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Author(s)	Orito, Kazuhiko
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Synthetic Studies of Heterocyclic Compounds II

—— Synthesis of 3-Benzazepines ——

Kazuhiko ORITO*

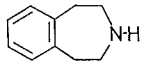
(Received June 30, 1979)

Abstract

Recent progress on the preparation of 3-benzazepines is described, in six types (Type 1 to 6) of ring closure or ring enlargement reactions.

Introduction

A number of 3-benzazepines have been known to have pharmacological activities[1,2], especially, as useful agents with analgesic, anorectic, antibacterial, antidepressant, antihypertensive and ganglion blocking properties. The skeleton of 1, 2, 4, 5-tetrahydro-3 H-3-benzazepine **1** has also been found in the isopavine **2**, rhoeadine **3** and cephalotaxine **4** alkaloids[3,4]. In these context, many synthetic approaches to the 3-benzazepine skeleton have been developed and some basic reactions to lead to this skeleton are herein described.



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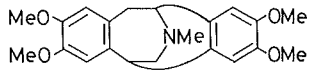
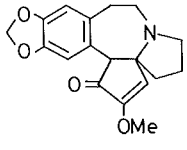
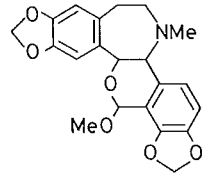


