CYCLIZATION AND CYCLOADDITION REACTIONS OF HETEROEPINS, CONJUGATED SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS[1)]

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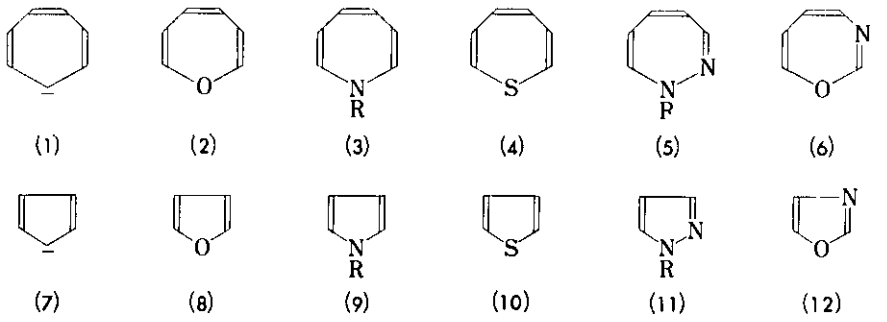
Abstract This review describes the recent advances in the chemistry of heteroepins, especially the thermally and photochemically induced reactions of 1H-azepine, 1H-1,2-diazepines and 1,3-oxazepine derivatives as well as the synthesis of these hetercyclic compounds.

Introduction

Conjugated seven-membered heterocyclic compounds are generally called heteroepins. A large number of heteroepins is so far known, e.g., oxepin (2), azepine (3), and thiepin (4), etc., which contain one heteroatom, and diazepine (5) and oxazepine (6), etc., which contain two heteroatoms. The heteroepins containing three heteroatoms are also known. All these compounds have 8π-electrons in their rings and are isoelectronic with the cycloheptatrienylide anion (1). Recently, heterocyclic polyenes have been roughly classified into two categories, i.e., aromatic and anti-aromatic compounds.[2)] According to this device, heteroepins belong to a class of compounds containing 4nπ-electrons in the (4n-1)-membered ring. On the other hand, furan (8), pyrrole (9), thiophen (10), pyrazole (11), and oxazole (12), which are five-membered analogs corresponding to heteroepins (1) ∿ (6) and isoelectronic with the cyclopentadienide anion (7), belong to a class of compounds containing (4n+2)π-electrons in the (4n+1)-membered ring. These five-membered heterocycles have been extensively studied as aromatic compounds for a long period and have become the basis of the modern heterocyclic chemistry and the organic precision industry. On the contrary, the history of the heteroepin chemistry is relatively new, and especially the studies on monocyclic heteroepins were started around 1960.[3)]



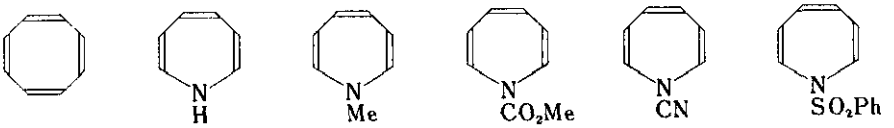
(1) (2) (3) (4) (5) (6)

(7) (8) (9) (10) (11) (12)

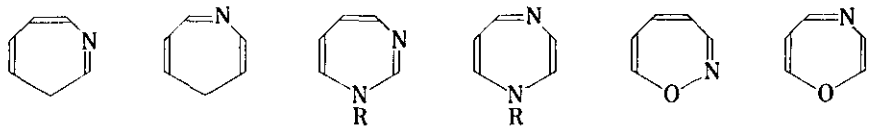
Scheme 1

The characteristic points of the heteroepins are that the lone-pair electrons on the heteroatom are localized and the double bonds of them are alternating. If the molecules possess plane structures, they should show the anti-aromatic character due to 8π-electrons. However, this character has not been clearly observed in the heteroepins except 1H-azepine. These molecules have a boat structure and behave like cyclic polyenes such as cycloheptatriene and cyclooctatetraene. Therefore, various kinds of intramolecular cyclization and intermolecular cycloaddition reactions can be expected although electrophilic and nucleophilic substitution reactions observed in aromatic compounds are not expected to occur easily. For these reasons, this paper describes mainly photochemically and thermally induced cyclization and cycloaddition reactions of the heteroepins.

In order to understand the heteroepin chemistry well, the following points should be noted. One point is that the reactivities of the heteroepins are compared with those of cycloheptatriene or cyclooctatetraene as well as the corresponding five-membered heterocycles. Another point is to consider whether the variety of heteroatoms influences the reactivities of the heteroepins or not. The reactivity or instability arising from the functional groups such as vinyl ethers or enamines in the heteroepin ring should be noted especially under ionic conditions. It is of interest to note the difference in the chemical behavior between 1H-azepines (3a) and 2H- and 3H-azepines (14 and 15). It is also interesting to consider the differences in chemical behavior between 1,2-isomers (5, 18) and 1,3-isomers (6, 16) in diazepines and oxazepins. In the heteroepins shown in schemes 1 and 2, there are unknown compounds such as thiepin (4), 1,2-oxazepine (18) and 1,4-oxazepine (19).



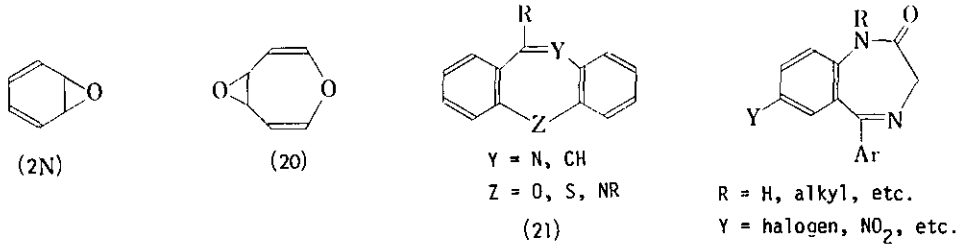
(13) (3a) (3b) (3c) (3d) (3e)



(14) (15) (16) (17) (18) (19)

Scheme 2

It is noteworthy, furthermore, to discuss the heteroepin chemistry from the standpoint of biochemical and pharmaceutical interest in addition to organic chemistry. Benzene oxide (2N), a valence isomer of oxepin (2), is an important intermediate in the conversion of aromatic compounds into phenols in vivo. In addition, (2N) is considered to make bonds with DNA or RNA because of its high reactivity and thus (2N) is of strong interest in connection with celltoxin and carcinogenic activity.[4] There is one theory that derivatives of oxepin and homooxepin (20) take part in the biosynthesis of aflatoxin, etc.[5] A large number of benzene-condensed derivatives of azepines and diazepines have biological activities.[6a] Diazepines (22) having a skeleton of 1,3-dihydro-5-arylbezodiazepine-2-one are well known as tranquillizers.[7] The variety of the heteroepin structure seems to stimulate further studies on applying them.



(2N) (20) Y = N, CH; Z = O, S, NR (21) R = H, alkyl, etc.; Y = halogen, NO_2, etc. (22)

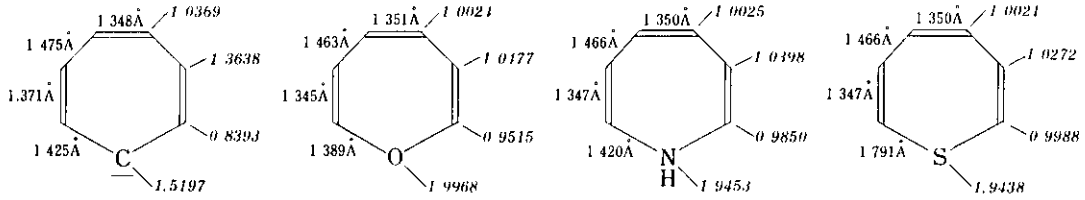
Scheme 3

In this review we wish to describe chiefly the heteroepins containing one or two heteroatoms in order to keep it to a reasonable size. There are some reviews concerning them.[8~11] These reviews, however, have been published before 1970 and, therefore, the present review covers the works that have been reported since 1970. The reviews concerning oxepins and thiepins have been recently reported by Murata[12a] and Jerina,[12b] and so we have eliminated these heterocycles chemistry in this article except for comparisons with other heteroepins. We have also left out borepins[13b] and silepins[2,13a] which contain boron and silicon, respectively, in the seven-membered ring, but instead showed only their references here.

I. Molecular structures and physical properties

We have pointed out that the heteroepins behave like cyclic polyenes. We wish to investigate here their molecular structures and physical properties. According to SCF-MO calculations reported

by Dewar, the resonance energies, bond lengths, and π-electron densities of heteroepins are obtained as shown in scheme 4.[14] It is clear that a single bond and a double bond are alternatively localized and the bond lengths are in accord with those of polyenes. Resonance energies (E_R) are small but negative values in 1H-azepine (3a) and thiepin (4) although oxepin (2) has a nearly zero value. Judging from these values, it can be expected that all of them are nonaromatic compounds with high reactivities. It can be predicted from the detailed investigation of these values, however, that oxepin (2) is slightly more stable than 1H-azepine (3a) and thiepin (4).

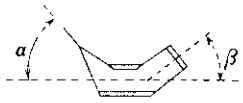


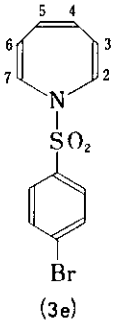
(1) (2) (3a) (4)

E_R=0.12kcal/mol E_R=−0.18kcal/mol E_R=−1.45kcal/mol

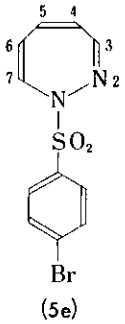
Scheme 4 Bond length, π-electron density, and resonance energy of (1) and its hetero-analogs.

Results of the X-ray crystallographic analyses of 1H-azepine derivative (3e),[15] 1H-1,2-diazepine derivative (5e),[16] and oxazepine derivative (23)[17] are shown in Table 1, although there is no report on oxepins. Comparison of (3e) and (5e) with Dewar's calculation seem to indicate the following important facts. (i) All these heteroepins have a boat form and clearly show bond-alternation. (ii) In mono- and di-azepines a lone-pair of electrons on the nitrogen atom is located at the endo position and to some extent has sp^2 character. As the electron withdrawing property of the N-substituent becomes weak (e.g., when an arylsulfonyl group changes to an alkoxycarbonyl group), the deviation of the ring from a plane becomes larger and the C_4-C_5 double bond becomes longer. (iii) In 1H-1,2-diazepines the imine double bond is localized and the butadiene framework is slightly stabilized by the resonance.

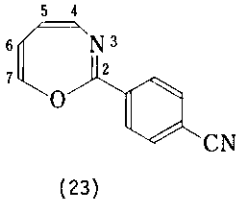




(3e)



(5e)



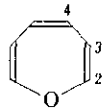
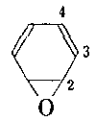
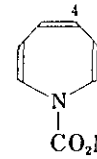
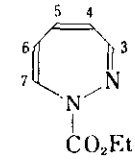
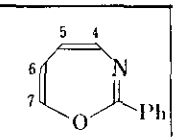
(23)

Table I X-ray Crystallographic Analyses of Heteroepins Derivatives

Compounds	(3e)	(5e)	(23)
α	51.8°	61.8°	54.8°
β	28.1°	27.6°	27.2°
N or O(1)-N or C(2)	1.43Å	1.447Å	1.329Å
C or N(2)-C or N(3)	1.38	1.255	1.281
C or N(3)-C(4)	1.44	1.460	1.415
C(4)-C(5)	1.34	1.326	1.336
C(5)-C(6)	1.46	1.436	1.443
C(6)-C(7)	1.37	1.333	1.331
C(7)-N or O(1)	1.45	1.428	1.394

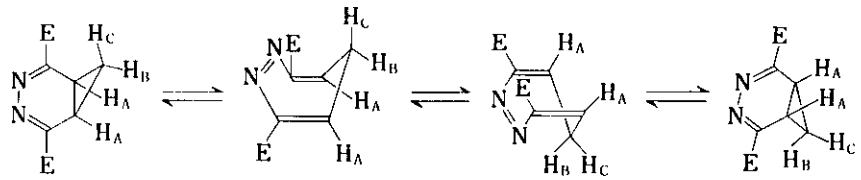
The measurement of the pmr spectra of the heteroepins is a useful method to investigate the extent of their aromaticity. The pmr spectra of a large number of heteroepin derivatives have been reported and the chemical shift of typical compounds is shown in Table II, indicating that the ring protons are located in the region of olefinic protons. Similarly to that of the X-ray crystallographic analyses this result indicates that the heteroepins belong to a class of cyclic polyolefins. For a comparison, the pmr spectrum of benzene oxide (2N) is also exhibited in Table II, indicating that α-protons appear at fairly high fields. The ^{13}C nmr spectrum is useful for the investigation of the equilibrium between oxepin (2) and benzene oxide (2N). The α-carbon signal of (2) appears at 141.8 ppm, whereas that of (2N) appears at 56.6ppm.[18]

Table II Pmr Spectra of Several Heteroepin Derivatives.

Position \ Compounds	 (2)	 (2N)	 (3c)	 (5c)	 (24)
2	δ 5.7	δ 4.0	δ 5.95	—	—
3	5.7	6.3	5.51	δ 6.23	—
4	6.3	6.3	6.15	5.75	δ 5.91
5	6.3	6.3	6.15	6.55	5.82
6	5.7	6.3	5.51	6.25	5.95
7	5.7	4.0	5.95	7.40	7.00

Furthermore, the temperature dependence of the nmr spectra is available for the thermodynamic studies of the equilibrium between the heteroepins and the norcaradiene structures, e.g., the equilibrium between oxepin and benzene oxide,[19] or the characterization of degenerate isomerization and inversion observed in 3,4-diazanorcaradienes (25).[20] It is also useful for the calculation

of the kinetic parameters of the equilibrium between two norcacadienes ($25N_1$, $25N_2$).[20]

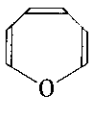
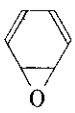
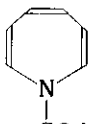
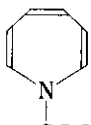
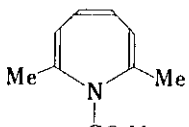
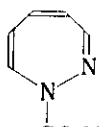
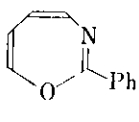


$(25N_1)$ $(25C_1)$ $(25C_2)$ $(25N_2)$

Scheme 5 $E=CO_2R$

Electron spectroscopy serves as a method for the investigation of the electronic states in heteroepins. UV spectra of the typical examples are shown in Table III. The UV spectrum of (2) is quite different from that of (2N).[8b] In the UV spectra of azepines, a small absorption band observed at > 300 nm disappears on the introduction of substituents at the C_2 and C_7 positions as shown in (26), or of an electron withdrawing substituent such as the arylsulfonyl group at the N_1 position as shown in (30). Therefore, this absorption may arise from the interaction between the N_1 lone-pair and π-electrons.[8e]

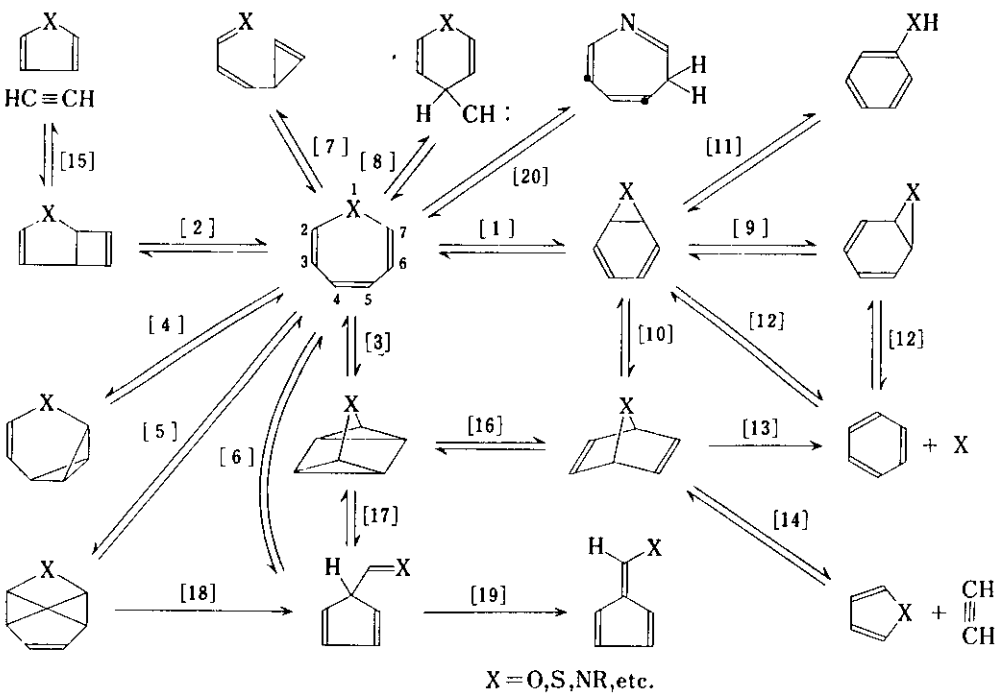
Table III UV Spectra of Heteroepin Derivatives.

Compounds	 (2)	 (2N)	 (3c)	 (3e)	 (26)	 (5c)	 (24)
Solv	iso-octane	iso-octane	ethanol	ethanol	ethanol	ethanol	ethanol
UV Absorption Maximum (nm)	305 (2.95)	271 (3.15)	207.5 (4.34) 242sh. (3.43) 318 (2.83)	205 (3.34) 266 (3.48)	215 (4.29) 230sh. (3.58) 285 (3.32)	228 (4.03) 355 (2.38)	238 (4.15) 323 (3.66) ~400 tailing

2. Valence bond isomerization

Valence bond isomerization and its attendant reactions such as ring opening and rearrangement reactions are formally summarized in scheme 6 using general formulas. Path [1] shows thermally allowed isomerizations between the heteroepins and the norcaradiene structures, and path [2] shows the photochemically allowed equilibrium between the heteroepins and the bicyclo[3.2.0]

heptadiene derivatives. Both path [1] and [2] are often observed in the reactions of the heteroepins. Isomerizations to quadricyclane structures, path [3], and to valene type isomers, path [4], are also known. Path [3] is a (π2a + π2a + π2a) process, where the C_2-C_4, C_5-C_6, and C_3-C_6 bonds are newly formed. Path [5] would give cross-type isomers. As examples of ring contraction, are given paths [6] and [7] in which a five- and a three-membered ring are formed, respectively. These ring contractions can be explained either by a 1,3- or by a 1,5- shift of the C-X bond. In addition, path [8] involving the formation of a six-membered ring by a 1,2-carbon shift can be formally considered. In this case, a carbene mechanism should be taken into account in order to match the balance of the electrons involved in this reaction. Rearrangements of the norcaradiene system are found in a 1,5-carbon shift called a walking process path [9] and a 1,3-carbon shift giving the norbornadiene system path [10]. Ring opening reactions in the norcaradiene lead to the aromatizing processes shown in paths [11] and [12], the latter implying elimination of a functional group X. Path [13] from the norbornadiene system and path [15] from the bicyclo[3.2.0]heptadiene system can be postulated as ring cleavage reaction to give cyclo-



Scheme 6 Possible valence isomerizations and related reactions of heteroepin derivatives.

pentadiene and acetylene derivatives. Path [16] showing the equilibrium between the quadricyclane system and the norbornadiene system is well known as a photochemical reaction. Besides path [16], path [17] giving cyclopentadiene derivatives and [18] affording fulvenes can be formally considered, the former involving the rupture of the three σ-bonds of the quadricyclane structures and the latter involving the rupture of the two σ-bonds of the cross type isomer obtained by path [5]. In the case of X=NH, furthermore, the isomerizations caused by a 1,3-, a 1,5-, and a 1,7-hydrogen shift, path [20], would be possible.

