

NEW-TYPED HETEROCYCLIC COMPOUNDS

Tadashi SasakiInstitute of Applied Organic Chemistry, Faculty of Engineering
Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464, Japan

The recent advance in new-typed heterocyclic compound is reviewed focused on 1) new heterocyclic systems of heteroaromatic character and 2) saturated fused polycyclic heterocycles.

Introduction

It is noteworthy that approximately 65% of the published papers in organic chemistry are estimated to be concerned with heterocyclic chemistry.¹ Therefore, the word, "new-typed" of the title should not be understood as hitherto unknown heterocyclic compounds in the rather extensive nature of this field, because the severe limitation imposed by this review does not allow to survey all the literatures published even only in recent one year. Thus, this review is focused on the synthesis of heterocyclic compounds having new skeletons since 1970. Furthermore, chemistry of small-, medium- and large-ring heterocycles is not dealt with in this review. Also, chemistry of heteroannulenes is excluded.

Heteroaromaticity² is discussed as a standard for the stability of heterocyclic compounds, as aromaticity is used for that of hydrocarbon compounds of conjugated cyclic polyolefins. Both 5-membered and 6-membered heterocycles can be regarded as a hetero-analog of benzene which is classified as a 6π -system by the Hückel rule. Depending on the sort, number and sequence of heteroatoms, a large number of heteroaromatic compounds are conceivable. By contrast, such a standard for the stability of saturated ring systems has been rarely discussed. Nevertheless, it is known that the stability of saturated monocyclic compounds increases with the ring-size from 3 to 5, 6 and begins to decrease from 7 up to 11. Large ring systems of more than 14 membered-ring are again stabilized. These phenomena are explained in terms of the ring-strain energy. Cyclohexane which is considered to be strain-free has two conformational isomers of chair- and boat-form. The boat conformation is less stable than the chair form by 6 Kcal/mole, largely owing to

torsional strain. But the conformation of cyclohexane is locked by introducing a suitable substituent. Even in the fused polycyclic saturated systems, an involved cyclohexane ring is often conformationally frozen and can take only one conformation. This is the case for many heterocyclic compounds which naturally exist. So far, chemistry of such fused polycyclic heterocycles has not been discussed from this point of view. Therefore, those heterocyclic compounds, which stimulate the author's own interest, are surveyed in chapter 2 of this review. It should be also pointed out that the unsaturated systems mentioned in chapter 1 have planar structures, whereas the saturated systems discussed in chapter 2 have structures of three dimensions.

1. New Heterocyclic Systems of Heteroaromatic Characters

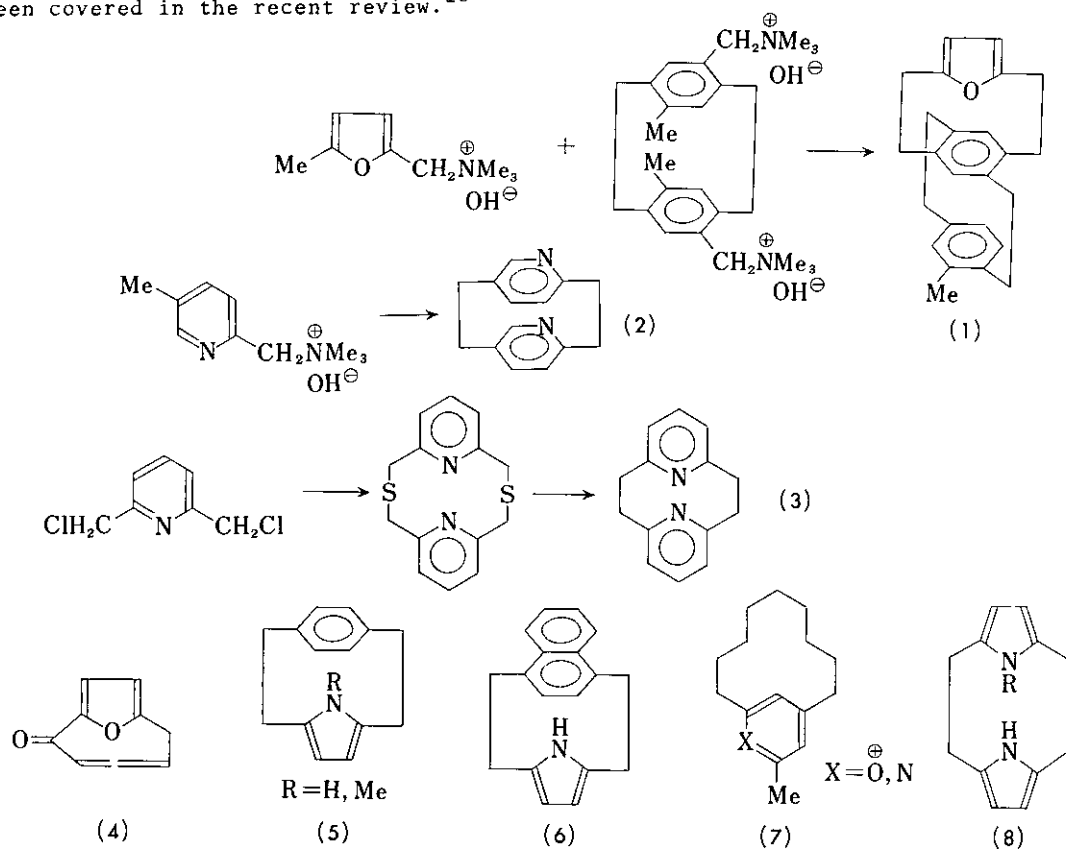
As in the case of aromatic compounds, heteroaromatic compounds can be subdivided into benzenoid- and nonbenzenoid-systems. However, this chapter is divided into 5 sections as follows; 1.1 Monocyclic Systems including heterocyclophanes, heterofulvenes and heterofulvalenes, 1.2 Fused Polycyclic Systems including heterohericenes and heterocirculenes, 1.3 Mesomeric Compounds, 1.4 New Heterocyclic Systems Based on the Extended Definition of Heteroatoms, 1.5 Miscellaneous.

1.1 Monocyclic Heterocycles

1.1.1 Heterocyclophane

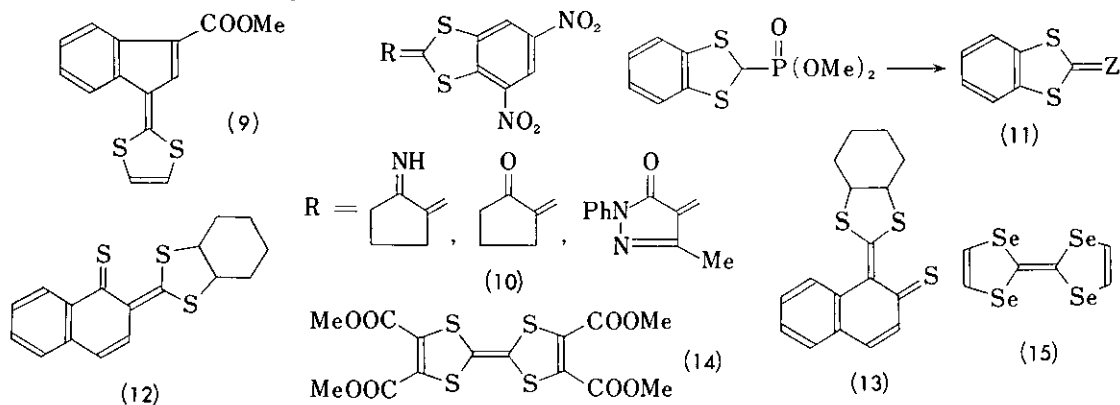
In a review "Cyclophane Chemistry" by Cram, heterocyclophanes were not mentioned. However, it is interesting to compare heterocyclophanes with the corresponding benzenoid cyclophanes by the ring basicities. The interaction of benzene ring and heterocyclic ring is expected to be weaker than that of two benzene rings. Bruhin and Jenny⁴ synthesized triple-layered heterocyclophane (1) by heating double-layered p-cyclophane with furan derivatives. In the similar way, [2,2](2,5)pyridinophane [(2), one of four isomers] was synthesized. The synthesis of [2,2]metapyridinophane [3] by Martel⁵ via sulfide and sulfone intermediates is a widely applicable method. The syntheses of allenefuranophane [4] by Sondheimer et al.⁶, [5] and [6] by Keehn et al.⁷, metaheterophane [7] by Pradamante et al.⁸, and [2,2](1,4)-naphthaleno[2,5]thiophenecyclophane and its furan derivatives by Misumi et al.⁹ have been reported. The structures of these compounds were discussed on the basis of NMR spectra. Yoshida et al.¹⁰ synthesized cyclophane porphyrin. The syntheses of [2,2]heterophane by Wong¹¹ and [2,2](2,5)pyrrolophane by Keehn et al.¹² have

been covered in the recent review.¹³



1.1.2 Heterofulvenes, Heterofulvalenes

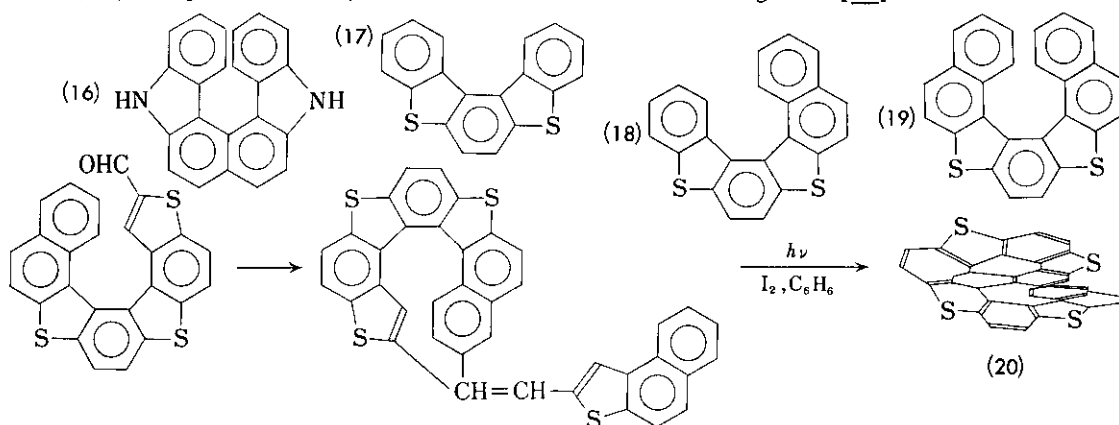
A review by Bergmann¹⁴ revealed about 20 sorts of heterofulvenes. In 1969, Seitz¹⁵ presented a review of heteroanalogues of sesquifulvalene, where the heteroatoms were sulfur and oxygen. In the monograph titled on "Aromaticity" by Yoshida and Osawa,¹⁶ 8 heterofulvenes and heterofulvalenes were discussed. Chemistry of sulfur compounds such as dithia-fulvene, -fulvalene and tetrathiafulvene, -fulvalene has been well investigated as a result of their stability and availability.



