEPINES

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Review articles on 1,2-, 1,3- and 1,4-diazepines (1,2), benzodiazepines (3) and 1,3-diazepines (4) have appeared previously. The present review covers the literature on 1,2-diazepines from 1966 to early 1975.

CONTENTS



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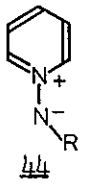
## 1. MONOCYCLIC 1,2-DIAZEPINES

### 1-1 Synthesis

#### (1H)-1,2-Diazepines

Streith, Snieckus and Sasaki originally reported the synthesis of (1H)-1,2-diazepines unsubstituted at the ring carbon atoms (e.g. compounds 1 and 2, table 1) via the photoinduced rearrangement of the corresponding 1-iminopyridinium ylides 44 (5-12). The reaction



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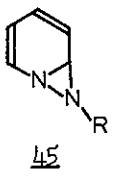

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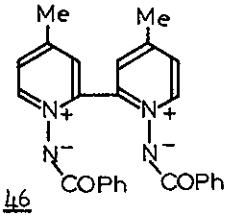

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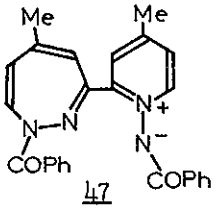

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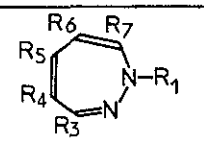
is a general one and yields are usually high. In the past the main difficulty encountered with this procedure has been the synthesis of the 1-iminopyridinium ylides 44 from the corresponding pyridine derivatives. This problem has now been overcome by the use of O-mesityl-sulphonylhydroxylamine (MSH) (13-15) to effect the nitrogen-nitrogen coupling reaction and a large number of ring-carbon substituted (1H)-1,2-diazepines 3-38 (see table 1) have now been prepared. For instance the synthesis of 4 and 6-halo-(1H)-1,2-diazepines 25-30, 32 and 33 could only be achieved by using MSH for the preparation of the corresponding photoactive 1-iminopyridinium ylides 44 (16). The photorearrangement presumably proceeds via the 1,7-diazanorcaradiene intermediate 45, by initial photoinduced electrocyclisation of the aromatic 1,3-dipole 44, followed by a thermally allowed disrotatory tautomerism to yield the (1H)-1,2-diazepines. As yet however, bicyclic inter-

Table 1 : (1H)-1,2-Diazepines

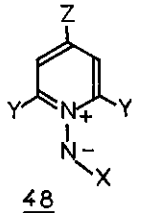



| Compound | $R_1$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|---|
| 1 | $CO_2{}^iPr$ | H | H | H | H | H | 19 |
| 2 | $CO_2Et$ | H | H | H | H | H | 5-12 |
| 3 | " | Me | H | H | H | H | 10-12 |
| 4 | " | H | H | Me | H | H | 10-12,19 |
| 5 | " | Me | H | Me | H | H | 11,12 |
| 6 | " | H | Me | H | H | H | 12,18 |
| 7 | " | Me | H | H | Me | H | 12 |
| 8 | " | H | Me | H | Me | H | 10,12 |
| 9 | " | H | Me | Me | H | H | 12 |
| 10 | " | Me | H | H | H | Me | 10,12 |
| 11 | " | Me | H | Me | H | Me | 12 |
| 12 | " | H | H | H | Me | H | 18 |
| 13 | " | H | H | Ph | H | H | 19 |
| 14 | " | H | H | $N(Me)_2$ | H | H | 10 |
| 15 | " | H | $CO_2Et$ | H | H | H | 18 |
| 16 | " | H | H | $CONHCHPh$ $CH_3$ | H | H | 27 |
| 17 | " | CN | H | H | H | H | 6 |
| 18 | Ac | H | H | H | H | H | 9 |
| 19 | Ac | Me | H | H | H | H | 8,9 |
| 20 | Ac | Me | H | H | H | Me | 9,19 |
| 21 | Ac | H | Me | H | H | H | 28 |
| 22 | COPh | H | H | H | H | H | 6,10 |
| 23 | " | H | H | Me | H | H | 16 |
| 24 | " | H | CN | H | H | H | 16 |
| 25 | " | H | Cl | H | H | H | 16 |
| 26 | " | H | H | H | Cl | H | 16 |
| 27 | " | H | Br | H | H | H | 16 |
| 28 | " | H | H | H | Br | H | 16 |

Table 1 - continued

| Compound | $R_1$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|---|
| 29 | COPh | H | I | H | H | H | 16 |
| 30 | " | H | H | H | I | H | 16 |
| 31 | " | H | Ph | H | H | H | 16 |
| 32 | " | H | F | H | H | H | 16 |
| 33 | " | H | H | H | F | H | 16 |
| 34 | $SO_2Ph$ | H | H | H | H | H | 6 |
| 35 | " | Me | H | H | H | H | 29 |
| 36 | Ts | H | H | H | H | H | 6,10 |
| 37 | $SO_2Me$ | Me | H | Me | H | Me | 29 |
| 38 | $CO_2$-Cholesteryl | H | H | H | H | H | 27 |
| 39 | Me | Ph | H | Ph | H | Ph | 24,25 |
| 40 | Me | Ph | H | p-ClPh | H | Ph | 25 |
| 41 | Me | Ph | H | p-$N(Me)_2$Ph | H | Ph | 25 |
| 42 | Ac | Ph | H | Ph | H | Ph | 30 |
| 43 | $CO_2Et$ | Ph | H | Ph | H | Ph | 30 |

mediates of type 45 have not been isolated, chemically trapped or observed as transient species in flash photolysis (17). N-Iminopyridinium ylides bearing methyl or cyano groups in the 2-position cyclised regiospecifically to the C-6 position, ultimately yielding the 3-methyl and 3-cyano-(1H)-1,2-diazepines 19 and 17 exclusively (18). Most 3-substituted ylides, however, cyclised at both the C-2 and C-6 positions, yielding the 6-substituted diazepines 12, 26, 28, 30 and 33 and the 4-substituted diazepines 6, 25, 27, 29 and 32 respectively. The exceptions were the 3-cyano and 3-carbethoxy ylides which gave exclusively the 4-substituted diazepines 24 and 15 (16,18). Besides the expected diazepines 29 and 30 the 4-phenyldiazepine 31 was isolated from



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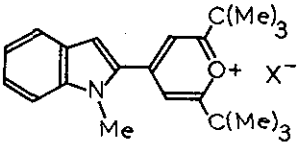
| | a | b | c | d | e |
|---|---|---|---|---|---|
| X | $CO_2Et$ | $CO_2Et$ | CN | CSNHR | Ph |
| Y | H | H | H | H | Ph |
| Z | $CO_2Et$ | p-Cl-COPh | H | H | Ph |

the photolysis of the 3-iodo ylide (16). By the photolysis of the N,N'-dibenzoylimino-2,2'-bipyridinium betaine 46, Tamura et al obtained the monodiazepine 47. Surprisingly, further irradiation of compound 47 did not yield the corresponding bidiazepine (15). This photochemical diazepine synthesis has only failed in a small number of cases. For instance, the pyridinium ylides 48a (10), 48b (19), 48c (20), 48d (21) and 48e (22), did not isomerise on uv irradiation to diazepines but instead N-N bond cleavage was observed. As yet this dependence of the photochemical reactivity on the substitution has not been rationalised. 1-Methyl-3,5,7-triaryl-(1H)-1,2-diazepines 39-41 have been prepared by the reaction of methylhydrazine with pyrylium and thiopyrylium salts. This



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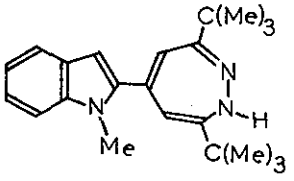

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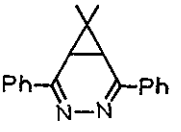

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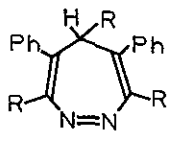
insertion reaction, originally reported by Klingsberg (23), was shown to be quite general for thiopyrylium salts (24,25). However if great care is not taken in this reaction then pyrazolines rather than diazepines are formed. A (1H)-1-phenyldiazepine derivative was not obtained when methylhydrazine was replaced by phenyl-

hydrazine (25). The reaction was successful when hydrazine was reacted with 2,6-di-tert-butyl-4-(1-methylindole-2-yl)-pyrylium perchlorate 49, the 1-unsubstituted (1H)-diazepine 50 being obtained (26).

(4H)-1,2-Diazepines

(4H)-1,2-Diazepines 51-66 (see table 2) have been prepared by the reaction of hydrazine with thiopyrylium (25,31) or pyrylium salts (25,26,32-34). In almost all cases quantitative yields were obtained. A new and original photochemical synthesis of the (4H)-1,2-diazepine 67 by the photolysis of the 3,4-diazanorcaradiene 68 has been reported (35). The authors have shown that this remarkable photoreaction proceeds via a "photochemical walk process" involving the first $\pi\pi^*$ singlet excited state. The (5H)-1,2-diazepine 69 was not formed from the cycloaddition of 1,2-diphenylcyclopropenes and s-tetrazines, as originally reported (36), but instead the 3,4-diazanorcaradiene 70 was obtained (37-40). High temperature isomerisation of the compound 70 was shown by X-ray analysis to give the (4H)-1,2-diazepine 71 (41). The instability of (5H)-diazepines of type 69 was accounted for by the diminished stability of heterocyclic compounds containing N=N double bonds (e.g. the well known 1-pyrazoline, 2-pyrazoline rearrangement) which is attributed to the lower energy (ca 50 kcal/mole) of the N=N double bond compared with C=N or C=C double bonds (40,42).



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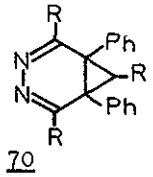

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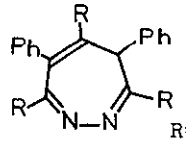

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R=Me
Ph
$CO_2Me$

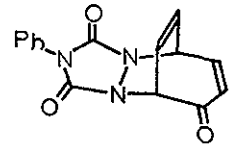

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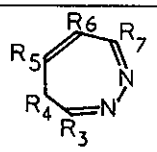
Table 2 : (4H)-1,2-Diazepines

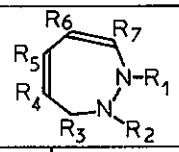



| Compound | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|
| 51 | Ph | H | Ph | H | Ph | 25,31-34 |
| 52 | Ph | H | p-MePh | H | Ph | 33 |
| 53 | Ph | H | p-MeOPh | H | Ph | 33 |
| 54 | Ph | H | p-ClPh | H | Ph | 25,33 |
| 55 | Ph | H | p-BrPh | H | Ph | 33 |
| 56 | Ph | H | p-$NO_2$Ph | H | Ph | 33 |
| 57 | Ph | H | m-$NO_2$Ph | H | Ph | 33 |
| 58 | p-MePh | H | p-MeOPh | H | p-MePh | 33 |
| 59 | p-MePh | H | m-$NO_2$Ph | H | p-MePh | 33 |
| 60 | p-BrPh | H | Ph | H | p-BrPh | 33 |
| 61 | p-BrPh | H | p-$NO_2$Ph | H | p-BrPh | 33 |
| 62 | Ph | H | p-$NMe_2$Ph | H | Ph | 25,31 |
| 63 | Ph | H | Ph | Me | Ph | 43 |
| 64 | Ph | H | Ph | Ph | Ph | 43 |
| 65 | p-IPh | Ph | Ph | Ph | p-IPh | 41 |
| 66 | Ph | H | 2-(1-methyl-pyrrolyl) | Ph | H | 26 |
| 67 | Ph | diMe | H | H | Ph | 35 |

## 2,3-Dihydro-(1H)-1,2-diazepines

2,3-Dihydro-(1H)-1,2-diazepines 72-79 (see table 3) were obtained in acceptable yields by sodium borohydride reduction (44) or hydroboration (45) of the corresponding fully unsaturated compounds.

