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REVIEW

1-Benzazepines

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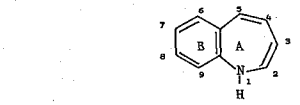
Fusion of benzene and azepine rings leads to three isomeric benzazepines. Kasparek[1] reviewed the chemistry, mainly the synthesis, of these benzazepines up to 1972. In this review focussing are on the synthesis of 1-benzazepines, which appeared between 1972 and 1984, and the reactions of 1-benzazepines which are not the main theme of Kasparek's review. 1-Benzazepine has three isomers, 1H-1-benzazepine **1**, 3H-1-benzazepine **2** and 5H-1-benzazepine **3**. None of these is synthesized. The manner which is used in Kasparek's review is also used in this review for the classification of the synthesis and the reactions are surveyed according to three major compounds, tetrahydro-1-benzazepines, dihydro-1-benzazepines and 1-benzazepines.



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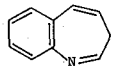

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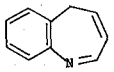

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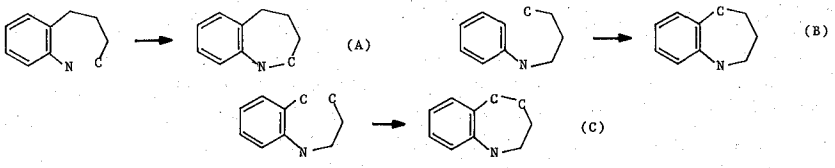

I SYNTHESIS

Synthetic methods are categolized into four parts, i.e., 1 Cyclization, 2 Nitrogen insertion, 3 Ring enlargement, 4 rearrangement.

1. Cyclization reaction

There are three types of cyclization reactions which have appeared in literatures. The first approach is the classical one and no noticeable report concerning with method (A) has reported since 1972. The major reaction which constitutes type (B) cyclization is Friedel-Crafts reaction. Intramolecular Friedel-Crafts alkylation finds its utility in the case where it is possible to generate the stable carbenium ion as the reaction intermediate.[1] But Friedel-Crafts acylation for method (B) has found no solid promise

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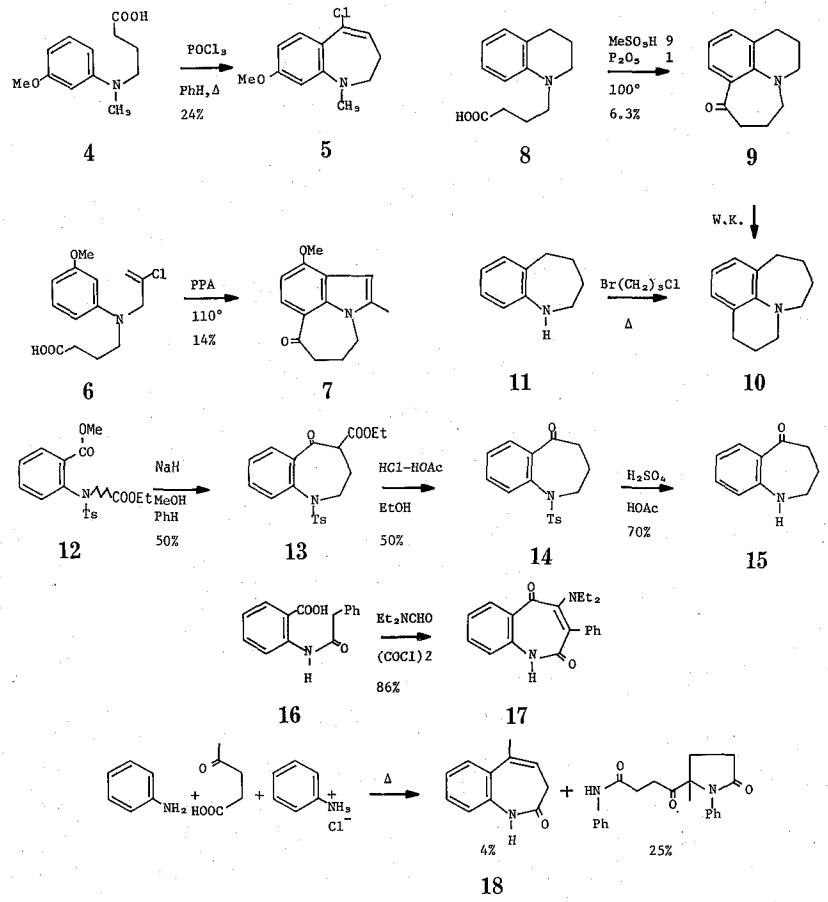
to succeed. Intramolecular acylation of **4** was carried out by phosphoryl chloride but the yield of **5** was 24% at best. Other reagents provide no promise.[2] New example is added in this area. When **6** is heated in polyphosphoric acid (PPA), double cyclization occured and **7** was obtained in 14% yield.[3] In this reaction Friedel-Crafts acylation took place at first then acid-catalyzed amino-Claisen rearrangement and subsequent cyclization into **7** followed since N-2-carboxyethyl-2-methylindole does not give any cyclization product under this reaction condition. We have also tried Friedel-Crafts acylation. When acid **8** was heated in a mix of methanesulfonic acid and phosphorous pentoxide (9: 1) at 100°C for 3 h, the cyclized product **9** was obtained in 6.3% yield after tedeous separation. The structure of **9** was confirmed by reducing by Wolff–Kishner reaction and comparing with 2,3,5,6,7,8-hexahydro-1H-1-benzazepino[3, 2, 1–ij] quinoline **10** which was prepared from 2,3,4,5-tetrahydro-1H-1-benzazepine **11**.[4] For hydrocarbons Friedel-Crafts acylation is an effective reaction to construct fused seven-membered ring[5] but the type (B) approach to form 1-benzazepine skeletone seems to be fruitless.

