SYNTHESIS OF AZAMODIFIED ADAMANTANE DERIVATIVES VIA BRIDGEHEAD- AND BRIDGE IMINES. A NEW ASPECT IN THE CHEMISTRY OF HETEROADAMANTANE DERIVATIVES

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Abstract—Recent advances in the chemistry of heteroadamantane derivatives, in particular synthesis and reactions of azamodified adamantane derivatives, have been reviewed emphasizing the synthetic utility of bridgehead imines as well as bridge imines.

1. INTRODUCTION

Three dimensional polycyclic compounds constructed by spirocyclic, fusedcyclic (or fusocyclic), and bridgedcyclic (or pontecyclic) rings[1] and their combination have drawn considerable attention in recent years from their unique physical, chemical, and biological[2] properties. Heteroanalogues of these polycycles have characteristic unique rigid stereochemistry as well as fixed conformations of heteroatoms,[3] and are of particular interest as novel typed heterocycles.[4] Although a wide variety of structurally, functionally, and biologically interesting classes of compounds like cryptands,[5] some alkaloids,[6] and cyclonucleosides[7] may fall under this category in a broad sense, this review is focused on heteromodified adamantane and related derivatives, in particular aza-modified type compounds, as one of so-called heterocage compounds in a more narrow sense. Studies on such heteromodified adamantanes seem to be not extensive compared to the carbocyclic systems. This might be due to the lack of efficient synthetic routes to the heteroanalogues. For adamantane and related stabilomers, the efficient synthetic routes have been developed by the acid-catalyzed rearrangement, i.e., adamantane rearrangement, found by Schleyer in 1957,[8] and now, adamantane 1, 1-methyladamantane, and 1,3-dimethyladamantane can be available commercially even in industrial scale.[9,10] Such efficient synthetic routes for heteroanalogues have been the subjects of intensive interest for organic chemists[11] with the exception of long known hexamethylenetetramine (urotoropin)[12] 2. Several types of diheterotricycloundecane series have been recently developed by Ganter.[13] These are only a few but biologically very interesting natural products that possess heteroadamantane skeletons. For examples, tetrodotoxin[14] 3

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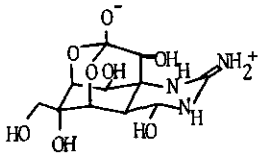

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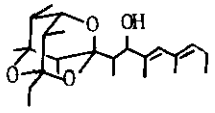

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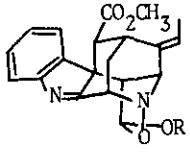

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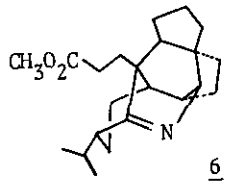
from puffer fish involves dioxaadamantane ring, muamvatin[15] 4 isolated recently from the Fijian S. normalis has a novel trioxaadamantane skeleton, and the indole alkaloid narelin[16] 5 from alstonia scholaris has 2-azaadamantane ring, respectively.

There are several excelent reviews on the chemistry of adamantane,[17,18] and heteroadamantanes.[11] The emphasis in this report is on recent synthetic approaches to some aza-modified adamantanes and related chemistry starting from readily available carbocycles like adamantane.

2. SYNTHESIS, REACTIVITY AND SYNTHETIC APPLICATION OF BRIDGEHEAD IMINES

The chemistry of carbocyclic bridgehead olefins have been a topic of current interests for over sixty years.[19-20] On the contrary, studies on bridgehead imines as one of heteroanalogues of bridgehead olefins have been the subject of keen interst for only about fifteen years. The preparation of unusually stable bridge head imine 6 from methyl homoseco-daphniphyllate, a derivative of Daphniphylline alkaloids, by Toda, Yamamura, and Hirata in 1970[22] prompted studies on synthesis of bridgehead imines via photolysis of bridgehead azide[23] or lead tetraacetate oxidation of bicyclic lactams.[24]



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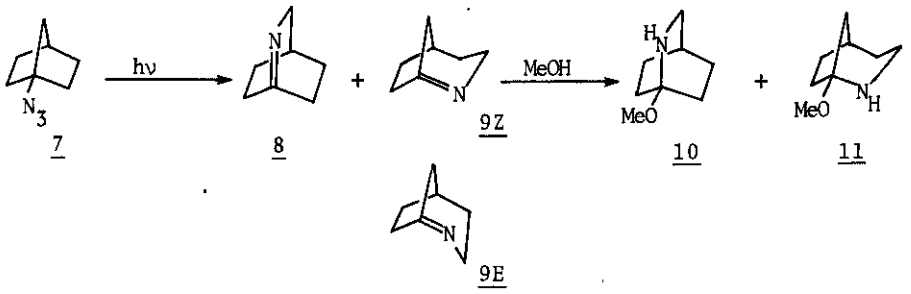
2.1. Bridgehead Imines and Azamodified Adamantane Derivatives via Bridgehead Azides