isopavine 2



cephalotaxinone 3

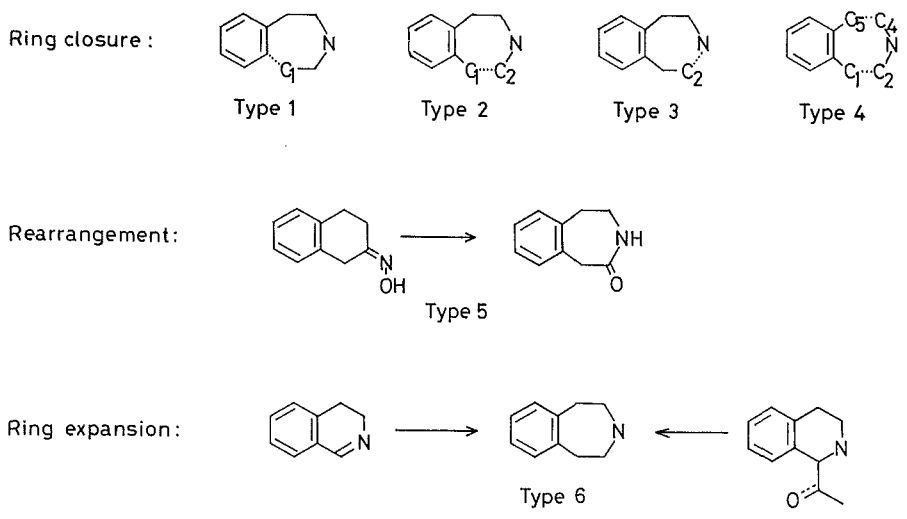


rhoeadine 4

Discussion

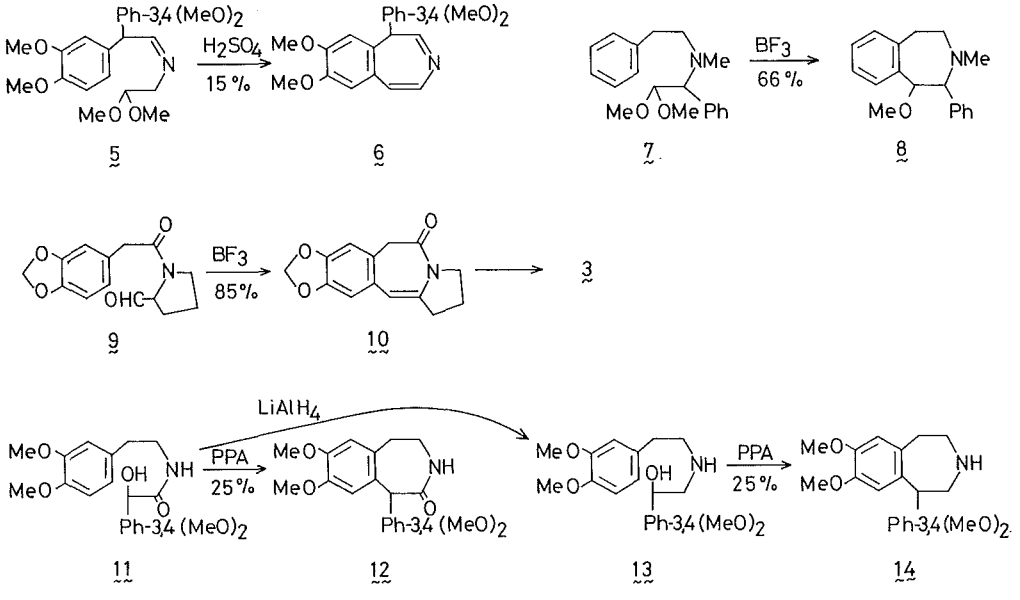
The methods for the preparation of 3-benzazepines will be presented in the six types of the synthetic reactions. Ring closure with the bond formation between aromatic ring and C_1-carbon mainly by electrophilic aromatic substitution reactions is shown as the Type 1. Similarly, the formations of C_1-C_2 bond (Type 2), and C_2-nitrogen bond (Type 3), as well as the two C-C bond formation in the Type 4, lead to the 3-benzazepine ring system. Beckmann rearrangement of β-tetralone oxime is discussed in the Type 5. The Type 6 includes the reaction of 3, 4-dihydroisoquinoline with diazomethane and the ring expansion reaction of 1-hydroxymethyl or 1-benzoyl derivatives of 1, 2, 3, 4-tetrahydroisoquinolines.

* Department of Chemical Process Engineering, Faculty of Engineering, Hokkaido University.



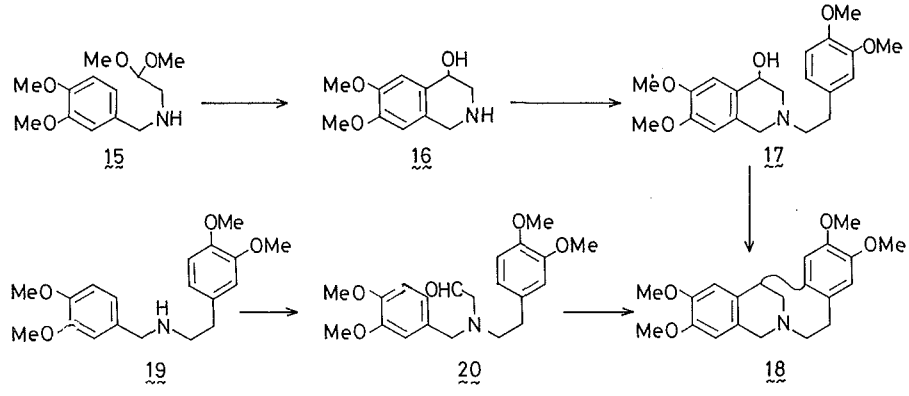
Type 1. ring closure, Ar–C

The most popular cyclization reaction arises from the electrophilic substitution reaction at the aromatic ring. In 1903, Fritsch[5] initiated the acid-catalyzed cyclization of the aminoacetal **5** to 1 H-3-benzazepine **6**, the structure of which was confirmed later by Sainsbury et al[6]. The β-aminoaldehyde **7** was also cyclized to 1, 2-dihydro-3 H-3-benzazepine **8** in the presence of Lewis acid in good yield[7]. Auerbach and Weinreb[8] applied this method to **9** to form the benzazepine **10**, which played a important role in the synthesis of cephalotaxine alkaloid **3**[8,9]. The mandelamide **11** cyclized on treatment with polyphosphoric acid to the benzazepin-2-one **12**[10,11], and the similar cyclization of the amino alcohol **13**, prepared by lithium

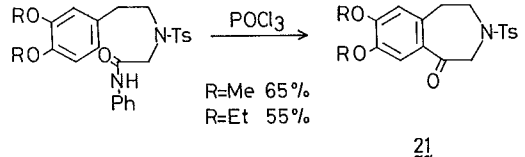


aluminum hydride reduction of the amide **11**, provided 1, 2, 4, 5-tetrahydro-3 H-3-benzazepine **14**[11].