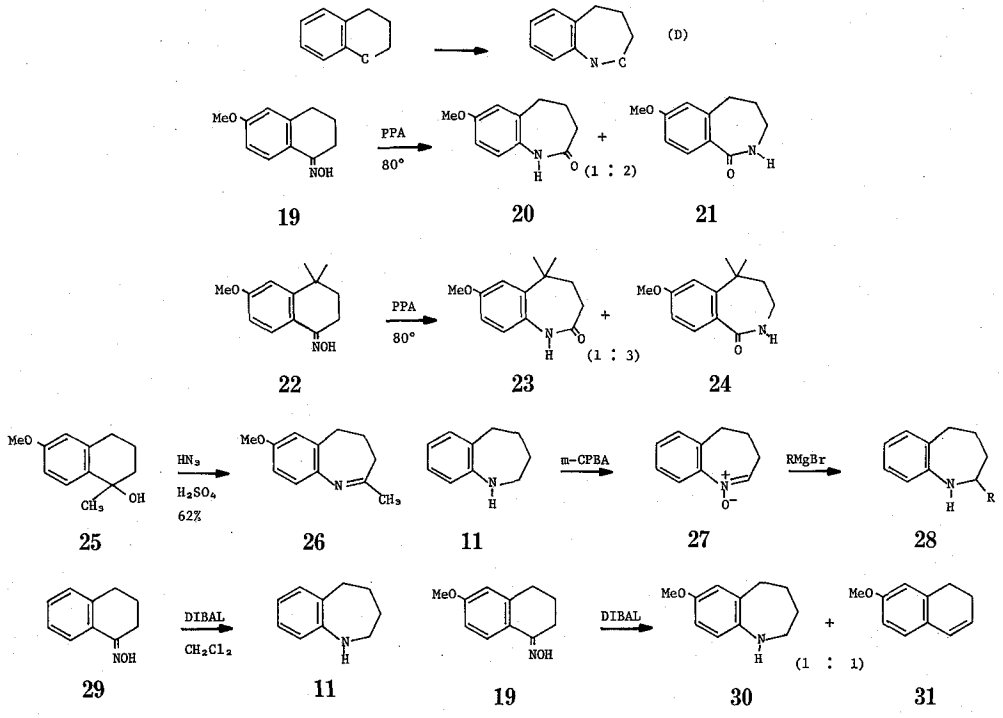


For type (C) reaction, Dieckmann, aldole and acyloin condensations are studied. Among them, Dieckmann condensation has been studied most extensively and the

typical application is the reaction of **12**. It is possible to prepare **14** and **15** in hundreds grams scale, thus this method constitutes the major entry into 1-bezazepine chemistry.[6] Tosyl group is essential in this reaction because no cyclization takes place when nitrogen is not protected and acetyl group is used as protecting group. Aldole and acyloin condensations are seldom used for type (C) reaction. Recently Vilsmeyer reaction is used in this area. When **16** was subjected to Vilsmeyer–Haack reaction condition, **17** was formed in good yield.[7] Condensation of laevulinic acid with aniline is reinvestigated. The structure of the major product is corrected. The yield of **18** is poor but this reaction is simple so that it can still find application, especially when activating substituent (8-OCH_3) locates on aromatic ring (25% yield).[8]

2. Nitrogen insertion reaction

Beckmann and Schmidt rearrangements have played major roles in this field (D). There are many reports concerning with these reactions to prepare tetrahydro-1-benzazepines. The major drawback for these reactions is the formation of by-product,