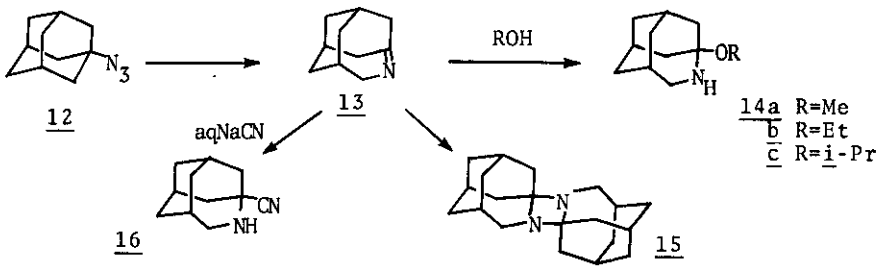
The ring expansion of 1-azidonorbornane 7 to methoxyamines 10 and 11 via photolysis in methanol was first reported by Lwowski et al[23] but a solvent-participated mechanism rather than the bridgehead imines (8, 9Z, and 9E) mechanism was prefered at that time (Scheme 1).[23,25]

Several years later, 1-azidoadamantane 12 was photolyzed in alcoholic solvents and in hydrocarbons by Quast and Eckert[26], or in the presence of cyanide by Sasaki, Eguchi, and Okano[27] to afford alcohol adducts 14a-c, dimer 15, and aminonitrile 16, respectively (Scheme 2).



7 8 9Z 9E 10 11

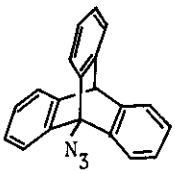
Scheme 1



12 13 16 15

14a R=Me
b R=Et
c R=i-Pr

Scheme 2



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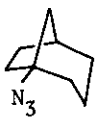

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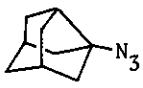

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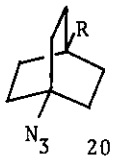

20a R=H
b R=Me

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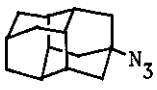

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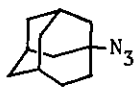

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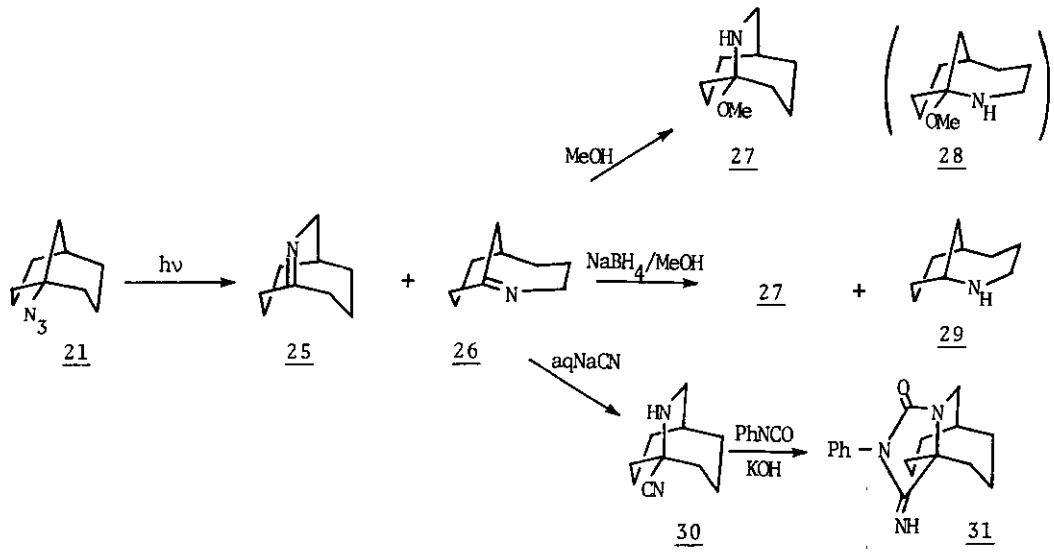
Several other bridgehead azides 17, and 18, and 20b were also decomposed photolytically or thermally (flash vacuum pyrolysis) by Quast[28,29] and Becker et al.[30] The intermediacy of the corresponding bridgehead imines was postulated. On the other hand, Sasaki, Eguchi, Okano et al. reported acidolytic and photolytic ring expansions of a series of bridgehead azides 19-24 in order to clarify the reactivity of the corresponding bridgehead imines and to develop synthetic routes to azamodified adamantane derivatives.[31-34]

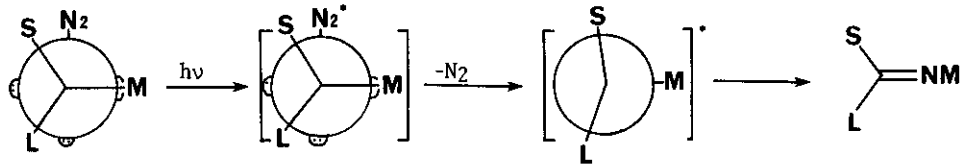
There are no regiochemical problem in the ring expansion on N atom for the symmetrical bridgehead azides 12, 17, 20 and 22 (i.e., the three shiftable carbons are equivalent). The corresponding bridgehead imines are easily trapped with methanol and hydrogen cyanide to afford useful bridgehead substituted azapolycycles. However, regiochemical problem arises in the ring expansion or bridgehead imine-formation for the unsymmetrical bridgehead azides where the shiftable bridged carbons are not equivalent. For example,