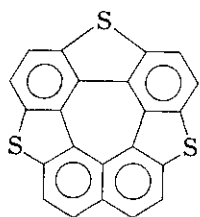
From an interest of the biological activity, Seitz et al.¹⁷ have synthesized dithiafulvene [9]. Takashima et al.¹⁸ have synthesized dithiafulvene [10] from dithiocarboxylic acids. Inamoto's synthesis¹⁸ of 3,4-benzodithiafulvene [11] as well as [12] and [13]¹⁹ was based on Wittig reaction. Tetrathiafulvalene [14] and tetraselenafulvalene [15] by Cava et al.²⁰ and tetrathiafulvalenes substituted with two functional groups by Pittman, Jr. et al.²¹ were of special interest, since their charge-transfer complexes with tetracyanoquinodimethane were shown to possess the characters as electron conductors.²²

1.2 Polycyclic Heterocycles - Heterohelicenes, Heterocirculenes

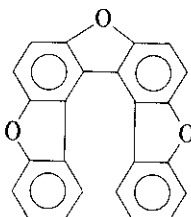
The name helicene was proposed by Newman²³ based on the fact that the continuance of ortho-fused benzene rings makes a helical molecule. The first example of heterohelicene was 5,10-dihydrocarbazolo[3,4-c]carbazole [16] by Fuchs et al.²⁴ Later, Wynberg et al.²⁵ synthesized several benzo-analogs of [17]²⁶ such as hexa-



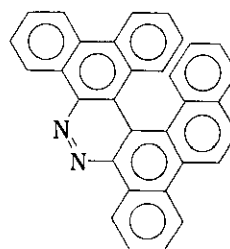
heterohelicene [18], heptaheterohelicene [19], and undecaheterohelicene [20], whose preparation is outlined above. Wynberg et al.²⁵ also reported the synthesis of [7]heterocirculene [21] by cyclization reaction. In a similar way, heterocirculene [22] was synthesized by Hogberg.²⁷ Chemistry of this field has been further expanded by Wynberg et al.²⁸ Recently, a facile synthesis of diaza-[7]helicene [23] was reported by Rau et al.²⁹



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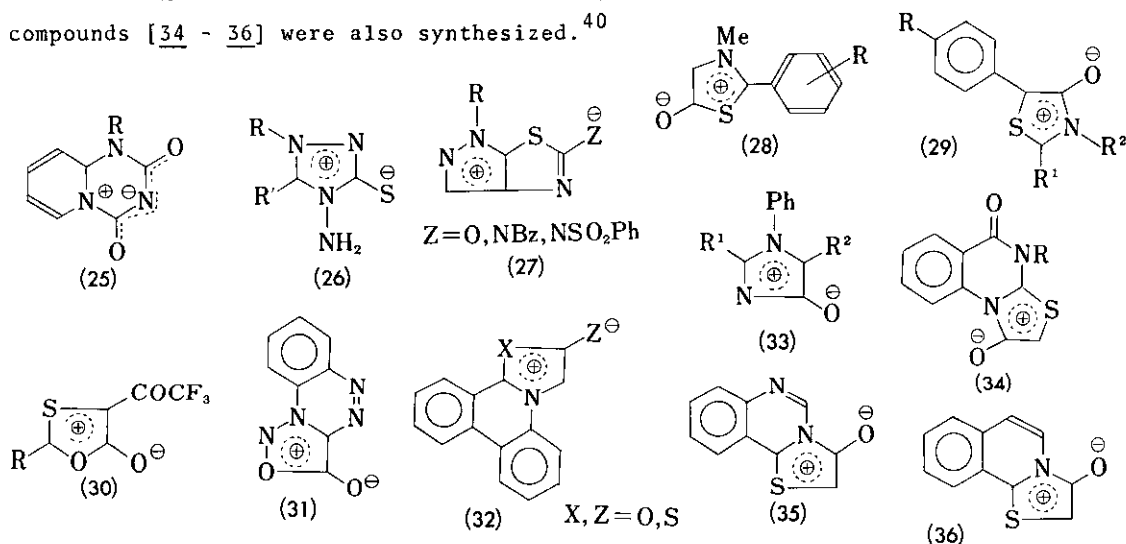
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1.3 Mesoionic Compounds

In contrast to the hydrocarbon aromatic compounds, heteroaromatic compounds include the unique class of compounds like the titled one. Sydnone [24] is the representative compound which was first synthesized in 1939. Its stability was attributed to the heteroaromaticity. Many organic chemists have paid much interest in its unique chemical properties and an increasing number of reports in this field has been published. Chemistry of mesoionic compounds was reviewed by Ohta and Kato³⁰ in 1971 and more recently by Ollis and Ramsden³¹. Therefore, this sections covers only recent papers. Mesoionic six-membered heterocyclic compound [25] was synthesized by Kappe³². Aminotriazolethione [26] and fused mesoionic compound [27] were reported by Lagaris.³³ Simple preparations of [28] by Elgendy³⁴, and [29] by Bandy³⁵ are known. In the course of study on mesoionic compounds, Masuda et al.³⁶ described the synthesis of [30]. Preston³⁷ synthesized fused mesoionic compound [31]. Compounds [32]³⁸ and [33]³⁹ were reported by Potts et al. Fused-cyclic mesoionic compounds [34 - 36] were also synthesized.⁴⁰



1.4 New-typed Heterocyclic Compounds Based on the Extended Definition of

Heteroatoms

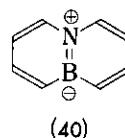
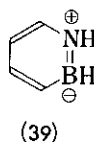
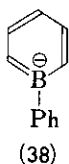
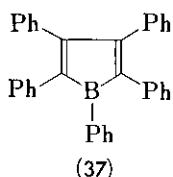
Previously, the author¹ defined heterocyclic compounds as "cyclic compounds whose ring is composed of more than one hetero(non-carbon) atoms". In periodic table, all atoms of valence 2 and more can be regarded as heteroatoms. But on restricting to organic heterocyclic compounds with covalent bonds, heteroatoms should be confined to be non-metallic atoms. These are further subdivided into 100% non-metallic atoms such as C, N, O, P, S, Se indicated by a square and 75% non-

metalloids such as B, Si, As, Te indicated by a one-corner-lacked square in Table 1. Among these heteroatoms, O and N are most frequently found in the naturally occurring organic compounds. The next ones are S and P. In contrast, these last two are involved as forms of many inorganic compounds such sulfates and phosphates. In Chem. Abstr., B, Si, P, As, Te are described in 29-organometallics.

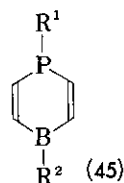
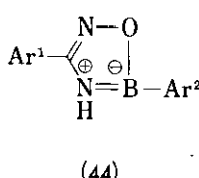
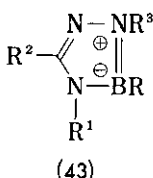
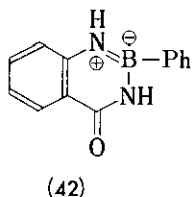
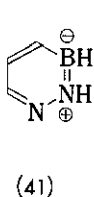
	I	II	III	IV	V	VI	VII	0
1	H							He
2	Li	Be	B	C	N	O	F	Ne
3	Na	Mg	Al	Si	P	S	Cl	Ar
4	K	Ca	Sc	Ge	As	Se	Br	Kr
					Sb	Te		
						Po		

1.4.1 Boron (III-group)

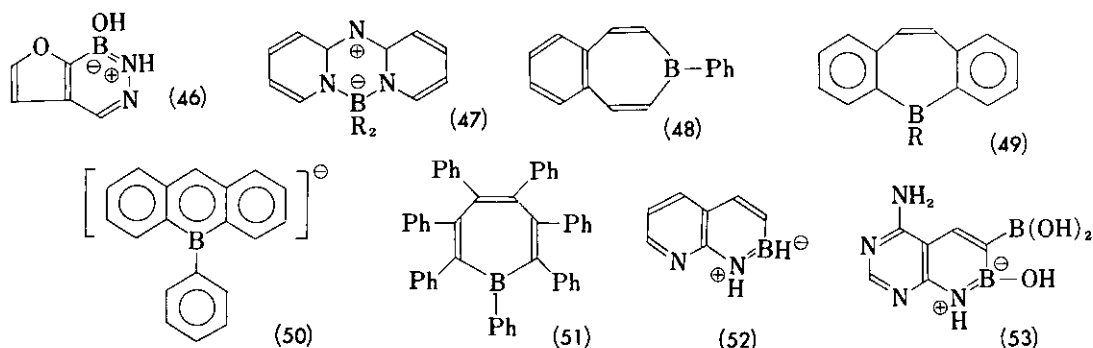
Braye et al.⁴¹ reported that pentaphenylborole [37] was a colorless solid, inactive to amines and stable both in ethanol and in the air. However, Eisch et al.⁴² reexamined and found that [37] was very reactive green solid (mp 120 °C) which was characterized as a 1:1 complex with pyridine (mp 180-182 °C). The expected anti-aromatic character of [37] was confirmed by NMR. The first example



of borabenzene was 1-phenylborabenzene anion [38] which was reported as a ligand of transition metal π -complex.⁴³ One year later, it was isolated by Ashe and Shu⁴⁴ and its aromatic character was confirmed by NMR. In 1967, Dewar et al.⁴⁵ synthesized unstable borazarene [39], whose synthesis was further improved in the next year. 10,9-Borazonaphthalene [40] which was more stable than [39] was also synthesized. By this time, 19 boron-aromatic compounds have been synthesized.⁴⁶



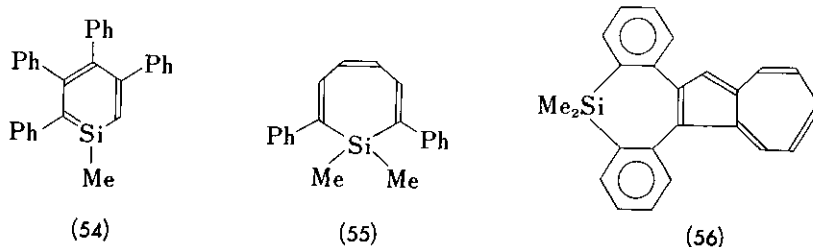
3,2-Borazapyridine [41] synthesized by Gronowitz⁴⁸ was more stable than [39]. 2,3-Borazaroquinone [42] and 2,3-Borazaroquinoline N-oxide were reported by Yale.⁴⁷ 5,1,3,4-Boratriazole [43] was synthesized and demonstrated to be aromatic by Dewar et al.⁴⁹ Syntheses of 1,3,5,2-oxadiazaborole [44] by Yale⁴⁷ and 1-bora-phosphacyclohexadiene [45] by Berger⁵⁰ were reported. 4,5-Borazarofuro[2,3-c]pyridine [46] by Floretin et al.⁵¹ and Dorokhov's [47]⁵² are heterocyclic compounds with