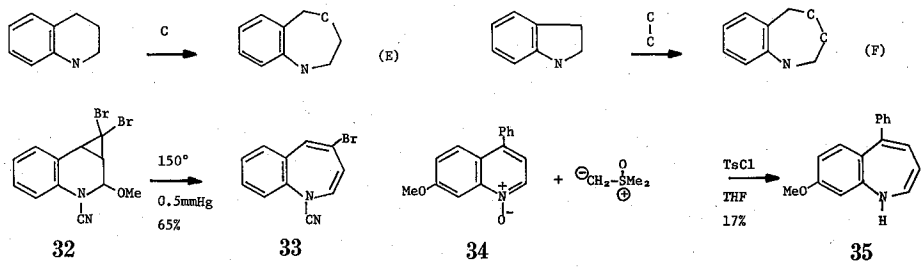
the isomer of 1-benzazepines. In these reactions the introduction of electron donating group at para position of aromatic ring decreases the yield of 1-benzazepine derivative and increases the yield of 2-benzazepine derivative. Beckmann rearrangement of 1-tetralone oxime **29** took place in favor of tetrahydro-1-benzazepin-2-one but the reaction of **19** proceeded in favor of 2-benzazepine derivative **21** over 1-benzazepine derivative **20**. The ratio of 2-benzazepine derivative is further increased in the reaction of **22**.[9] Similar trend is reported in Schmidt rearrangement of 1-tetralone. When Schmidt rearrangement was adopted to alcohol **25**, 2-methyl-1-benzazepine

derivative **26** was formed. In this reaction alkyl substituent was introduced into C–2.[10] The preparation of 2-alkyl-tetrahydro-1-benzazepine was carried out by the oxidation of **11** with m-chloroperbenzoic acid and Grignard reaction of nitrone **27**. The yield of **28** was moderate.[11]

Yamamoto et al have used diisobutylaluminum hydride (DIBAL) as the catalyst for Beckmann rearrangement as well as the reducing agent for amide in one pot procedure.[12] By this method oxime **29** was directly reduced into **11** and the purity of the product was high. But when this reaction was applied to **19**, the product was a mix of **30** and **31** (1 : 1). The presence of methoxy group again reduced the yield of 1-benzazepine derivative **30**.[4]

3. Ring enlargement reaction

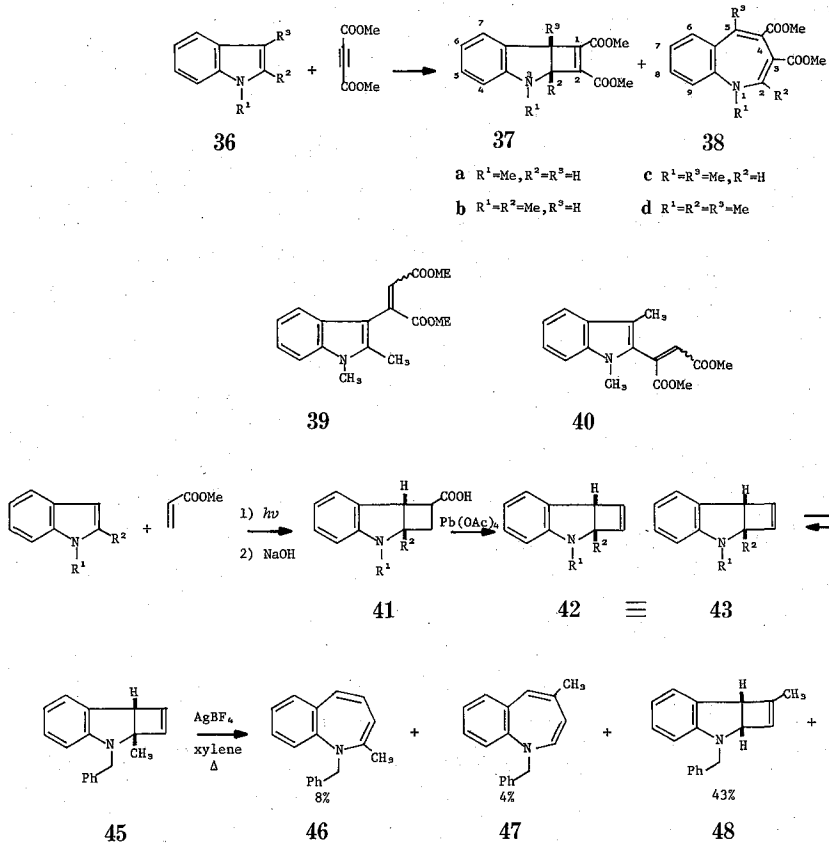
Two types of ring enlargement (E) and (F) are reported for the preparation of 1-benzazepine skeletone. After 1972, the efforts are focussed onto type (F) reaction and also on the behaviers of reaction products. The first report concerning with type (E) reaction is that the dibromocyclopropane ring was opened by the contact with silver nitrate or by refluxing in pyridine.[13a] Heating is also found to be effective.



32 33 34 35

When **32** was heated under reduced pressure, **33** was obtained in 65% yield.[13b] The presence of electron releasing group on aromatic ring does not increase the yield of ring-expanded product. Product **33** polymerized when exposed to acid. The analogues of **32** with dichlorocyclopropane ring are stable enough to distill under heating.[13b] New method to introduce one carbon into quinoline A ring has appeared.[14] The reaction of ylide with N-oxide **34** produced **35** as brown crystals. The major product in this reaction is dimeric quinoline. When other quinoline N-oxide is used in this reaction no 1-benzazepine derivative is formed. The property of **35**, mp 82–83°C is unique since many attempts at isolating 1H-1-benzazepines have failed due to its instability.

