Chemistry of 3-Azabicyclo[3.3.1]nonanes

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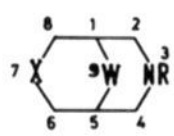
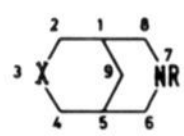
I. Introduction

Several 3-azabicyclo[3.3.1]nonanes (**1**), 3,7-diazabicyclo[3.3.1]nonanes (**2**), 3,9-diazabicyclo[3.3.1]nonanes (**3**), 3-oxa-7-azabicyclo[3.3.1]nonanes (**4**), and 3-thia-7-azabicyclo[3.3.1]nonanes (**5**), designated in this review,





1 X = CH_2, W = CH_2 (3-ABN)

2 X = NR, W = CH_2 (3,7-DABN)

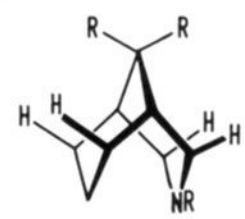
3 X = CH_2, W = NR (3,9-DABN)

4 X = O (3-O-7-ABN)

5 X = S (3-T-7-ABN)

respectively, as 3-ABN, 3,7-DABN, 3,9-DABN, 3-O-7-ABN, and 3-T-7-ABN, have been synthesized and studied widely in view of the various conformational possibilities and intramolecular interactions. They also occur in the skeleton of several diterpene alkaloids.[1-5]

The conformational analysis of azabicyclo[3.3.1]nonanes with substituents at the 9-position is complicated because of the close similarity of steric factors on both sides of the one-carbon bridge when the two rings adopt a chair–chair conformation (**6**). The case is different



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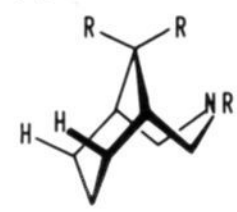

7

when the rings adopt chair–boat (**7**), boat–chair (**8**), or boat–boat (**9**) conformations, causing different steric

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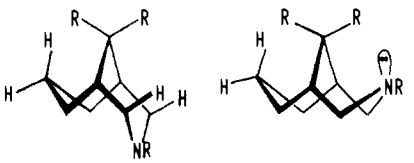
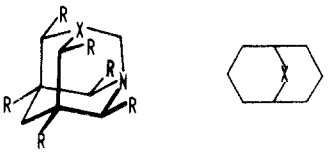


8 9

environments and intramolecular interactions for the 9-substituents. Compared with alicyclic and saturated heterocyclic six-membered rings which show marked differences in reactivities and physical properties between axial and equatorial epimers,[6-18] the 3-ABNs and related systems exhibit little difference between the 9-substituted epimeric pairs. However, specific methods of conformational analysis of these systems have been developed.

The close resemblence of aza- and diazaadamantanes (10) in conformation and stereochemistry[19-24] to the



10 X = CH or N 11 X = BR, NR, O or S

3-ABNs has caused significant progress in the azabicyclononane studies. The ease of formation of 3-ABNs from simple ketones and aldehydes through the Mannich reaction[25] without the involvement of complicated reaction conditions and reagents and the ready availability of a reactive carbonyl group in most of the ABNs prepared may also be considered as important reasons for the widespread studies on ABNs. However, 9-heterabicyclo[3.3.1]nonanes (11) have also been prepared and studied, and some of them (e.g., 9-borabicyclo-[3.3.1]nonane, 9-BBN) are even being used as synthetic reagents.[26-31] The stereochemical studies and conformational effects examined are of greater importance in 3-ABNs than in 9-ABNs. A number of patents on 3-ABN derivatives exist, indicating their usefulness in design of drugs.

Reviews on similar systems have appeared.[32-44]

II. Scope and Limitations

This review is confined to 3-azabicyclo[3.3.1]nonanes with additional heteroatoms, if any, at positions 7 and 9. Importance has been given to the synthetic methods, stereochemical investigations, and reactions. The literature has been reviewed through mid-1980. Probable mechanisms of reactions have been omitted. A few of the *Chemical Abstracts* descriptions of the patented syntheses and biological activities have been left out if found repetitive or of minor importance. In addition to these omissions, a few more could have resulted and, therefore, we offer our apologies in advance for any such inadvertent omissions.

III. Nomenclature

Bicyclic hydrocarbons having two rings with two common atoms take the name of the hydrocarbon with the same number of carbon atoms as the total number of ring atoms in the bicyclic system, irrespective of whether the ring atoms are carbon or other heteroatoms. For alicyclic systems the prefix bicyclo- is employed and for saturated heterocyclic systems an appropriate prefix, such as thiabicyclo-, azabicyclo-, etc., is employed. The prefix is immediately followed, within square brackets, by the number of ring atoms in each of the three rings connecting the two bridgeheads in descending order. The system is numbered commencing from one of the bridgeheads, proceeding along the longest possible ring (irrespective of the presence of any heteroatom) to the second bridgehead and from there along the next longer bridgehead to the first, and finally along the smallest bridge.

If two rings are of equal size, preference is given to that containing the heteroatom. If two rings of equal size contain two different heteroatoms, that containing the heavy heteroatom is numbered first if the heteroatoms belong to the same period. If they belong to the same group the light atom is numbered first.[45]

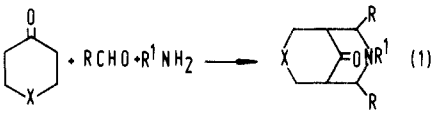
IV. Synthetic Methods

A. 3-Azabicyclo[3.3.1]nonanes

Synthesis through the Mannich reaction may be considered as one of the simple routes to many substituted 3-ABNs usually containing a carbonyl group at a suitable position so that many derivatives can be prepared easily. The 3-ABNs are also synthesized by α,α'-annelation of cyclic ketones or via enamines which usually lead to 6-substituted products often containing the secondary base from which the enamine is prepared. A less convenient and old method is cyclization of 1,3-disubstituted cyclohexanes. The last method also serves as a method of formation of 3-thiabicyclo[3.3.1]nonanes.

1. Mannich Reaction

Even though Mannich reaction[25] is one of the oldest reactions, most of the earlier literature reports deal with only acyclic or monocyclic disubstituted Mannich products. By this reaction, a six-membered cyclic ketone reacts with a primary amine and a suitable aldehyde to form 3-ABNs (eq 1). Sometimes instead of



(1)

the azabicyclic ketone disubstituted cyclic ketones are obtained. This happens mostly in concentrated solutions and when formaldehyde is the aldehyde component.

Baliah et al., following their synthetic and stereochemical studies[12,17,18,46-50] on 2,6-diarylpiperidin-4-ones (12), synthesized many azabicyclic compounds with

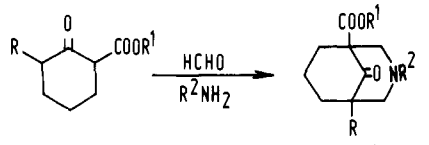
12 R = H, alkyl or aryl 13

heteroatoms at the 3 and 7 positions. Aromatic aldehydes have been employed as the aldehyde component.

In both piperidinone series and azabicyclic series the incorporation of two aryl groups makes the products

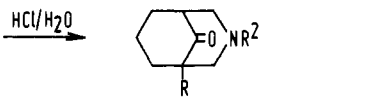
poorly soluble in common organic solvents. However, the two aryl groups are useful since 2,6-diarylpiperidines exist in a single chair conformation with the two aryl groups in 1,3-cis positions acting as conformation-holding groups (13). The two aryl groups in 3-ABNs keep the piperidine ring in either chair or boat conformation exclusively, the 3-ABNs stand as convenient models for the study of conformational effects at the 9 position.

With the use of formaldehyde or paraformaldehyde a large number of 3-ABNs have been prepared. Formaldehyde and phenethylamine react with an alcoholic solution of ethyl 3-methyl-2-oxocyclohexanecarboxylate (14) to yield ethyl 5-methyl-9-oxo-3-phenethyl-3-ABN-1-carboxylate (15). This after hydrolysis and decar-



14 R=CH$_3$, R^1=CH$_2$CH$_3$ 15 R=CH$_3$, R^2=CH$_2$Ph

16 R=COOCH$_3$, R^1=R^2=CH$_3$

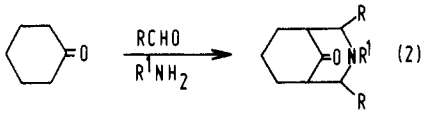


17 R=CH$_3$, R^2=CH$_2$Ph

18 R=H, R^2=CH$_3$

boxylation gives 1-methyl-3-phenethyl-3-ABN-9-one[51] (17). Similarly, dimethyl 2-oxo-cyclohexane-1,3-decarboxylate condenses with formaldehyde and methylamine to yield the 3-ABN 16[52,53] which on hydrolysis produces the amino ketone 18.[54,55] Instead of methylamine, phenethylamine has also been used.[56]

The difficulties encountered in the earlier synthesis of 3-ABN-9-ones employing 2-oxocyclohexane-1,3-dicarboxylic esters were surmounted in the synthesis of 3-alkyl-3-ABN-9-one (19) directly from cyclohexanone[57] (eq 2). Use of ammonium acetate instead of primary



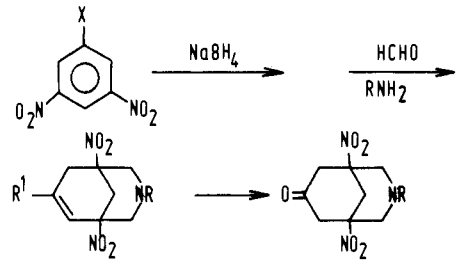
(2)

19 R=H, R^1=CH$_3$

20 R=Aryl, R^1=H

amine and an aromatic aldehyde for formaldehyde results in the formation of 2,4-diaryl-3-ABNs (20) along with diarylidenecyclohexanones.[58-60] Two crystalline modifications of 20 have been isolated.[61] Cyclopentanone fails to condense in a similar way,[62] while 4-alkylcyclohexanones, 2-alkylcyclohexanones, and 2-decalone yield substituted 3-ABNs.[63]

Not only carbonyl compounds but 1,3-dinitrocyclohexanes also have been employed for the synthesis of 3-ABNs. The amide 21 has been synthesized by reducing 3,5-dinitrobenzamide with $NaBH_4$ followed immediately by Mannich condensation with methylamine and formaldehyde.[64] A solution of 21 in methanol or THF, on treatment with sodium hypochlorite and dilute HCl, yields the amino ketone 25. By a similar reduc-



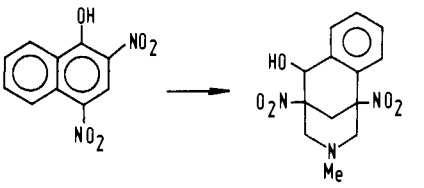
21 R=CH$_3$, R^1=CONH$_2$ 25 R=CH$_3$

22 R=CH$_3$, R^1=OCH$_3$ 26 R=CH$_2$CH$_3$

23 R=CH$_2$CH$_3$, R^1=OCH$_3$ 27 R=CH$_2$Ph

24 R=CH$_2$Ph, R^1=OCH$_3$

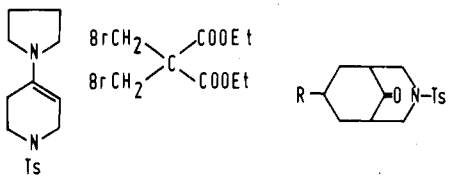
tion and condensation method 3,5-dinitroanisole forms the vinyl ether 22 which on hydrolysis gives 25. This method is also employed for the formation of vinyl ethers 23 and 24 by use of ethylamine and benzylamine, respectively.[64] The amino ketones 26 and 27 are obtained by acid treatment of 23 and 24. The nitronaphthol 28 produces a 3-ABN (29) while with 2,4-dinitrophenol complicated reactions occur.[64]



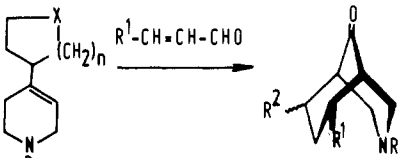
28 29

2. By α,α'-Annelation of Cyclic Ketones or through Enamines

With the development of enamine syntheses, formation of 3-ABNs has become possible through this route. The pyrrolidine enamine (30) of *N*-tosylpiperidin-4-one reacts with $(BrCH_2)_2C(COOEt)_2$ in the presence of 1 equiv of Et_3N to give 80% 3-ABN-9-one[65,66] (31). The



30 31 R=COOEt



32 R=CH$_3$, CH$_2$Ph 33 R=CH$_3$, CH$_2$Ph

X=O, CH$_2$; n=1,2 R^2=pyrrolidinyl

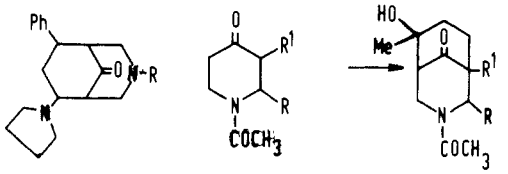
R^1=H, Me, Ph morpholinyl

piperidinyl

tetrahydropyridines (32) react with acrolein to give 6-substituted 3-ABN-9-ones[67,68] (33). Crotonaldehyde has been used instead of acrolein. By a similar treatment, cinnamaldehyde forms 6,8-disubstituted 3-ABNs[69] (34).

Michael addition of methyl vinyl ketone to 1-acetyl-2-benzoyl-3-carbethoxy-4-piperidinone (35) in the presence of triethylamine in methanol produces 1-carbethoxy-2-benzoyl-3-acetyl-6-methyl-6-hydroxy-3-

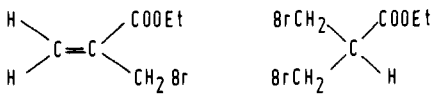
ABN-9-one[70] (36). This reaction has been investigated



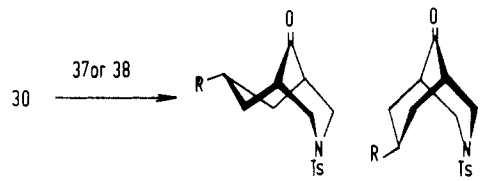
34 35 R = COPh, R¹ = COOEt 36 R = COPh, R¹ = COOEt

by UV spectrophotometry, and the rate of the reaction is found to be proportional to the concentration of the enolate form of 35.

When ethyl α-(bromomethyl)acrylate (37) or β,β'-dibromoisobutyrate (38) is condensed with the enamine of N-(arylsulfonyl)piperidinone (30), N-tosyl-3-ABN derivatives (39, 40) are obtained.[71] When the reaction



37 38



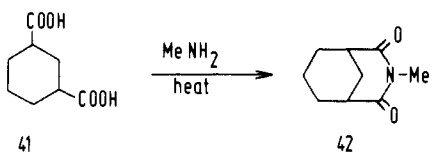
39 40

is carried out by adding the bromo ester 37 in ethanol to a refluxing solution of enamine in acetonitrile, the yield of 3-tosyl-3-ABN-9-one is about 58%. Alternatively, in the reaction of enamine with bromo ester 38, in acetonitrile to which 2.2 equiv of triethylamine have been added, the yield increases to 80%. The lower yield in the first case may be due to elimination of HBr from the ester before cyclization.[71]

3. By Intramolecular Cyclizations

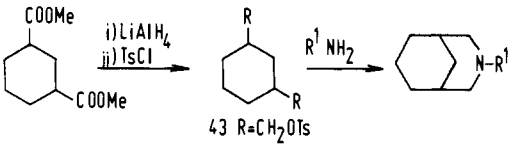
Monocyclic compounds with suitable 1,3-substituents undergo intramolecular reactions with cyclizing agents to form 3-ABN derivatives. Cyclohexane-1,3-dicarboxylic acid and its derivatives have been used for the formation of both 3-aza- and 3-thiabicyclo[3.3.1]-nonanes. In most of the earlier work isophthalic acid was the essential starting material for the formation of 1,3-disubstituted cyclohexanes.

Cyclohexane-1,3-dicarboxylic acid (41) on treatment with ammonia or a primary amine forms the corresponding N-alkyl-3-ABN-2,4-dione[72,73] (42).



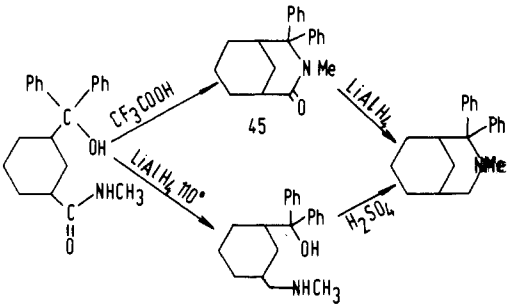
41 42

Hexahydroisophthalic acid (41) reacts with acetyl chloride and then with an amine to yield 42. The amine may be alkyl or dimethylaminoalkyl or an arylamine.[74] Similarly, hexahydroisophthalic anhydride reacts with N,N-dimethylcadaverine to form N-(5-dimethylamino-amyl)-3-ABN.[75] All the substituted 3-ABN-2,4-diones have been reduced by using $LiAlH_4$. Another earlier route to N-alkyl-3-ABNs is the cyclization of the ditosylate of *cis*- and *trans*-1,3-bis(hydroxymethyl)cyclohexanes (43) with an amine.[76]



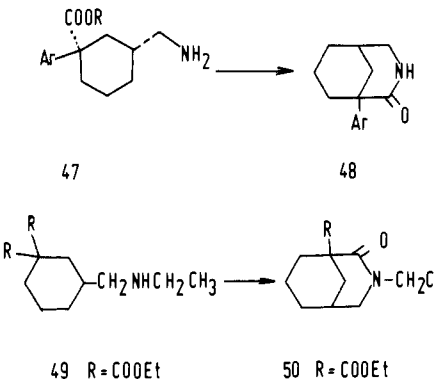
43 R = CH_2OTs

Intramolecular acid-catalyzed cyclization of suitable 1,3-bifunctional cyclohexanes also yields 3-ABNs.[77,78] The amide 44 on treatment with CF_3COOH gives the 3-ABN-2-one 45 which can be reduced to 2,2-diphenyl-3-ABN (46). Alternatively, 44 is reduced with



44 46

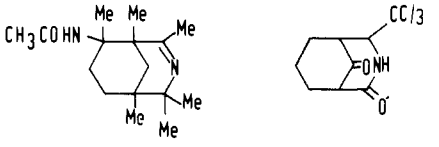
$LiAlH_4$ and then treated with 30% H_2SO_4 to yield 46. The amine 47 cyclizes to give 1-aryl-3-ABN-2-one (48). N-Ethyl-(3,3-dicarbethoxycyclohexyl)methylamine (49) is formed in 50% yield on heating for 20 h under reduced pressure.[79]



47 48

49 R = COOEt 50 R = COOEt

The reaction of 2,3-dimethyl-1,3-butadiene with acetonitrile in the presence of sulfuric acid gives the 3-azabicyclo[3.3.1]nonene 51.[80,81] Enamines react with



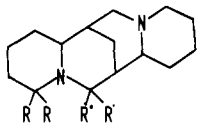
51 52

1,2,2,2-tetrachloroethyl isocyanate, yielding 3-ABN-2,9 dione (52) through an intramolecular substitution.[82]

B. 3,7-Diazabicyclo[3.3.1]nonanes

This is one of the oldest azabicyclic systems synthesized through the Mannich reaction[25,83,84] and from pyridine derivatives.[85] Petrenkokrischenko has obtained 3,7-DABNs (bispidines) as byproducts during the preparation of piperidin-4-ones from ketones, aldehydes, and amines.[25] In recent years the bispidines have

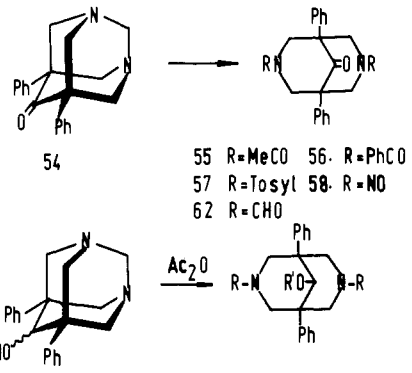
attracted attention for study of their crystal structures, stereochemistry, intramolecular interactions, formation from 1,3-diazaadamantanes, and conversion to diazaadamantanes. The 3,7-DABN skeleton is present in lupin alkaloids[1-5] (53).



53 Sparteine (R = R' = H)
Lupanine (RR' = =O, R' = H)
Aphylline (R = H, R'R' = =O)

1. By Ring Fission of Diazaadamantanes

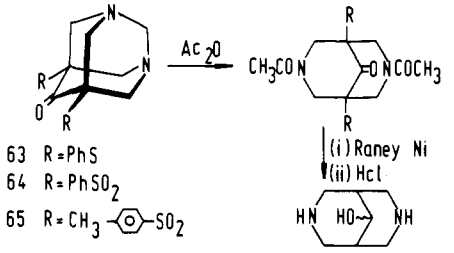
Diazaadamantanes cleave under acidic conditions to yield 3,7-DABNs. Reaction of 5,7-diphenyl-1,3-diazaadamantan-6-one (54) with acetic anhydride or acetyl chloride produces 3,7-diacetyl-1,5-diphenyl-3,7-DABN-9-one[22,86,87] (55). Reaction of 5,7-diphenyl-1,3-diazaadamantan-6-ol (59) with acetic anhydride gives either 1,5-diphenyl-3,7-diacetylbispidin-9-ol (60) or 1,5-diphenyl-3,7,9-triacetylbispidine (61) depending upon the conditions.[88,89] The diazaadamantanone reacts with benzoyl chloride also, yielding 3,7-dibenzoyl-3,7-DABN[22] (56). Similarly, it reacts with a variety of other reagents also such as *p*-toluenesulfonyl chloride and nitrous acid to give substituted 3,7-DABNs[22,89] (57, 58). Dichlorocarbene in alkaline medium reacts with 54, yielding 1,5-diphenyl-3,7-diformyl-3,7-DABN-9-one[90] (62).