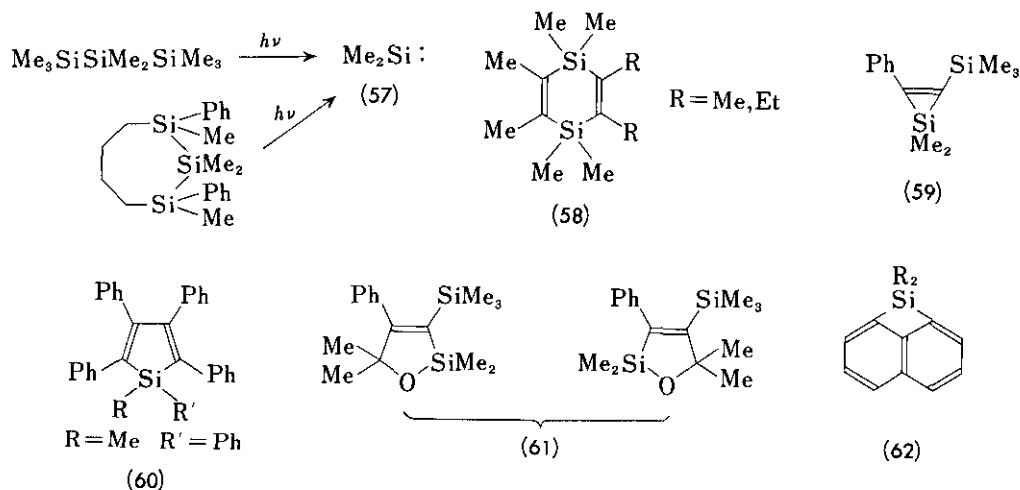
B-N Bonds in the ring. The other reported benzo-cyclic compounds are 3-benzoborepin [48]⁵³, dibenzoborepin [49]⁵⁴, and boraanthracene anion [50].⁵⁵ Recently synthesis of heptaphenylborepin [51]⁵⁶ has been reported. Matterson et al.⁵⁷ synthesized 7,8-borazaroquinazolines [52,53] which were inactive in the standard P388 leukemia screening test.

1.4.2 Silicon (IV-group)

The chemistry of heterocyclic compounds containing P, As, Sb, Bi and Si was reviewed in "The Chemistry of Heterocyclic Compounds," Vol. 1 (A. Weissberger, ed., 1950). Its complementary volume was published in 1970. Therefore, this review only surveys the literatures published since 1971. Märkl and Merz⁵⁸ have synthesized the precursor of silabenzene [54], but its conversion into [54] was unsuccessful. Syntheses of silepin [55] by Barton et al.⁵⁹ and fused silepin [56] by Müller⁶⁰ were stimulated by successful syntheses of benzo[d]silepin⁶¹, dibenzo[b,f]silepin⁶² and tribenzo[b,d,f]silepin.⁶³ In 1974, Kumada⁶⁴ and Sakurai⁶⁵



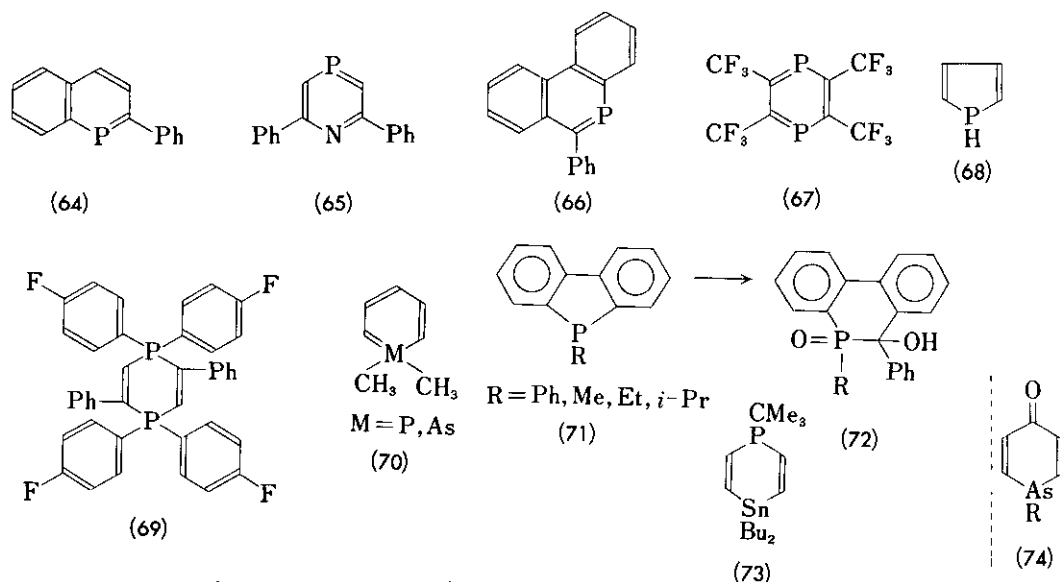
reported sililene [57] which was an important intermediate for other silicon heterocycles. Atwell and Uhlman⁶⁶⁾ have synthesized [58] which was also prepared from 1-silacyclopentene [59] by Kumada et al.⁶⁷ Seyferth and Vick⁶⁸ investigated the



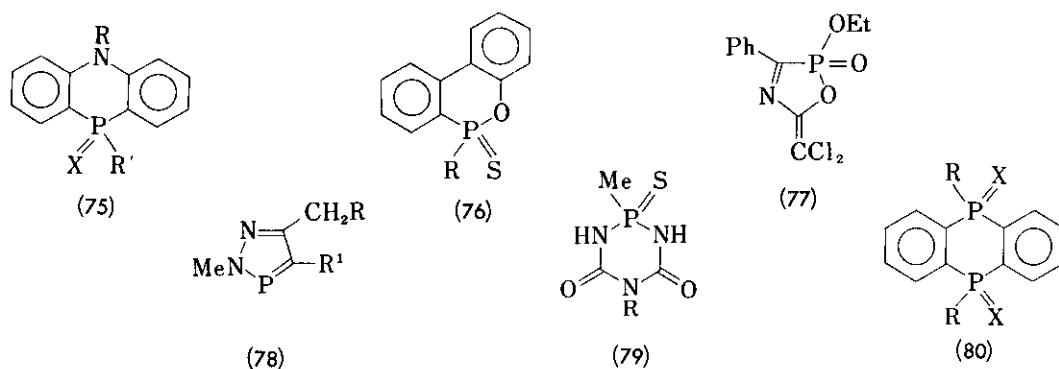
insertion reaction of [57] to silacycloprenes. Oxidation of silacyclopentadiene [60] was investigated by Mahajan et al.⁶⁹ Kumada et al.⁷⁰ reported about the conversion of [59] into [61]. 1,1-Dialkyl-naphtho[1,8-bc]silete [62] was synthesized by Yang and Shechter.⁷¹

1.4.3 Phosphorous, Arsenic, Antimony (V-group)

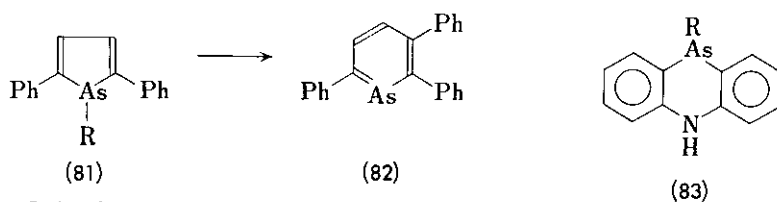
As mentioned above (1.4.2), this section covers only the recent literatures. Ashe⁷² synthesized phosphabenzene, arsabenzene, stibabenzene and bismabenzene [63], and studied their chemical properties. Phosphabenzene and arsabenzene were rather stable at room temperature, but easily oxidized in the air. By contrast, stibabenzene polymerized even at -80°C . Märkl et al.⁷³ have synthesized phosphabenzene derivatives such as 2-phenyl-1-phosphanaphthalene [64] and 1-aza-4-phosphabenzene [65]. 9-Phenylphosphaphenanthrene [66] was synthesized by Schäfer et al.⁷⁴ and diphosphabenzene [67] was reported by Kobayashi et al.⁷⁵ The unsubstituted five-membered compound, phosphole [68] was prepared by Byre et al.⁷⁶ Williams et al.⁷⁷ synthesized [69] and Ashe⁷⁸ reported [70]. Conversion of dibenzophosphole [71] to dibenzo[b,d]phosphorineoxide [72] was investigated by Allen and Oades.⁷⁹ The synthesis of 1,4-dihydro-1-phospha-4-stannabenzene [73] was reported by Märkl and Matthes.⁸⁰ Alkylation⁸¹ of arsacyclohexadienone [74] and halogenation⁸² of phosphorine (phosphabenzene) were reported. Stepanov's 5-methyl-5,10-dihydropheno-



phosphazine [75]⁸³, Bhatia's [76]⁸⁴, Drach's phosphaoxazolone [77]⁸⁵, Luber's diazaphosphole [78]⁸⁶, Roesky's triazaphosphorinone [79]⁸⁷, and Kovaeva's 5,10-dihydrophosphanthrene [80]⁸⁸ are phosphorous heterocycles reported recently. Chemistry of



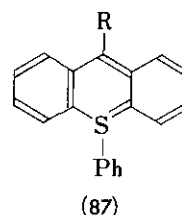
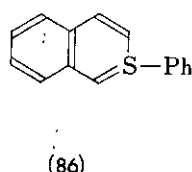
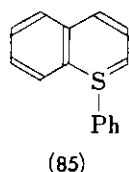
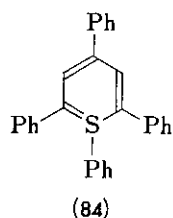
arsole has been extensively studied by Märkl. Conversion of arsole [81] to arsa-benzene [82] was reported.^{73d} Following the synthesis of 10-R-phenoxyarsine, Gravilov and co-workers⁸⁹ reported the synthesis of 5,10-dihydrophenarsazine derivatives.



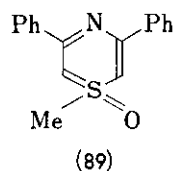
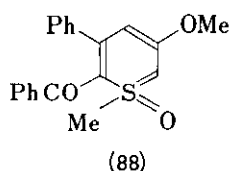
1.4.4 Sulfur, Selenium, Tellurium

Chemistry of thiabenzene is rather young in comparison with that of thiophene.

