CYCLOHEPTA[b][1,4]BENZOXAZINE AND ITS RELATED COMPOUNDS. SOME NOVEL ASPECTS IN HETEROCYCLIC CHEMISTRY[1]

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Abstract - Chemistry of cyclohepta[b][1,4]benzoxazines and their S- and O-analogues as well as of the related compounds without annulated benzene ring is reviewed. Differing from usual, unreactive heterocycle-annulated tropylium compounds, title compounds are usually very reactive, especially towards 1,4-difunctional nucleophiles such as *o*-phenylenediamine, ethylenediamine and their S- and O-analogues. Reactivities towards alkali and oxidizing agents are comparatively described in view of the difference of the heteroatoms.

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This paper is dedicated to the memory of the late Professor Tetsuji Kametani.

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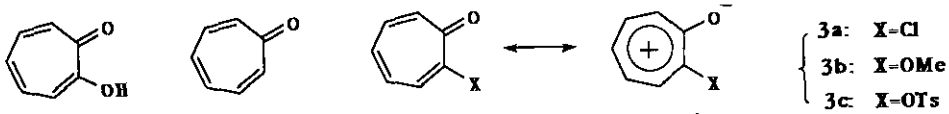
1. INTRODUCTION

1.1 Hetero-Annulated Troponoids

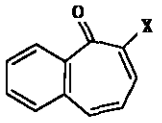
Since the synthesis of tropolone (**1**) and tropones (**2** and **3**) in early 1950's,



1 **2** **3a-c** **3***

a number of troponoids annulated with benzenoid, hetero-aromatic, or alicyclic ring (e.g. **4**, **5**, and **6**) have also been prepared.[2]

Meanwhile we found that monocyclic reactive troponoids **3** having a good leaving group at C-2 easily reacted with various nucleophiles to give e.g. heterocycles **7** (X, Y, Z = CR, NH_2, SH, OH) and trisubstituted azulenes **8** (X^1, X^3 = COOR, COR, CN,



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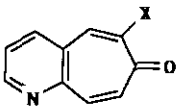

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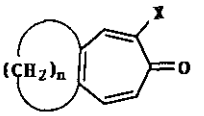
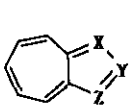


6

X^2 = OH, NH_2) in very high yield.[2] However, almost all of these annulated compounds (**4-6**: X = OMe, Cl) did not show the reactivity of monocyclic reactive troponoid having considerable contribution of 6π-electronic system **3***. Exceptionally, naturally occurring colchicine **9** (and its related compounds) was found to



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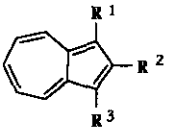

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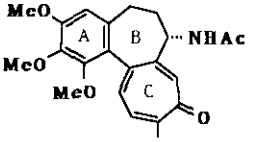

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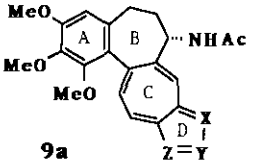


9a

exhibit similar characteristics as those of monocyclic reactive troponoids **3**, easily giving heterocyclic compounds and azulenes having annulated five-membered ring D like **9a**.[2b,3]

Later we found two types of heterocyclic compounds, cyclohepta[b]furan-2-ones (**10**: X = O, NH)[4,5] and cyclohepta[b][1,4]benzoxazines and its analogues (**11**: X = O, S, NR)[1] to exhibit interesting characteristics owing to the contribution of 6π-tropylium system (**10a**, **11a**), as well as their tendency of facile hetero-ring

10 10a

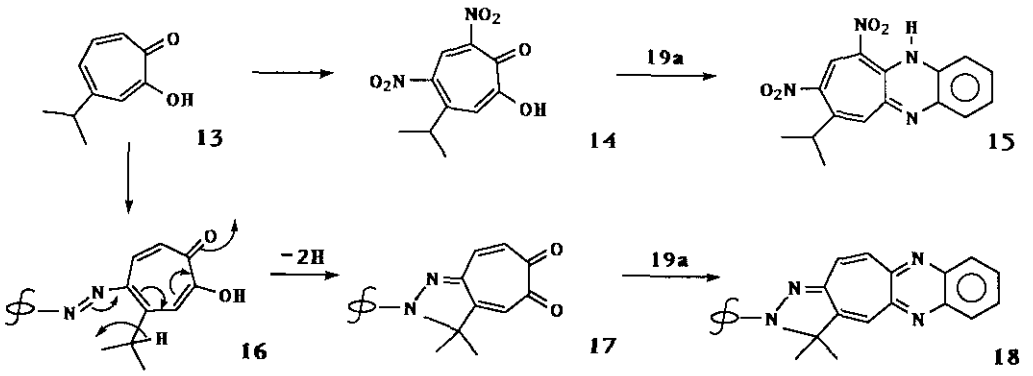
11 11a

12 12a

opening, especially in the case of **10** and **11** (X = O). In this paper, I would like to review our study on the chemistry of the type **11** and their related compounds without benzene ring **12** (X = O, S, NR).

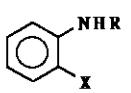
1.2 Early Studies on Quinoxalo- and Pyrazinotropones

About 40 years ago, we obtained two types of quinoxaline derivatives **15** and **18** from naturally occurring tropolone, hinokitiol (β-thujaplicin, **13**).[6] Namely, differing from **13** its dinitro derivative **14** easily afforded **15** with o-phenylenediamine (**19a**, OPD),[6,7] and dark purple pigments "hinopurpurins" **17**, easily derived



Scheme 1.

from 5-arylazohinokitiol (**16**) also gave quinoxalines **18** with OPD[6,8] (Scheme 1). Later, we obtained quinoxalo[2,3-d]tropone (**22**) by strong acid hydrolysis of the

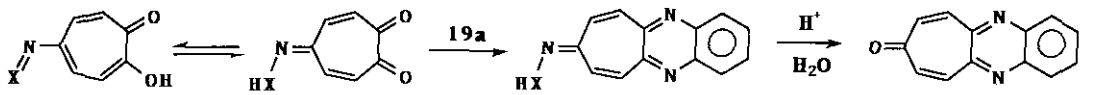


19a-e

	X	R	
19a	NH_2	H	(OPD)
19b	NH_2	Me	
19c	NHMe	Me	

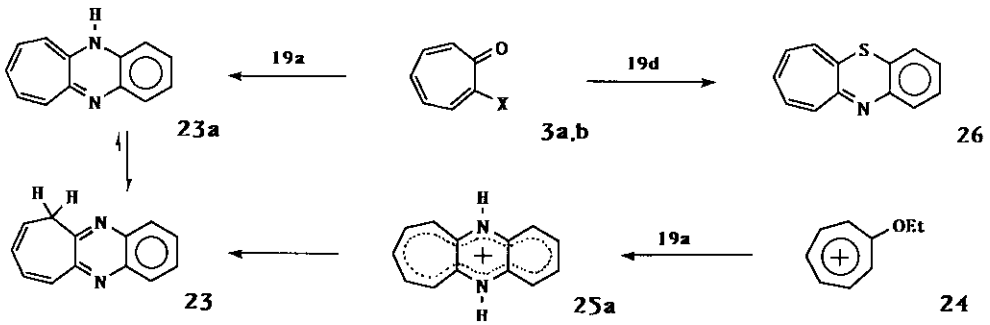
	X	R	
19d	SH	H	(OAT)
19e	OH	H	(OAP)

oxime or arylhydrazone **21** (X = O, NH), prepared from 5-nitroso- or 5-arylazotropolone (**20**: X = O, NH) with OPD.[9]



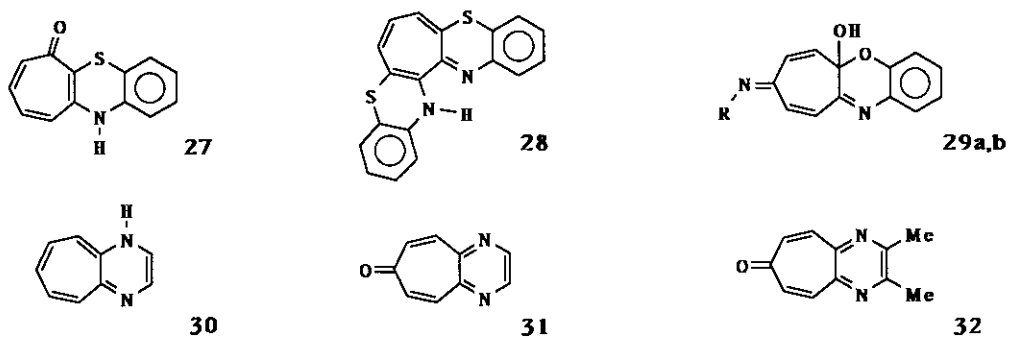
20 **20a** **21** **22**

Then we synthesized[10] the parent compound **23a** of **15**, **18**, and **22** as well as its methyl homologue by the reaction of **3a,b** with OPD and its methyl derivatives, **19b,c** (Scheme 2). However, we were unable to determine the position of H-atom of **23a**, because any appropriate instrument such as nmr was not available at that time.



Scheme 2.

Later in 1971, Fukunaga[11] reported that the reaction of ethoxytropylium salt **24** with **OPD** gave greenish black crystals **25** which reversibly changed to the quinoxalotropylidene (**23**) on neutralization. By comparison of the nmr spectrum with those of the structurally similar compounds, he pointed out that the cation **25** had the resonance stabilized, peripheral 16π-electron system (**25a**). He also considered that our colorless specimen reported as benzo[b]tropazine[10] might have been a dimer of his quinoxalotropylidene (**23**), but he did not study the structure of the dimer any further. We also synthesized benzo[b]tropothiazine (**26**), its related compounds **27**, **28**,[12] and O-analogues **29a,b** (R = OH or NNHR'),[13] by the reaction of some reactive troponoids with o-aminobenzenethiol (**19d**, **OAT**) or of 5-nitroso- and 5-arylazotropone with o-aminophenol (**19e**, **OAP**).



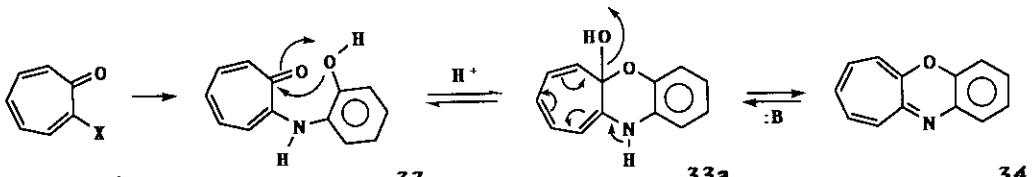
Synthesis of cyclohepta[b]pyrazine (**30**),[14a] pyrazinotropone (**31**)[14b] and its dimethyl derivative **32**[15] was also reported. However we could not confirm the structure of **30** (existence of pyrazine ring) because of unavailability of nmr at that time. As it was necessary to examine these systems (**11** and **12**: X = NR, S,

and O) more closely, synthesis of O-analogues of these compounds **23** and **26**, namely cyclohepta[b][1,4]benzoxazine (**34**) was undertaken first. This study has unexpectedly resulted in the discovery of several very interesting features of these compounds.

2. CYCLOHEPTA[b][1,4]BENZOXAZINES

2.1 Cyclohepta[b][1,4]benzoxazine

Compound **34** is easily obtained via 2-(o-hydroxyanilino)tropone (**33**) by the condensation of **3a,b** and o-aminophenol (**OAP**, **19e**), and **34** is readily hydrolyzed by alkali to regenerate **33**, which subsequently gives tropolone (**1**) and **OAP** by heating with excess alkali.[16]



3a,b **33** **33a** **34**

Red-colored cations **34a** and **26a** respectively formed from **34** and **26** in strong acid have been found by their nmr spectra to have the 6π-benzenoid-6π-tropylium

a

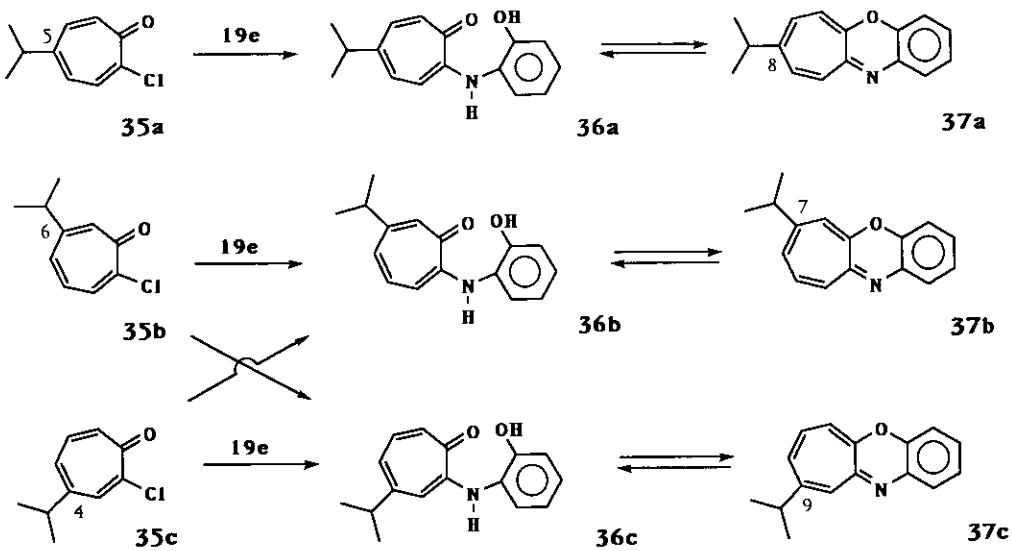
34a **26a**

system,[16] which is different from that of the previously mentioned Fukunaga's green colored cation **25a**.[11]

It was generally known that the reactive troponoids **3** give the normal substitution products at C-2 or so-called ciné-substitution products at C-7, depending upon the kind of the leaving group, the nucleophile, solvent, and other reaction conditions.[2]

In order to confirm the substitution position of the troponoid nucleus with the amino group of **OAP**, three isopropyl-2-chlorotropones (**35a-c**) were heated with **OAP** in acetic acid. As shown in Scheme 3, 5-isopropyl compound **35a** provides a single compound **37a** in high yield, whereas **35b** and **35c** give an almost 1:1-mixture of **37b** and **37c**.[17] This evidence excludes the ciné-substitution pathway, but the reason why the isomeric mixtures **37b** and **37c** were produced from either of **35b** and **35c**

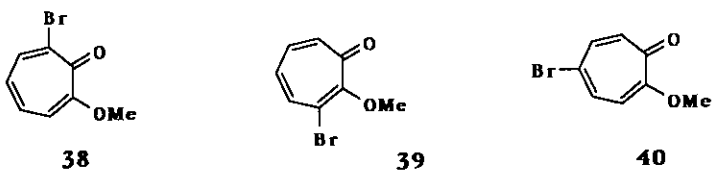
remained unestablished at that time.



Scheme 3.

2.2 6-Bromocyclohepta[b][1,4]benzoxazine

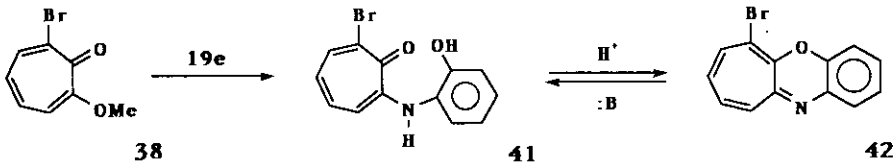
We then compared the reaction of **OAP** with three isomeric bromo-methoxytropones **38-40** and encountered various unexpected results which sometimes led us to make an erroneous assumption with regard to some of the reaction products and pathways.[1,18]



38 **39** **40**

When 2-bromo-7-methoxytropone (**38**) and **OAP** are refluxed in acetic acid, a mixture of 70% of 2-bromo-7-(o-hydroxyanilino)tropone (**41**) is obtained besides 5% of orange compound **B** and a trace of dark violet pigment **A**. The major product **41** readily gives the ring-closed 6-bromocyclohepta[b][1,4]benzoxazine (**42**) on heating in acetic acid containing a trace of conc. H_2SO_4.[18] Compound **42** quantitatively reverts back to **41** by alkali. Such a facile, reversible opening and closing of the heterocyclic ring have turned out to be one of characteristic features of cyclohepta[b][1,4]benzoxazine system.