Table 3 : 2,3-Dihydro-(1H)-1,2-diazepines



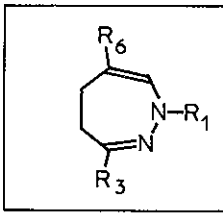

| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|---|---|
| 72 | Ac | H | H | H | H | H | H | 44 |
| 73 | Ac | H | Me | H | H | H | H | 44 |
| 74 | Ac | H | H | H | Me | H | H | 44 |
| 75 | Ac | H | H | Me | H | Me | H | 44 |
| 76 | Ac | H | Me | H | H | H | Me | 44 |
| 77 | $CO_2Et$ | H | H | H | H | H | H | 44,45 |
| 78 | $CO_2Et$ | H | H | H | Me | H | H | 45 |
| 79 | COPh | H | H | H | H | H | H | 45 |
| 80 | Ac | Ac | H | H | H | H | H | 44 |
| 81 | Ac | Ac | Me | H | H | H | H | 44 |
| 82 | Ac | Ac | H | H | Me | H | H | 44 |
| 83 | $CO_2Et$ | Ac | H | H | H | H | H | 44 |
| 84 | Ac | Ts | H | H | H | H | H | 44 |
| 85 | CONHPh | $CO_2Me$ | $CH_2CO_2Me$ | H | H | H | H | 46 |

Some of these dihydro derivatives were unstable under normal laboratory conditions, but could be readily stabilised by acylation or by sulphonylation at N-2, thus yielding the 1,2-disubstituted derivatives 80-84 (44). The 1,2-disubstituted 2,3-dihydrodiazepine 85 was obtained by uv irradiation of the triazolinedione, tropone cycloadduct 86, however, the structure 85 has not yet been unambiguously proved (46).

4,5-Dihydro-(1H)-1,2-diazepines

The title compounds 87 and 89 were prepared by the cycloaddition of diazomethane and 1,2-disubstituted cyclobutenes. The initially formed 1-pyrazoline, on treatment with hydrogen chloride gas in

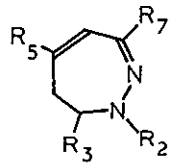
aprotic media, gave the seven membered heterocycles quantitatively. The acylation of the diazepine 87 with acetic anhydride gave the 1-acetyl derivative 88 (47).



| | $R_1$ | $R_3$ | $R_6$ |
|---|---|---|---|
| 87 | H | $CO_2Me$ | $CO_2Me$ |
| 88 | Ac | $CO_2Me$ | $CO_2Me$ |
| 89 | H | CN | CN |

3,4-Dihydro-(2H)-1,2-diazepines

The 3,4-dihydro-(2H)-1,2-diazepines 90-92 were prepared by sodium methoxide deacylation of the corresponding 2,3-dihydro-(1H)-derivatives 72-74. Compounds 90-92 were unstable but could be stabilised by acylation or tosylation at N-2 affording compounds 93-95 (44). The 2-benzoyldiazepine 96 was obtained by NBS treatment of the 4,5,6,7-tetrahydro-(1H)-derivative 106 (see table 4) (48).



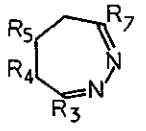
| | 90 | 91 | 92 | 93 | 94 | 95 | 96 |
|---|---|---|---|---|---|---|---|
| $R_2$ | H | H | H | Ac | Ac | Ts | COPh |
| $R_3$ | H | Me | H | H | H | H | H |
| $R_5$ | H | H | Me | H | Me | H | H |
| $R_7$ | H | H | H | H | H | H | Ph |

5,6-Dihydro-(4H)-1,2-diazepines

Diazepine 97 was prepared by catalytic hydrogenation of the (4H)-derivative 51 (25). Compounds 98 and 99 were obtained by condensation of 1,3-dibenzoylpropanes with hydrazine (1,49-51).

A mixture of the 5,6-dihydro-(4H)-1,2-diazepine 100 and the tetra-

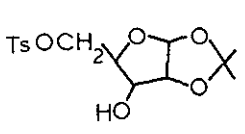
hydro derivative 112 (see table 4) was obtained by catalytic hydrogenation of the fully unsaturated diazepine 67 (35). The diazepine 100 was also prepared for structure correlation purposes by reaction of 2,2-dimethyl-1,5-diphenyl-1,5-pentanedione with hydrazine (35).



| | $R_3$ | $R_4$ | $R_5$ | $R_7$ |
|---|---|---|---|---|
| 97 | Ph | $H_2$ | Ph,H | Ph |
| 98 | Ph | $H_2$ | $H_2$ | Ph |
| 99 | Ph | $H_2$ | Me,H | Ph |
| 100 | Ph | $Me_2$ | $H_2$ | Ph |

4,5,6,7-Tetrahydro-(1H)-1,2-diazepines

Compound 101 (see table 4) was one of the catalytic hydrogenation products of the fully unsaturated (1H)-diazepine 2, the other product being the hexahydrodiazepine 122 (see table 5) (6,10,12, 45). 4,5,6-Trihydroxy-1-methyldiazepine 102 was obtained by reaction of the furanose 113 with methylhydrazine followed by sulphurous acid hydrolysis of the resulting α-methylhydrazine derivative 114 and treatment of the acyclic hydrolysis product 115



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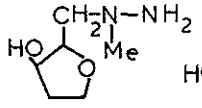

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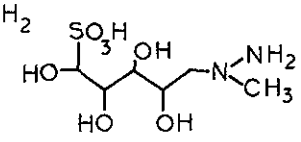

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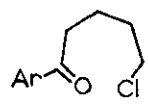

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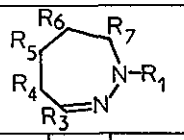
with barium hydroxide. Acetylation of compound 102 yielded the triacetate 103 whereas treatment with trimethylsilyl chloride gave the tris-trimethylsilyl ether 104. Careful analysis of the nmr spectrum of 102 showed that it exists in the chair conformation. Its circular dichroism spectra displayed a positive Cotton effect (52). *Synthesis of the diazepines* 105-111 has been achieved in

Table 4 : 4,5,6,7-Tetrahydro-(1H)-1,2-diazepines

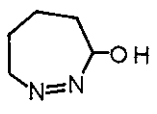


| Compound | $R_1$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Ref. |
|---|---|---|---|---|---|---|---|
| 101 | $CO_2Et$ | H | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 6,10,45 |
| 102 | $CH_3$ | H | OH,H | OH,H | OH,H | $H_2$ | 52 |
| 103 | $CH_3$ | H | OAc,H | OAc,H | OAc,H | $H_2$ | 52 |
| 104 | $CH_3$ | H | $OSi(Me)_3$,H | $OSi(Me)_3$,H | $OSi(Me)_3$,H | $H_2$ | 52 |
| 105 | H | Ph | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 106 | COPh | Ph | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 107 | Me | Ph | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 108 | 2-(morpholine-N-yl)-ethyl | Ph | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 109 | Me | p-ClPh | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 110 | 2-(morpholine-N-yl)-ethyl | p-ClPh | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 111 | 2-(pyrrolidine-N-yl)-ethyl | p-ClPh | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 48 |
| 112 | H | Ph | $Me_2$ | $H_2$ | $H_2$ | Ph,H | 35 |

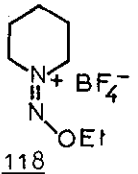
good yields by the reaction of substituted hydrazines with δ-chloroaryl ketones 116 (48).

4,5,6,7-Tetrahydro-(3H)-1,2-diazepin-3-ol

The title compound 117 was prepared by treatment of the six-membered ethoxydiazenium fluoroborate 118 with sodium carbonate (1,53) whereas treatment of 118 with hydroxide anion gave the fourteen membered diazepinol dimer 119 (54).



117



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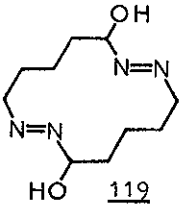
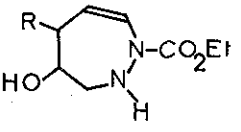


119



120 R = H
121 R = Me

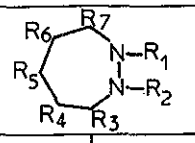
## 2,3,4,5-Tetrahydro-(1H)-1,2-diazepin-4-ols

The title compounds 120 and 121 were the alternative hydroboration products of diazepines 2 and 4 respectively (45).

## Hexahydro-1,2-diazepines

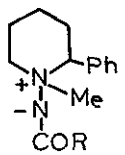
The 1,2-disubstituted hexahydro derivatives 123 and 124 (see table 5) were obtained under Schotten-Baumann conditions from the monosubstituted compound 122 (6,10). The perhydro diazepines 125 and

Table 5 : Hexahydro-1,2-diazepines




| Compound | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|---|---|
| 122 | $CO_2Et$ | H | $H_2$ | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 6,10,12,45 |
| 123 | COPh | COPh | $H_2$ | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 10 |
| 124 | $CO_2Et$ | $CO_2Et$ | $H_2$ | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 6 |
| 125 | Me | Ac | Ph,H | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 55 |
| 126 | Me | $CO_2Et$ | Ph,H | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 55 |
| 127 | Me | H | $H_2$ | Ph,m-MeOPh | $H_2$ | $H_2$ | $H_2$ | 56 |
| 128 | Me | Me | $H_2$ | $H_2$ | $H_2$ | $H_2$ | $H_2$ | 57 |
| 129 | $CF_3$ | $CF_3$ | carbonyl | $F_2$ | $F_2$ | $F_2$ | carbonyl | 58 |

126 have been prepared by vacuum pyrolysis of the mesoionic 1-methyl-2-phenylpiperidine-1-acylimides 130. Confirmation of the structure of compounds 125 and 126 was obtained by an independent synthesis. The nmr spectra of 125 and 126 were temperature dependent. An investigation revealed that three conformations exist for the acetyl compound and two for the carbethoxy compounds (55). A multistep synthesis of the perhydro diazepine 127 starting with 1-(3-methoxyphenyl)-phenylacetonitrile has recently been described (56). The compound

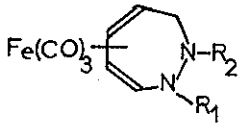



130

128 has been synthesised by reaction of glutaraldehyde with N,N'-dimethylhydrazine in the presence of sodium cyanoborohydride (57). Perfluoro-(1,2-dimethylperhydro-1,2-diazepine-3,7-dione) 129 was prepared by reaction of perfluoroglutaryl fluoride with tetrafluoroformaldazine in the presence of caesium fluoride. This is a new synthetic route to perfluoro heterocyclic compounds and is effective with a large number of difunctional perfluoroacyl fluorides (58).

