# SYNTHESIS AND REACTIVITY OF 2-AZABICYCLO[2.2.1]HEPTANES, HEPTENES AND HEPTADIENES

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Abstract - It is purpose of this review to cover all known methods of preparation of 2-azabicyclo[2.2.1]heptanes, heptenes, and heptadienes. The reactivity of these systems will then be discussed, stressing their synthetic potential as it has already been demonstrated for example in the field of nucleoside antibiotics.

CONTENTS

## 1. Introduction

Earliest studies originated at the turn of the century[1] and the parent system has been known since the mid-sixties[2]; almost all the work has been carried out within the past twenty years.

The rigidity of the ring system has been taken advantage of in physico-chemical studies : thus low temperature $^1H$ NMR spectral experiments allowed studies of nitrogen inversion barriers both invertomers being observed[3].

Study of optically active material by means of Optical Dispersion and Circular Dichroism allowed separation of solvent and conformational effects. Comparison with pyroglutamic acid made possible a model study of conformation of polypeptides in solution[4].

The existence of nitrenium ion which is of important theoretical interest was best demonstrated on 2-azabicyclo[2.2.1]heptanes through rearrangement mechanism studies by Gassmann and co-workers : thus there was evidence of both singlet and triplet states of this divalent charged species. This work has been reviewed[5].

The present review will focus on the chemistry of the 2-azabicyclo[2.2.1]heptyl system, dealing with methods of preparation and properties. Synthetic applications will separately be delineated.

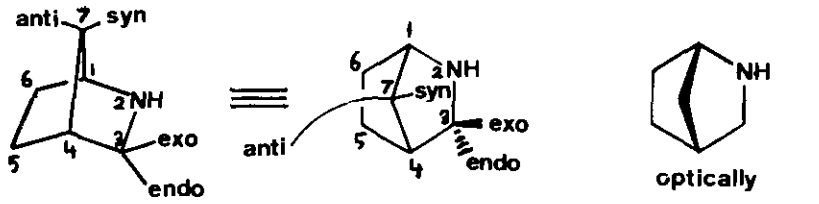


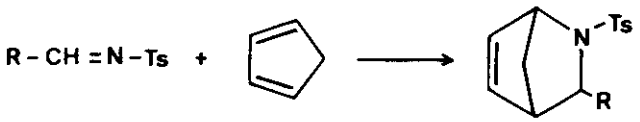

Fig.1

Figure 1 shows appropriate numbering and the conventional representation which will be adopted throughout ; note that this does not imply the material to be optically active although this will be the case in a few instances (accordingly the bonds linking C-7 will be put forward).

2. Methods of preparation

a) Diels-Alder cycloadditions

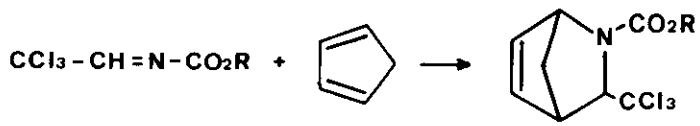
Kreske and Albrecht[6,7] were the first to use a Diels-Alder reaction in the preparation of a 2-azabicyclo[2.2.1]heptyl derivative ; thus, activated imine 1 was condensed with cyclopentadiene to give adduct 2 in excellent yield.




1: R = $CCl_3$ 2: R = $CCl_3$

3: R = $CF_3$ 4: R = $CF_3$

Afterwards, the stereochemical outcome of this reaction was studied and shown to afford kinetically endo-2 and thermodynamically exo-2[8,9]. Use of the more reactive imine 3 gave immediately and in quantitative yield a mixture of endo and exo 4 in a 43 : 57 ratio. Similarly, when cyclopentadiene was condensed with imine 5, adduct 6 was obtained. This was characterised as its dibromo derivative[10].

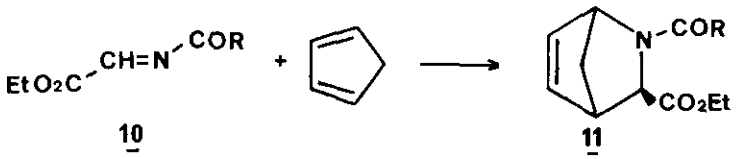



5: R = Bu 6: R = Bu

7: R = Me 8, 9: R = Me

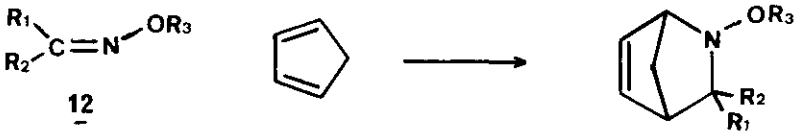
Unambigous assignment of endo and exo structures of the adducts 8 and 9 obtained on reacting activated imine 7 with cyclopentadiene, was made possible by a detailed NMR spectral analysis. This showed the coupling constants $J_{3-4}$ to be 0 and 3 Hz respectively. Adducts 8 and 9 were produced in a 2 : 1 ratio[11]. However this ratio was found to be 1 : 1 subsequently by other workers[9].

A single compound, exo 11 was isolated in fair to good yield when in situ generated trans imine 10 was condensed with cyclopentadiene. The NMR spectrum exhibited two sets of protons but this was shown to be due to hindered rotation about the amide bond[12].




10 11

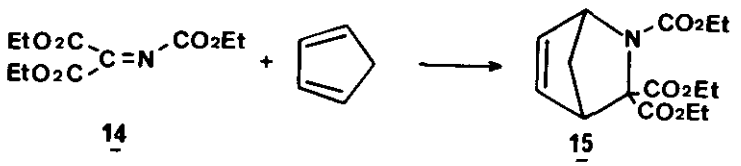
Type 12 oximes, which are air and water stable compounds, were shown by Fleury et al. to undergo Diels-Alder cycloadditions[13-15,59]. Depending on the substituents, the reactivity order was shown to be $R_1$ or $R_2$ = CN >> COOR > $CONH_2$ and $R_3$ = Tos > Mes > $pNO_2Bz$ > Bz. Thus, when $R_1$ = $R_2$ = CN, 12 reacts with cyclopentadiene to give adduct 13 independantly of $R_3$ ; on the other hand when $R_1$ = CN, $R_2$ = COOR, and $R_3$ = Bz, 12 can be recovered. Based on spectral information and chemical reactivity of the endo C-3 substituent, the cyano group was shown in every case to occupy the exo position.



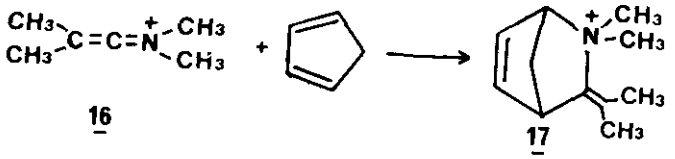

12 13

**$R_1$ : CN , $CO_2R$ , $CONH_2$**
**$R_2$ : CN , $CO_2R$ , $CONH_2$**
**$R_3$ : Tos ; Mes , p $NO_2Bz$ , Bz**

A final example of the condensation of cyclopentadiene with an activated imine is its cycloaddition with 14 to give 15[16]. A somewhat closely related reaction involves electron deficient iminium 16 to give 17 in 85 % yield ; alternate structures have been eliminated on ground of spectral properties and chemical reactivity[17].