Similar treatment of 3-bromo-2-methoxytropone (**39**) with **OAP** affords, to our



38 41 42

surprise, more than twelve colorful products, which are easily separated by reversed phase hplc, and these products were conveniently called as A, B, ...L, according to their decreasing R_f values of tlc.[19] Compounds A and B either from 38 or 39 are the same compounds;[16] structures of these compounds are shown in Chart 1.[19]

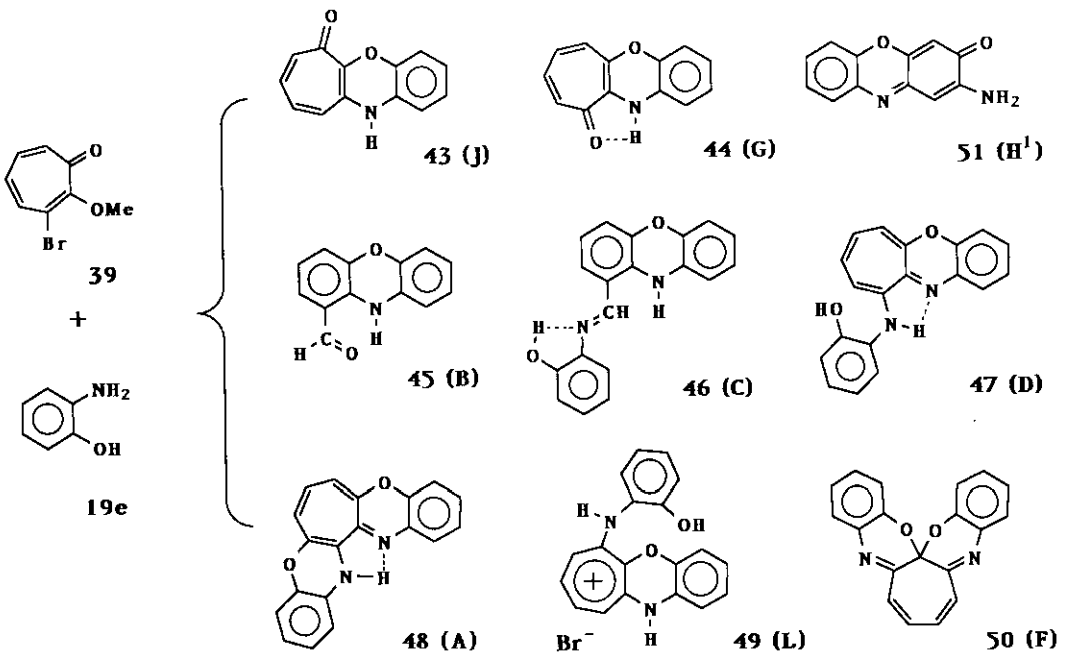
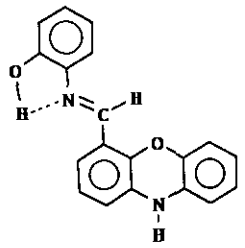


Chart 1.

Among these compounds, J and G are 1:1-condensation products, and others (A, B, C, D, F, and L) are 1:2-condensation products and their secondary product (B). 2-Amino-3H-phenoxazine-3-one (51, H^1) is the coupling product of OAP and usually produced in these reactions. These compounds (43-50) are later found to be more easily obtained by the reaction of OAP and 42 which is presumed one of the reaction intermediates in the above reaction.[20] For example, when 42 and OAP are heated in acetic acid at 120 ^{o}C, 10- and 6-substituted products (D and L) and their dehydro-cyclized products (A and F) are obtained besides a small amount of

the rearranged products **B** (1-formylphenoxazine).



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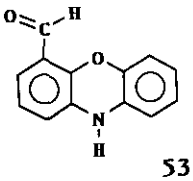
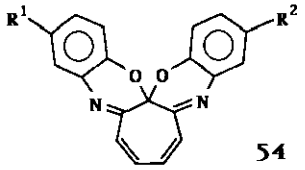


53

In methanol, the reaction proceeds very faster, and 50% of **D**, 10% of **41**, and 30% yield of **C** are produced at 50 °C. When the reactants are kept at 5 °C, the ratio of these products reverses and more than 70% yield of **C** is produced. However, if a base such as **DABCO** is added to the reactants, surprisingly, the Schiff base **52** of 4-formylphenoxazine (**53**) is obtained as the main product.

Compound **49** (**L**), which is produced as the stable HBr salt on heating **42** with **OAP** in acetic acid, is easily dehydrogenated by air oxidation to give the acetal **50** (**F**), upon basification.[19] Compound **F** regenerates **L** upon zinc dust reduction in acetic acid. Various substitution products of **F** (**54**: R^1, R^2 = H, Me, Cl) and naphtho analogue **55** can also be prepared by the similar method.[21,22] Compounds **F** (**50** and **54**) containing a chiral center in the molecule are resolved in optically



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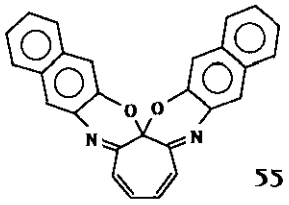

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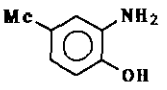


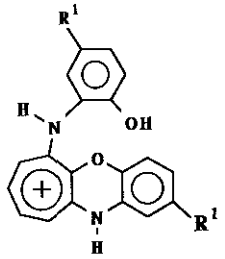
56 (MeOAP)

pure formes by hplc on a chiral poly(triphenylmethylmethacrylate) column.[23] These compounds show very large optical rotations (e.g. $[\alpha]_D$ of **50**: +4600°) comparable to helicene. From the X-ray analysis[23] of the (-)-3,12-dichloro derivative (**54**: R^1 = R^2 = Cl) and also by theoretical calculation of cd spectra,[22] the levorotatory compound **54** has an S-absolute configuration.

2.3 Intermolecular Heterocycle-Exchange Reactions.

To examine generality of such an unprecedented complex reaction of **39** and **OAP**, reaction of 6-bromo compound **42** with 2-amino-4-methylphenol (**56**, **MeOAP**) was studied. The reaction turned out extremely complex, and many products were

formed simultaneously, showing about 30 peaks by the hplc analysis.[24b] We found that **54**, **57**, **58**, and **59** consist of a set of comparable amount of three components, which contain two, one or none of the methyl groups in the molecule.



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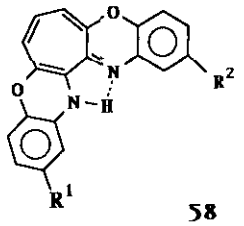

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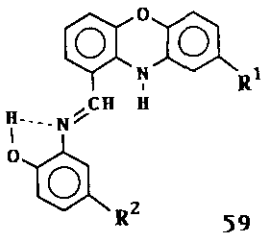

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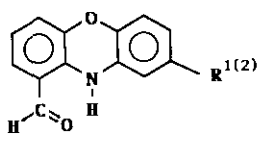
Moreover, **60**, ring-opened product **61** and coupling product **62** (H^1) also exist as a mixture of parent compound and its monomethyl products (R^1, R^2 = H, Me), suggesting that a certain kind of interconversion between substrate and the reagent is



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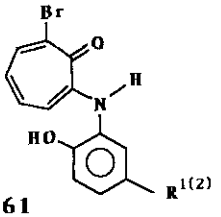

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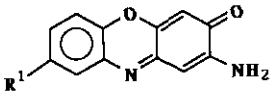

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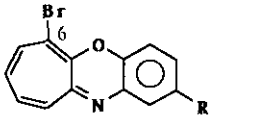
taking place to produce intermediate compounds such as **63** and **64** (R = H or Me). Therefore, preference of the reaction between the heterocyclic conversion and the bromine-substitution was examined. The reaction of bromine-free isopropyl



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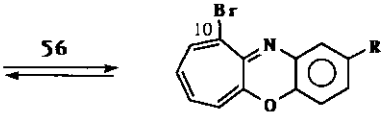

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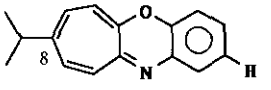
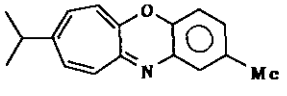


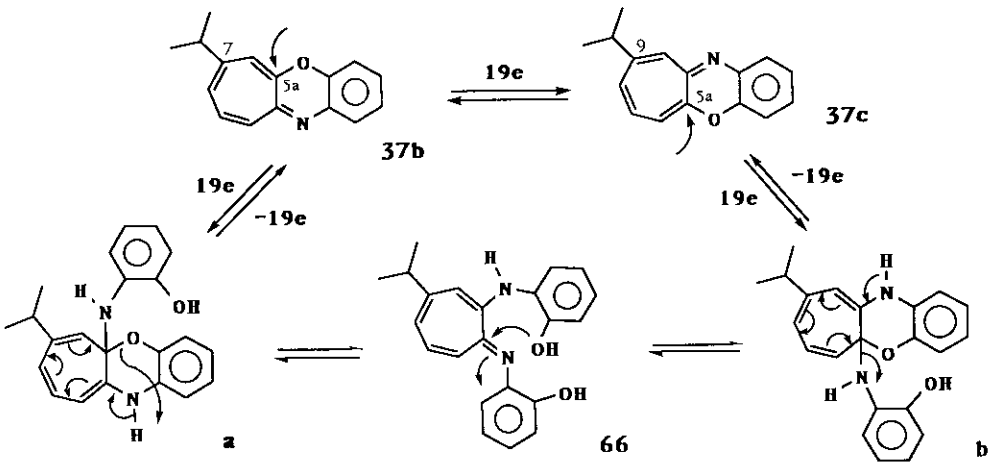
37a



65

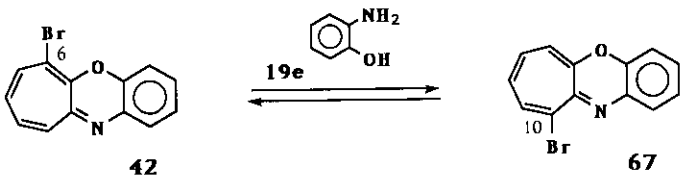
derivatives **37a-c** with **OAP** and **MeOAP** was chosen first, in order to avoid the complications caused by the bromine substitution reaction.[20a,24] When 8-isopropyl compound **37a** and **MeOAP** are dissolved in methanol and allowed to stand at room temperature, an additional peak due to methyl-containing product **65** gradually begins to appear in the hplc chromatogram and an equilibrium reaches within a few

hours. when the reaction of **37b** and **37c** with **OAP** is examined, a mixture of an equal amount of both compounds is always produced, even if either of the single compounds **37b** and **37c** is used as the starting material. From these pieces of evidence we concluded the reaction pathway involving the ring-opened 2-amino-troponeimine intermediate **66**, which is formed by the nucleophilic attack of the amino group of **OAP** at C-5a of **37b** or **37c** (Scheme 4).[24]



Scheme 4.

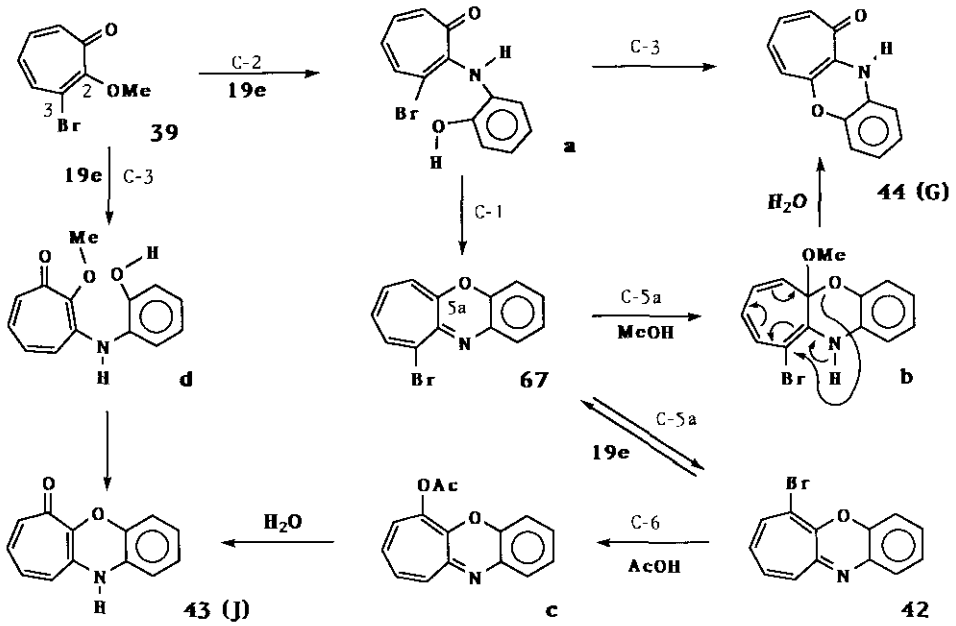
The reaction between 6-bromo compound **42** and **OAP** was then studied by the same method in methanol or in acetic acid. The ring exchange reaction proceeds surprisingly fast in methanol at 5 °C, giving the 10-bromo compound **67** in pure crystals. This confirmed our assumption of the heterocycle-exchange reaction (**42** → **67**),[20,24b]



2.4 Possible Pathways of the Reaction of 3-Bromo-2-methoxytropone and OAP.

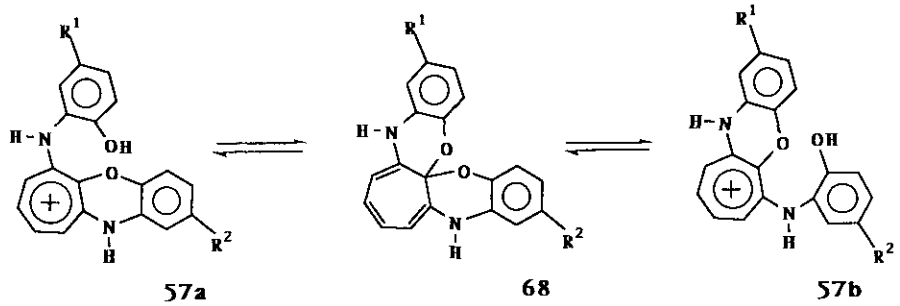
The possible pathways of the unusual reaction of **39** (and **42**) with **OAP** were then proposed.[20] As arylamines such as p-toluidine and p-methoxyaniline were confirmed to undergo substitution exclusively with C-2 methoxy group of **39**,[20] the most favorable, first intermediate of the reaction of **39** with **OAP** was considered to be 2-substituted intermediate **a**, which then gives either **44** (**G**) or 10-bromo compound

67 according to the site of the ring-closure of **b**. Compound **67** readily rearranges to **42** by the heterocyclic exchange reaction. Then these bromo compounds **67** and **42** have been proved to quantitatively give oxazolotropones **44** (**G**) and **43** (**J**), respectively, in hot acetic acid according to the pathways shown in Scheme 5.[25] 10-Bromo compound **67** is very reactive and quantitatively transformed into **44** on standing in methanol overnight at room temperature. Several competing pathways usually exist in these area. Meanwhile, Sasakawa et al. obtained C-3 substituted compound besides ciné-substituted compound at C-7 by the reaction of **39** with morpholine.[26] Therefore, the formation of **43** via intermediate **d** (substitution at C-3) may also be possible (Scheme 5).