54 55 R = MeCO 56 R = PhCO
57 R = Tosyl 58 R = NO
62 R = CHO

59 60 R = CH_3CO, R' = H
61 R = R' = CH_3CO

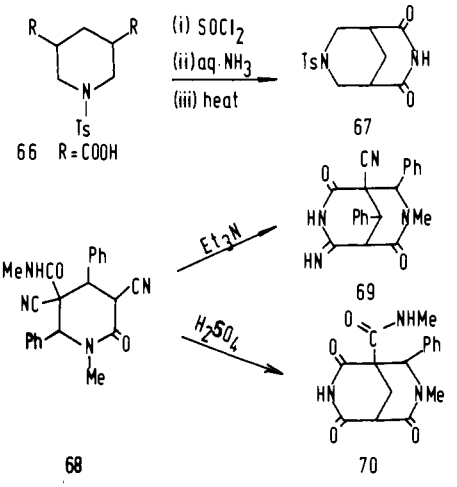
Diazaadamantanes with sulfur-containing substituents at 5,7 positions (63–65) are also cleaved by acetic anhydride[91,92] to yield bispidine derivatives.



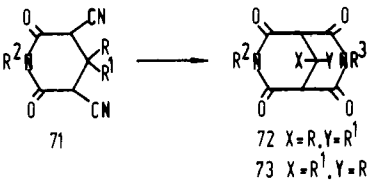
63 R = PhS
64 R = $PhSO_2$
65 R = CH_3-C$_6$H$_4$-SO_2

2. By Intramolecular Cyclizations

N-Tosylpiperidine-3,5-dicarboxylic acid (66) on conversion to the acid chloride and treatment with ammonia forms the diamide of 66, which on heating produces 67.[91,93,94] The 1-cyano derivative 69 and 1-methylcarbamoyl derivative 70 could be easily obtained from 1-methyl-4,6-diphenyl-5-(methylcarbamoyl)-3,5-dicyanopiperidin-2-one (68) by treatment with triethylamine and sulfuric acid, respectively.[34,95] Similarly, the imide 71 forms isomeric diimides 72 and 73 when treated with H_2SO_4.[96,97]



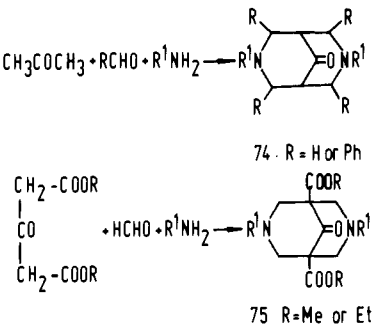
66 R = COOH
67
68
69
70



71
72 X = R, Y = R^1
73 X = R^1, Y = R

3. Mannich Reaction

A mixture of acetone, a suitable aldehyde, and a primary amine in the ratio of 1:4:2 yields bispidine derivatives (74). Acetonedicarboxylic acid and its esters may be employed in the place of acetone. Dimethyl or diethyl acetonedicarboxylate reacts with formaldehyde and primary amine to yield dimethyl or diethyl 3,7-dialkyl-9-oxo-3,7-DABN-1,5-dicarboxylate (75) at a pH below 6.[84,98-101] The primary amines employed frequently are ethylamine, methylamine, and benzylamine. Benzylamine is found to react more readily with HCHO and ketones than do most primary amines.[102]

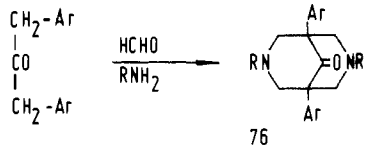


74 R = H or Ph

75 R = Me or Et

The 3,7-DABNs can also be prepared in two steps, first by synthesizing the piperidin-4-one and then by condensing it with suitable aldehyde and amine components.[98] By this stepwise method different pairs of substituents may be incorporated in the rings.

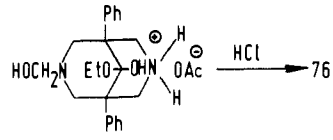
Dibenzyl ketone has also been used to a larger extent as the ketone component in the Mannich reaction. In this way 1,5-diaryl-3,7-DABN-9-ones (76) are obtained.[103] The aryl group may be phenyl, *p*-chlorophenyl, *p*-anisyl, or *o*-methoxyphenyl groups.[101,104-108] The Mannich reaction between dibenzyl ketone and a



76

series of ammonium salts indicates that the reaction does not depend on the type of ammonium salt used.

In the reaction of dibenzyl ketone, paraformaldehyde, and ammonium acetate 1,5-diphenyl-3-hydroxymethyl-9-ethoxy-9-hydroxy-3,7-DABN acetate (77) is



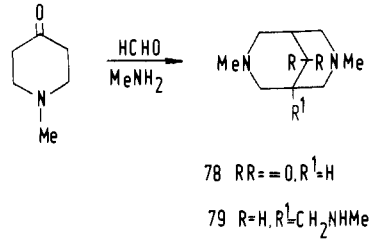
77

also formed sometimes, along with the normal product.[108,109] However, 77 can be converted to 76 by treatment with 4 N HCl.

Dibenzyl ketone after nitration also undergoes Mannich reaction to give the corresponding 3,7-DABNs.[110]

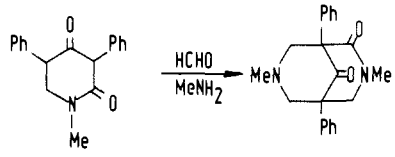
On introduction of methyl substituents in the ortho positions of the phenyl groups of dibenzyl ketone the ease of formation of 3,7-DABN decreases. Bispidines are formed from 1-phenyl-3-(*o*-tolyl)-propan-2-one almost as easily as from 1,3-diphenylpropan-2-one. With 1,3-bis(*o*-tolyl)propan-2-one the two products, 3,7-DABN and piperidinone, are formed in a 1:2 ratio. As the number of *o*-methyl groups increases further, even piperidinones are not formed.[111]

Treatment of 1-methylpiperidin-4-one with formaldehyde and methylamine gives a mixture of 78 and 79.[112] When acetic acid is employed as the solvent, only



78 RR=O, R¹=H

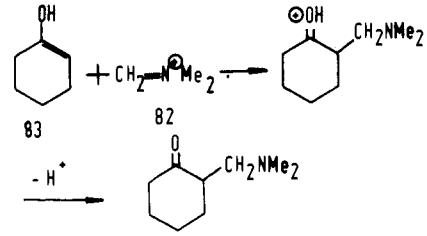
79 R=H, R¹=CH₂NHMe



80 81

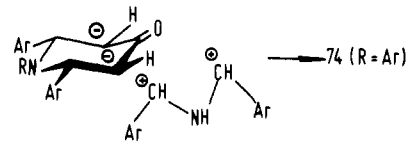
78 is obtained, in 10% yield. 3,7-DABN-2,9-dione (81) is obtained when 80 condenses with formaldehyde and methylamine.[113]

The mechanism of the Mannich reaction is believed[114,115] to involve electrophilic attack by an iminium salt (e.g., 82) on the enol (e.g., 83) of the active methylene compound. This mechanism requires stepwise reaction, condensation at one α position of the ketone followed by an intramolecular condensation at the second α position, in order that 3-ABNs are formed. However, in the formation of diaryl- and tetraaryl-3-ABN derivatives, the bulkiness of the substituent (84) may resist flipping needed for further condensation from axial side. The formation of ABNs from conformationally rigid systems suggests a concerted reaction of the diiminium salt (86) with the dicarbanion (85) of the ketone. The arylidenecyclohexanones formed[60] along with 3-ABNs are due to stepwise reaction.



83 82

84

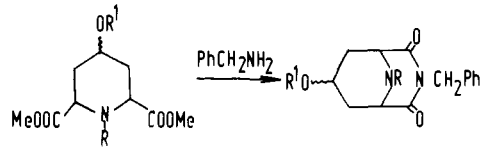


85 86

C. 3,9-Diazabicyclo[3.3.1]nonanes

The 3,9-DABN skeleton has been built up mostly by cyclization reactions employing piperidine-2,6-dicarboxylic acid and its derivatives as starting materials. The interest in 3,9-DABN is very narrow except that Nikitskaya et al. have studied the biological effects of several 3,9-DABN derivatives.[116-120]

Dimethyl 4-hydroxy-1-methylpiperidine-2,6-dicarboxylate (87) reacts with benzylamine at high temperatures to yield 3-benzyl-9-methyl-3,9-DABN-2,4-dione derivatives[121-124] (90). Similarly, 1-benzyl-



87 Me, R¹=H

88 R=CH₂Ph, R¹=H

89 R=CH₂Ph, R¹=Me

90 R=Me, R¹=H

91 R=CH₂Ph, R¹=H

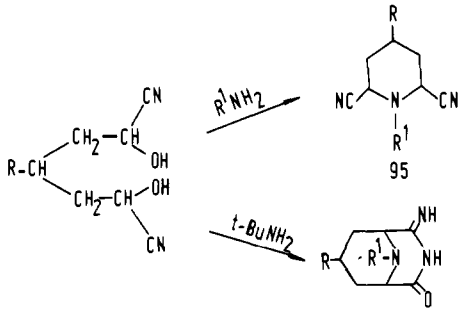
92 R=CH₂Ph, R=Me

piperidine 88 gives 91.[125] The benzyl group at the 3 and 9 positions is readily removed by treatment with palladium chloride and hydrogen. The 4-methoxypiperidine derivative 89 gives the 7-methoxy-3,9-DABN 92.[126]

Reaction of the dicyanohydrins (93 and 94) of glutaraldehyde and methylglutaraldehyde with simple alkylamines yields 2,6-dicyanopiperidines (95) whereas with *tert*-butylamine the 3,9-DABN derivative 96 is also obtained as a byproduct.[127]

D. 3-Oxa-7-azabicyclo[3.3.1]nonanes

The 3-O-7-ABNs have also been obtained through a Mannich reaction by condensing a tetrahydropyran-4-one with an aldehyde and an amine. Condensation of *cis*- and *trans*-2,6-diphenyl-tetrahydropyran-4-ones (97)

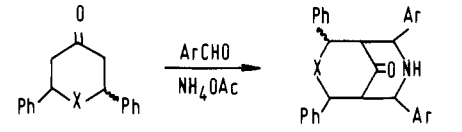


93 R=H
94 R=Me

96 R^1 = t-Bu

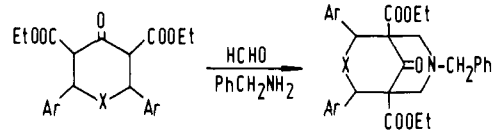
95

with aromatic aldehydes and ammonium acetate yields 2,4-diphenyl-6,8-diaryl-3-O-7-ABN-9-ones[128,129] (98).



97 X=O
103 X=S

98 X=O
104 X=S

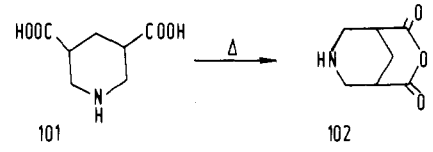


99 X=O
105 X=S

100 X=O
106 X=S

Condensation of 3,5-dicarbethoxy esters (99) with HCHO and benzylamine gives 100.[130,131]

The cyclic anhydride (102) of *cis*-piperidine-3,5-dicarboxylic acid (101) may be regarded as a 3-O-7-ABN derivative.[132]



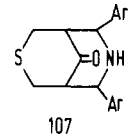
101

102

The interesting fact in 2,4-diphenyl-3-O-7-ABNs and 3-T-7-ABNs is that both cis and trans derivatives have been obtained[128,129] and studied whereas in 3-ABNs and 3,7-DABNs only cis products have been obtained. This is due to the availability of both *cis*- and *trans*-2,6-diaryltetrahydropyranones and 2,6-diaryltetrahydrothiopyranones for condensation while only *cis*-2,6-diarylpiperidin-4-ones are available. Since the piperidones are formed by Mannich condensation through fast equilibrium steps, the more stable 2,6-diequatorial products are formed. On the other hand, in the formation of either 2,6-diaryltetrahydropyranone or 2,6-diaryltetrahydrothiopyranone stepwise addition of H_2O or H_2S across double bonds conjugated to carbonyl groups leads to both cis and trans products depending upon the direction of addition in the second step.

E. 3-Thia-7-azabicyclo[3.3.1]nonanes

Interest on 3-T-7-ABNs is much less than that of 3-ABNs and 3,7-DABNs. Almost all the 3-T-7-ABNs have been prepared through the Mannich reaction. 2,4-Diphenyl-6,8-diaryl-3-T-7-ABN-9-ones (104) are formed when *cis*- or *trans*-2,4-diphenyltetrahydrothiopyran-4-ones (103) are condensed with aromatic aldehydes and ammonium acetate in ethanol.[133,134] Similarly, condensation of 105 with formaldehyde and benzylamine in ethanol results in diethyl 2,4-bis(2-pyridyl)-7-benzyl-9-oxo-3-T-7-ABN-1,5-dicarboxylate[130,135,136] (106). Simple tetrahydrothiopyranone condenses with an aldehyde and ammonium acetate to yield 6,8-diaryl-3-T-7-ABN-9-one[136a] (107).



107

V. Stereochemistry

A. Introduction

Apart from a few distorted structures, substituted bicyclo[3.3.1]nonanes exist in any of the three conformations 108–110, all of which are free from bond-angle

Chair-Chair 108 | Chair-boat 109 | boat-boat 110

strain. In most cases the chair–chair conformation with slight ring flattening is favored.[137-140] In the twin-chair conformation the actual distance between the C-3 and C-7 carbons is 3.06 Å while the ideal value is 2.52 Å. Flattening occurs in order to minimize the transannular interaction between the endo-axial hydrogen atoms at the C-3 and C-7 positions. If these hydrogens are replaced by bulky groups, one of the rings assumes a boat form.

In heterocyclic systems the possibility of a six-membered ring acquiring the boat conformation is higher due to the decrease in some of the interactions present in the boat form of cyclohexane and also due to intramolecular hydrogen bonding and other attractive interactions between the heteroatoms and the substituent.

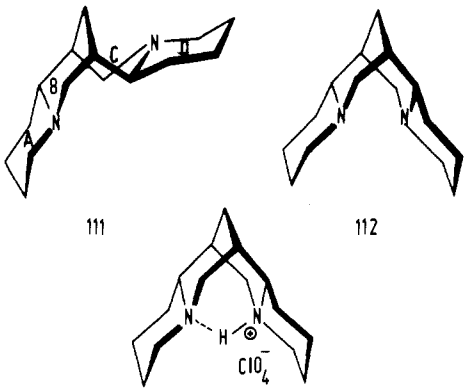
Various methods such as IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy, X-ray diffraction, dipole moment measurements, polarizability, kinetic methods, and pK_a measurements have been employed for the determination of conformation and configuration of 3-ABN compounds.

The conformations of alkaloids containing the DABN skeleton have also been studied. The C rings of sparteine (111) and α-isosparteine (112) have been shown to prefer the boat and chair conformations, respectively.[141-145] However, the monoperchlorate (113) of sparteine adopts the chair–chair conformation.[141,145a]

B. Determination of Conformations and Configurations

1. IR Spectroscopic Method

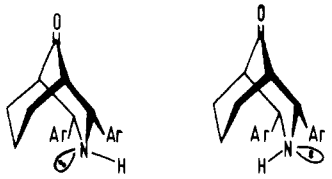
The IR spectra of 3-ABNs in the region of C–H stretching vibrations contain additional bands that are shifted to the low-frequency region relative to the



111 112 113

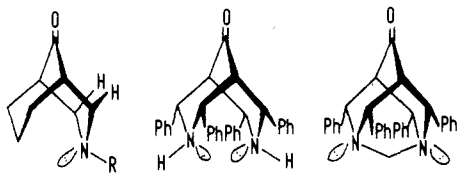
normal C–H stretching vibrations.[61] These bands were first detected by Bohlmann[146] and therefore are known as Bohlmann bands. Bohlmann bands arise because of interaction of the p electrons of nitrogen with the anticoplanar C–H bonds in piperidine derivatives.[147,148] In a conformer with an axial p pair of electrons on nitrogen, the p pair forms a trans arrangement with axial C–H bonds,[149,150] whereas in the conformer with an equatorial p pair on nitrogen, the p pair forms only a gauche arrangement with both the axial and equatorial C–H bonds.

Crystals of different forms (**114**, **115**) have been isolated by recrystallizing 2,4-diphenyl-3-ABN-9-one in a nonpolar solvent and polar solvent, respectively.[151-153] The IR spectra of crystalline samples of **114** and **115** differ substantially in the region of C–H stretching vibrations.[61] The IR spectrum of a sample of **114** in this region contains eight bands, four of which lie in the Bohlmann region (2750, 2790, 2810, and 2840 cm^{-1}), whereas the IR spectrum of a sample of **115** contains two bands in the C–H stretching region (2860 and 2927 cm^{-1}) but no absorption bands in the Bohlmann region.



114 115

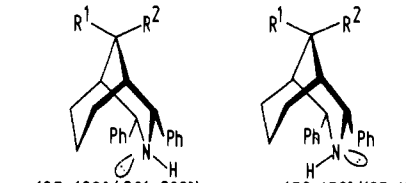
The unsubstituted 3-methyl-3-ABN-9-one and 2,4,6,8-tetraphenyl-3-ABN-9-one also exhibit Bohlmann bands.[57,61] The former shows three peaks in the 2600–2800-cm^{-1} region (2800, 2750, 2700 cm^{-1}). This indicates that the favored conformation has at least two hydrogen atoms trans and coplanar with the unshared electron pair on the nitrogen atom. The conformation is, therefore, represented by **116**. From the point of view of the orientation of the p electrons on nitrogen, 3,7-DABN-9-ones and diazaadamantan-9-ones may be regarded as epimers (**117**, **118**).



116 117 118

A quantitative study of the 2900–2500-cm^{-1} region of the IR spectra of 15 alkaloids of the sparteine series[154] has confirmed the suggestion that the area under which "trans bands" (T bands) occur is from just below 2800–2700 cm^{-1}. It has been suggested that the lower frequency of the T band compared with the normal C–H region may be due to charge delocalization of the nitrogen lone pair of electrons to the α axial C–H bonds.[154]

The conformational effect of the p pair in 2,4-diphenyl-3-ABN-9-ols,[155] obtained by catalytic hydrogenation of the ketone, on the IR spectra has been examined.[156] In the high-melting isomer (**119**) the lone pair was expected to be oriented endo to the ring and thus cause Bohlmann bands.[146,157] In the low-melting isomer, the lone pair was postulated to be equatorial. The C–O stretching absorption band for the isomer **119** is at low frequency (1031 cm^{-1}) and is narrower than the analogous band (1062 cm^{-1}) for isomer **120**. This has led to the idea that the high-melting isomer has OH to the side of the piperidine ring (**119**) and the low-melting isomer has OH equatorial to the piperidine ring. This view has been arrived at by two independent groups who employed IR and ^1H NMR spectroscopic data.[156,158,159] But ^{13}C NMR studies[160] conclusively establish that the configurations are the reverse of those represented by **119** and **120**. The basis for assigning structures **121** and **122** can be found in the section on ^{13}C NMR spectroscopy.

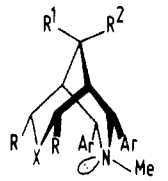


mp 195-196° (201-202°) mp 158-159° (135-136°)

119 R^1=OH, R^2=H 120 R^1=H, R^2=OH

121 R^1=H, R^2=OH 122 R^1=OH, R^2=H

In the *N*-methyl derivatives of 2,4-diaryl-3-ABNs, 2,4-diphenyl-6,8-diaryl-3,7-DABNs, and 2,4-diphenyl-6,8-diaryl-3-T-7-ABNs, the appearance of the Bohlmann bands indicates that the lone pair is axial and the *N*-methyl equatorial (**123**) in all the cases irrespective of whether the aryl groups possess ortho substitutents or para substituents.[161] This offers additional support to chair–chair conformation for these compounds.

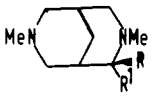


123 R=H, Ph

X=CH_2, NH, S

123a R^1=OH, R^2=CH_2COOEt

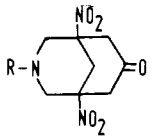
Comparison of the IR spectra of *N*,*N*′-dialkylbispidines[162] with those of **124**, **125**, and **126** indicates considerable similarity in regard to appearance and intensity of Bohlmann (trans) bands centered at 2778 cm^{-1}. The intensity of these bands is proportional to the number of C–H bonds anticoplanar to the nitrogen lone pairs.[163] On the basis of the number and intensity of Bohlmann bands it has been concluded that **124**, **125**,



124 R=H, R^1=Me
125 R=H, R^1=i-Pr
126 R=Me, R^1=H

and **126** have the same number of C–H bonds anticoplanar to the nitrogen lone pair and that the 2-alkyl substituents in these compounds are equatorial.