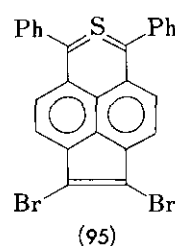
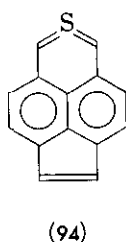
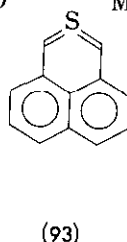
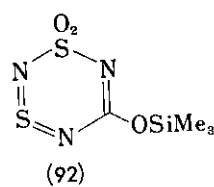
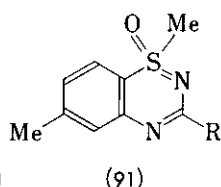
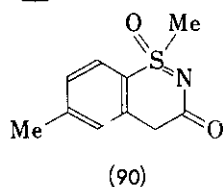
However, some thiabenzene derivatives [84] - [87] were synthesized by Price and co-workers⁹¹ from 1961 through 1963. Thiabenzene [84], redbrown powder, is most



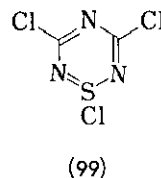
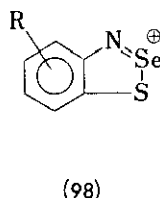
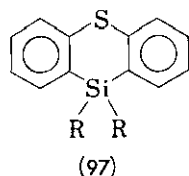
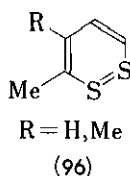
unstable one and easily oxidized. But the aromaticity of thiabenzene ring was confirmed by NMR. Its benzo-derivatives showed increased stability. The stabilized thiabenzenesulfoxide [88] was synthesized by Kishida.⁹² König⁹³ synthesized 4-azathiabenzene-1-oxide [89]. Cram and Williams⁹⁴ also reported the synthesis of



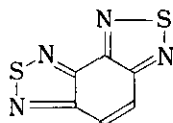
3-azathianaphthalene-1-oxide [90] and 2,4-diazathianaphthalene-1-oxide [91] as well as thiabenzenesulfoxide. Interestingly, compound [92]⁹⁵ has a -N=S=N- bond in the ring. 2-Thiaphenylene [93]⁹⁶ was also synthesized. Acenaphtho[5,6-cd]thiopyran [94]⁹⁷ was unstable and rapidly decomposed to yellow polymeric substance. Compound [95] and its tetraphenyl derivative were isolated as stable dark-green crystals.⁹⁸



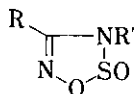
The following compounds were recently synthesized; dithiabenzene [96]⁹⁹, 9-thia-10-silaanthracene [97]¹⁰⁰, benzo-1,2,3-thiaselenazolium salt [98]¹⁰¹, and 1,2,4,6-



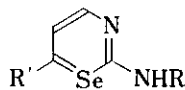
thiatriazine [99].¹⁰² The synthesis of 2,7,1,3,6,8-dithiatetraaza-as-indacene [100] by Tashiro et al.¹⁰³ was patented. Selenopyrones and selenobenzenes were prepared in one-step.¹⁰⁴ Preparation of 1,2,3,5-oxathiadiazole-2-oxide [101]¹⁰⁵ and the patented synthesis of 2-amino-1,3-selenazinium salt¹⁰⁶ were reported.



(100)



(101)



(102)

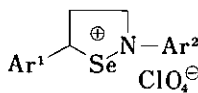
In 1970 Magdesieva presented a review which surveyed the chemistry of selenophenes, five-membered heterocycles, published in 1960's. In 1946, according to that review, Yur'ev has synthesized selenophene by heating furan and hydrogen selenide in the presence of magnesium oxide at 450°C. Ten years later in 1956, Perveev et al. have prepared various selenophene derivatives by ring-close reactions. Selenophenes have been used for practical purpose as antioxidants for silicone liquids, extractants for separation and extraction of metals, antibacterials, antifungals, antihistaminics and psychotropic drugs.

By contrast, tellurophene was first synthesized in 1966 by Mack from butadiene and sodium telluride, but no experimental details were reported. In 1972¹⁰⁸, its synthesis was reexamined. In 1977, the chemistry of tellurophene was reviewed by Magdesieva.¹⁰⁹

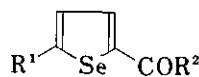
Benzo[b]selenophene and benzo[b]tellurophene were prepared by Piette et al.¹¹⁰ by the same method as used for the synthesis of benzothiophene. A review of chemistry of selenazoles, which contain nitrogen and selenium as heteroatoms, was presented in 1963.¹¹¹ While some substituted selenazoles were already reported in 1889, unsubstituted selenazole has not yet been synthesized. Liebscher and Hartmann have synthesized [103]^{112a}, [104]^{112b}, and [105]^{112c}. Industrial preparation of selenophene was also reported.¹¹³ The reported polycyclic compounds are



(103)



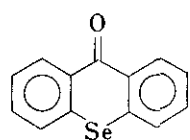
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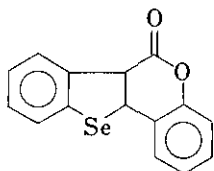
(105)

selenoquisanthone [106]¹¹⁴, benzo[b]selenophene-2(3H)-one [107]¹¹⁵, and 2,3-dihydroseleno[2,3-b]quinoline [108].¹¹⁵ The one-step synthesis of 2-(N-acetyl-

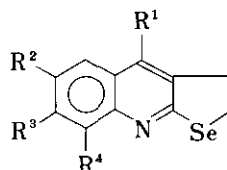
anilino]-4-formylselenazole [109]¹¹⁶ and the patented one-step synthesis of substituted 2-aminoselenazoles [110]¹¹⁷ and 2,5-disubstituted selenophene [111]¹¹⁸



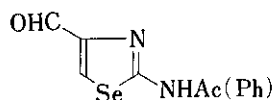
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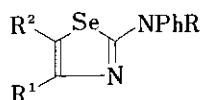
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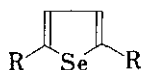
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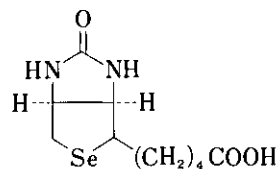
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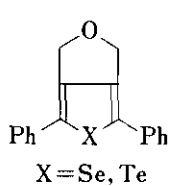
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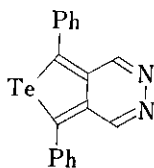
(112)

were described. Total synthesis of selenobiotin [112],¹¹⁹ synthesis of benz[b]-selenophene analogs¹²⁰ of gramine, tryptamine and tryptophane, synthetic approach of seleno analogs of benz[a]anthracene and dibenz[a,h]anthracene¹²¹, and synthesis of selenolo[2,3-c]- and selenolo[3,2-c]pyriliun salts¹²² were reported.

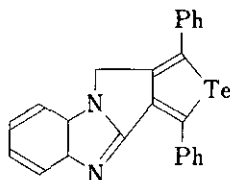
The recent synthesized tellurophenes are as follows; 2,5-disubstituted tellurophenes¹²³, 4,6-diphenyl-1H,3H-selenolo- and -telluro[3,4-c]furans [113]¹²⁴, new fused-cyclic tellurophenes [114 and 115]¹²⁵, 2,3-dihydrotellurolo[2,3-b]-quinoline [116]¹²⁶ and 2,5-dihydrotellurolo[3,4-c]tellurophene [117].¹²⁷



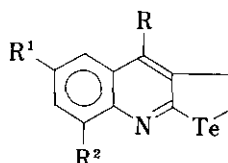
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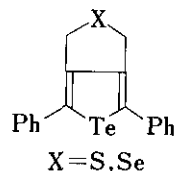
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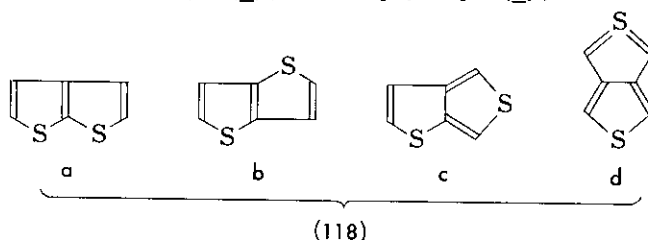
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1.5 Miscellaneous

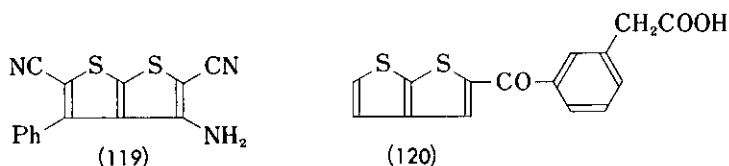
As mentioned in "Introduction", the aim of this review is to survey the synthesis of new-typed heterocyclic compounds. Within the limitations of 5- and 6-membered heteroaromatic compounds which contain oxygen, nitrogen and sulfur as heteroatoms, new heteroaromatic systems have been rarely reported. Therefore, this section is mainly focused on the fused polycyclic heterocycles composed of more than two hetero-rings. Usually, benzo-heterocycles are prepared from benzene derivatives and fused heterocycles are prepared by constructing an additional hetero-

cyclic ring on the basic heterocyclic ring. As seen in sections 1.1.1 and 1.2, many thiophene derivatives were prepared owing to the similar stability of thiophene ring like benzene ring. Therefore, this section describes mainly fused polycyclic compounds containing a thiophene ring. Furthermore, some other interesting heterocycles are also mentioned here.

Thienothiophenes [118], which are composed of two thiophene rings, have four possible isomers; thieno[2,3-b]- (a), thieno[3,2-b]- (b), thieno[3,4-b]- (c),

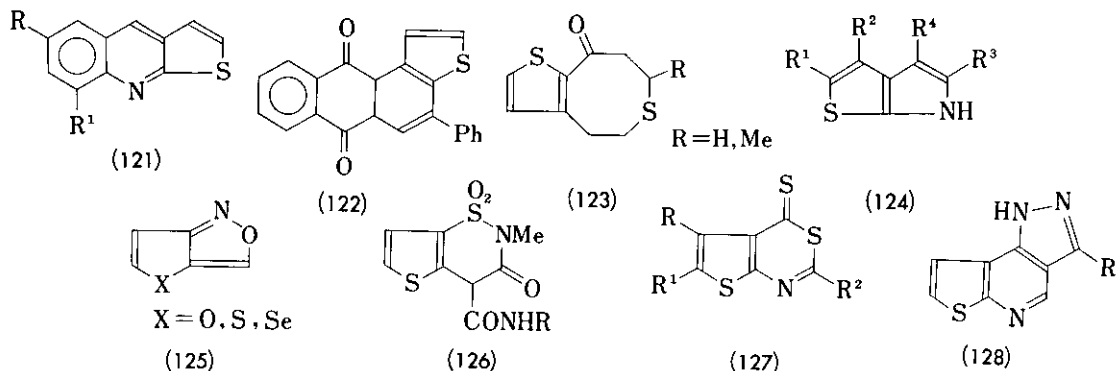


thieno[3,4-c]thiophene (d). Compound [118d] contains tetravalent sulfur and is called nonclassical thiophthene. No its oxygen- and nitrogen-analogs exist owing to their lack of d-orbitals. Classical thiophenes [118a,b,c] were described by Wynberg and Zwanenburg.¹²⁹ Cava and co-workers¹²⁸ isolated the substituted derivatives of [118d]. This sort of compounds is usually unstable and readily undergoes 1,4-cycloaddition. The review was published in 1976.¹³¹ The recent reports de-



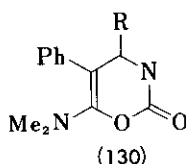
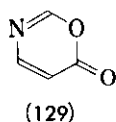
scribed the synthesis of [119]¹³⁰ and preparation of [120]¹³² as antipyretics.