Scheme 3

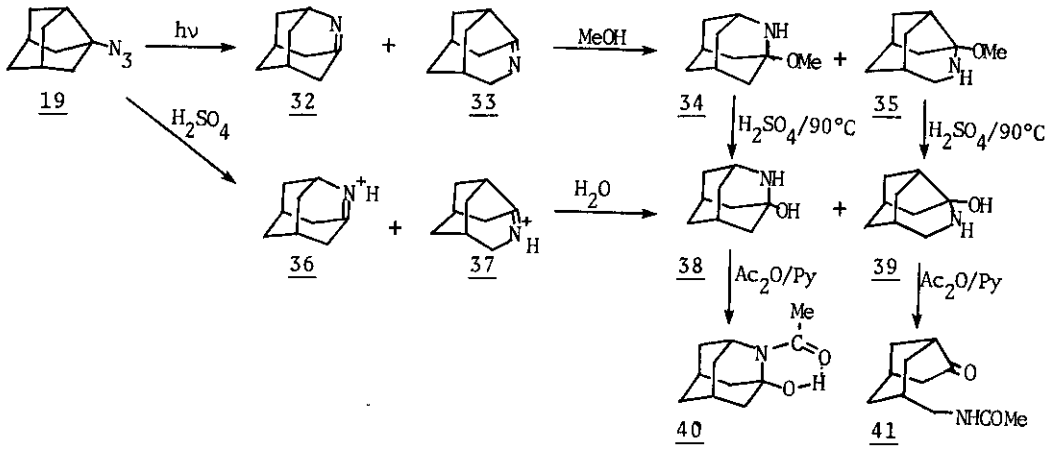
photolytic decomposition of the azide 21 in methanol (Scheme 3) should produce two isomeric methoxyamines 27 and 28, however, only 27 could be isolated in 18% yield.[31] While the reaction in the presence of $NaBH_4$ gave both 27 (26% yield) and an amine 29 (40% yield). The reaction in the presence of sodium cyanide gave also only cyanoamine 30 which gave a novel hydantoin derivative 31. These results

demonstrate clearly the lower reactivity (or a stability) of the bridgehead imine 26 compared to 25 rather than regioselective ring expansion[30] of 21 (there seems no notable comformational preference in terms of the Abramovitch-Kyba model, Scheme 4).[35]



Scheme 4

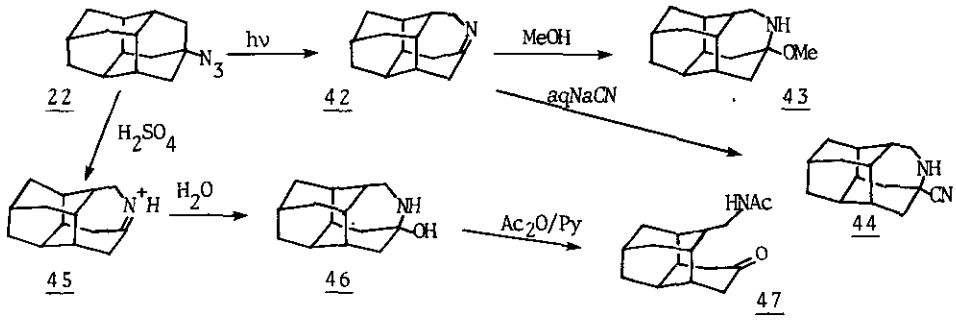
Highly strained, and hence, very reactive bridgehead imines, 2-azaadamant-1-ene 32 and 4-azaprotoadamant-3-ene 33 should be formed in the decomposition of 3-azidonoradamantane 19. The photolysis in methanol afforded methoxyamines 34 and 35 in 38 and 42% yields (Scheme 5)[31,32]. These products were correlated with the products (38 and 39) of acidolysis, in which, interestingly, 2-azaadamantane product 38 was produced more regioselectively. Such regioselective ring expansions to adamantane skeleton are also recognized in the ring expansions via 3-noradamantylcarbene[36] and -carbinylcation.[37]



Scheme 5

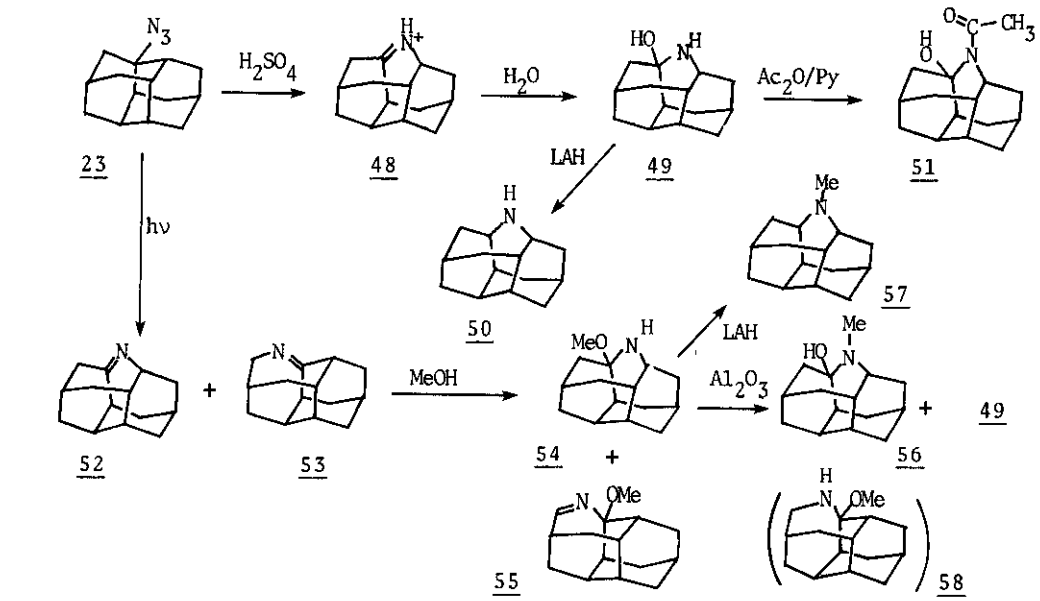
The intermediacy of reactive bridgehead imines 13, 25, 32 and 33 in the above photolytic ring expansions was supported by photolysis of the azides 12, 21 and 19 at 77 K in a hydrocarbon matrix, followed by treatment with methanol at 195 K to afford the corresponding methoxyamines.[31] The spectral (ir and uv etc.) evidences of these strained imines have been reported using matrix-isolation experiments at 10-14K in nitrogen or argon matrix by Sheridan,[38] Michl[39-41] and Dunkin[42] et al. The additions of dibutylamine[43] and carbon dioxide[40] to 32 have been reported also.