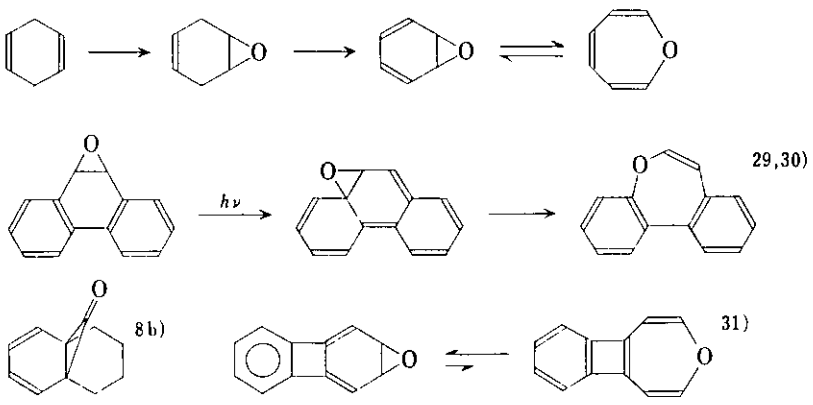
One may have a doubt whether these paths shown in scheme 6 actually exist because fairly bold suggestions are involved. However, most of the paths have been found more or less in the published reports. These paths seem to have a paticular significance when viewed from the reversible reactions because they may be useful for the synthetic design of heteroepins and hetero-norcaradiene derivatives. We would like to explain concrete examples hereinafter.

2.1 Syntheses of heteroepins using valence bond isomerizations

In early days of the heteroepin chemistry (prior to ca. 1965), syntheses of benzazepine and benzodiazepine derivatives were attempted from the viewpoint of pharmaceutical interest. Relating to these topics, interested readers should refer to the reviews written by Popp,[9a] Takase,[8d] Sternbach,[7] Rosowsky,[8f] Lloyd,[9b] and Kaspararek.[6b] Since 1960, new synthetic methods using valence bond isomerization involving cyclization or cycloaddition reactions have appeared. Vogel's oxepin synthesis[8b] and Hafner's azepine synthesis[8a] are given as these examples. In 1966 Kaneko[10a,b] and Buchardt[10c] synthesized polysubstituted 1,3-oxazepines by the photoreaction of aromatic N-oxides. Prinzbach reported the synthesis of oxepin[21] and azepine[22] using the thermal ring opening reactions of the quadricyclane system. Since 1968, interesting synthetic methods of 1,2-diazepines using the photoreactions of pyridinium-N-ylides have been successively reported by Streith,[23] Sasaki,[24] and Snieckus,[25b] et al.. The synthesis of a diazanorcaradiene system reported by Maier in 1965[25a] and that of 5H-1,2-diazepines reported by Sauer using addition reaction of tetrazines are also noteworthy.[26] The latter is particularly interesting because this method is available for the syntheses of several derivatives of azepines, diazepines, and triazepines. Mukai's method to prepare 1,3-oxazepines using the photochemical ring opening of the bicyclo[3.2.0]heptadiene system is worth-while because it is the only method for the synthesis of mono-substituted 1,3-oxazepines.[27] Although a large number of heteroepins have been synthesized besides those descrived above, the explanation of these examples will be left out and only the synthetic paths along with the references are represented by chemical formulas in order to keep this review to a reasonable size. The classification is done according to the ways of Scheme 6.

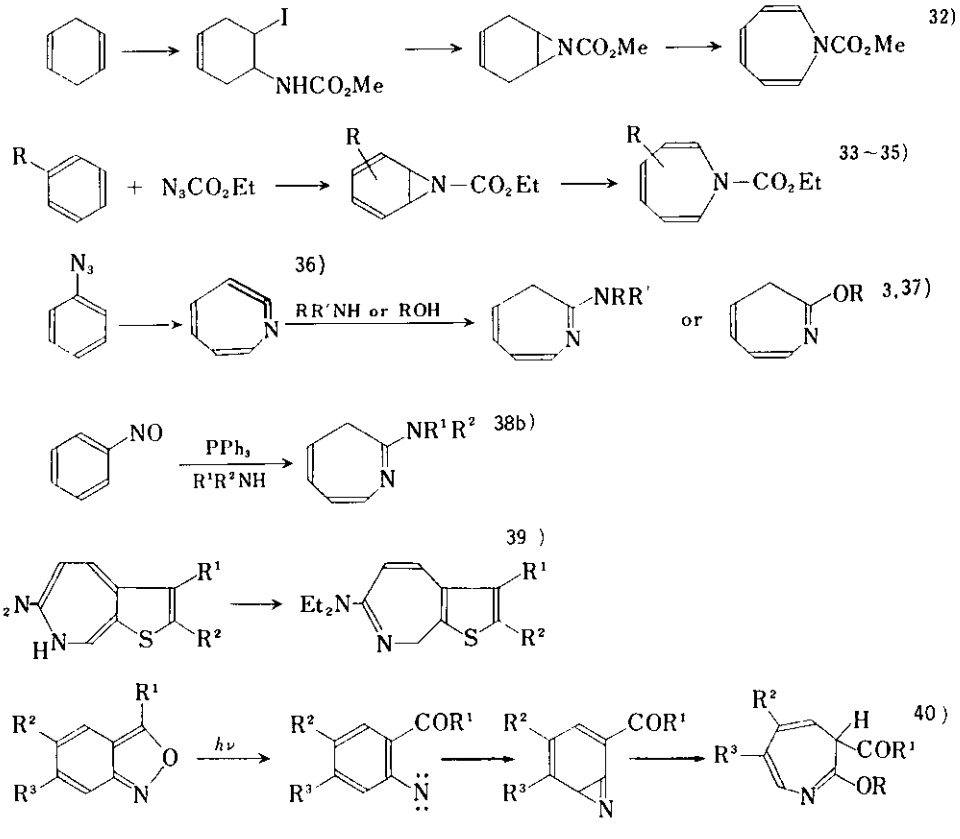
2.1.1 Synthetic Paths via The Norcaradiene System. (Path [1] in Scheme 6)

(A) via Benzene Oxides



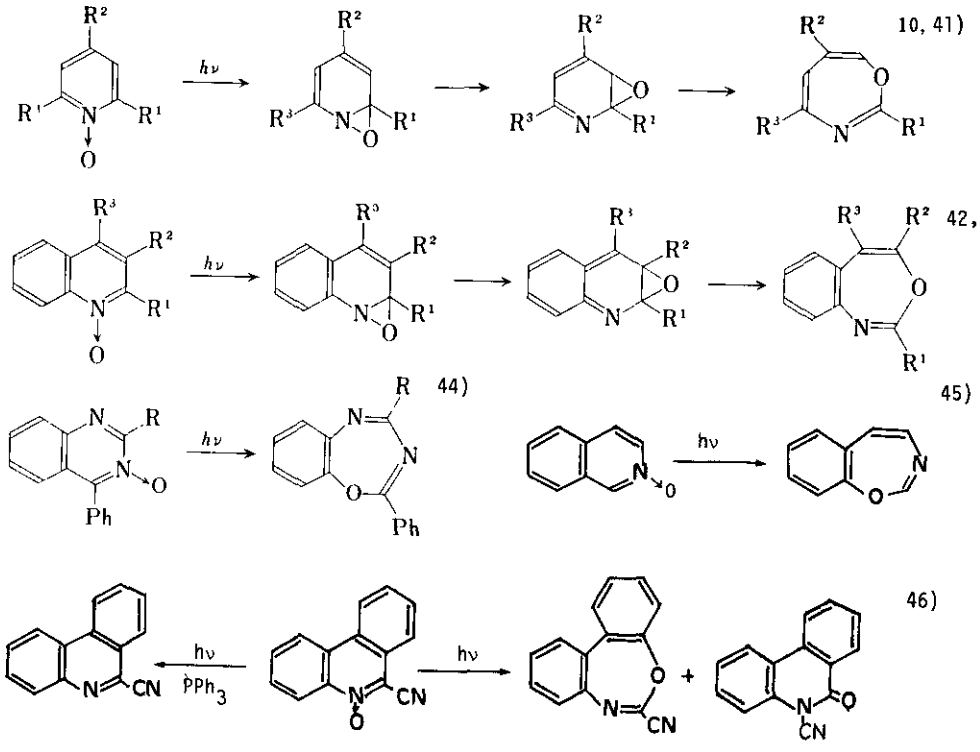
Scheme 7

(B) via Benzene Imines and Their Analogs



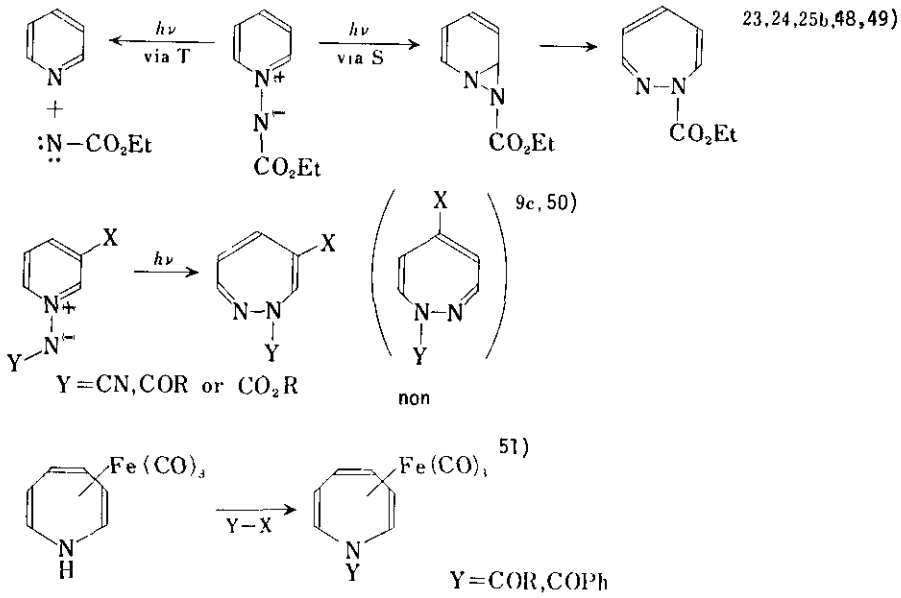
Scheme 8

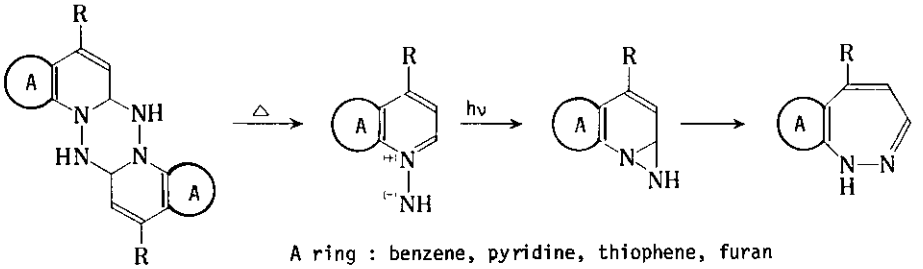
(C) Photoreactions of Aromatic Amine N-Oxides

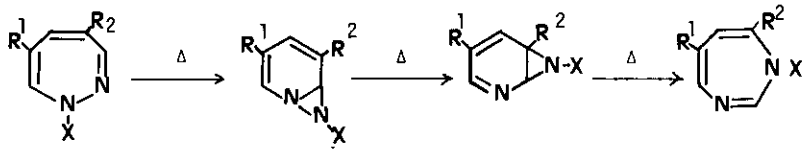


Scheme 9

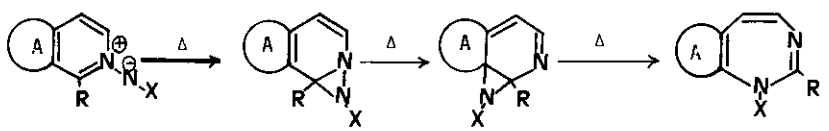
(D) Photoreactions of Aromatic Amine N-Ylides







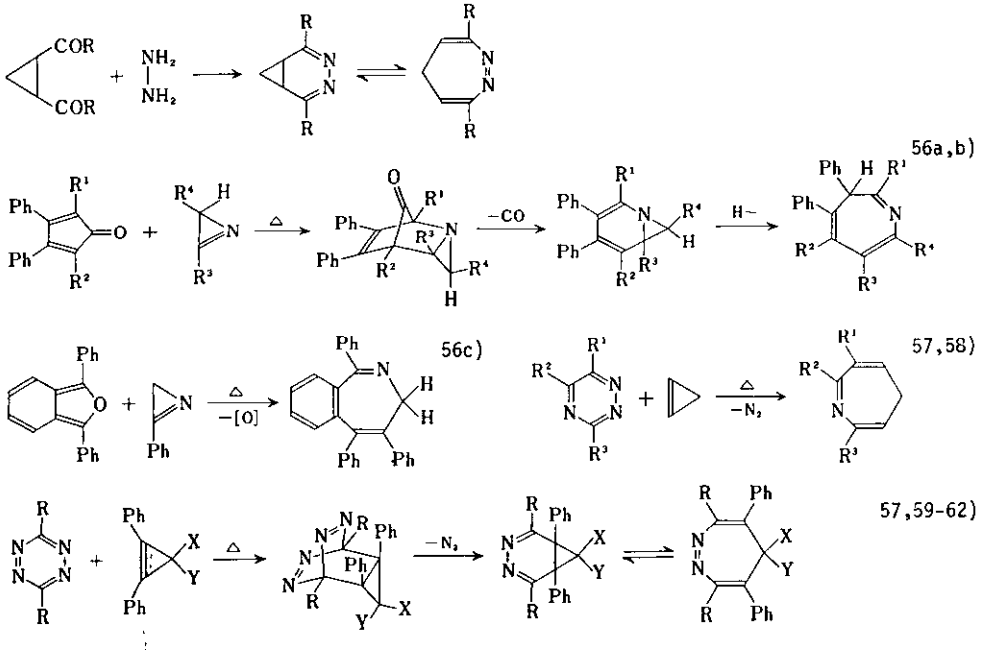
R^1 and R^2 = electron donating group (Me, OMe, NEt_2,etc.)



R = Me or COOR

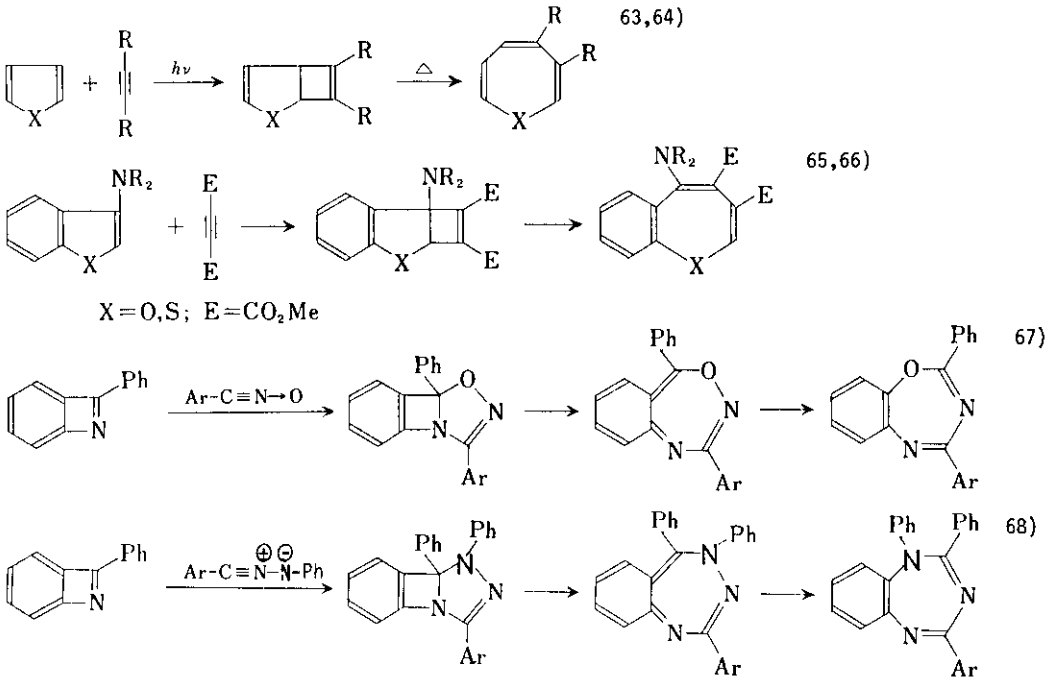
Scheme 10

(E) via Azanorcaradienes Resulting from Cycloaddition Reactions



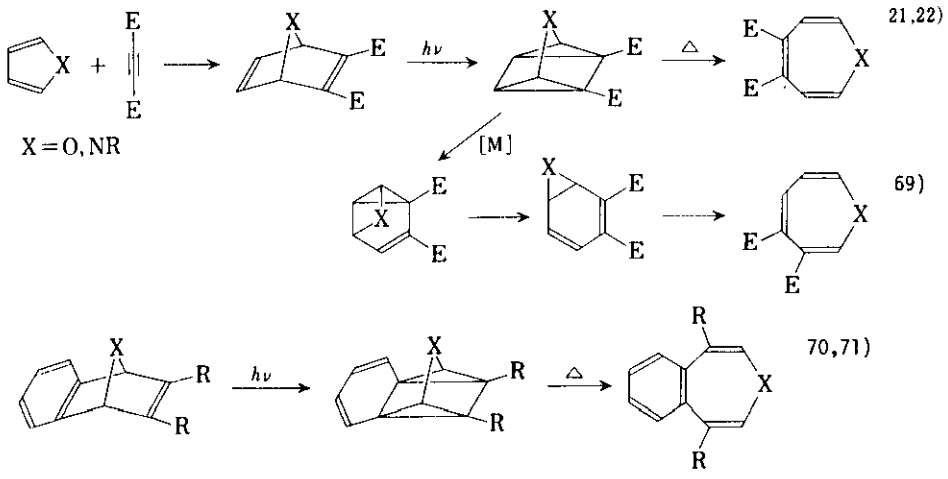
Scheme 11

2.1.2 Synthetic Methods via The Bicyclo[3.2.0]heptadiene System (path [15] in Scheme 6)



Scheme 12

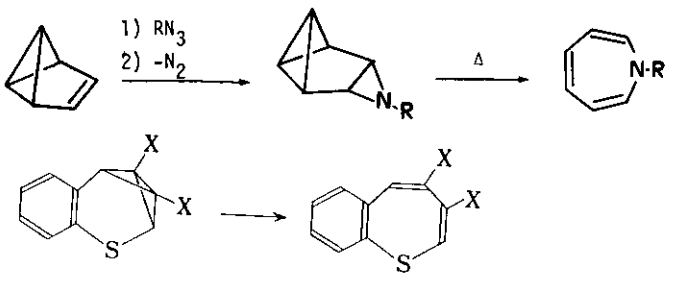
2.1.3 Synthetic Methods via The Quadricyclane System (path [3] in Scheme 6)