## 1,2-Diazepine-transition metal complexes

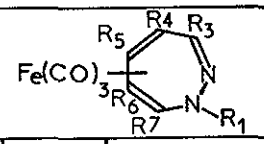
The (1H)-1,2-diazepine-iron-tricarbonyl complexes 131-143 (see table 6) and the 2,3-dihydro-(1H)-1,2-diazepine-iron-tricarbonyl complexes 144 - 147 have been prepared by treating the corresponding free diazepines with a suspension of iron-nonacarbonyl in benzene (5,6,19,27,28,44,59,60). Complexes derived from 2,3-dihydro compounds have also been obtained by sodium borohydride



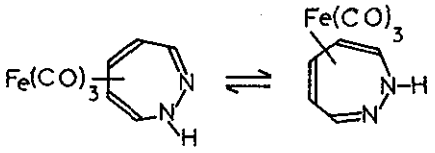

| | 144 | 145 | 146 | 147 |
|---|---|---|---|---|
| $R_1$ | $CO_2Et$ | Ac | $CO_2Et$ | Ac |
| $R_2$ | H | H | Ac | Ac |

reduction of the corresponding fully unsaturated complexes (44). X-ray crystallographic analysis of the iron complexes has shown that the metal is linked to the butadiene moiety via a Diels-Alder like cycloaddition (27). Complexation of iron to the diene moiety of the diazepine ring has been confirmed by Mössbauer, ir, nmr and mass spectroscopy (28,60). The temperature dependence of the nmr spectrum of the ring unsubstituted complex 137 has been attributed to simultaneous tautomerism and fluxionality between

Table 6 : (1H)-1,2-Diazepine-iron tricarbonyl-complexes

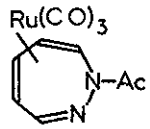



| Compound | $R_1$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|---|
| 131 | Me | Ph | H | Ph | H | Ph | 28,59 |
| 132 | Ac | H | H | H | H | H | 28,44,60 |
| 133 | Ac | Me | H | H | H | H | 19,28,60 |
| 134 | Ac | H | Me | H | H | H | 28 |
| 135 | Ts | H | H | H | H | H | 28 |
| 136 | COPh | H | H | H | H | H | 28 |
| 137 | H | H | H | H | H | H | 60 |
| 138 | H | Me | H | H | H | H | 60 |
| 139 | H | H | H | Me | H | H | 60 |
| 140 | $CO_2Et$ | H | H | H | H | H | 5,6,44,60 |
| 141 | $CH_2Ph$ | H | H | H | H | H | 60 |
| 142 | $CO_2{}^iPr$ | H | H | H | H | H | 19,27 |
| 143 | Ac | H | H | Me | H | H | 60 |

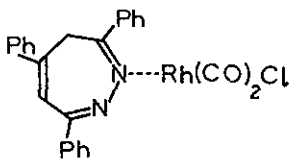



137 a 137 b

structures 137a and 137b, having the same energy content (60). Whereas the ruthenium tricarbonyl complex 148 has been reported to have a similar structure to that of the iron tricarbonyl complexes (28) X-ray analysis of the rhodium chloro-dicarbonyl complex 149 indicated that coordination occurred




148

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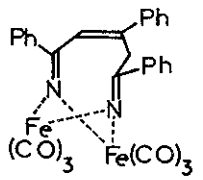


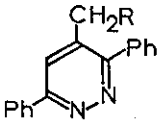

150

between the metal and one of the ring-nitrogen atoms (59). Complexation of iron-nonacarbonyl with 3,5,7-triphenyl-(4H)-diazepine 51 resulted in N-N bond cleavage and formation of a nitrogen bridged complex. X-ray analysis showed its structure to be the [5.1.1]-bicyclic compound 150. This is the first example of an unsaturated eight-membered metalocyclic ring system(61).

## 1-2 Chemistry

### Reduction and oxidation

Catalytic hydrogenation of the (1H)-1,2-diazepines 1-43 leads to reduction of the $\Delta^4$ and $\Delta^6$ double bonds, the reduction of the imine double bond occurring only under more drastic conditions (6,8,10,12,45). On the other hand reduction with either sodium borohydride (44) or diisobutyl aluminium hydride (DIBAL) (45) results in selective reduction of the imine double bond and formation of the 2,3-dihydro-(1H)-diazepines 72-79. Hydroboration of (1H)-1,2-diazepines gave both the 2,3-dihydro derivatives 77-79 and the 4-hydroxy-2,3,4,5-tetrahydro compounds 120 and 121 (45). Treatment of the 5,6-dihydro-(4H)-1,2-diazepines 97 - 99 with N-bromo or N-chlorosuccinimide resulted in ring contraction to the pyridazine derivatives 151 and 152 (R = H,Me,Ph) (49,50).
The isolation of the 3,4-diazanorcaradiene 153 has been cited as

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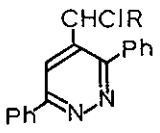
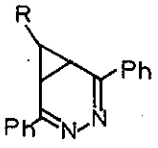


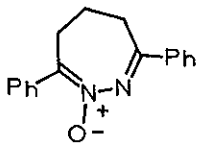

152



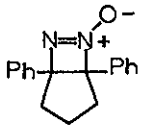

153


154

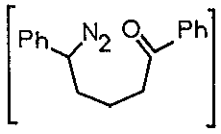
evidence for its intermediacy in this remarkable reaction which presumably proceeds by a chlorination-dehydrochlorination mechanism. Careful mechanistic investigations have shown that an excess of NCS leads to compound 152 via a radical process whilst protonation of 153 leads to compound 151, via the diazanorcaradiene monohydrochloride (153 , HCl) (50)*. The treatment of the diazepine 98 with chlorine gas in methylene chloride resulted in a mixture of compound 153 (R = H) and the tetrachlorodiazepine 154 (51). Oxidation of the diazepine 98 in ethereal trifluoroperacetic acid in the presence of sodium carbonate gave the diazepine mono-N-oxide 155. The photochemical reactivity of the N-oxide 155 has been explored, its uv irradiation resulting in the formation of the bicyclic N-oxide 156, and the diazoketone 157, the latter compound rearranging to 1,5-diphenyl-4-penten-1-one 158 (62,63).




155




156

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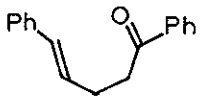


158

Base induced reactions

The base induced ring contraction of (1H)-1,2-diazepines to 2-aminopyridine derivatives was initially thought to proceed via the bicyclic tautomer 45 (6,8). It has been shown subsequently, however, that careful treatment of the diazepine 1 with sodium

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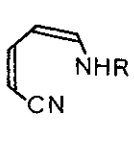
* The same reaction of compound 98 with NBS has been reported recently (51). However, surprisingly, references 49 and 50 are not quoted.

isopropoxide in isopropanol leads initially to the cis-cis diene 159 which, on further exposure to base, ring-closes to a 2-amino-pyridine (19,64). The base catalysed ring opening of (1H)-1,2-diazepines bearing a hydrogen atom at C-3 has been shown to be quite general and it has been successfully carried out with compounds 1, 2, 4, 6, 12, 13, 18, 22, 34 and 36 (64,65). It should be noted that many other heterocyclic systems containing an $sp^2$ nitrogen atom attached to an electron withdrawing hetero atom or group ring-open in base to give nitriles (see for instance reference 66). The stability of the 3-methyldiazepine 19 to base (19) coupled with methyl labeling experiments (64) has led to the assertion that the 3-H is the reactive site towards basic species in (1H)-1,2-diazepines. The reactivity of (1H)-1,2-diazepine-iron tricarbonyl complexes towards base was found to be quite different. For example, sodium methoxide treatment of the complex 140 afforded the ring-unsubstituted complex 137 (60). The apparent lack of 3-H acidity in these complexes is possibly due to the difference in conformation of the $C_7$-$N_1$-$N_2$-$C_3$ moiety in the complexed and uncomplexed rings (27). Base induced deacylation of iron tricarbonyl-(1H)-1,2-diazepine complexes has been observed with the 3-methyl and 5-methyl compounds 133 and 143 (60). Sodium methoxide treatment of the 2,3-dihydro-(1H)-1,2-diazepines 72, 80 and 84 led to the corresponding 3,4-dihydro-(2H)-diazepines 90, 93 and 95 (44). In contrast to the above mentioned base catalysed ring-opening of the fully unsaturated compounds, base induced ring-opening of the 2,3-dihydro derivatives is thought to involve the intermediacy of the anion 160 (R = H,Ac). When this reaction was carried out in

deuterated methanol, C-4 and C-6 deuterated products were isolated (44). Treatment of the 4,5-dihydro-(1H)-1,2-diazepines 87 and 89 with potassium hydroxide resulted in N-1 deprotonation and formation of the anion 161 (R = $CO_2Me$,CN) (47). Reaction of the

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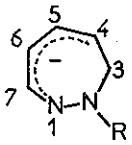


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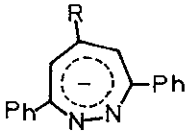
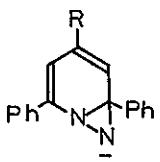
161

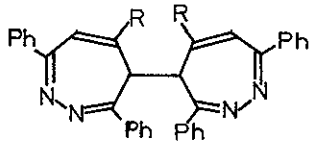



162




163

(4H)-1,2-diazepines 51, 52 and 54 with lithium diisopropylamide resulted in the formation of corresponding cyclic anions of type 162 in 50% yield. In the presence of deuterated acids the anion 162 reverted back to the (4H)-diazepine and from the degree of deuteration the pKa value of the diazepine 51 was estimated to be ca 30. Treatment with acids caused the anion 162 to dimerise, yielding compound 164. The reaction of compounds 51, 52 and 54

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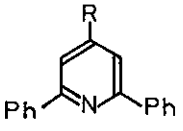


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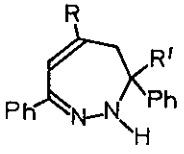


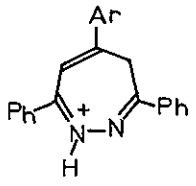

166

with a sodium-potassium alloy in THF at -20° gave the corresponding pyridine derivatives 165, presumably via the valence tautomer 163. Treatment of compound 51, with butyllithium, however, gave the adduct 166 (R' = nBu or tBu), reflecting the low acidity of the C-4 protons of (4H)-1,2-diazepines (67).