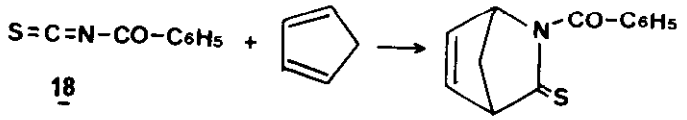



14 15




16 17

Among other types of dienophiles condensed with cyclopentadiene to give 1 : 1 adducts, benzoyl isothiocyanate 18[18] and sulfonyl cyanide of type 19 were described[19,65]. Iron-substituted cyclopentadiene reacted with isocyanate 20 to give anti 7-substituted 21[20].

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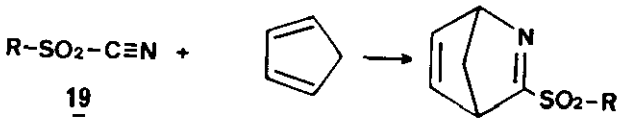


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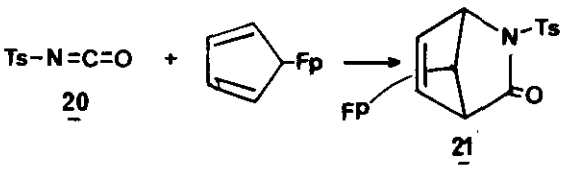


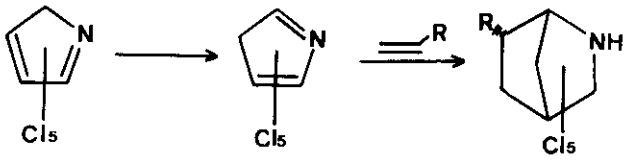

20 21

Fp ≡ $h^5$-$C_5H_5Fe(CO)_2$

Final mention has to be made of the postulated 2-azabicyclo[2.2.1]heptane structures which were believed to be intermediates in the reactions of substituted cyclopentadienones with cyanide derivatives ; pyridines were isolated as final products[21,22].

It is appropriate at this point to mention that (4+2) cycloadditions of iminodienophiles have been reviewed[23] although there is little overlap with the work presented above.

*Another totally different* cycloaddition has been found to give 2-azanorbornenes : reaction of an activated azacyclopentadiene with simple olefins. This reaction, whose first example was not expected since X-ray proof of structure had been necessary to correct previous result[24], can be viewed as *in situ* isomerisation of 1-azadiene 22 to 2-azadiene 23.



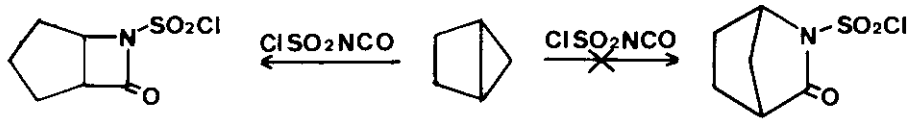

22 23 24

Thus cycloadditions of 23 have been obtained with styrene[24], vinyl acetate[25], and trans piperylene[26]. A noteworthy aspect is the endo position of substituent R in derivative 24.

b) Rearrangement reactions

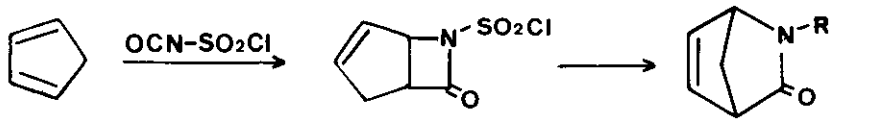
Two examples of this type have appeared in the literature.

It has been reported[27,28] that addition of chlorosulfonyl isocyanate to 25 afforded, among other products, lactam 26. These results were later denied, however, when Jagt and Van Leusen[29] proved that these reactions produced isomeric 27. This correction was the agreed upon by the previous workers[30,31].




27 25 26

The second example refers to the spontaneous complete rearrangement of adduct 28 to 29 within 5 hours as demonstrated by IR spectroscopy monitoring[32]. The structure of 29 was proven on reduced 30 by a detailed NMR spectral analysis (spin decoupling and europium induced shifts).




28

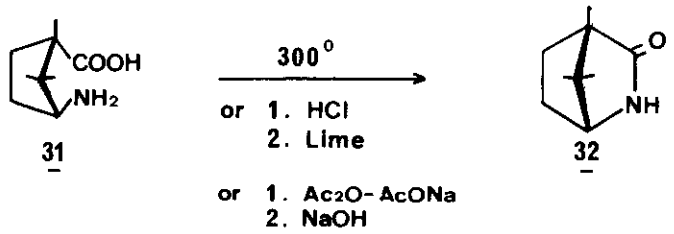
29: R = SO2Cl

30: R = H

c) Other ring closures

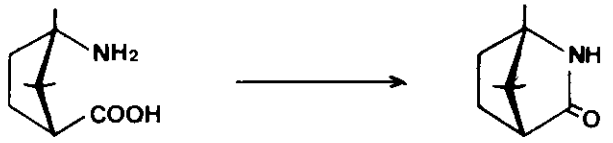
This section is concerned with ring closures from adequately substituted cyclopentanes or pyrrolidines ; thus a variety of substituted azanorbornanes are available, some of them in optically active form.

Noyes has been the first on record[1] to assign a 2-azabicyclo[2.2.1]heptane structure ; of interest is that the compounds are optically active since they are derived from chiral source. Aminolauric acid 31 was heated, or the corresponding acid chloride was reacted with lime, to yield lactam 32[1,33]. 32 can be obtained as well by reaction of acetic anhydride with 31 followed by alkaline treatment[34,37], although another structure had been earlier proposed[36].



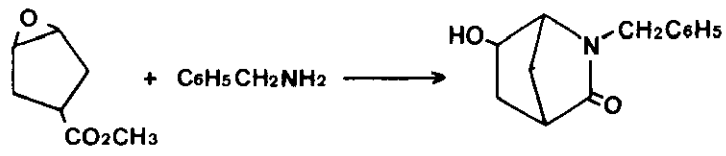

31 32

Similarly isomeric lactam 34 can be derived from amino-dihydrocampholytic acid 33 by thermolysis[37] or acetic anhydride treatment followed by base[34,38].



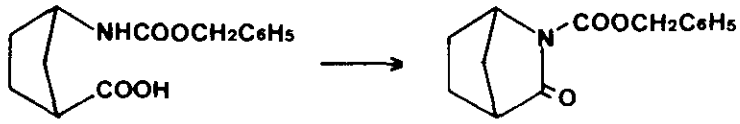

33 34

Another lactam, 36 was produced by symmetrical opening of the 35 epoxide ring by benzylamine ; 6-functionalised 36 was synthesized as an intermediate for conformationally rigid analogues of acetylcholine[38].