4- and 1-Azidodiamantanes 22 and 23 afford cleanly azahomodiamantane derivatives by photolytic and acidolytic ring expansions (Scheme 6 and 7).[34] The ring expansion of 22 is quite similar to that of 1-azidoadamantane 13 (Scheme 2) and provides an efficient route to 10-aza-2(3)-homodiamantane derivatives. On the other hand, unsymmetrical 1-azidodiamantane 23 gives 12-aza-1(2)-homodiamantane

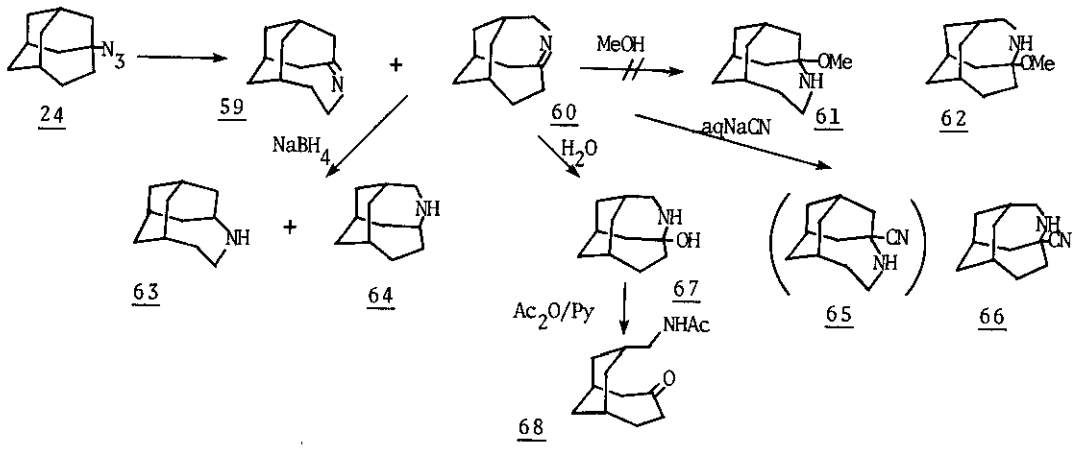


Scheme 6

derivative[49] regioselectively only on acidolytic ring expansion, but on photolysis in methanol, 23 affords methoxyamine 54 and methoxyimine 55. Very facile O→N Me migration of 54 occurs on alumina column as well as on lithium aluminum hydride reduction to afford 56 and 57, respectively. Another expected methoxyamine 58 could not be isolable (Scheme 7). These unusual behaviors of 52, 53, and their derivatives may be due to their very crowded and constrained molecular geometry.