Acid catalysed rearrangements and protonations

(1H)-1,2-Diazepines rearrange to N-iminopyridinium ylides 44 on

treatment with acid (6,8,19,68). The intermediacy of the bicyclic tautomer 45 has been suggested and this postulation is supported by the acid catalysed rearrangement of an isolated bicyclic diaziridine to an N-iminopyridinium salt (69). This rearrangement, coupled with the thermal isomerisation of (1H)-1,2-diazepines to 2-aminopyridine derivatives (19,64) (see below, thermal reactivity) constitutes the main evidence for the existence of the bicyclic compound 45. It is likely that the tautomer 45 is only present in very low concentration since it could not be detected by low temperature nmr or trapped by various cycloaddition reactions (20, 70,71,72). (4H)-1,2-Diazepines, on acid treatment gave both

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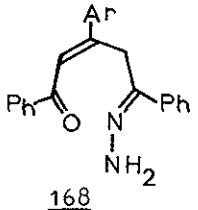


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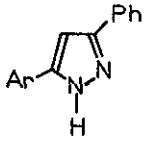


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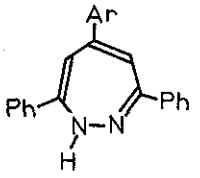


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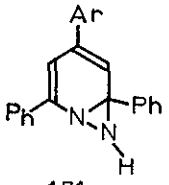


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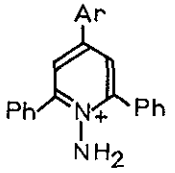


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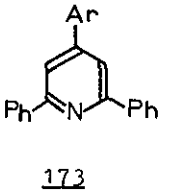


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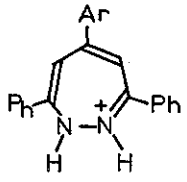


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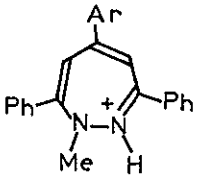


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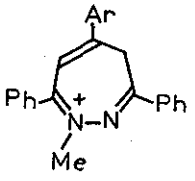


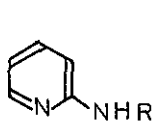

176

pyrazole 169 and pyridine derivatives 173. The pyrazoles are thought to arise from acyclic intermediates of type 168 and the pyridines from the bicyclic diaziridines 171 via a protonation-deprotonation process involving (1H)-1,2-diazepines 170. The protonation of the (4H)-1,2-diazepines 51, 54 and 62 and the (1H)-1,2-diazepines 40 and 41 was initially reported to yield the planar cations 174 and 175 respectively (1,2,23). Protonation has since been shown by nmr studies to occur at N-1 for (4H)- and at C-4 for (1H)-1,2-diazepines, yielding the non-planar cations 167 and 176, respectively (68,73). The boat conformation of the protonated and unprotonated (4H) derivatives as well as the position of the extra proton in the cation 167 has been ascertained by X-ray crystallographic analysis (74). However, deuteration of 167 occurred at C-4 and C-6, this mode of exchange being attributed to tautomerism between the cations 167 and 174 (68,73). Variable temperature nmr spectra of the protonated diazepine 167 (Ar = Ph) showed a ring-inversion process with an activation energy in the region of 10 kcal/mole (68,73). This value is low compared with the activation energy for ring-inversion of the free base 51 ($\Delta G^{\neq}$ = 17 kcal/mole) (33,43,68). The above difference in activation energy has been attributed to the repulsive interaction between the skewed N-1 and N-2 lone pairs in the planar transition state during ring inversion of the free base. Mono-protonation at N-1 results in a decrease in the repulsive interaction thus lowering the energy barrier to ring inversion. In contrast to the above mentioned acid-induced rearrangements and protonations, treatment of the 1-ethoxycarbonyl-(1H)-1,2-diazepines 2, 4, 11, 13 and 17

with either formic acid, trifluoroacetic acid or boron trifluoride resulted in dimerisation via a [4π + 2π] cycloaddition reaction (75).

Thermal reactivity

On heating (1H)-1,2-diazepines undergo two types of rearrangements, a) ring-contraction to 2-aminopyridine derivatives of type 177 (19,30,64) and b) ring-opening leading to diene-aminonitriles of type 159 (6,8,19). Methyl labeling experiments have shown that compounds of type 177 are formed via N-N bond cleavage in the bicyclic tautomer 45 and not by ring closure of the acyclic isomer 159 thus proving the existence of a valence tautomeric equilibrium between (1H)-1,2-diazepines and diazanorcaradienes 45 (64). 5,6-Dihydro-(4H)-1,2-diazepines 97 and 98 on pyrolysis at 250-300° gave the corresponding pyridine derivatives 178 (R=H,Ph) and ammonia. This unusual reaction has been supposed to proceed via a

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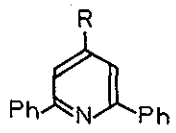


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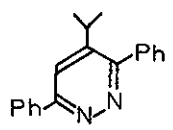


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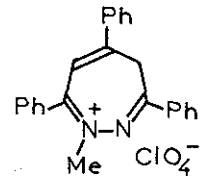



180

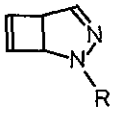
radical mechanism (76). However, further details were not given by the authors. The thermally-induced ring-contraction of the (4H)-1,2-diazepine 67 has been reported to give both the 3,4-diazanorcaradiene compound 68 and the pyridazine 179 the latter presumably arising via the intermediacy of 68. Treatment of compound 67 with acid also resulted in the formation of the pyridazine 179 (35).

Electrophilic substitutions

Acylation of the (4H)-diazepine 51 with acetyl chloride or ethyl chloroformate occurred at N-2 to afford the corresponding acylated (1H)-diazepines 42 and 43 (30). Treatment of the unstable N-unsubstituted 3,4-dihydro-(2H)-diazepine 90 with acetic anhydride yielded the N-acetyl compound 93 whereas sulphonylation of the (1H)-2,3-dihydro derivative 72 gave the tosyl compound 84 (44). Reaction of the N-unsubstituted iron tricarbonyl-(1H)-1,2-diazepine complex 137 with acetyl chloride in the presence of sodium hydride led to the formation of the corresponding N-acetyl complex 132 whilst its reaction with benzyl bromide in the presence of n-butyllithium resulted in the formation of the N-benzyl complex 141 (60). Methylation of compound 51 with methyl iodide in alkali afforded the (1H)-derivative 39 in 70% yield (25) whereas its treatment with methyl fluorosulphonate and perchloric acid yielded the diazepinium perchlorate 180 (68).

Photochemical reactivity

(1H)-1,2-Diazepines, like many other seven-membered cyclic dienes undergo photoinduced electrocyclic ring-closure of the butadiene moiety yielding 2,3-diaza [3.2.0] bicyclic heptadienes of type 181 (19,30,77). This reaction is quite general and has been found to

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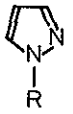


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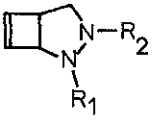


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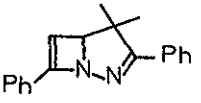


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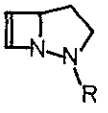
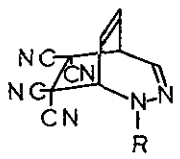



185

occur with a large number of (1H)-1,2-diazepines (77,78). In two cases however the bicyclic photoisomer could not be isolated, the reaction leading instead to the formation of the pyrazole 182 presumably via a non-concerted loss of a substituted acetylene fragment (30,78). The 2,3-dihydro-(1H)-1,2-diazepines 72-85 underwent a similar photoinduced electrocyclic ring-closure yielding the corresponding [3.2.0] bicyclic compounds 183 even more readily and in higher yields (44,45). The facile isomerisation of the latter dihydro species and their higher reactivity towards dienophiles (see below) when compared to their fully unsaturated counterparts has been ascribed to the planar conformation of their butadiene moiety, as shown by X-ray analysis (27) and Dreiding models (45). Diazepines containing no butadiene moiety but instead an azabutadiene moiety (e.g. the (4H)-1,2-diazepine 67 and the (2H)-3,4-dihydrodiazepines 90-96) photocyclise to yield the 1,2-diaza [3.2.0] bicyclic compounds 184 and 185 respectively (35,44). Similar reactions in both the (4H)-1,2-diazepin-4-one (79-81) and the (3H)-1,2-diazepin-3-one series (82) have been reported.

Cycloaddition reactions

- $[4\pi + 2\pi]$ Cycloadditions : although highly conjugated the $\Delta^4$- $\Delta^6$ butadiene moiety of (1H)-1,2-diazepines is not very reactive towards dienophiles. No reaction was observed with maleic anhydride or dimethylacetylene dicarboxylate (12). However, highly reactive dienophiles such as TCNE (11,12) or 4-phenyl-1,2,4-triazoline-3,5-dione (46,72,83) did react yielding the expected cycloadducts 186 and 187. (1H)-1,2-Diazepines bearing an alkoxycarbonyl function at N-1 dimerised in acidic media yielding the $(\Delta^4,\Delta^6) + \Delta^6$ cyclo-



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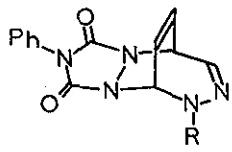

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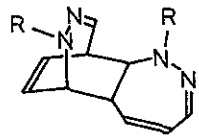
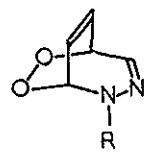


188

adduct 188 (75). The cycloaddition of singlet oxygen to (1H)-1,2-diazepines leads to the photoxide 189 (84). As mentioned in the previous section the 2,3-dihydro-(1H)-1,2-diazepines 72-85 show a higher reactivity towards dienophiles. The TCNE (45) and the triazolinedione (44) cycloadducts 190 and 191 were readily obtained from these compounds.