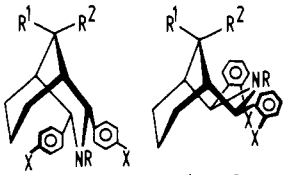
The IR spectra of 3-alkyl-1,5-dinitro-3-ABN-7-ones have been examined.[64] Since the carbonyl stretching frequencies of the amino ketones **127**, **128**, and **129** are



127 R=Me
128 R=Et
129 R=Ph

identical in $CHCl_3$ and exhibit a negligible variation in CCl_4, it has been suggested that the amine and carbonyl functions in these compounds exert no interaction on each other. The values are higher (1732 ± 3 cm^{-1}) than simple 3-ABNs (1717 and 1706 cm^{-1})[164] but of the same order as 1,5-diphenylbicyclo[3.3.1]nonane-3,7-dione.[137]

The epimeric pairs of 3-ABN-9-ols (**130** and **131**) with

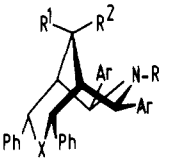


130 R^1=H, R^2=OH
131 R^1=OH, R^2=H
132 R^1=H, R^2=OH
133 R^1=OH, R_2=H

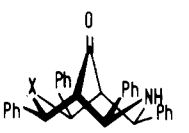
phenyl or para-substituted phenyl groups at 2 and 4 positions show broad absorption bands due to bonded OH. Since each pair shows the same type of absorption, the conformation of these alcohols is expected to correspond to twin-chair.[158] The isomer ratios of the alcohols in the MPV and sodium–alcohol reductions,[165] relative rates of acetylation[159] of alcohols, relative rates of hydrolysis of the esters,[166] dipole moment studies,[167] and ^1H NMR,[168] ^{13}C NMR,[160] and mass[169] spectral studies support this view.

However, the proposed chair–boat conformation for the 3-ABN-9-ols with ortho-substituted aryl groups at the 2 and 4 positions[158,159,165,166] (**132** and **133**) are contradictory to ^1H NMR,[168] ^{13}C NMR,[160] and mass[169] spectral data. The two hydroxyl bands, one at 3520–3500 cm^{-1} and another at 3570 cm^{-1}, interpreted[158] as due to intermolecular and intramolecular hydrogen bonding, respectively, may actually be due to intermolecularly bonded and nonbonded hydroxyls. Since ^{13}C NMR data establish[160] the conformation as twin-chair as in the case of other 2,4-diaryl-3-ABNs, the nonbonded OH might have resulted out of hindrance by the ortho substituents of the aryl groups when they are oriented toward OH.

The IR spectra of 2,4,6,8-tetraphenyl derivatives of 3-ABN, 3,7-DABN, 3-T-7-ABN, and 3-O-7-ABN have been examined and the configurations of the ABN-9-ols (**134** and **135**) established. Presence of intramolecular



134 R^1=H, R^2=OH
135 R^1=OH, R^2=H

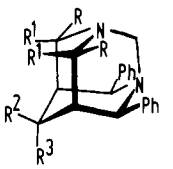


136

hydrogen bonding, between the 9-OH group and the nitrogen, in the β forms indicates that the newly formed piperidine ring is in boat conformation and that the OH in β forms is endo to the boat side[134] (**134**).

The α isomers show a free OH, indicating that the OH is oriented to the chair side (**135**). However, the α isomers of 3-T-7-ABN show intermolecular H bonding.[134]

Azerbaev et al. have proposed a twin-boat conformation (**136**) for 2,4,6,8-tetraphenyl-3,7-DABN-9-one[59] and a twin-chair conformation for the corresponding alcohols.[135,136] It has also been stated that the tetraphenylbispidines were converted to tetraphenyldiazaadamantanes[24,137] (**137**). The fact that two alco-



137 R^1=H, R=Ph
R^2=H, R^3=OH
138 R=R^1=Me
R^2=R^3=H

hols have been obtained[134] from tetraphenylbispidines supports the chair–boat conformation. The other two conformations, chair–chair and boat–boat, would give only one alcohol. Moreover, Dreiding models of 4,8,9,10-tetraphenyl-1,3-diazatricyclo[3.3.1.$1^{3,7}$]decan-6-ol[136] (**137**) and 4,4,10,10-tetramethyl-8,9-diphenyl-1,3-diazatricyclo[3.3.1.$1^{3,7}$]decane[170] (**138**) show severe interactions. Hence it appears that the chair–boat conformation is more probable for tetraphenyl-3,7-DABNs. The various postulates need to be confirmed.

Epimeric 3-methyl-3-ABN-9-ols (**139**, **140**) show no

139 R^1=H, R^2=OH
140 R=OH, R^2=H

evidence of intramolecular hydrogen bonding and therefore have been assigned the chair–chair conformation.[171]

2. ^1H NMR Spectroscopy

Proton magnetic resonance (^1H NMR) spectroscopy has proved to be very effective in resolving conformational and configurational features in azabicyclic sys-

tems.[172-174] More recently carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy has been shown to be a powerful tool for such studies.[172,175-185]

Equilibrium constants for chair–chair to chair–boat transformations of 3-methyl-3-ABN hydrochloride (141) and 3-benzyl-3-ABN hydrochloride (142) have been

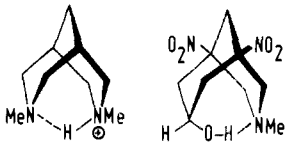
141 R=Me

142 R=PhCH$_2$

determined from NMR spectral measurements.[186] 141 is found to exist in the chair–chair conformation 5 times as often as in chair–boat while 142 exists in the chair-boat form at least 33% of the time. The hydriodide of 3-methyl-3-ABN is shown to exist in the chair–boat conformation exclusively.[187]

IR and NMR spectra and dipole moment data indicate that 1,5-diphenyl-3,7-DABN-9-one exists in the chair–chair conformation. In the corresponding alcohols intramolecular H bonding stabilizes the boat form.[188] The corresponding benzyl derivative also exists in the chair–chair conformation.[189]

3,7-Dimethyl-3,7-DABN forms only a monoperchlorate, and this has a symmetrical structure (143)

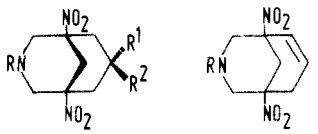


143 145

which shows a sharp singlet for the methyl protons. The basicity is supported by pK_a measurements also.[190] The greater upfield shift suggests that both N atoms carry partial but equal positive charges.

The NMR spectrum of 3,7-dimethyl-3,7-DABN supports[190] the view that this substance exists in the chair–chair conformation. The close similarity of the chemical shifts of the γ-methylene protons of bispidine and those of *N*-methylpiperidine proves the chair conformation since the latter shows a marked preference for chair conformation with the methyl group equatorial.[191]

On the basis of the J_{HCOH} value, the conformation of 1,5-dinitro-3-methyl-3-ABN-7-*endo*-ol (144) has been



144 R=Me, R^1=OH, R^2=H

146 R=Me, R^{1}R^2=O

147 R=Et, R^{1}R^2=O

148 R=CH$_2$Ph, R^{1}R^2=O

149 R=Me

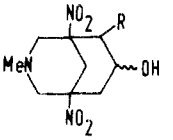
150 R=Et

151 R=CH$_2$Ph

determined.[64] J_{HCOH} is known[192-200] to exhibit a dependence on the dihedral angle (θ) analogous to the Karplus rotation,[201] $J_{HCOH} = A \cos^2 \theta$. Large values of J_{HCOH}^{trans} (ca.12 Hz) have been reported for compounds in which the OH hydrogen is constrained by H bonding to be anti to the carbinol hydrogen. A similar value of J_{HCOH} (ca.12 Hz) for the amino alcohol 144 indicates a transoid arrangement (θ = 180°) of the H–C–OH bonds in accord with the H-bonded chair–chair structure (145).

The *N*-methyl group of the amino ketones 146, 147, and 148 gives signals at 2.41 (s), 2.64 (q), 1.03 (*t*, *J* = 7 Hz), 7.30 (m), and 3.68 (s, benzylic H).[64] The close similarity of these values with those of the corresponding vinyl ethers and 3-ABN-6-enes (149–151) indicates the absence of any interaction between C=O and nitrogen.

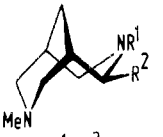
Half-band width[202] also establishes the configuration of 3-ABN-7-ols.[64] In the NMR spectrum of 152 the



152

broad multiplet at δ 4.55 due to the carbinol proton has a half-band width of 20 Hz, indicating diaxial coupling of this proton with the C-6 and C-8 protons. In the spectrum of 144 the half-band width of 11 Hz for the multiplet at δ 4.20 due to the C-7 proton provides additional support for the intramolecular bonding.

The configurations of 2-alkylbispidines are derived from the IR and NMR spectra. The appearance of signals between δ 2.60 and 3.10 (3 H) in the NMR spectra[203] of 153, 154, 155, and 156 indicates an equa-



153 R^1=R^2=Me

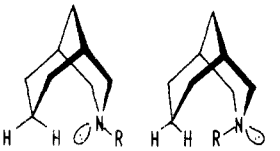
154 R^1=Me, R^2=i-Pr

155 R^1=PhCH$_2$, R^2=Me

156 R^1=Me, R^2=Et

torial orientation of the 2-alkyl groups on the basis of the postulate that protons in this region of the spectrum are gauche to the nitrogen lone pairs, with other N- and C-aliphatic protons appearing upfield from these.[115,204]

However, it has been shown that the δ_{ae} criterion is inadequate for the determination of lone-pair stereochemistry.[205] Proof for this is provided by NMR spectra observations on 3-alkyl-3-ABNs (157, 158). It is pos-



157 158

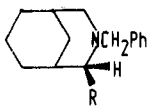
sible to reverse the NH group in this compound by adding methanol to the solution. The change is reflected in the chemical shift of the 7-endo proton, whereas no change is observed in δ_{ae}. It has also been shown that substituents on nitrogen have a considerable effect on the chemical shift of the α protons, the axial proton being more shielded.[205]

The extent of chemical shift nonequivalence of benzylic methylene protons in ^1H NMR spectroscopy[206] has been utilized for the determination of relative configurations and conformational analysis of piperidines,[207]

piperazines,[208] and 3-ABNs.[172,187,209] Nonequivalence is observed in cyclic systems if the benzyl group is vicinal to a single equatorial alkyl substituent, as in **159**.[208]

159 160

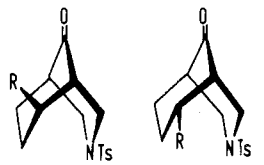
However, if the substituent is axial, as in **160**, nonequivalence will not be observed. By examination of the nonequivalence of the benzylic protons it has been shown that the 3-benzyl-3,7-DABNs with 2-methyl (**161**) or 2-ethyl substituents prefers a flattened chair–



161 R=Me
162 R=Et
163 R=i-Pr

chair conformation. Introduction of an isopropyl group (**163**) causes a change in favor of the chair–boat conformation. The 2-methyl and 2-ethyl groups are axial, as evidenced from the lack of observable nonequivalence of the benzylic protons in the NMR spectrum of monoperchlorates.[172] Conversion of the salt to the free base causes the *N*-benzyl methylene protons to appear as an AB quartet in the NMR spectrum which indicates that the 2-methyl group is now equatorial.[206-208,210]

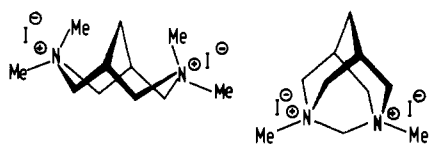
The ^{1}H NMR spectra of **164**, **166**, and **168** show an



164 R=OH 165 R=OH
166 R=OAc 167 R=OAc
168 R=OMs 169 R=OMs

absorption at δ 4.55 ($W_{1/2}$ = 10 Hz) indicative of an equtorial proton (H-6). The OH at 6-position, therefore, occupies an exo position.[211] The spectra of **165**, **167**, and **169** with various amounts of shift reagent Eu(FOD)$_3$ indicate that H-6 is axial ($W_{1/2}$ = 20 Hz) in all cases. No evidence is present for the occurrence of an intramolecular N···HO interaction.[211] The acetate (**167**) and mesylate (**169**) clearly exhibit the pattern for an axial hydrogen at C-6, δ 5.09 ($W_{1/2}$ = 23 Hz) and 5.05 ($W_{1/2}$ = 23 Hz), respectively. **166** and **168** show δ 5.46 ($W_{1/2}$ = 7 Hz) and 5.44 ($W_{1/2}$ = 7 Hz), respectively.

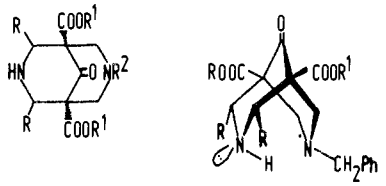
When *N*,*N*′-dimethylbispidine reacts with diiodomethane, different products are formed depending upon the conditions. Equimolar amounts form 1:2 adduct (**170**). But addition of dilute solution of diamine in



170 171

ethanol forms **171**. In the NMR spectrum of **171** the poorly resolved doublet due to the four *N*-methylene groups is similar to those for the corresponding methylene protons in symmetrically 1,3-substituted adamantanes.[190]

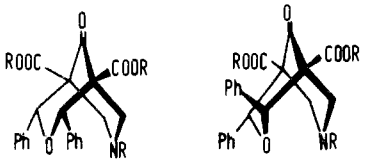
The 220-MHz NMR spectra of **172** (R = 2-pyridyl, 3-pyridyl, 4-pyridyl, or 6-methyl-2-pyridyl; R^1 = methyl or ethyl; R^2 = methyl or benzyl) establish the presence of coupling between *vicinal* NH and CH protons in (3-pyridyl)-2-substituted compounds of this series.[212] In the spectrum of **172** (R = 3-pyridyl; R^1 = methyl; R^2



172 173

= benzyl) the NH absorption appears as a triplet at δ 4.61 and the H(2,4) appears as doublet at δ 4.93. The coupling constant, $J_{NH/CH}$ is 12.5 Hz. When R^1 = ethyl the NH triplet and H(2,4) doublets appear at δ 4.61 and 4.58, respectively. The value of the coupling constant indicates a chair–chair conformation[212] (**173**).

The ^{1}H NMR spectra of the two isomers of 2,4-diphenyl-3-O-7-ABN-9-one derivatives (**174** and **175**) have

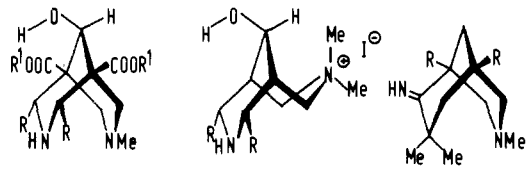


174 175

been recorded.[131] The protons at C-2 and C-4 of the isomer **174** shows a singlet. For the protons H(6,8) and H(6′,8′) an AB quartet with geminal coupling constant of 12 Hz appears. Thus the NMR spectrum indicates a symmetrical structure. The conformation must, therefore, be twin-chair, with 2,4-*cis*-phenyl substituents.[131] In the 220-MHz NMR spectrum of **175** complex signals appear between δ 3 and 4, comprising a H(6,8) doublet and two octets for the methylene protons of COOCH$_2$CH$_3$ groups at δ 3.72 and 3.39. The octet arises due to the magnetic nonequivalence of the CH$_2$ protons and can happen only if the phenyl groups are trans, and not due to chair–boat conformation. Thus the isomers may be identified as cis and trans isomers, respectively, and represented by structures **174** and **175**. Such cis–trans isomers in the case of 2,6-diaryltetrahydropyran-4-ones (**97**) and 2,6-diaryltetrahydrothiopyran-4-ones (**103**) are known.[128,134,213-215]

The 3,7-DABN-9-ol **176** has been prepared by NaBH$_4$ reduction of the ketone and its NMR spectrum studied.[216] The signals of the geminal methylene protons at the 6 and 8 positions form an AB quartet, $J_{66'}$ (=$J_{88'}$) being 12.0 Hz. The OH portion is found to have coupled with the geminal C-9 proton (J = 6 Hz).[216]

In the methiodide **177** the downfield and upfield shifts of the two NCH$_3^+$ protons and the greater coupling constant for 6,6′ protons indicate that the ring B has flipped to the boat form. The ring A cannot flip owing to the presence of bulky aryl groups in 1,3-cis diequatorial positions. Moreover, irradiation at the resonance frequency of the signals of the *N*-methyl

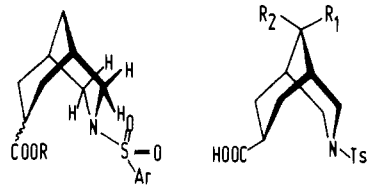


176 R =  177 R =  178

protons (δ 3.10) induces an NOE on H-9, causing an increase of 10% in the intensity of the signal for H-9, whereas the intensity of the OH signal is not affected. This confirms that the ring B has flipped to the boat form.[216]

In the spectrum of **178** long-range couplings are observed for the isolated AB systems for the protons on C-2, C-4, C-8, and C-9.[217] Of these protons the only one that resonates as a two-line signal is the axial H-4β at δ 1.51 which has a 10.0-Hz geminal coupling to the equatorial H-4α at δ 2.70. The H-4α resonates as a doublet (10.0 Hz) of triplets (1.5 Hz) as the rigid nature of the molecule is such that four-bond couplings through a "W" arrangement of σ bonds are observed to both H-9α and H-2α.[217] Similar four-bond couplings are observed for H-2α, H-2β, H-8β, H-9α, and H-9β also.

The *N*-methylene protons in the *N*-tosyl-3-ABN derivative **179** constitute an AA′BB′ system in which the



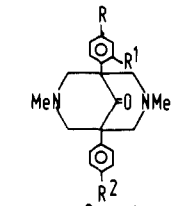
179 R = Me, Et, H 180 R^1 = H, R^2 = OH

181 R = OH, R^2 = H

low-field A part comprises the equatorial protons and the high-field B part the axial ones.[71] The equatorial protons which are in the N—S=O plane are shifted downfield considerably as a result of the deshielding by the S=O functions. Thus equatorial protons are found between δ 3.5 and 4.0 while the axial ones absorb around δ 2.5–3.5, leading to a difference of δ 0.5–1.4 for the two halves of the AA′BB′ system.

The extremely low-field absorption of H-7 in acids **180** and **181** has been explained by assuming a chair conformation for the B ring in which H-7 is said to be situated in the plane of O=S=O group symmetricaly with respect to the oxygen atoms.[71] However, this nearness of H-7 to the tosyl group can happen only if the tosyl group is in the endo position, which seems to be far less probable. Therefore, the downfield shift for H-7 should be due to some other reason, such as partial attraction between H-7 and lone pair on nitrogen and approach of COOH of another molecule near H-7 to form OH···N hydrogen bonding.

The NMR spectrum of 1-(*o*-nitrophenyl)-5-phenyl-3,7-dimethyl-3,7-DABN-9-one (**182a**) shows two sets of quartets for the C-2, C-4, C-6, and C-8 methylene protons while that of 1,5-diphenyl- or 1,5-bis(*p*-nitrophenyl)-3,7-dimethyl-3,7-DABN-9-one (**182a**) shows a symmetrical neat quartet. The *o*-nitro group causes nonequivalence amoung the C-2,8-axial protons and C-4,6-axial protons. In a similar way the equatorial protons are also differenciated. This clearly shows that



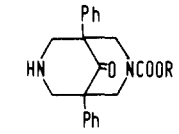
182a R = R^2 = H, R^1 = NO_2

182b R = R^2 = NO_2, R^1 = H

182c R = R^2 = H, R^1 = Me

the nitro group in **182a** is oriented to the side of the C-2 and C-8 carbons.[110] The reason appears to be that dipole–dipole repulsion between C=O and NO_2 forces the nitro group away from the carbonyl. The related 1-phenyl-5-*o*-tolyl-3,7-dimethyl-3,7-DABN-9-one (182c) weakly exhibits this differentiation.[111]

The NMR spectrum of **183** shows a doublet at δ 4.92



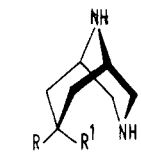
183

assigned to the equatorial protons of the C-2 and C-4 attached to N–COOR (J_{AB} = 13.5 Hz). The signal for the other methylene protons appear at δ 3.74.[86] This establishes the equatorial nature of the COOR groups and thereby the chair–chair conformation.

1,5-Diphenyl-3-tosyl-3,7-DABN-9-one also shows nonequivalence for C-2, C-4, C-6, and C-8 protons, the absorptions being C-2, C-4 equatorial H at δ 4.51 (J_{AB} = 11.5 Hz), C-6, C-8 equatorial H at 4.02 ($J_{A_1B_1}$ = 14 Hz), C-6, C-8 axial H at 3.58, and C-2, C-4 axial H at 3.28.[86]

1,5-Diphenyl-3-ethyl-7-methyl-3,7-DABN-9-one and 1,5-diphenyl-3-benzyl-7-methyl-3,7-DABN-9-one also show related NMR spectral behavior.[218]

The conformations of 3,9-DABN-7-ol (**184a**) and 7-methoxy-3,9-DABN (**184b**) have been determined by



184a R = H, R^1 = OH

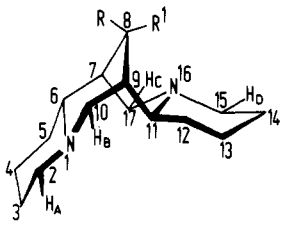
184b R = OMe, R^1 = H

NMR data.[219] **184a** is found to occupy the chair–chair conformation with axial OH involved in H-bonding to 3-N and with some distortion of the bicyclic ring angles. **184c** also exists in a chair–chair conformation, but with an equatorial OMe group.[219]

^{1}H NMR data of the N-CH_2 protons and H_7 of *N*-tosyl-3-ABNs (derivatives of **40**) indicate the preferred conformations.[71] Owing to the deshielding of the tosyl group the absorption of the endo H-7 in the chair form of the cyclohexane ring is shifted considerably downfield compared with the absorption of the exo H-7 in the boat form. Substitution of the endo C-7 hydrogen increases the conformational energy of the twin-chair, thus favoring the chair-boat form.[71]

The endo configuration of the C-7 proton in 7-benzoyl-3-tosyl-3-ABN-9-one is established by its half-band width ($W_{1/2}$ = 28 Hz), compatible with the chair–boat conformation.[71] Epimerization with EtO-Na/EtOH gives the more stable twin-chair isomer in which the absorption of the axial H-7 ($W_{1/2}$ = 23 Hz) is shifted 2 ppm downfield (5.27 ppm) as a result of deshielding the tosyl group.