Scheme 13

2.1.4 Other Synthetic Methods

(A) via The Valene System

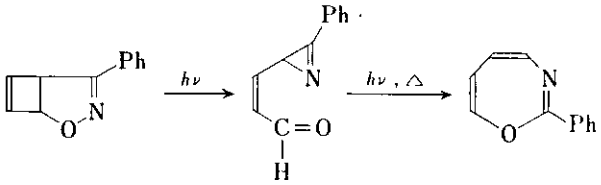


72)

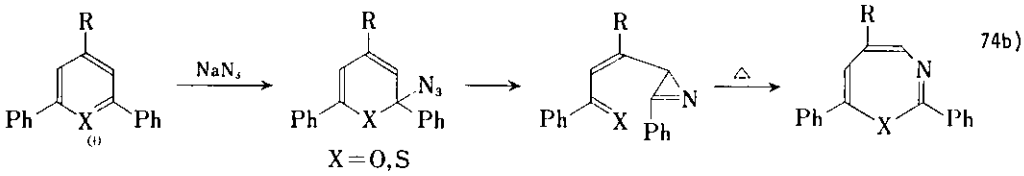
73)

Scheme 14

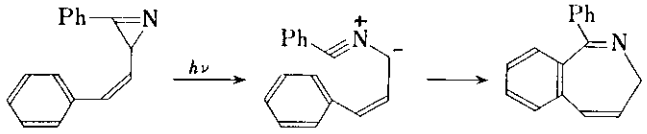
(B) via Path [7] in Scheme 6



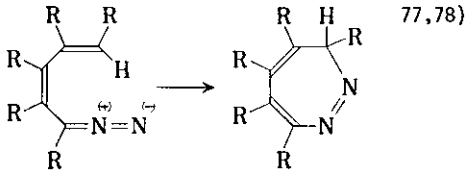
11)



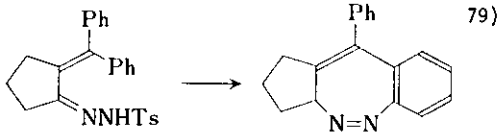
74b)



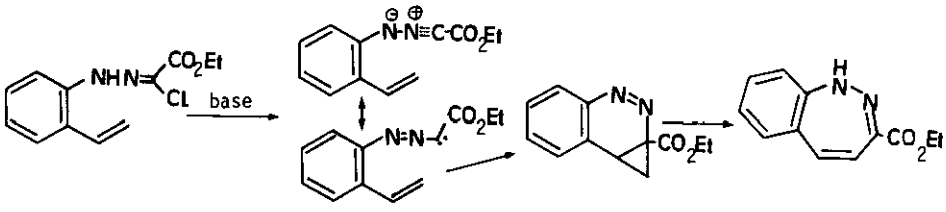
75)



77,78)



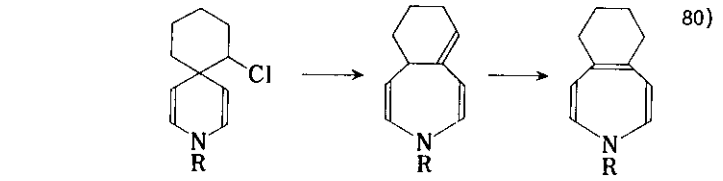
79)

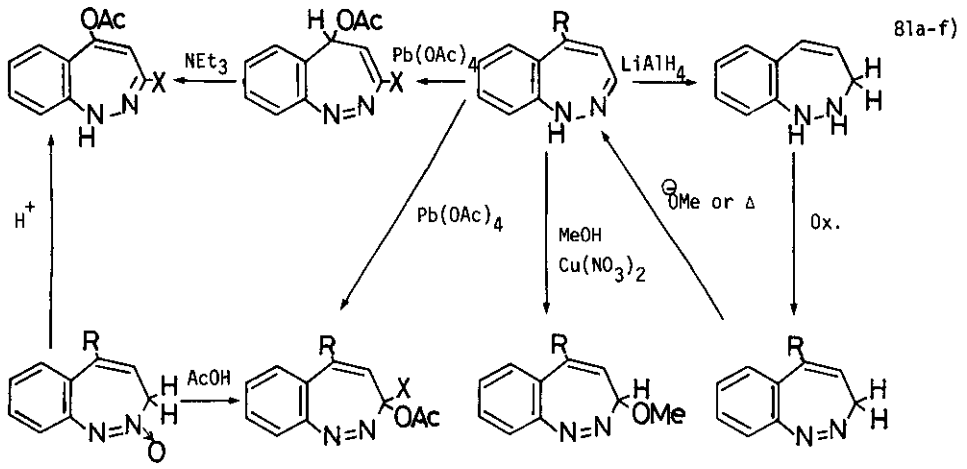


76)

Scheme 15

(C) via Paths [8] and [20] in Scheme 6





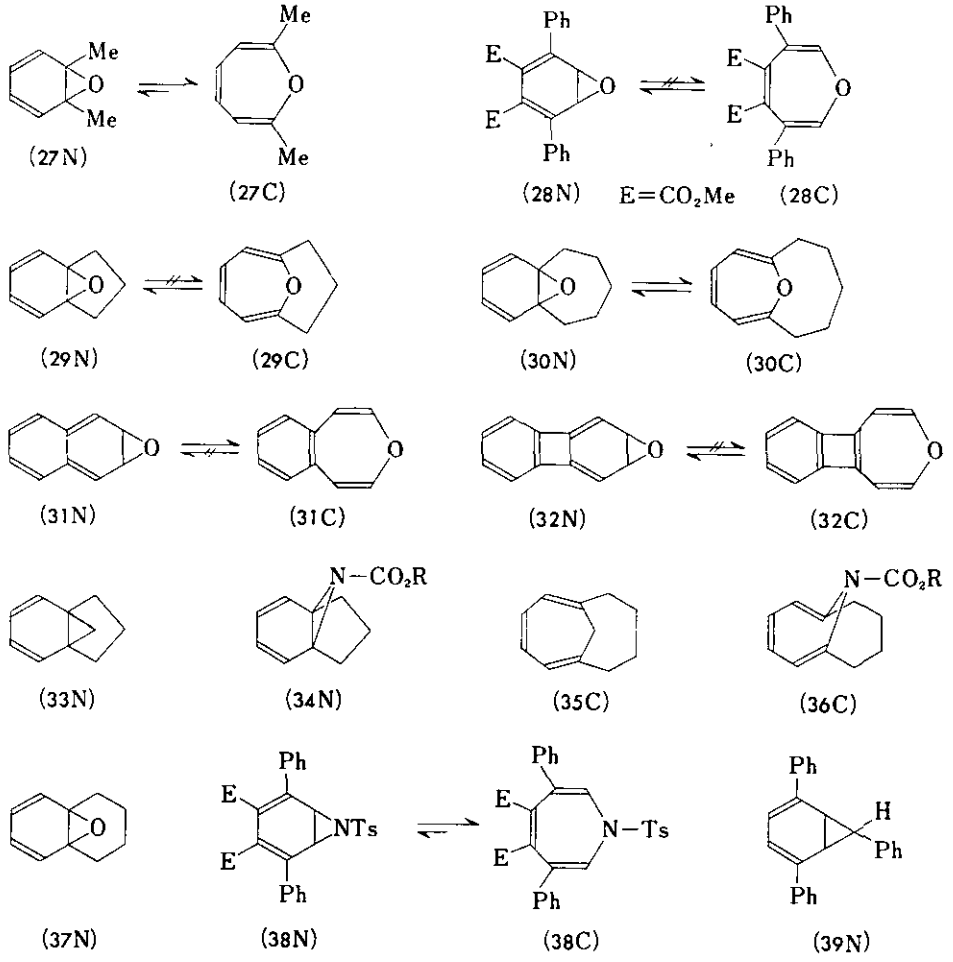
Scheme 16

2.2 Problems with the norcaradiene system

2.3.1 Stability of the norcaradiene system

There are several problems with the valence bond isomerization between the cycloheptatriene system (C-form) and the norcaradiene system (N-form), whether or not a heteroatom is contained in the ring. There are some reviews dealing with this problem. Maier[8c] and Toda[82] discussed mainly the corresponding carbon compounds. Vogel[8b] and Paquette[83] dealt with the heteroepins.

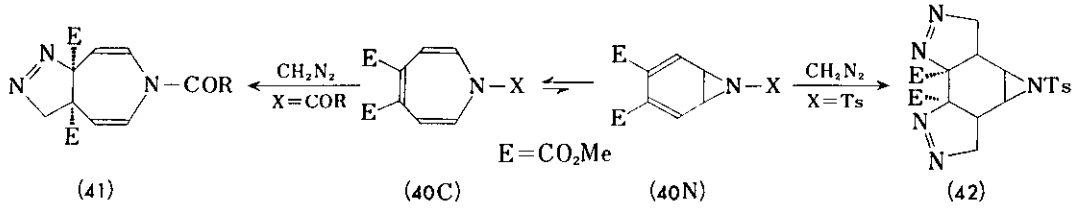
Two factors governing these isomerizations can be supposed, i.e., substituent effect and structural effect. Typical examples are as follows. Oxepin (27C) is more stable than benzene oxide (27N) because of the steric effect of the methyl groups. On the contrary, (28N) is more stable than (28C) because of the conjugation of the phenyl groups and the electronic effect of the methoxycarbonyl groups. The tightening effect due to the methylene chain observed in (29) and (30), and loss of naphthalene resonance in (31) are important factors in each case. Benzene oxide (32N) is more stable than (32C) due to the instability of the cyclobutadiene moiety in (32C).



Scheme 17

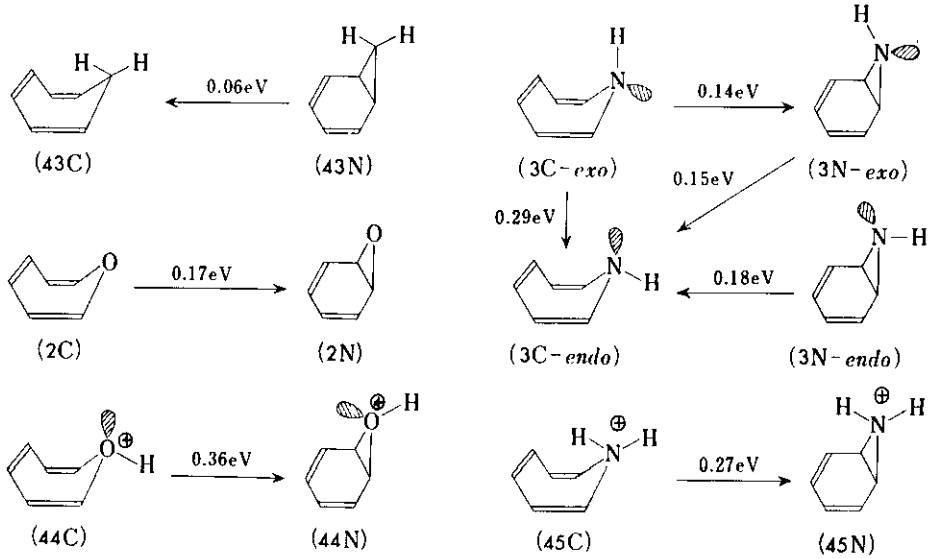
In Scheme 17, we would like to compare the equilibrium between valence isomers in oxepins, azepines and cycloheptatrienes with each other. Compounds (29), (33), and (34) all exist in the N-form due to the strong tightness by three methylenes. When the number of the methylene chain is four, the tightness becomes weaker and thus, in (35) and (36) the C-form is dominant. On the other hand, oxepin (37) possessing four methylenes still has the N-form as a stable form. When the methylene chain becomes five, the equilibrium between the N- and C-forms takes place, as observed in oxepin (30). N-Tosyl-1H-azepine (38) has the N-form and the C-form in a ratio of 3:97, while the corresponding oxepin (28) exists exclusively in the N-form.[84] Despite the β-phenyl and γ-methoxycarbonyl substituents which are recognized to stabilize the N-form, the

heptatrienes possessing a cyano group at the C_7-position or three phenyl groups at the C_2, C_5, and C_7-position take the N-form as stable structure. These experimental facts indicate that in the equilibrium between the C-form and the N-form, the tendency to occupy the N-form increases in the order of oxepins > cycloheptatrienes > 1H-azepines. 4,5-Dimethoxycarbonylazepine (40) possessing a carbonyl substituent on the nitrogen-atom reacts at the C_4-C_5 bond with diazomethane to give an adduct (41) (Scheme 18). In contrast, azepine (40) possessing a tosyl group reacts from the N-form to give a 2:1 adduct (42) as a major product. The formation of (42) gives an indirect proof of the presence of (40N) although (40N) could not be spectroscopically observed.[84, 85] This result indicates that a tosyl group stabilizes the N-system more than a carbonyl group, which is in accord with Hoffmann's theoretical suggestion[86] "the introduction of electron withdrawing groups into the C_7-position stabilizes the N-system."



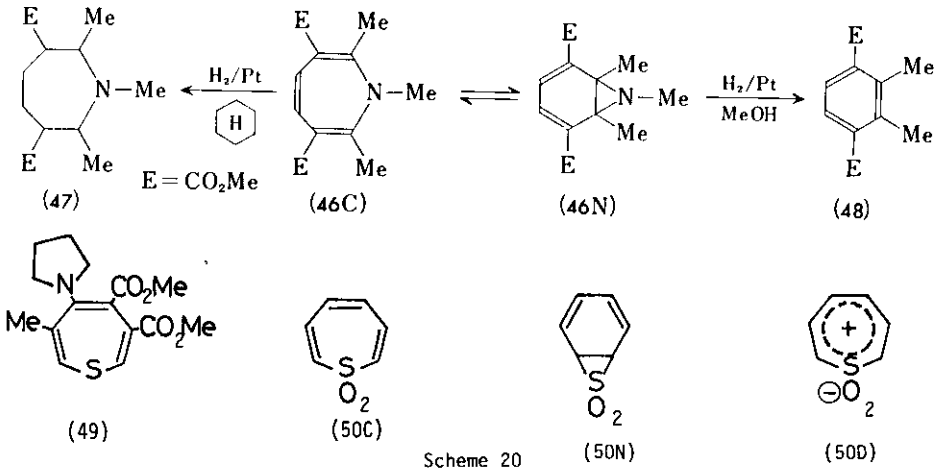
Scheme 18

Next we wish to discuss the equilibrium between the C-form and N-form of oxepin (2C), 1H-azepin (3C), and cycloheptatriene (43C) on the basis of the Extended Hückel MO calculation reported by Störhrer[87] as shown in Scheme 19. In this Scheme the arrows show the stabilizing direction and the values over the arrows indicate the energy difference.



Scheme 19

Attention should be given to the important role of the lone-pair of electrons on the nitrogen-atom in azepine (3C). When the electrons are located at the exo position, the N-form is more stable, whereas in the case of the endo position, the C-form becomes more stable. This idea seems to be correct because there is an experimental fact that in the deuterium exchange of the C_7-position of (43C), the exo proton is dominantly exchanged.[88] As shown in Scheme 19, this calculation reveals that the stability of the norcaradiene form increases in the order of oxepin > cycloheptatriene > 1H-azepine, supporting the experimental results described before. This calculation also indicates that in the protonated state the oxepins and azepines take the N-form (44N) and (45N), respectively, as the stable structure. However, it is difficult to prove experimentally the correctness of this calculation because both oxepins and azepines are unstable to acid. In this connection, there is an interesting report (see Scheme 20). In aprotic solvents, N-methylazepine derivative (46) is reduced to give the seven-membered amine (47), while in protic solvents, a benzene derivative (48) is obtained.[89] This fact can be rationalized by considering that the protonation make the equilibrium to (46N) which becomes an intermediate of the reaction.

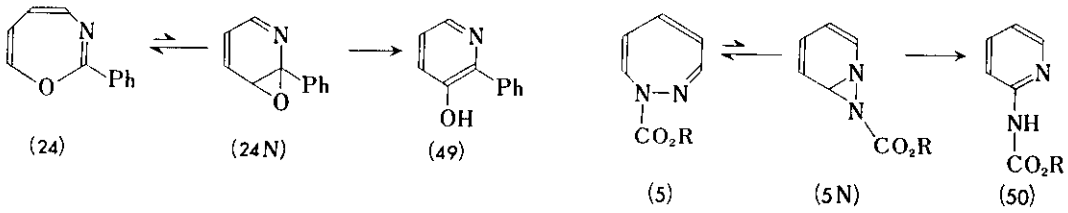


Scheme 20

On the other hand, thiepins strongly tend to lose sulfur to give the corresponding benzene derivatives via thianorcaradienes.[12] Therefore, unsubstituted thiepin (4) has never been obtained and even a derivative (49), the first identified monocyclic thiepine, was not isolated due to the ready sulfur elimination.[90] In contrast to thiepins, thiepin sulfone (50) is isolated as stable crystals and is shown to exist as a triene form (50C) from its UV and NMR spectrum.[91] The detailed X-ray analysis indicates, however, that although (50) takes the boat form as expected, there is a small contribution from a delocalized structure (50D).[92]

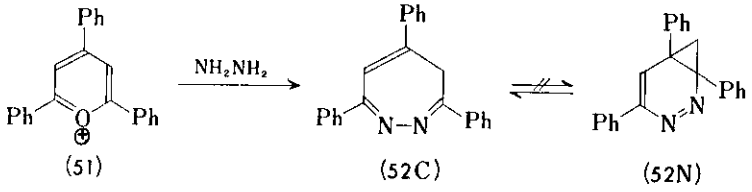
The following reason for the high stability of the sulfone can be given besides the contribution of (50D). The equilibrium between the triene form (50C) and the norcaradiene form (50N) lies to (50C). Furthermore, the sulfur dioxide elimination requires more activation energy than the sulfur elimination.