Type (F) reaction has attracted many chemists. A series of studies are conducted with substituted indoles **36**. When a solution of 1-methylindole **36a** and dimethyl acetylenedicarboxylates (DMAD) in absolute acetonitrile was refluxed for 6 days, 1-benzazepine derivative **38a** was formed as one of seven products.[15] However if a solution of this mixture in benzene was irradiated at 10°C by medium-pressure Hg lamp in the presence of benzophenone as sensitizer, the smooth reaction took place and a mixture of **37a** and **38a** was obtained.[16] The major product **37a** is deep orange oil and formed intramolecular CT complex. This product was thermally transfered into **38a** while standing at ambient temperature. Irradiation of **38a** gave an equilibrium



36 37 38

a R^1=Me, R^2=R^3=H
b R^1=R^2=Me, R^3=H
c R^1=R^3=Me, R^2=H
d R^1=R^2=R^3=Me

39 40

41 42 ≡ 43 44

45 46 47 48 45

between **38a** (70%) and **37a** (30%).

Sensitized photocycloaddition of 1,2-dimethylindole **36b** and DMAD also gave a mixture of **37b** and **38b** along with the secondary product **39**. Warming at 40°C readily converted **37b** into **38b**. Irradiation of **38b** also sets an equilibrium between **37b** and **38b**.

Reaction of 1,3-dimethylindole **36c** is complicated. When an equimolar amount of 1,3-dimethylindole **36c** and DMAD was treated with excess boron trifluoride in ether at 15°C, **37c** was produced. Although it was unable to isolate this product in pure state, the crude product was warmed and transformed into **38c** in 10% overall yield. The adduct **40** was the major product in this reaction.[17] The similar reaction in carbon tetrachloride at 0–4°C afforded **37c** (30%), **38c** (8%) and **40** (40%) after separation. In the crude product of this reaction, **38c** was not detected but it was formed during the process of isolation. On heating benzene solution, **37c** was ring-expanded into **38c**.[18] When an equimolar mixture of 1,3-dimethylindole **36c** and DMAD in benzene was irradiated in the presence of sensitizer, **37c** was formed with six other products. If two fold excess of DMAD was used at 10°C, **37c** predominated in the reaction products and no **38c** was formed, though **38c** rather than **37c** was isolated when the reaction was carried out at ambient temperature. These obser-

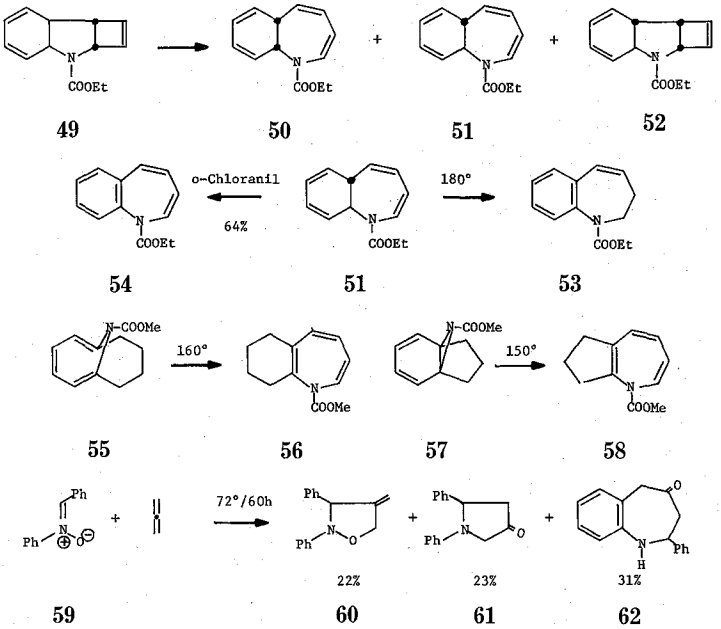
vations conclude that the primary photochemical process is the cycloaddition and followed by thermal ring opening. 1-Benzazepine derivative **38c** in benzene at 10°C was photolyzed into **37c** in 71% yield.[17]

The behaviors of 1,2,3-trimethylindole **36d** under these reaction conditions are much more simple. When a mixture of **36d** and DMAD (molar ratio 1: 1) was treated with a few drops of boron trifluoride etherate, **37d** was formed in 82% yield which was thermally transformed into **38d** in 83% yield.[18]

Ikeda et al have established the general method for the preparation of 1-benzazepines starting from indoles.[19] Indole and 2-methylindole are used after protecting NH bond with either benzoyl or benzyl groups. Yield for each step is good except decarboxylation stage. It requires heating up to more than 300°C to transfer **43** into **44** thermally. So, effective reaction condition for this conversion was investigated in details. The addition of silver tetrafluoroborate lowered the reaction temperature considerably and allowed to form an equilibrium between **43** and **44**. The equilibration is also attained by the irradiation of **44**. Interesting rearrangements occurred when **45** was heated in the presence of tetrafluoroborate. The reaction mechanisms for these reactions are proposed. Since the conrotatory ring opening of cyclobutene ring is prohibited by ring strain, biradical mechanism is considered to be most plausible under thermal condition. However, the participation of nitrogen lone pair and subsequent disrotatory ring opening is not totally ruled out. For the rearrangement of **45**, the initial coordination of silver cation on nitrogen and subsequent N–C bond cleavage to form cyclobutenyl cation are proposed.