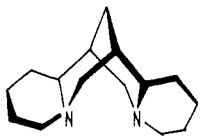
From the NMR spectra[145] of sparteine (**185**) and its



185 R=H, R¹=H
186 R=OH, R¹=H
187 R=H, R¹=OH
188 R=H, R¹=OAc

deuterated analogues (17-d_2, 2,17-d_4, 6,10,17-d_5), the signals for the 4 protons which appear downfield have been assigned: H_A δ 2.63, H_B 2.51, H_C 2.32, H_D 2.76. The signal at δ 1.04 has been assigned to the C-8 H_E proton. The spectra are in accordance with conformation **185**. Two 8-hydroxysparteines (**186** and **187**) have been isolated and studied.[145] The shifts of the C-8 protons are at δ 4.34 and 3.47. This shows that the proton at C-8 is situated above the free electron pair at N-16 in **186** whereas in **187** a hydrogen bond exists between the OH group and the N-16 atom. Similarly the two 8-acetoxysparteines also show different chemical shifts of the C-8 protons (δ 5.28 and 2.53). The high-field position has been attributed to the interaction of the acetyl group with the N-16 atom (**188**).

In β-isosparteine (**189**) both tertiary protons at C-6 and C-11 are arranged in the position cis to the free electron pair, and all NMR signals of the α protons are downfield.[145]

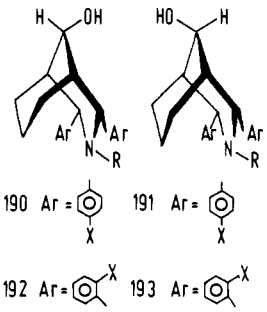


189

3. ^{13}C NMR Spectroscopic Methods

Eliel et al. have examined the ^{13}C NMR spectra of a series of about 50 2,4-diaryl-3-ABNs and established the configurations and conformations of several 2,4-diaryl-3-ABN-9-ols.[160] Assignment of configurations has been made on grounds of γ-gauche effect[177-185] of the OH group on the C-6 and C-8 or C-2 and C-4 carbons. The upfield shift has been observed for the N-containing ring in endo alcohols (e.g., **190**) and for the carbocyclic ring in exo alcohols (e.g., **191**).

The idea[158,159,165] that 2,4-diaryl-3-ABN-9-ols with ortho substituents on the aryl groups occupy chair–boat conformations has been dropped because the ^{13}C NMR studies[160] show that not only the 2,4-diaryl-3-ABNs with para substituents but also those with ortho substituents (e.g., **192** and **193**) occupy chair–chair conformation.



190 Ar = 191 Ar =

192 Ar = 193 Ar =

The 7-*tert*-butyl-2,4-diphenyl-3-ABNs also adopt chair-chair conformations.

The configurations of the 3-ABN-9-ols with para-substituted aryl groups are the reverse of what had been reported previously,[152,158,159,165] and the configurations of the alcohols with ortho-substituted aryl groups are the same as those predicted.[152,158,159,165]

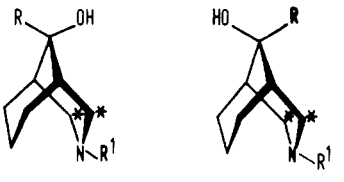
In the ^{13}C NMR spectra of **161**, **162**, and **163** the upfield shift of the benzylic methylene carbons indicates a steric congestion due to the presence of the 2-alkyl group. The spectral positions of C-7 and the benzylic carbon provide unambiguous evidence regarding the conformation of **161**, **162**, and **163**.[172] A 5.0-ppm upfield shift of C-7 is seen in **163** relative to 3-benzyl-3-ABN. This difference has been attributed to a gauche relationship of the endo hydrogen with the endo hydrogens at C-2 and C-4. This interaction has also been proposed to account for the ~5-ppm upfield shift of C-7 in the spectra of chair–boat conformers with respect to those of chair–chair conformers in the closely related 9-ABN-3-ols.[176]

Comparison of the calculated and observed ^{13}C chemical shifts for the various carbons of about 70 3-ABNs and bicyclo[3.3.1]nonanes indicates that for C-7 without alkyl substituents an upfield shift of about 4.9 ± 0.4 ppm is to be included. This additive factor could not be employed when substituents are present in the C-7 carbon. This may be due to the resistance to flattening of the cyclohexane ring when a substituent is incorporated in the 7 position.[168] The variation could be related to the bulkiness of the 7-alkyl substituent.

4. Mass Spectrometry

Mass spectrometry has been made use of for the determination of conformations of 3-ABN systems to a lesser extent compared with other usual spectroscopic techniques. A strain-based driving force for loss of a hydrogen atom from the molecular ions of various epimeric azabicycloalkanes has been proposed.[220]

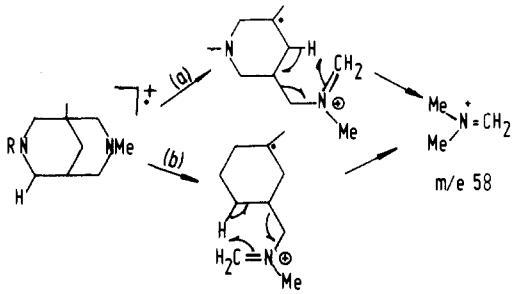
The mass spectra of 3-alkyl-3-ABN-9-ols (**194**, **195**)



194 R=H, R¹=Me 195 R=H, R¹=Me

exhibit $[M - 1]^+$ fragmentation. Deuterium labeling at the bridgehead carbons and at the one-carbon bridge gives rise to no ion at m/e $[M - 2]$ ruling out the possibility of H-atom fragmentation from these positions. However, on the basis of the known behavior for β

CHART I

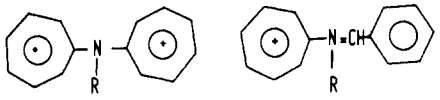


cleavage of amines[221] it has been concluded[220] that the hydrogens on α-carbons (to N) are eliminated. The intensity of the $[M - 1]^+$ peaks are also found to depend on the bulkiness of the 9-substituents. In the epimers **194** and **195** with differing R groups, those with the larger group facing the heterocyclic bridge always exhibit significantly more intense $[M - 1]^+$ ions. This has been attributed to a 1,3 interaction.[220]

In the 6-substituted-3-ABN series two major fragmentations have been observed,[222] the first arising from breakdown of azabicyclononyl ring about C_6–C_8, the second initiated by loss of electron from *N*-Me. However, these also correspond to β cleavage of amines.[221]

The configurations of some bicyclo[*n*.3.1]alkanols have been established[223] by using the effect of distance between abstracted hydrogen and hydroxyl oxygen for the elimination of H_2O. It has been clearly demonstrated that any one abstractable secondary hydrogen must be present within 1.8 Å from the HO^+ in order that H_2O is eliminated.[224-227] The proximity effect could not be made use of for determining configurations of 9-substituents in chair–chair conformations. However, in boat–chair or chair–boat conformations use of this technique is possible. The mass spectra of 2,4-diaryl-3-ABN-9-ols do not exhibit an $[M - 18]^+$ peak, indicating that no secondary hydrogen is close to the OH.[168] This also establishes the chair-chair conformation for 2,4-diaryl-3-ABNs.

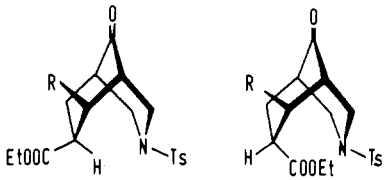
The mass spectra of 2,4-diaryl-3-ABN-9-ones with various aryl groups show that the cleavage between bridgehead carbons and benzylic carbons for the formation of ditropyliumamine (**196**) and the imino derivative (**197**) is the major fragmentation mode.[169] This arises because of stabilization of the fragments.



196 197

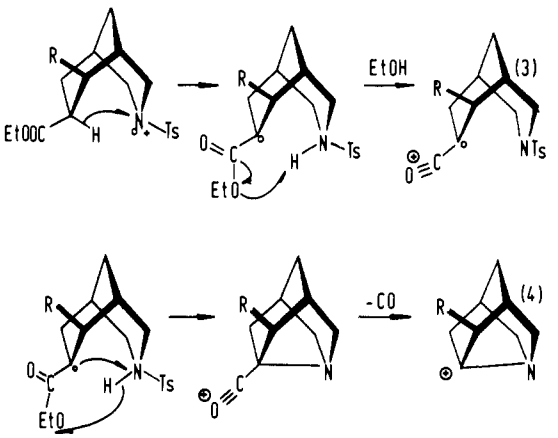
Mass spectrometry has been employed for establishing the configurations of the C-7 substituents of the *N*-tosyl-7-carbethoxy-3-ABNs.[228] The molecular ions of compounds **198** and **200** eliminate a molecule of ethanol whereas this decomposition is not observed for the molecular ions of compounds **199** and **201**.

In the *exo*-COOR series the transfer of a hydrogen from C-7 to the charge-localized nitrogen atom occurs through a six-membered transition state.[228] This transfer is not possible for the endo series (eq 3). In the spectra of **198** and **200** appropriate diffuse peaks are also found for the loss of a tosyl radical from $[M - EtOH]^+$ ion. This happens because of an anchimeric assistance as shown in eq 4.



198 R = COOEt 199 R = COOEt

200 R = H 201 R = H



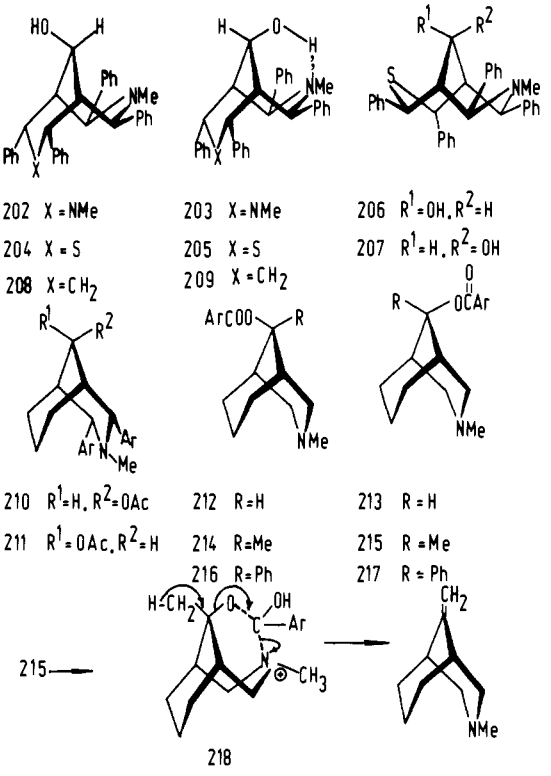
The mass spectra of a series of N,N′-disubstituted bispidine derivatives have been investigated.[229] The important feature observed in the spectra is the common base peak (*m*/*e* 58) which results from the generation of *N*,*N*′-dimethylformimmonium ion as indicated in Chart I. In 3-ABNs this peak is of lesser importance. Deuteration of bridge heads in *N*,*N*′-dimethylbispidine causes an increase in the intensity of the *m*/*e* 59 peak, indicating participation of a methylene bridge hydrogen (path a). However, the base peak remains at *m*/*e* 58, indicating also the involvement of an *N*-methylene hydrogen as in path b.

5. Kinetic Methods

The kinetic method of conformational analysis is one of the earliest successful techniques in establishing the relative conformation and configurations of isomeric pairs of cyclic systems.[6-18,230,231] However, this technique could not be employed successfully for establishing the configurations of ABN-9-ols[159] or their derivatives[166] since the OH or OR group is axial with respect to either of the two rings and thus has almost the same steric environments. The configurations of some of the pairs of alcohols which were derived by kinetics of acetylation are in fact the reverse of their actual relative configurations which have been established by ^{13}C NMR spectral studies.[160]

The α and β isomers of 3,7-dimethyl-2,4,6,8-tetraphenyl-3,7-DABN-9-ol (**202** and **203**) have almost the same rates of acetylation.[232] In the case of 7-methyl-*cis*-2,4-*cis*-6,8-tetraphenyl-3-T-7-ABN-9-ol (**204** and **205**) the α isomer (**204**) reacts at a much faster rate than the β isomer (**205**). The higher rate of the α isomer has been explained in terms of longer C–S bond length which causes greater separation of the axial hydrogens at C-2 and C-4, facilitating attack by the reagent from the chair side.[232]

On the basis of the lower reaction rate of the α isomer of 7-methyl-*trans*-2,4-*cis*-6,8-tetraphenyl-3-T-7-ABN-9-ol (**206**) compared with that of **204**, a boat–boat conformation has been proposed for **206**. The corre-



sponding β isomer (**207**) shows intramolecular hydrogen bonding.

Epimeric **208** and **209** exhibit a reversal of trend in the rates of acetylation. The β isomer (**209**) is acetylated nearly 3 times as fast as the α isomer (**208**). It has been explained in terms of steric hindrance by phenyl groups and axial hydrogens at C-6 and C-8.

The conformations and configurations of alcohols **202** to **209** need to be confirmed by other techniques.

Second-order rate constants for alkaline hydrolysis of 9-acetoxy-3-methyl-2,4-diaryl-3-ABNs (**210, 211**) in 95% ethanol show small rate ratios (1.3–1.9) between the epimeric pairs.[166] This may be due to the absence of steric factors in the transition state or to similarities in the conformation on both sides of the one-carbon bridge. In the light of new ideas on conformation and configuration of **210** and **211**, the lower rate of the trans isomer (**210**, Ar = *o*-tolyl) seems to be due to steric hindrance caused by the *o*-methyl groups which are necessarily oriented to the side of the 9-endo substituent.

The similar relative rates of solvolysis of each pair of 9-(*p*-nitrobenzoyloxy)-3-ABNs (**212–217**) suggest that in none of the cases does the nonbonded electron pair on nitrogen provide substantial aid to ionization of the C–O bond.[233] Simple ester hydrolysis takes place with the secondary alcohols **212** and **213** while ionization followed by fragmentation is the process occurring with the tertiary phenylcarbinol derivatives **216** and **217**. The tertiary methylcarbinol derivatives **214** and **215** are intermediate in behavior, giving products expected from ester hydrolysis and ionization. The ester **215** produces a substantial amount of an elimination product which is explained to be formed via a cyclic intermediate (**218**).

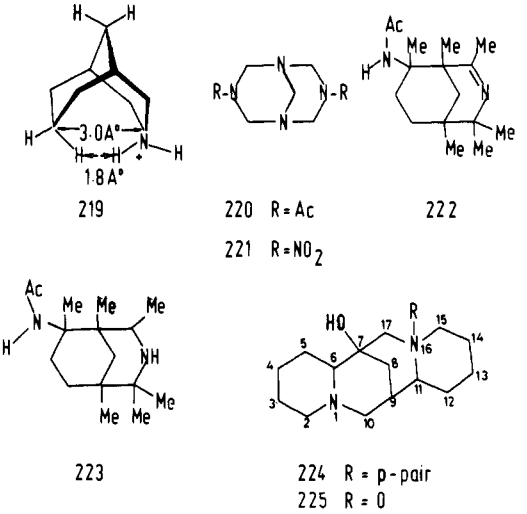
6. *X-ray Crystallography*

Many X-ray crystal and molecular structure determinations have been performed on 3-ABNs, 3,7-DABNs, and sparteine-type alkaloids. In many cases they have yielded conclusive evidence for conformation and configuration.

Crystals of 2,4-diphenyl-3-ABN-9-one belonging to the monoclinic and orthorhombic systems have been studied by X-ray crystallography.[234] The monoclinic crystals have space group C_2 or C_m with $a = 13.871 \pm 0.001$, $b = 35.780 \pm 0.003$, $c = 12.856 \pm 0.001$ Å and $\beta = 92 \pm 0.5°$; d(exptl) = 1.20 and d(calcd) = 1.22 for $Z = 16$. The orthorhombic crystals have space group $C_{mc}2_1$, with $a = 20.838 \pm 0.002$, $b = 10.532 \pm 0.001$, and $c = 7.231 \pm 0.001$ Å; d(exptl) = 1.225 and d(calcd) = 1.227 for $Z = 4$.

Two crystalline modifications have been found for 1,5-dinitro-3-methyl-3-ABN-7-one.[235] One is monoclinic, space group $P2_1/C$ with $a = 8.018$, $b = 20.247$, $c = 8.346$ Å; $\beta = 123.97°$; $Z = 4$ and d(X-ray) = 1.434. The other modification is orthorhombic, space group P_{ccn}, with $a = 18.877$, $b = 11.031$, $c = 10.707$ Å; $Z = 8$ and d(X-ray) = 1.446. Both structures show high thermal motion (or disorder) especially of the nitro groups. The conformation of the ring is chair-chair (with equatorial methyl group at nitrogen) for the monoclinic and orthorhombic modifications.[235] In both forms the NO_2 group orientation does not conform to the appropriate mirror symmetry of the substituted ABN skeleton. One NO_2 group (N_1) closely eclipses C_1–C_2 in both forms. The other nitro group is nearly perpendicular to C_5–C_4 in the first but eclipses C_5–C_6 in the second. The molecules of the two forms are thus conformational isomers. The ring containing the C=O group is less puckered than the one containing the N atom. The N···C=O distances are 2.76 and 2.69 Å and the deviations of the carbonyl from the plane of its three neighbors are 0.023 and 0.054 Å, respectively, in both cases towards the nucleophile N.

The HBr salt of 3-methyl-3-ABN exists in chair–chair conformation with slight deformation of bond angle.[236] It has a tetragonal structure, $a = 14.01$ Å, $c = 9.43$ Å, $Z = 8$, space group $P\bar{4}2_1C$. The two rings are flattened to a slight extent (**219**).



The molecules of 3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (**220**) and 3,7-dinitro-1,3,5,7-tetraazabicyclo[3.3.1]nonane (**221**) exist in a chair–chair conformation.[237]

The crystal and molecular structure of 1,2,4,4,5,8-hexamethyl-8-(*N*-acetamido)-3-ABN-2-ene (**222**) has been studied.[80] This compound crystallizes in mono-

clinic system; space group $P2_1/n$, a = 32.385, b = 6.526, c = 7.778 Å; β = 88.43°; Z = 4. Because of the introduction of the double bond, some interactions with the endo H atom at C-7 are not present. The conformation of the cyclohexane ring resembles a slightly flattened chair. The distance of the atoms C_7 and C_9 to the plane through C_1–C_5–C_6–C_8, which are 0.604 and –0.719 Å, respectively, confirm this conformation.[238] The N_3···C_7 nonbonded separation is 3.13 Å.

The saturated analogue[239] of **222** (**223**) crystallizes in the monoclinic form, space group $C2/c$ with Z = 8. The cell dimensions are a = 19.409, b = 18.368, c = 10.258 Å; β = 117.478°.

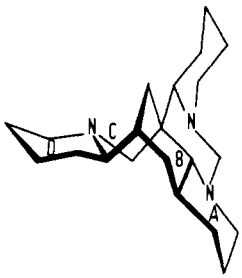
In this compound the hydrogen of the NH is located in the exo position. The displacement of the N_3 atom from the plane through C_1–C_2–C_4–C_5 is –0.589 Å. The deviation of the bridge atom C_9 from this plane is 0.718 Å. Consequently, the piperidine ring presents a slightly flattened chair conformation. In the other ring the deviations of the C_7 and C_9 atoms from the plane through C_1–C_5–C_6–C_8 are 0.616 and –0.723 Å, respectively. Since there is no severe interaction between the endo hydrogen atom at C_7 and the H atom at N_3, the chair–chair conformation is close to the ideal, the distance N_3···C_7 being 2.880 Å. However, the angles C_4–C_5–C_6 (113.1°) and C_2–C_1–C_8 (116.6°) are greater than the tetrahedral value.[239]

The conformations of sparteine group of alkaloids have been determined by X-ray crystallographic studies. Crystals of 7-hydroxy-β-isosparteine perchlorate (**224**) are found to be orthorhombic, with space group $P2_12_12_1$.[240] The unit cell dimensions are a = 13.04, b = 13.19, c = 9.59 Å. The number of molecules in unit cell is 4. The molecule is called by convention[241,242] trans,trans (while α-isosparteine is called cis,cis and sparteine is cis,trans), and all four of the six-membered rings are found to be in chair conformation. The OH has been shown to be attached to C_7, contrary to earlier reports[242] which indicate that OH is attached to the bridge atom C_8. The two N atoms are close to each other (2.68 Å). The hydrogen from $HClO_4$ is situated in a position only 1.04 Å from one nitrogen and 1.84 Å from the other. Thus this hydrogen is covalently bonded to N_{16} and hydrogen bonded to N_1[145a] (**113**).