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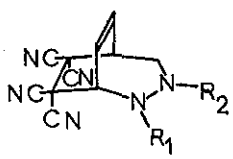

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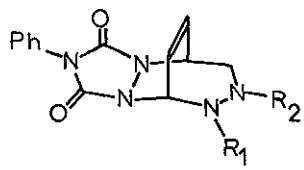
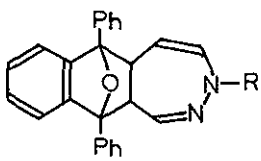
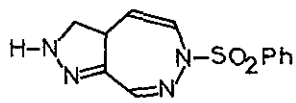


191

- [2π + 4π] Cycloadditions : diphenylisobenzofuran adds slowly to the $\Delta^4$ double bond of (1H)-1,2-diazepines to yield the cycloadduct 192 (20,83). A number of interesting results have been obtained from cycloadditions involving diazoalkanes (70-72,85). For example



192



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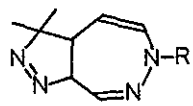
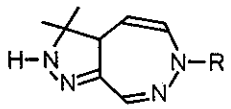


194

diazomethane reacted only with the 1-benzenesulphonyldiazepine 34 yielding regiospecifically the 2-pyrazolinodiazepine 193 whereas the more reactive diazopropane adds to the $\Delta^4$ double bond of a large number of (1H)-1,2-diazepines yielding the 1- and 2-pyrazoline



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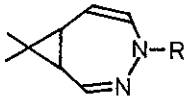

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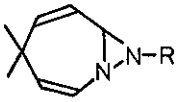
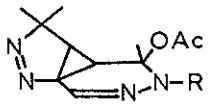


197

derivatives 194 and 195. Compound 194 isomerises in solution to the more stable adduct 195. Flash pyrolysis of the pyrazolines 194 and 195 resulted in the expulsion of nitrogen and the formation of the homodiazepines 196. No azahomoazepine 197 could be detected in this reaction by the variable temperature nmr technique (72). The structure of compound 195 (R=$CO_2$Et) deduced from its nmr spectrum was confirmed by X-ray analysis of its lead tetraacetate oxidation product 198 (71).



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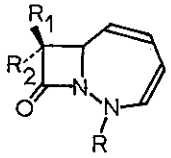


199

- [2π + 2π] Cycloaddition reactions with the imine double bond : ketenes add regiospecifically to the $\Delta^2$ imine double bond of (1H)-1,2-diazepines to yield the $C_7$-$C_8$ trans-aza-9-nonanes 199 (86). Isocyanates reacted readily with 1,2-diazepines but did not form stable products (78).

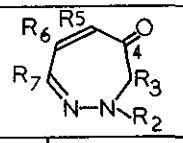
## 2. MONOCYCLIC 1,2-DIAZEPINONES

### 2-1 Synthesis

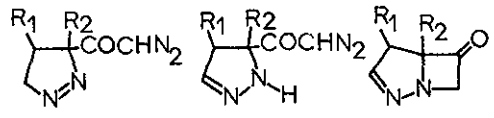
#### 2-1-1 (4H)-1,2-Diazepin-4-ones and their derivatives

5-Methyl-6-phenyl-2,3-dihydro-(4H)-1,2-diazepin-4-one 200 (see table 7) was originally prepared by mild acid treatment of either the 3-diazoacetyl-pyrazolines 210a and 211a or the bicyclic intermediate 212a (1,2,87,88). Treatment of compound 200 with dimethylsulphate led to the 2-methyl derivative 201. The 2-acyl-derivatives

Table 7 : 2,3-Dihydro-(4H)-1,2-diazepin-4-ones



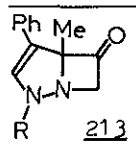
| Compound | $R_2$ | $R_3$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|
| 200 | H | H | Me | Ph | H | 1,87,88 |
| 201 | Me | H | Me | Ph | H | 1,87,88 |
| 202 | H | CHOHPh | Me | Ph | H | 1,87,88 |
| 203 | COPh | H | Me | Ph | H | 89 |
| 204 | Ac | H | Me | Ph | H | 90 |
| 205 | $CH_2CH_2CN$ | H | Me | Ph | H | 91 |
| 206 | $CH_2CH_2CO_2H$ | H | Me | Ph | H | 91 |
| 207 | H | H | Ph | Ph | H | 92 |
| 208 | H | H | Me | $CO_2Me$ | H | 92 |
| 209 | Ts | H | Me | Ph | H | 81 |



210 211 212

| | $R_1$ | $R_2$ |
|---|---|---|
| a | Ph | Me |
| b | Ph | Ph |
| c | $CO_2Me$ | Me |
| d | Ph | Br |
| e | Ph | $CO_2Et$ |

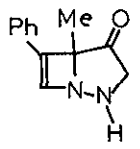
203 and 204 were prepared by reaction of the bicyclic ketone 213a with acyl chlorides in pyridine (89) or by treatment of the diazepinone 200 with acyl chlorides in alkali (90). The reaction of compound 200 with tosyl chloride in the presence of sodium hydride led to the 2-tosyldiazepinone 209 (81). Base-catalysed addition of electrophilic olefins to 200 resulted in the formation of the 2-cyanoethyl and 2-carboxyethyl derivatives 205 and 206 (91). Aldol condensation of 200 with benzaldehyde gave the 3α-hydroxybenzyl compound 202 (1). The 5,6-diphenyl derivative 207 and the 5-methyl-6-carbomethoxy derivative 208 were prepared from the corresponding 3-diazoacetylpyrazolines 210b and 210c. However, the 5-bromo-6-phenyl as well as the 5-carboethoxy-6-phenyldiazepinones could not be prepared by the same method from compounds 210d and 210e respectively (92).



213
a) R=Ac
b) R=Ts
c) R=COPh

## 1,5-Dihydro-(4H)-1,2-diazepin-4-ones

The title compound 214 (see table 8) was prepared either by treatment of compound 223 with base at room temperature or by treatment of compound 200 with base at high temperature (79). Reaction of the 1,7-dihydro tautomer 227 with base or irradiation of the betaine



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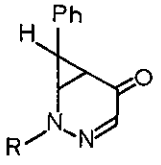
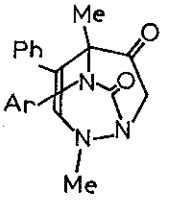
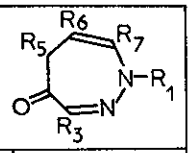


224 a) R = H
b) R = Ac



235

Table 8 : 1,5-Dihydro-(4H)-1,2-diazepin-4-ones



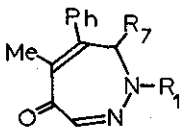

| Compound | $R_1$ | $R_3$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|
| 214 | H | H | Me | Ph | H | 79 |
| 215 | Me | H | Me | Ph | H | 69,79 |
| 216 | H | H | Me | $CO_2Me$ | H | 92 |
| 217 | Ac | H | Me | Ph | H | 90 |
| 218 | Ac | H | Ph | Ph | H | 90,93 |
| 219 | H | H | Ph | Ph | H | 90,93 |
| 220 | PhCO | H | Me | Ph | H | 90 |
| 221 | p-MeOPhCO | H | Me | Ph | H | 90 |
| 222 | p-$NO_2$PhCO | H | Me | Ph | H | 90 |

256a led to formation of the 1-methyl derivative 215 (69,79). The 1-acyl derivatives 217, 218, 220-222 were obtained by treatment of the corresponding N-unsubstituted derivatives 214 and 219 with either acyl chlorides or ketenes (90). Preparation of the 5,6-diphenyl derivatives 218 and 219 was achieved by base treatment of the corresponding 2,3-dihydro compound 207 (90) or by photo-isomerisation of the diazabicyclo[4.1.0]heptenone 224 which was obtained by treating the 3-diazoacetylpyrazoline 211b with base (93). Compound 216 was detected by means of nmr spectroscopy in a DMSO solution of compound 208 containing sodium methoxide but it could not be isolated (92).

1,7-Dihydro-(4H)-1,2-diazepin-4-ones

The title compound 227 was prepared by room temperature rearrangement of the betaine 256a, the latter compound being obtained after alkaline methylation of the 2,3-dihydro compound 200 with

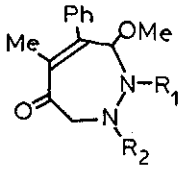
dimethyl sulphate (94). Preparation of the 1-acyl derivatives 229 and 230 was carried out in a similar way but the intermediate diazepinone betaines 256b and 256c could not be isolated (95). The N-unsubstituted diazepinone 226 could not be isolated or detected during the treatment of compound 200 with base probably because of the higher stability of the 1,5-dihydro tautomer 214 (79). Compound 226 has been obtained, however, by base hydrolysis of the 1-acetyl derivative 229 (95). The 1-benzoyl (96) and 1-tosyl (81) derivatives 225 and 228 were obtained by NBS treatment of the 1,2,3,7-tetrahydro compounds 231 and 233 respectively.




| | 225 | 226 | 227 | 228 | 229 | 230 |
|---|---|---|---|---|---|---|
| $R_1$ | COPh | H | Me | Ts | Ac | COPh |
| $R_7$ | OMe | H | H | OMe | H | H |

1,2,3,7-Tetrahydro-(4H)-1,2-diazepin-4-ones

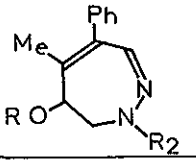
The title compound 231 was prepared by treatment of the 2,3-dihydrodiazepinone 200 with benzoyl chloride in the presence of amines (89). The 1-acetyl and the 1-tosyl homologues 232 and 233 were obtained by heating methanolic solutions (containing a trace amount of a carboxylic acid) of the bicyclic ketones 213a and 213b respectively (81,89). The 1-methyl-2-arylamido derivatives of type 234 were isolated by heating the betaine-arylisocyanate cyclo-adducts 235 (Ar = p-$NO_2$Ph, Ph, p-MeOPh) in methanol (97).



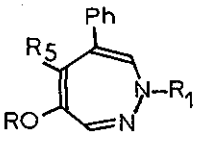

| | 231 | 232 | 233 | 234 |
|---|---|---|---|---|
| $R_1$ | COPh | Ac | Ts | Me |
| $R_2$ | H | H | H | CONHAr |

## 1,2-Diazepin-4-ols and derivatives

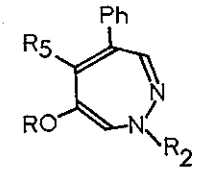
Selective sodium borohydride reduction of the 2,3-dihydrodiazepinones 200 and 204 gave the corresponding diazepinols 236 and 237 (98). The N-unsubstituted diazepinols 242 and 247 have been postulated as intermediates in the base-catalysed interconversion of the three dihydro diazepinone tautomers, i.e. 2,3-dihydro 200, 1,5-dihydro 214 and 1,7-dihydro 226 (79,95). The 4-acetoxy and 4-benzoyloxy



| | 236 | 237 | 238 | 239 | 240 | 241 |
|---|---|---|---|---|---|---|
| $R_2$ | H | Ac | Me | COPh | Ac | Ac |
| R | H | H | H | H | Ac | Ts |



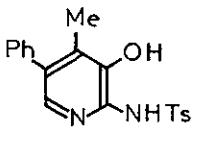
| | 242 | 243 | 244 | 245 | 246 |
|---|---|---|---|---|---|
| $R_1$ | H | Ac | COPh | Ac | COPh |
| $R_5$ | Me | Me | Me | Ph | Ph |
| R | H | Ac | COPh | Ac | COPh |



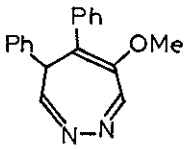
| | 247 | 248 | 249 | 250 |
|---|---|---|---|---|
| $R_2$ | H | Ts | Ac | Ac |
| $R_5$ | Me | Me | Me | Ph |
| R | H | H | Ac | Ac |

diazepines 243-246 were prepared by reacting the 1,5-dihydrodiazepinones 214 and 219 with either acetic anhydride or benzoyl chloride in pyridine at 80° (90). Using a similar procedure the 4-acetoxydiazepines 249 and 250 were prepared from the corresponding 2,3-dihydrodiazepinones 200 and 207 (90). Compound 250 could also be obtained by acetylation of the bicyclic ketone 224a (93). The 2-tosyldiazepinol 248 has been postulated as an

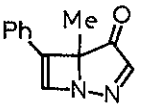
intermediate in the base-catalysed conversion of the diazepinone 209 to the pyridine derivative 251 (81). Methylation of compound 224a with trimethyl oxonium fluoroborate resulted in the formation



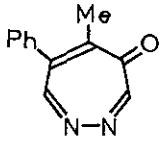

251



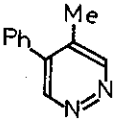

252



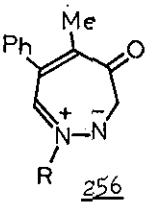

253




254




255




256

a) R = Me
b) R = Ac
c) R = COPh

of the (6H)-4-methoxydiazepine 252 (93). (4H)-1,2-Diazepin-4-ones containing only $sp^2$ nitrogen atoms could not be isolated in this series. The diazatropone 254, however, has been postulated as an intermediate in the formation of the pyridazine derivative 255 following thermolysis of the bicyclic ketone 253 (99).