Scheme 7

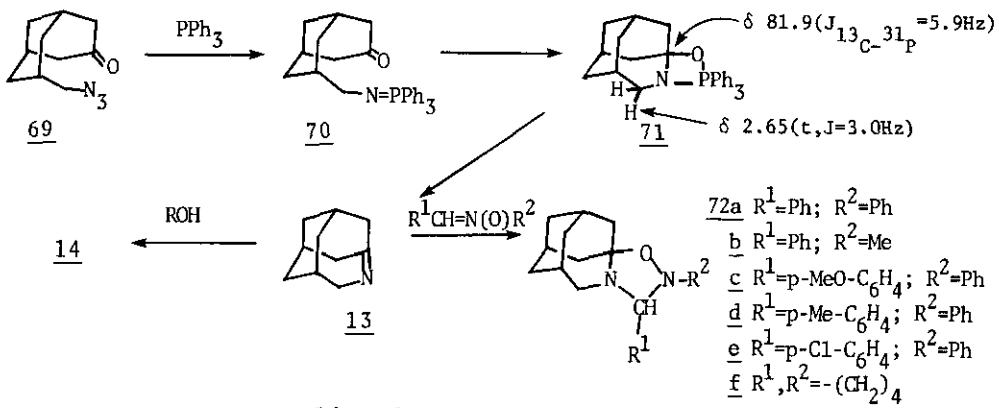


Scheme 8

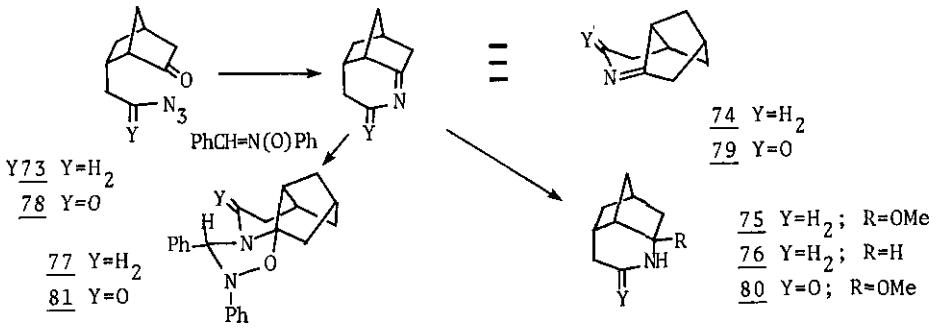
The photolytic ring expansion of 3-azidohomoadamantane 24 affords bridgehead imines 59 and 60, both of them, however, do not give isolable MeOH adducts 61 and 62 (Scheme 8).[33] Their sodium borohydride reduction gives 4-azatricyclo-[5.3.1.1^{3,9}]dodecane[44] 63 and 5-azatricyclo[4.4.1.1^{3,9}]dodecane 64 in a 1:2 ratio (70%). Among the possible adducts of HCN and H_2O to 59 and 60, only the adducts 66 and 67 are isolable, and hence, the bridgehead imine 59 behaves similarly to so-called "hyperstable" olefins[20,45] (the olefinic strain, OS value is 1.8 kcal/mol for the corresponding carbocyclic system by MM2 calculation, see Figure 1).

2.2 Bridgehead Imines and Azamodified Adamantane Derivatives via Intramolecular Aza-Wittig Reaction

The above described photorearrangement of bridgehead azides provides a general route to bridgehead imines but suffers from serious disadvantages because unsymmetrical azides generally afford a mixture of bridgehead imines due to non-regioselective ring expansion, moreover the reagents applicable to generated imines are restricted to photostable ones like MeOH, HCN, and H^-. The lead tetraacetate oxidation of the parent azapolycycles is only useful for very limited precursors.[24] In view of the above, the development of regiospecific routes to bridgehead imines is highly desirable. As one of these methods, the intramolecular aza-Wittig route have been developed as summarized in Scheme 9 and 10.[46] The Staudinger reaction[47] of ketoazide 69 with triphenylphosphine gives iminophosphorane 70 which affords the bridgehead imine 13 via 71. The intermediate

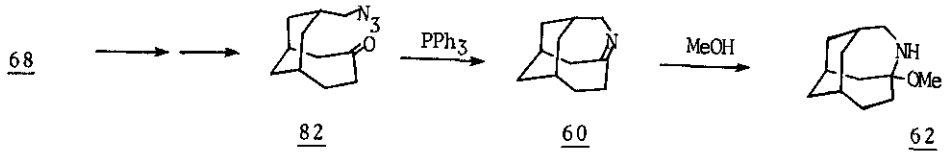


Scheme 9



Scheme 10

formation of 71 could be observed by ^{1}H and ^{13}C nmr spectra as indicated in Scheme 9. The advantage of this route is demonstrated by trap of the imine 13 with nitrones affording novel adducts 72 in high yields. This route was successfully applicable to 4-azahomobrend-3(4)-enes 74, 79 (Scheme 10) and 5-azatricyclo-[4.4.1.$1^{3,9}$]dodec-5(6)-ene 60 (Scheme 11). The MeOH adduct 75 is not isolable but the adduct 80 from 5-oxo-imine 79 is isolable. Both nitrone adducts 77 and 81 are obtained in high yields. On the other hand, the imine 60 from 82 and triphenylphosphine, previously generated as a regioisomeric mixture by photolysis of 24, gives unstable MeOH adduct 62 as evidenced by ^{1}H nmr signal at δ 3.42 but its isolation was again not successful. These results demonstrate clearly the utility of the intramolecular aza-Wittig route to some bridgehead imines.



82 60 62

Scheme 11

2.3. Reactivity of Bridgehead Imines

From the above results, it turns out that bridgehead imines (Anti-Bredt imine) involving E-1-azacycloheptene or E-1-azacyclohexene moiety are highly reactive affording stable MeOH and HCN adducts, while bridgehead imines involving an

E-1-azacyclooctene or larger ring are unreactive and do not give stable MeOH and HCN adducts. However, sodium borohydride reduction of these unreactive imines provdies an efficient route to novel azamodified adamantane skeletons. Furthermore, nitrone adducts can be obtained efficiently by generating bridgehead imines via intramolecular aza-Wittig route. The reactivity of bridgehead imines examined is summarized in Figure 1. This order corresponds to the Wiseman's rule for carbocyclic systems.[48] Some of the spectral data and calculation results from recent reports on Anti-Bredt imines are summarized in Table 1. Finally, it should be added that 1-azido-4-methylcubane has been reported recently to afford homoprismane carbonitrile on photolysis but trideuteriomethoxyazahomocubane on thermolysis in CD_3OD at 100°C.[49] The latter may be formed presumably via the solvent participated mechanism rather than via the bridgehead imine,[49] although details are not known yet.