The structure proposed for sparteine N_{16}-oxide (**225**) sesquiperchlorate on the basis of chemical behavior and IR spectra has been confirmed by X-ray crystal structure studies.[243,244] All the rings are in the chair conformation. This is analogous to the results obtained from NMR spectra.[244] In sparteine and its derivatives in solution the inversion of N_{16} can readily take place, transforming the ring C into a boat form.[143,145] However, the chair conformation stabilized by hydrogen bonding enhances the basicity of the N-oxide.[244-247]

The structure of α-isosparteine monohydrate (**112**) has also been determined.[242] The space group is $C222_1$, a = 20.18, b = 10.61, c = 6.84 Å, Z = 4. The four rings of the molecule have the chair form, with both outer rings trans to the methylene bridge.

The alkaloid **226**, jamine from *Ormosia jamaicensis*, belongs to space group $P\bar{1}$, with a = 6.79, b = 10.61, c = 13.41 Å; α = 95°, β = 97° 20′, and γ = 103° 55′. Of the six six-membered rings, five exist in chair form and one in boat form. The 3-ABN part exists in chair–boat conformation.[248,249]



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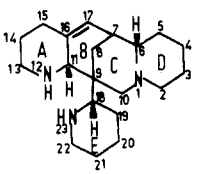


227

Another alkaloid, podopetaline (**227**), belonging to this group has the same relative configuration[250] at C_6, C_{11}, and C_{18} as jamine[248] and ormosanine.[249] There is, however, an important difference between the conformation of podopetaline and that of jamine and ormosanine.

Rings A, C, D, and E in podopetaline are in the chair conformation and ring B, which contains the C_{16}–C_{17} double bond, has five carbon atoms essentially coplanar and C_8 out of plane (sofa conformation). The chair form for ring C and cis C/D ring junction contrasts with the conformation of jamine, which has a boat form for ring C and the C/D ring junction trans.

Jamine and ormosanine have a trans C/D conformation because steric interaction between C_{16}–H and the nitrogen lone pair (at N_1 in the quinolizidine moiety) makes the cis form less stable. In podopetaline the chair–chair conformations for rings C and D and the cis C/D junction represent the more stable conformation.[250]

7. Other Methods

Dipole moment calculations[251] prove that 3-methyl-3-ABN-9-one exists in the chair–chair conformation and not in a chair–boat conformation. The observed dipole moment in benzene solution at 25 °C is 2.89 ± 0.03 D. This value is close to the value (~2.7 D) expected for the chair–chair conformation and differs significantly from the expected value (~3.8 D) for the chair–boat conformation.

The calculated dipole moments for the chair–chair, chair–boat, and boat–boat conformations for 3,7-dimethyl-3,7-DABN are 1.10, 1.10, and 1.84 D, respectively.[190] Though the observed value (2.02 D) is closer to the boat–boat conformation, a flattened chair–chair conformation also can have a value up to 1.90 D. On the basis of previous reports, a flattened chair–chair conformation has been assigned.[190]

The nitroxide **228b** has a dipole moment of 5.2 D in benzene at 25 °C, this suggests a chair–chair conformation for the ring, either with an axial-type N–O bond or a slight distortion of the piperidinoxyl ring.[252]

228a R=O R^1=I
228b R=O R^1=H

229 R=NO
230 $R=NO_2$

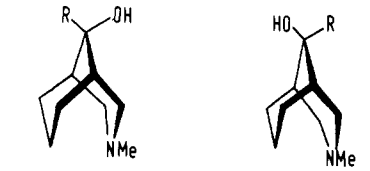
The measured dipole moments for **229** and **230** are 6.8 and 6.9 D, respectively. The high value suggests a

chair–chair conformation since the calculated values for **229** and **230** are ca. 7 and 8 D, respectively, while those for the chair–boat conformations are less than 4.6 D.[253]

1,5-Diphenyl-3,7-DABN derivatives have been assigned the chair–boat conformation on the basis of spectral and dipole moment studies.[188]

3-Alkyl-7-methyl-3,7-DABNs titrate as monoamines, and none of them form stable disalts. The stabilizing factor is the possibility of intramolecular hydrogen bonding between nitrogens which produces an adamantane-like structure.[190] Since the pK_a value of *N*,*N*′-dimethylbispidine is 11.88, it is more basic than *N*-methylpiperidine (pK_a = 10.08).

The pK_a values of epimeric 3-methyl-9-alkyl-3-ABN-9-ols[254] suggest that the β isomer of any stereochemical pair is the stronger base. Thus **231a** is stronger than **232a** and **231b** is stronger than **232b**.



231a R=Me
231b R=Ph

232a R=Me
232b R=Ph

The structures of *N*,*N*′-dimethylbispidine and 3-ABN·HBr have been assigned by calculating the energy differences by LCAO–MO methods.[209] In 3-ABN·HBr and *N*,*N*′-dimethylbispidine, the minimum energies are present when the distance between 3 and 7 atoms are 2.9 and 2.5 Å, respectively, which are close to the distance in the normal chair–chair conformation. Calculations for boat–chair and boat–boat conformations have yielded higher energy values. Therefore, it has been concluded that these compounds exist in a normal or near-normal chair–chair form at room temperature.

The high-resolution ESR spectra[252] of the nitroxides **228a** and **228b** have been studied, and the N–O bond has been shown to occupy an axial (endo) position.

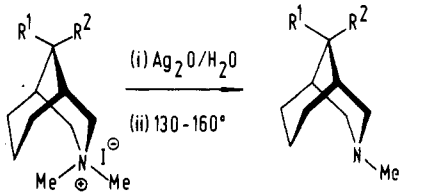
VI. Reactions and Their Stereochemistry

A. Reactions at Nitrogen

In most of the 3-ABNs, alkylation at nitrogen has been carried out easily with alkylating agents.[58,78,106,107,165,190,218,255-258] 3-ABNs are alkylated with (i) and HCOOH–HCHO mixture, (ii) alkyl halides with a mild base, and (iii) alkyl sulfates in alkaline medium.

The stereochemistry of alkylation at nitrogen has been studied in detail.[259] The reactions of 3-ABN-9-one (**19**) and 3-ABN-9-ols (**139**, **140**) with trideuteriomethyl *p*-toluenesulfonate have been examined to determine the degree of stereoselectivity with which the trideuteriomethyl group is introduced to form a quaternary ammonium salt. Salts of **139** and **140** in NMR give signals for *N*-Me protons. The *N*-methyl signals appear at two different positions for the two isomers. In the case of **139** and **140**, the salt is oxidized to the ketone and then the positions of the signals for *N*-methyl protons are ascertained and the stereochemistry of alkylation determined. In the chair–chair conformation the peak for an equatorial *N*-methyl group appears at lower field and that for an axial *N*-methyl appears at higher field. From the area of the different peaks the ratio of N-alkylated products is found out. On the basis of the NMR spectral results it has been concluded that the direction of alkylating agent is independent of the nature of steric arrangements of the oxygen function. The alkylating agent attacks from a direction syn to the oxygen function. With methyl *p*-toluenesulfonate and methyl bromoacetate the same trends have also been observed.[259-261]

The methiodide **233a** on conversion to the hydroxide and subsequent thermal decomposition forms O-alkylated product **234a**, among others, by intramolecular

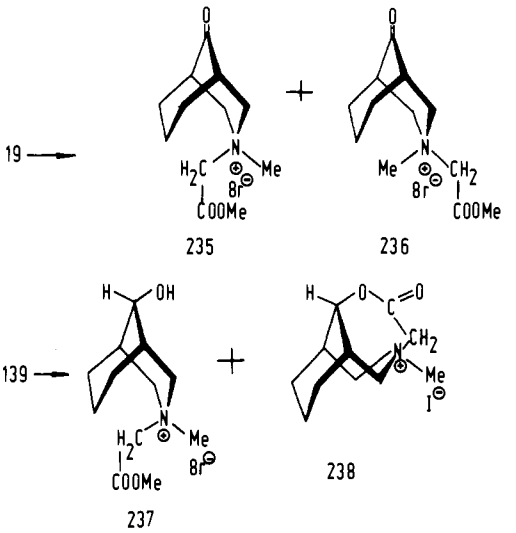


233a R^1=H, R^2=OH
233b R^1=OH, R^2=H

234a R^1=H, R^2=OMe
234b R^1=OMe, R^2=H

transfer. The methiodide **234b** undergoes O-alkylation by an intermolecular process and at a slow rate.[259]

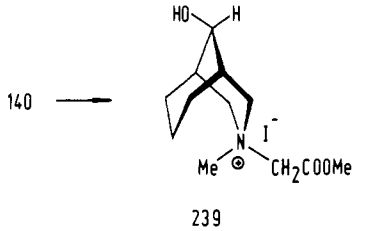
Alkylation of 3-ABN-9-one with methyl bromoacetate gives almost equal amounts of the keto esters **235** and **236**.[260] Alkylation of the endo alcohol **139** gives a



235 236

237 238

mixture of the hydroxy ester **237** (ca. 25%) and the lactone **238** (ca. 75%). Alkylation of the exo alcohol gives a single quaternary salt (**239**).[260]



239

The difference in protonation and quaternization of 1,5-diphenyl-3,7-dimethylbispidin-9-one (**76**) and the corresponding alcohol has been related to their conformation.[262]

The orientation of the lone pair of electrons on nitrogen in 3-ABNs has been predicted. The NH hy-

drogen undergoes inversion depending upon the solvent. In polar solvents the lone pair is equatorial in a chair–chair conformation, and in nonpolar solvents it is axial.[153,263]

On the basis of NMR and IR spectral studies the NH compound is reported to have an equatorial lone pair while the *N*-methyl compound has an axial lone pair.[264]

Urea derivatives containing the 3-ABN skeleton (**242**) have been obtained[265] by treating *N*-amino-3-ABN·HCl (**240**) with NaOMe and the urethane **241** at 110–120 °C.

240 241 242 R=NHCONHSO$_2$Ar

The kinetics of N-alkylation of 2,6-diarylpiperidine derivatives and 2,4-diaryl-3-ABN derivatives has been studied.[266] The alkylation rates in piperidines are found to depend upon both electronic factors and flattening effects due to substitutents at the 3- and 5-positions. In 3-ABNs with different aryl substituents the rate constants varied widely depending upon the presence or absence of ortho substituents. It has also been shown that quaternization is not possible in 2,4-diaryl-3-ABNs because of steric hindrance caused by the adjacent aryl groups.[266]

^{13}C NMR spectral investigations of *N*-methyl-2,4-diaryl-3-ABNs show that in the *N*-Me compounds the signals due to the ortho and meta carbons of the aryl groups are doubled.[160] The doubling disappears on raising the temperature and is probably due to restricted rotation of the aryl groups. In the NH series this type of doubling has not been observed.[160]

B. Reactions of Carbonyl Groups

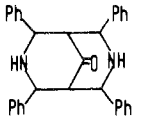
The carbonyl group in 3-ABN-9-ones is found to be less reactive than the carbonyl in other heterocyclic ketones. One of the reasons given is that the interaction between C=O group and the increased electron density on the nitrogen makes C=O less reactive.[129] The C=O group of 3-ABNs can be hydrogenated by using PtO_2[129,171,286] or Raney nickel.[266] Isomeric alcohols are formed in each case except simple 3,7-DABNs.

1,5-Diphenyl-3,7-dimethyl-3,7-DABN-9-one (**76**) on reduction with $LiAlH_4$ or Raney nickel gives the 9-hydroxy compound.[113,171] Other 3,7-dialkyl analogues of **76** also have been reduced to the corresponding bispidin-9-ols.[87]

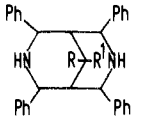
2,4-Diaryl-3-ABN-9-ones and 2,4,6,8-tetraaryl-3,7-DABN-9-ones on reduction by the MPV method, sodium–alcohol, $NaBH_4$, or catalytic hydrogenation produce epimeric pairs of alcohols.[134,155,165] Determination of the ratio of the pairs of alcohols formed usually provides sufficient evidence to predict the conformations and configurations in six-membered heterocyclic alcohols. The results obtained from isomer ratios in 3-ABN-9-ols often lead to wrong conclusions.[160,165] Caution is needed in correlating isomer ratios with configurations of alcohols.

It has been reported[156,165,266] that **20** gives the endo alcohol predominantly on reduction with aluminum isopropoxide and almost exclusively in the reduction with Pt/H_2 or Raney nickel, while reduction with sodium borohydride or Na/alcohol produces more of the exo alcohol. However, ^{13}C NMR investigations of the alcohols reveal[160] that the actual configurations are the reverse of those proposed earlier.[156,165,266] Thus it is evident that the predominant alcohol in MPV reduction and catalytic hydrogenation is really the exo isomer and that formed in reduction with $NaBH_4$ or Na/alcohol is the endo isomer.

Though several workers obtained only one alcohol in the reductions of 2,4,6,8-tetraphenyl-3,7-DABN-9-one (**243**), MPV reduction gives two isomers of the alcohol.



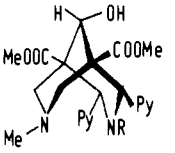
243



R^1=H or OH
R^2=OH or H

The conformation of the two rings should therefore be chair–boat since neither chair–chair nor boat–boat forms would give two isomers because of the presence of C_2 symmetry. In related tetraphenyl derivatives of 3-O-7-ABN and 3-ABN the newly formed piperidine ring assumes the boat form during its formation. On reduction, these ketones give different proportions of α and β isomers, depending upon the method of reduction as in the case of unsubstituted 3-ABN-9-ones.[171].

$NaBH_4$ reduction of 1,5-dicarbalkoxy-2,4-bis(pyridyl)-3,7-DABN-9-ones (**172**) yields one alcohol only (**244**), with very high stereoselectivity.[216] The stereo-



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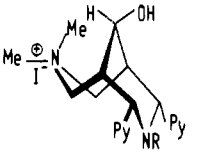
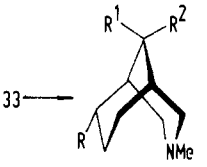


245

chemistry of the methiodide **245** has been determined by NOE measurements.[216]

Difficultly separable mixture of isomeric 3-methyl-6-cycloalkylamino-3-ABN-9-ones (**33**) on reduction with $NaBH_4$ gives mixtures of 3-ABN-9-ols (**246**, **247**) which

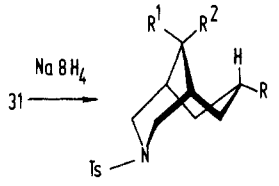


246 R^1=OH, R^2=H
247 R^1=H, R^2=OH

have been separated by GLC.[261] The resistance of **246** to ester formation[262] and IR frequency for free OH absorption at 3610 cm^{-1} point to the OH group being anti to the *N*-methyl and syn to the cycloalkylamino group. **247** shows intramolecular hydrogen-bonding.

The C=O group at the 9-position of several 3-ABNs has been reduced to CH_2 by Wolf–Kishner methods[165,267] or by treating the ketone with BF_3 and 1,2-ethanedithiol followed by desulfurization.[19]

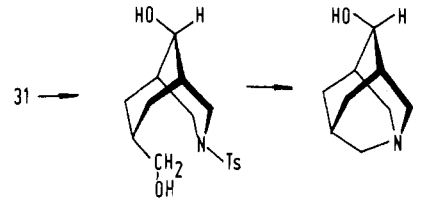
3-Tosyl-7-carbethoxy-3-ABN-9-one (**31**) on reduction with $NaBH_4$ gives a mixture of **248** and **249** in a 4:1 ratio. The OH thus prefers to go to the hindered position. On the other hand, $LiAlH_4$ reduction gives



248 R=COOEt, R^1=H, R^2=OH

249 R=COOEt, R^1=OH, R^2=H

250. Since **250** undergoes detosylation readily to give

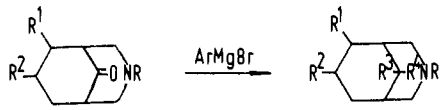


250

an azaadamantanol, the conformation sould be chair–chair with the OH oriented to the side of the cyclohexane ring.[19]

The carbonyl group at the 9-position undergoes addition reactions with Grignard reagents and alkyllithium to give a mixture of α and β alcohols. The presence of a nitrogen atom does not have greater influence on the stereochemistry.[254] Reaction of 3-methyl-3-ABN-9-one with organometallic reagents in THF or ether produces mixtures of tertiary alcohols,[67,269,270] with exo alcohol upto 61–69% yield and the rest endo (31–39% yield). The organometallic reagents employed are CH_3Mg Br, $(CH_3)_2Mg$, CH_3Li, PhMgBr, and PhLi.

1-Methyl-3-phenethyl-3-ABN-9-one (**17**) and 3-benzyl-7-methyl-6-pyrrolidinyl-3-ABN-9-one (**251**) react with PhMgBr to give the corresponding tertiary alcohols.[51,67] The stereochemistry of the products is not



251 R^1 =  , R^2=Me

R = $PhCH_2$

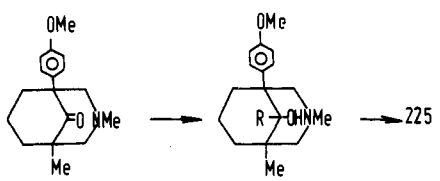
R^3 = Ar or OH

R^4 = OH or Ar

252 = R^1 =  , R^2=Me, R^3 = p-Tolyl, R^4=OH

known. *p*-Tolyllithium has been employed to get the tertiary alcohol **252**.[67]

Addition of EtOC≡CLi to the 3-ABN-9-one **253** gives 41% of the acetylinic tertiary alcohol **254**. Hydration followed by hydrolysis gives the acid **255**.[271]

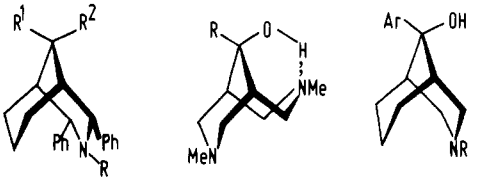


253

254 R=C≡C-OMe

255 R=CH_2COOH

The acetylenic alcohols[155,272-274] **256** and **257** are formed from 2,4-diphenyl-3-ABN-9-one by three methods: (i) reaction with acetylene in either containing KOH, (ii) reaction with acetylene in ammonia containing sodium, and (iii) reaction with HC≡CMgBr. The first two methods give 70–86% of **256** while the third gives only 26% of **256**. Hydrogenation of **256** over Raney nickel and palladium has been reported to be five times faster than that of **257**.[272]



256 R^1=OH, R^2=C≡CH

257 R^1=C≡CH, R^2=OH

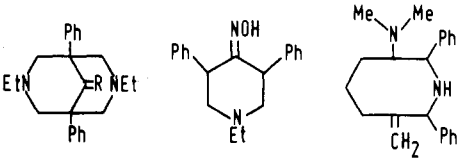
258 R = aryl

259

When *N,N'*-dimethyl-3,7-DABN-9-one is treated with ArLi followed by an acid chloride or alkyl halide, the products are **258**.[275] These compounds are reported to exist in a chair–boat conformation in which the piperidine ring to which the OH is syn is in the boat form.

N-Alkyl-9-aryl-3-ABN-9-ols (**259**) have been obtained by treating 3-methyl-3-ABN-9-one with an arylmagnesium halide.[276] The tertiary alcohols have also been converted to the methyl ethers.

The carbonyl at the 9-position reacts with hydroxylamine to give oximes. 1,5-Diphenyl-3,7-diethyl-3,7-DABN-9-one (**74**, R = Et) on treatment with hydroxylamine in acetic acid forms **260** and **261**. The extent of rupture of the 3-ABN skeleton depends upon the time of reaction.[70,103]



260 R=NOH

261

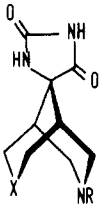
262

2,4-Diphenyl-3-ABN-9-one oxime has been converted,[277,278] through several steps, to 7-(dimethylamino)-1-methyl-3-methylene-2,8-diphenyl-1-azacyclooctane (**262**). The oxime has also been reduced to amines.[188]

N-Tosyl-3-ABN-9-one derivatives (**31**) have been converted to amines by reduction of the oximes.[19]

1,5-Diaryl-3,7-DABN-9-ones (**74**) and some simple 3,7-DABN-9-ones fail to react with carbonyl reagents except hydrazine.[90,162] In the first case the reason seems to be the steric hindrance caused by the phenyl groups at bridgehead positions and not due to chair–boat conformation. In the second case the failure has been ascribed to an amide-like character.[162]

The spirohydantoin skeleton (**263** and **264**) has been built up at the 9-position from 3-alkyl-3-ABNs and 3-methyl-7-alkyl-3,7-DABNs.[279]

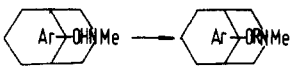


263 X=CH_2

264 X=NR

C. Reactions of OH Groups

O-Alkylation of tertiary 3-ABN alcohols has been carried out.[70,280,281] 3-Methyl-9β-hydroxy-9α-phenyl-3-ABN (**265**) reacts with ethanol in the presence of concentrated H_2SO_4 to yield the 9β-ethoxy derivative. The



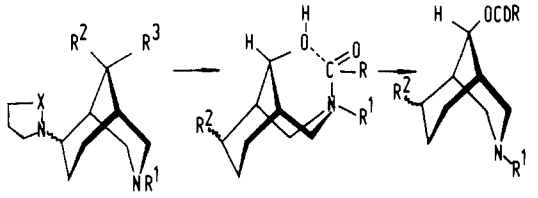
R=Et, Me

265

corresponding methyl ester can also be produced similarly.[70,280,281]

O-Alkylation of 2,4-diphenyl-3-ABN-9-ols fails to take place with simple aliphatic alcohols and acid, dialkyl sulfate, or NaH/CH_3I.[168]

However, acetylation occurs with much more ease with common acylating agents.[159] The 3-ABN-9-ol **266** reacts with Ac_2O, $MeSO_2Cl$, $(EtCO)_2O$, and C_6H_5COCl to yield the corresponding esters.[67,282] Acetylenic alcohols also could be benzoylated.[283]



266 R^1=COPh R^2=H, R^3=OH

267 R^2=H

269 R^2=OH, R^3=H

268 R^2 = -N(X)

270 R^2=H, R^3=OH

House et al. carried out a series of investigations and reported[171] that unsubstituted 3-methyl-3-azabicyclo-[3.3.1]nonan-9-ols and analogues in which the OH group is syn to the *N*-methyl group react with *p*-nitrobenzoyl chloride in $CHCl_3$ at room temperature to yield the corresponding *p*-nitrobenzoates. Their anti isomers, however, are inert under these conditions. It has been suggested[171] that the facile esterification of the syn-oriented compounds proceeds by an intramolecular N- to O-acyl transfer through the intermediacy of an acylammonium complex as shown by structures **267** and **268**. When this observation is employed, the configurations of 6-(1-azacycloalkyl)-3-ABN-9-ols (**269** and **270**) have been established.[68,284]

The solvolysis rates of 3-alkyl-3-ABN-9-methanesulfonate and 9-alkyl-9-ABN-3-methane-sulfonate have been compared and correlated with the electronic and steric properties of the N-substituents.[285]

D. Reactions at Bridgehead Positions

Many synthetic routes for 3-ABNs and 3,7-DABNs involve the decarboxylation of the carboxyl group present in the 1- and/or 5-positions. Decarboxylation has been carried out by heating with dilute acid.