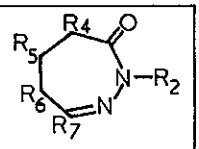
Diazepinium betaines

The 1-methyldiazepinium betaine 256a was isolated from the reaction of the 2,3-dihydrodiazepinone 200 with either dimethyl sulphate in aqueous alkali (94,100) or, more cleanly, by reaction with diazomethane in the presence of boron trifluoride (91). 1-Acyldiazepinium betaines 256b,c could not be isolated. The latter compounds, however, have been shown to be intermediates in the thermal rearrangement of the bicyclic ketones 213a,c by means of trapping experiments (95).

2-1-2 (3H)-1,2-Diazepin-3-ones

The 2,4,5,6-tetrahydro-(3H)-1,2-diazepin-3-ones 257-265 (see table 9) were prepared via the condensation of substituted hydrazines with δ-keto acids (101-104). This reaction was proved to be quite general and failed only in a few cases (e.g. when hydrazine itself or sterically hindered keto acids were used). The synthesis of the

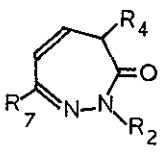
Table 9: 2,4,5,6-Tetrahydro-(3H)-1,2-diazepin-3-ones




| Compound | $R_2$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Reference |
|---|---|---|---|---|---|---|
| 257 | H | $H_2$ | $H_2$ | $H_2$ | Ph | 101,103,104 |
| 258 | Me | Me,H | $H_2$ | $H_2$ | Ph | 101 |
| 259 | Me | $H_2$ | $H_2$ | Ph,H | Me | 101 |
| 260 | H | $H_2$ | Me,H | $H_2$ | Ph | 101 |
| 261 | Me | $H_2$ | $H_2$ | $H_2$ | 2-thienyl | 101 |
| 262 | Me | $H_2$ | $H_2$ | $H_2$ | Ph | 55,102 |
| 263 | Me | $H_2$ | $H_2$ | $H_2$ | p-ClPh | 102 |
| 264 | Me | $Me_2$ | $H_2$ | $H_2$ | Ph | 102 |
| 265 | Me | $H_2$ | $H_2$ | $Me_2$ | Ph | 102 |
| 266 | Me | $H_2$ | $H_2$ | Br,H | Ph | 102 |
| 267 | Me | $H_2$ | $H_2$ | Br,H | p-ClPh | 102 |

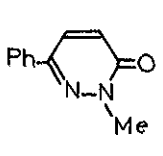
diazepinone 262 could also be achieved via the condensation of ethyl 4-benzoylbutyrate with methylhydrazine (55). This new heterocyclic system was proved to be quite interesting pharmacologically : compounds of this type showed psychotropic and analgesic activity and hence a large number of them have now been prepared (103,104). Reaction of these tetrahydro derivatives with NBS afforded the 6-bromodiazepinones 266 and 267 which, on further

treatment with lithium bromide in the presence of collidine and sodium carbonate, were dehydrobrominated, yielding the 2,4-dihydro derivatives 269 and 270 (102). Another original synthesis of this

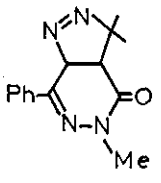


| | $R_2$ | $R_4$ | $R_7$ |
|---|---|---|---|
| 268 | Me | $Me_2$ | Ph |
| 269 | Me | $H_2$ | Ph |
| 270 | Me | $H_2$ | p-ClPh |

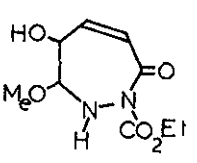
2,4-dihydrodiazepinone system has been reported : a cycloaddition involving the pyridazone 271 and diazopropane yielded the stable pyrazoline 272 which on further heating or uv irradiation afforded compound 268 (105). 1,2,6,7-Tetrahydro-(3H)-1,2-diazepin-3-one 273 was obtained by photolysis of the (1H)-1,2-diazepine-singlet oxygen cycloadduct 189 in methanol (84). The hexahydro-1,2-diazepin-3-one 274 was prepared by thermally induced ring closure of the hydrazine 275 (56).



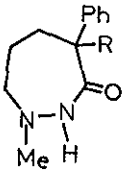
271



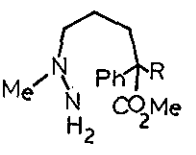
272



273



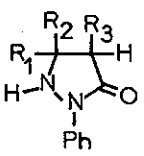
274 (R = m-MeOPh)



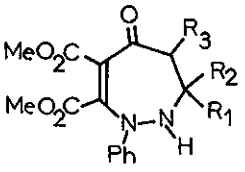
275

## 2-1-3 (5H)-1,2-Diazepin-5-ones

Only a few members of this series have been synthesized. Reaction of dimethyl acetylene dicarboxylate with pyrazolidinones of type 276 has been reported to afford the 1,2,3,4-tetrahydro-(5H)-1,2-diazepin-5-ones 277a-c (106). The structure of these diazepinones was proposed on the basis of spectroscopic data and confirmed by



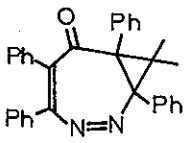
276



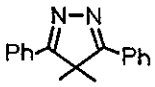
277

| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | Me | Me | H |
| b | Me | H | H |
| c | H | H | Me |

X-ray analysis of compound 277a.



278



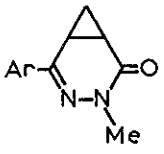
279

No mechanism for this unusual reaction has been proposed by the authors. The synthesis of 3,4-homo-(5H)-1,2-diazepin-5-one 278 has been achieved via the thermal rearrangement of the cycloadduct obtained from diphenylcyclopropenone and 4,4-dimethyl-3,5-diphenyl-isopyrazole 279 (107).

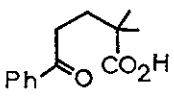
## 2-2 Chemistry

### Reduction and oxidation

Lithium aluminium hydride treatment of the tetrahydrodiazepinone 262 resulted in selective reduction of the amidic carbonyl function to afford the 4,5,6,7-tetrahydro-(1H)-1,2-diazepine 107 (48,55). Whereas NBS treatment of diazepinones 262 and 263 resulted in selective bromination at the imine α-position to yield the 6-bromo-derivatives 266 and 267, the 6,6-dimethyl-diazepinone 265 was unreactive towards NBS, proving the inertness of the carbonyl α-position (102). Prolonged treatment of compounds 266 and 267 with lithium bromide resulted in 1,2-elimination and



280

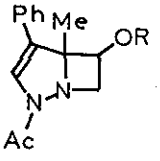


281

formation of the 2,4-dihydrodiazepinones 269 and 270. Reaction of 266 and 267 with triton B, however, resulted in 1,3-elimination and formation of the 3,4-diazabicyclo[4.1.0]heptenones of type 280 (102). Alkaline hydrolysis of the dihydrodiazepinone 268 resulted in ring-opening and formation of the δ-keto acid 281 (105).

Electrophilic substitutions

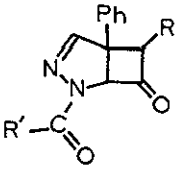
Acylation or sulphonylation of the diazepinone 200 can occur at both nitrogen atoms and may be directed by careful choice of reaction conditions to give either seven-membered rings or bicyclic derivatives. The treatment of compound 200 with acid chlorides in the presence of tertiary amines (88-91,95) or with tosyl chloride in the presence of sodium hydride (81) resulted in N-1 substitution leading to the bicyclic ketones 213a-c. When the diazepinol 236 was treated with acetic anhydride in pyridine, the bicyclic ester




a) R = H

b) R = Ac

282




a) R = Me

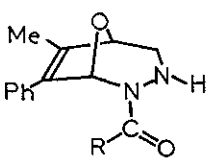
b) R = Ph

R' = Me, Ph

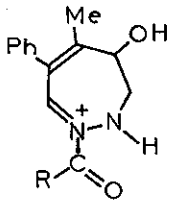
283

282b was isolated (98). N-2 Substitutions were observed when the 1,5-dihydrodiazepinones 214 and 219 were treated with acid chlorides in dimethylaniline, the bicyclic heptenones 283 being obtained (90). Treatment of the diazepinol 236 with acetic anhydride only gave the transannular oxides of type 284. The bicyclic alcohol 282a was initially postulated as an intermediate in this reaction (98). However, it has been shown that (even though compound 282a was converted to 284 on treatment with organic acids,

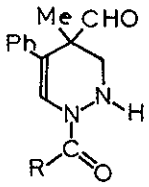
pyridine hydrochloride or dimethylaniline) this isomerisation is not the major pathway from 236 to 284. Intermediacy of the diazepinium cation 285 has since been postulated to account for the formation of the two types of acylated compounds, i.e. oxide 284 and tetrahydropyridazines 286 (108).




284




285

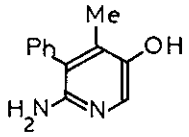



286

a) R = Me
b) R = Ph

Ring contraction to six-membered rings involving diazanorcaradiene intermediates

Alkaline treatment of diazepinone 200 resulted in the formation of the two aminopyridines 287 and 288 (94,109,110). From a careful investigation of the interconversion between the 2,3-dihydro 200, 1,5-dihydro 214 and 1,7-dihydro 226 diazepinones via an enolisation and tautomerisation pathway it was concluded that the 1,7-diazabicyclo[4.1.0]heptadienols 289 and 290 were the likely intermediates in these reactions (79). Confirmation of this mechanism was provided by the isolation and characterisation of the diaziridine 291 following photoisomerisation of the betaine 256a.