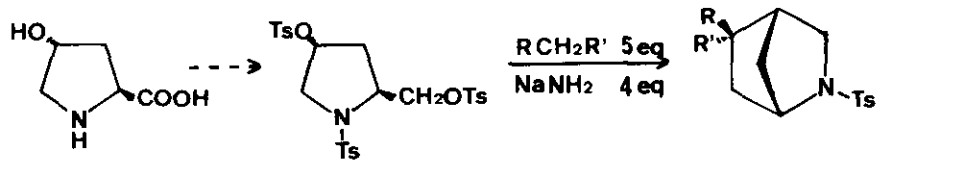

35 36

The last example of this type of these reactions occurred during the synthesis of (±)-myxoviromycine[39] : on standing in vacuo 37 gave 38 as a by-product.




37 38

In addition to the camphor derived series, another chiral source, namely hydroxyproline, has been used in the construction of optically active azanorbornanes. Besides the often much desired chirality, the main advantage of these compounds lies in the absence of methyl groups attached to the skeleton (compare to 32 and 34). Thus tritosylated 39 was reacted with an excess of phenylacetonitrile anion to give a 75 % yield of epimeric 40 and 41 in a 3 : 2 ratio[40,41].




39

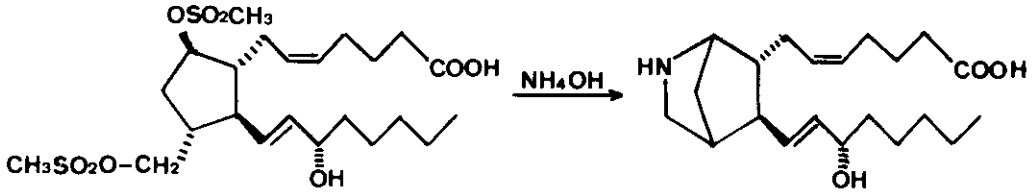
40 : R = CN , R' = C6H5

41 : R = C6H5 , R' = CN

42 : R = R' = COOC2H5

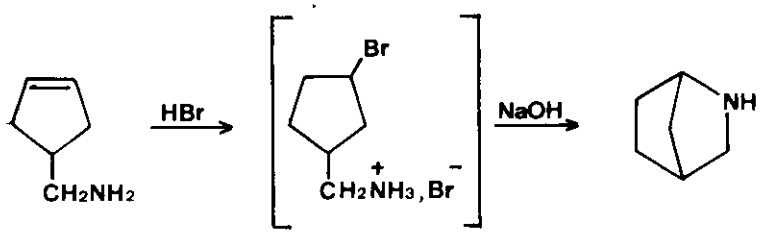
Condensing 39 with symmetrical diethyl malonate gave a single compound 42 in over 80 % yield[38,42,43].

The last two examples of chiral syntheses belong to the prostaglandin field and involve double displacement of $PGA_2$-derived bismesylate 43 by aqueous ammonium hydroxide to give the stable endoperoxide analogue 44[44,45]. It is of interest from a conceptual point of view to note that introduction of nitrogen and ring closure are performed simultaneously.



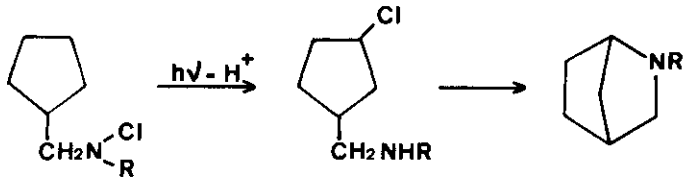

43 44

A related internal displacement has been used in the synthesis of the parent compound. Amino derivative 45 was converted into the bromo derivative which was immediately reacted with sodium hydroxide to give 46 in ca. 50 % yield. The distilled product was contaminated with starting material but could be purified as its acetate[2,46].



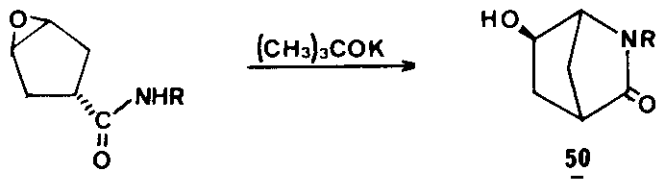

45 46

Starting with an N-halo derivative takes advantage of its strong preference for δ-hydrogen abstraction through a 6-membered ring transition state. This results in regiospecific Hoffmann-Löfler-Freytag rearrangement of aminocyclopentane 47 to give 48 whose basification allows ring formation[2,46]. In this way, N-alkyl derivatives have been prepared[47,48].



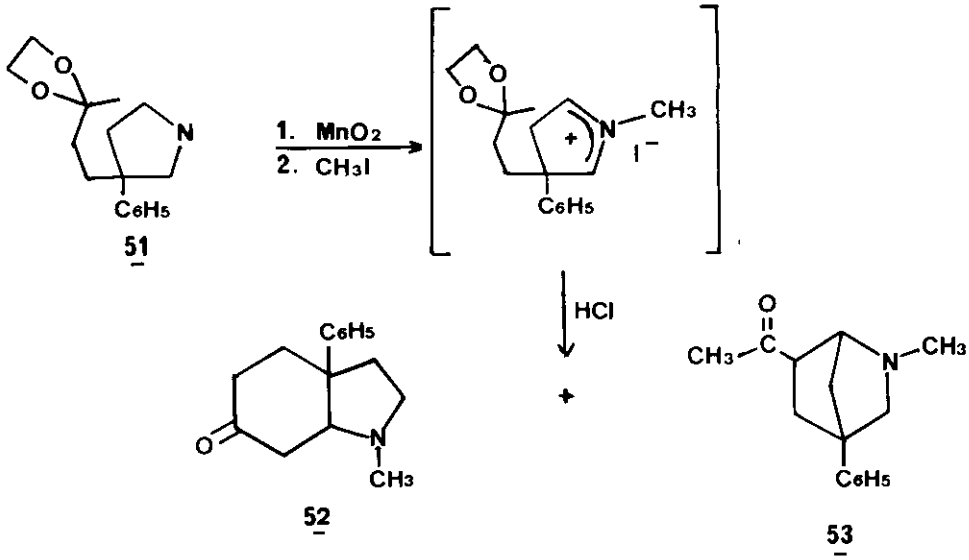

47 48 49

Intramolecular epoxide ring opening by amides has been used to form, in strongly basic medium, a 80 % yield of lactam 50. Interestingly, when an amine was used instead of an amide, this reaction failed[49].




50

Finally, besides the major product 52, 53 could be isolated from ring closure in acidic medium of the iminium species derived from 51[50].