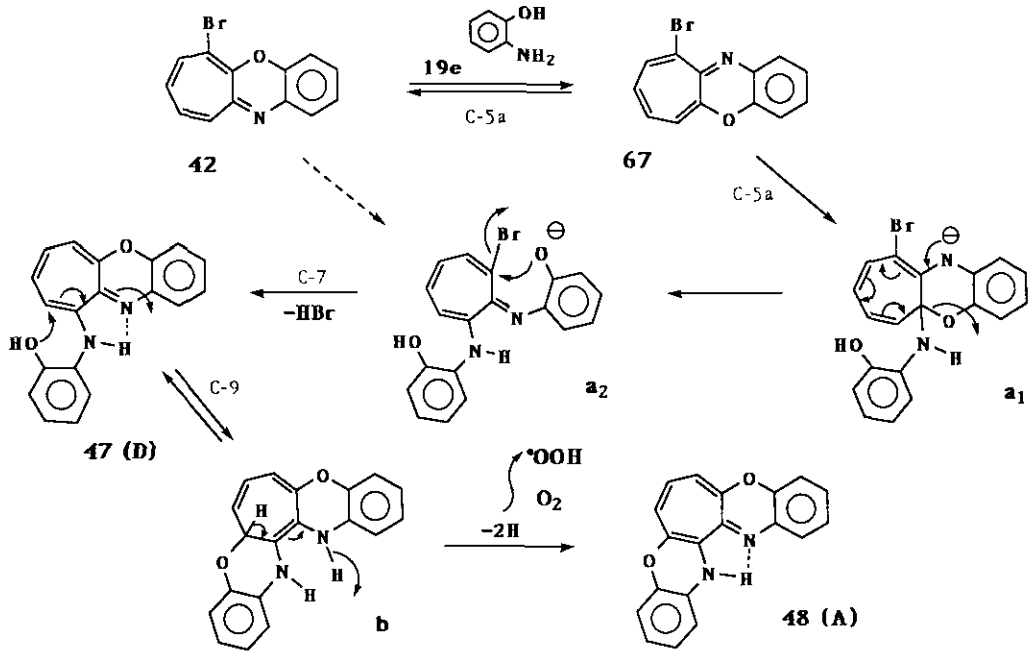
Scheme 5.

The possible reaction pathways for the formation of a variety of 1:2-condensation products were then disclosed by the discovery of the heterocycle-exchange reaction. Compound **49** or **57** (**L**) is a normal substitution product, and through the heterocyclic exchange reaction, a dynamic equilibrium is assumed to exist between **57a** and **57b**. Upon basification or on alumina column, unstable ring-closed intermediate **68** was easily autoxidized to give **50** (**F**) or **54** (Scheme 6).[20] As for the reaction path from **42** to **47** (**D**), our experimental facts[20] as well as theoretical calculation[27] pointed out that C-5a of the benzo[*b*]tropoxazine system



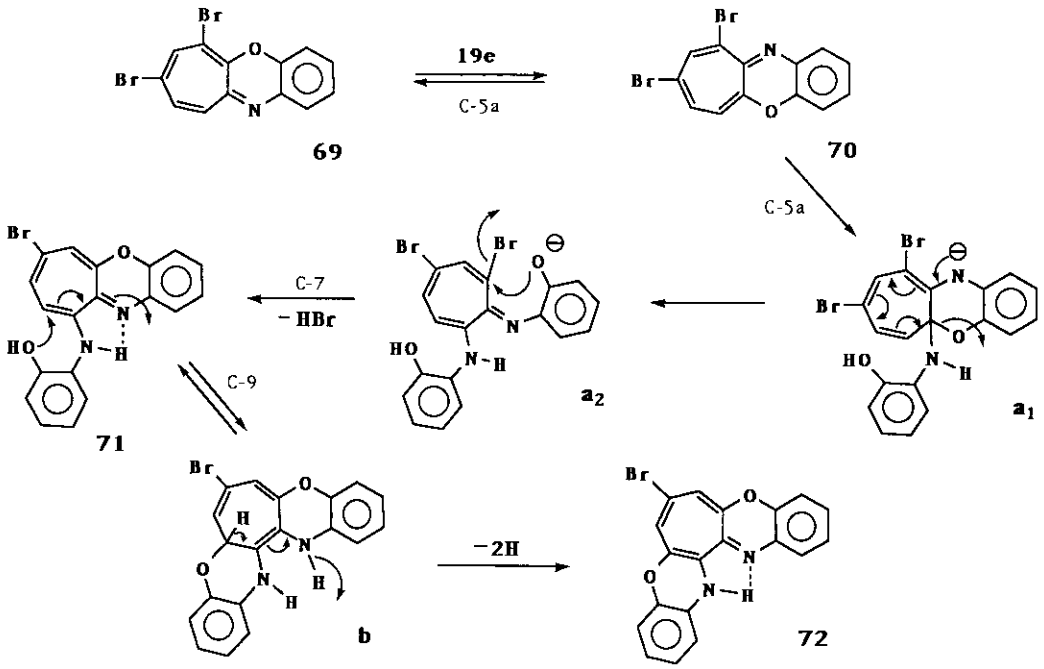
Scheme 6.

(11) is the most favored position for nucleophilic attack. Moreover, we found that 10-bromo compound **67** is far more reactive than 6-bromo isomer **42**.[20a,24b] Therefore we assume that the amino group of **OAP** first attacks C-5a of **67**, followed by ring-opening a_1 and then bromine substitution a_2 proceeds to give **47** (D).[20] This compound is readily transformed to **48** (A) by ring-closure at C-9 of **b**, followed by dehydrogenation (Scheme 7). Hydroperoxyl radical (HOO·) which is

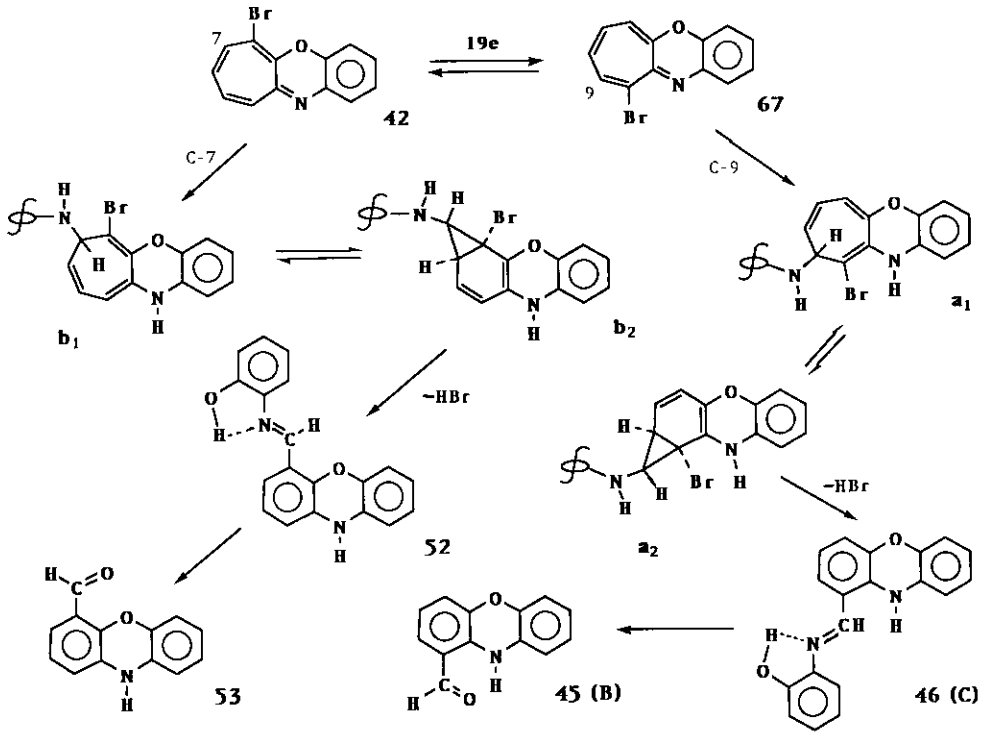


Scheme 7.

expected to be liberated during the autoxidation of **47**, oxidizes the reagent **OAP** to the dehydrodimer **51**. In consequence, **51** always accompanies as one of the product in the reaction of this series. This reaction pathway is supported by the fact that 6,8-dibromo compound **69** affords 7-bromo compound **71** and **72** through



Scheme 8.



Scheme 9.

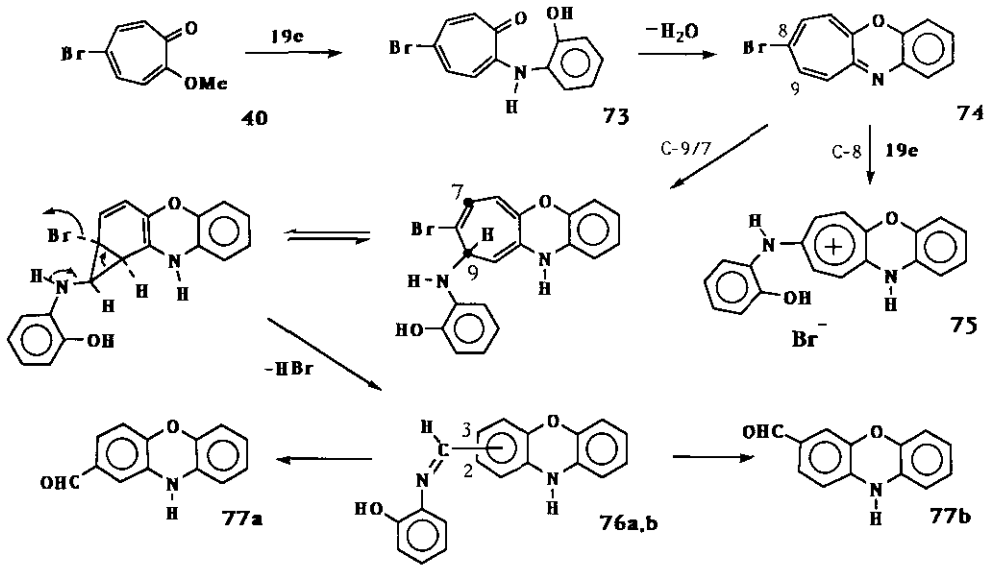
similar ways (Scheme 8).[28] This type of an unprecedented intramolecular heterocycle transposition on the 7-membered nucleus appears to be very common in this series, so we always had to be very careful to assign the structural formulas and the reaction pathways.

The formation of Schiff base **46** (C) is best explained by addition of **OAP** at C-9 of **67**, followed by ring contraction through a norcaradiene accompanied by the removal of HBr (Scheme 9).[28] If a strong base such as **DABCO** is added to the reaction mixture of **42** and **OAP** in methanol, a different kind of the Schiff base **52** is obtained, which is hydrolyzed to 4-formylphenoxazine (**53**). Note that the heterocycle-exchange reaction of **42** to **67** is strongly restricted under basic conditions (Scheme 9).

2.5 8-Bromocyclohepta[b][1,4]benzoxazine

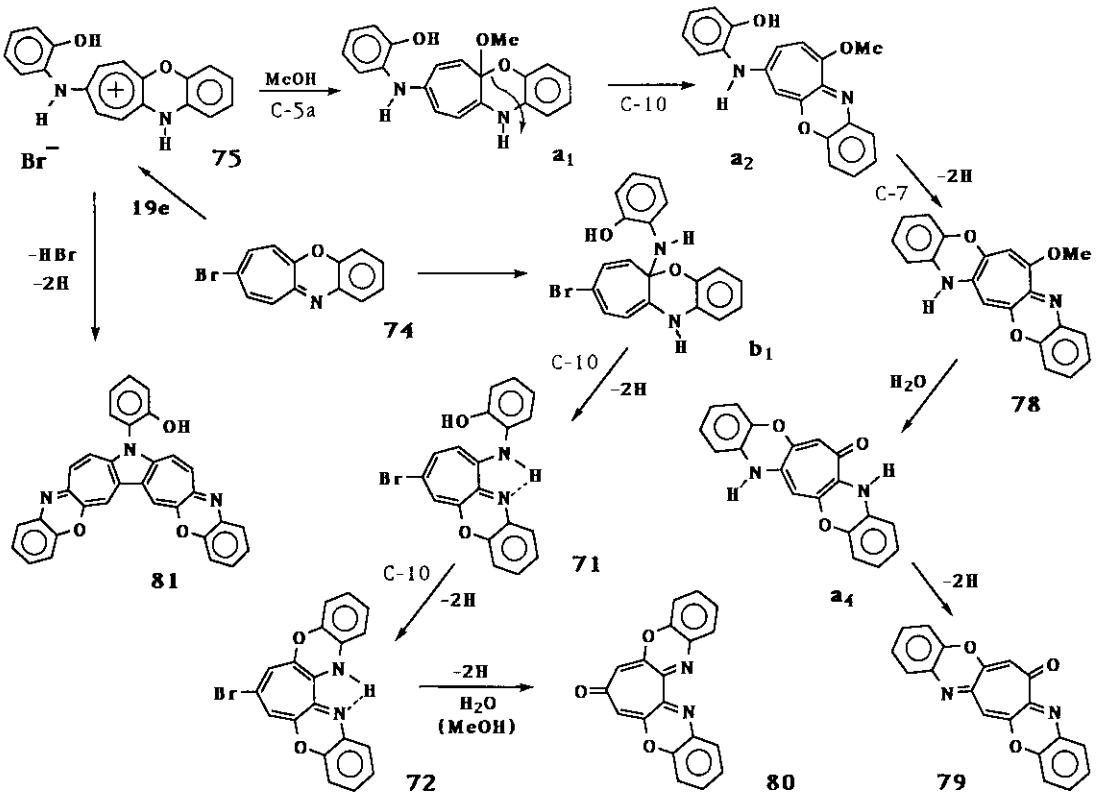
Although heterocycle-exchange reaction of 8-bromobenzo[b]tropoxazine (**74**), which is obtained from 5-bromo-2-methoxytropone (**40**) and **OAP** via **73**, do not give isomer by heterocyclic exchange reaction, the reaction of **40** with **OAP** is far more complex than those of **38** and **39**. Heating of **40** with two equivalents of **OAP** in acetic acid gives 10% each of **73** and **74**, and 70-80% of **75** as HBr salt. 2- (**77a**) and 3-formylphenoxazines (**77b**) are also produced (2% each)(Scheme 10).[28]

Various compounds such as tropoquinonoids **78**, **79**, and **80**, and dark violet pigment



Scheme 10.

81, among other products, were easily derived from 8-bromo compound **74** and **OAP** in methanol, by the repeated substitutions and cyclizations followed by dehydrogenation (Scheme 11).[28b] It is one of characteristic features of the compound in



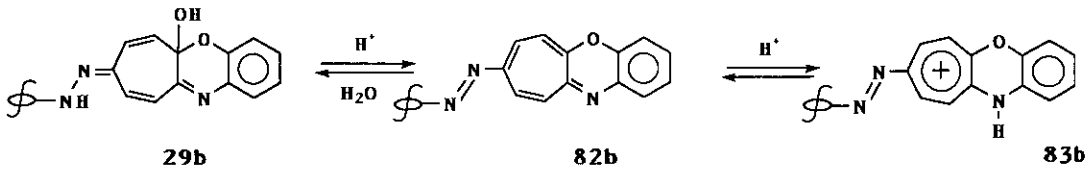
Scheme 11.

this system to give fully conjugated, quinonoid compounds. The dimeric compound **51** is always produced in such cases.