Table 1. Some reported spectral data of bridgehead imines.

Imines	$\nu_{C=^{14}N}$, cm^{-1}		$\lambda_{n\pi^*}$[h], nm		$\lambda_{\pi\pi^*}$[h], nm		ΔH_f°[i], kcal/mol
	exptl	calcd	exptl	calcd	exptl	calcd	
32[a]	1451	1472	495	575	252	262	66.9
9E[b]	1475	1523	400	512	238	264	70.1
8[b]	1481	1493	400	493	237	283	66.2
9Z[b,c]	1586	1591	298	346	202	228	45.4
33[a]	1591	1585	314	376	204	229	55.9
13[a,d,e]	1600	1595	302	380	214	226	35.6
83b[e]	1601						
60[f]	1640						
$Me_2C=NMe$[g]	1669	1669	240	333	182	177	0.5

[a] Ref. 40 [b] Ref. 41. [c] Ref. 38. [d] Ref. 39. [e] 5-Me derivative of 83.
[f] S. Eguchi, T. Okano, and H. Takeuchi, unpublished results. [g] I. R. Dunkin and O. C. Thompson, Tetrahedron Lett., 1980, 21, 3813. [h] Converted values from the reported ν values. [i] Force field calculations on MNDO optimization.

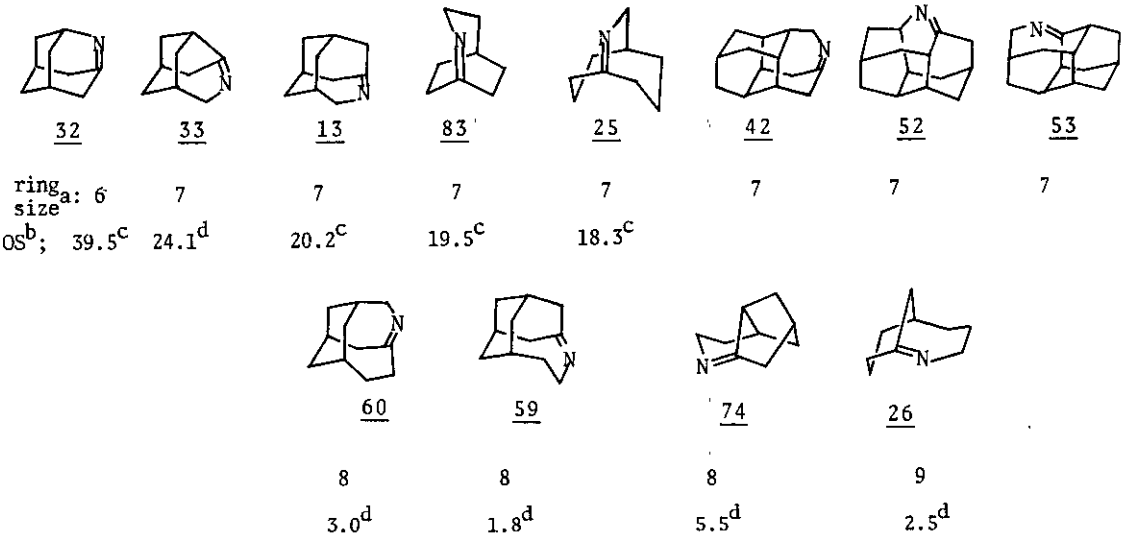


Fig 1. Qualitative reactivity order of bridgehead imines.

[a] Ring size of (E)-azacycloalkene moiety. [b] The OS values in kcal/mol of the corresponding bridgehead alkenes. [c] Ref. 20 (calculated by Allinger's MMI force field program). [d] Calculated by MM2 program (a modified Allinger's MM2 program by Prof. E. Ōsawa).

2.4. Synthesis of [3,4]Fused 4-Azahomoadamantane Heterocycles

The HCN and MeOH adducts of bridgehead imines are useful intermediates for aza-modified adamantane derivatives. For examples, various types of [3,4]fused 4-azahomoadamantane heterocyclic ring systems can be obtainable from 3-cyano- and 3-methoxy-4-azahomoadamantanes. Some examples are shown in Figure 2.[27,50]