4. Rearrangement

When triene **49** was exposed under light of low-pressure coil at −78°C, a mixture of **50**, **51** and **52** was formed.[20] The isolated product **51** rearranged into **53** when



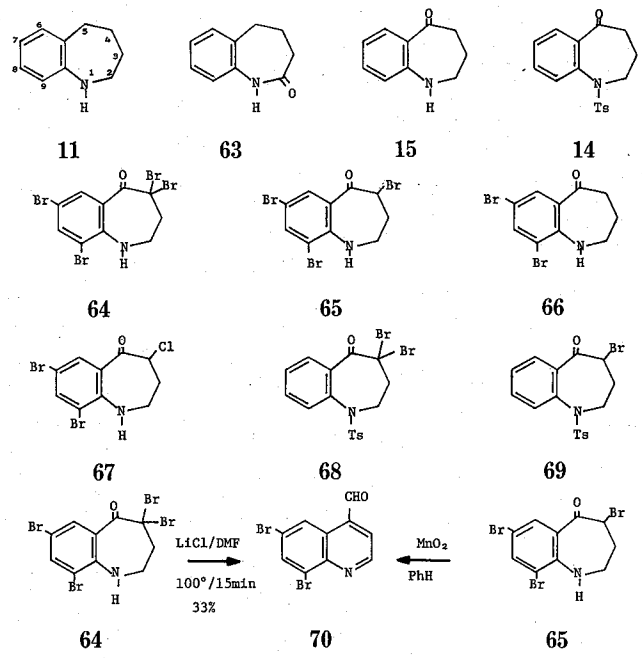
heated at 180°C and also was dehydrogenated into **54** when treated with o-chloranil at ambient temperature. The catalytic hydrogenation of **54** saturated two double bonds in azepine ring. Paquette has reported the thermal rearrangement of **55** and **57**. Reaction mechanism involves initial valence tautomerization for **55** then 1,5-shift of nitrogen and Cope rearrangement.[21] The reaction of nitrone **59** with allene in a sealed tube gave three products **60**, **61** and **62**. 1-Benzazepine derivative **62** is the major product. Both **61** and **62** are derived from the addition isomer of **60** via diradical intermediate.[11] Among the approaches to construct 1-benzazepine skeletone by type (E) method, Wagner–Meerwein rearrangement should be explored more and this approach should reserve more promise than the methods known due to its versatilities.

II REACTIONS

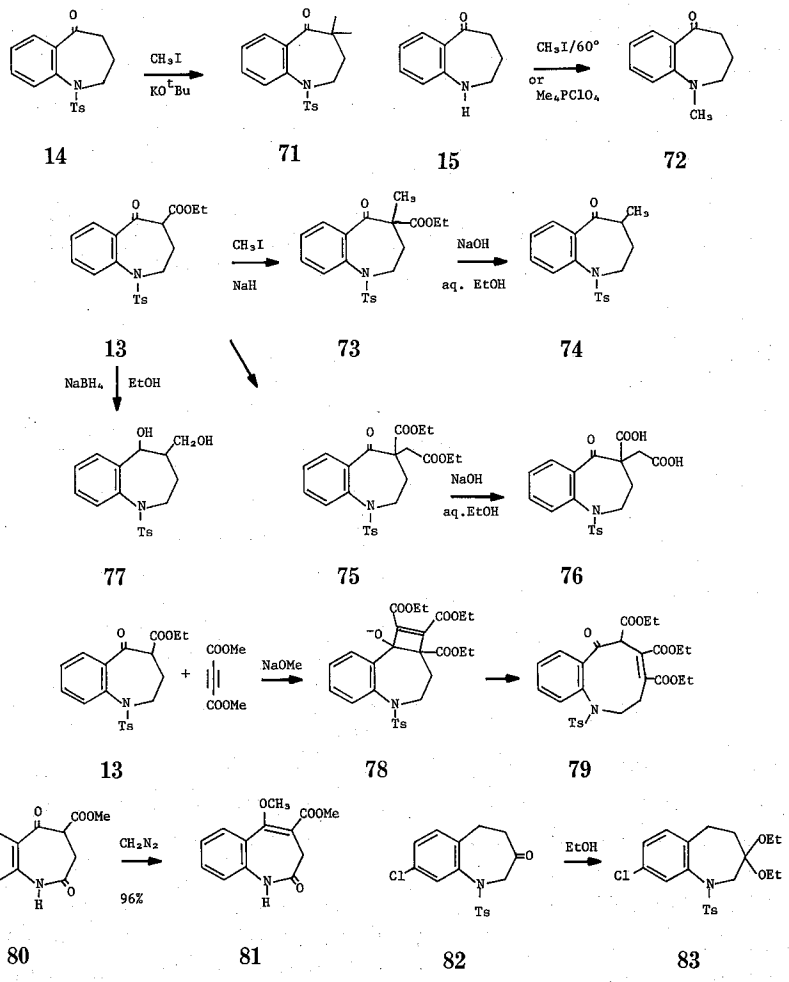
Reactions of 1-benzazepines are surveyed basing upon three compounds, tetrahydro-1-benzazepine, dihydro-1-benzazepine and 1-benzazepine. Novel and unique reactions are center of discussion.