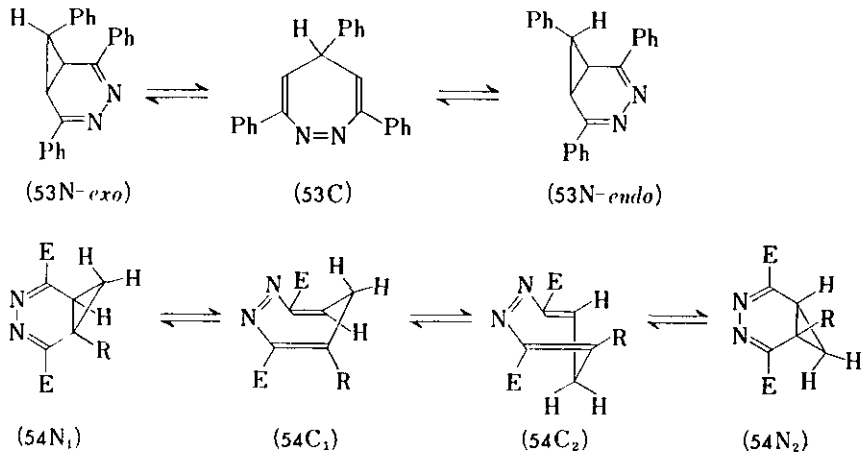
1,3-Oxazepine (24) and 1H-1,2-diazepine (5) exist as the triene form and the existence of the norcaradiene form has never been identified even by spectroscopic methods. However, the fact that 2-phenyl- 3-hydroxypyridine[91] and 2-alkoxyaminopyridine[9c] are readily obtained by thermolysis or the reaction with acid proves indirectly the presence of (24N) and (5N) (see Scheme 21).



Scheme 21

Next we would like to explain the problems concerning 3,4-diazanorcaradienes and their valence isomers in Scheme 22. The syntheses of these compounds are relatively easy. For example, 4H-1,2-diazepines (52C) have been obtained by the reaction of pyrylium salts (51) with hydrazine . Diazo-compounds such as (53) and (54) have been obtained by the method described in section 2.2. There is a large number of reports concerning the valence isomerizations of these compounds. It should be noted here that the direction of the equilibrium in the diazepine (52)[92] is quite different from that in (53).[20b] The former has the triene form as the stable one, while the latter takes the norcaradiene form. This can be clearly explained by considering that the C=N bond energy (145 kcal/mol) is larger than the N=N bond energy (92 kcal/mol) and this difference overcomes the energy disadvantage (ca. 15 kcal/mol) attributed to the energy difference between the C-form and the N-form. The unstable triene form is regarded as an intermediate in the endo-exo isomerization occuring at 170-180°C (53N-endo $\rightleftarrows$ 53N-exo).[20b]



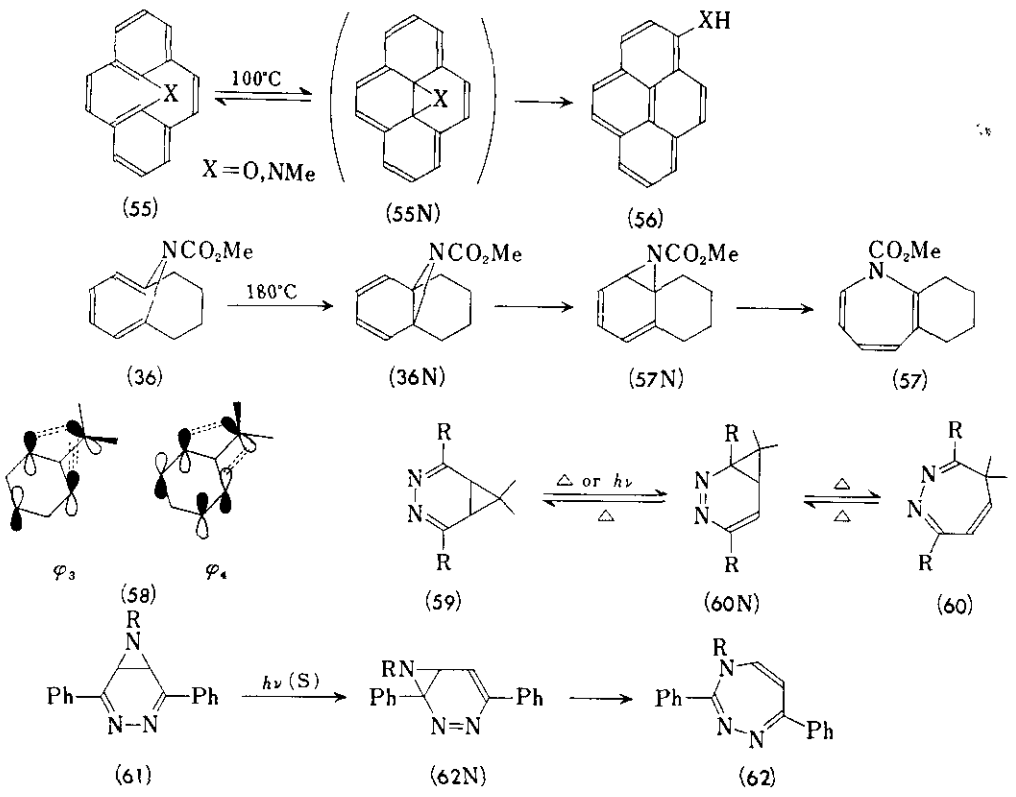


Scheme 22

This kind of thermal isomerization has been also studied in 5H-1,2-diazepine derivatives (54) in which the activation parameters for the thermal equilibrium ($N_1 \rightleftarrows N_2$, topomerization) were obtained (Ea=15.3 ± 0.1 Kcal/mol, $\Delta S^{\neq}$=-0.16 ± 0.34 eu).[57] It was clarified, furthermore, that the ring inversion ($C_1 \rightleftarrows C_2$) between the triene forms (54C) is involved in this topomerization and the rate determing step is this ring inversion instead of the valence isomerization.

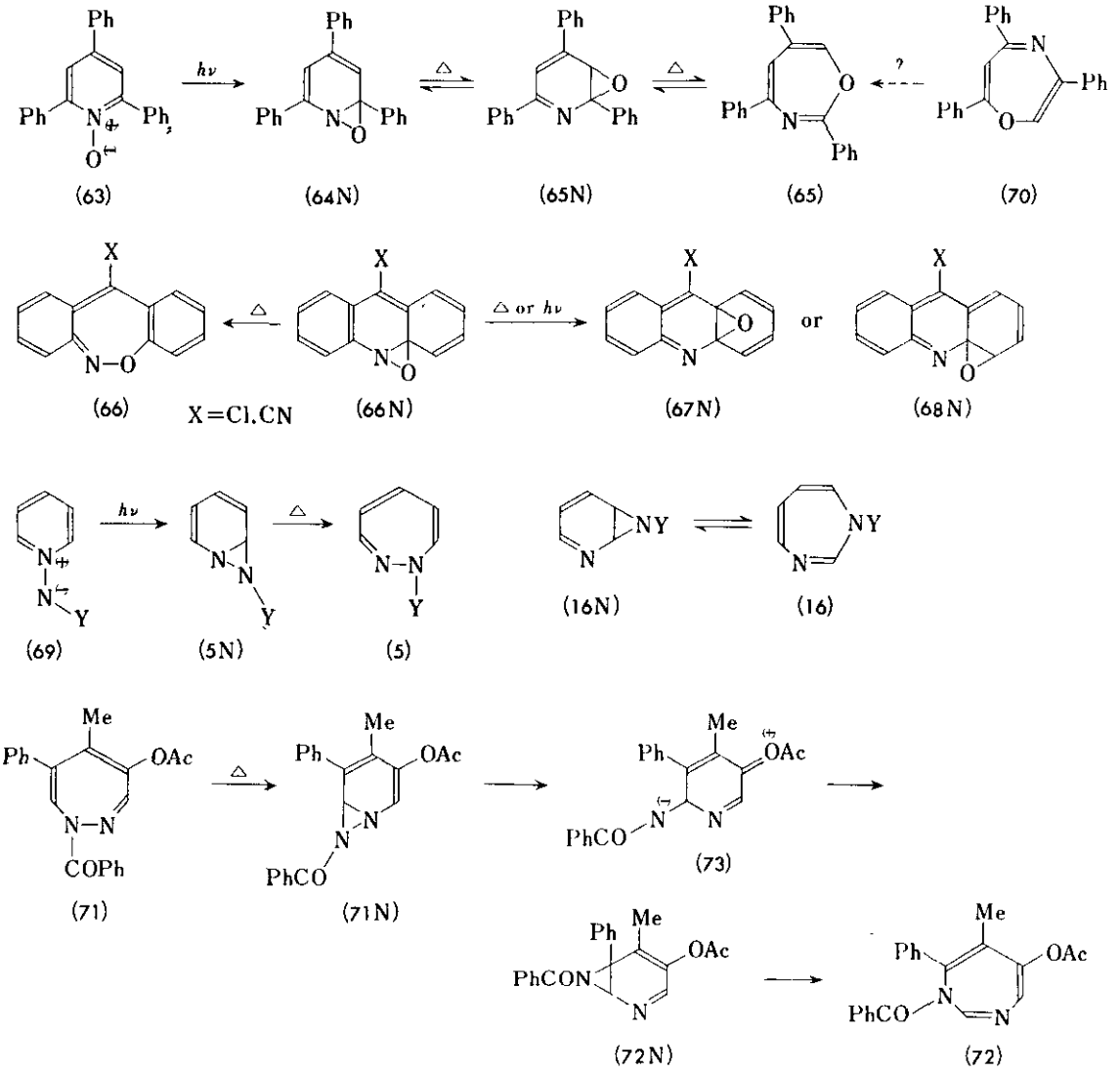
2.2.2 Walking reactions

With regard to the reactions of the norcaradienes, a walking process is of particular interest. This reaction has already been introduced in path [9] shown in Scheme 6 and in section 2.2.1.[29,30,40,41,42,55] The walking reaction of a cyclopropane ring on the carbon skeleton is well known as the Berson-Willcott rearrangement.[93] In addition, the walking reaction of an oxirane[10] and an aziridine ring[55] is also known. As shown in Scheme 23, hetero[2.2]metacyclophane-1,9-diene (55) upon heating affords pyrene derivatives (56).[94] Azepine (36) rearranges to an isomer (57) by thermolysis at 180°C.[38] These reactions can be explained by the walking of a hetero three-membered ring in the norcaradiene form (55N) or (36N) postulated as intermediates. This kind of walking reactions is both thermally and photochemically allowed from the standpoint of the orbital symmetry rule. Cyclohexadienyl orbitals ϕ_3 and ϕ_4 shown in (58) should be considered as the frontier orbitals to explain these reactions. In ϕ_3 the stereochemistry of the rearranging atom is retention (Vibot mechanism), whereas in ϕ_4 it is inversion (Sliter mechanism). Zimmerman et al. have found, in fact, that the isomerization of (59) to (60) occurs not only as a thermal reaction[95,96] but also as a photochemical one.[97] Matsuura et. al. have found a photochemical N-walking reacton of (61) to (62N) giving triazepine (62).[98]



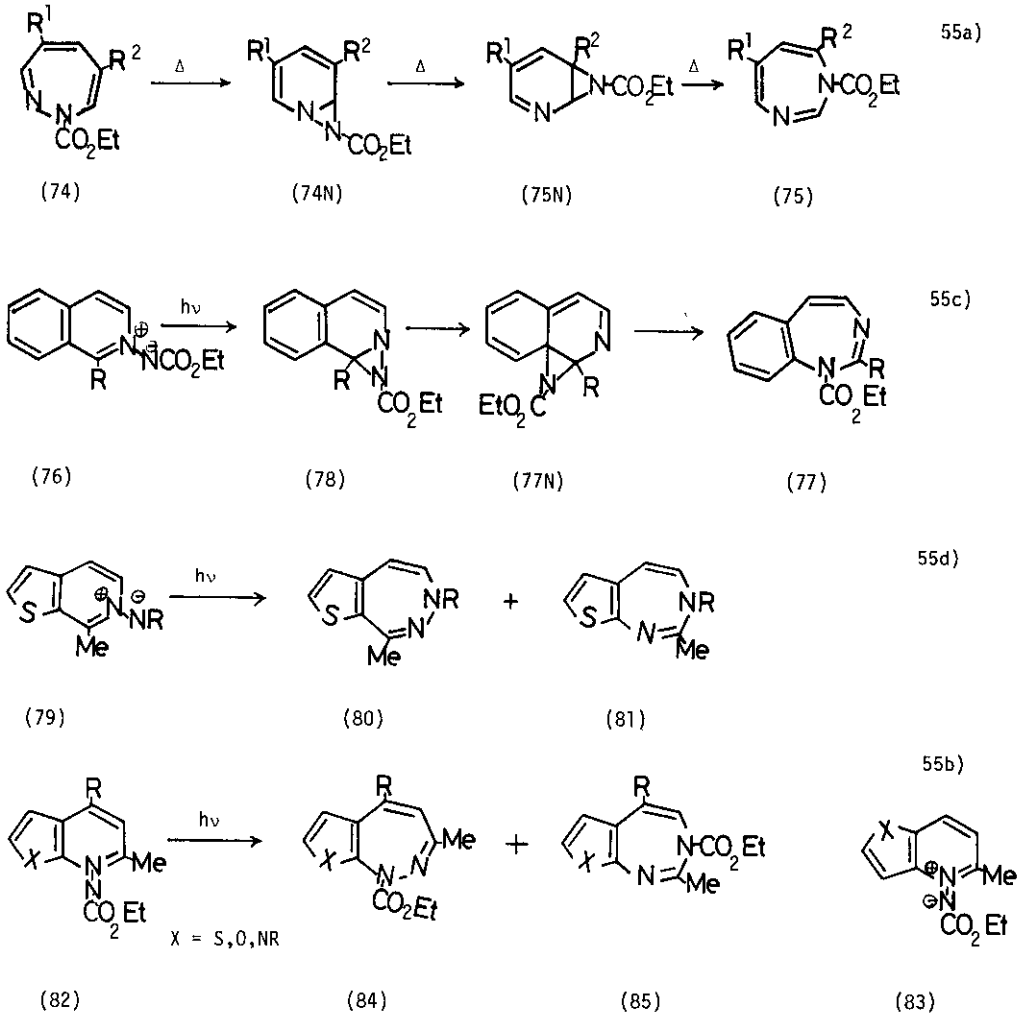
Scheme 23

One of our interests in connection with these walking processes is the difference between oxazepines and diazepines (see Scheme 24). As described in section 2.2.1, it is well known that pyridine N-oxide (63) affords a good yield of 1,3-oxazepine (65) upon irradiation, in which the walking process of oxanorcaradiene (64N) to (65N) is involved. The 1,2-oxazepines in general appear to be intermediates and there is only one example for the 1,2-oxazepines isolated, which is dibenzo-[c,f]-1,2-oxazepine (66) reported by Kaneko.[99a] The walking reaction of the corresponding norcaradiene (66N) to the isomers (67N) and (68N) is found in the photoreaction of acridine-10-oxide.[99b] In this connection, it is interesting to investigate whether 1,4-oxazepine (70) rearranges to 1,3-oxazepine (65) although no monomeric 1,4-oxazepine is known. Contrary to 1,2-oxazepines, 1H-1,2-diazepines (5) are readily obtained by the photoreaction of 1-iminopyridinium ylides (69) as described in section 2.2.1.[9c] Although the intervention of azanorcaradienes (5N) is presumed, the walking reaction to 1H-1,3-diazepine (16N) is in general difficult. Recently, Moore et al. have found a novel reaction, in which 1,2-diazepines (71) rearranges to 1,3-diazepines (72).[100b] This reaction was considered to require the walking of nitrogen on diazanorcaradiene. However, then it seems to proceed via a stable ionic intermediate (73) rather than by a concerted mechanism because diazepines containing no acetyl group do not



Scheme 24-I

undergo this reaction. More recently, Tsuchiya et al. have found that thermolysis of the 1H-1,2-diazepines (74) having an electron-donating substituent in the 4- or 6-position affords the corresponding 1,3-diazepine derivatives (75) by the walking process of an aziridine ring via (74N) and (75N).[55a] Irradiation of isoquinolinium ylide (76) gives 1,3-benzodiazepines (77) in which intermediates (78) and (77N) are also suggested.[55c] When thienopyrilium ylides (79) are irradiated, the corresponding 1,2- (80) and 1,3-diazepine derivatives (81) are obtained(Scheme 24-II).[55d]