Fused polycyclic thiophenes are named with a prefix "thieno". There have been many



reports on thienopyridines and the review was also published in 1977.¹³³ Thieno-[2,3-b]quinoline [121] was synthesized from aniline through three steps.¹³⁴ The

syntheses of anthra[2,1-b]thiophene [122]¹³⁵, tetrahydrothienothiocin [123]¹³⁶, thieno[2,3-b]pyrrole [124]¹³⁷, furo-, thieno-, seleno[3,2-c]isoxazoles [125]¹³⁸, thieno[2,3-e]isothiazolium salt¹³⁹, 2H-thieno[2,3-e]-1,2-thiazinecarboxylamide [126]¹⁴⁰ as an antiinflammatory agent, flavone, thioflavone, thiophene isoster of quisanthone¹⁴¹, thienothiazinethione [127]¹⁴² and thieno[3,2-e]pyrazolo[4,3-c]-pyridine [128]¹⁴³ were reported. An increasing number of reports concerning fused tricyclic compounds has been published, but still many systems remain unknown and to be investigated. The followings are monocyclic, but new-typed compounds which were recently synthesized; 1,3-oxazine-6-one [129] as a precursor of azacyclobutadiene in 1975¹⁴⁴ and 2H-1,3-oxazin-2-one [130] in 1976.¹⁴⁵



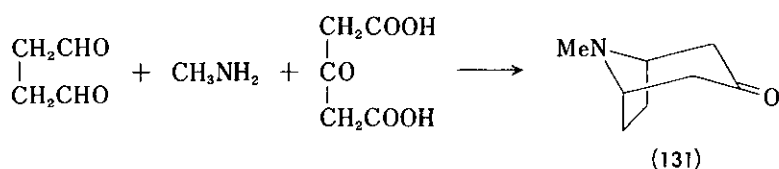
2. Saturated Fused Polycyclic Heterocycles

As mentioned in "Introduction", molecular flexibilities of saturated fused polycyclic systems are restricted by bridged atoms, resulting in total stabilization of the molecules with less strain energy. However, it has been rather difficult to synthesize these fused polycyclic systems by simple methods. The recent progress of cycloaddition reactions, especially pericyclic reactions, has been giving a solution to these problems, and they became one of new fields of heterocyclic chemistry. This chapter is subdivided into two sections describing chemistry of saturated bridged heterocycles (section 2.1) and synthesis of hetero-adamantanes and heterotwistanes (section 2.2).

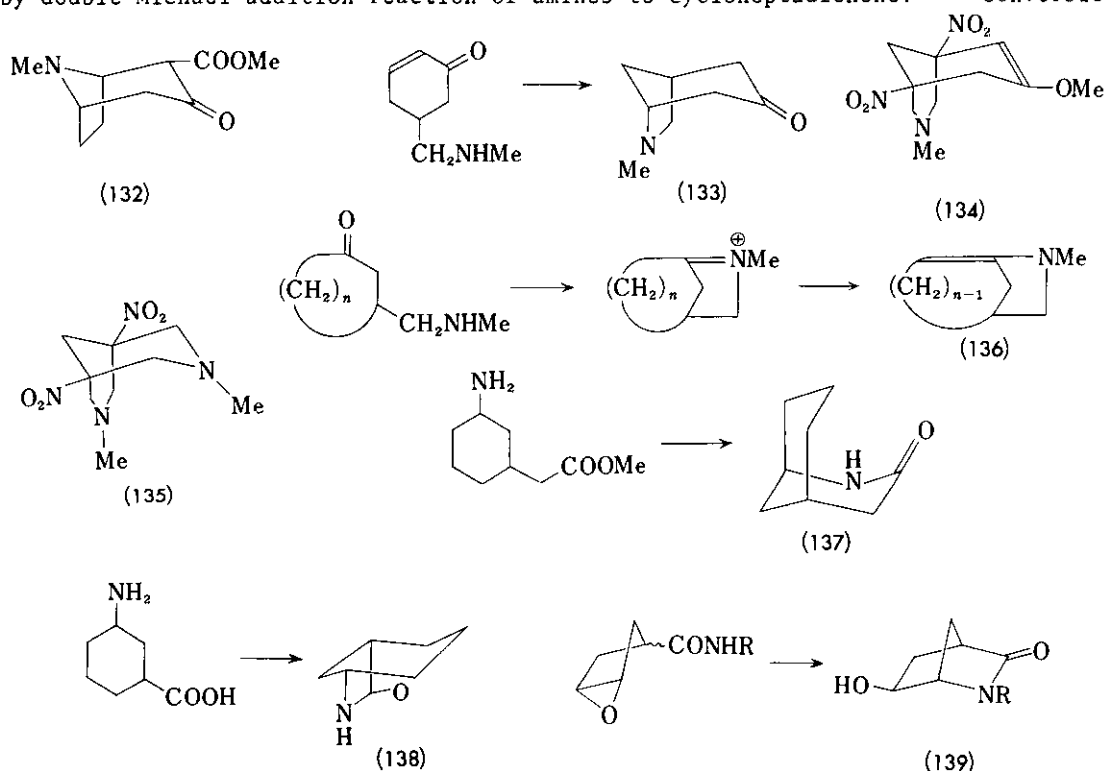
2.1 Saturated Bridged Heterocycles

2.1.1 Nitrogen Heterocycles

This class of compounds can be synthesized mainly by four methods as follows,
a) Mannich-type Reactions Carbon-nitrogen bond can be formed by nucleophilic addition of nitrogen to the electron-deficient double bonds. The Robinson-Schöpf reaction in tropinone [131] synthesis is a historically well-known example. Bottini¹⁴⁶ and Mukai¹⁴⁷ independently reported the above reaction of N-alkylamine with cycloheptadienone and cyclooctadienone instead of succinic dialdehyde and acetone-dicarboxylic acid, but the yield were low. Slightly improved results were obtained in the similar reaction of N-allylamine. Syntheses of [132]¹⁴⁸ by the modified



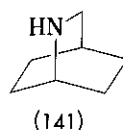
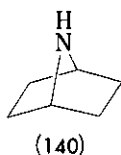
Robinson-Schöpf reaction and [132]¹⁴⁹ by intramolecular Michael addition were reported. 3-Azabicyclononanes were obtained from the reaction of methylamine, formaldehyde and NaBH₄-reduction products of substituted m-dinitrobenzenes. For instance, [134] was prepared from dinitroanisole in 66% yield and [135] was synthesized from dinitrophenol.¹⁵⁰ 8-Azabicyclo[3.2.1]octane systems were synthesized by double Michael addition reaction of amines to cycloheptadienone.¹⁵¹ Conversions



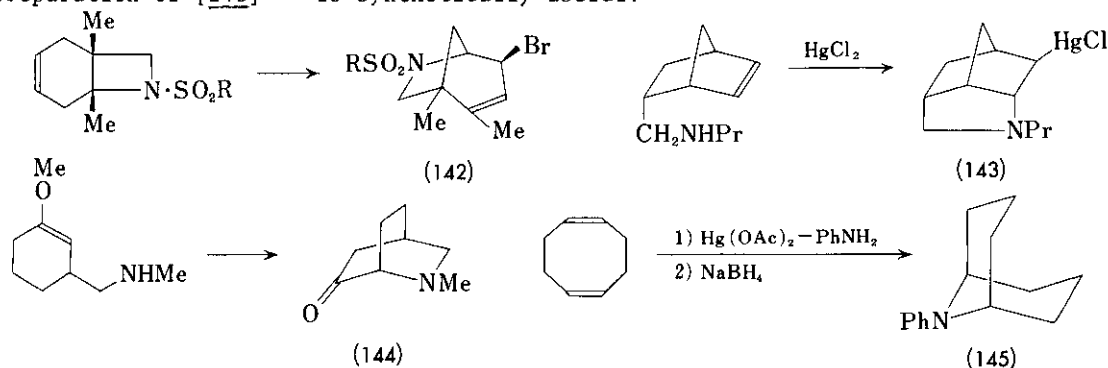
of monocyclic aminoketones into bicyclic enamines [136]¹⁵² and bicyclic amides [137 and 138]¹⁵³ were reported. Reaction of cyclododecanone with methylamine and formaldehyde¹⁵⁶, and synthesis of [139]¹⁵⁵ were also described.

b) Nucleophilic Attack of Nitrogen Fraser and Swingle¹⁵⁶ synthesized 7-azabicyclo[2.2.1]heptane [140] through 5 steps from p-hydroxyacetoanilide. Schneider

and Lehmann¹⁵⁷ prepared azabicyclo[2.2.2]octane [141] from 1-amino-4-ethoxycarbonyl-



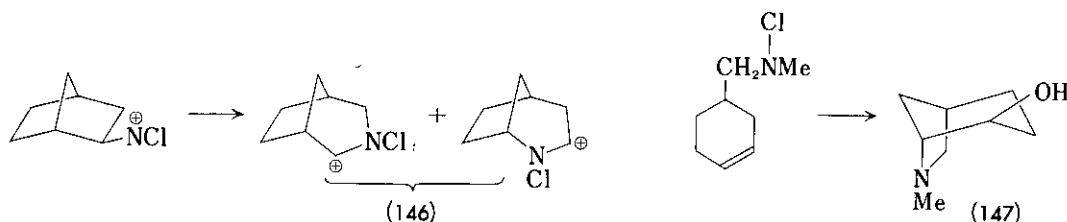
cyclohexane by reductive ring-closure. Syntheses of [142] by Paquette¹⁵⁸, [143] by Perie¹⁵⁹ and [144] by Furstoss¹⁶⁰ were recently reported. The high-yield (80%) preparation of [145]¹⁶¹ is synthetically useful.