2.6 8-Arylazo and 8-Nitroso Derivatives

Earlier study[13] of the reaction between 5-nitroso- and 5-arylazotropolones (**20a,b**) and **OAP** (vide supra) was reinvestigated, and we found the ring-closed hemiacetals **29a,b** were obtained quantitatively, when an ethanolic solution of **20a,b** was refluxed with **OAP**.[29] When **29b** (ϕ = phenyl or p-tolyl) was left in acetic acid in the presence of a small amount of H_2SO_4, they underwent dehydration to give 8-arylazocyclohepta[b][1,4]benzoxazine (**82b**), and then formed the cation **83b** in the presence of strong acid (Scheme 12).

Cation **83b** is converted back to the hemiacetal **29b** in ethanol, even in the

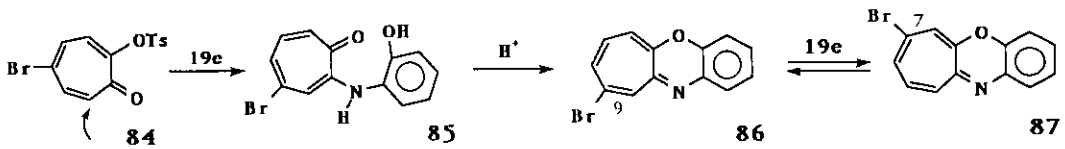


Scheme 12.

presence of a small amount of 2M hydrochloric acid, and hydrolyzed quantitatively by alkali into 5-arylazotropolone (**20b**) and **OAP**. 8-Nitroso compound **82a** (nitroso analogue of **82b**) was not obtained in a pure form, but hydrolyzed into 5-nitroso-tropolone (**20a**) and **OAP**.

2.7 Oxazinotropones and Tautomerism

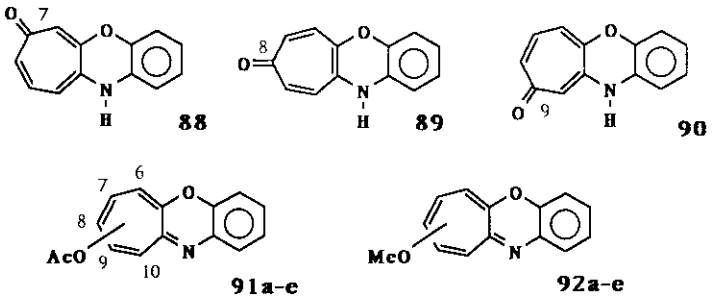
Various bromo derivatives of cyclohepta[b][1,4]benzoxazine (**34**) are obtained by direct bromination of **34**, or by the reaction of appropriate bromo-2-methoxy-tropones with **OAP** via anilino-bromotropones[25] (e.g. **33**). When the ring closure of o-anilino-bromotropones is carried out, care must be taken because the complex intermolecular shift of bromine atom by the disprotionation concurrently occurs especially when a too much quantity of conc. H_2SO_4 is used in aerial conditions.[30] The 7- and 9-bromo derivatives (**86** and **87**), which are not available by direct bromination of **34**, can be produced using ciné-substitution of the tosylate **84**, followed by ring-closure and heterocyclic exchange reaction with **OAP** as shown in Scheme 13.[25]



Scheme 13.

All possible isomeric bromo compounds **34**, **67**, **74**, **86**, and **87** can be led to the corresponding isomeric tropones (**43**, **44**, and **88-90**) via acetoxy compounds **91a-e**. Most of tropones (except **44**) exist as keto forms, but give methyl ethers **92a-d** with diazomethane in ether; **44** does not react with diazomethane or acetic anhydride in the presence of a trace amount of conc. H_2SO_4 due to its strong intramolecular H-bonding.

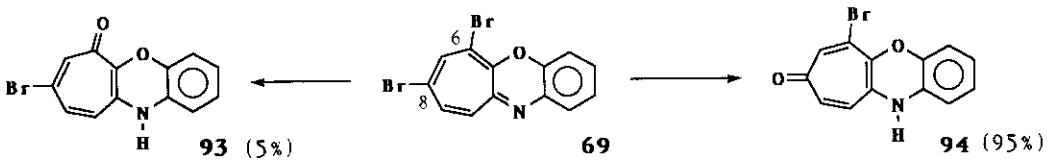
Similarly, 6,8-dibromotropone derivative **69** affords isomeric bromotropones **93** and



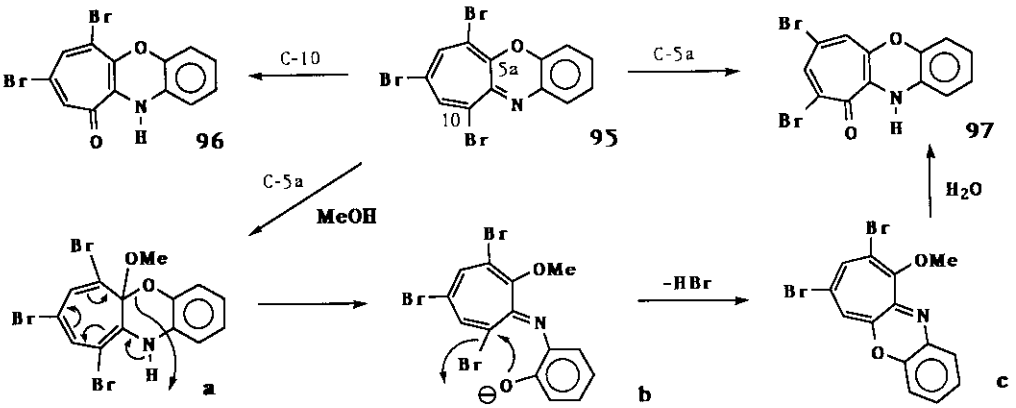
91, 92	Fometional group at
a	C-6
b	C-7
c	C-8
d	C-9
e	C-10

Chart 2.

room temperature dibromo tropones **96** and **97**, both of which unexpectedlly give the same tropone **44** by zinc dust reduction in acetic acid.



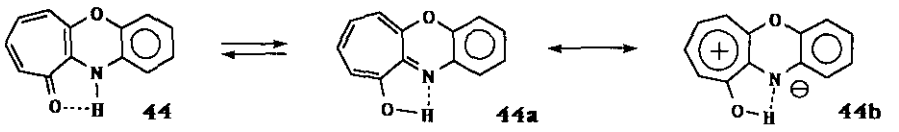
Possible pathways for the formation of **97** by ring-transposition followed by hydrolysis are shown in Scheme 14.[25]



Scheme 14.

Tautomerism of these tropones has been studied by spectroscopy and by theoretical calculations. The resonance energies and the heat of formation are calculated by means of HMO and molecular geometry by MINDO/3 optimizations. In all cases, except **44**, the MINDO/3-optimized geometries are planar and exhibit appreciable bond alternation and preference of the keto forms. Compound **44**, which shows considerable different properties compared with its isomers, is believed to be

considerable different properties compared with its isomers, is believed to be stabilized by the intramolecular H-bonded structure **44a**, and its remarkable bathochromic shift of the electron spectra is due to the 6π-benzenoid-6π-tropylium charge transfer form **44b**.[25]

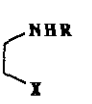


3. CYCLOHEPTA[b][1,4]BENZOTHIAZINES AND THEIR N-ANALOGUES

3.1 The Heterocycle-Exchange Reactions with OAT and OPD

The above-mentioned heterocycle-exchange reaction of **34** can be extended by using o-aminobenzenethiol (**OAT**) and o-phenylenediamine (**OPD**) and its N-methyl derivatives (**19a-c**) and aliphatic 1,2-bifunctional reagents **98a-d**.[31]

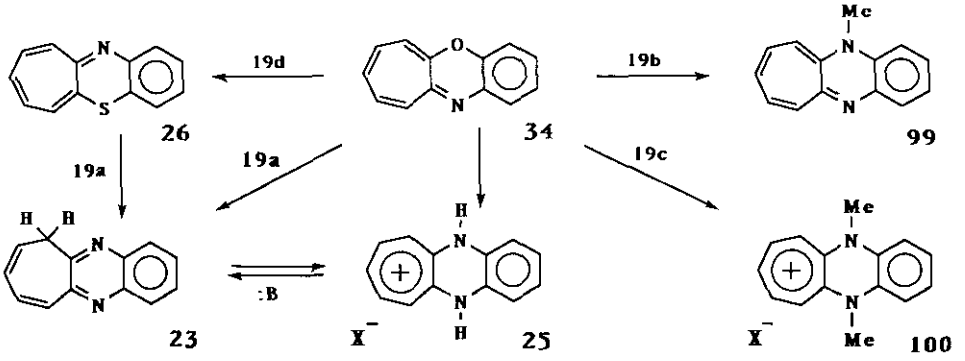
Treatment of **34** with an excess of **OAT** in methanol at room temperature gives cyclohepta[b][1,4]benzothiazine (**26**) in high yield. Similarly, both **34** and **26**[31b]



98a-d

	X	R
98a	NH_2	H
98b	NH_2	Me
98c	SH	H
98d	OH	H

can be led to quinoxaline **23** by the reaction of **OPD**.[31] Conversion of **34** to N-methyl derivative **99** and N,N'-dimethyl cation **100** is also possible by the heterocycle exchange with N-monomethyl- and N,N'-dimethyl-**OPD**s (**19b,c**), respectively (Scheme 15). The reverse reaction of **23** and **26** to **34** did not take place

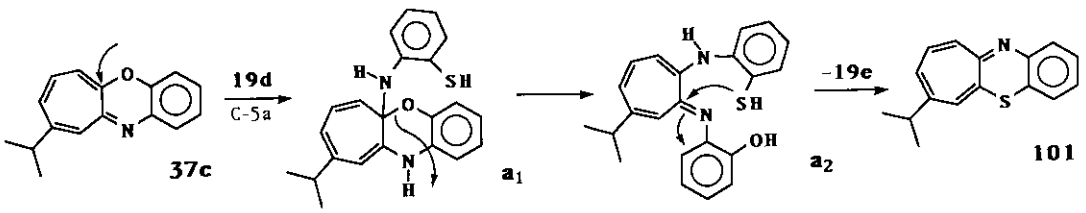


Scheme 15.

apparently because of the less favorable nucleophilicity of **OAP**.

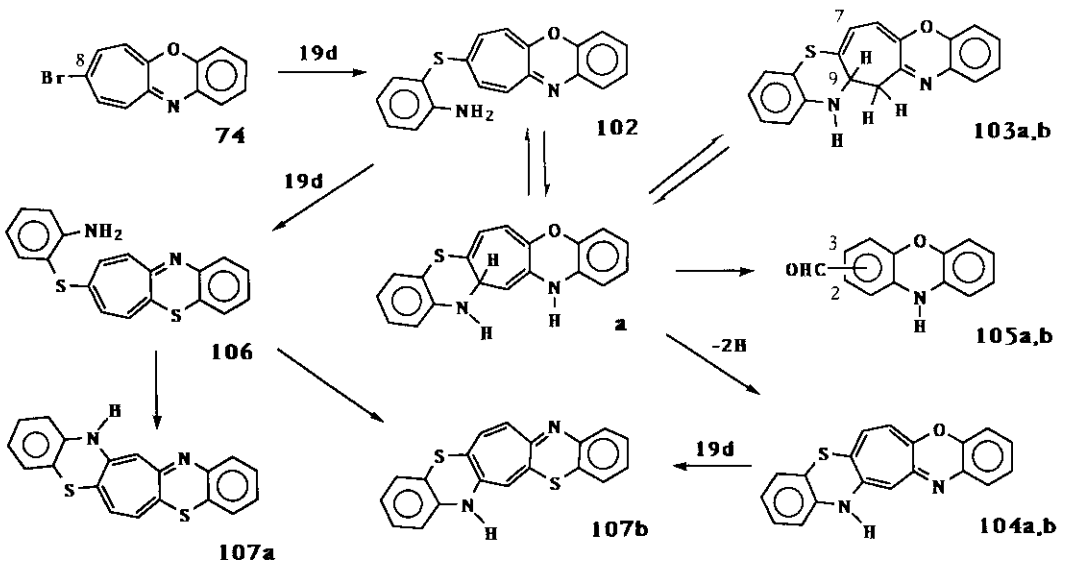
It is very interesting to note that not only the cation **100** and the previously mentioned Fukunaga's cation **25a**, but also the free N-methyl compound **99** has almost the same deep green color and very similar absorption curves.[32]

9-Isopropylcyclohepta[b][1,4]benzoxazine (**37c**) and **OAT** give thiazine analogue **101** which does not isomerize anymore with **OAT**[31] (Scheme 16).



Scheme 16.

More examples of facile hetero-ring close and/or heterocycle-exchange reactions of 8-bromo compound **74** with **OAT** are shown in Scheme 17. The S-substituted compound **102** is exclusively produced from **74** and **OAT** in methanol in one minute at room temperature. Surprisingly, this compound **102** gradually changes in methanol containing **OAT** at room temperature to a mixture of about 10 compounds, consisting of the ring-closed products at C-7 and C-9 (**103a,b**), dehydrogenated pigments (**104a,b**) and even their S-oxides, 2- and 3-formylphenoxazines (**105a,b**), which are

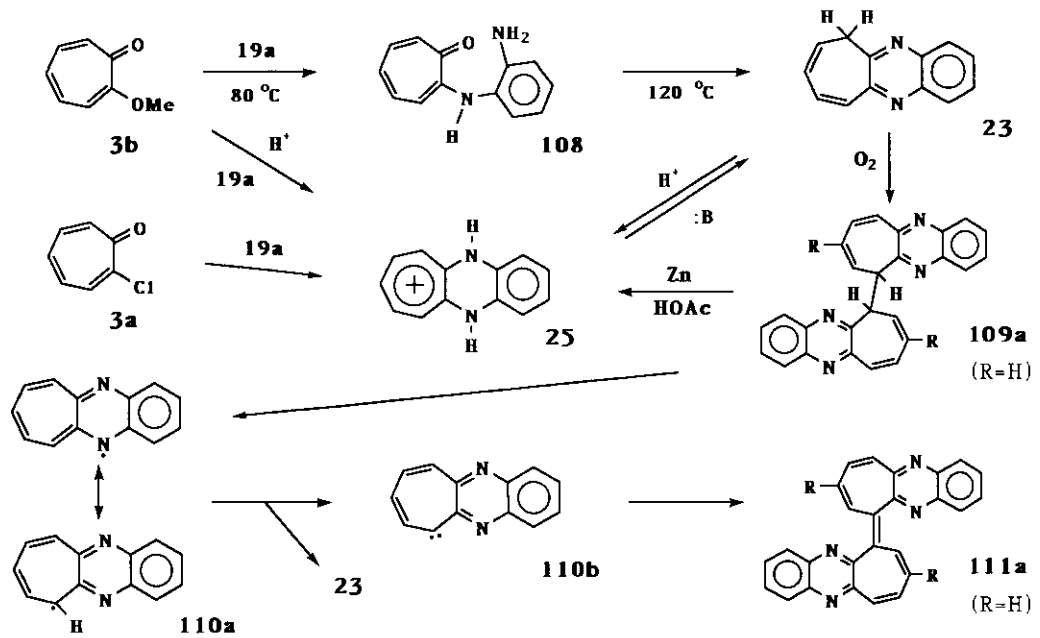


Scheme 17.

produced by saponification of the rearranged products (Schiff bases) from the intermediate **a** via its norcaradiene form. Heterocycle-exchanged products **106** and their dehydrocyclized products **107a,b** are also produced by the reactions of **102** with another molecule of **OAT**. Compounds **107a,b**, having two annulated benzothiazine rings are also derived from **104a,b** and **OAT** by the hetero-ring exchange reaction, or directly from **106** by the ring-closure at C-7 and C-9 followed by dehydrogenation (Scheme 17).[31b]