Scheme 24-II

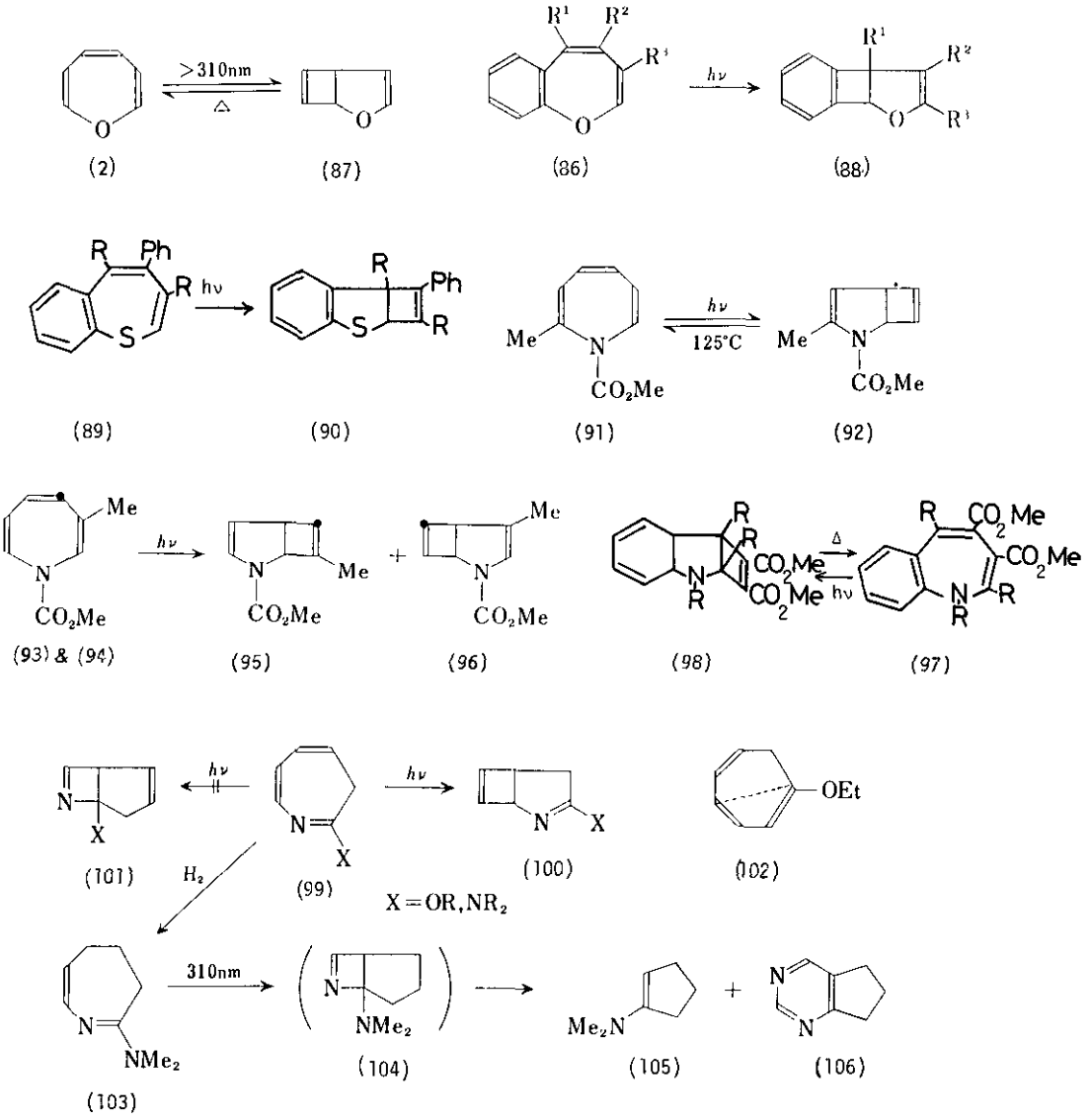
Similarly, photolysis of pyridinium ylides, (82) or (83), condensed with thiophene, furan, and pyrrole affords the corresponding 1,3-diazepine derivatives such as (84) and (85) via the walking process.[55b] In the reaction paths such as [10], [11], and [12] in Scheme 6, which all involve the norcaradienes, the fragmentation and rearrangement reactions should not be overlooked. It is noteworthy that aromatizations exemplified by paths [11] and [12] are often observed, whereas reactions via path [11] are rarely found.

2.3 Valence bond isomerization with the bicyclo[3.2.0]heptadiene system

The orbital symmetry rule predicts that the cycloheptatriene structure is thermally convertible to the norcaradiene structure and photochemically to the bicyclo[3.2.0]heptadiene structure. In fact, a large number of heteroepins undergo (2+2) cyclization reaction upon irradiation to give the bicyclic compounds. Concerning these reactions, attention should be paid to the following points. (i) When there are two possibilities for the direction of ring closure, peri-selectivity often appears. (ii) The ring opening reactions reverting to the heteroepins are thermally forbidden, but they take place at relatively lower temperatures compared with the corresponding hydrocarbons. This may be attributed to the lone-pair of electrons on a heteroatom. (iii) When the ring closure products are photochemically or thermally unstable, they suffer secondary reaction. For example, path [15] in Scheme 6 described in section 2.1 is one of the usually encountered reactions. In addition, new reactions such as an aza-di-π-methane rearrangement have recently been reported. Keeping these points in mind, we wish to discuss the (2+2) type reactions according to the structure of the substrates in Schemes 25, 26 and 27.

2.3.1 Examples in oxepins and azepines

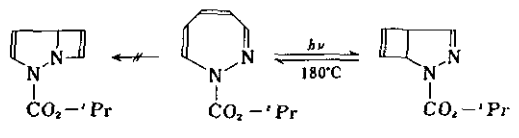
It has been found that the photoreactions of oxepin derivatives (2)[101] and (86)[102] affording (87) and (88) are dependent on the wavelength and the yields are higher using the light with wavelength above 310 nm. A similar type of reaction has been observed in the photoreaction of 1-benzothiepins (89),[103,104] where the reaction giving (90) is much slower than that of the corresponding 1-benzoxepins. This may be explained by the lower π-bond order of the butadiene skeleton of 1-benzothiepin. Irradiation of 2-methyl-1H-azepine (91) selectively gives a ring closure product (92) because of the steric interaction between the methyl group and the N-substituent. In contrast, in the case of 3-methyl (93) and 4-methyl derivative (94), two products (95) and (96) are obtained in a ratio of 1 : 1.[104] Benzazepine derivatives (97) undergo the similar photochemical cyclization to (98) which revert to (97) on heating.[7] Irradiation of 3H-azepine derivative (99) affords only one isomer (100) without the formation of another isomer (101).[106] This is in sharp contrast to the photo-ring closure of 1-ethoxycycloheptatriene (102), in which the ring closure occurs at the C_1 and C_4-positions. This reason may be attributed to the inertness of the amidine group ($N{=}C{-}NMe_2$) or the imidate group (N=C-OR). When the reaction site is limited, however, the C=N bond takes part in the photoreaction. For instance, dihydro-compound (103) gives a bicyclic compound (104) which immediately undergoes secondary reactions to give (105) and (106).[107]



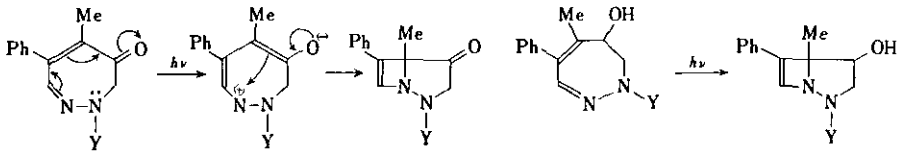
Scheme 25

2.3.2 Examples in diazepines

Photocyclization reactions of 1H-, 3H- and 4H-1,2-diazepine derivatives are described here. The photochemical ring closure of 1H-1,2-diazepine (107) shows the regioselectivity and gives only a product (108) without the formation of (109) involving the participation of the C=N bond.[55,108] However, when the reaction sites are limited as in the case of dihydro-compounds such as (110) and



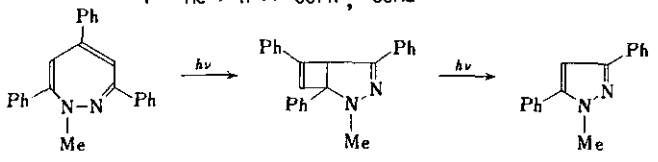
(109) (107) (108)



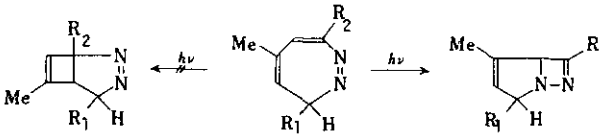
(110) (114) (112) (111) (113)

Y = Me > H >> COPh, COMe

Y = COMe, COPh>Me, H

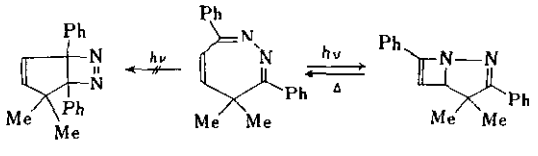


(115) (117) (116)

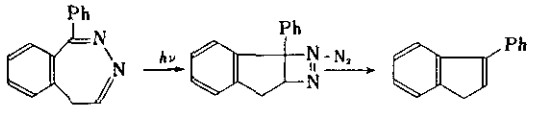


$R_1=R_2=H$
$R_1=H, R_2=Me$
$E=CO_2Et$

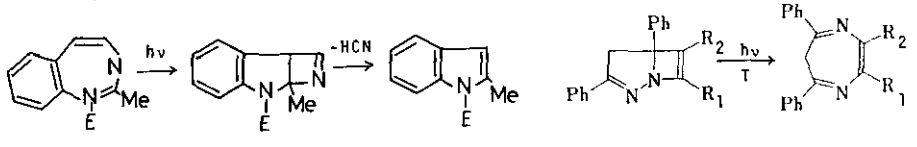
(120) (118) (122)



(121) (119) (123) (124) (125)



(126) (127) (128) (129) (130)



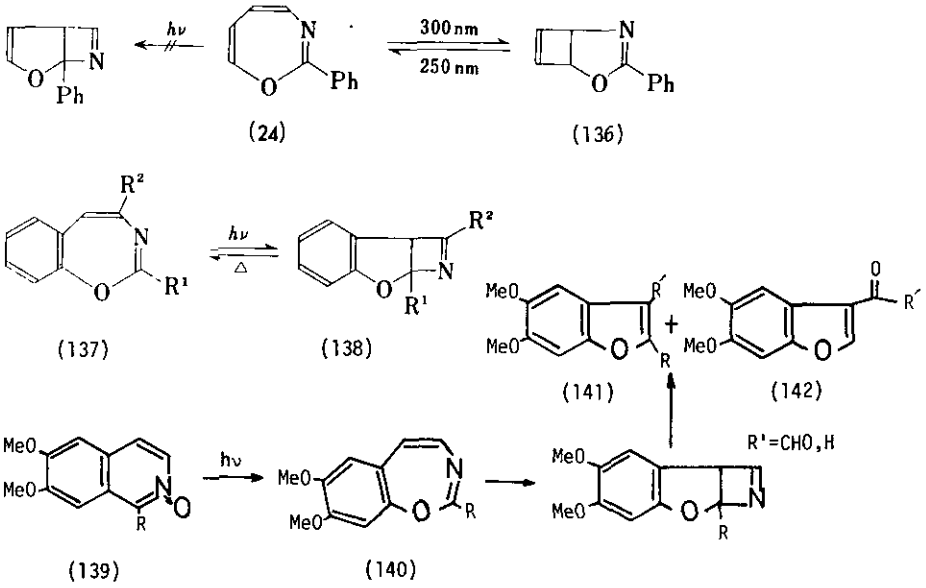
(131) (133) (132) (134) (135)

Scheme 26

(111), the C=N bond takes part in the photoreaction to give (112) and (113), respectively.[109] It is of interest to note that the N-substituent effect of the ketone (110) appears opposite to that of the alcohol (111) in the photoreaction. Namely, in (110) the electron donating groups accelerate the ring closure, whereas in (111) the electron withdrawing groups do so. This fact may be explained by considering a polar excited state such as (114) in the former and the n-π* excitation of the C=N bond in the latter. Irradiation of N-methyl-3,5,7-triphenyl-1,2-diazepine (115) affords N-methylpyrazole (116) in 82% yield which is formed by elimination of phenylacetylene from the initially formed ring closure product (117).[110] In the photochemical reactions of 3H- (118)[111,112] and 4H-1,2-diazepine (119),[113] the ring closure to azo compounds (120) and (121) does not occur and instead, the closure to (122) and (123), thermodynamically stable compounds, occurs. Benzo-1,2-diazepines (124) give the similar products (125) upon irradiation.[113] On the other hand, upon irradiation of 5H-2,3-benzodiazepine (126), the double bonds of the benzene ring remains unchanged and instead, an azo bond is formed. However, intermediate (127) is too unstable to be isolated and easily eliminates nitrogen to give an indene derivative (128).[77] 1,3-Diazepines (129) undergo the photochemical (2+2) cycloaddition without the participation of the C=N bond to give bicyclic compounds (130) which revert to (129) upon heating.[55a] In contrast, irradiation of benzo-1,3-diazepines (131) resulted in the ring closure including the C=N bond to produce intermediate (133), which then converted into indene (132) with the elimination of HCN.[55c,d] Recently, it has been found that 1,2-diazabicyclo[3.2.0]heptadiene (134) undergoes a photorearrangement with a remarkable skeletal change to give diazepine (135). This reaction is called an aza-di-π-methane rearrangement.[114] Sensitizing and quenching experiments clarified that the reaction takes place from the triplet state.

2.3.3 Examples in the 1,3-oxazepines

Different from the polysubstituted 1,3-oxazepines, the monosubstituted derivative (24) undergoes a ring closure reaction upon irradiation, where the direction selectivity is observed, and a bicyclic compound (136) is obtained without the participation of the C=N bond.[115] Compound (136) reverts to (24) on irradiation with the shorter wavelength light. In contrast, benz-1,3-oxazepine (137) affords azetine (138) because the benzene ring is not involved in the reaction diene.[116] Photolysis of the N-oxide of alkaloid papaverine affords benzo-1,3-oxazepine (140), benzofuranes (141) and (142), where ring closure product is regarded as an intermediate.[117]



Scheme 27

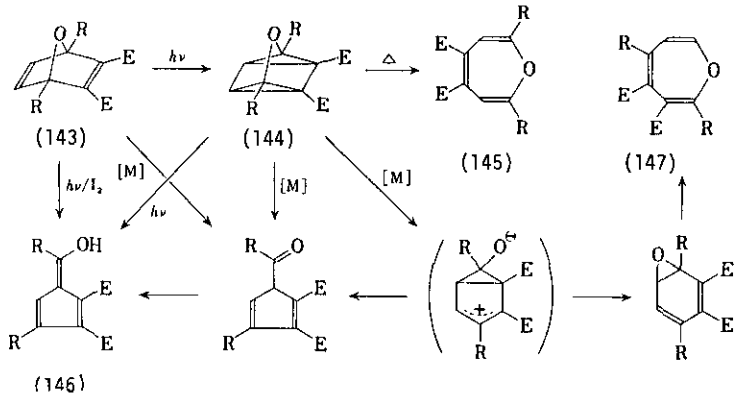
2.4 Rearrangement and ring opening reactions accompanied by valence bond isomerizations

The valence bond isomerization, the related rearrangement, and the ring opening reactions are summarized in section 2.1 (Scheme 6). In the previous sections, the aromatization path, [11] and [12], and the acetylene elimination path [15] have been described. The paths that have not been explained are comprised of paths [16], [17], [18], and [19] dealing with the rearrangement to five-membered ring compounds, and path [20] dealing with the hydrogen shift observed in the azepine. These paths are explained in the following two sections.

2.4.1 Rearrangement to fulvene and pyrrole derivatives

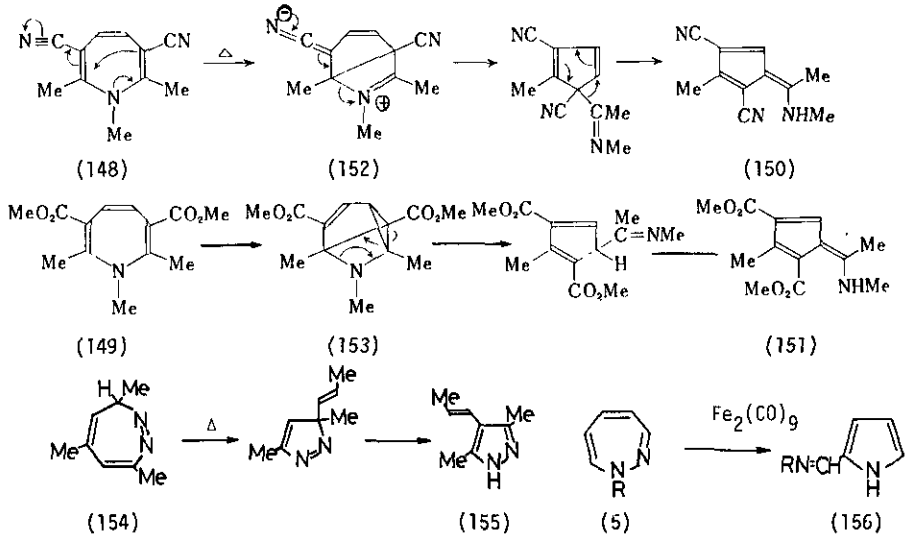
As described in section 2.2.3, oxepin (145) was synthesized by the thermolysis of oxaquadricyclane (144) which was obtained by the irradiation of 7-oxanorbornadiene (143). Compounds (143) and (144) give 6-hydroxyfulvene (146) and another oxepin (147) upon treating with Rh(I) or Pt(II) complex,[69a,b] or irradiation in the presence of iodine.[69c] The reaction mechanism is shown in Scheme 28.