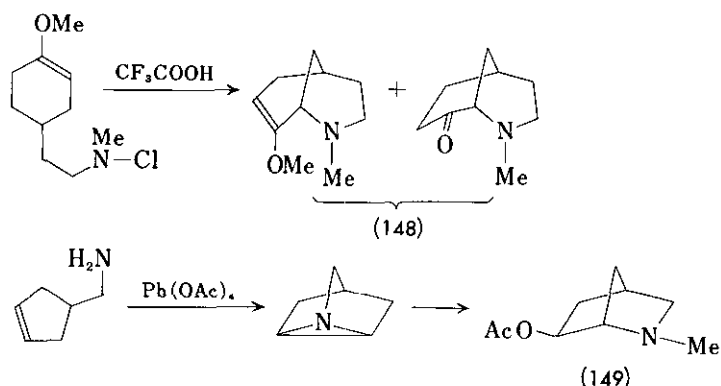
c) Electron-Deficient Nitrogen Species

Ring-formation or ring-expansion reactions of nitrenium ions formed by solvolysis of N-haloamines are known as the

Hofmann-Löffler-Freytag reaction which has been widely used to synthesize nitrogen heterocycles. Kovacic et al.¹⁶² utilized this reaction to make [146] and presented a review of its chemistry.¹⁶³ Gassmann¹⁶⁴ reported the preparation of [147] by intramolecular double-bond addition of nitrenium ion and also revealed the review.¹⁶⁵

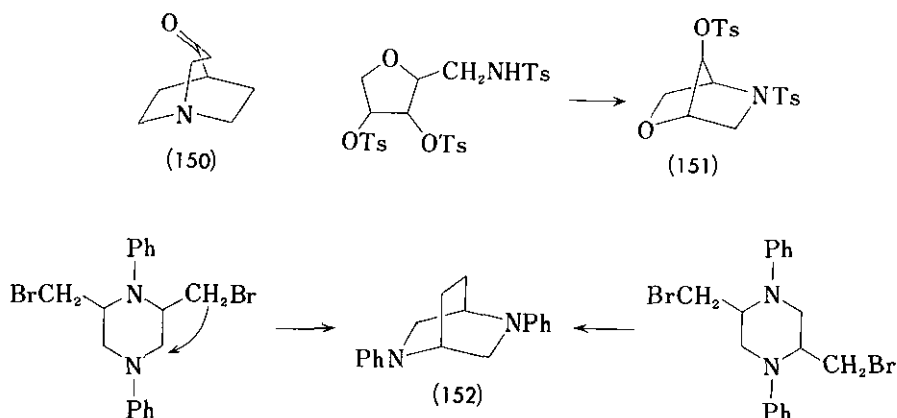


1-Azatwistane was elegantly synthesized by intramolecular double-bond addition of the carbon-radical which in turn was formed by photolysis of N-haloamines in the acidic media.¹⁶⁶ Chow et al.¹⁶⁷ have developed the method using nitrosoamines instead of haloamines, and described the review. Other methods by photolysis of haloamines in the presence of titanium tetrachloride¹⁶⁸, and photolysis of azides¹⁶⁹ were also reported. Kovacic et al.¹⁷⁰ found that aluminum chloride catalyzed the reaction of dihaloamines. Syntheses of [148]¹⁷¹ and [149]¹⁷² were also reported.

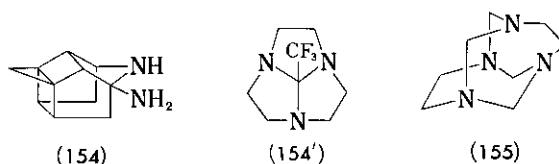
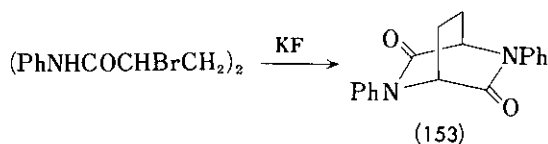


d) Cycloaddition Reaction When cyclic dienes and/or cyclic dienophiles are used in the cycloaddition reaction, bicyclic and tricyclic systems are formed in one-step. By choosing heterodienes and heterodienophiles, many interesting heterocyclic compounds can be prepared in one-step. Therefore, it has been main interest to develop new heterodienes and heterodienophiles. Since many reports have been published in this field, this section only deals with review published in 1977. They are concerning pericyclic reactions of cumulenes¹⁷³, cycloaddition reactions of enones¹⁷⁴, synthesis of quinazoline alkaloids by intramolecular cycloaddition of iminoketenes¹⁷⁵, thermal cycloaddition reaction of tropilium compounds¹⁷⁶, 1,3-dipolar cycloaddition of X=Y components¹⁷⁷, and the monograph by Imoto.¹⁷⁸

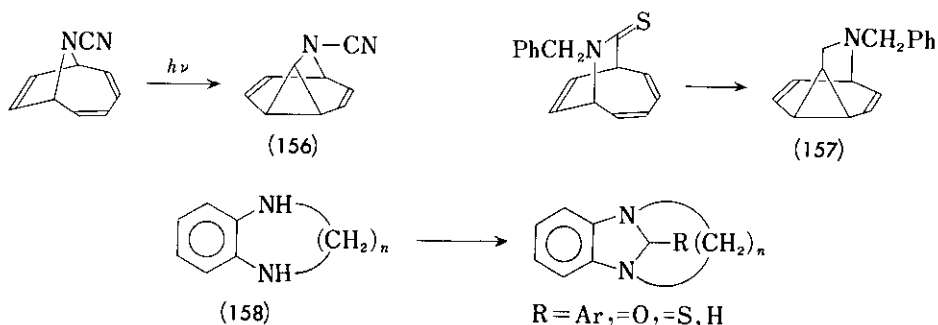
e) Miscellaneous Reactions This section includes ring-expansion reaction, ring-contraction reaction and ring-isomerization by solvolysis. The synthesis of 1-azabicyclo[3.2.2]nonane [150]¹⁷⁹ by ring-expansion reaction of quinuclidin-3-one with diazomethane, and solvolytic preparations of oxaazabicycloheptane [151]¹⁸⁰,



diazabicyclooctane [152]¹⁸¹, diazabicyclodione [153]¹⁸², aza-bird cage compound [154]¹⁸³, 10-trifluoromethyl-1,4,7-triaza-tricyclo[5.2.1.0^{4,10}]decane [154']¹⁸⁴, and tetracin [155]¹⁸⁵ have been reported. 2-Azabicyclo[2.2.2]octane was converted



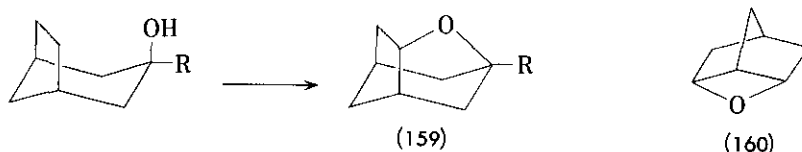
to 7-azabicyclo[3.2.1]oct-2-one in 25% yield.¹⁸⁶ 9-Azababaralane [156]¹⁸⁷ and aza-bullvalene [157]¹⁸⁸ were photochemically prepared. 3-Azabicyclo[3.3.1]nonanes were synthesized from acrolein and enamine of piperidone.¹⁸⁹ Ring-close reactions of cyclic diamines [158]¹⁹⁰ were also known.



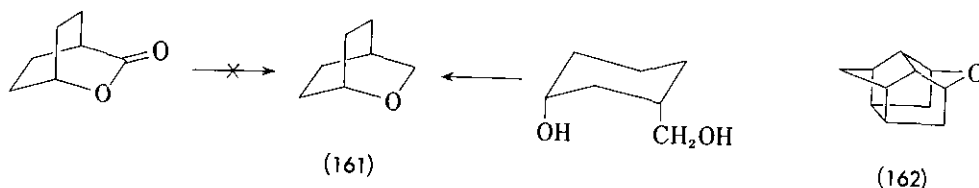
2.1.2 Oxygen Heterocycles

The following three methods are most widely used.

a) Ether-Formation by Hydrogen-Abstraction of Alkoxy Radicals Generated by Oxidation of Alcohols Brun and co-workers¹⁹¹ prepared the cyclic ether [159] in 50% yield by treating the alcohol in benzene with lead tetraacetate in the presence of calcium carbonate. Compound [160] was similarly synthesized.¹⁹³ Such ether bond formation by lead tetraacetate was recently reviewed.¹⁹²

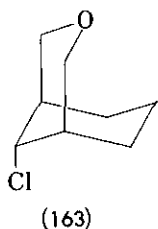


b) Nucleophilic Attack of Oxygen 2-Oxabicyclo[2.2.2]octane [161] was not obtained by reduction of the corresponding lactone, but prepared from cyclohexane-alcohol by tosylation followed by base-treatment.¹⁹⁴ Oxy-bird cage compound [162]¹⁸³

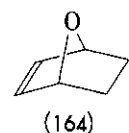


was similarly synthesized by us. Ganter et al.¹⁹⁵ obtained the isomeric mixture of oxabicyclo[3.3.1]nonanes and oxabicyclo[4.2.1]octanes by treating cycloocta-1,5-diene with mercuric acetate, potassium iodide, and iodine. Paquette and Storm¹⁹⁶

investigated the reactivity of the related compounds. The reaction of olefins and formaldehyde in the acidic media giving methadioxane is known as Prins reaction. Stapp and Randall¹⁹⁷ prepared oxabicyclo-[3.3.1]nonane [163] in 50% yield by treating a mixture of cyclohexene and paraformaldehyde with hydrochloric acid at low temperature. The similar reaction with 1-phenylcyclohexene was also reported.¹⁹⁸



c) Cycloaddition Reaction Many oxabicyclo[2.2.1]heptene systems have been prepared by [4+2] cycloaddition reaction of furan and the appropriate dienophiles.



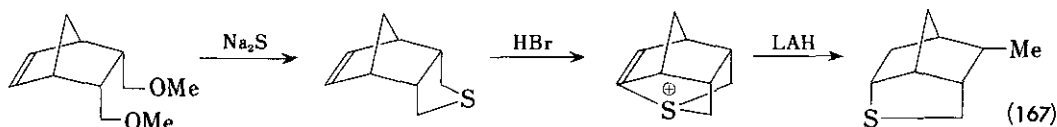
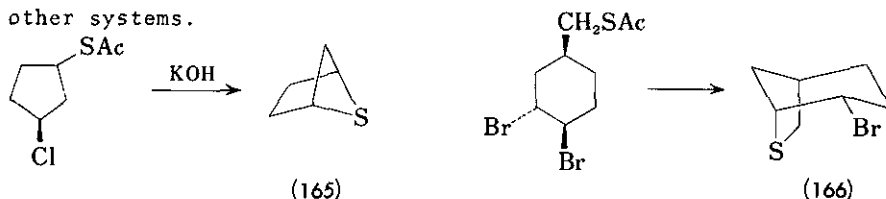
The review was published.¹⁹⁹ Besides the reviews mentioned in 2.1.1d, the reviews concerning cationic polar cycloaddition reactions (by Bradsher)²⁰⁰ and intramolecular 1,3-dipolar cycloaddition reactions (by Padwa)²⁰¹ are available.