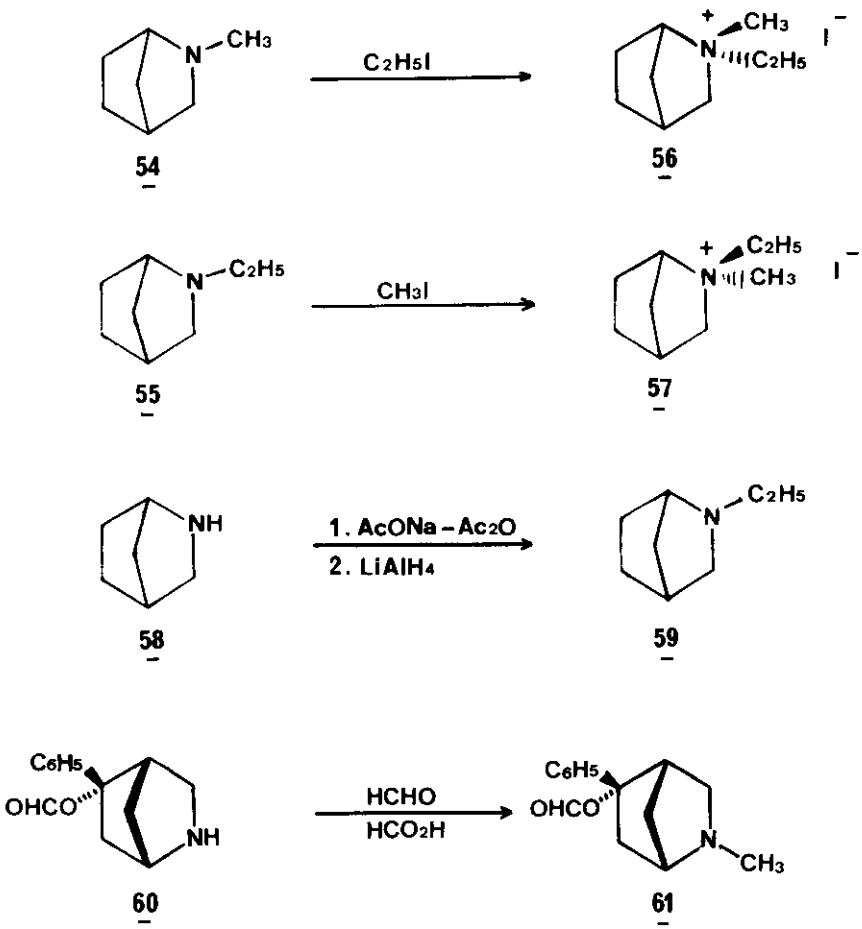



51 52 53

3. Reactivity

a) Reactions directly involving nitrogen

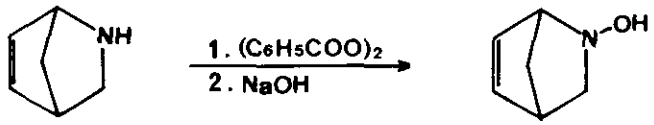
One of the simplest reactions, alkylation of the nitrogen of tertiary amines, proved to be exceptionally stereospecific ; thus ammonium derivatives 56 and 57 can be specifically isolated from quaternisation of 54 and 55 respectively. They were proved to be epimerically pure products, and this demonstrated that although the exo position is less hindered, the Curtin-Hammet principle of least motion during transition state is respected[2].



Formation of the N-ethyl derivative 59 starting with secondary amine 58 could be accomplished by reduction of the acetyl derivative[2].

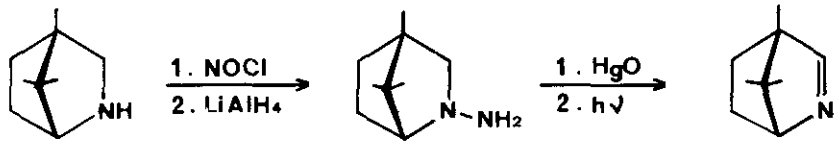
The N-methyl derivative 61 was obtained in 71 % yield by reacting 60 with formaldehyde in formic acid[40].

Oxydation of 30 with benzoyl peroxide, followed by basification, gave hydroxylamine 62 in ca. 50 % yield[51].



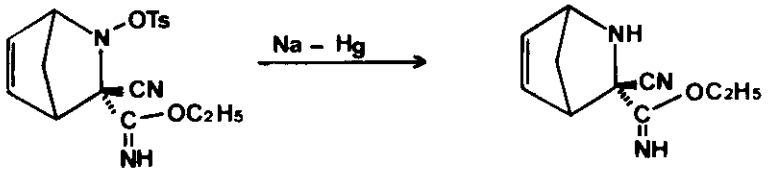

30 62

Other reactions of secondary amines involve N-chlorination with sodium hypochlorite[3,35] and N-nitrosation with nitrosyl chloride. Further transformation gives access to imine 63 among other products[52].

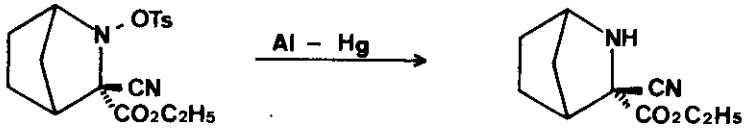



63

Reduction of the nitrogen-oxygen bond of 64 to give 65 was accomplished by sodium amalgam[15]. Similarly 66 could be reduced to 67 in 60 % yield by use of aluminum amalgam[53,54].




64 65

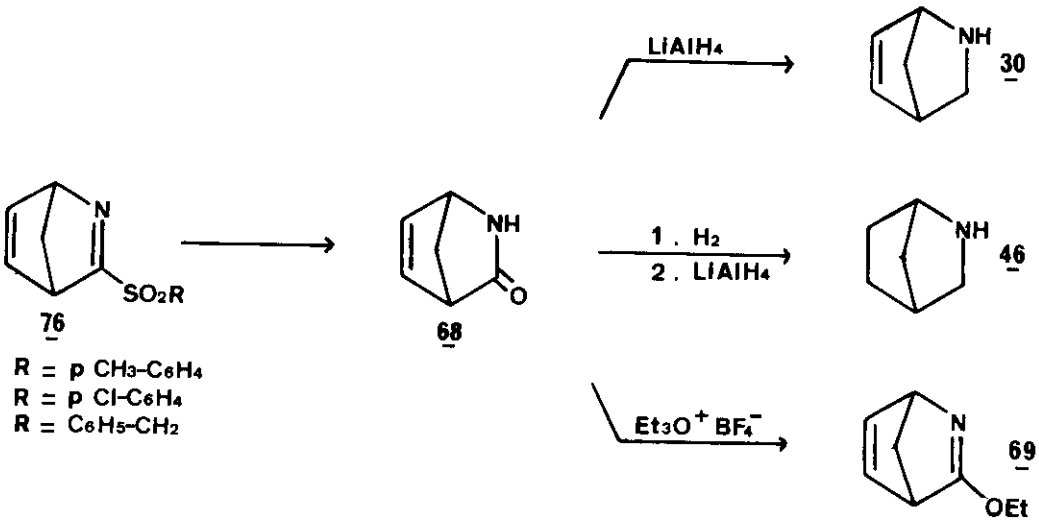



66 67

When a lactam moiety was present as in 2-azabicyclo[2.2.1]heptan-3-ones, nitrogen could be benzylated, benzoylated[35], or nitrosated by action of sodium nitrite and hydrochloric acid[33,34,37,55].