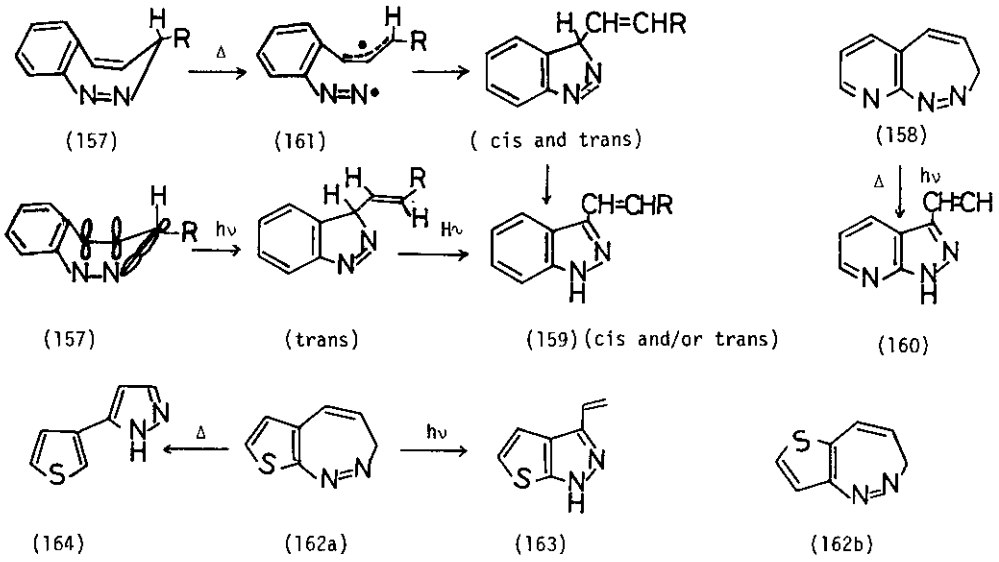
As shown in Scheme 29, in the presence of electron withdrawing groups such as cyano or carbonyl groups, 1H-azepines (148) and (149) easily rearrange upon heating to 6-aminofulvene derivatives (150) and (151), respectively.[80,118,119] There are several proposals relating to the mechanism of this rearrangement and two explanations are described in Scheme 29. One involves an ionic structure (152) as an intermediate[80] and the other involves a bridged structure (153).[118]



Scheme 28

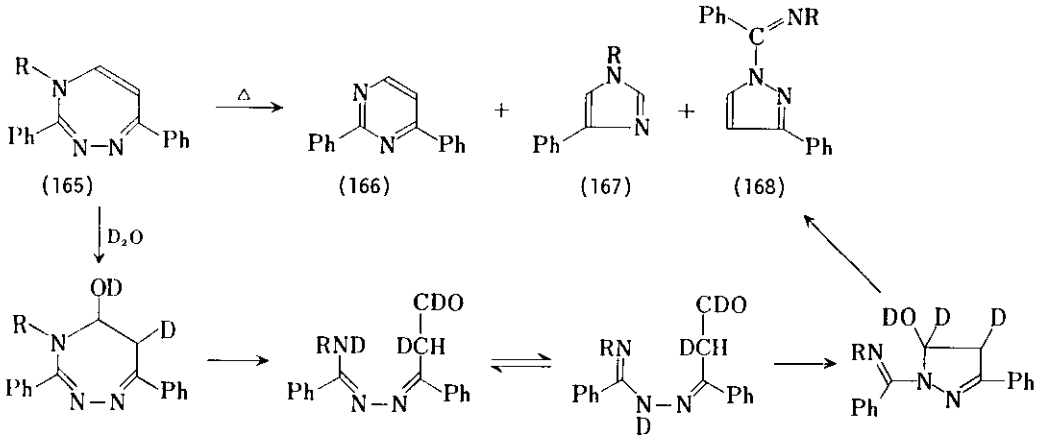
Thermolysis of 3H-1,2-diazepines (154) gives pyrazoles (155) by ring contraction.[120] Upon treating with $Fe_2(CO)_9$, 1H-1,2-diazepines (5) also undergo rearrangement to give pyrroles (156).[121] Both heat- and light-induced rearrangements of 3H-1,2-benzo-(157) and pyridodiazepines (158) lead to 3-vinylindazoles, (159) and (160), fused with pyridine rings.[81,122] It should be noted that the thermolysis occurs in stepwise manner via diradical intermediate (161), whereas the photolysis takes place in concerted manner giving trans-indazole.[122] On the other hand, Tsuchiya et al. have found that 3H-1,2-thienodiazepines (162a,b) show different behavior to light and heat.[122b] Thus, photolysis of (162a) affords the corresponding condensed 3-vinylpyrazoles (163), whereas the thermolysis gives the thienylpyrazoles (164) via a [1,5]-hydrogen shift followed by a [1,3]-carbon shift.[122b]





Scheme 29

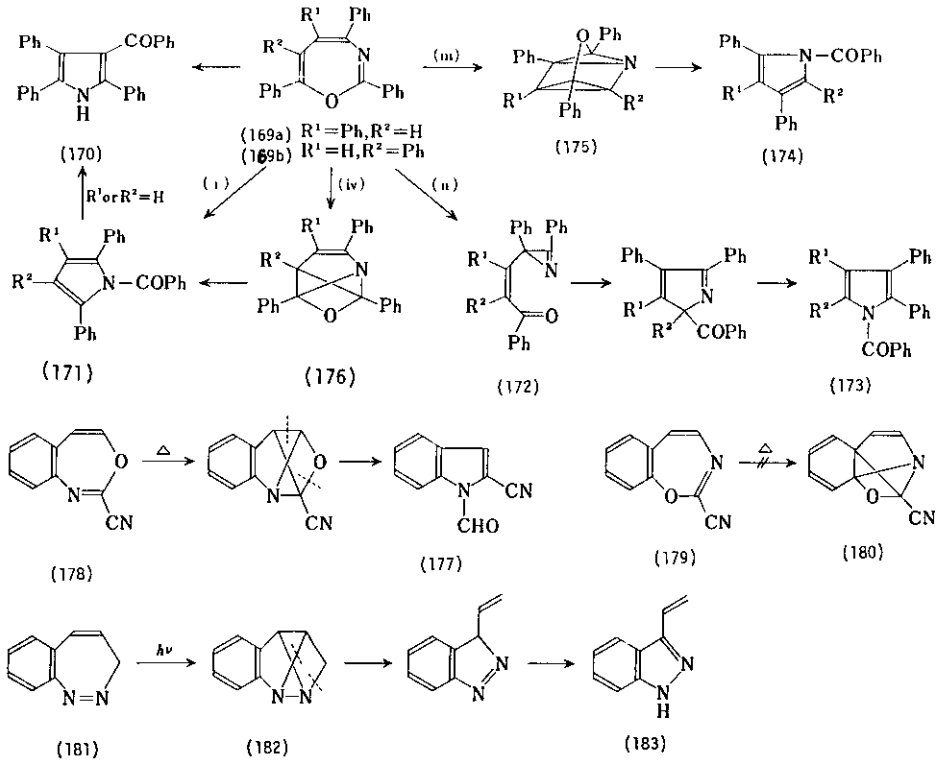
Matsuura et.al. have discovered that thermolysis of 1,2,4-triazepine derivatives (165) affords pyrimidine (166), imidazole (167), and N-substituted pyrazole (168) as major products and clarified the mechanism by using deuterium-labelling experiments.[84b] The summary is shown in Scheme 30.



Scheme 30

As to the 1,3-oxazepines, tetraphenyl substituted derivatives (169), upon heating at 240°C readily rearrange to pyrrole derivative (170).[123] Since N-benzoylpyrrole derivatives are known to rearrange thermally to the α- and β-benzoyl pyrroles, the mechanism shown in Scheme 31 is postulated for the formation of benzoylpyrroles; it involves (i) the formation of (171) by a 1,3-carbon shift, (ii) the formation of (172) by a 1,5-carbon shift followed by a ring closure to (173), (iii) the formation of (172) via quadricyclane (175), and (iv) the formation of (171) via the cross structure (176).

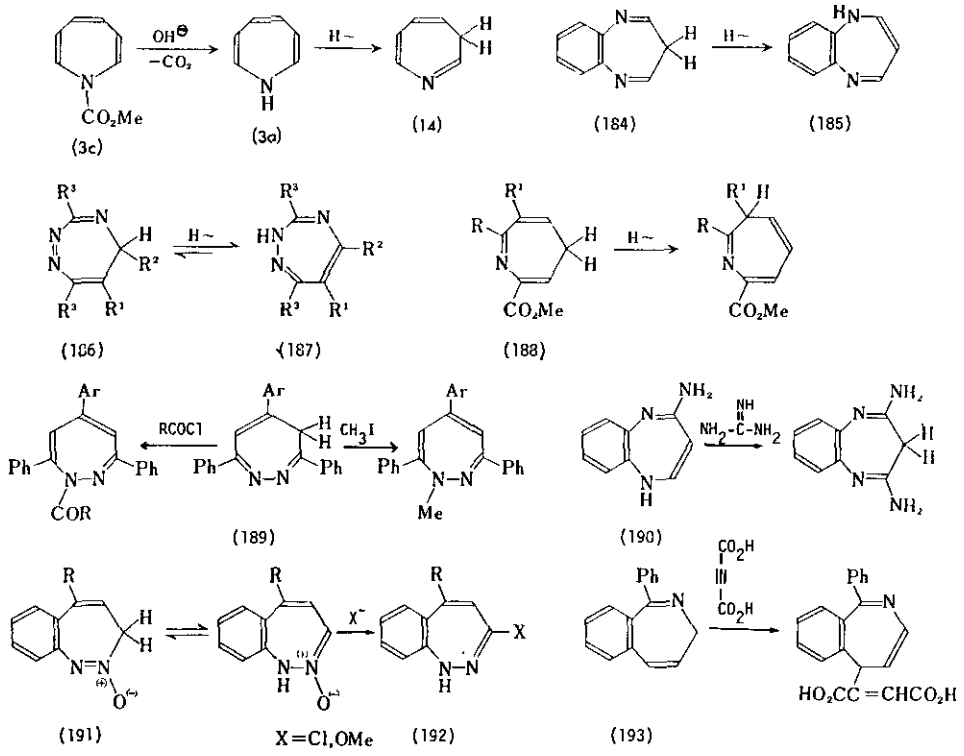
Mukai et al. reported that mechanism (ii) and (iii) can be excluded because thermolyses of (169a) and (169b) give the same product (173).[11] The path (iv) seems to be more plausible than the path (i) because the formation of N-formyl indene (177) from benzo-1,3-oxazepine (178) can be explained, by path (iv), but not by (i). In addition, the fact that an isomer (179), possessing a structure similar to that of (178), is stable under the same conditions seems to support the correctness of the path (iv), because the rearrangement of (179) to (180) requires loss of the benzene resonance in contrast to the case of (178). Tsuchiya et al. also pointed out that irradiation of 3H-benzodiazepin (181) produces vinyl benzopyrazole (183) whose precursor is considered to be the cross structure intermediate (182).[124]



Scheme 31

2.4.2 Proton shift in the azepine derivatives

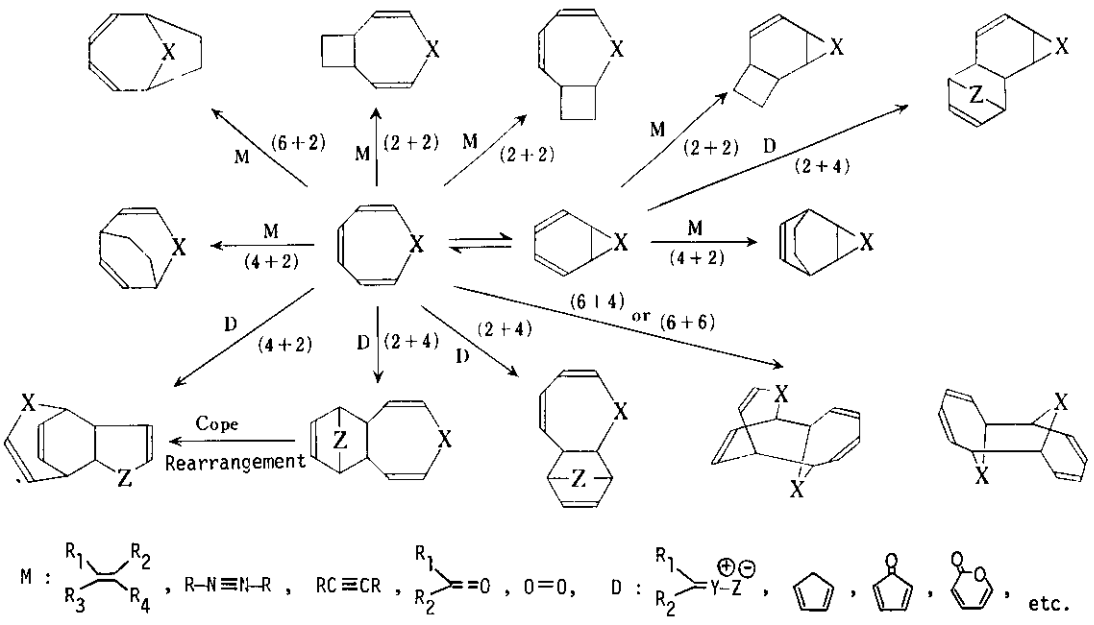
When N-ethoxycarbonyl-1H-azepine (3c) was hydrolyzed with alkali to give 1H-azepine (3a), the product immediately isomerized to 3H-azepine (14).[8a] Dewar's MO calculation reveals that (14) is 0.11 kcal/mol more stable than (3a).[14] In contrast, there exists an example for the rearrangement of 3H-diazepine (184) to 1H-diazepine (185).[9b] These reactions are available for the judgement of the thermodynamical stability in the azepine system.[81] The following reactions are regarded as examples of this kind of proton shift, the reversible reaction between (186) and (187),[60-62,125] and the isomerization of (188).[57] Some other related examples are shown in Scheme 32, i.e., methylation or benzoylation of 4H-1,2-diazepine (189),[126] amination of 1H-1,5-benzodiazepine (190),[127a] synthesis of 3-substituted benzodiazepine (192) from N-oxide (191),[127b] and the ene reaction of benzazepine (193).[75] For details of them, the references should be referred to.



Scheme 32

3. Intermolecular cycloaddition reaction

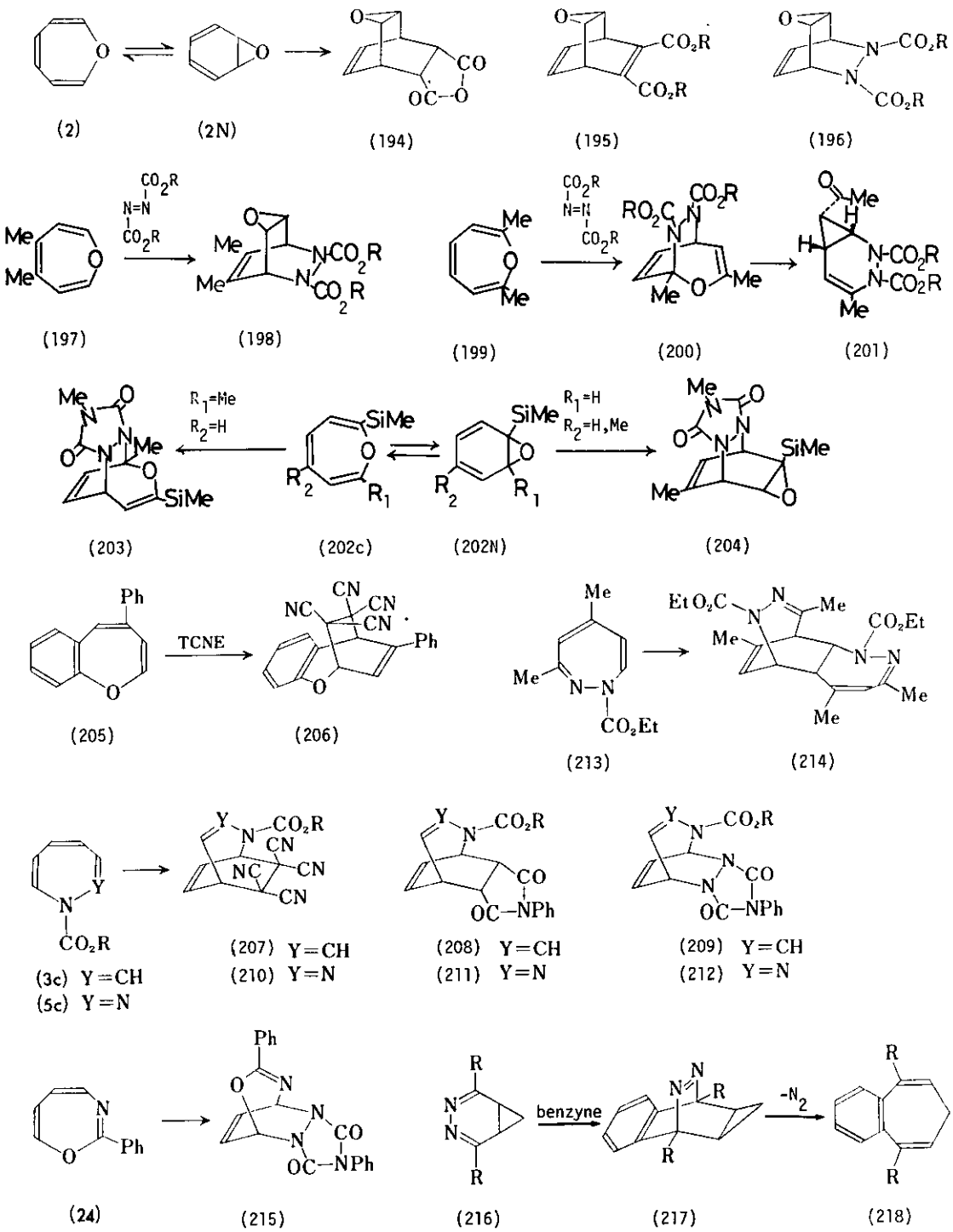
The heteroepins undergo cycloaddition reactions with unsaturated molecules because they behave like cyclic polyenes possessing boat form. The problem points of these reactions are that the heteroepins possess a lot of reaction sites and can behave as monoene, diene, and triene, according to the kind of reactants. It is also possible for them undergo the cycloaddition reaction as the norcaradiene form. It is of interest, furthermore, to consider how the included heteroatom influences these reactions. Before going into details, we wish to introduce the possible types of cycloaddition reactions in Scheme 33. Monoenes (M) and dienes (D) are shown as the reactants in this Scheme. Although (M) is described as ethylene and (D) as a cyclopentadiene form, they should be extended to other multipe bonds, including triple bonds or heteroatoms.