2.1.3 Sulfur Heterocycles

Generally transannular reaction of sulfur compounds is easier than that of corresponding oxygen compounds. The following three methods are most widely used for synthesis.

a) Nucleophilic Attack of Sulfur The reactions proceed in increased ease because of the increased nucleophilicity of sulfur in comparison with nitrogen and oxygen analogs. 5-Thiabicyclo[2.1.1]hexane [165]²⁰² and thiabicyclo[3.2.1]-

octane [166]²⁰³ were prepared by this method. Sulfur-carbon bond formation by reaction of alcohol and sodium sulfide was applied to the synthesis of 2-methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane [167].²⁰⁴ This method was widely used for synthesis of other systems.

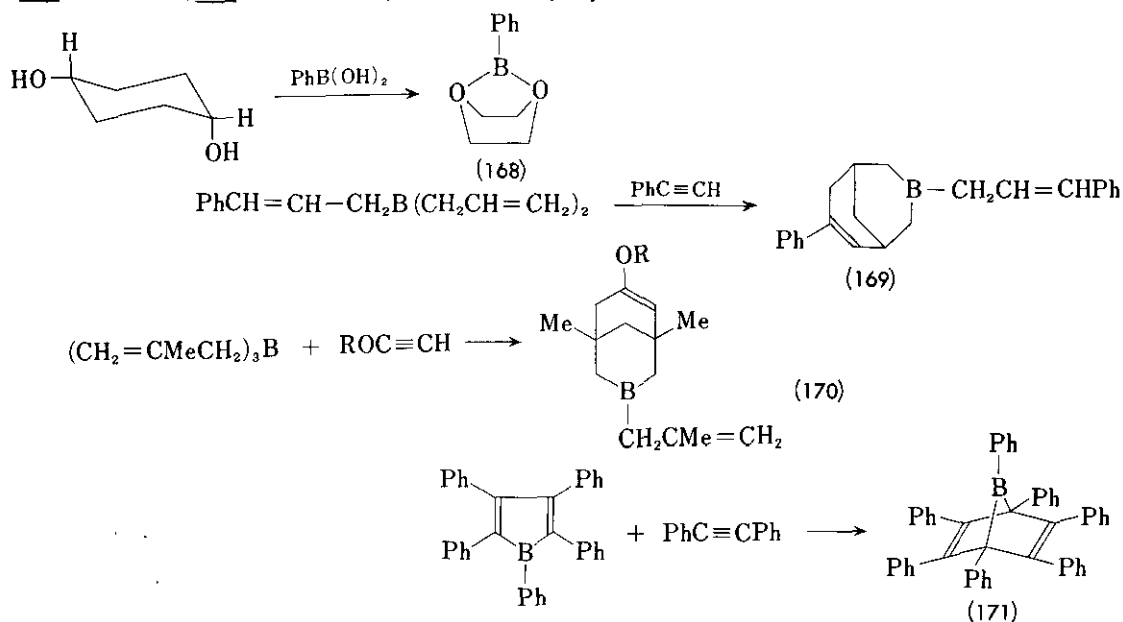


b) Use of Sulfur Dichloride This compound corresponds to haloamines mentioned in 2.1.1c. No correspondents are available to oxygen analogs. Its application to the synthesis of heteroadamantane is discussed in section 2.2.

c) Cycloaddition Reactions Thiophene is a sulfur analog of furan mentioned in 2.1.2c, but is less reactive in cycloaddition reaction. However, thioketones, sulfur dioxide, sulfur monoxide, and thiophosgene are often used as dienophiles. Development of new sulfur-containing diene and dienophiles will be hoped.

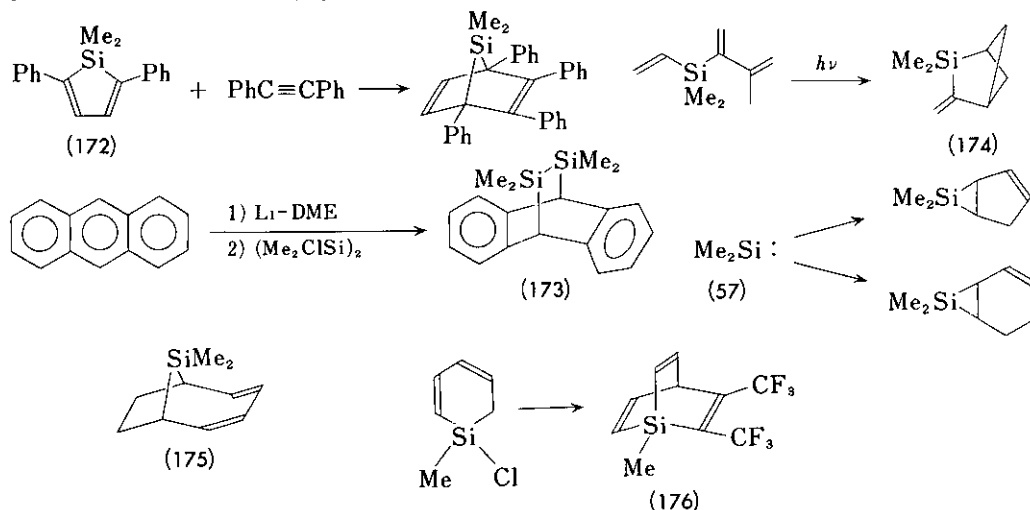
2.1.4 Boron Heterocycles

Finch et al.²⁰⁵ prepared [168] by condensation reaction. Compound [169]²⁰⁶, [170]²⁰⁷ and [171]²⁰⁸ were synthesized by cycloaddition reaction.



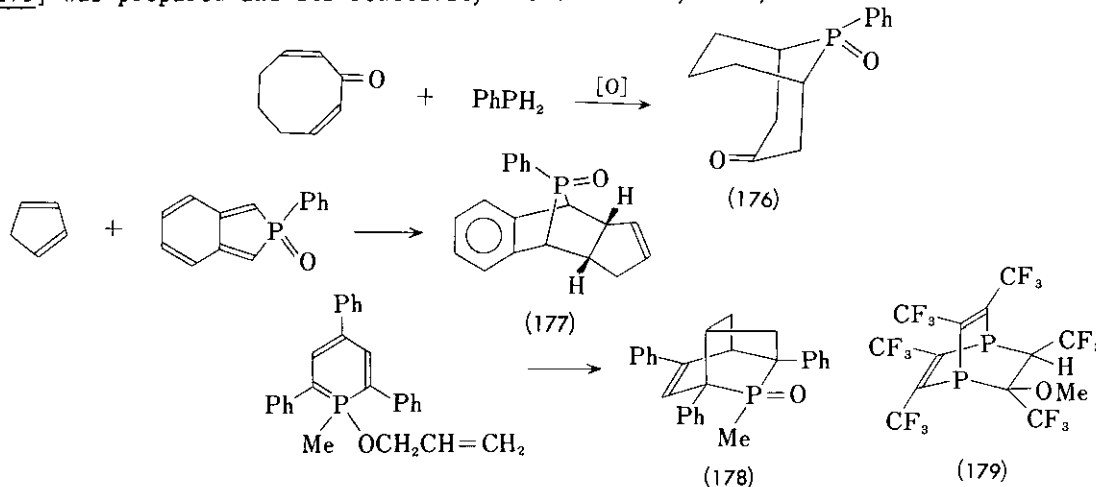
2.1.5 Silicon Heterocycles

The cycloaddition reaction of [172] was reported in 1971.²⁰⁹ On heating, Me_2Si was easily eliminated from the product. Preparation of [173]²¹⁰ and photochemical formation of [174]²¹¹ were reported. Cycloaddition of dimethylsililene [57] to olefins was described.²¹² Preparation and reactivity of [175] were investigated.²¹³ Compound [176] was synthesized by Barton and Banasiak.²¹⁴



2.1.6 Phosphorus Heterocycles

Phenylphosphene dichloride is closely related to haloamine [2.1.1c] and sulfur dichloride [2.1.3b], and some reactions are described in the monograph, "1,4-Cycloaddition Reactions" published in 1967. The recent reports described the syntheses of [176]²¹⁶ by addition of phenylphosphine [177]²¹⁷, by cycloaddition of isophosphorindole oxide, and [178]²¹⁸ by intramolecular cycloaddition. Diphosphabarrelene [179] was prepared and its reactivity was studied by Kobayashi et al.²¹⁹



2.2 Heteroadamantanes, Heterotwistanes

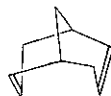
Both adamantane and twistane are tricyclic stable crystalline compounds having $C_{10}H_{16}$ formulae. Chemistry of heteroadamantanes was described in the recent monograph titled "Adamantane".²²⁰ Therefore, this section only covers the recent papers.

2.2.1 Nitrogen Heterocycles

1- and 2-Azaadamantanes have been known for a long time. But synthesis of these compounds has been mostly developed since 1970. The preparation of these compound by method 2.1.1b is efficient. Synthesis by a method 2.1.1a was also investigated. Stetter and co-workers reported the synthesis of 2-azaadamantane from diketone [180] and bicyclononadiene [181]. No other syntheses have been reported.