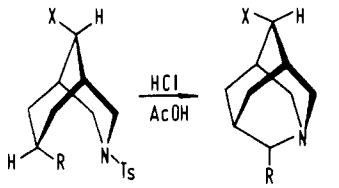
The decarboxylation at bridgehead positions of 3-ABNs without bulky substituents at 2,4,6,8 position is comparatively easy. This has been ascribed to the overlap of the intermediate carbanion orbitals with the π orbitals of the adjacent carbonyls. Ease of decarboxylation is related to the dihedral angle between the carbanion and the carbonyl group.[51,79,286]

However, results obtained from deuterium exchange and decarboxylation experiments[287] reveal that decarboxylation does not proceed through the usual cyclic mechanism even if one considers 3-ABNs as borderline cases for the existence of compounds with a bridgehead double bond.[288] The probable course of decarboxylation seems to involve opening and closing of the 3-ABN skeleton.[287]

Bromination of 2,4-diaryl-3-ABN-9-one does not give the 1-bromo derivative but cleaves the ring to give dibenzylidenecyclohexanone.[168]

E. Cyclizations

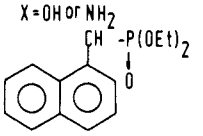
Compound **271** undergoes detosylation and cyclization in HCl–AcOH to yield azaadamantane derivatives[19,20] (**272**). Quinine analogues containing azaa-



271 $R=CH_2OH$, $X=OH$ or NH_2

272 R=H, X=OH or NH_2

274 R = CH_2



273

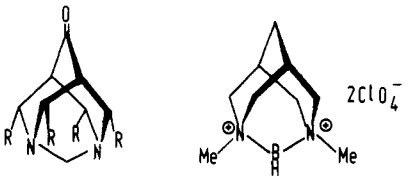
damantane skeleton have been obtained.[289] The alcohol **271** (X = H) is oxidized to the aldehyde, condensed with the phosphonate **273**, and cyclized to azaadamantane derivative **274**.

The insertion reaction of the carbene produced at the C-9 position of 3-methyl-3-ABN proceeds[290] exclusively into the side opposite to the *N*-methyl group, yielding 3-methyl-3-azatricyclo[6.1.0.0^{5,9}]nonane (**275**) while that

275 276 277

of a carbene at bridge carbon C-8 of 3-methyl-3-azabicyclo[3.2.1]octane is to the same side of the *N*-methyl group to give 2-methyl-2-azabicyclo[5.1.0.0^{4,8}]octane (**276**).

3,7-DABN sulfate when treated with HCHO and HCOOH forms 1,3-diazaadamantane-1-methonium sulfate[21] (**277**). 3,7-DABN when refluxed with benzene and paraformaldehyde forms[291] diazaadamantane (**10**, X = N, R = H). Similarly, 1,5-diphenyl-3,7-DABN-9-one (**76**) and its *N*,*N*′-diacetyl derivative (**55**) when heated with HCHO yield 100% 5,7-diphenyl-1,3-diazaadamantane.[22,23,88,292] 2,4,6,8-Tetraphenyl-3,7-DABN-9-one (**74**) and the alcohol are also claimed[24,136] to react with paraformaldehyde to give diazaadamantanes (**278**). A paper chromatography method has been described for identifying the 1,3-diazaadamantanes and 3,7-DABNs.[293]

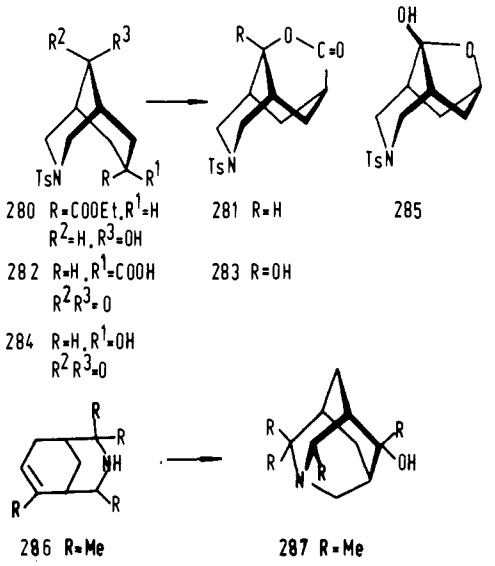


278 R = Ph 279

The diphenyladamantan-6-one and bis(carbomethoxy)adamantan-6-one can, however, be prepared directly from the ketone, HCHO, and ammonium acetate.[22,90]

1,3-Dimethyl-3,7-DABN is reported to react with $NaBH_4/ClO_4^-$ with the formation of 1,3-dimethyl-2-boronia-1,3-diazaadamantane perchlorate[294] (**279**).

A few cases of lactone formation in 3-ABNs are known. An attempt to cleave the tosyl group in ethyl *N*-tosyl-9-*exo*-hydroxy-3-ABN-7-*endo*-carboxylate (**280**)



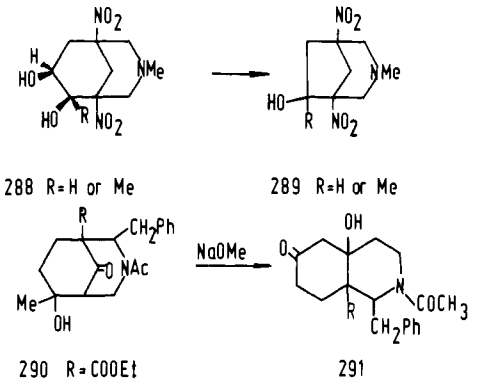
280 R=COOEt, R^1=H, R^2=H, R^3=OH
281 R=H
285
282 R=H, R^1=COOH, R^2R^3=O
283 R=OH
284 R=H, R^1=OH, R^2R^3=O
286 R=Me
287 R=Me

has resulted in the formation of the lactone **281**.[65] ^{13}C NMR studies at various temperatures indicate that an equilibrium exists between **282** and **283**.[295] In a similar way the *N*-tosyl-7-*exo*-hydroxy-3-ABN-9-one (**284**) is shown to exist in equilibrium with the hemiacetal **285**.[296] The unsaturated 3-ABN derivative **286** when heated with HCHO gives substituted azaadamantanol[297] (**287**).

F. Other Reactions

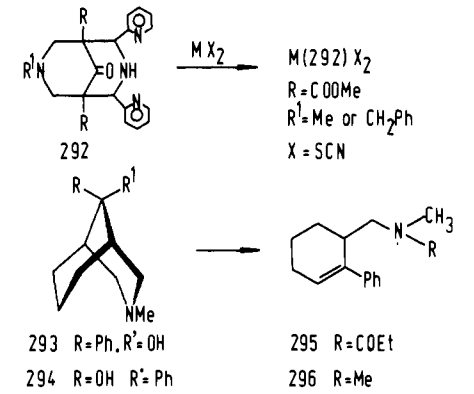
Several substituted 3-ABNs undergo a novel rearrangement involving ring contraction to form 3-azabicyclo[3.2.1]octane derivatives.[64] Thus the 1,5-dinitro-3-ABN derivative **288** on exposure to sodium metaperiodate in methanol for 18 h under nitrogen is converted into 1,5-dinitro-3-methyl-3-azabicyclo[3.2.1]octan-6-ol (**289**). 1-Carbethoxy-2-benzyl-3-acetyl-6-methyl-6-hydroxy-3-ABN-9-one (**290**) on treatment with NaOMe in MeOH yields 1-benzyl-2-acetyl-6-oxo-9-carbethoxy-10-hydroxydecahydroisoquinoline (**291**). This has been shown as a second-order reaction, first order with respect to the substrate and first order with respect to NaOMe, and favored at low temperatures.[70]

3-ABNs with pyridyl substituents at 2- and 4-positions serve as polydentate ligands and form complexes.[289] Compound **292** reacts with an equimolar quantity of transition-metal salts to give complexes of general formula M(**292**)X_2 where X is SCN and M may be Mn,



288 R=H or Me
289 R=H or Me
290 R=COOEt
291

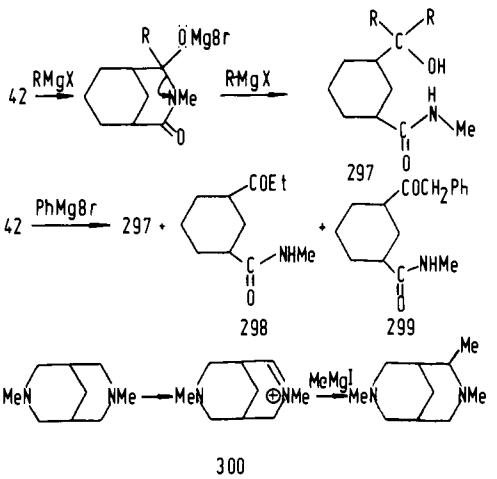
Ni, Co, Fe, and Cd.[299] The structures of these complexes have been characterized by IR and NMR spectral data.[130]



292
M(292)X_2
R=COOMe
R^1=Me or CH_2Ph
X=SCN
293 R=Ph, R'=OH
294 R=OH R'=Ph
295 R=COEt
296 R=Me

Heating the 9α- or 9β-hydroxy compound **293** or **294** in propionic anhydride at 100 °C gives the corresponding propionate while treatment of either **293** or **294** in propionic anhydride at 160 °C affords a mixture of **295** and **296**. A possible path for the formation of **295** and **296** may be a kind of fragmentation reaction.[300]

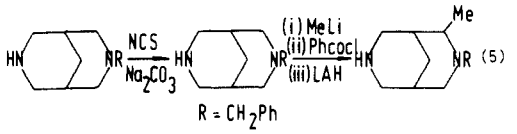
3-Methyl-3-ABN-2,4-dione (**42**) reacts with RMgX with ring opening[301] to yield **297**. When the Grignard reagent is PhMgBr, two more products, **298** and **299**, are also formed along with **297**.



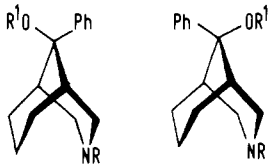
300

Alkyl groups can be introduced at the 2-position of 3-ABNs. Treatment of 3,7-dimethyl-3,7-DABN with excess mercuric acetate[172,203,302,303] using 33% acetic anhydride in acetic acid as solvent furnishes a aldimmonium ion **300**. This on reaction with excess alkylmagnesium iodide produces the 2-alkyl derivative of 3,7-DABN. Alkylation of *N*-benzylbispidines is

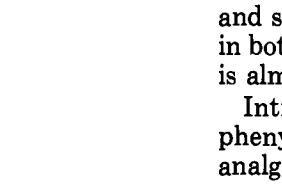
carried out in a different way by employing *N*-chlorosuccinimide (eq 5).



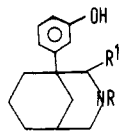
Oxidation of *N,N'*-dimethylbispidine with excess mercuric acetate in 5% aqueous HOAc produces the 3,7-dimethyl-3,7-DABN-2-one.[203] Instead oxidation by the same reagent using 33% acetic anhydride in HOAc and treating the resulting aldimmonium ion in methanol give 2-methoxy-3,7-dimethyl-3,7-DABN.[203]



301a R = R^1 = Me
301b R = Me, R^1 = Ph
301c R = CH_2Ph, R^1 = Me
301d R = CH_2Ph, R^1 = Ar



302a
302b
302c
302d



303 R = H, Me, n-Pr, $-C_5H_{11}$
$CH_2CH{=}CH_2$, $-CH_2-$
R^1 = H, Me, $CH_2-CH{=}CMe_2$
CH_2CH_2Ph

Microbiological oxygenation of 3-benzyl-3-ABN with *Sporotrichum sulfurescens* gives 3-benzyl-*endo*-3-ABN-6-ol.[304,305] It has been proposed that *S. sulfurescens* attack at saturated carbon approximately 5.5Å from an electron-rich center such as ketone or amide carbonyl oxygen. Hydroxylation of 3-benzyl-3-ABN with *Rhizopus arrhizus*[305] forms a mixture of *endo*- and *exo*-3-benzyl-3-ABN-6-ols.

The C-7 position in both bicyclo[3.3.1]nonanes and 3-ABNs is inactive toward chemical transformations[211,306] as a result of the chair–chair conformation. 3-Tosyl-2-hydroxy-3-ABN-9-ones (**164** and **165**) are resistant to dehydration with a variety of reagents. Derivatives of **164** and **165** (**166, 168, 167, 169**) also fail to undergo elimination with various reagents except in NaOAc/HOAc, in which case along with substitution elimination also takes place to the tune of about 44%.[211]

VII. Biological Activity

Many derivatives of 3-ABN are found to possess useful biological activities.[307] In a study involving 26 3-ABN derivatives, the analgesic activity has been determined by employing the Haffner tail pinch method and compared with those of meperidine hydrochloride and morphine hydrochloride. Good analgesic activities are reported to be shown by 9-alkoxy or 9-aryloxy derivatives **301** and **302**.[308,309] 3-Allyl-9-α-phenyl-9-β-methoxy-3-ABN lacks narcotic antagonism while weak antagonism is exhibited by the 9-β-phenyl-9-α-methoxy isomer.[310]

The citrate salt of 3-methyl-9-phenyl-9-*endo*-methoxy-9-ABN (**302a**) has an analgesic potency approximately 3 times greater than that of meperidine.[308-313] The activity has been determined by mechanical, chemical, and thermal stimulation methods in mice and rats. Adverse side effects such as mydriasis, hypotension, and local irritation are reportedly less pronounced with **302a** than in meperidine at equianalgesic doses.[309,313]

Similar antagonism to analgetic effects by nalorphine, rapid development of tolerance to analgetic effects, antitussive effect, potentiation of thiopental anaesthetic, and slight respiratory depression have been observed in both the drugs.[308,309,313,314] The acute toxicity of **302a** is almost similar to that of meperidine.

Introduction of a *m*-methoxy substituent in the phenyl group of **302** results in radical potentiation of analgesic and antitussive activities.[280,315,313] *N*-Carbamates of these derivatives exhibit appreciable antiinflammatory effects with analgesic activities.[256,280,316] Similarly, 3-methyl-9-*exo*-benzoyl-3-ABN has local anaesthetic activity comparable with that of procaine hydrochloride.[313] The simple 3-ABN is effective against influenza infection.[317]

Replacement of amino hydrogen in 3-ABN by a linear chain of 2–5 carbon atoms carrying at the end an amino group disubstituted with Me or Et gives diamines having powerful ganglioplegic and hypotensive properties.[74,75,318-320]

However, the corresponding 3-alkyl-3-dialkylaminoalkyl-3-ABN hydrochlorides and mono and bis quaternary salts exhibit only a low degree of hypotensive activity. By comparison with very highly active compounds in the closely related 2-azabicyclo[4.3.0]nonane (isoindole) series, it has been concluded that changing the bridging in the bicyclic ring from the [4.3.0] to [3.3.1] structure results in marked reduction or almost complete loss of hypotensive activity.[74]

Several 6-substituted 3-ABNs are found to be useful as sedatives, analgesics, antipyretics, and psycholaleptic and hypoglycemic agents.[67,321] 3,7-Dimethyl-6-pyrrolidino-9-hydroxy-3-ABN was the most effective hypoglycemic agent and had the least toxicity of the drugs tested.[322]

A series of N-substituted 1-(3-hydroxyphenyl)-3-ABNs (**303**) has been examined by structure–activity relationships. In agreement with earlier work[323,324] on *N*-alkylpiperidines and other similar ring systems it was concluded that replacement of an *N*-methyl group of **303** by a propyl or an allyl group would result in an increase in the antagonist activity.[78] None of the 1-phenyl-3-ABN derivatives shows any analgesic activity. The *N*-methyl derivatives of **303** show narcotic analgesic activity. Replacement of *N*-methyl by a propyl or allyl group increase antagonist activity.

The 3,7-DABNs possess good antiarrhythmic potencies,[325] but they are also quite toxic, as indicated by LD_{50} values.[326] The 1,5-diphenyl-3,7-DABNs are local anaesthetics but have negligible analgesic or physiological activities.[101,327] Some of them possess hypotensive activity[328] and activity for miocardia.[329] *N,N'*-Dibenzyl derivatives are found to be antiphlogistic, and antithrombic.[330]

Quaternary salts of certain α,ω-bis(9-methyl-3,9-DABN-9-yl)alkanes are found to exhibit neuromuscular blocking activity[121,122,331-334] which is explained as resulting from depolarization at motor end plate. Some 3,9-DABNs possess neuroleptic activity.[335]

Many 3,9-DABNs are found to possess weak central cholinolytic action,[336] curarelike activity,[337] a slight local anesthetic effect,[337] and other activities.[338] The quaternary salts obtained from 3,9-DABNs with various alkyl substituents have been found to possess curariform properties which vary directly with the length of the polymethylene chain and ganglioblocking activity which varied inversely with the number of carbon atoms in the chain. The neuromuscular block induced by these compounds is decreased by proserine and ditilin and enhanced by diplacin.[339]

VIII. Summary and Conclusion

In the foregoing sections we have attempted to review comprehensively the numerous studies on 3-ABNs. The review establishes that in spite of the simplicity of the methods available both for the synthesis and determination of the stereochemistry of 3-ABNs, 3,7-DABNs, etc., there remains a large number of stereochemical assignments to be explored. In many cases the substituents have been incorporated in the skeleton with a view to examining the biological activities but without any further attempt to establish the configuration and conformation of the rings. In this regard ^{13}C NMR spectroscopy, X-ray crystallography, and advanced methods of ^{1}H NMR spectroscopy may prove to be of much use over other techniques.

It is surprising that different configurational and conformational assignments have been made even for simpler easily obtainable tetraarylbispidines and their derivatives. Since the tetraaryl derivatives can exist in a single conformation only and cannot flip to the other, further study on these systems is required.

Regardless of the above possibilities, probably the most important area awaiting exploration is the study of limiting factors which determine the conformation and the product spread in the case of epimeric pairs of substituted 3-ABNs. Quantitative studies and theoretical calculations are also needed.