Scheme 33 Addition Reactions of the Heteroepins with Monoenes (M) and Dienes (D)

3.1 Reaction as dienes; (4+2) cycloaddition reaction

In the thermal cycloaddition reaction of heteroepins, they have the most opportunity to behave as dienes. As shown in Scheme 34. oxepin (2) undergoes cycloaddition reaction with many dienophiles through benzene oxide (2N). For example, it reacts with maleic anhydride, dimethyl acetylenedicarboxylate (DMAD),and azodicarboxylic diester to give (4+2) adducts (194), (195),


(2)
(2N)
(194)
(195)
(196)
(197)
(198)
(199)
(200)
(201)
(203)
(202c)
(202N)
(204)
(205)
(206)
(213)
(214)
(3c) Y=CH
(5c) Y=N
(207) Y=CH
(210) Y=N
(208) Y=CH
(211) Y=N
(209) Y=CH
(212) Y=N
(24)
(215)
(216)
(217)
(218)
TCNE
benzyne
-N2

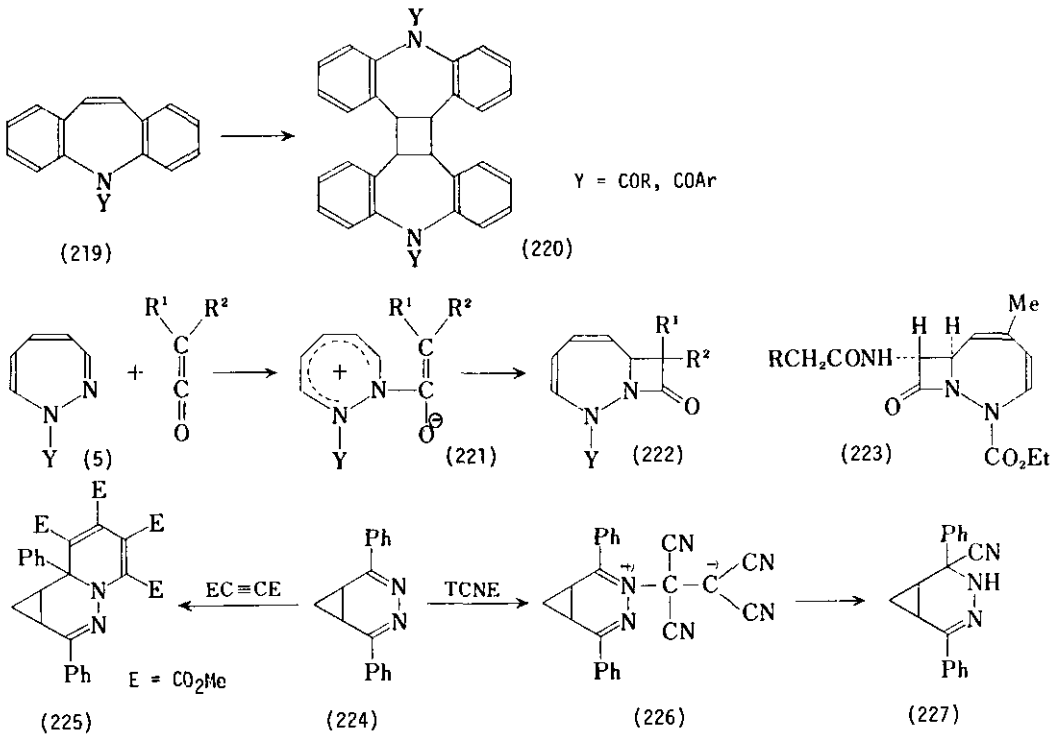
Scheme 34

and (196), respectively.[128] Reaction of 4,5-dimethyloxepin (197) with azodicarboxylic diester gives the similar adduct (198),[129a] whereas 2,6-dimethyloxepin (199) reacts as the triene form to give the adduct (200) which readily isomerizes to (201) by the Claisen rearrangement.[129b] Reaction of oxepins (202) with N-methyltriazolinedione is also affected by substituents, in which only the 2,6-disubstituted oxepins (203) react as the triene form.[130] These substituent effects can be rationalized by the idea that 2,6-disubstituted oxepins take the triene form (202c) as the stable one and there is little contribution of the benzene oxide structure (202N) in them. Benzoxepin (205) reacts with tetracyanoethylene (TCNE) through the triene structure to give an adduct (206).[131] On the other hand, N-alkoxycarbonyl-1H-azepine (3c) does not react with maleic anhydride, DMAD, and so on,[132] but it reacts with stronger dienophiles such as TCNE, N-phenylmaleimide, and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to give adducts (207), (208), and (209).[133,134] The cycloaddition reaction of N-ethoxycarbonyl-1H-1,2-diazepine (5c) is similar to those of (3c) because it does not react with maleic anhydride and DMAD etc., while it reacts with stronger dienophiles such as TCNE and PTAD to give Diels-Alder type adducts (210) and (211), and (212).[9c,24,135] The 1H-1,2-diazepine derivative (213) undergoes a dimerization reaction to give a (4+2) adduct (214) in the presence of acid catalyst such as boron trifluoride or trifluoroacetic acid.[135]

Polysubstituted 1,3-oxazepine, which are readily synthesized, are inert to cycloaddition reactions.[96] 2-Phenyl derivative (24) does not also react with maleic anhydride, DMAD, and TCNE, but it reacts with PTAD to give a (4+2) adduct (215).[136] 3,4-Diazanorcaradiene (216) reacts with benzyne to give a (4+2) adduct (217) which immediately eliminates nitrogen to give (218). The addition reaction of (216) serves as a new method for the synthesis of tropilidene derivatives because (216) also reacts with acetylenes with loss of nitrogen.[137] It should be noted that the Diels-Alder reactions described above occur exclusively at the 2,5-position (4,7-position) of the heteroepins.

3.2 Reaction as monoenes; (2+2), (2+4) or (6+2) cycloaddition reactions

As shown in Scheme 35, photodimerization of dibenzazepine (219) to give (220) is known as an example of (2+2) cycloaddition reactions.[138] Although this kind of reaction is in general thermally forbidden, 1H-1,2-diazepines (5) react with ketenes via an ionic intermediate (221) to give adducts (222).[139a] This reaction is available for the synthesis of bicyclo[5.2.0]-compounds (223) which are interesting as cephalosporin analogues.[139b] 3,4-Diazanorcaradiene (224) undergoes a (2+2+2) addition reactions with two equivalents of DMAD to give (225).[20b] Compound (224) also undergoes an ionic reaction with TCNE via an intermediate (226) to give (227), instead of a cycloaddition reaction.[20b]

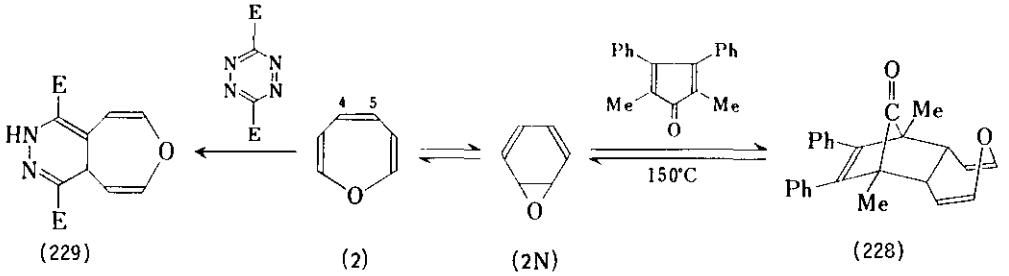


Scheme 35

There are a large number of examples in which the heteroepins behave as dienophiles in the Diels-Alder reaction. Cyclopentadienes, cyclopentadienones, α-pyrones, isobenzofuran, and 1,3-dipolar reagents, etc. are known as reacting dienes. Examples of these reactions will be discussed below.

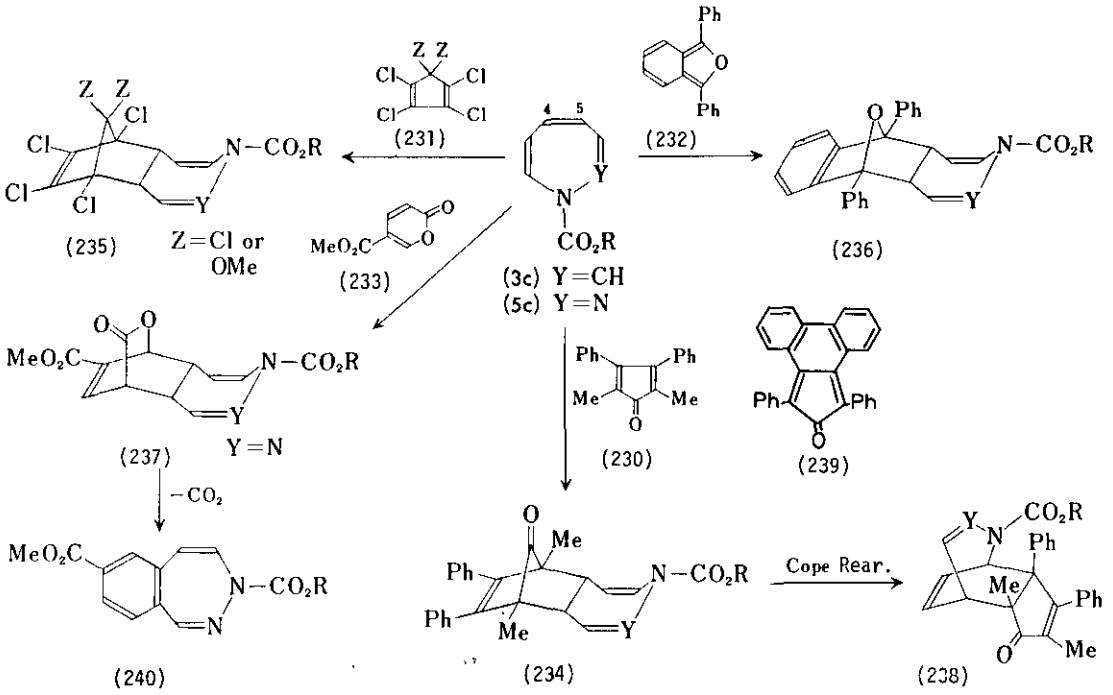
(A) Oxepins

Oxepin (2) undergoes cycloaddition reactions at the C_4-C_5 bond with a cyclopentadienone derivative[118] and a 1,2,4,5-tetrazine derivative[141] to give (228) and (229), respectively. It is noteworthy that (2) does not react through benzene oxide structure (2N). It seems interesting, furthermore, that (228) undergoes neither the Cope rearrangement nor a decarbonylation reaction, and instead reverts to (2) at 150°C.



(B) 1H-Azepines

1H-Azepine (3c) undergoes cycloaddition reactions with cyclopentadienone (230),[133] cyclopentadiene (231),[142] isobenzofuran (232),[133] and α-pyrone (233)[143] to give 1 : 1 adducts (234)-(237). It should be noted that in all cases, peri-selectivity is observed, in which the reaction site is the C_4-C_5 bond of (3c). In the reaction with (230), an initially formed adduct (234) undergoes the Cope rearrangement to afford another (4+2) adduct (238).[144] The reaction with phenylcyclone (239) is quite similar to that with (230).[145] Furthermore, the azepine (3c) undergoes a cycloaddition reaction with diazomethane, in which there are two reaction sites, i.e., the C_4-C_5 double bond of (3c) and the C_2-C_3 double bond of (3N) as described in Scheme 18.

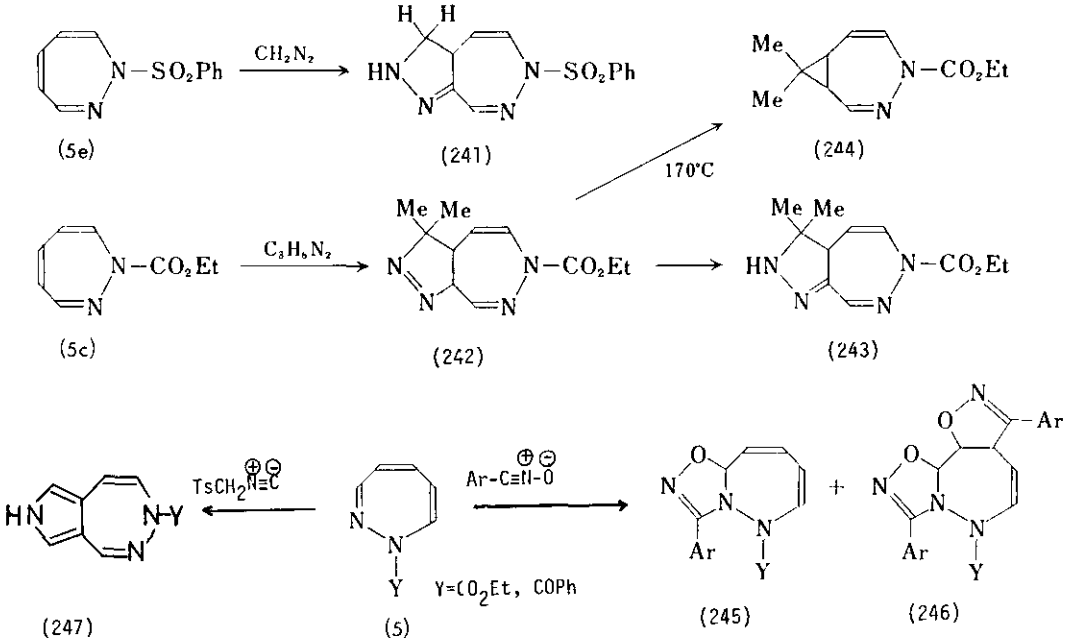


Scheme 36

(C) 1H-1,2-Diazepines

As shown in Scheme 36, the cycloaddition reaction of 1H-1,2-diazepines (5) is similar to those of 1H-azepines (3c) except in the reaction with α-pyrone carboxylic ester in which, without the isolation of a (2+4) adduct (237), decarboxylation occurs to give benzodiazepine (240) in low yield.[143] As shown in Scheme 37, N-phenylsulfonyl-1H-1,2-diazepine (5e) undergoes an

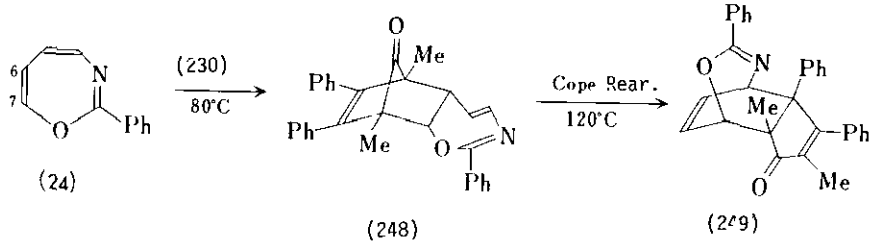
addition reaction with diazomethane at the C_4-C_5 bond to give a 1 : 1 adduct (241).[146a] N-Ethoxycarbonyl derivative (5c) reacts with diazoisopropane to afford adducts (242) and (243).[146] Upon heating of (242), loss of nitrogen leads to homodiazepine (244) in good yield. This reaction is interesting from the synthetic standpoint. Streith et. al. have recently found that nitrile oxides react peri-selectively with the 1H-1,2-diazepines (5) to give a 1 : 1 adduct (245) along with a 1 : 2 adduct (246).[147] Tosylmethyl isocyanide reacts with the diazepines (5) to afford pyrrolodiazepines (247).[148]



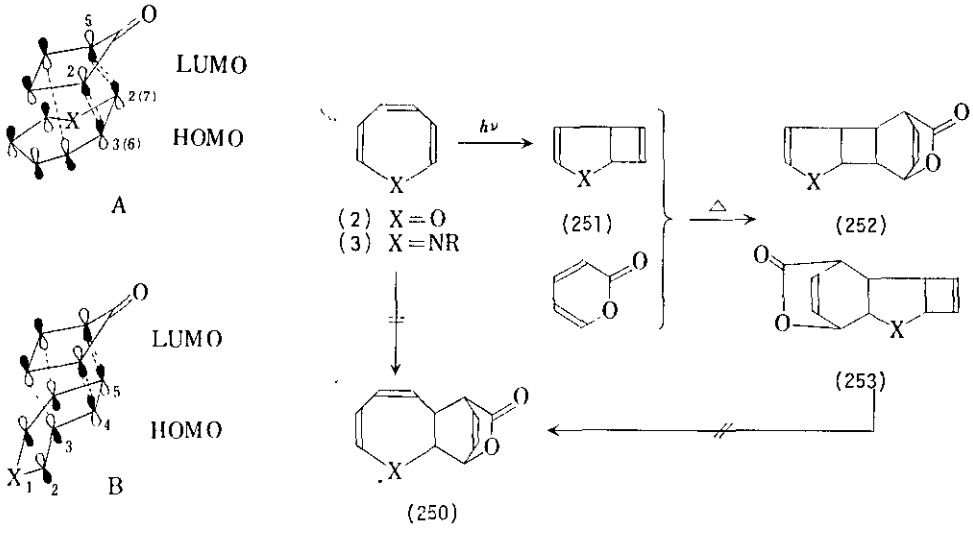
Scheme 37

(D) 1,3-Oxazepines

2-Phenyl-1,3-oxazepine (24) reacts with cyclopentadienone (230) to give a (2+4) adduct (248) which undergoes the Cope rearrangement to afford a (4+2) adduct (249) in good yield. The initial addition with (230) occurs at the C_6-C_7 bond of (24).[144]



Now we wish to discuss the peri- and stereo-selectivity observed in the cycloaddition reactions of oxepin (2), azepine (3c), diazepine (5c), and oxazepine (24) with dienone (230). Because (230) is an electron defficient diene and the heteroepins are regarded as electron donating dienophiles, these addition reactions are understandable in terms of the inverse Diels-Alder reactions. Therefore, these reactions follow the interaction between the HOMO of the heteroepins and the LUMO of the dienone (230) as shown in Scheme 38. In the transition state, the orbitals of the C_2-C_3 (C_6-C_7) bond and the C_4-C_5 bond of the heteroepins have the bonding overlap with that of the C_2-C_5 bond of (230), indicating that both A and B are possible transition states. It is conceivable, furthermore, that the formation of the endo adducts is dominant because of the presence of the β-orbital interaction shown in A and B.



Scheme 38

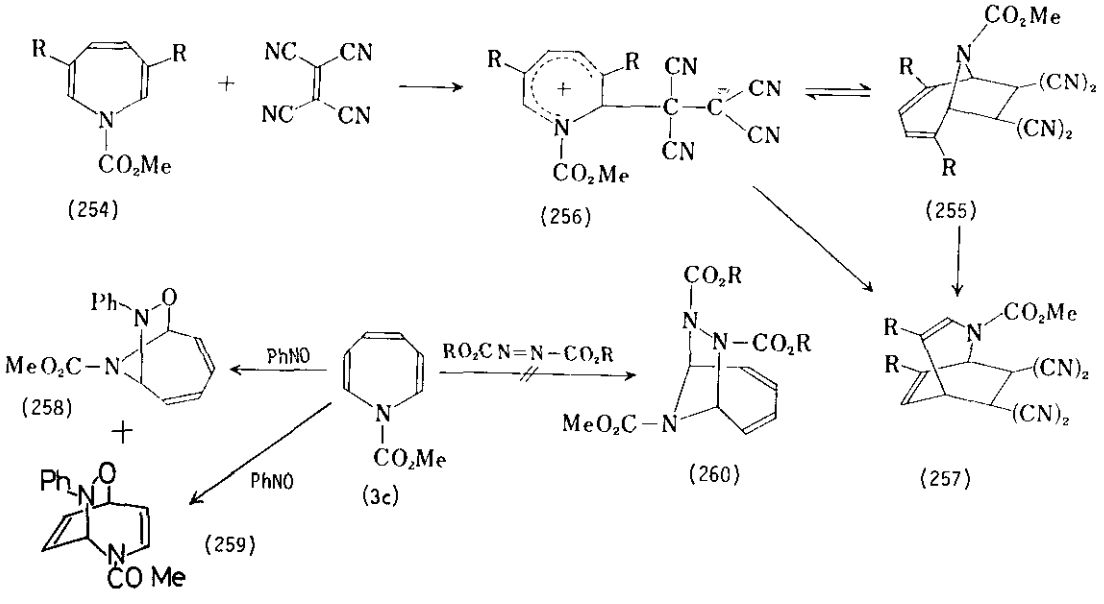
It should be noted here that only 2-phenyl-1,3-oxazepine reacts at the C_6-C_7 bond (A), whereas three other heteroepins react at the C_4-C_5 bond (B). The selectivity of the cycloaddition of dienone (230) to cycloheptatriene is similar to the case of the 1,3-oxazepine. The X-ray analyses described before show that these heteroepins take the boat conformation and that there is not much difference concerning the stereochemistry and the bond lengths in them. Therefore, electronic factors may be the most important and further studies are expected to clarify these points.