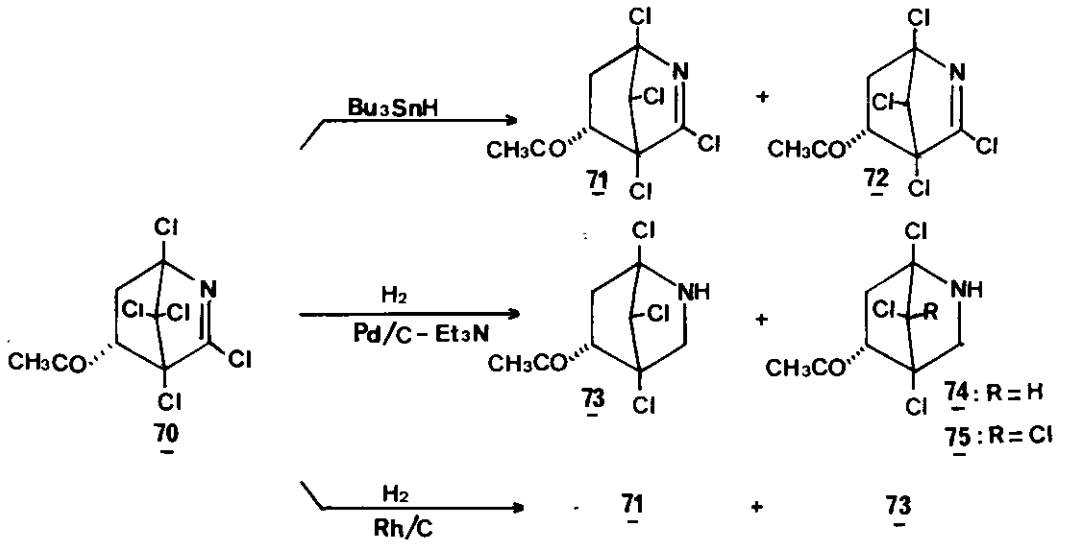
b) Reactions not directly involving nitrogen

Lactam such as 68 can be reduced to bicyclic amines 30 and 46[32,38]. By action of Meerwein's reagent, diene 69 could be obtained in 80 % yield ; however it resinified on standing[32].



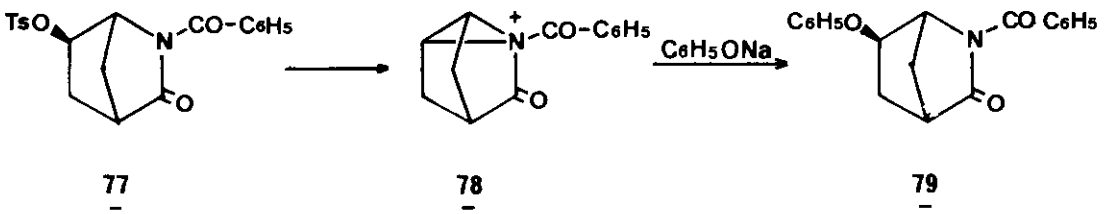
Besides simple transformation such as reduction or bromination of double bonds of 2-aza-bicyclo[2.2.1]heptenes[15,56], classical functional transformations have been performed on functional groups (ketones, alcohols, esters) linked to the heterocyclic system[15,38,40,42,43,49,54,58,59].

Special mention has to be made of the reduction of polyhalogenated 70 which, depending of the reducing agents, gave rise to various products[25]. With tributyltin hydride, 71 and 72 were almost quantitatively obtained in a 4 : 6 ratio. Catalytic hydrogenation in the presence of palladium produced 73, 74 and 75 ; if rhodium was used as a catalyst, 71 and 73 were formed.



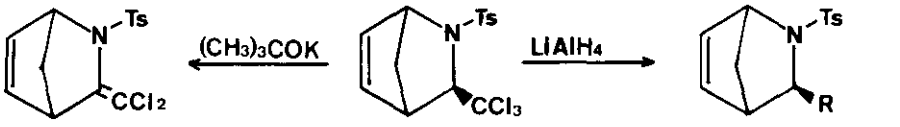

Other reactions of interest include the acidic or basic hydrolysis of 76 which permitted the preparation of the synthetically useful lactam 68[19].

The reaction of 6-substituted 77 was shown to proceed with nitrogen participation to form aziridinium ion 78. 78 was then attacked by the nucleophile ; retention of configuration was proven by X-ray crystallographic determination of the product, 79[58].



Final mention should be made of chloroalkyl-substituted azanorbornanes. Hydrochloric acid elimination from 80 gave 81 [56], and potassium tert-butoxide treatment of 82 gave 83[57]. However from lithium aluminium hydride treatment of 82, monochlorinated 84 and dichlorinated 85 could be isolated. From the exo stereochemistry of the products, direct nucleophilic attack by the hydride was inferred instead of reduction of intermediate 83[57].


80 81




83 82

84 : R = $CH_2Cl$
85 : R = $CHCl_2$

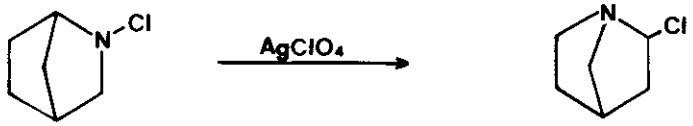
c) Transpositions

An interesting aspect of 2-azabicyclo[2.2.1]heptane chemistry lies in the modification of the ring system giving access to rearranged products.

The more trivial of these reactions is the retro Diels-Alder reaction of azanorbornenes which may occur at somewhat low temperatures, ca. 75°C, giving cyclopentadiene and the corresponding imines[57,59]. Therefore, if further synthetic elaboration is required, the double bond must be protected in some way.

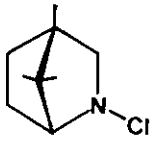
Rearrangement of the Wagner-Meerwein type reaction have been throughly studied especially by Gassmann et al. in their quest for nitrenium ions[5]. In all cases, a leaving group was attached to nigrogen.

Thus, the simple chloro derivative 86 rearranged to 87 in a concerted process, a crucial role being played by silver ion through rate acceleration[60].

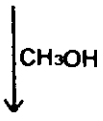


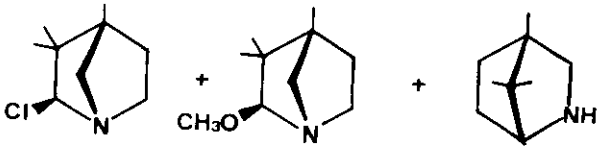

86 87

Similar rearrangement could be effected by simple heating of 88 in methanol (half-life of 83 minutes at 70°C) but was markedly accelerated (at least $10^3$ times) by silver ion catalysis, 89 being formed as the major product[60,61].