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IX. References

(1) Wiesner, K.; Valenta, Z. *Prog. Chem. Org. Nat. Prod.* **1958**, *16*, 26.
(2) Shimizu, B.; Ogiso, A.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 774.
(3) Henry, T. A. "Plank Alkaloids"; J. and A. Churchill Ltd.: London, 1956; p 75.
(4) Hart, N. K.; Jones, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1967**, *20*, 561.
(5) Pelletier, S. W. "Chemistry of the Alkaloids"; Van Nostrand: New York, 1970; p 503.
(6) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962, p 204.
(7) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965; p 71.
(8) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.
(9) Eliel, E. L.; Lukach, C. A. *J. Am. Chem. Soc.* **1957**, *79*, 5986.
(10) Eliel, E. L.; Biros, F. J. *J. Am. Chem. Soc.* **1966**, *88*, 3334.
(11) Baliah, V.; Chellathurai, T. *Indian J. Chem.* **1971**, *9*, 1092.
(12) Radhakrishnan, T. R.; Balasubramanian, M.; Baliah, V. *Indian J. Chem.* **1973**, *11*, 562.
(13) Balasubramanian, M.; D'sSouza, A. *Indian J. Chem.* **1970**, *8*, 23.
(14) Baliah, V.; Bhavani, N.; Chandrasekaran, J. *Indian J. Chem.* **1978**, *16B*, 943.
(15) Baliah, V.; Mangalam, G. *Indian J. Chem.* **1978**, *16B*, 827.
(16) Reisse, J. "Conformational Analysis": Chiurdoglu, G. Ed.; Academic Press: New York, 1971; p 219.
(17) Balasubramanian, M.; Padma, N. *Tetrahedron* **1963**, *19*, 2135.
(18) Baliah, V.; Chandrasekaran, J. *Indian J. Chem.* **1977**, *15B*, 558.
(19) Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc. D* **1970**, *4*, 197.
(20) Speckamp, W. N.; Van Oosterhout, H. *Heterocycles* **1977**, *7*, 165.
(21) Smissman, E. E.; Weis, J. A. *J. Heterocycl. Chem.* **1968**, *5*, 405.
(22) Stetter, H.; Schafter, J.; Dieminger, K. *Chem. Ber.* **1958**, *91*, 598.
(23) Mannich, C.; Mohs, P. *Chem. Ber.* **1930**, *63B*, 608.
(24) Chiavarelli, S.; Settimj, G.; Rabagliati, F. M. *Gazz. Chim. Ital.* **1960**, *90*, 311.
(25) Blicke, F. F. *Org. React.* **1942**, *1*, 303.
(26) House, H. O. "Modern Synthetic Reactions"; W. A. Benzamin, Inc.: Manila, 1972; p 135.
(27) Brown, H. C., Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.
(28) Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, *98*, 5297.
(29) Jacob, III, P.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 579.
(30) Kramer, G. W.; Brown, H. C. *J. Organometal. Chem.* **1975**, *90*, C1.
(31) Sinclair, J. A., Molander, G. A.; Brown, H. C. *J. Am. Chem. soc.* **1977**, *99*, 954.
(32) Wiberg, K. B. *Adv. Alicycl. Chem.* **1968**, *2*, 185.
(33) Meinwald, J.; Meinwald, Y. C. *Adv. Alicycl. Chem.* **1966**, *1*, 1.
(34) Rubtsov, M. Y.; Mikhlina, E. E.; Yakhontov, L. N. *Russ. Chem. Rev. (Engl. Transl.)* **1960**, *29*, 37.
(35) Stoll, A.; Jucker, E. *Angew. Chem.* **1954**, *66*, 376.
(36) Lark, J. C. *Diss. Abstr.* **1965**, *26*, 94.
(37) Flegal, C. A. *Diss. Abstr. B* **1969**, *29*, 3675.
(38) Fort, R. C.; Schleyer, P. v. R. *Chem. Rev.* **1964**, *64*, 277.
(39) Bingham, R. C.; Schleyer, P. V. R. *Fortschr. Chem. Forsch.* **1971**, *18*, 1.
(40) Buchanan, C. L. *Topics Carbocycl. Chem.* **1969**, *1*, 199.
(41) Ganter, C. *Topics Current Chem.* **1976**, *67*, 1.
(42) Zefirov, N. S.; Rogozina, S. V. *Russ. Chem. Rev. (Engl. Transl.)* **1973**, *42*, 190.
(43) Zefirov, N. S. *Russ. Chem Rev. (Engl. Transl.)* **1975**, *44*, 196.
(44) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 286.
(45) IUPAC, "Nomenclature of Organic Chemistry," 2nd ed.; Butterworths: London, 1966; p 32.
(46) Baliah, V.; Chandrasekaran, J.; Natarajan, A. *Indian J. Chem.* **1977**, *15B*, 829.
(47) Radhakrishnan, T. R.; Balasubramanian, M.; Baliah, V. *Indian J. Chem.* **1973**, *11*, 318.
(48) Baliah, V.; Ekambaram, A. *J. Indian Chem. Soc.* **1955**, *32*, 274.
(49) Baliah, V.; Gopalakrishnan, V. *J. Indian Chem. Soc.* **1954**, *31*, 250.
(50) Baliah, V.; Gopalakrishnan, V.; Govindarajan, T. S. *J. Indian Chem. Soc.* **1954**, *31*, 832.
(51) Iwai, I.; Kurabayashi, M. Japan Patent 6723941, 1967; *Chem. Abstr.* **1968**, *69*, 35982y.
(52) Schneider, W.; Goetz, H. *Arch. Pharm.* **1961**, *294*, 506.
(53) Schneider, W.; Gotz, H. *Naturwissenschaften* **1960**, *47*, 397.
(54) Rossi, S.; Butta, W. *Ann. Chim. (Rome)* **1962**, *52*, 381; *Chem. Abstr.* **1962**, *57*, 9810i.
(55) Blicke, F. F.; McCarty, F. J. *J. Org. Chem.* **1959**, *24*, 1379.
(56) Iwai, I.; Kurabayashi, M. Japan Patent 13950, 1967; *Chem. Abstr.* **1968**, *68*, 114442e.
(57) House, H. O.; Wickham, P. P.; Muller, H. C. *J. Am. Chem. Soc.* **1962**, *84*, 3139.
(58) Azerbaev, I. N.; Omarov, T. T.; Al'mukhanova, K. A. *Kratk-Tezisv-Vses. Soveshch. Probl. Mekh. Geteroliticheskikh Reakts.* **1974**, *150*; *Chem. Abstr.* **1976**, *85*, 77503d.
(59) Azerbaev, I. N.; Omarov, T. T.; Gubasheva, A. Sh.; Al'mukhanova, K. A.; Baisalbaeva, S. A. *Vestn. Akad. Nauk. Kaz. SSR* **1975**, *2*, 47; *Chem. Abstr.* **1975**, *82*, 156245n.

(60) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1971**, *9*, 1020.
(61) Azerbaev, I. N.; Omarov, T. T.; Al'mukhanova, K.; Baisalbaeva, S. A. *Zh. Org. Khim.* **1976**, *12*, 1207.
(62) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1977**, *15B*, 798.
(63) Jeyaraman, R.; Chockalingam, KN.; Rajendran, T. *Indian J. Chem.* **1980**, *198*, 519.
(64) Wall, R. T. *Tetrahedron* **1970**, *26*, 2107.
(65) Speckamp, W. N.; Dijkink, J.; Huisman, H. O. *J. Chem. Soc. D* **1970**, *4*, 196.
(66) Stetter, H.; Reinartz, W. *Chem. Ber.* **1972**, *105*, 2773.
(67) Yoshitomi Pharmaceutical Industries Ltd., French Patent 1 557 671, 1969; *Chem. Abstr.* **1969**, *72*, 43472j.
(68) Britten, A. Z.; O'Sullivan, J. *Chem. Ind. (London)* **1972**, 336.
(69) Curran, A. C. W. U.S. Patent 3 829 427, 1974; *Chem. Abstr.* **1974**, *81*, 135998z.
(70) Becker, H. G. O.; Bergmann, G.; Sozabo, L. *J. Prakt. Chem.* **1968**, *37*, 47.
(71) Bok, Th. R.; Speckamp, W. N. *Tetrahedron*, **1979**, *35*, 267.
(72) The configuration of the cyclohexane derivative must be cis in order that two axial substituents react to form a new ring. However, the cis-trans mixture may also be used.
(73) Schneider, W.; Gotz, H. *Naturwissenschaften* **1960**, *47*, 61.
(74) Rice, L. M.; Grogan, C. H. *J. Org. Chem.* **1958**, *23*, 844.
(75) Rossi, S.; Valvo, C. *Chim. Ind. (Milan)* **1960**, *42*, 637.
(76) Leonard, N. J.; Conrow, K.; Sauess, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 5185.
(77) Schill, D.; Schneider, W. *Arch. Pharm.* **1975**, *308*, 925.
(78) Takeda, M.; Kawaramori, M.; Noguchi, K.; Nurimoto, S. *Chem. Pharm. Bull.* **1977**, 25, 1777.
(79) Ferris, J. P.; Miller, N. C. *J. Am. Chem. Soc.* **1963**, *85*, 1325.
(80) Garcia-Blanco, S.; Florencio, F.; Smith-Verdier, P. *Acta Crystallogr., Sect B* **1976**, *32*, 1382.
(81) Lora-Tamayo, M.; Garcia-Munoz, G.; Madronero, R. *Bull. Soc. Chim. Fr.* **1958**, *1334*.
(82) Sinitsa, A. D.; Nebogatova, L. O. *Zh. Org. Khim.* **1978**, *14*, 522.
(83) Reichert, B. "Die Mannich Reaktion"; Springer-Verlag: Berlin, 1959.
(84) Mannich, C.; Veit, F. *Chem. Ber.* **1935**, *68B*, 506.
(85) Galinovsky, F.; Langer, H. *Monatsh.* **1955**, *86*, 449.
(86) Misiti, D.; Chiavarelli, S. *Gazz. Chim. Ital.* **1966**, *96*, 1696.
(87) Chiavarelli, S.; Settimj, G. *Gazz. Chim. Ital.* **1958**, *88*, 1253.
(88) Chiavarelli, S.; Settimj. G. *Gazz. Chim. Ital.* **1958**, *88*, 1234.
(89) Chiavarelli, S.; Fennoy, L. V. *J. Org. Chem.* **1961**, *26*, 4895.
(90) Sasaki, T.; Eguchi, S.; Kiriyama, T.; Sakito, Y. *J. Org. Chem.* **1973**, *38*, 1648.
(91) Stetter, H.; Dieminger, K.; Rauscher, E. *Chem. Ber.* **1959**, *92*, 2057.
(92) Kuznetsov, A. I.; Yakushev, P. F.; Unkovskii, B. V. *Zn. Org. Khim.* **1974**, *10*, 841.
(93) Stetter, H.; Merten, R. *Chem. Ber.* **1957**, *90*, 868.
(94) Stetter, H.; Hennig, H. *Chem. Ber.* **1955**, *88*, 789.
(95) Dietz, G.; Fiedler, W.; Faust, G. *Chem. Ber.* **1969**, *102*, 4147.
(96) Hoerlein, U.; Kurz, T.; Lipinski, D. *Chem. Ber.* **1977**, *110*, 3894.
(97) Hoerlein, V. *Eur. J. Med. Chem.-Chim. Ther.* **1977**. *12*, 301; *Chem. Abstr.* **1977**, *87*, 201499q.
(98) Hennig, H.; Pesch, W. *Arch. Pharm.* **1974**, *307*, 569.
(99) Steck, E. A.; Fletcher, L. T.; Brundage, R. P. *J. Org. Chem.* **1963**. *28*, 2233.
(100) Anet, E. L. F. J.; Hughes, G. K.; Marmion, D.; Ritche, E. *Aust. J. Sci. Res.* **1950**, *3A*, 330.
(101) Kyi, Z-Y.; Wilson, W. *J. Chem. Soc.* **1951**, 1706.
(102) Mannich, C.; Hieronimus, O. *Chem. Ber.* **1942**, *75B*, 49.
(103) Andrisano, R.; Angeloni, A.; Gottarelli, G. *Gazz. Chim. Ital.* **1967**, *97*, 1762.
(104) Chiavarelli, S.; Toeffler, H. F.; Fennoy, L. V.; Landi Vittory, R.; Mazzeo, P. *Farmaco*, Ed. *Sci.* **1965**, *20*, 408.
(105) Gottarelli, G. *Tetrahedron Lett.* **1965**, 2813.
(106) Chiavarelli, S.; Toeffler, F.; Landi-Vittory, R.; Mazzeo, P. *Gazz. Chim. Ital.* **1964**, *94*, 1021.
(107) Chiavarelli, S.; Settimj, G. *Gazz. Chim. Ital.* **1957**, *87*, 109.
(108) Chiavarelli, S.; Toffler, F.; Gramiccivani, L.; Valsecchi, G. P. *Gazz. Chim. Ital.* **1968**, *98*, 1126.
(109) Chiavarelli, S.; Toffler, F.; Mazzeo, P.; Gramiccioni, L. *Farmaco, Ed. Sci.* **1968**, *23*, 360; *Chem. Abstr.* **1968**, *69*, 52115k.
(110) Settimj, G.; Landi-Vittory, R.; Monache, F. D.; Chiavarelli, S. *Gazz. Chim. Ital.* **1966**, *96*, 311.
(111) Misiti, D.; Settimj, G.; Mantovani, P.; Chiavarelli, S. *Gazz. Chim. Ital.* **1970**, *100*, 495.
(112) Smissman, E. E.; Ruenitz, P. C.; Weis, J. A. *J. Org. Chem.* **1975**, *40*, 251.
(113) Hohenlohe-Oehringen, K. *Monatsh.* **1963**, *94*, 1208.
(114) Cummings, T. F.; Shelton, J. R. *J. Org. Chem.* **1960**, *25*, 419.
(115) Fernandez, J. E.; Fowler, J. S.; Glaros, S. J. *J. Org. Chem.* **1965**, *30*, 2787.
(116) Nikitskaya, E. S.; Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1970**, 1372; *Chem. Abstr.* **1971**, *74*, 87867n.
(117) Medvedev, B. A.; Nikitskaya, E. S. *Khim.-Farm. Zh.* **1970**, *4*, 13. *Chem. Abstr.* **1970**, *72*, 132668v.
(118) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Zh. Obshch. Khim.* **1962**, *32*, 3684.
(119) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Khim. Geterotsikl. Soedin., Sb. 1: Azotsod. Geterots.* **1967**, 445. *Chem. Abstr.* **1969**, *70*, 77832a.
(120) Nikitskaya, E. S.; Levkoeva, E. I., Usovskaya, V. S.; Rubtsov, M. V. *Khim. Geterotsikl. Soedin., Akad. Nauk Lat. SSR.* **1965**, 296; *Chem. Abstr.* **1965**, *63*, 6982h.
(121) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Zh. Obshch. Khim.* **1961**, *31*, 3202; *Chem. Abstr.* **1962**, *56*, 15491i.
(122) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Zh. Obshch. Khim.* **1962**, 32, 2886; *Chem. Abstr.* **1963**, *58*, 9064a.
(123) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Zh. Obshch. Khim.* **1960**, *30*, 3306; *Chem. Abstr.* **1961**, *55*, 18743b.
(124) Cignarella, G.; Maffii, G.; Testa, E. *Gazz. Chim. Ital.* **1963**, *93*, 226.
(125) Nikitskaya, E. S.; Levkoeva, E. I.; Usovskaya, V. S.; Rubtsov, M. V. *Zh. Org. Khim.* **1965**, *1*, 174; *Chem. Abstr.* **1965**, *62*, 14678a.
(126) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Khim. Geterotsikl. Soedin., Sb. 1: Azotsod. Geterots.* **1967**, 445; *Chem. Abstr.* **1969**, 70, 77832a.
(127) Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1962**, 27, 1298.
(128) Baliah, V.; Mangalam, G. *Indian J. Chem.* **1978**, *16B*, 234.
(129) Azerbaev, I. N.; Omarov, T. T.; Gubasheva, A. Sh. *Dokl. Resp. Nauchno-Tekh. Konf. Neftekhim.: 3rd* **1974**, *1*, 437; *Chem. Abstr.* **1975**, *83*, 178789r.
(130) Haller, R. *Arzeimittel*-Forsch. **1965**, *15*, 1327.
(131) Haller, R.; Unholzer, H. *Arch. Pharm.* **1972**, *305*, 855.
(132) Hahn, W. E.; Korzeiniewski, C. *Soc. Sci. Lodg., Acta Chim.* **1971**, *16*, 113; *Chem. Abstr.* **1972**, *76*, 126724b.
(133) Baliah, V.; Usha, R. *Indian J. Chem.* **1972**, *10*, 319.
(134) Baliah, V.; Usha, R. *Indian J. Chem.* **1977**, *15B*, 684.
(135) Haller, R. *Arzneimittel*-Forsch. **1963**, *13*, 1117.
(136) Haller, R. *Arch. Pharm.* **1965**, *298*, 306. (a) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1977**, *15B*, 91.
(137) Eglinton, G.; Martin, J.; Parker, W. *J. Chem. Soc.* **1965**, 1243.
(138) Appleton, R. A.; Egan, C.; Evans, J. M.; Graham, S. H.; Dixon, J. R. *J. Chem. Soc. C* **1968**, 1110.
(139) Brown, W. A. C.; Martin, J.; Sim, G. A. *J. Chem. Soc.* **1965**, 1844.
(140) Webb, N. C.; Becker, M. R. *J. Chem. Soc. B* **1967**, 1317.
(141) Skolik, J.; Wiewiorowski, M.; Krueger, P. J. *J. Mol. Struct.* **1970**, *5*, 461.
(142) Leonard, N. J.; Thomas, P. D.; Gash, V. M. *J. Am. Chem. Soc.* **1955**, 77, 1552.
(143) Wiewiorowski, M.; Edwards, O. E.; Bratek-Wiewiorowska, M. D. *Can. J. Chem.* **1967**, *45*, 1447.
(144) Sadykov, A. S.; Kamayev, F. G.; Korenevsky, V. A.; Leont'ev, V. B.; Ustynyuk, Yu. A. *Org. Magn. Reson.* **1972**, *4*, 837.
(145) Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Lett.* **1965**, 2705. (a) Borowiak, T. E.; Kokii, N. G.; Struchkov, Y. T. *Zh. Strukt. Khim.* **1973**. 14, 387; *Chem. Abstr.* **1973**, *79*, 24503y.
(146) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
(147) Bohlmann, F. *Chem. Ber.* **1959**, *92*, 1798.
(148) Hamlow, H. P.; Okuda, S.; Nakagawa, N. *Tetrahedron Lett.* **1964**, 2553.
(149) Masamune, T.; Takasugi, M. *Chem. Commun.* **1967**, 625.
(150) Agashkin, S. V.; Artyukhin, V. I.; Sokolov, D. V.; Zhaparov, T.; Khludneva, K. I.; Litvineko, G. S. *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.* **1969**, *5*, 46.
(151) Azerbaev, I. N.; Omarov, T. T.; Al'mukhanova, K. *Zh. Obshch. Khim.* **1975**, *45*, 1403; *Chem. Abstr.* **1975**, *83*, 96262z.
(152) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1978**, *16B*, 597.
(153) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1978**, *16B*, 1127.
(154) Wiewiorowski, M.; Skolik, J. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1962**, *10*, 1.
(155) Azerbaev, I. N.; Omarov, T. T.; Al'mukhanova, K. A. *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.* **1975**, *25*, 56; *Chem. Abstr.* **1971**, *84*, 30827b.
(156) Azerbaev, I. N.; Omarov, T. T. *Zh. Org. Khim.* **1976**, *12*, 2475.
(157) Omarov, T. T.; Cheravatova, N. K. *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.* **1978**, *28*, 41 *Chem. Abstr.* **1978** *89*, 162926W.
(158) Baliah, V.; Jeyaraman, R. *Indian. J. Chem.* **1977**, *15B*, 852.
(159) Baliah, V.; Jeyaraman. R. *Indian J. Chem.* **1977**, *15B*, 832.
(160) Eliel, E. L.; Morris Natschke, S.; Manoharan, M.; Ganapathy, K.; Jeyaraman, R.; Jawaharsingh, C. B., Avila, S. *Tetrahedron* (submitted for publication).
(161) Jawaharsingh, C. B.; Manoharan, S.; Jeyaraman, R.; Avila, S., unpublished results.
(162) Smissman, E. E.; Ruenitz, P. C. *J. Org. Chem.* **1976**, *41*, 1593.
(163) La Londe, R. T.; Wong, C. F.; Das, K. C. *J. Am. Chem. Soc.* **1973**, *95*, 6342.
(164) Zbinden, R.; Hall, H. K. *J. Am. Chem. Soc.* **1960**, *82*, 1215.
(165) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1977**, *15B*, 791.
(166) Ganapathy, K.; Gopalakrishnan, V.; Jeyaraman, R. *Indian J. Chem.* **1979**, *17B*, 417.
(167) Baliah, V.; Pandiarajan, K. private communication.