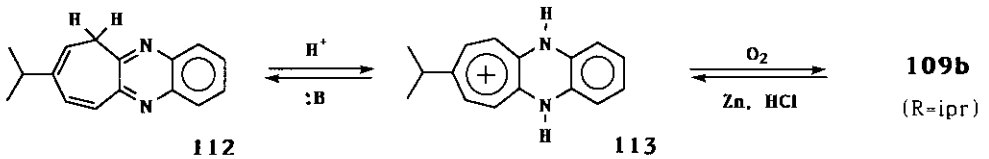
3.2 Reinvestigation of the Reaction of Reactive Troponoids and OPD

Since the Fukunaga's result described in Section 1.2 was not published yet, we have reinvestigated[32] the reaction of reactive troponoids (**3a,b**) with **19a** (OPD) as shown in Scheme 18. Heating of an ethanolic solution of **3b** (X = OMe) with OPD in a sealed tube at 80 °C and 120 °C gives 2-(o-aminoanilino)tropone (**108**) and quinoxaline (**23**), respectively in high yields. If **3a** (X = Cl) or **3b** is reacted under acidic conditions, the dark green salt of the cation **25** is directly obtained. Compound **23** is easily oxidized in air, especially under basic conditions, giving the dimeric compound **109a**. We obtained white crystals by alumina chromatography of **23**, which turned out to be the autoxidized dimer **109a**



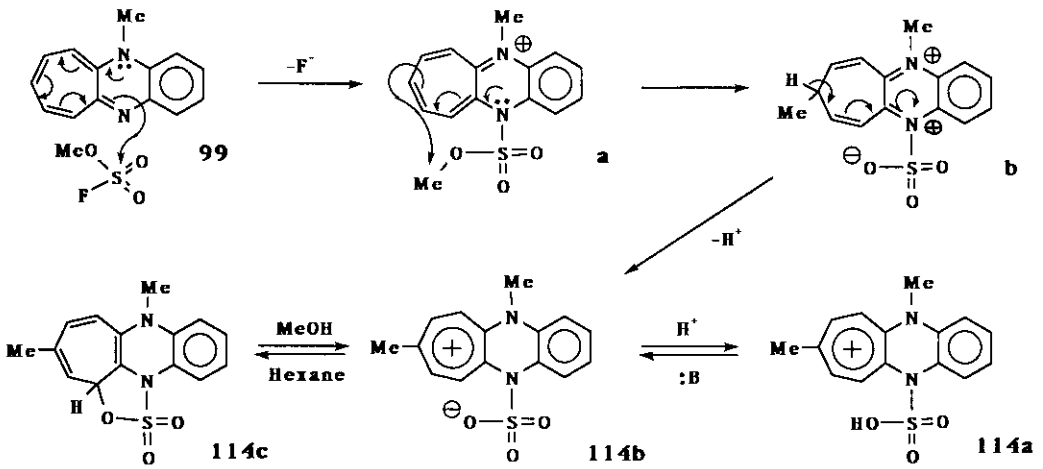
Scheme 18.

(R = H) as suspected earlier by Fukunaga;[11] the structure of **109a** has now been determined by nmr spectral data. Reduction of **109a** with zinc dust in acetic acid reproduces the cation **25** quantitatively. Heating of **109a** at 220 °C under vacuum gives **23** and a reddish brown substance, the latter being presumed to be a fulvalene **111a** (R = H) on the basis of mass spectroscopy and uv spectrum: carbene **110b** formed by disproportionation of radical **110a** is suggested as the most likely intermediate to give **111a** (Scheme 18). To make sure the characteristics of the cyclohepta[b]quinoxaline system, we have also studied the isopropyl derivatives **112**, **113** and dimer **109b**, and the physicochemical properties of these compounds are quite similar to those of their parent compounds.[32]



Electronic structures of the cations **25**, **26a**, and **34a**, as well as **99** and **100** have been established on the basis of spectral data,[33] which indicate that these cations have a similar 6π-benzenoid-6π-tropylium π-electron system. 16π-peripheral system (**25a**)[11] considered by Fukunaga should be considered as 25. The deep color of these cations is assumed due to the intramolecular charge transfer.[34]

A little later Mukai et al.[35] also obtained the cation **100** (as iodide salt) by



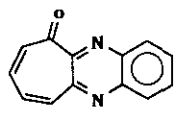
Scheme 19.

methylation of **99** with methyl iodide. On the contrary, our attempted methylation of **99** with magic methyl surprisingly afforded green needles **114a** having molecular composition of $C_{15}H_{14}N_2O_3S$. This compound exhibits the same visible absorptions (at 616, 676, and 680 nm) as those of **100** in methanol. In hexane the longest-wavelength absorption becomes at 434 nm (**114c**) but its green color is recovered in methanol (**114b**) or by adding a slight amount of acid (**114a**).

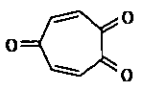
Detailed examination of spectral data has confirmed that **114** takes different structures (**114a-c**) according to the solvent system employed. Although the mechanism of this unusual reaction has not been clarified yet, one of the possible pathways is shown in Scheme 19.[32]

3.3 Quinoxalotropones having two Tropone Rings

After our earlier study of quinoxalotropone (**22**) and quinoxalohinopurpurins **18**, Itô and his coworkers[36] obtained **22** and its isomer **115** by the reaction of p- and o-tropoquinones (**116** and **117**) with OPD, while Asao[37] obtained tricyclic ditropone



115



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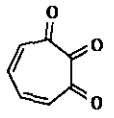

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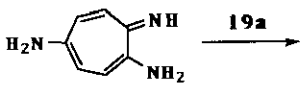

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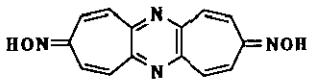

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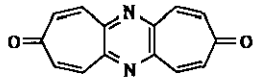
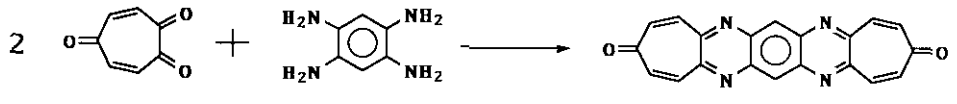


120

120 from 2,5-diaminotroponeimine and nitrosotropone (**20**) as shown above. More recently, Takeshita et al.[38] synthesized pentacyclic ditropone **121** from **116** and tetraaminobenzene (**121**).



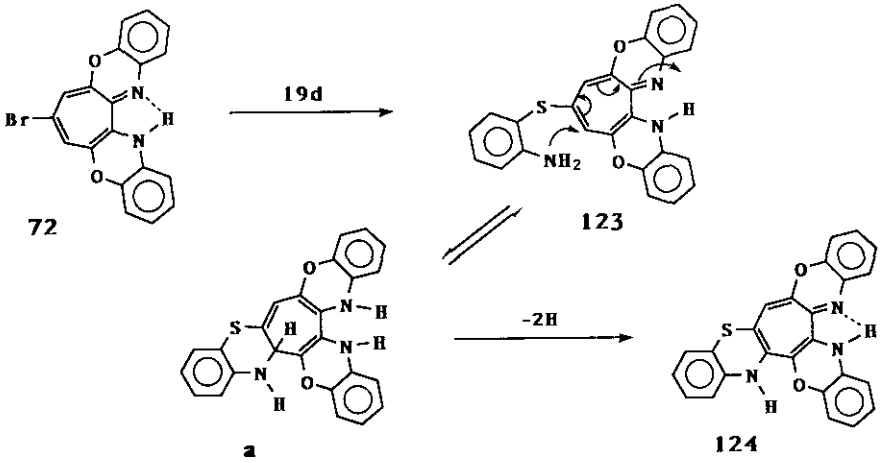
116 **121** **122**

3.4 Polyannulated Systems

We have then tried to synthesize tropylium compounds having triannulated heterocycles and found further examples of interesting transposition of heterocyclic

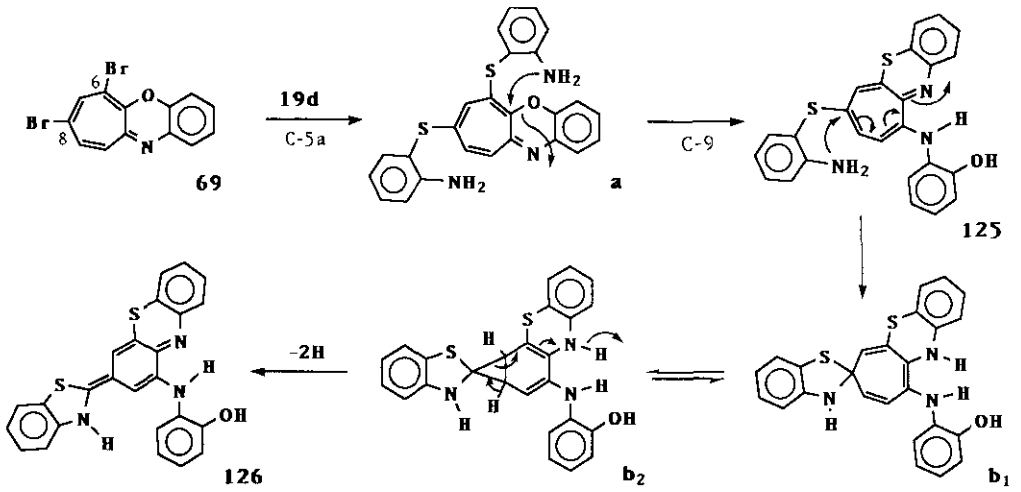
ring on the seven-membered nucleus as well as some rearrangement reactions to o- and p-benzoquinonoid compounds during the attempted synthesis. Some examples are shown in the following Schemes.

Symmetrical bromo compound **72** does not react with **OAP**, because the ring system is highly stabilized by the intramolecular H-bonding. However, when **72** and **OAT** are allowed to stand overnight at room temperature, S-substitution compound **123** is obtained in a high yield. This compound is then cyclodehydrogenated in acetic acid by anodic oxidation, giving the reddish violet, triannulated compound **124**[39] (Scheme 20).



Scheme 20.

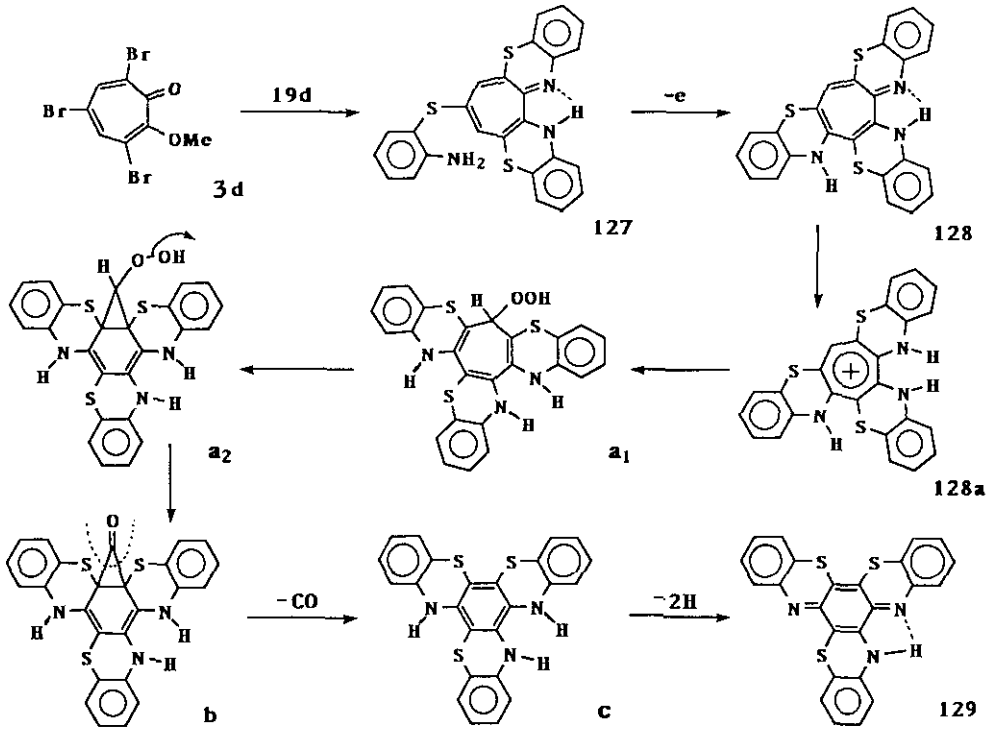
Reaction of **69** with an excess of **OAT** in methanol-chloroform at room temperature



Scheme 21.

for 1 day gives red needles **125** via di-S-substituted intermediate **a** followed by the ring conversion as shown in Scheme 21. An attempt at ring-closure of **125** by anodic oxidation causes ring contraction to give p-benzoquinone-diimide **126** as brownish yellow crystals. Possible pathways for this rearrangement are considered to proceed via spiro intermediate $\mathbf{b}_1$ and its norcaradiene form $\mathbf{b}_2$, followed by the oxidative H-abstraction (Scheme 21).[39]

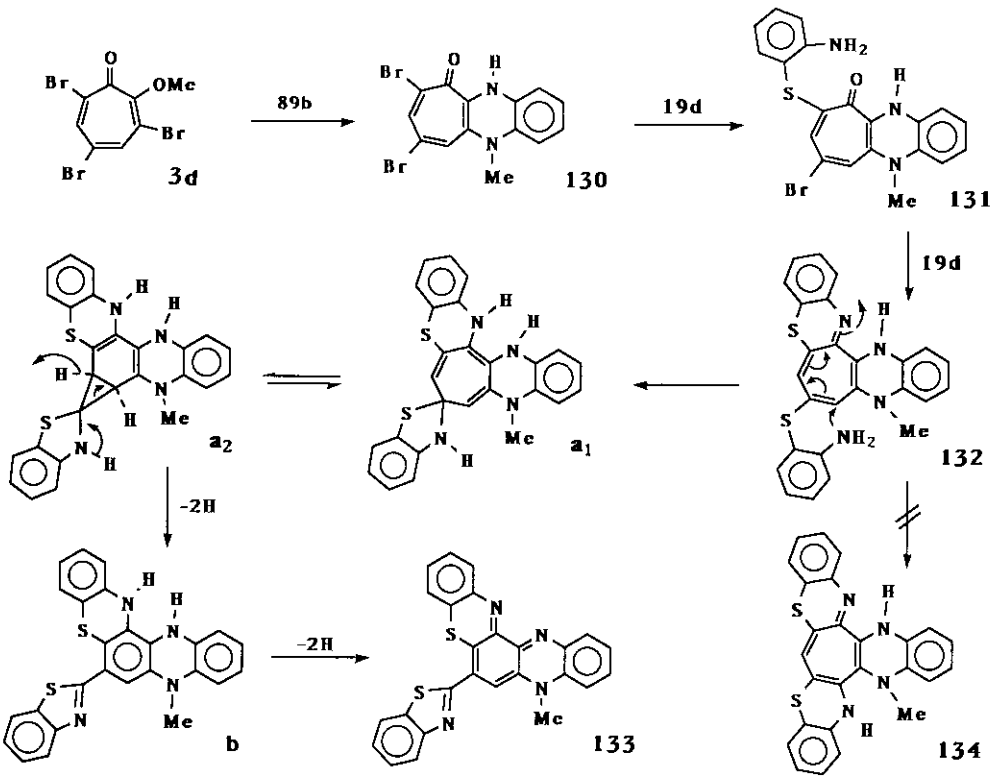
We have then tried to synthesize tropylium compound **128** having triannulated benzothiazine rings. Namely, treatment of 3,5,7-tribromo-2-methoxytropone (**3d**) with an excess of **OAT** at room temperature gives **127**, which with **DDQ** in acetic acid changes to blue violet crystals **129** having one-cabon-less p-benzoquinonoid structure. However, the desired compound **128** can be prepared by electro-chemical oxidation of **127**. Red crystals **128** is easily converted via deep green colored cation **128a** in air or with **DDQ** in acetic acid into **129**, presumably via hydroperoxide $\mathbf{a}_1$ and its norcaradiene form $\mathbf{a}_2$ followed by decarbonylation and dehydrogenation[39] (Scheme 22).