88

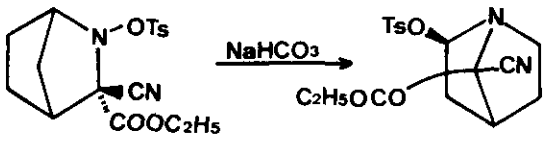



89 90

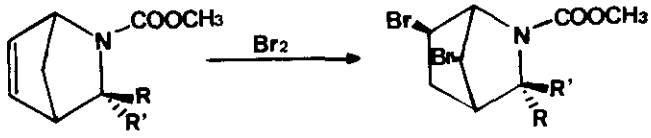
Occurrence of 90, albeit in low yield, was suggestive in those solvolytic studies of the discrete existence of singlet and triplet states of nitrenium ions[5,61].

The same type of rearrangement was shown to occur[15,59,62,63] when the N-O-tosyl derivative 91 was kept in dioxane-water in the presence of sodium bicarbonate. 92 was isolated as the sole product although the reaction was much slower (half-life of 25 days) than was the case of N-chloro derivatives (see above).



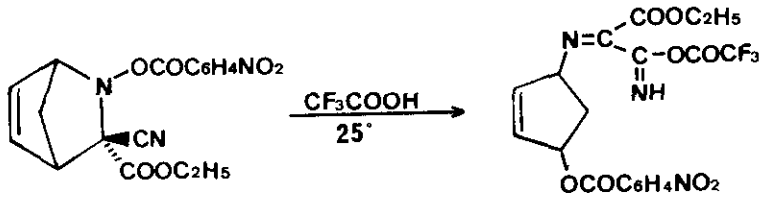

91 92

Bromination of endo 93 gave exo 94 whereas exo 95 converted to 96. Inversion of configuration at C-3 demonstrated nitrogen participation in the process[56].



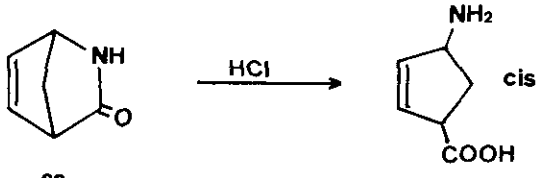

93 : R=H , R'=CCl3
95 : R=CCl3 , R'=H
94 : R=H , R'=CCl3
96 : R=CCl3 , R'=H

When the amine function is substituted by an acyloxy group, the corresponding derivatives are stable in conditions in which N-sulfonyloxy compounds are rearranged (see above). However in acidic medium, a fast ring opening reaction occurs to give cis and trans cyclopentenes 97 in a 2 : 1 ratio[15].



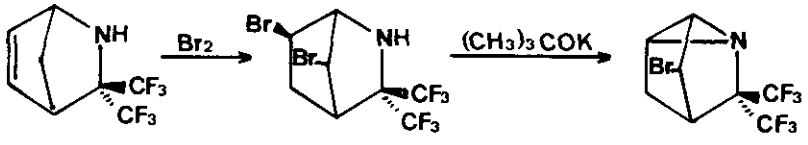

97

Another ring opening reaction is known to yield cis 1,3-disubstituted cyclopentane derivatives : lactam 68 could be hydrolysed to synthetically useful 98[19,64] ; advantage can then be taken of the cis relationship of substituents.




68 98

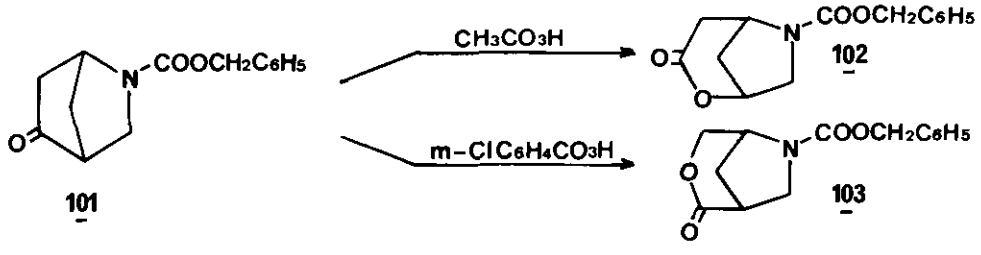
Azanortricyclene 100 is obtained by bromination and base treatment of 99. This demonstrated bromine to be exo[56].




99 100

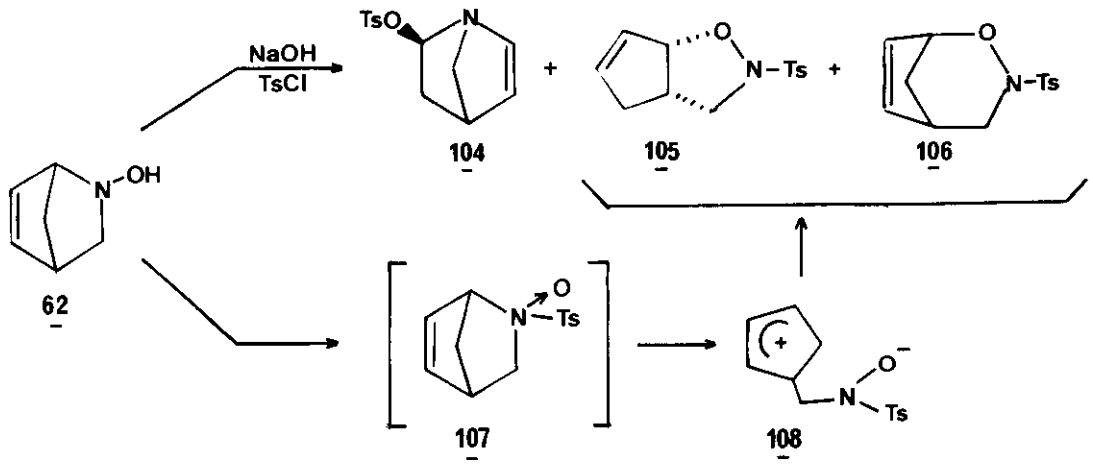
Ring enlargments have been observed in two cases.

Bayer-Villiger type oxidation has been performed regioselectively on 101 using peracetic acid to give 102 in 65 % yield (however 102 was not very stable since it was hydrolysed during purification) ; if m-chloroperbenzoic acid was used, isomeric lactone 103 could be isolated as well[66].