1. Tetrahydro-1-benzazepines

2,3,4,5-Tetrahydro-1-benzazepine **11** is stable and gave nitrone **27** by the oxidation with m-chloroperbenzoic acid, *vide supra*. Dehydrogenation of **11** with 40% Pd–C gave a mixture of quinoline and methylquinolines.[22] Amide **63** opens lactam ring by acid treatment but if double bond is present in lactam ring this reaction becomes severer. 2,3,4,5-Tetrahydro-1-benzazepin-5-one **15** is readily available and its chemistry is most widely studied. The ketone **15** is colored yellow but this color disappeares if nitrogen lone pair is trapped by tosyl group and the reactivity of carbonyl group increases. Thus the controlled bromination of **14** allowed the selective substi-



tution of active methylene[23] but bromination of **15** gave a mixture of the products which were brominated at aromatic ring and active methylene. Reaction of **15** with excess bromine gave a single product **64**.[23] When a solution of **64** in ethanol was refluxed with sodium bicarbonate, debrominated products **65** and **66** were formed.[24] Heating **65** with lithium chloride in dimethylformamide (DMF) yielded **67** instead of dehydrobromination product. Many attempts at introducing double bond by dehydrobrominating **68** and **69** failed and the starting materials were recovered.[23] When **64** was treated with lithium chloride in DMF, **70** was formed in 33% yield. This product was also the product when **65** was oxidized with manganese dioxide.[25] Dehydrobrominating agents are ineffective to **65**. The alkylation of **14** takes place at active methylene and that of **15** occurs at nitrogen.[26] Ester groups of **73** and **75** were