Scheme 22.

Treatment of **3d** with N-methyl-OPD (**19b**) gives dibromo compound **130** (68%), which

in turn condenses with **OAT** in chloroform to give the mono-S-substituted compound **131** (86%). When a mixture of **131** and **OAT** is heated at 100 °C in a sealed tube or further kept standing at room temperature for a day, a rearranged product **133** having o-benzoquinonediimine structure is obtained, instead of the expected triannulated tropylium compound **134**. The rearranged product **133** is presumed to be produced from **132** via spiro intermediates (a_1, a_2) followed by dehydrogenation as shown in Scheme 23.



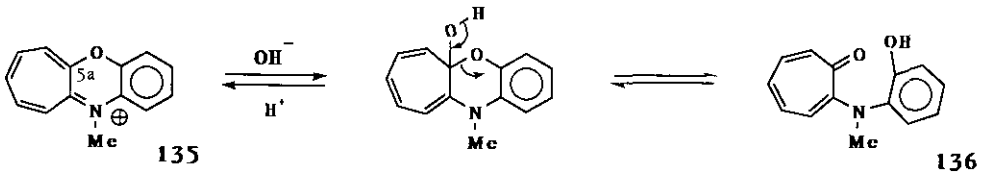
Scheme 23.

4. COMPARISON OF THE REACTIVITY TO NUCLEOPHILES

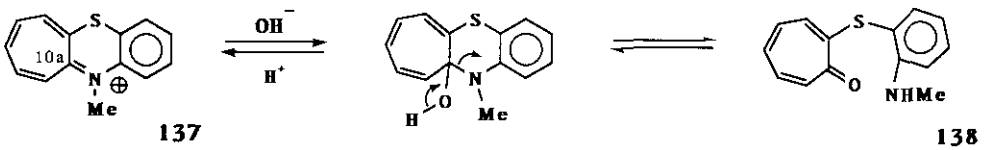
Comparative study on the reactivity of cyclohepta[b][1,4]benzoxazine (**34**) and its S- (**26**) and N-analogues (**99**) and their N-methylated cations (**135**, **137**, and **100**) to nucleophiles, such as water, alkali, hydrogenperoxide, and m-chloroperbenzoic acid (**MCPBA**), was made as follows.

4.1 Reactions with Alkali (and Water)

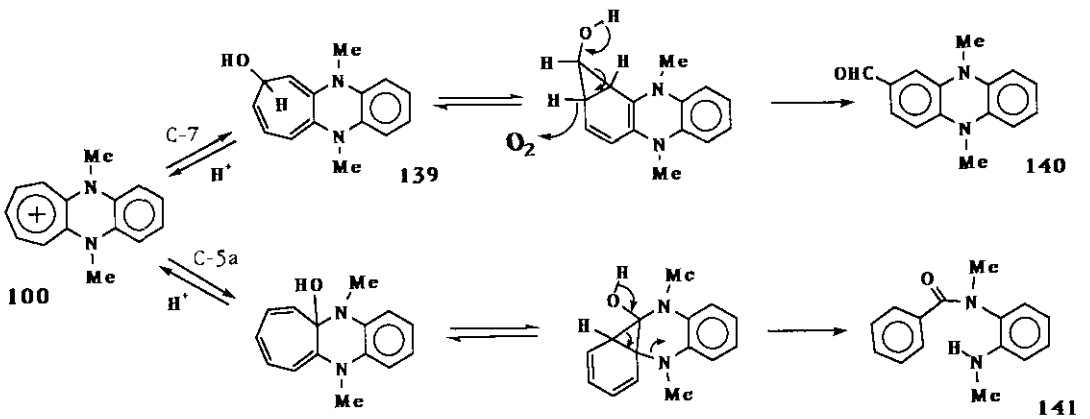
As mentioned earlier, facile ring opening by alkali and ring-closure by acid is one of the characteristic features of cyclohepta[b][1,4]benzoxazine system; treatment with an excess of warm alkali results in complete saponification to tropolone and **OAP**. N-Methyl cation **135** is readily saponified to aminotropone **136**, even with water at room temperature, by the attack of water (hydroxide ion) as a nucleophile at C-5a.



Although its S-analogue **26** is stable to warm alkali, N-methyl cation **137** is saponified with cold alkali to give 2-(o-methylaminophenyl)thiotropone (**138**) by an attack of OH^- at C-10a.[32,40]



On the contrary, N-methyl compound **99** is quite stable to warm alkali, whereas the N,N'-dimethyl cation **100** gives colorless conjugate base **139**, but is restored to **100** upon acidification. When a methanolic solution of **100** is allowed to stand at

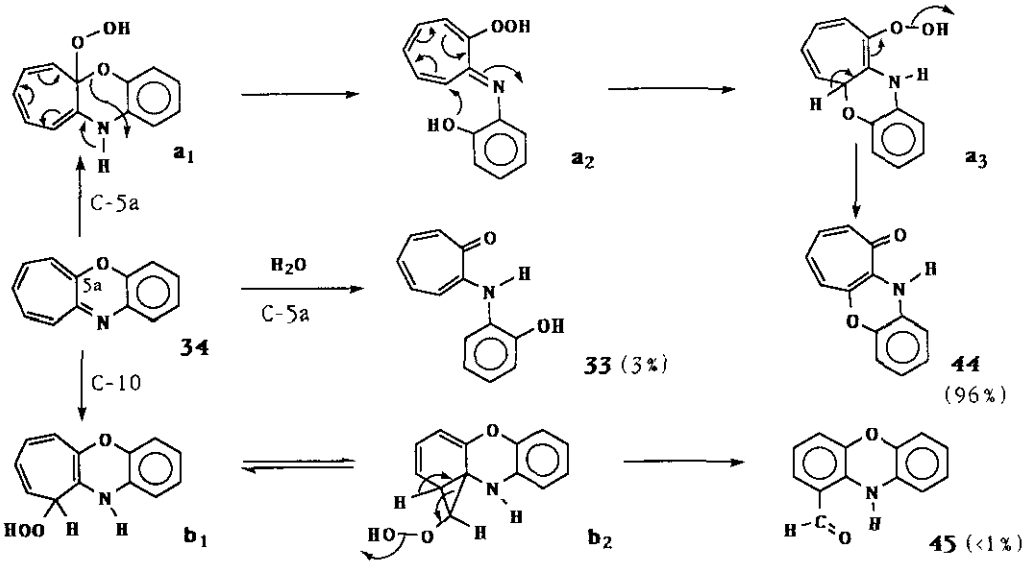


Scheme 24.

room temperature overnight, various products are formed (accompanied by autoxidation), from which dimethylphenazinecarbaldehyde (**140**, 6.5%) and benzamide **141** (11%) are isolated. Possible pathways for the reaction are shown in Scheme 24. In concentrated methanolic alkali, **100** rearranges to benzamide **141** in 98% yield.[32] As mentioned before cyclohepta[b]quinoxaline (**23**) is quite unstable under alkaline conditions and easily gives dehydro dimer **109a**.[32]

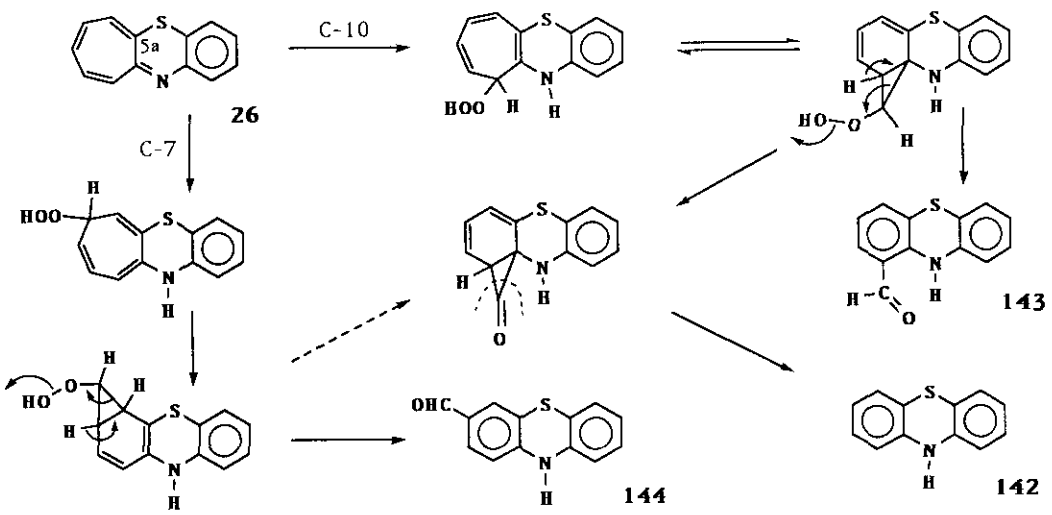
4.2 Reactions with Hydrogenperoxide

The reactions of cyclohepta[b][1,4]benzoxazine (**34**) and its S- and N-analogues with H_2O_2 have been examined for a comparison of the effect of the hetero atoms. Treatment of **34** with H_2O_2 in methanol at room temperature gives almost exclusively oxazinotropone **44**, besides a trace amount of rearranged **45** and some ring-opened **33**, as shown in Scheme 25.[32,40]



Scheme 25.

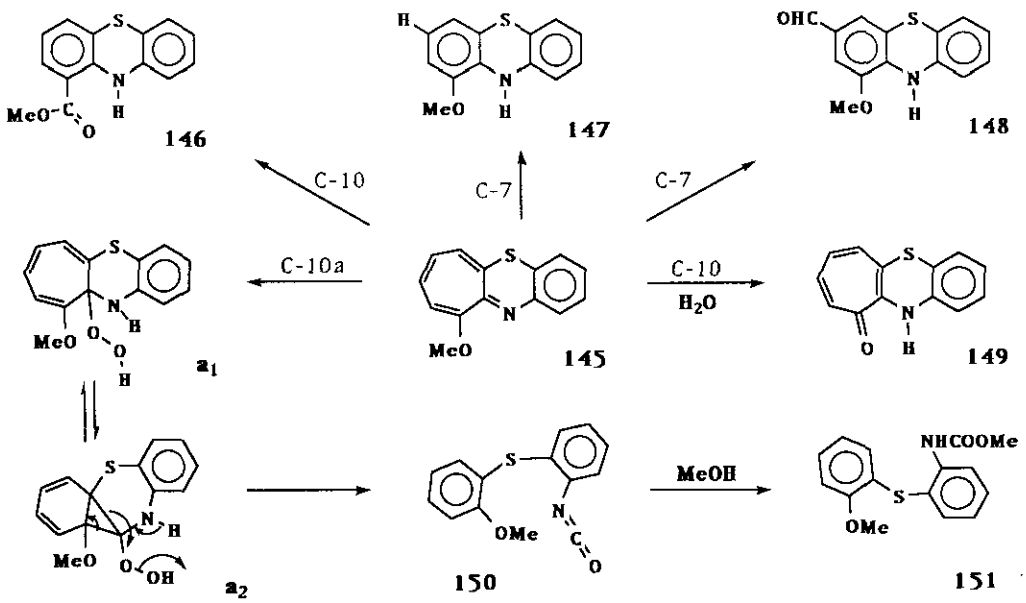
S-Analogue **26** reacts with H_2O_2 in methanol more slowly than **34**, producing many kinds of rearranged products, 10H-phenothiazine (**142**), its 1- and 3-formyl derivatives (**143, 144**), and their respective S-oxides and S-dioxides[40] (Scheme 26). Then, in order to confirm the sites of the peroxide attack on the seven-membered nucleus, compound **145** which bears a methoxyl group at C-10 has been studied as shown in Scheme 27.[40] All of these products bear a methoxyl group and afford their respective S-oxides and S-dioxides with excess reagent. **151** is assumed to



Scheme 26.

be formed through the C-10a attacked intermediates a_1 and a_2 and rearranged isocyanate **150**, while **149** is saponified product of **145** by the attack of water (in solvent methanol) at C-10.

On the other hand, oxidation of N-analogue **23** with H_2O_2 in acetic acid gives mainly the dehydro dimer **109a** and a small amount of **115**.[32]



Scheme 27.

4.3 Theoretical Calculations of Electronic Structures and Reactivities[41]

To obtain further informations about the above-mentioned very complex reactions, theoretical calculations[27] on the electronic structures and reactivities of cyclohepta[b][1,4]benzoxazines and their N- and S-analogues were carried out by means of HMO[42] and MNDO,[43] and compared with the experimental results.

The geometry optimizations were carried out with optimization of all geometrical parameters with no assumption whatsoever. In N-methylated compounds, the MNDO optimized geometries were significantly nonplanar, and some of those structures are shown in Chart 3 and Figure 1.

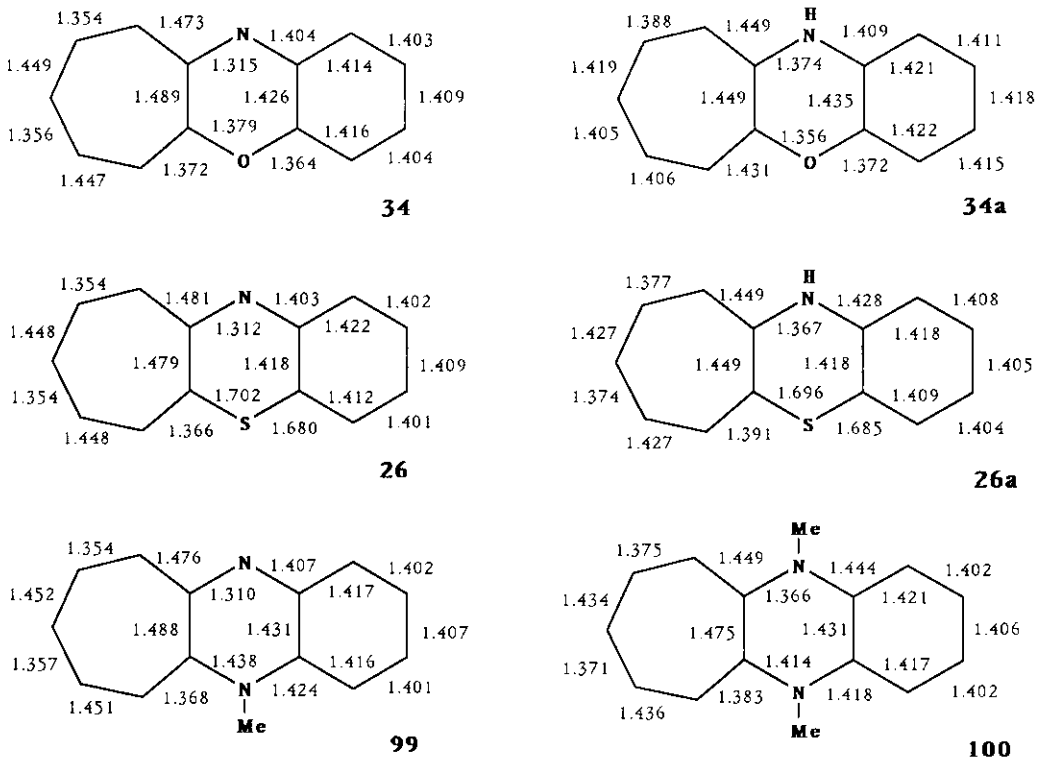


Chart 3. The optimized Geometries of **34**, **34a**, **26**, **26a**, **99**, and **100** calculated by using the MNDO. The units of bond lengths are in Angstrom.[27]

Table 1 lists the frontier electron density $f_r^{(-)}$[45] for nucleophilic reaction calculated by the HMO method.[42]

For **34**, **34a**, and **135**, the values of $f_r^{(-)}$ give the order of C-5a > C-10 > C-7.