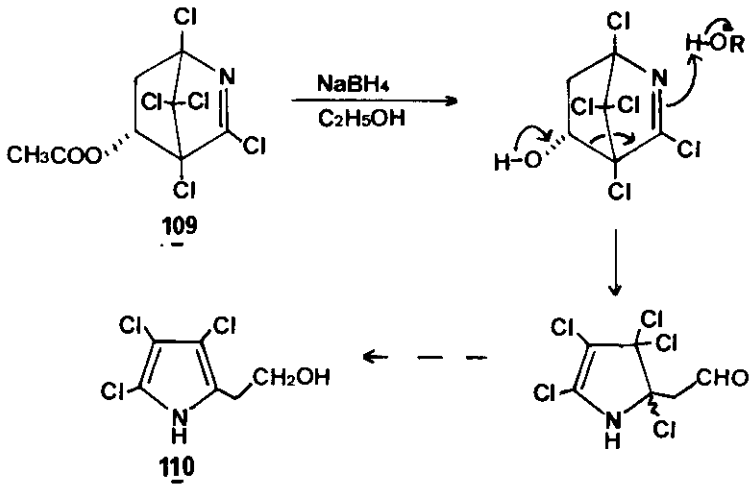



101 102 103

The other example is related to formation of 106 ; in addition to 105, whose structure was proven by X-ray analysis, and to Wagner-Meerwein type rearranged 104, 106 could be detected. Its formation was best explained by breakdown of intermediate 107 into 108 ; although isolated yield of 106 was low (2 %), its isolation is interesting.




Finally, mention has to be made of reduction of polychlorinated 109 which yielded pyrrole 110. The following mechanistic pathway has been proposed[25].



## 4. Synthetic applications

Use of 2-azabicyclo[2.2.1]heptanes as aminocyclopentanes precursors and as such, their potential power has been elegantly demonstrated in the preparation of complex molecules by several workers. To illustrate this point the chemistry involved will now be described.

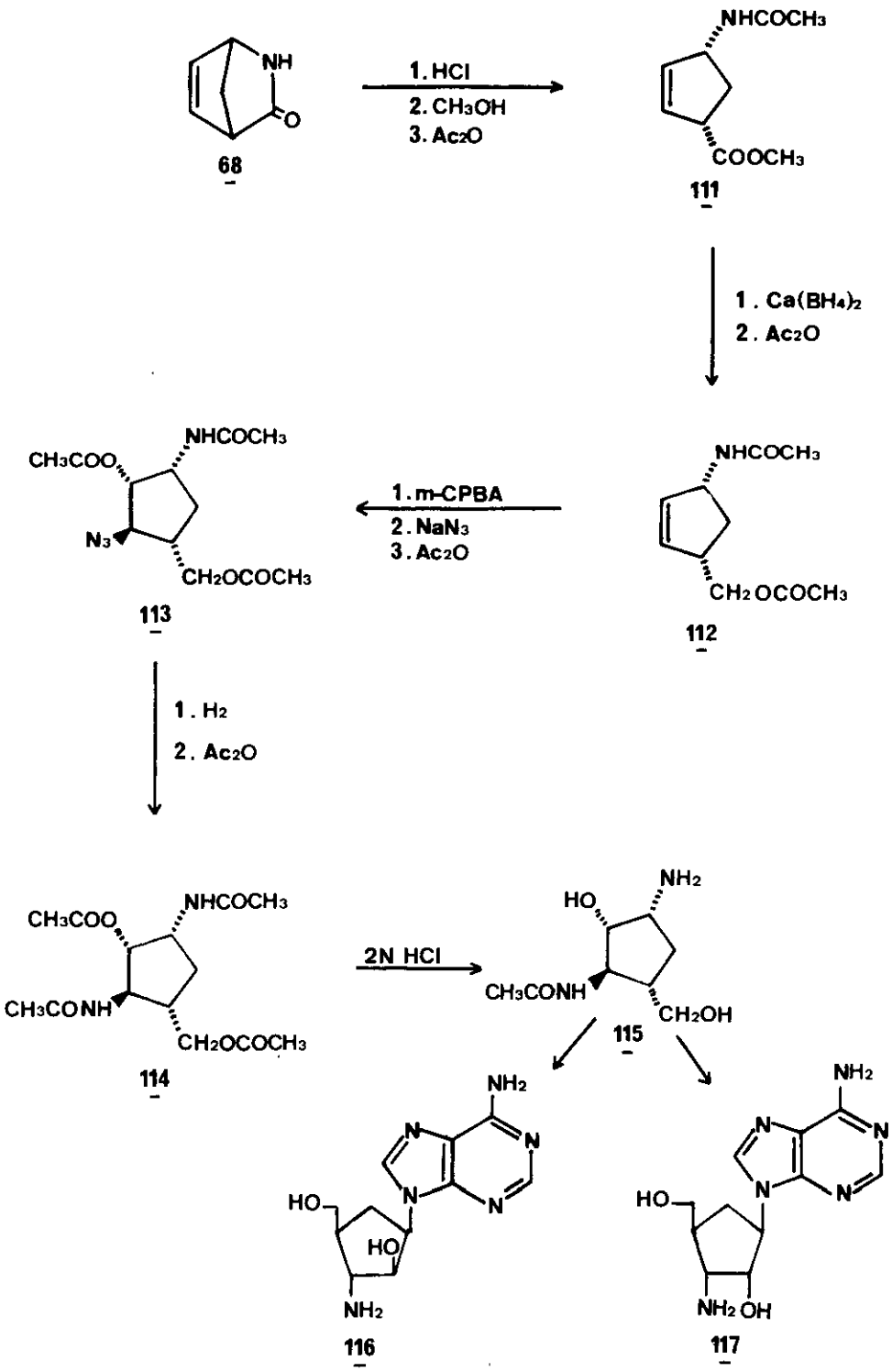
### a) Carbocyclic analogues of puromycin

Readily available lactam 68[19] was hydrolyzed to the corresponding cis-amino acid which was esterified and acylated in a conventional manner to give 111 in 89 % overall yield. Reduction of the ester group leaving intact the amide function was best performed with calcium borohydride. After acetylation 112 was obtained in 94 % yield. Epoxidation of the double bond followed by opening of the cis-epoxide by sodium azide gave predominantly 113. This was explained by attack of azide nucleophile at the position farthest from the acetamido group, which was presumably due to inductive effects. 113 was easily separated as its acetate. Catalytic hydrogenation of 113 followed by acetylation gave 114 in 84 % yield. The tetraacetyl derivative thus obtained was then selectively deacylated to 115 using somewhat mildly acidic conditions ; that one of the amides was more readily hydrolysed was best explained by the presence of a cis-hydroxyl group, and this avoided use of different protective groups for the two amino functions. The final steps of the synthesis depended on standard nucleoside chemistry : condensation of 115 with 5-amino-4,6-dichloropyrimidine, then ring closure with diethoxymethylacetate, and lastly amination of the intermediate chloropurine gave 116 after final deprotections. Epimerisation at C-2' (through an oxazoline intermediate) gave similarly access to the ribo analogue 117[64,69].