14 71 15 72

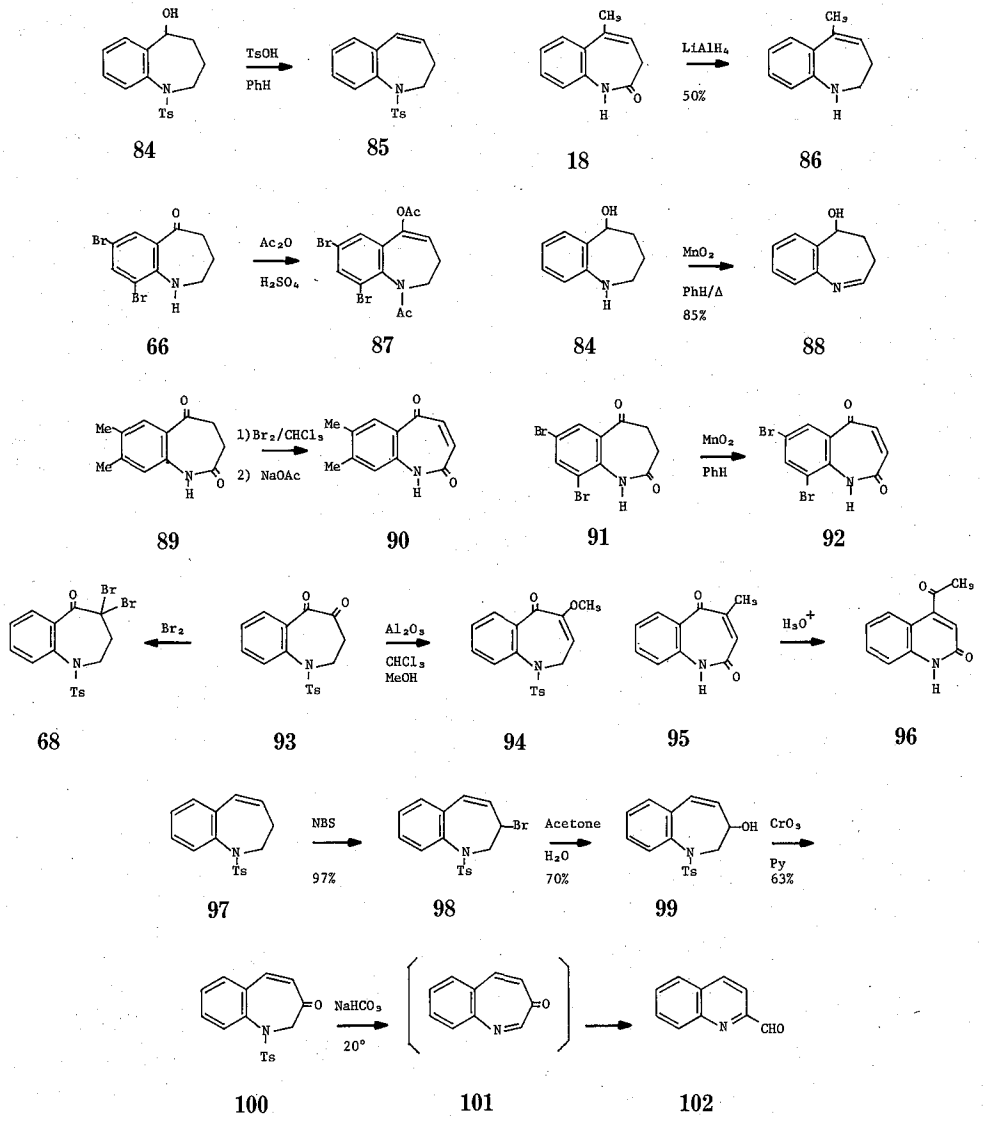
13 73 74

77 75 76

13 78 79

80 81 82 83

hydrolyzed by sodium hydroxide but the carboxyl group of **76**, β-ketoacid, remained.[27] Sodium borohydride in ethanol reduced both ketone and ester groups of **13** and gave dialcohol **77** in good yield.[27] Enolate of **13** generated with sodium methoxide reacted with DMAD and gave **79** *via* **78** in high yield.[27] β-Ketoesters are in equilibrium with



84 85 18 86

66 87 84 88

89 90 91 92

68 93 94 95 96

97 98 99

100 101 102

enol form so that **80** was methylated by diazomethane.[28] Carbonyl group of **82** is quite reactive and was readily converted into ketal **83** by warming in ethanol, although dechlorinated ketone does not have this reactivity.[29]

2. Dihydro-1-benzazepines

Benzylalcohol **84** is quite susceptible to dehydration and gave **85** in good yield.[24] Reduction of amide **18** also afforded 2,3-dihydro-1-benzazepine derivative **86**. Amides **18** was prepared by condensation reaction.[8,30] Dehydrogenation with dichlorodicyano-1,4-benzoquinone (DDQ) is effective for the preparation of unsaturated amide when methyl group of **18** is substituted with phenyl group.[31] It is also possible to locate double bond by enol ester formation as shown by the transformation of **66** into **87**.[24]

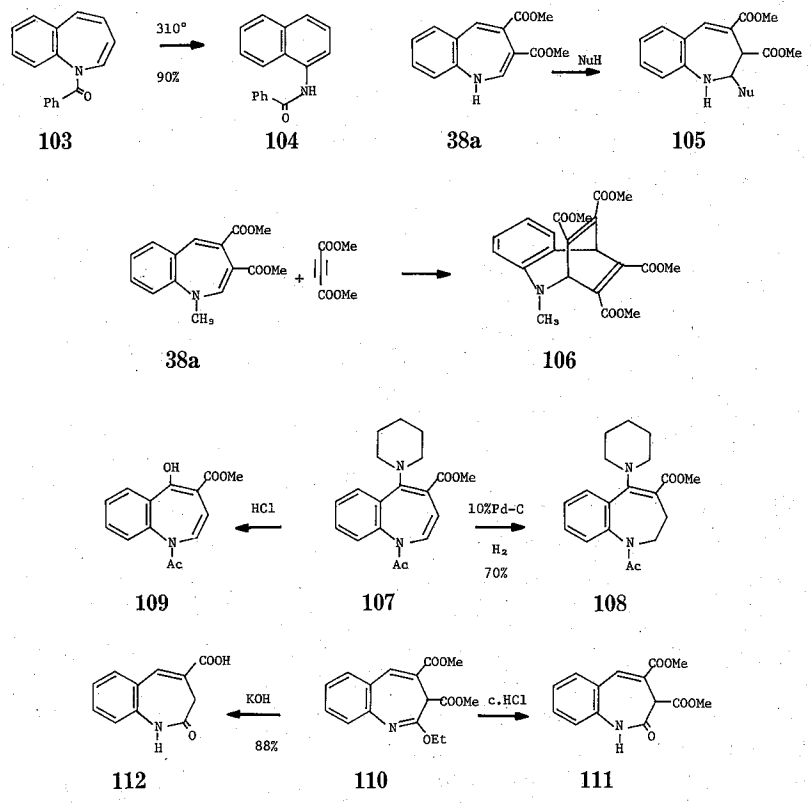
Manganese dioxide does not work on alcohol of **84** but on amine of **84**. Thus