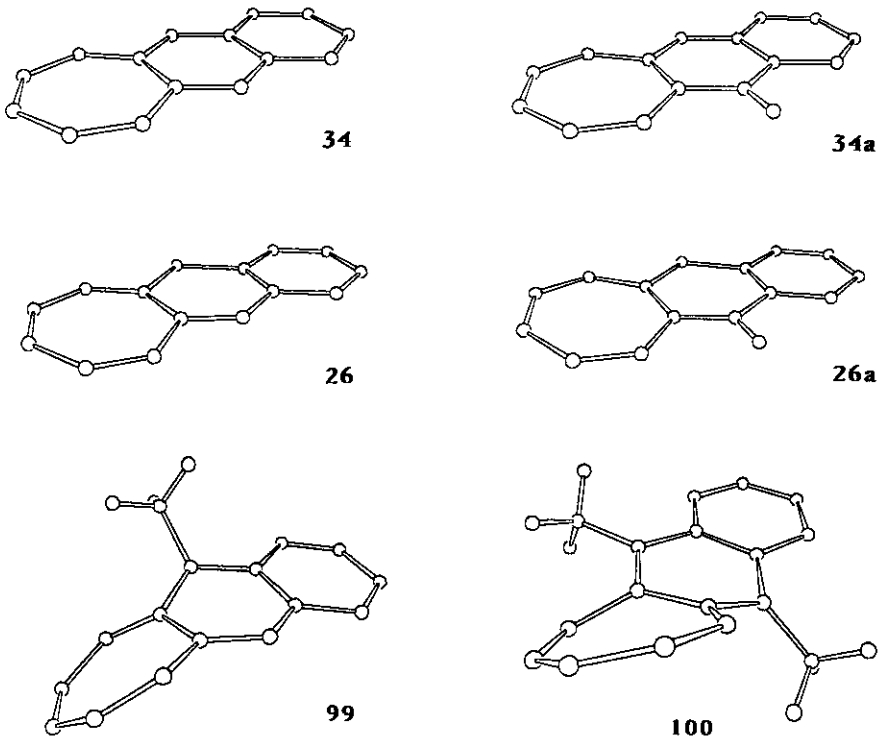


Figure 1. ORTEP[44] Plots of **34, 34a, 26, 26a, 99,** and **100.**[27]

The next LUMO (NLUMO) coefficient magnitudes of **34** and **135** are in the order of C-5a > C-7 > C-10. The predicted attacking sites of the nucleophile (alkali or

Table 1. Reactivity Indexes of Selected Compounds

Compd.	$f_r^{(-)}$		
34	C-5a (0.541)	C-10 (0.511)	C-7 (0.413)
26	C-5a (0.534)	C-10 (0.499)	C-7 (0.419)
145	C-5a (0.510)	C-10 (0.486)	C-7 (0.375)
34a	C-5a (0.550)	C-10 (0.502)	C-7 (0.239)
135	C-5a (0.552)	C-10 (0.529)	C-7 (0.414)
26a	C-5a (0.537)	C-10 (0.478)	C-7 (0.454)
137	C-5a (0.544)	C-10 (0.495)	C-7 (0.423)
100	C-7 (0.480)	C-5a (0.260)	

H_2O_2) agree with the experimental results.[27]

Compound **100** was attacked by the alkali at the position of C-5a or C-7 on experimental data.[32] The values of $f_r^{(-)}$ of **100** give the order of C-7 > C-5a. The NLUMO coefficient magnitudes of **100** are in the order of C-7 > C-5a. The predicted attacking sites also agree with the experimental results.

For **26**, **145**, and **137**, however, the $f_r^{(-)}$ magnitudes give the order of C-5a > C-10 > C-7. The predicted attacking site from the reactivity indexes such as LUMO coefficients and $f_r^{(-)}$ does not agree with the experimental results that showed the attack of H_2O_2 at the C-10 or C-7 position.[40]

CNDO/2[46] calculation which allows inclusion of 3d atomic orbitals of S atom was carried out using MNDO optimized geometries of **26** and **145**. The LUMO coefficient magnitudes of **26** are in the order of C-5a > C-7 > C-10, whereas those of **145** are C-10 > C-7 > C-5a.

In the case of O- and N-analogues, the position having the larger NLUMO coefficients suggests the preferred sites of attack by nucleophiles, whereas in the S-analogues the position having the larger LUMO coefficient (from the results of calculated CNDO/2 which allows to include **3d** atomic orbitals of S atom) suggests the preferred sites of attack by nucleophiles.

4.4 Reactions with MCPBA

Inspection of time-dependent hplc of the reaction of cyclohepta[b][1,4]benzothiazine (**26**) with **MCPBA** in chloroform indicates the rapid formation of many polar products at short retention time (6-10 min). These are presumed to be reversible Michael type addition compounds of **26** with **MCPBA**. Then stable products appear at less polar part (retention time 26-60 min). The products (with 2 equivalents of **MCPBA**) isolated are mainly thiazinotropone **149** and its S-mono- and S-dioxide **153** and **154**, and smaller amounts of 1:2-condensation products (**28** and **156-158**, besides unidentified resinous products) as shown in Chart 4.[47] This reaction proceeds very rapidly in chloroform at room temperature to afford 2-troponylaminophenylthio substitution (**157** and **158**) besides benzothiazino-annulation (**28** and **155**). A small amount of benzothiazinotropolone ester **156** is also produced. This unusual reaction may start via C-5a adduct by **MCPBA** followed by radical cleavage to benzoyl radical and troponylaminophenylthio radical **160**. The radical **160** in turn attacks various site in the seven-membered nucleus or

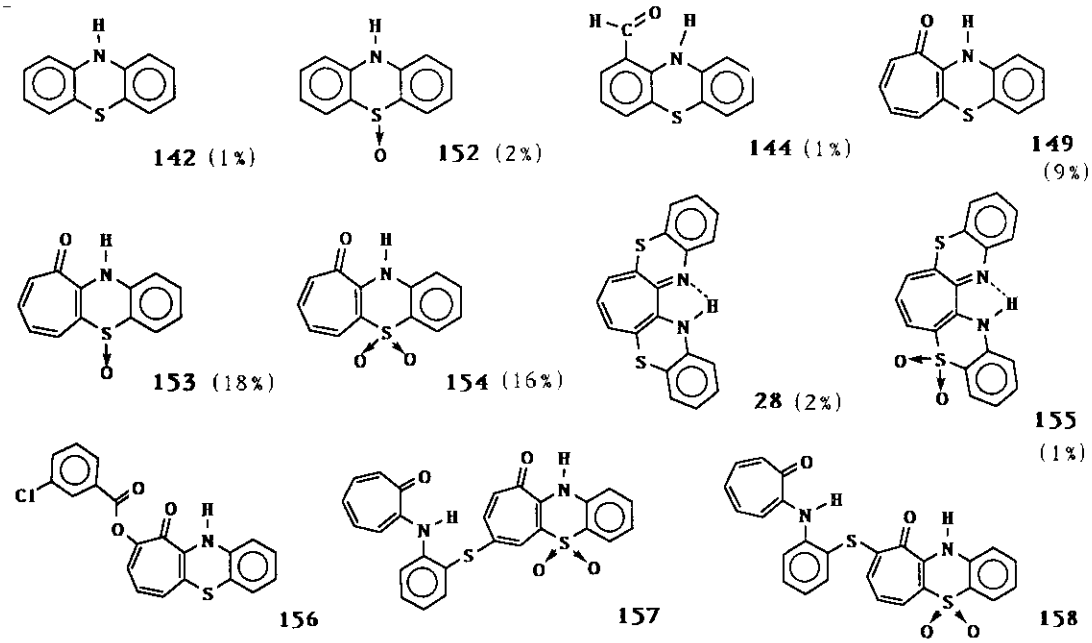
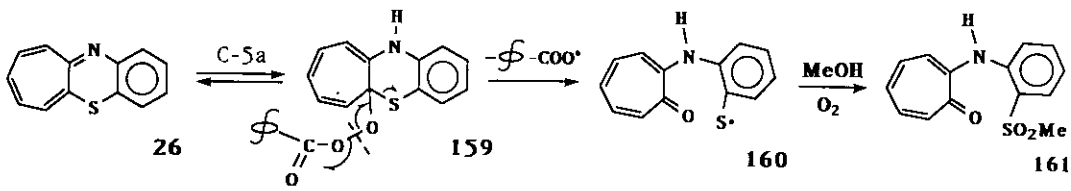


Chart 4.

close benzothiazino ring eliminating troponoid ring.

When this **MCPBA** oxidation is conducted in chloroform-methanol solution, more than 50% yield of the sulfinic methyl ester **161** are obtained besides **149** and its S-oxide, but the dimeric compounds **28** and **155-158** are not detectable in the reaction mixture.



4.5 Thermolysis of Compound 131

When a benzene or chloroform solution of **131** is heated at 100 °C for 20 hours, or an acetic acid solution of **131** is electrically oxidized, surprisingly many variety of compounds **162-170** are formed.[39,48] It should especially be noted that various benzothiazinotropones **165-170** are found among the products. Although the reasonable reaction pathways are difficult to postulate at present, we may be able to explain them in terms of exchange (substitution) reactions of the substrates

with H·, Br·, and OAT radical **171**, which may be produced under such conditions (Chart 5).

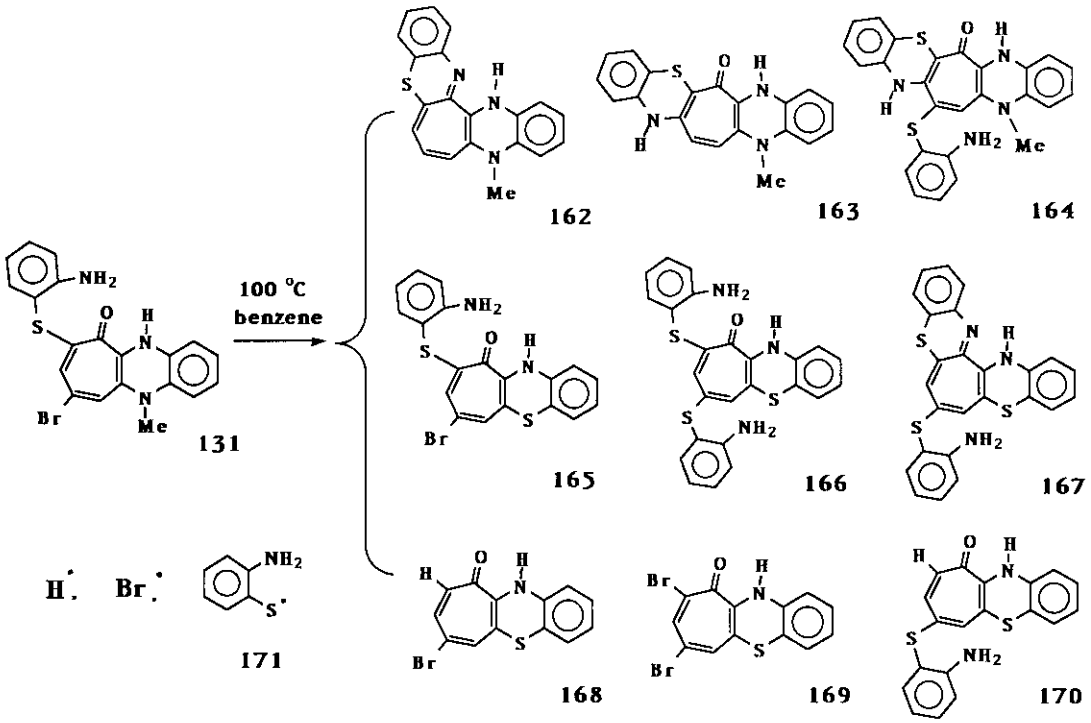
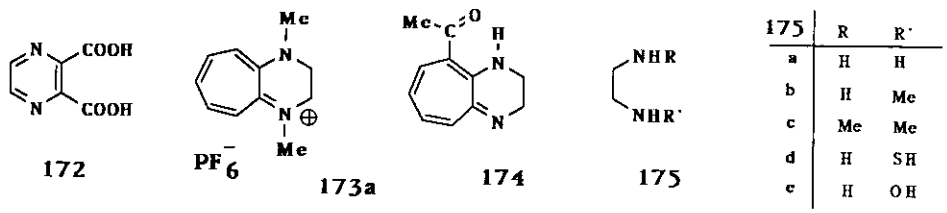


Chart 5.

5. 2,3-DIHYDRO-1H-CYCLOHEPTA[b]PYRAZINE AND ITS ANALOGUES

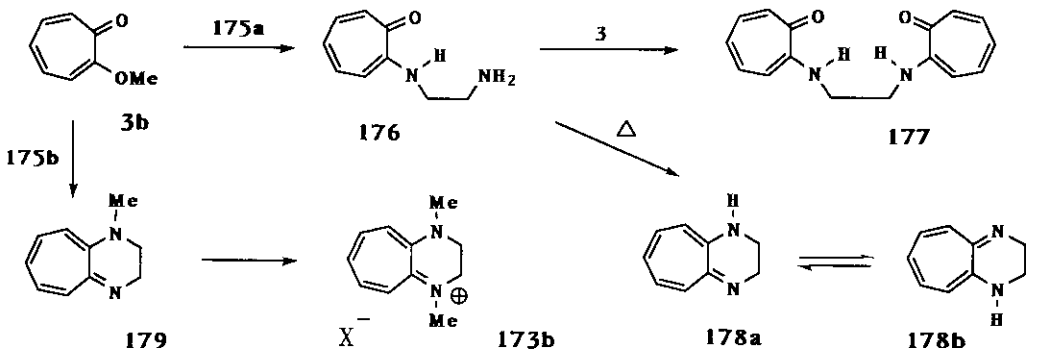
5.1 2,3-Dihydro-1H-cyclohepta[b]pyrazine

In relation to the noteworthy high reactivity of cyclohepta[b][1,4]benzoxazine and its S- and N-analogues, we were interested in the study of the heterocycles (**12** or **30**) without the annulated benzene ring. Structures for earlier-mentioned pyrazinotropone **31** and its parent compound **30** had been assigned by the formation of pyrazine-2,3-dicarboxylic acid (**172**) on $KMnO_4$ oxidation.[14] Without any convenient facilities like nmr at those time, we could not determine whether their heterocyclic ring had pyrazine or dihydropyrazine structure. Later, Wilson et



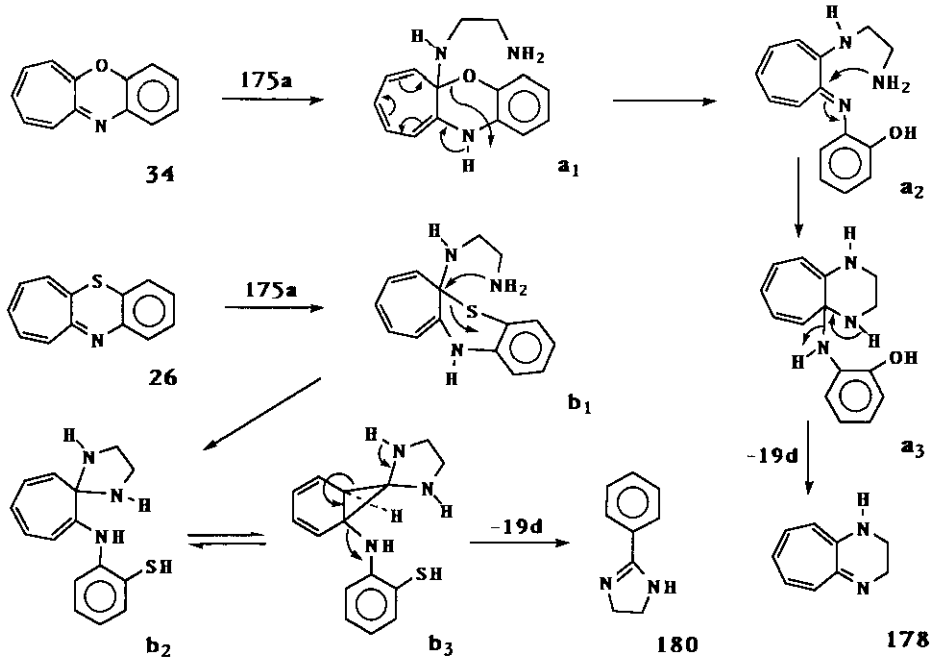
175	R	R'
a	H	H
b	H	Me
c	Me	Me
d	H	SH
e	H	OH

al[49] synthesized N,N'-dimethyl-2,3-dihydrocyclohepta[b]pyrazinium salt (173a), while Matsumura and coworkers reported the synthesis of 5-acetyl derivatives of 2,3-dihydrocyclohepta[b]pyrazine (174).[50] Therefore, we recently reinvestigated our previous study of the reaction between the reactive troponoids 3a,b and ethylenediamine or its related bifunctional reagents 175a-c, and compared their reactivity.