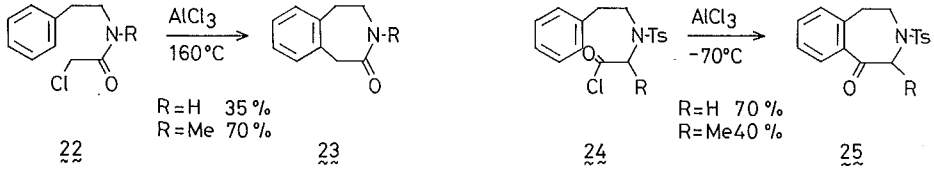
The scheme (**15**–**20**) is the reaction sequences often applied to the total synthesis of isopavine alkaloids[2]. The acid treatment of 1, 2, 3, 4-tetrahydro-4-hydroxy-2-phenethylisoquinoline **17**, prepared by interaction of **16** with phenethyl bromide, gave the benzazepine **18**[12,13], substantiating that cyclization reaction of N-benzyl-phenethylaminoaldehyde **20** to **18** proceeds *via* 4-hydroxyisoquinoline **17**[13].



Ring closure of Bischler-Napieralski type to benzazepin-1-one **21** has been known. When glycine anilide of N-*p*-tosyl-phenethylamine was treated with wet phosphoryl chloride, **21** was obtained in 65% yield[14]. However, removal of the tosyl group has not been achieved.