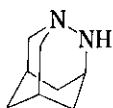


(180)

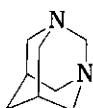


(181)

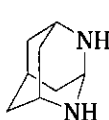
Diazaadamantane has five isomers of 1,2- [182], 1,3- [183], 2,4- [184], 1,4- [185] and 2,6-diazaadamantane [186]. 1,3-Diazaadamantane is the oldest one which was



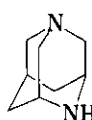
(182)



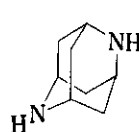
(183)



(184)



(185)



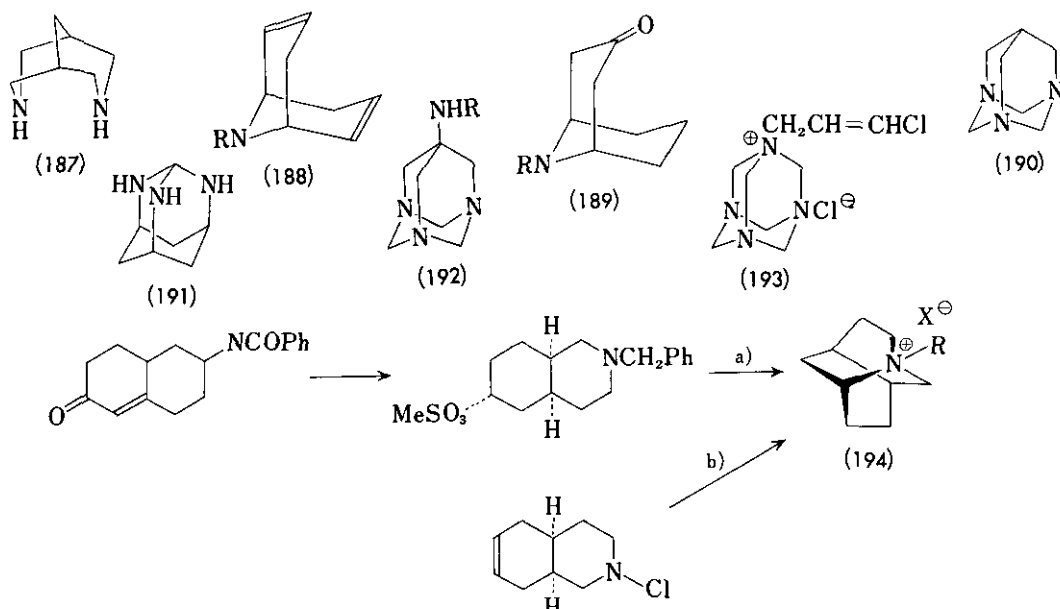
(186)

synthesized from bispidine [187], and most well investigated. Some of its derivatives are as toxic as strychnine. 2,6-Diazaadamantane was synthesized from [188] and [189]. The other isomers still remain unknown.

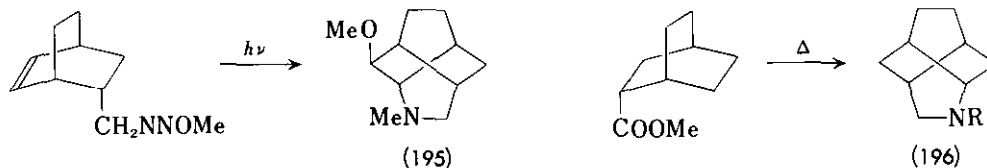
Among the possible 11 isomer of triazaadamantane, only [190] with all nitrogens at bridgeheads and [191] with all nitrogens at bridges were synthesized by Stetter in 1970, but N-unsubstituted compound of [191] is still unknown. Nelson synthesized [192] in 92-99% yield.²²¹

Tetraazaadamantanes with all nitrogen bridgeheads have been known for a long time. A compound [193], antifungals, was patented by Dow-Chemicals.²²²

1-Azatwistane [194] was synthesized in three different ways in 1970. The first two methods, Deslongchamps' method (a) and Pereman's method, are variations of section 2.1.1b, and the third one, Heusler's method (b) is variation of section 2.1.1c.

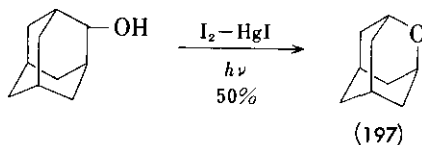


In each case, key cyclization reaction proceeded in moderate yields. 2-Azatwistane was first synthesized by Lworskii et al. in 1971. Lockhart and co-workers²²³ synthesized [195]. Compound [196] was prepared by Furstoss and Waegell.²²⁴ Diaza-twistane is still unknown.



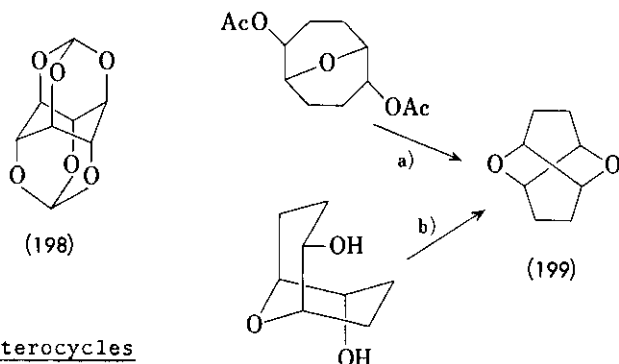
2.2.2 Oxygen Heterocycles

2-Oxaadamantane [197] was synthesized in 4 different ways. Reduction of diketone [180] followed by intramolecular dehydration (method 1) and simultaneous ring close by catalytic hydrogenation (method 2) were reported by Stetter et al. before 1970. Compound [181] was used as a starting material in Zifirov's method (method 3). In Gill's method, adamantanol was converted to oxaadamantane (method 4).



Both 2,4- and 2,6-isomers of dioxaadmantane were synthesized by Stetter before 1970. All three isomers of trioxaadmantane have been synthesized, but the reported unsubstituted compound is only 2,4,10-oxaadmantane. Only 2,4,6,8-isomer

of tetraoxaadamantane was synthesized. None of pentaoxaadamantanes are known so far. Hexaoxadiamantane [198] was reported in 1969. In 1970, dioxatwistane [199] was synthesized by Ganter's method (a) and Dittman's method (b). Synthesis of monooxatwistane was reported in 1975.²³⁵

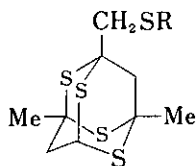


2.2.3 Sulfur Heterocycles

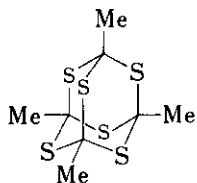
Thiaadamantane [200] is the only heteroadamantane which occurs in nature. It was found in the tar of Iranian kerosine. The synthesis was reported by Stetter et al. in 1960.



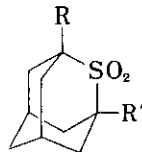
Two isomers of substituted dithiaadamantane were synthesized. Trithiaadamantane are still unknown. 2,4,6,8-Tetrathiaadamantane was synthesized, but 2,4,6,9-isomer remains unknown. Synthesis of [201] was reported.²²⁶ Pentathiaadamantane is not yet reported. Hexathiaadamantane is the oldest known heteroadamantane. 1,3,5,7-Tetramethyl-2,4,6,8,9,10-hexathiaadamantane [202] was synthesized from thioacetic acid and zinc chloride, or bromine, acetyl chloride and liquid hydrogen sulfide. Its original structure was revised by Pregda (1951) who synthesized the unsubstituted compound. Recently, reactivity of 2-thiaadamantane sulfone [203] was investigated.²²⁷ In the studies on dithiatwistane, Ganter²²⁸ obtained dithiaisotwistane [204].



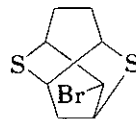
(201)



(202)



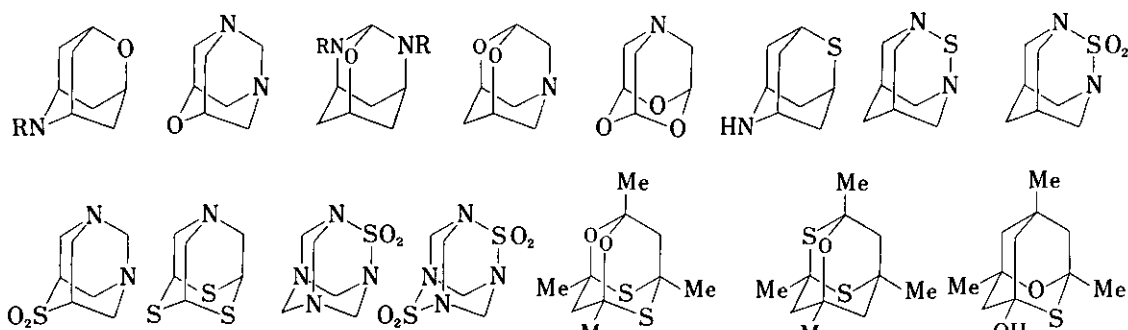
(203)



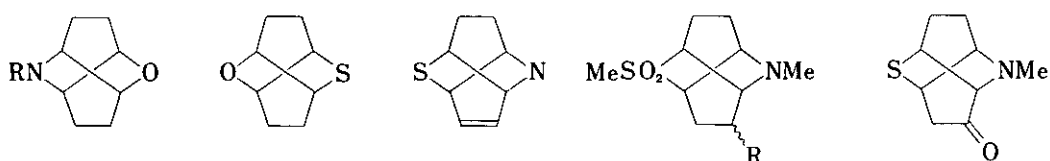
(204)

2.2.4 Heterocycles Containing More Than Two Nitrogen, Oxygen, and Sulfur

Polyheteroadamantanes are as follows;



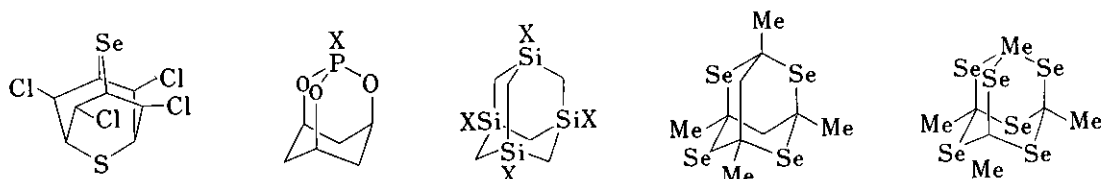
The following are heterotwistanes. The first two compounds have been known.



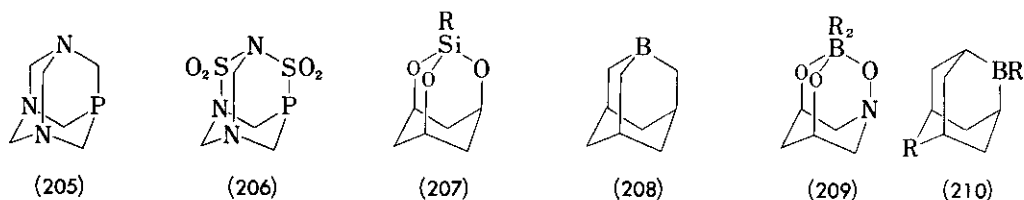
The last three compounds were recently synthesized.²³⁴

2.2.5 Miscellaneous

The following compounds have been known.



The recent reports describe preparations of 1,3,5-triaza-7-phosphaadamantane [205], 2,4-dithia-1,3,5-triaza-7-phosphaadamantane-2,2-dioxide [206]²³⁰, 2,4,10-trioxa-3-silaadamantane [2-7]²³¹, 1-boraadamantane [208]²³², 1-bora-2,8,9-trioxa-7-azaadamantane [209]²³³ and 2-boraadamantane [210].²³⁵



(205)

(206)

(207)

(208)

(209)

(210)

Conclusion

This review has been concerned with new-typed heterocyclic compounds. The number of reports in this field is increasing but only limited number of literatures which attract author's own interest have been described here. Furthermore, lack of space does not allow to discuss the details for each case.

The author is happy if this review is useful to the readers.

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