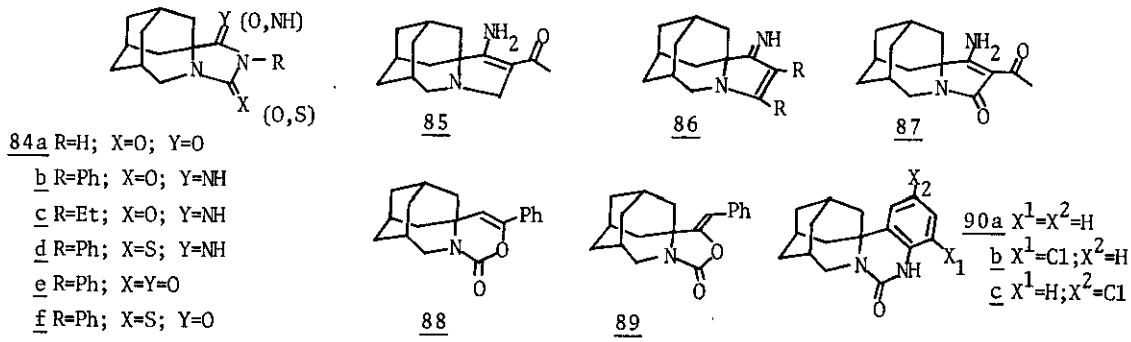


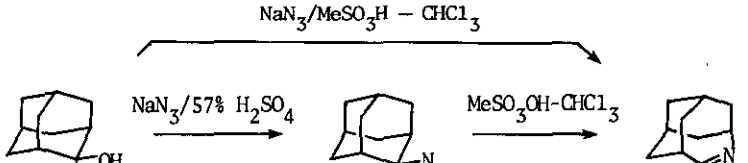
Fig 2. Some examples of [3,4]-fused 4-azahomoadamantane heterocycles.

3. SYNTHESIS AND SYNTHETIC APPLICATION OF BRIDGE IMINES

Bridge imines are less strained compared with bridgehead imines and are expected to behave as normal Schiff base. General synthetic routes to cyclic imines involve condensation reactions, addition reactions, rearrangement reactions as well as oxidation and reduction reactions.[51] As the synthetic routes to polycylic bridge imines, a) ring expansions of bridge azides[52] and b) Beckmann rearrangements[53] or Schmidt reactions[54], followed by reductions[55] or alkylations[56] are attractive ones. The latter routes require generally multi-step procedure and suffer from the disadvantage of concurrent Beckmann- or Schmidt fission reactions, in particular for rigid polycycles like adamantane ring.[57] The bridge azides route may be efficient if there is no regiochemical problem in the ring-expansions on N atom via dinitrogen loss.

3.1. Bridge Imines via Acidolysis of Bridge Azides

2-Alkyl- and 2-aryl-2-azidoadamantanes 92b-f are readily obtainable from the corresponding alcohols (Scheme 12).[58] However, 2-azidoadamantane 92a can not be prepared by this substitution reaction via 2-adamantyl cation but can be prepared from 2-aminoadamantane via the diazo-transfer method[58] or from 2-bromoadamantane by using trimethylsilylazide and stannic chloride.[59]

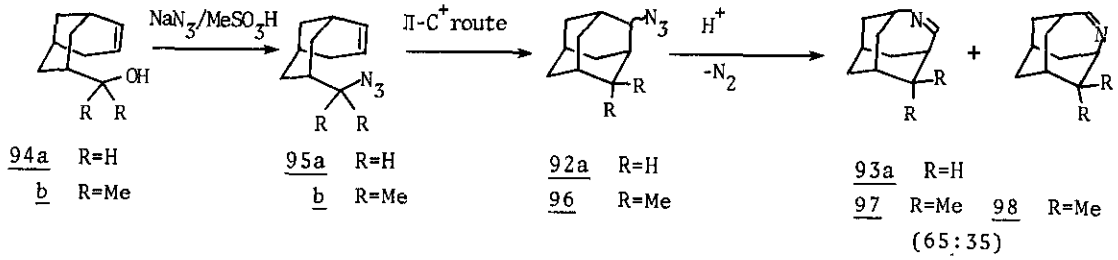


91a	R=H	92	87%[a]	67%,[b] 62%,[c] 66%[d]
b	R=Me		92%	69%, 58%, 75%
c	R=Et		91%	82%, 68%
d	R=n-Bu		75%	75%, 89%
e	R=Ph		90%	0%, 36%
f	R=PhCH$_2$		71%	47%,[e] 55%[e]

[a] 92a is prepared from 2-adamantylamine. [b] By acidolysis from 92.
[c] By photolysis from 92. [d] By acidolysis from 91. [e] Obtained as 5-COPh derivative.

Scheme 12

Acidolytic ring expansion of these 2-azidoadamantanes affords 5-alkyl-4-azahomoadamant-4-enes 93 in good yields. 5-Unsubstituted 4-azahomoadamant-4-ene 93a is obtainable more conveniently directly from the alcohol 91a on teatment with $NaN_3/CHCl_3$-CH_3SO_3H. However, 5-phenyl derivative 93e can not be obtained at all by the acidolytic decomposition because of exclusive phenyl migration on N atom (cf. however, photolytic route described below). These bridge imines 93a-d can be handled at room temperature but decompose gradually by moisture and air, therefore, they can be stored as their hydrochloride. However, 5-benzyl derivative is extemely unstable to air and isolable only as 5-benzoyl derivative 93f.



94a R=H
b R=Me

95a R=H
b R=Me

92a R=H
96 R=Me

93a R=H
97 R=Me 98 R=Me
(65:35)

Scheme 13

The Π-C^+ route cyclization of azidobicyclononenes 95a,b provides a novel route to 2-azidoadamantane derivatives, of which acidolytic ring expansion affords also 4-azahomoadamant-4-ene derivatives, 93a, 97 and 98 (Scheme 13).[60]

3.2. Bridge Imines via Photolysis of Bridge Azides

The photolytic ring expansion of 2-azidoadamantane derivatives 92a,b,e,f affords also the corresponding 4-azahomoadamant-4-enes (Scheme 12).[61] This route gives 5-phenyl derivative 93e in a moderate yield but again 5-benzyl derivative is isolated as 5-benzoyl derivative 93f after the air oxidation.