Scheme 28.

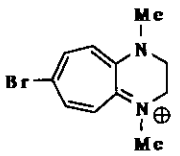
2-(2-Aminoethylamino)tropone (176, 95%) and 2,2'-(1,2-ethanediamine)bistropone (177, 4%) are obtained by refluxing ethanolic solution of 3b with 175a. Heating



Scheme 29.

of **176** in a sealed tube at 120 °C gives 2,3-dihydro-1H-cyclohepta[b]pyrazine (**178**) in quantitative yield.[51] Its nmr spectral data indicates that this compound exists in rapidly interchanging tautomeric forms **178a** and **178b** (Scheme 28). Compound **178** is not converted to cyclohepta[b]pyrazine (**30**) by attempted dehydrogenation with *DDQ* or trityl salt. N-Methyl derivative **179** and N,N'-dimethyl cation (**173b**) are obtained by the reaction of **3b** with **175b** and methylation of **179** with magic methyl, respectively.

Compound **178** is also produced from benzoxazine **34** by heterocycle-exchange reaction with **175a**, while S-analogue **26** exclusively gave 2-phenyl-4,5-dihydro-1H-imidazole (**180**) by the same treatment with **175a** as shown in Scheme 29. It is specially



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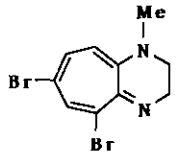

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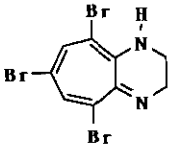
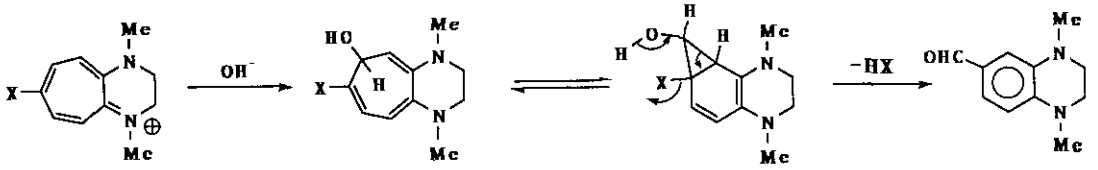


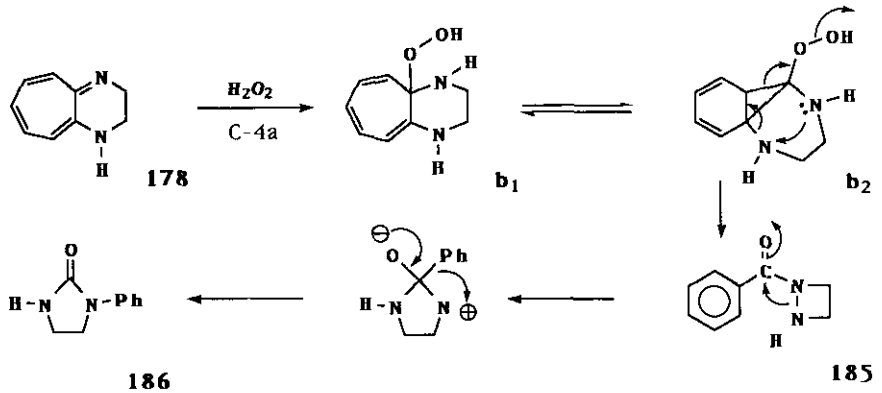
183

noted that the aliphatic amino group in an intermediate b_1 displaces C-S bond before ring-opening as shown in Scheme 29.



173 or 181 a_1 a_2 (X=H, Br) **184**

N,N'-Dimethyl cation **173** gives, with excess bromine in acetic acid, 7-bromo compound **181** exclusively, while **179** and **178** give mostly dibromo **182** and tribromo



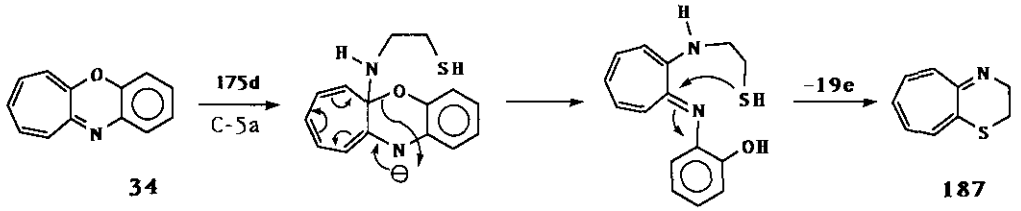
178 b_1 b_2 **185** **186**

Scheme 30.

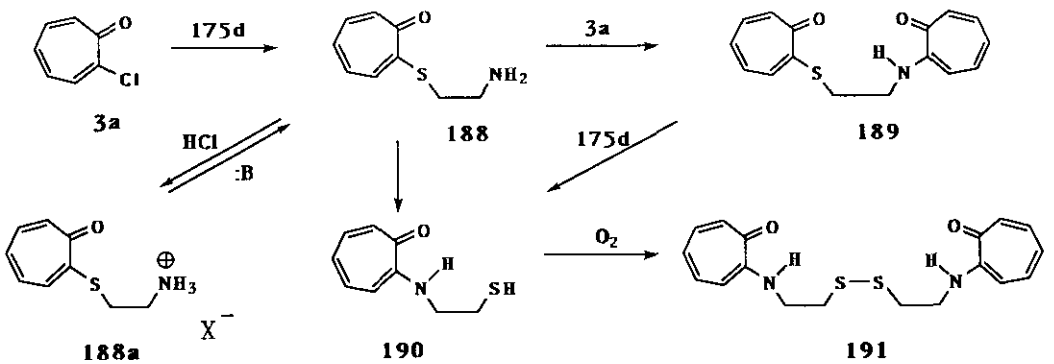
compound **183** under similar conditions, presumably by the steric effect of N-methyl group. While **178** and **179** are easily saponified by warm alkali into tropolone and **175a,b**, dimethyl cation **173** or its bromo compound **181** rearranges to 1,2,3,4-tetrahydro-1,4-dimethylquinoxaline-6-carbaldehyde (**184**). Treatment of **178** with H_2O_2 in methanol affords 1-phenylimidazolin-2-one (**186**), presumably formed through involving unstable 1-benzoyldiazetidine (**185**) as shown below in Scheme 30.[51]

5.2 2,3-Dihydro-1H-cyclohepta[b][1,4]thiazine

S-Analogue **187** of **178** is produced by heterocycle-exchange of benzoxazine **34** with 2-aminoethanethiol (**175d**). However, in our attempt to produce the same compound



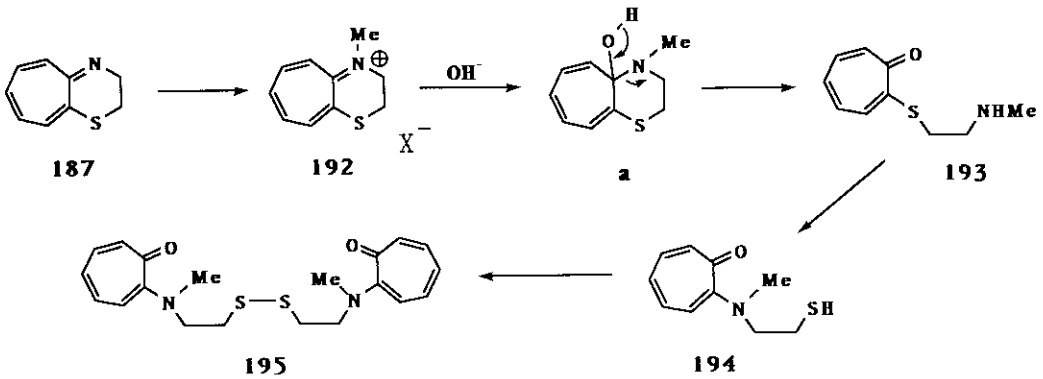
187 by the reaction of 2-chlorotropone (**3a**) with **175d**, we have encountered a quite unexpected phenomenon. Namely, hydrochloride **188a** (X = Cl) is immediately obtained (75% yield) by adding 2-3 drops of conc. HCl to a mixture of **3a** and **175d** at 0-5 °C. When a methanolic solution of free compound **188**, obtained by neutralizing **188a** with triethylamine, is treated with another molecule of **3a**, 2-[2-(2-troponyl)thioethylamino]tropone (**189**) is produced in a high yield. However, N,N'-bis(2-troponyl)-2-aminoethanedisulfide (**191**) is obtained via unstable 2-(2-mercaptoethylamino)tropone (**190**), when free amine **188** is allowed to stand in methanol for 1 day, or when a methanolic solution of **189** and **175d** is left in open-



Scheme 31.

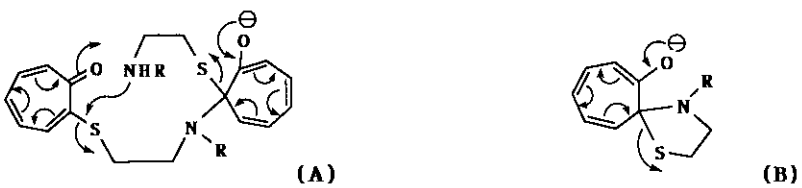
air for several hours. We have examined time-dependent hplc of the reaction of **3a** and **175d** to have useful information of the sequence of the reaction, and the possible reaction pathways are shown in Scheme 31.

Upon heating HCl salt **188a** in ethanol at 120 °C for 2 hours (sealed tube), the expected dihydrocycloheptathiazine **187** is obtained in a high yield. Treatment of this compound with magic methyl affords N-methyl cation **192** (X = FSO_3), which is, differing from its parent compound **187**, very unstable to alkali and gives disulfide **195** on standing in open air, via ring-opened **193** and its isomerized compound **194** (Scheme 32).



Scheme 32.

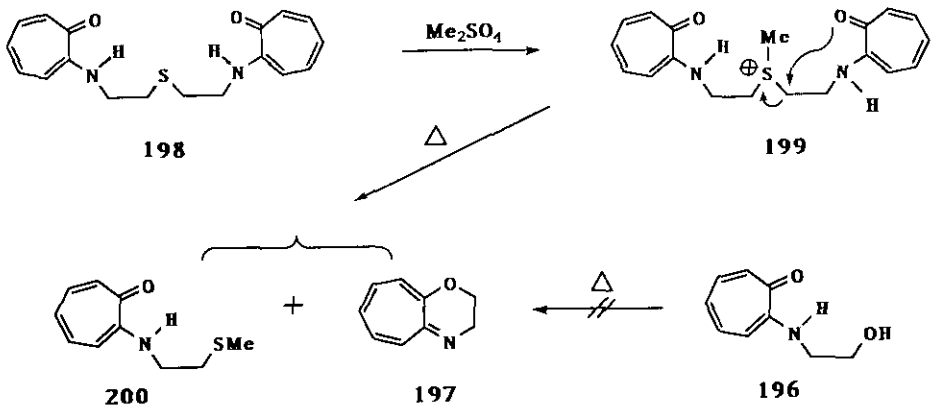
These two closely resembled reactions are likely to proceed through the intermolecular bimolecular (A), or intramolecular intermediate (B), because these rearrangement undergoes without addition of any extra reagent (**175d**). These unprecedented, facile exchange of the bifunctional side chain (Schemes 31 and 32), could be explained in terms of HSAB principle.



5.3 2,3-Dihydro-1H-cyclohepta[b][1,4]oxazine

2-(2-Hydroxyethylamino)tropone (**196**), obtained from **3a,b** and 2-aminoethanol (**175e**), does not give the oxazine **197**, because of weaker nucleophilicity of aliphatic hydroxyl group. However, we have obtained **197** and **200** by refluxing **198** in toluene with dimethyl sulfate,[52] presumably through thermal decomposition of

S-methylated compound **199** (Scheme 33). Oxazine **197** is unstable and easily changes to unidentified resinous substance on standing in open air.



Scheme 33.

6. *CONCLUSION*

So far described are synthesis and reactivities of cyclohepta[b][1,4]benzoxazine (**11**: X = O), 2,3-dihydrocyclohepta[b][1,4]oxazine (**12**: X = O), and their S- and N-analogues. Generally these compounds are readily obtained by the condensation of reactive troponoid **3** (X = Cl, OMe) with 1,2-bifunctional nucleophilic reagents (**19a-c** and **98a-d**). However, the reactions of isomeric bromo-2-methoxytropones (**38-40**) having two leaving groups, in particular **39** and **40**, with **OAP** and **OPD** become extremely complex. Detailed studies on these complex mechanism have led us to the discovery of interesting, unprecedented reactions of various type. For the reactive troponoids **38-40** the attack of the amino group of **OAP** usually takes place MeO at C-2. Then, ring-closure often proceeds competitively by the attack at the vicinal carbonyl (C-1) or bromine (C-3), followed by elimination of H_2O or HBr (Scheme 5). Even when no bromine atom is present at the ring-closure site of the nucleus, addition of the phenolic OH group and the subsequent autoxidation produces a conjugate tropylium system or benzenoid compounds by the rearrangement via norcaradiene tautomers (e.g. Schemes 10 and 11). It is particularly noteworthy that the initially formed cyclohepta[b][1,4]benzoxazines often suffer further nucleophilic attack of another molecule of **OAP** at C-5a, resulting in either the heterocycle-exchange to exclude the initial **OAP** (e.g. Schemes 8 and 9) or the hetero-ring transposition by the intramolecular migration

of the halfliberated initial **OAP** (e.g. Schemes 11, 17, and 21). Autoxidation of these intermediates produces polycyclic tropylium systems and also ·OOH (or H_2O_2); the latter involves in further oxidation of various substrates, thus causing the extremely complex reactions.

The SH group of reagents **19d** and **175d** tends to preferentially attack Br atom on the troponoid nucleus, followed by ring closure with the ortho-amino group (Schemes 17, 21, and 22). The functional group exchange of the nucleus-substituted S- with the side-chain amino-group often takes place intra- or intermolecularly (Schemes 31 and 32).

Also found are the facile formation of polyannulated tropylium systems from the *benzoxazine series by the ring-closure* and subsequent dehydroganation and the rearrangement to yield the o- and p-benzoquinonoid compounds (Schemes 21, 22, and 23). Upon heating the benzothiazino-annulated compounds in benzene or chloroform, *hetero-ring substitution and exchange reactions presumably of radical* type are observed (Chart 5).

These experimental results presented in this review explicitly demonstrate the diversity of the reactivities of troponoid compounds. In the meantime, we have found that the time-dependent hplc (and tlc) technique for this type of work is very useful for studies on the reaction processes and optimization of the synthetic products, because some of these reactions proceeds extremely fast (Scheme 17) and others reach equilibrium very slowly.

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