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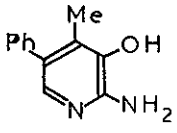


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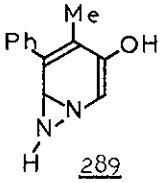


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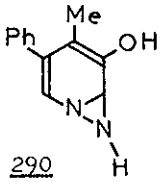
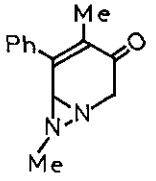



290

Compound 291 led to 292 in the presence of sodium methoxide (69). The higher reactivity of the tosyl diazepinone 209 towards base was attributed to the higher acidity of the C-3 protons (as evidenced by facile C-3 deuteration) favouring enolisation and valence isomerisation (81). The intermediacy of the 2,3-diazanorcaradienone 293 has been postulated in the alkoxide catalysed conversion of the tosyl diazepinone 209 into the dihydro pyridazine 294 (81).

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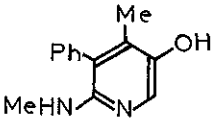


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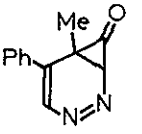


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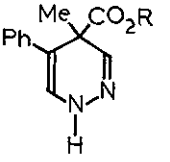
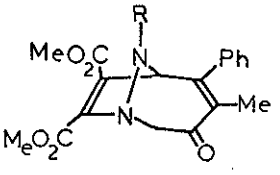



294

Cycloaddition reactions

The 1-methyl-2,3-dihydrodiazepinium betaine 256a undergoes 1,3 and 1,5-cycloaddition reactions involving the 4π azomethine-imine system (N-2,N-1,C-7) and the extended 6π system (N-2,N-1,C-7,C-6, C-5) respectively. Dimethyl acetylene dicarboxylate gave the 1,3-cycloadduct 295 (R=Me) whereas ketene gave the 1,5-adduct 296. The arylisocyanate 1,5-cycloadduct 235 rearranged to the more

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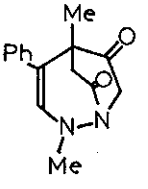


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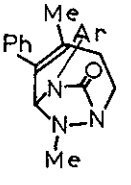


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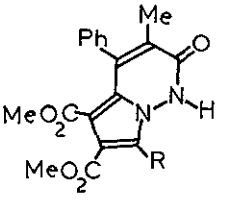
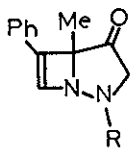



298

stable 1,3-adduct 297 (97). Bimolecular reaction of the betaines 256 are restricted by their facile thermal rearrangement to the 1,7-dihydrodiazepinones 227, 229 and 230 via a [1,5] sigmatropic shift (95,97). For example the possibility of a concerted cycloaddition involving the extended 6π system of compounds 256 and several dienes was explored but only the corresponding 1,7-dihydro derivatives could be isolated. On heating or on treatment with acid or base the 1,3-cycloadducts 295 (R = Me,Ac,COPh,p-BrPhCO) underwent an unusual reaction yielding the pyrrolopyridazinones 298 and formaldehyde. The structure of the bicyclic compounds 298 was confirmed by X-ray analysis (111).

Photochemical reactivity

2,3-Dihydro-(4H)-1,2-diazepin-4-ones (see table 7) undergo facile photoinduced ring-closure of their azabutadiene moiety (cf. 1,2-diazepines), yielding the 1,2-diazabicyclo[3.2.0]heptenones 299 (79-81). The 2,3-dihydrodiazepinols 236-239 and the esters 240 and 241 on photocyclisation gave a mixture of exo and endo isomers 300 and 301, the exo isomer always being the major product (80).

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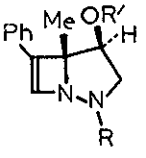
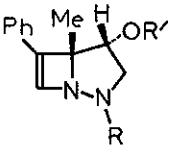
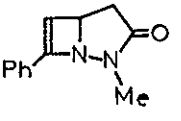



300




301




302

Sodium borohydride reduction of compound 299 was found to be an effective preparative pathway to the endo isomer 301. Photoexcitation of the 2,4-dihydrodiazepinone 269 gave the 3-oxo-1,2-

diazabicyclo[3.2.0]heptene 302 (82). Another type of photoisomerisation occurred when the diazepinium betaine 256a was irradiated at low temperature. The 1,7-diazabicyclo[4.1.0]heptenone 291 was obtained, resulting from photoinduced electrocyclisation of the 1,3-dipolar system. A trace amount of the 1,5-dihydrodiazepine 215 was also obtained in this reaction. It is not clear whether compound 215 resulted from a [1,3] sigmatropic shift in the starting material 256a or from a photochemical reaction of the 1,7-dihydrodiazepinone 227 which could be formed thermally from the starting material in the reaction mixture (69).

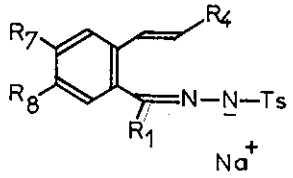
## 3. POLYCYCLIC 1,2-DIAZEPINES

### 3-1 Synthesis

#### 3-1-1 Benzodiazepines

##### (1H)-2,3-Benzodiazepines

The (1H)-2,3-benzodiazepines 303-312 (see table 10) were prepared by electrocyclic ring-closure of the α-aryldiazoalkenes 314 which, in turn, were prepared by thermal decomposition of the corresponding tosylhydrazone sodium salts 313 (112,113). The involvement of diazo-

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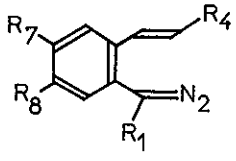
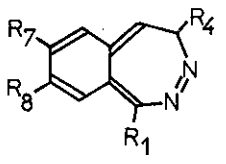
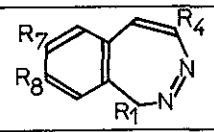



314




315

Table 10 : (1H)-2,3-Benzodiazepines



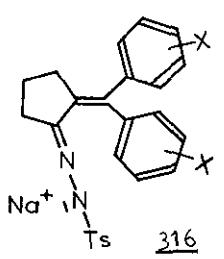

| Compound | $R_1$ | $R_4$ | $R_7$ | $R_8$ | Reference |
|---|---|---|---|---|---|
| 303 | H | H | H | H | 113 |
| 304 | H | H | OMe | OMe | 113 |
| 305 | Me | H | H | H | 112,113 |
| 306 | Et | H | H | H | 113 |
| 307 | Ph | H | H | H | 113 |
| 308 | Ph | H | OMe | OMe | 113 |
| 309 | H | Ph | H | H | 113 |
| 310 | Me | Ph | H | H | 112,113 |
| 311 | p-MePh | Ph | H | H | 112,113 |
| 312 | Me | H | OMe | OMe | 116 |

compounds in these reactions was indicated by a deep-red coloration observed in the early stages of the cyclisations and by trapping experiments (114). The (4H)-benzodiazepines 315, previously assigned as the cyclisation products (115,116), have been postulated as intermediates, being themselves converted into the isolated (1H)-derivatives via a symmetry-allowed [1,5] sigmatropic hydrogen shift. The (1H)-2,3-benzodiazepine structure assigned to the product was suggested by nmr and mass spectral studies and confirmed by X-ray analysis of compound 310. The nmr spectrum of compound 303 was found to be temperature dependent, the barrier to ring inversion being approximately 15 Kcal/mole (113).

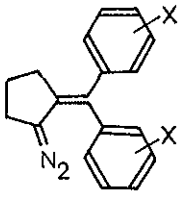
(3H)-1,2-Benzodiazepines

The title compounds 318 were prepared by thermal decomposition of the tosylhydrazone salts of the α-diarylmethylene cyclopentanones

316 (114,117). The benzodiazepines were obtained from the resulting diazoalkenes 317 via a 1,7-electrocyclic ring-closure. In contrast to the related reaction of the diazoalkenes 314, this reaction was found to be extremely sensitive to steric factors.



316



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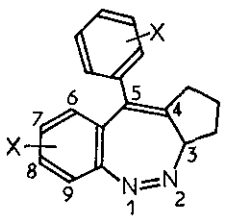
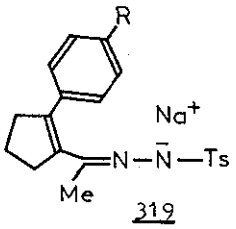


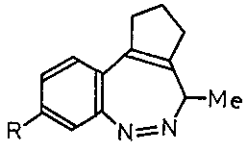
318

| | a | b | c | d | e |
|---|---|---|---|---|---|
| X | H | 8-Me,p-Me | 9-OMe,m-OMe | 8-$CF_3$,p-$CF_3$ | 8-F,p-F |

The (3H)-1,2-benzodiazepines 320 have been obtained using a similar method, i.e. the thermal decomposition of the tosylhydrazone salts of type 319 (118).



319

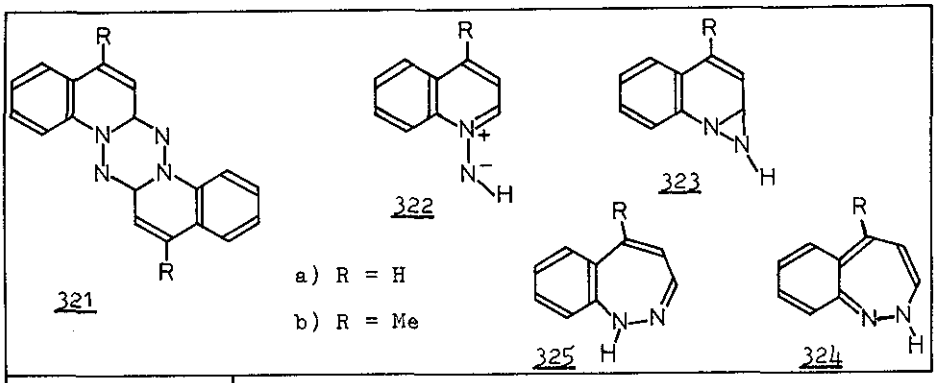


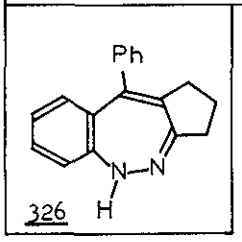
320

a) R = H
b) R = Me
c) R = F

(1H)-1,2-Benzodiazepines

(1H)-1,2-Benzodiazepines 325 were obtained by photolysis of the N-iminoquinolinium ylide dimers 321. The equilibration of compound 321 to the monomer, ylide 322, followed by photoinduced electrocyclisation to compound 323, ring expansion to the (2H)-benzodiazepine

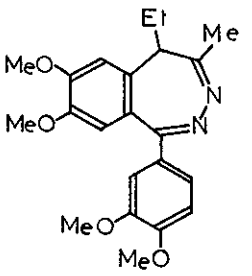


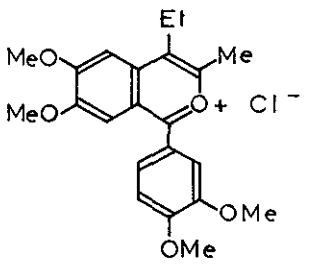



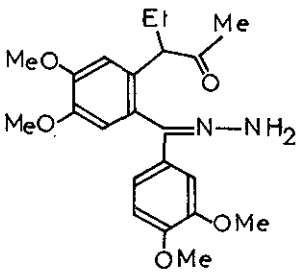

324 and finally a [1,7] hydrogen shift has been postulated as a reasonable mechanism for this reaction (119). The (1H)-1,2-benzodiazepine 326 was isolated from acid or base treatment of the (3H) derivative 318a (114).