(168) Avila, S. M.Sc. Thesis, American College, Madurai, 1980.
(169) Jeyaraman, R.; Jawaharsingh, C. B.; Avila, S. unpublished results.
(170) Azerbaev, I. N.; Omarov, T. T.; Baisalbaeva, S. A. *Zh. Obshch. Khim.* **1975**, *45*, 1404; *Chem. Abstr.* **1975**, *83*, 114343h.
(171) House, H. O.; Muller, H. C.; Pitt, C. G.; Wickham, P. *J. Org. Chem.* **1963**, *28*, 2407.
(172) Ruenitz, P. C. *J. Org. Chem.* **1978**, *43*, 2910.
(173) Lambert, J. B. *Acc. Chem. Res.* **1971**, *4*, 87.
(174) Chen, C. Y.; Le Fevre, R. J. W. *J. Chem. Soc. B* **1966**, 539.
(175) Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* **1974**, *8*, 1.
(176) Wiseman, J. R.; Krabbenhoft, H. O. *J. Org. chem.* **1975**, *40*, 3222.
(177) Dalling, D. K.; Grant, D. M.; *J. Am. Chem. Soc.* **1972**, *94*, 5318.
(178) Dalling, D. K.; Grant, D. M.; Paul, E. G. *J. Am. Chem. Soc.* **1973**, *95*, 3718.
(179) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.
(180) Roberts, J. D.; Weigert, F. J.; Kroschwitz, J. I.; Reich, H. J. *J. Am. Chem. soc.* **1970**, *92*, 1338.
(181) Dalling, D. K.; Grant, D. M.; *J. Am. Chem. Soc.* **1967**, *89*, 6612.
(182) Pehk, T.; Lippmaa, E. *Org. Magn. Reson.* **1971**, *3*, 679.
(183) Lippmaa, E.; Pehk, T.; Paasivirta, J.; Belikova, N.; Plate, A. *Org. Magn. Reson.* **1970**, *2*, 581.
(184) Pehk, T.; Lippmaa, E.; Sevostjanova, V. V.; Krayuschkin, M. M.; Tarasova, A. I. *Org. Magn. Reson.* **1971**, *3*, 783.
(185) Eliel, E. L.; Bailey, W. F.; Kopp.; Willer, R. L.; Grant, D. M.; Bertrand, R.; Christensen, K. A.; Dalling, D. K.; Duch, M. W.; Wenkert, E.; Schell, F. M.; Cochran, D. W. *J. Am. Chem. Soc.* **1975**, *97*, 322.
(186) McKenna, J.; McKenna, J. M. *J. Chem. Soc. B* **1969**, 644.
(187) Lygo, R.; McKenna, J.; Sutherland, I. O. *Chem. Commun.* **1965**, 356.
(188) Scheiber, P.; Nador, K. *Acta Chim. Acad. Sci. Hung.* **1975**, *84*, 193.
(189) Johnson, R. A. *J. Org. Chem.* **1968**, *33*, 3627.
(190) Douglas, J. E.; Ratliff, T. B. *J. Org. Chem.* **1968**, *33*, 355.
(191) Allinger, N. L.; Carpenter, J. D. G.; Karkowski, F. M. *J. Am. Chem. Soc.* **1965**, *87*, 1232.
(192) Rader, C. P. *J. Am. Chem. Soc.* **1966**, *88*, 1713.
(193) Uebel, J. J.; Goodwin, H. W. *J. Org. Chem.* **1966**, *31*, 2040.
(194) Moniz, W. B.; Poranski, C. F.; Hall, T. N. *J. Am. Chem. Soc.* **1966**, *88*, 190.
(195) Paterson, L. K.; Hammaker, R. M. *J. Phys. Chem.* **1966**, *70*, 3745.
(196) Ouellette, R. J.; Marks, D. L.; Miller, D. *J. Am. Chem. Soc.* **1967**, *89*, 913.
(197) Bauld, N. L.; Rim, Y. S. *J. Org. Chem.* **1968**, *33*, 1303.
(198) Stolow, R. D.; Gallo, A. A. *Tetrahedron Lett.* **1968**, 3331.
(199) Kiefer, E. F.; Gericke, W.; Aminoto, S. T. *J. Am. Chem. Soc.* **1968**, *90*, 6246.
(200) Rader, C. P. *J. Am. Chem. Soc.* **1969**, *91*, 3248.
(201) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
(202) Hassner, A.; Heathcock, C. *J. Org. Chem.* **1964**, *29*, 1350 and references cited.
(203) Ruenitz, P. C.; Smissman, E. E. *J. Org. Chem.* **1977**, *42*, 937.
(204) Bohlmann, F.; Schumann, D.; Schulz, H. *Tetrahedron Lett.* **1965**, 173.
(205) Robinson, M. J. T. *Tetrahedron Lett.* **1968**, 1153.
(206) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307.
(207) Hill, R. K.; Chan, T. H. *Tetrahedron* **1965**, *21*, 2015.
(208) Lyle, R. E.; Thomas, J. J. *Tetrahedron Lett.* **1969**, 897.
(209) Chakrabarty, M. R.; Ellis, R. L.; Roberts, J. L. *J. Org. Chem.* **1970**, *35*, 541.
(210) Lyle, R. E.; Thomas, J. J.; Walsh, D. A. "Conformational Analysis"; Chiurdoglu, G. Ed.; Academic Press: New York, 1971; p 157.
(211) Bok, Th. R.; Speckamp, W. N. *Tetrahedron* **1977**, *33*, 787.
(212) Haller, R.; Unholzer, H. *arch. Pharm.* **1971**, *304*. 866.
(213) Baliah, V.; Chellathurai, T. *Indian J. Chem.* **1971**, *9*, 424.
(214) Baliah, V.; Bhavani, N. *Indian J. Chem.* **1978** *16B*, 776.
(215) Baliah, V.; Mangalam, G. *Indian J. Chem.* **1978**, *16B*, 213.
(216) Haller, R.; Unholzer, H. *Arch. Pharm.* **1971**, *304*, 654.
(217) Hawthorne, D. G.; Johns, S. R.; Willing, R. I. *Aust. J. Chem.* **1976**, *29*, 315.
(218) Settimj, G.; Landi-Vittory, R.; Galler, F.; Sarti, N.; Chiavarelli, S. *Gazz. Chim. Ital.* **1966**, *96*, 604.
(219) Vlavosa, T. F.; Nikitskaya, E. S.; Sheinker, Yu. N. *Dokl. Akad. Nauk SSR* **1969**, *188*, 1049; *Chem. Abstr.* **1970**, *72*, 11890.
(220) Bryant, III, W. M.; Burlingame, A. L.; House, H. O.; Pitt, C. G.; Tefertiller, B. A. *J. Org. Chem.* **1966**, *31*, 3120.
(221) Longevialle, P.; Alazard, J. P.; Lusinchi, X. *Org. Mass. Spectrom.* **1974**, *9*, 480.
(222) Britten, A. Z.; O'Sullivan, J. *Org. Mass Spectrom.* **1974**, *8*, 109.
(223) MacLeod, J. K.; Wells, R. J. *J. Am. Chem. Soc.* **1973**, *95*, 2387.
(224) Green, M. M.; Bafus, D.; Franklin, J. L. *Org. Mass Spectrom.* **1975**, *10*, 679.
(225) Green, M. M.; Cook, R. J.; Schwale, J. M.; Roy, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 3076.
(226) Budzikiewicz, H.; Djerassi, C.; Williams, D. H. "Mass Spectrometry of Organic Compounds"; Holden-Day: San Francisco, 1967; p 157.
(227) Cable, J.; MacLeod, J. K.; Vegar, M. R.; Wells, R. J. *Org. Mass Spectrom.* **1973**, *1*, 1137.
(228) Dekkers, A. W. J. D.; Nibbering, N. M. M.; Speckamp, W. N. *Tetrahedron* **1972**, *28*, 1829.
(229) Ruenitz, P. C.; Smissman, E. E.; Wright, D. S. *J. Heterocycl. Chem.* **1977**, *14*, 423.
(230) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. "Conformational Analysis"; Wiley-Interscience: New York, 1965; p 72.
(231) Eliel, E. L.; Della, E. W.; Williams, T. H. *Tetrahedron Lett.* **1963**, 831.
(232) Baliah, V.; Usha, R. *Indian J. Chem.* **1977**, *15B*, 734.
(233) House, H. O.; Bryant, W. M. *J. Org. Chem.* **1966**, *31*, 3482.
(234) Suleimanov, Kh.; Shalamov, A. E.; Omarov, T. T.; Burassbaev, M. *Zh. Vestn. Akad. Nauk. Kaz. SSR* **1977**, 61; *Chem. Abstr.* **1977**, *86*, 149063f.
(235) Kaftory, M.; Dunitz, J. D. *Acta Crystallogr., Sect. B* **1976**, *32*, 1.
(236) Dobler, M.; Dunitz, J. D. *Helv. Chim. Acta* **1964**, *47*, 695.
(237) Choi, C. S.; Santoro, A.; Abel, J. E. *Acta Crystallogr., Sect. B*, **1976**, *32*, 354.
(238) Brown, W. A. C.; Martin, J.; Sim, C. A. *J. Am. Chem. Soc.* **1965**, *87*, 1844.
(239) Garcia-Blanco, S.; Florencio, F.; Smith-Verdier, P. *Acta Crystallogr., Sect. B* **1976**, *32*, 1386.
(240) Pinkerton, J. M. H.; Steinrauf, L. K. *J. Org. Chem.* **1967**, *32*, 1828.
(241) Marion, L.; Leonard, N. J. *Can. J. Chem.* **1951**, *29*, 355.
(242) Przybylska, M.; Barnes, W. H. *Acta Crystallogr.* **1953**, *6*, 377.
(243) Srivastava, S. N.; Przybylska, M. *Tetrahedron Lett.* **1968**, 2697.
(244) Srivastava, S. N.; Przybylska, M. *Acta Crystallogr., Sect. B* **1969**, *25*, 1651.
(245) Krueger, P. J.; Skolik, J. *Tetrahedron* **1967**, *25*, 1799.
(246) Baranowski, P.; Skolik, J.; Wiewirowski, M. *Tetrahedron* **1964**, *20*, 2383.
(247) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.
(248) Karle, I. L.; Karle, J. *Acta Crystallogr.* **1964**, *17*, 1356.
(249) Karle, I. L.; Karle, J. *Tetrahedron Lett.* **1963**, 2065.
(250) Hast, N. K.; Johns, S. R.; Lamberton, J. A.; Mackay, M. F.; Mathieson, A. M.; Satzke, L. *Tetrahedron Lett.* **1972**, 5333.
(251) Leonard, N. J.; Marrow, D. F.; Rogers, M. T. *J. Am. Chem. Soc.* **1957**, *79*, 5476.
(252) Motherwell, W. B.; Roberts, J. S. *Tetrahedron Lett.* **1972**, 4287.
(253) Hall, P. G.; Horsfall, G. S. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1280.
(254) House, H. O.; Bryant, W. M. *J. Org. Chem.* **1965**, *30*, 3634.
(255) Binnig, F.; Raschack, M.; Treiber, H. J. German Patent 2428792, 1976; *Chem. Abstr.* **1976**, *84*, 105675x.
(256) Sankyo Co. Ltd. British Patent 952137, 1964; *Chem. Abstr.* **1964**, *61*, 5614e.
(257) Chiavarelli, S.; Settimj, G. *Gazz. Chim. Ital.* **1958**, *88*, 1246.
(258) Jeyaraman, R.; Chockalingam, KN. *Indian J. Chem.* in press.
(259) House, H. O.; Pitt, C. G. *J. Org. Chem.* **1966**, *31*, 1062.
(260) House, H. O.; Tefertiller, B. A. *J. Org. Chem.* **1966**, *31*, 1068.
(261) Brown, D. R.; Lygo, R.; McKenna, J.; McKenna, J. M.; Hutley, B. G. *J. Chem. Soc. B* **1967**, *11*, 1184.
(262) Settimj, G.; Del Giudice, M. R.; D'Angelo, S.; Disimone, I. *Ann. Chim. (Rome)* **1974**, *64*, 281; *Chem. Abstr.* **1975**, *83*, 192319u.
(263) Pumphrey, N. W. J.; Robinson, M. J. T. *Chem. Ind. (London)* **1963**, 1093.
(264) Lambert, J. B.; Keske, R. G.; Carhart, R. E.; Jovanovich, A. P. *J. Am. Chem. Soc.* **1967**, *89*, 3761.
(265) Boehringer, C. F.; Sochne, G. M. B. H. British Patent 1110645, 1968; *Chem. Abstr.* **1968**, *69*, 52029k.
(266) Baliah, V.; Jeyaraman, R. Unpublished Results.
(267) Ruenitz, P. C.; Smissman, E. E. *J. Heterocycl. Chem.* **1976**, *13*, 1111.
(268) Bok, T. R.; Speckamp, W. N. Heterocycles **1979**, *12*, 343.
(269) Jeyaraman, R.; Jawaharsingh, C. B. Unpublished results.
(270) Azerbaev, I. N.; Omarov, T. T.; Baisalbaeva, S. A.; Bazalitskaya, V. S. *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **1976**, *26*, 55; *Chem. Abstr.* **1976**, *85*, 177361y.
(271) Shimizu, B.; Ogiso, A.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 766.

(272) Sokolov, D. V.; Cherevatova, N. K.; Omarov, T. T.; Kondaurov, G. N. *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **1978**, *28*, 37.
(273) Azerbaev, I. N.; Omarov, T. T.; Al'mukhanova, K.; Baisalbaeva, S. A.; Kondaurov, G. N. *Tezisky Dolk.-Vses. Kof. Chim. Atsetilena* **1975**, *5*, 392; *Chem. Abstr.* **1978**, *88*, 169915e.
(274) Azerbaev, I. I.; Baisalbaeva, S. A.; Omarov, T. T.; Bazalitskaya, V. S. *Izv. Akad. Nauk Kaz. SSR, Khim.* **1977**, *27*, 86; *Chem. Abstr.* **1977**, *87*, 151995a.
(275) Smissman, E. E.; Ruenitz, P. C. *J. Med. Chem.* **1976**, *19*, 184.
(276) Iwai, I.; Ohki, E.; Oida, S.; Takagi, H.; Ohashi, Y. German Patent 2257131, 1973; *Chem. Abstr.* **1973**, *79*, 53184a.
(277) Baliah, V.; Jeyaraman, R. *Indian J. Chem.* **1977**, *15B*, 796.
(278) Jeyaraman, R.; Thanaraj, A. E.; Chockalingam, KN. *Indian J. Chem.* **1980**, *19B*, 522.
(279) Trigo, G. G.; Galvez, E.; Avendano, C. *J. Heterocycl. Chem.* **1978**, *15*, 907.
(280) Ohki, E.; Oida, S.; Ohashi, Y.; Takagi, H. Japanese Patent 7461168, 1974; *Chem. Abstr.* **1974**, *81*, 135978t.
(281) Oida, S.; Kurabayashi, M.; Ohki, E. *Chem. Pharm. Bull.* **1966**, *14*, 1418.
(282) Iwai, I.; Ohki, E.; Oida, S.; Takagi, H. Japanese Patent 7018860, 1970; *Chem. Abstr.* **1970**, *73*, 66467w.
(283) Sokolov, D. V.; Omarov, T. T.; Cherevatova, N. K.; Alekseeva, N. N. *Izv. Akad. Nauk Kax. SSR, Ser. Khim.* **1978**, *28*, 47.
(284) Britten, A. Z.; O'sSullivan, J. *Tetrahedron* **1973**, *29*, 1331.
(285) Scheiber, P.; Kreiss, G.; Nador, K. *Arzneim. Forsch.* **1976**, *26*, 1797; *Chem. Abstr.* **1977**, *86*, 90097q.
(286) Shimizu, B.; Ogiso, A.; Iwai, I. *Chem. Pharm. Bull.* **1963**, *11*, 333.
(287) House, H. O.; Muller, H. C. *J. Org. Chem.* **1962**, *27*, 4436.
(288) Fawcett, F. S. *Chem. Rev.* **1950**, *47*, 219.
(289) Speckamp, W. N.; Dijkink, J. *heterocycles* **1974**, *2*, 291.
(290) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1968**, *16*, 654.
(291) Galik, V.; Landa, S. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1101.
(292) Kafka, Z.; Galik, V.; Safar, M. *Collect. Czech. Chem. Commun.* **1975**, *40*, 174.
(293) Kafka, Z.; Safar, M.; Galik, V. *Collect. Czech. Chem. Commun.* **1974**, *39*, 3268.
(294) Douglass, J. E.; Shih, H.; Fraas, R. E.; Craig, D. E. *J. Heterocycl. Chem.* **1970**, *7*, 1185.
(295) Van Oosterhout, H.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, *653*.
(296) Bok, T. R.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1978**, 657.
(297) Oui, K. H.; Delpech, B. French Patent 2358404, 1978; *Chem. Abstr.* **1978**, *89*, 197343f.
(298) Hung, Y. *Diss. Abstr., Int. B* **1976**, *37*, 762; *Chem. Abstr.* **1976**, *85*, 153266w.
(299) Haller, R. *Arch. Pharm.* **1969**, *302*, 113.
(300) Bohlmann, F.; Ottawa, N.; Keller, R.; Nebel, I.; Pollit, J. *Liebigs Ann. Chem.* **1954**, *587*, 162.
(301) Schill, D.; Schneider, W. *Arch. Pharm.* **1975**, *308*, 917.
(302) Schneider, W.; Goetz, H. *Liebigs Ann. Chem.* **1962**, *653*, 85.
(303) Rossi, S.; Butta, W.; Valvo, C. *Farmaco, Ed. Sci.* **1959**, *14*, 666.
(304) Johnson, R. A.; Herr, M. E.; Murray, H. C.; Reineke, L. M.; Fonkess, G. S. *J. Org. Chem.* **1968**, *33*, 3195.
(305) Johnson, R. A.; Murray, H. C.; Reineke, L. M. *J. Org. Chem.* **1969**, *34*, 3834.
(306) Momosa, T.; Atarashi, S.; Muraoka, O. *Tetrahedron. Lett.* **1974**, 3697.
(307) Tecle, H.; Hite, G. *Probl. Drug. Depend.* **1976**, 464; *Chem. Abstr.* **1978**, *88*, 69028z.
(308) Iwai, I.; Ohki, E.; Oida, S.; Takagi, H.; Ohashi, Y. German Patent 2103486, 1971; *Chem. Abstr.* **1971**, *75*, 88493v.
(309) Kobayashi, S.; Hasegawa, K.; Oshima, T.; Takagi, H. *Toxicol. Appl. Pharmacol.* **1970**, *17*, 344.
(310) Mori, M.; Kobayashi, S.; Iwata, N.; Hara, T.; Aoshima, S. *Sankyo Kenkyusho Nempo.* **1971**, *23*, 139; *Chem. Abstr.* **1972**, *77*, 28980h.
(311) Tommasini, R.; Paserini, N. *Farmaco, Ed. Sci.* **1958**, *13*, 302.
(312) Cain, C. K. *Annu. Rep. Med. Chem.* **1971**, *6*, 37.
(313) Ohki, E.; Oida, S.; Ohashi, Y.; Takagi, H.; Iwai, I. *Chem. Pharm. Bull.* **1970**, *18*, 2050.
(314) Hiltmann, R.; Hoffmeister, F.; Neimers, E.; Schlichting, U.; Wollwebber, H. *Arzneim.-Forsch.* **1974**, *24*, 548; *Chem. Abstr.* **1974**, *81*, 37463b.
(315) Ohki, E.; Oida, S.; Ohashi, Y.; Yoshida, A.; Kamoshita, K.; Takagi, H. *Chem. Pharm. Bull.* **1974**, *22*, 1014.
(316) Poletto, J. F.; Allen, G. R.; Littell, R.; Weiss, M. J. U.S. Patent 3801594, 1974; *Chem. Abstr.* **1974**, *81*, 3769r.
(317) Angier, R. B.; Murdock, K. C.; Clark, J. H. U.S. Patent 3459861, 1969; *Chem. Abstr.* **1969**, *71*, 112826w.
(318) Rossi, S.; Valvo, C.; Butta, W. *Gazz. Chim. Ital.* **1959**, *89*, 1164.
(319) Rossi, S. British Patent 833165, 1960; *Chem. Abstr.* **1960**, *54*, 18551h.
(320) Rossi, S. British Patent 824140, 1959; *Chem. Abstr.* **1960**, *54*, 11055f.
(321) Nakanishi, M.; Arimura, K.; Muro, T. Japanese Patent 6820184, 1968; *Chem. Abstr.* **1969**, *70*, 87594p.
(322) Takeuchi, S.; Fukano, T.; Dohi, C.; Inoue, Y. *Jpn. J. Pharmacol.* **1971**, *21*, 811; *Chem. Abstr.* **1972**, *77*, 541s.
(323) Takeda, M.; Tsukamoto, G.; Noguchi, K.; Saito, S.; Nurimoto, S. *Chem. Pharm. Bull.* **1976**, *24*, 2312.
(324) Takeda, M.; Kawamori, M.; Inoue, H.; Noguchi, K.; Nurimoto, S. *Chem. Pharm. Bull.* **1977**, *25*, 775.
(325) Rossi, C.; Figini, A.; Carpi, A. *Ann. 1st Super. Sanita* **1968**, *4*, 333; *Chem. Abstr.* **1969**, *70*, 85991s.
(326) Ruenitz, P. C.; Mokler, C. M. *J. Med. Chem.* **1977**, *20*, 1668.
(327) Chiavarelli, S.; Toffler, F.; Misiti, D. *Ann. 1st Super. Sanita* **1968**, *4*, 157; *Chem. Abstr.* **1968**, *70*, 68574r.
(328) Chiavarelli, S.; Del Carmine, R.; Michalek, H. *Ann. 1st Super. Sanita.* **1972**, *8*, 156; *Chem. Abstr.* **1973**, *78*, 24098z.
(329) Chiavarelli, S.; Settimj, G. *Farmaco, Ed. Sci.* **1961**, *16*, 313; *Chem. Abstr.* **1962**, *56*, 12900c.
(330) Binnig, F.; Friedrich, L.; Hofmann, H. P.; Kreiskott, H.; Raschack, M.; Mueller, C. German Patent 2726571, 1978; *Chem. Abstr.* **1979**, *90*, 121568h.
(331) Nikitskaya, E. S.; Usovskaya, V. S.; Rubtsov, M. V. *Khim. Geterotsikl. Soedin., Sb. Azotsoderzh. Geterots.* **1967**, *445*; *Chem. Abstr.* **1969**, *70*, 77832a.
(332) Rubtsov, M. V.; Mashkovskii, M. D.; Nikitskaya, E. S.; Medvedev, B. A.; Usovskaya, V. S. *J. Med. Pharm. Chem.* **1961**, *3*, 441.
(333) Mashkovskii, M. D.; Medvedev, B. A. Farmakol. *Toksikol.* **1960**, *23*, 493.
(334) Medvedev, B. A. *Farmakol. Toksikol.* **1962**, *25*, 320.
(335) Medvedev, B. A.; Mashkovskii, M. D. *Farmakol Toksikol.* **1972**, *35*, 401; *Chem. Abstr.* **1972**, *77*, 135105y.
(336) Nikitskaya, E. S.; Gerchikov, L. N. *Khim. Farm. Zh.* **1969**, *3*, 7; *Chem. Abstr.* **1969**, *71*, 30448k.
(337) Nikitskaya, D. S.; Usovskaya, V. S.; Rubtsov, M. V.; Demina, I.. G. *Khim.-Fharm. Zh.* **1967**, *1*, 32; *Chem. Abstr.* **1967**, *67*, 116863w.
(338) Steck. E. A. U.S. Patent 3196154, 1965; *Chem. Abstr.* **1965**, *63*, 11585h.
(339) Nikitskaya, E. S.; Medvedev, B. A. *Khim. Fharm. Zh.* **1968**, *2*, 9.