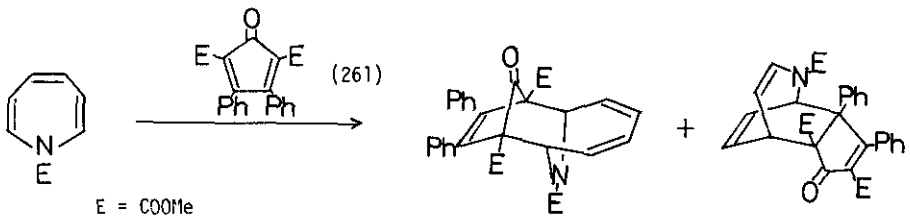
Next we would like to discuss the reaction of heteroepins with α-pyrones in Scheme 38 on the basis of the recent studies of Anastassiou[140] and Iida.[143] Attempts to obtain the adduct (250)

from heteroepins and α-pyrone have been unsuccessful. Instead, Anastassiou synthesized (252) and (253) using the thermal addition reaction of α-pyrone with bicyclo[3.2.0]heptadienes (251) which are readily obtained by irradiation of the heteroepins.[140] This method is unique with the idea that the reacting double bond was activated by the incorporation into a small ring.
On the other hand, Iida attempted the addition reaction of the heteroepins and α-pyrone substituted by an electronegative alkoxycarbonyl group which activates the diene. As described already in Scheme 36, (2+4) adducts of the heteroepins with α-pyrones are obtained although the yields are poor. These facts indicate that this is an inverse electron demand Diels-Alder reaction, in which the interaction between the LUMO of the α-pyrones and the HOMO of the heteroepines is important.

3.3 Reaction as trienes; (6+2), (6+4), and (6+6) cycloaddition reactions

As described in section 3.1, the cycloaddition reaction of 1H-azepines appears generally as a (4+2) type. When substituted at the C_3- and C_6-positions, however, the azepines undergo (6+2) addition reactions mainly because of steric hindrance (Scheme 39). Thus, 3,6-disubstituted azepines (254) react with TCNE to give adducts (255) and the yields are better when R is t-butyl than methyl.[35] Because (6+2) additions are thermally forbidden, they proceed stepwise via an ionic intermediate like (256). The (6+2) adduct (255) rearranges to the (4+2) adduct (257) upon heating at 140°C, in which (256) might be a possible intermediate. It is of interest to note that the (4+2) cycloaddition is in competitive relation with the (6+2) one.

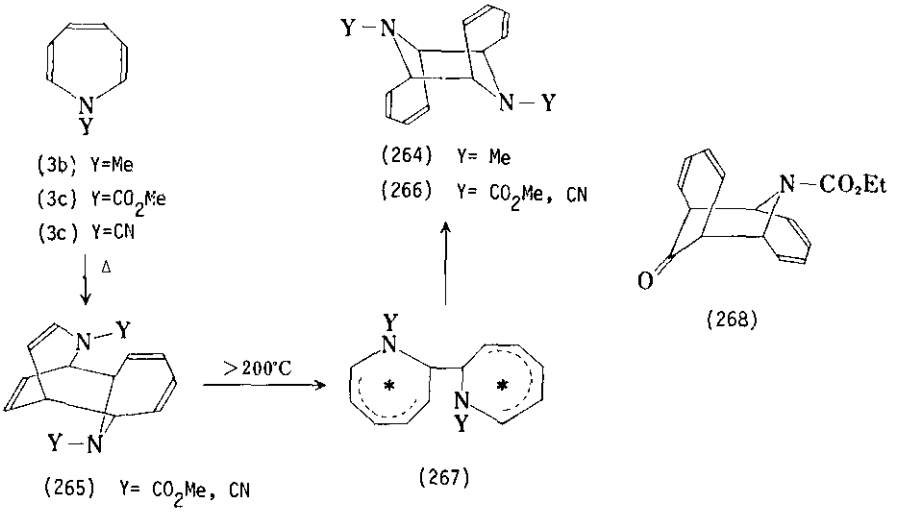




Scheme 39

1H-Azepine (3c) also undergoes a (6+2) cycloaddition reaction with nitrosobenzene to give an adduct (285) along with (4+2) adduct (259).[149] The addition reaction of (3c) with azodicarboxylic diester was also reported to give a (6+2) adduct (260).[150a] However, recently the structure of the adduct was corrected to be a (4+2) adduct like (259) based on its ^{13}C nmr spectrum.[150b] Reaction of the azepine (3c) with a cyclopentadienone derivative (261) affords a (6+4) adduct (262) along with a usual (4+2) adduct (263).[156]

Thermal dimerization of 1H-azepines is their general property and it has been studied in detail. As shown in Scheme 40. N-methylazepine (3b) undergoes dimerization below room temperatures to give a (6+6) dimer (264).[152] The temperature required for dimerization is strongly influenced by the nature of the substituents. N-Cyanoazepine (3d) dimerizes at 25°C,[153] whereas N-ethoxycarbonylazepine (3c) is relatively stable and dimerizes at 130°C.[154] The thermally allowed (6+4) adducts (265) are initially formed and rearrange upon heating at higher temperatures to the thermodynamically stable (6+6) dimers (266) via intermediates (267). As a (6+6) addition reaction between different molecules, 1H-azepine (3c) reacts with tropone to give an adduct (268).[155]

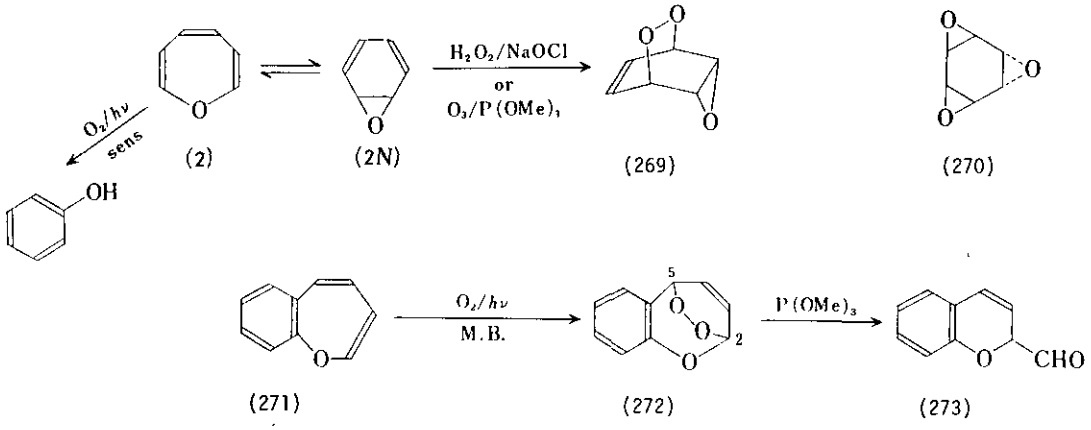


Scheme 40

4. Addition Reaction with Singlet Oxygen.

The addition reaction of singlet oxygen are in general considered to be electrophilic reactions requiring only a small energy barrier. Therefore, it is well known that singlet oxygen reacts easily with polyolefins such as cyclopentadiene and cycloheptatriene to give epoxides and peroxides. The reaction of singlet oxygen with five-membered heterocyclic compounds has also been studied in detail; the initial products are cyclic peroxides. In connection with these reactions, it is of interest to investigate what kind of addition reactions heteroepins undergo with singlet oxygen.

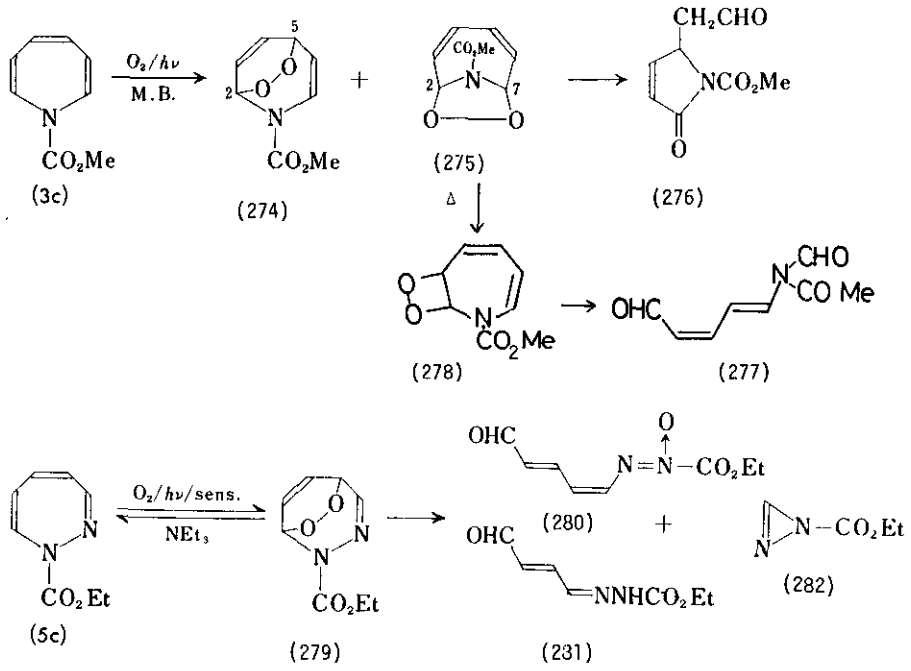
As shown in Scheme 41, sensitized photooxidation of oxepin (2) gives only phenol, while chemically generated singlet oxygen undergoes a 1,4-addition reaction with (2N), in which the addition occurs at the C_2 and C_5 positions to give peroxide (296). [156] This peroxide readily rearranges upon heating to benzene trioxide (270). On the other hand, sensitized photooxidation of benzoxepin (271) affords an endo-peroxide (272) which is derived by the addition at the C_2 and C_5 positions of the seven-membered ring. The adduct (272) is thermally stable, but it rearranges to an aldehyde (273) upon treatment with trimethyl phosphite.[157]



Scheme 41

Under the sensitized photooxidation, 1H-azepine (3C) gives 1,4-addition (274) and 1,6-addition products (275) in 63 and 25% yields, respectively.[158,159] Epi-dioxide (275) is found to be labile to heat, and it rearranges to the pyrrolinone derivative (276) when heated at 60°C in ethanol. On the other hand, in benzene at 60°C the epi-dioxide (275) affords fragmentation product (277), which is considered to be derived via 6,7-dioxetane (278) by the double cleavage reaction. The dioxetane is presumed to be a 1,5-oxygen migration product from (275).[159]

Photo-oxidation of 1H-1,2-diazepine (5c) also leads to the formation of 4,7-endo-peroxide (279) as a major product, accompanied by three minor products (280), (281), and (282) (see Scheme 42). In this reaction the initial process is probably the 4,7-addition reaction, because three minor products can be obtained from (279) under the same oxidation conditions.[160]



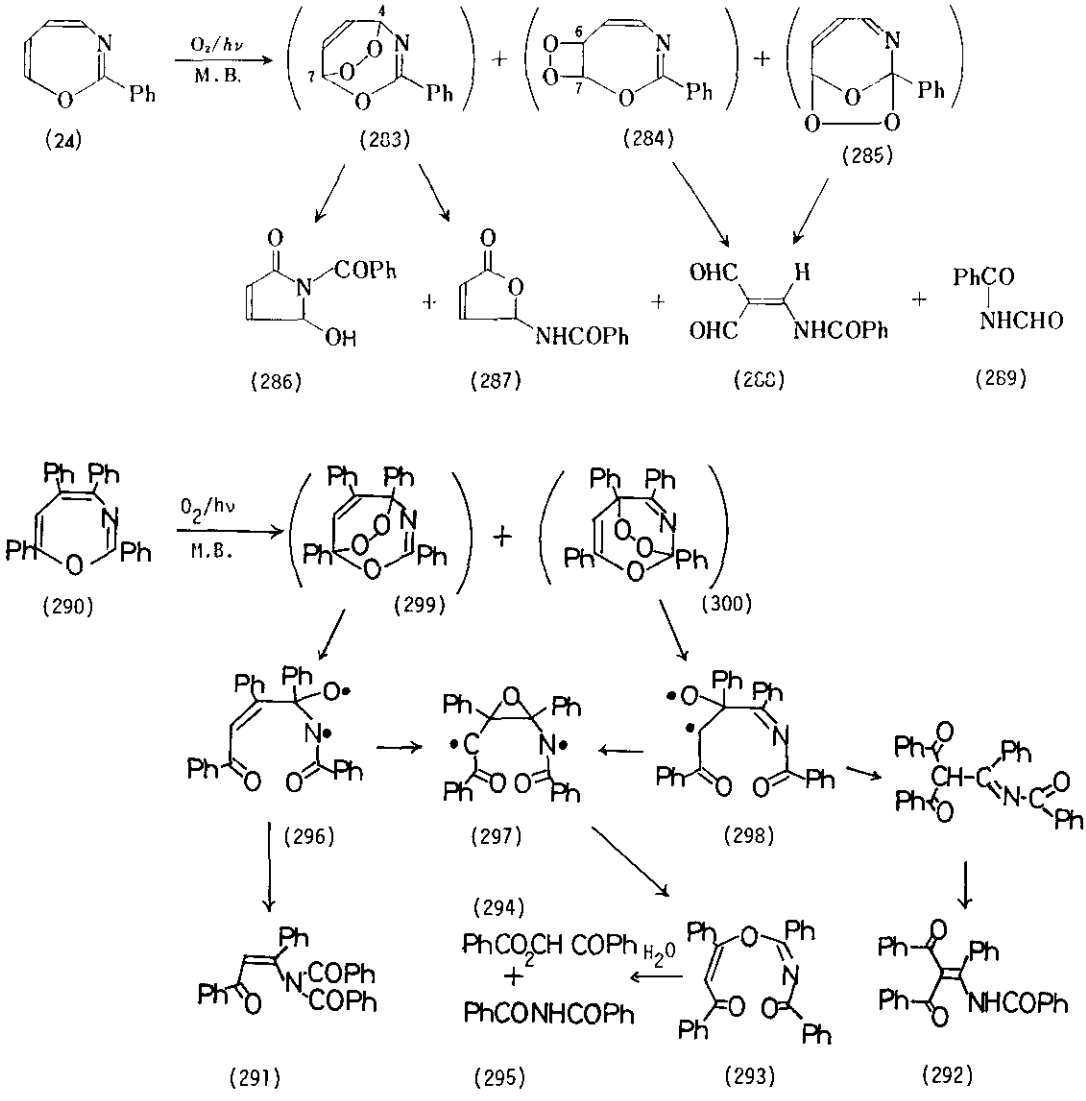
Scheme 42

In contrast to oxepins and azepines, the reaction of 1,3-oxazepines with singlet oxygen is more complex (see Scheme 43). Photo-oxidation of 2-phenyl oxazepine (24) does not give any expected cyclic peroxide such as (283), (284) or (285) at all, but instead affords their presumable decomposition products (286)-(289).[161] By comparing these products with the reaction paths of the photo-oxidation of oxazoles (12),[162] it is possible to deduce the relationship between the decomposition products obtained and their precursors. Thus, pyrrolinone (286) and butenolide (287) can be derived from the endo-peroxide (283). 6,7-Dioxetane (284) can afford (287) and an ethylidene malonaldehyde derivative (288). Furthermore, N-formyl-benzamide (289) and (288) can also be derived from 2,7-epodioxide (285) as shown in Scheme 43.

More recently, the reaction mechanism for the photooxidation of di-, tri- and tetraphenyl substituted 1,3-oxazepine derivatives has been studied.[159] As an example, the reaction of (290) with singlet oxygen is shown in Scheme 43, where five kinds of products (291)-(295) are produced

instead of the expected cyclic peroxides. The isolation of vinyl ether (293) which easily gives (294) and (295) on hydrolysis is noteworthy. Each of the products (291) to (293) can be derived from the diradical intermediates (296), (297), and (298). The expected endo-peroxides (299) and (300) can lead to the formation of these intermediates by O-O and C-O bond cleavages.

In the photo-oxidation of 2,4,7-triphenyl-1,3-oxazepine using ^{18}O-singlet oxygen, it is established that both 2,5-and 4,7-endo-peroxides are initially formed.[159]



Scheme 43

As mentioned before the addition reactions of singlet oxygen are in general considered to be electrophilic reactions requiring only a small energy barrier. Therefore, in the reaction with hetroepins, if all the oxygen adducts could be quantitatively evaluated, the electronic states of these heteroannulenes would have been estimated experimentally. If the heteroepin derivatives are regarded as various kinds of vinyl ethers or enamines, these studies of singlet oxygen addition reactions take another significance. From these view-points, further progress in this field is desired.

Closing words

In this review the heteroepin chemistry has been discussed mainly from the stand points of cyclization and cycloaddition reactions. In order to keep it at a reasonable size, we have had to leave out iron carbonyl complexes, metal compounds, and so on. In addition, although there are many details missing, we are happy if this review is useful for understanding what position the heteroepin-chemistry occupies in the heterocyclic compound chemistry. We would like to close this review, hoping that the heteroepin-chemistry will make progress as a basic chemistry and will sometime become useful for mankind.

Acknowledgement

This review contains our unpublished studies on 1H-azepine, 1H-1,2-diazepine, and 1,3-oxazepine derivatives. Those studies were supported by Grant-in-Aid for Chemical Research in Development and Utilization of Nitrogen-Organic Resources. The anthors are indebted to Professor T. Kametani who is a group leader of the above project for his encouragement throughout our works.

This monograph is dedicated to Professor Tetsuji Kametani on the occasion of his retirement from Pharmaceutical Institute, Tohoku University.

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