(5H)-2,3-Benzodiazepines

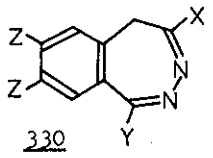
Compound 327 was prepared by reaction of hydrazine hydrate with the benzopyrylium salt 328, the reaction proceeding via the monohydrazone 329 (120-124). The structure of the benzodiazepine 327 was elucidated by means of detailed nmr and mass spectroscopic studies, none of the isomeric (3H)-2,3-benzodiazepine being observed (123).



(5H)-2,3-Benzodiazepines 330 were readily obtained by thermal or basic treatment of the corresponding (1H)-derivatives 307, 308, 310 and 311 (113, 116). The nmr spectra of compounds 330 were found to be temperature dependent, the energy barrier to ring inversion ranging from 19-22 Kcal/mole (113). These values are much higher than those reported for the parent monocyclic (4H)-diazepines (33, 43,68) suggesting a higher degree of ring-rigidity in the benzo-compounds.

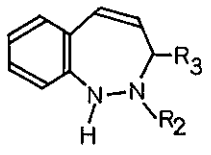


330

| | a | b | c | d |
|---|---|---|---|---|
| X | H | H | Ph | Ph |
| Y | Ph | Ph | Me | p-MePh |
| Z | H | OMe | H | H |

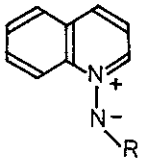
2,3-Dihydro-(1H)-1,2-benzodiazepines

The title compounds 331 and 332 were obtained by photolysis of the corresponding N-iminoquinolinium ylides 333 in ethanol or methanol (125-127). Confirmation of the structure of compound 331 was achieved by its conversion, via thermolysis in acetic acid, to the known ylide 333a (127). Compound 334 was isolated in quantitative yield by reduction of the fully unsaturated benzodiazepine 325b with either sodium borohydride in methanol or lithium aluminium



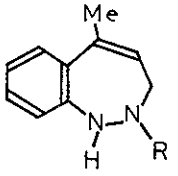
331 $R_2$ = $CO_2Et$, $R_3$ = OEt

332 $R_2$ = Ac, $R_3$ = OMe



333 a) R = Ac

b) R = $CO_2Et$



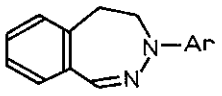
334 R = H

335 R = $CO_2Me$

hydride. The treatment of compound 325b with sodium borohydride in the presence of methyl chloroformate resulted in the formation of compound 335 (119).

3-Aryl-4,5-dihydro-(3H)-2,3-benzodiazepines

Compounds 336 (Ar = Ph, p-MePh, p-ClPh, p-$NO_2$Ph) were prepared by treatment of the dihydroisoquinolinium salts 337 with alkali, followed by reaction of the resulting pseudobase with mesitylsulphonylhydroxylamine (MSH). The intermediacy of the hydrazine derivative 338 has been postulated (128).

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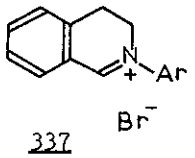


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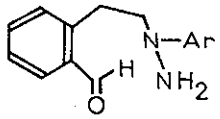
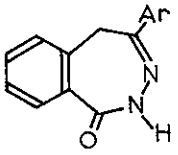



338

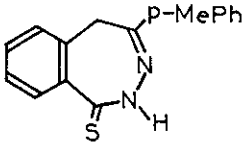
3-1-2 Benzodiazepinones

1-Aryl-3,5-dihydro-(4H)-2,3-benzodiazepin-4-ones 339-342 (see table 11) were prepared by condensation of o-aroylphenylacetic acids with substituted hydrazines in refluxing n-butanol (129), this method improving and extending the method originally reported by Halford et al (130). These benzodiazepines were found to have tranquillizing activity in mice and, consequently, a large number

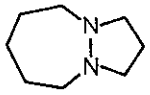



a) Ar=Ph
b) Ar=p-MePh
c) Ar=p-MeOPh

346

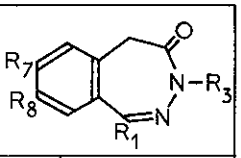



347




350

Table 11 : 3,5-Dihydro-(4H)-2,3-benzodiazepin-4-ones

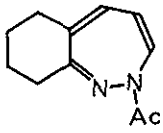


| Compound | $R_1$ | $R_3$ | $R_7$ | $R_8$ | Reference |
|---|---|---|---|---|---|
| 339 | Ph | H | H | H | 129 |
| 340 | Ph | Me | H | H | 129 |
| 341 | p-MeOPh | 2-(morpholine-N-yl)-ethyl | H | H | 129 |
| 342 | Ph | 2-(morpholine-N-yl)-ethyl | H | Cl | 129 |
| 343 | Me | Ph | OMe | OMe | 133 |
| 344 | Me | p-ClPh | OMe | OMe | 133 |
| 345 | Me | p-BrPh | OMe | OMe | 133 |

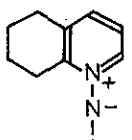
of these compounds have been prepared (131,132). A similar synthesis has been reported for compounds 343-345 which involves the use of N,N'-dicyclohexylcarbodiimide as the cyclising agent (133). The synthesis of the 4-aryl-2,5-dihydro-(1H)-2,3-benzodiazepin-1-ones 346 by the reaction of hydrazine with 3-arylisocoumarins was first reported in 1905 (134). More recently, a similar reaction involving 3-aryl-2-thioisocoumarins has been described (135). Reaction of compound 346b with phosphorus pentasulphide afforded the benzodiazepin-1-thione 347 (135).

### 3-1-3 Other polycyclic 1,2-diazepines

The synthesis of the 3,4-tetramethylene-(1H)-1,2-diazepine 348 has been achieved by photolysis of the N-acetylimino-5,6,7,8-tetrahydroquinolinium ylide 349 (136). The 1,2-trimethylene hexahydro-1,2-diazepine 350 has been prepared by the reaction of pyrazolidine with glutaraldehyde (57). Condensation of 1,4-dioxo compounds

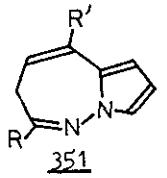


348



349

with 1-aminopyrrole afforded the (6H)-3a,4-diazaazulenes 351 (R = Me,Ph ; R' = Me,Ph). These compounds can be considered to be pyrrolo[1,2-b]-1,2-diazepines (137). Reaction of N-aminothiazolium salts of structure 352 (R = H,Me) with dimethylacetylene dicarboxylate in the presence of sodium carbonate led to a 1:2 adduct which was assigned structure 353 (138). A photochemical intramolecular oxygen insertion reaction with 2,2'-dinitrophenylmethanes followed by reductive coupling has been reported to give the mono- and di-N-oxides 354 and 355. Successive reduction of compounds 354 and 355 with magnesium in ethanol led quantitatively to the (11H)-dibenzo[c,f]-1,2-diazepin-11-one 356 (139).



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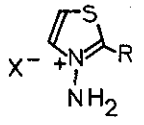

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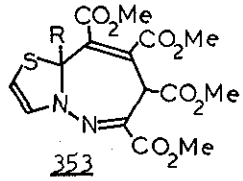

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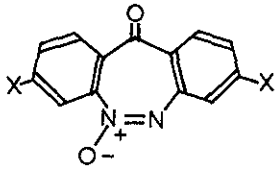

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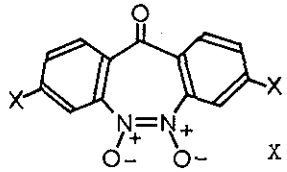
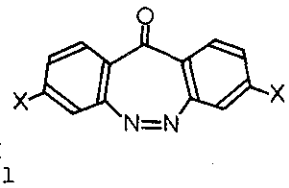


355

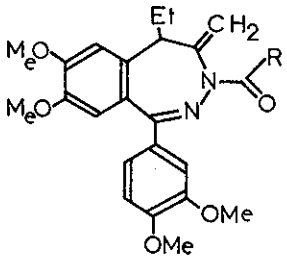
X = H
Cl
Br



356

## 3-2 Chemistry

The acylation of benzodiazepine 327 with either p-nitrobenzoyl chloride or acetic anhydride in pyridine resulted in C = N double bond migration and acylation at the N-3 position thus affording the 3-acyl-4-methylene derivatives 357(R = Ac,p-$NO_2$Ph). Catalytic hydro-



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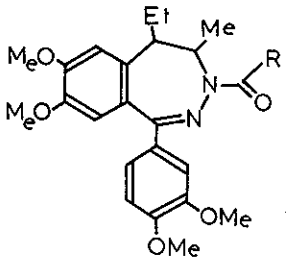

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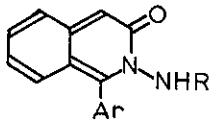

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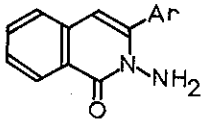
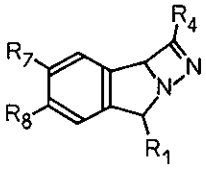


360



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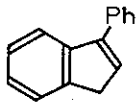
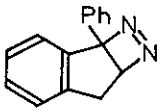


362



363

genation of compound 357 gave the (3H)-4,5-dihydro compound 358 (140). Catalytic reduction (Pd-C) of benzodiazepines 325 has been reported to give quinoline derivatives via N-N bond fission, recyclisation and deamination (119). Acid catalysed ring-contraction of the benzodiazepin-4-ones 339-342 resulted in the formation of the N-aminoisoquinolones 359 (129), and similarly the benzodiazepin-1-ones 346 ring-contracted to give the N-aminoisoquinolones 360 (135). Photolysis at 0°C of the (1H)-2,3-benzodiazepines 304, 305, 307, 309, 310 and 312 resulted in electrocyclisation of their 1,2-diazabutadiene moiety, yielding the novel tricyclic compounds of type 361 (116). Photolysis of the (5H)-benzodiazepine 330a, however, led to the indene 362 in high yield, presumably via electrocyclisation to the tricyclic compound 363 and expulsion of nitrogen (116).

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