84 produced **88** in good yield.[27] Preparation of 2,3-dihydro-1-benzazepin-5-one from saturated ketone has been unsuccessful. Reactions used are oxidation with selenium dioxide,[24] dehydrobromination with amines[23,24] or lithium chloride[24,25] and dehydration with phosphorous pentoxide.[23] However the preparation of 2,3-dihydro-1-benzazepin-2, 5-dione system has no problem and **90** was prepared from **89** by bromination and dehydrobromination reactions[32] and **92** was obtained from **91** by oxidation.[25] Diketone **93**, which is available from **14** or **68**, has unique reactivity. When **93** was purified by chromatography, enol ether **94** is formed.[26] The bromination of **93** gave **68**.[23] Unsaturated ketoamide **95** is directly available by Schmidt reaction of 2-methyl-1,4-naphthoquinone[1] and rearranged into **96** when **95** was heated in aqueous acid.[33]

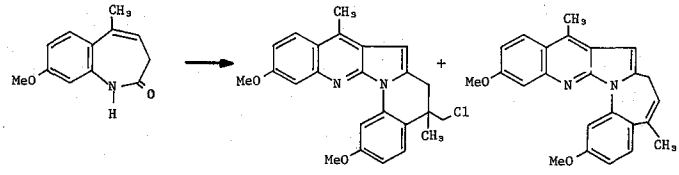
Different approach is used for the preparation of 1,2-dihydro-1-benzazepine-3-ones. Starting from **97**, **100** was synthesized in good yield. When protecting group of **100** is removed by sodium methoxide, bright purple product, possibly **101**, was formed. But it was unable to isolate **101** and the product isolated was **102** in poor yield after workup. The treatment of **100** with sodium hydride afforded dimeric product. Double bond of **100** does not react with osmium tetroxide nor with potassium permanganate.[24]

3. 1-Benzazepines

Preparation methods and some of porperties of 1-benzazepines are described in previous section. Notable among them is the equilibrium between 1H-1-benzazepines



38 and 2a,7b-dihydrocyclobut[b]indoles **37**. When **103** was heated to more than 300°C, rearrangement took place and **104** was formed in high yield. Benzyl group in place of benzoyl group does not allow this rearrangement.[17] Azepine ring is not aromatic and accepts nucleophilic attacks. Thus indole and methanol attack **38a** and gave the adduct **105** in 89% and 32% yields respectively.[15] Contrary to **54**, **38a** is not susceptible to catalytic hydrogenation but double bonds were reduced selectively. Sodium amalgum reduced **38a** to give 4,5-dihydro-1-benzazepine derivative and reduction with zinc powder in acid afforded 2,3-dihydrogenated product. Two double bonds in azepine ring is in conjugation so that Diels–Alder reaction of **38a** with DMAD gave the cycloadduct **106** in 75% yield.[15] Catalytic hydrogenation of **107** reduced one of double bonds and gave **108**. On the other hand aqueous acid hydrolyzed one of two enamines of **107** and produced **109**.[34]



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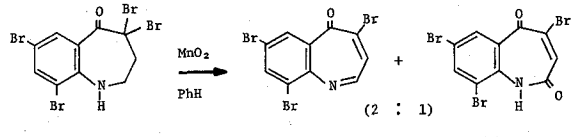
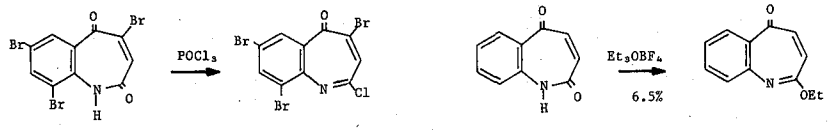
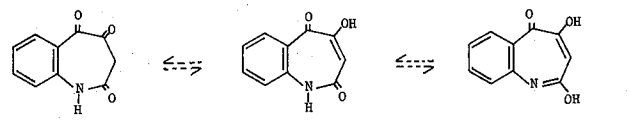


64 116 117



117 118 119 120



121 122 123

Number of 3H-1-benzazepines is scarce and their chemical behaviors are little studied. Acidic hydrolysis of **110** gave **111** and basic hydrolysis afforded **112** in 88% yield.[35] In order to prepare 3H-1-benzazepine derivative, amide **113** was treated with phosphorylchloride. The reaction products were dimeric **114** and **115**. The structures of these products were determined by X-ray analysis and the reaction mechanism is also discussed.[36]

As 5H-1-benzazepine derivative, **116** is prepared by the oxidation of **64** with manganese dioxide. Further oxidation of **116** produces **117** which was converted in **118** with phosphoryl chloride.[25] Similarly the reaction of **119** with Meerwein reagent

gave **120**. This product has no ring current according to NMR analysis.[37] Diketoamide **121** has yellow green color and is hardly soluble in organic solvent. However its IR spectrum indicates that it has no enol isomers such as **122** and **123**.[32]

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