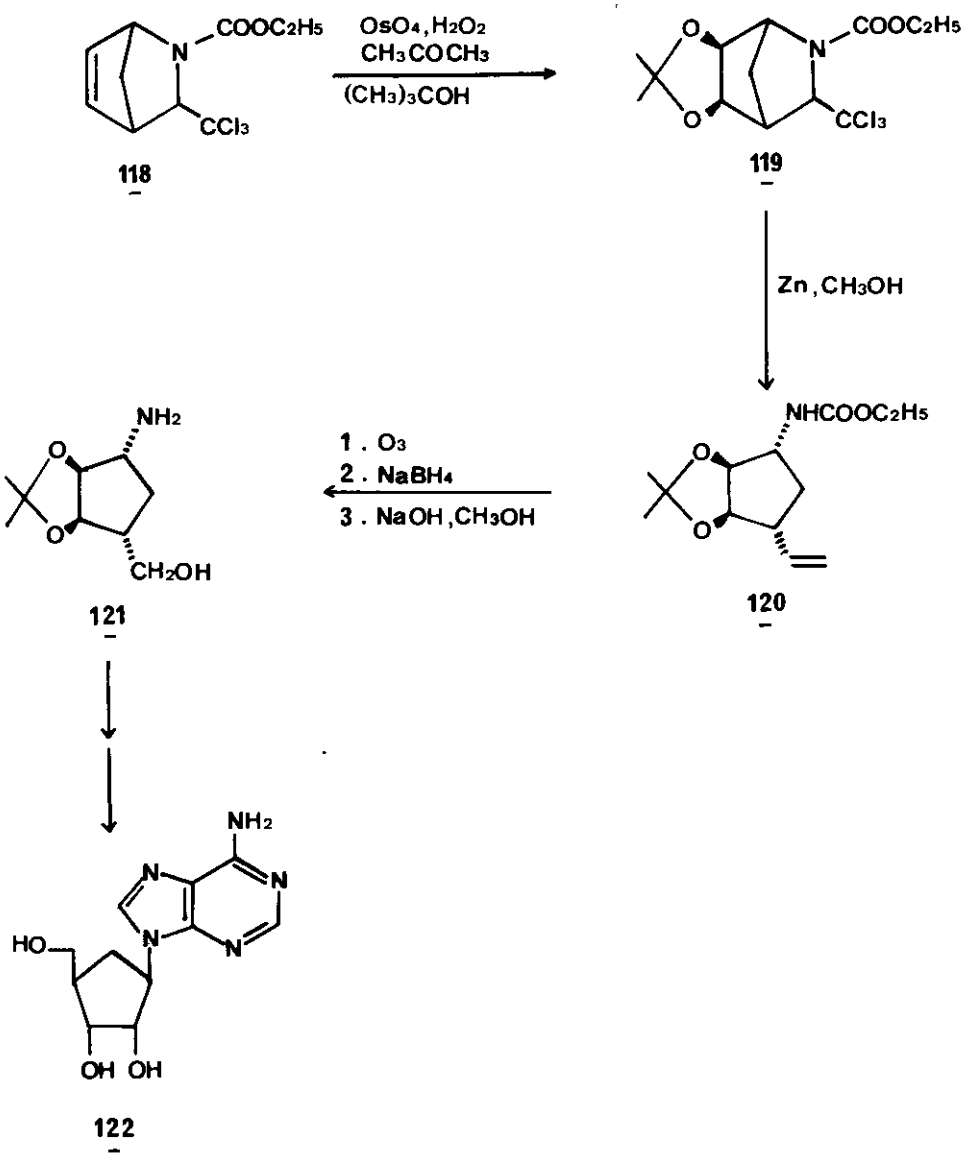
### b) Aristeromycin

A short total synthesis of this antibiotic has recently been proposed[68]. Starting with a mixture of endo and exo 118[11] catalytic osmylation in acetone gave endo and exo 119 in over 60 % yield. On refluxing with zinc powder in methanol, an interesting fragmentation reaction took place : halogen free olefin 120 was obtained in 57 % yield. The following steps of the synthesis were straightforward : ozonolysis of the double bond followed by reductive work-up and deprotection of the amine gave amino-alcohol 121. 121 is recognized as a synthetic intermediate of (±)-aristeromycin 122. This is an efficent and stereocontrolled synthesis.

**Synthesis of puromycin analogues**



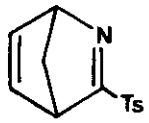
## Synthesis of aristeromycin




118 119 120 121 122

Synthesis of

(±)-methyl 3-(3-isocyano-6-oxabicyclo[3.1.0] hex-2-en-5-yl)-2-propenoate

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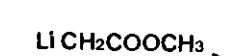


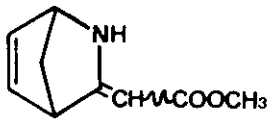


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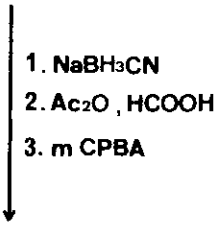


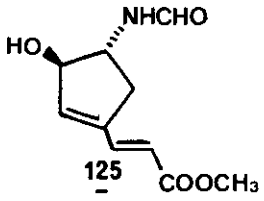


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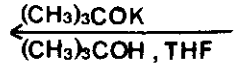


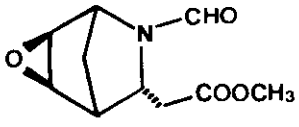


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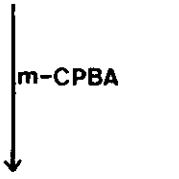


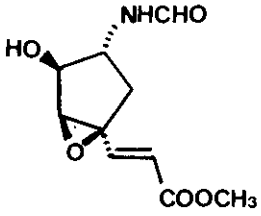


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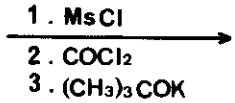


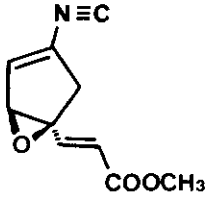


128

c) (±)-Methyl 3-(3-isocyano-6-oxabicyclo[3.1.0.]hex-2-en-5-yl)-2-propenoate

This unique structure was established by X-ray diffraction studies to a product which might be responsible for poor ruminant growth. Its synthesis which was recently announced[69] takes elegantly advantage of a unique fragmentation of appropriately substituted 2-azabicyclo[2.2.1] heptane 124. Latter compound had been obtained from known 76[19,65] as follows : reaction of 76 with 2 equivalents of methyl lithioacetate gave 123 in 81 % yield ; reduction in acidic medium of the conjugated double bond followed by N-formylation and epoxidation gave 124 in a 54 % overall yield. The key fragmentation step was performed by use of a large excess of potassium tert-butoxide, which caused ring opening as well as epoxide rearrangement, to give a 53 % yield of 125. Epoxidation of 125 could be performed regio- and stereospecifically to give 126 in 68 % yield. Final transformations to 127 involved hydroxyl elimination and elaboration of the isocyanide moiety.

## 5. Conclusion

2-azabicyclo[2.2.1]heptanes are now available by a number of synthetic methods. Among these, Diels-Alder cycloadditions for racemic material and internal nucleophilic displacement for chiral compounds are the most advantageous in terms of efficiency and versatility. The bicyclic systems thus obtained are of interest either intrinsically because of their rigidity or synthetically because of various ring opening and rearrangements which they are prone to. The synthetic potential of these compounds which some work has already elegantly demonstrated, seems promising, especially in the rich area of 5-membered ring compounds chemistry.

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