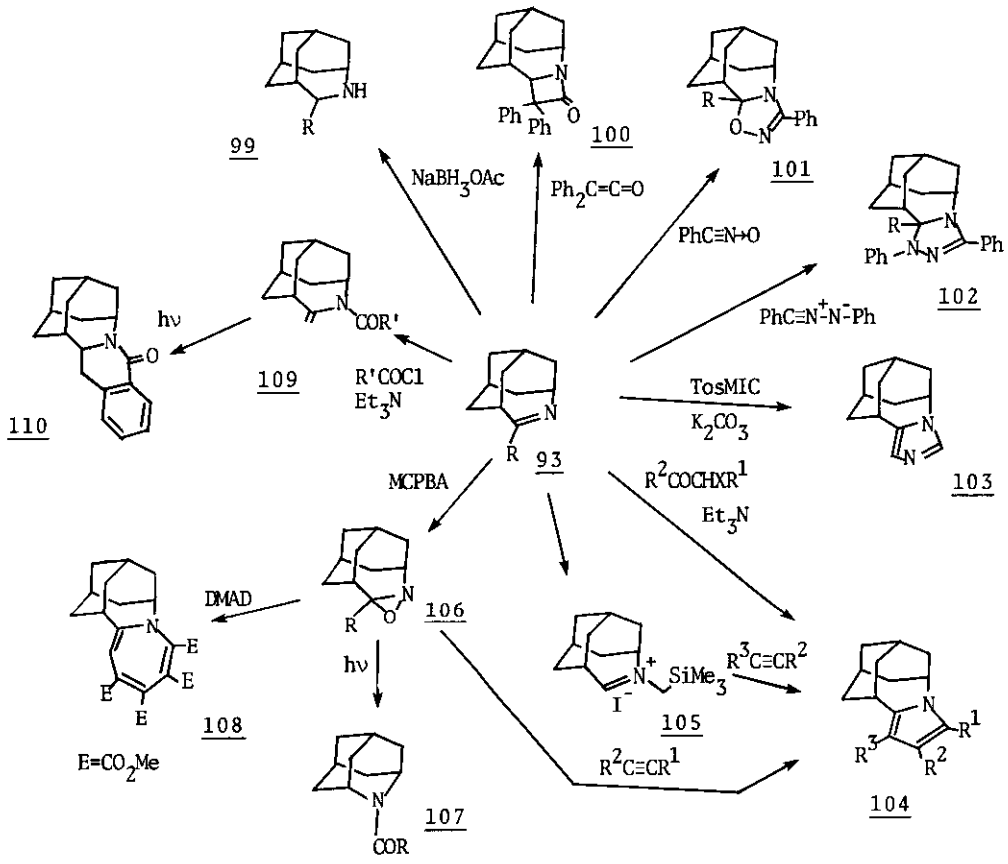
Synthesis of other bridge imines is not developed yet, though regiochemical problems as well as their stability depend on the design of carbocycles and functionalization.

3.3. Reactivity and Synthetic Application of Bridge Imines

Above-described 4-azahomoadamant-4-enes are generally stable imines and may be useful precursors for synthesis of [4,5]fused type 4-azahomoadamantane

heterocycles.

Some examples are summarized in Scheme 14. Simple reduction of 93 provides 5-substituted 4-azahomoadamantane derivatives 99.[61] Various types of cycloadditions using diphenylketene or 1,3-dipoles afford directly [4,5]fused 4-azahomoadamantane heterocycles 100-102.[61] The reaction with TosMIC gives imidazole 103.[61] The reaction of 93b-d with α-bromoketones gives the corresponding pyrrole derivatives 104 via enamine cyclization.[62] The pyrrole derivatives 104 were also



Scheme 14

obtainable via 1,3-dipolar cycloadditions of an azomethine ylide generated from trimethylsilylmethiodide 105 with alkynes,[62] and also via the thermal reaction[63] of alkynes with epoxy-4-azahomoadamantanes 106, which are readily prepared from the bridge imine via MCPBA oxidation. The reacion of 106b (R=Me) with dimethyl-

acetylenedicarboxylate gives also azepine derivative 108 as a minor product. Furthermore, the epoxy derivatives 106 can be converted to N-acyl-2-azaadamantanes 107 via photolytic ring contraction.[64] Usual acylation of 5-alkyl imines 93b-d in the presence of triethylamine affords the corresponding enamide derivatives 109 in good yields, which are readily converted to 4-azahomo-adamantano[4,5-b]-1',2',3',4'-tetrahydroisoquinolin-1'-one derivatives 110 via enamide photocyclization.[65]

4. CONCLUSION AND OUTLOOK

Bridgehead imines and bridge imines can be employed as useful intermediates in synthesis of azapolycycles, in particular azamodified adamantane derivatives, although their reactivity and stability have a very broad spectrum depending on the nitrogen containing ring size. Only the results obtained mainly from adamantane precursors are summarized here but the methods presented may be potentially applicable to a number of other polycarbocycles as convenient alternatives or complementary procedures for the Beckmann- and Schmidt nitrogen insertion routes.[53]

It is hoped that bridgehead imines as well as bridge imines will open up new vistas in nitrogen heterocyclic synthesis.

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