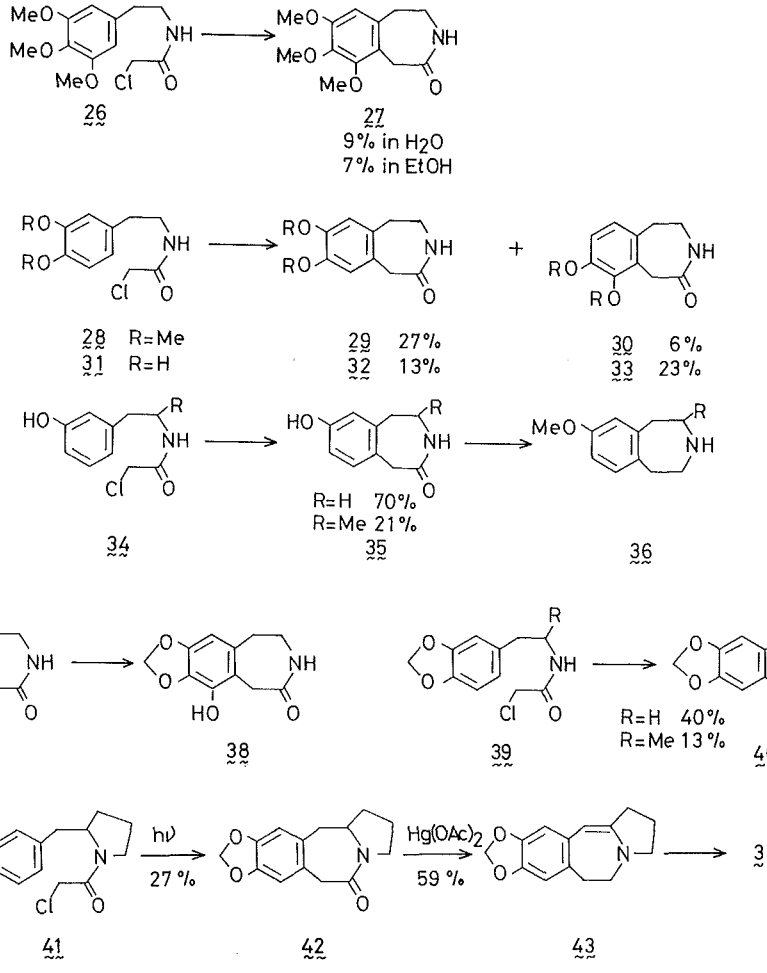


Friedel-Crafts cyclization could be employed to afford 1- or 2-oxo derivative of 3-benzazepines. In the alkylation reaction, N-chloroacetyl-phenethylamine **22** was heated with anhydrous aluminum chloride at 160°C to give 1, 2, 4, 5-tetrahydro-3 H-3-benzazepin-2-one **23** by Nair (R=H)[15] or Orito (R=CH_3)[16]. Intramolecular alkylation was performed in turn by low temperature operation of the acid chloride **24** to 1-oxo benzazepine **25** having *N*-tosyl group in question[17].

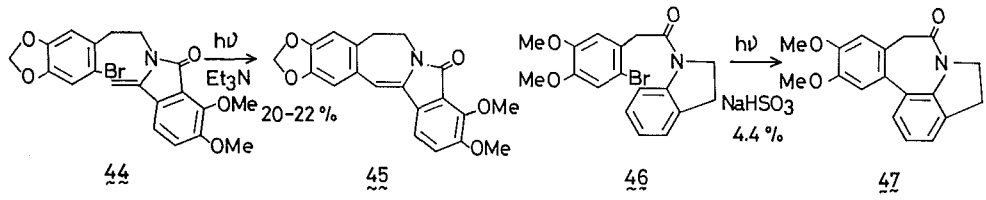


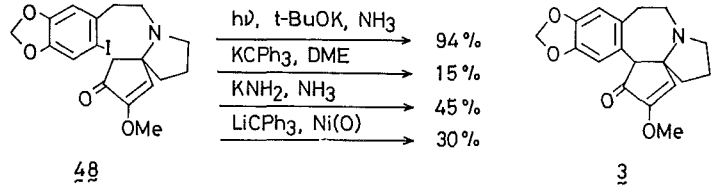
The compounds of the type **22** also cyclize under photochemical conditions. Yonemitsu and his co-workers[18~20] reported the irradiation of various chloroacetamides with ultra violet light 2537 Å in aqueous solution.

Many azepinones as well as isomeric benzazepinones for examples, **29**, **30** and **32**, **33** yielded, and, on further reductive procedure, were converted to the corresponding benzazepines such as the amine **36**[18]. A similar result was obtained in the conversion of **39** to **40** by Sniekus et al[22]. Dolby et al. applied this method to have the compound **42**, which gave the key precursor **43** in the synthesis of cephalotaxinone **3** by Auerbach et al[8,9].



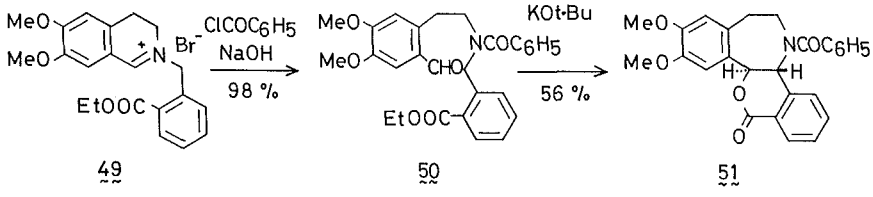
Photolysis of the enamide **44**[23], or **46**[24] furnished the benzazepine **45** or the dibenzazepine **47**. Intramolecular SRN 1 reaction was accomplished in the synthesis of cephalotaxine alkaloid **3** by Semmelhack[25]. That is photolysis of the iodide **48** in liq ammonia in the presence of potassium *t*-butoxide produced the cephalotaxinone **3**[25]. Other methods also could provide **3** but in lower yield[25~27].





Type 2. ring closure, C_1–C_2

Only one example of this type C_1–C_2 was achieved by Shamma, who introduced the new approach to trans B/C fused rhoeadine alkaloid analogue **51** due to intramolecular aldol-type condensation by the base treatment of the aldehyde **50** prepared from the salt **49**[28].

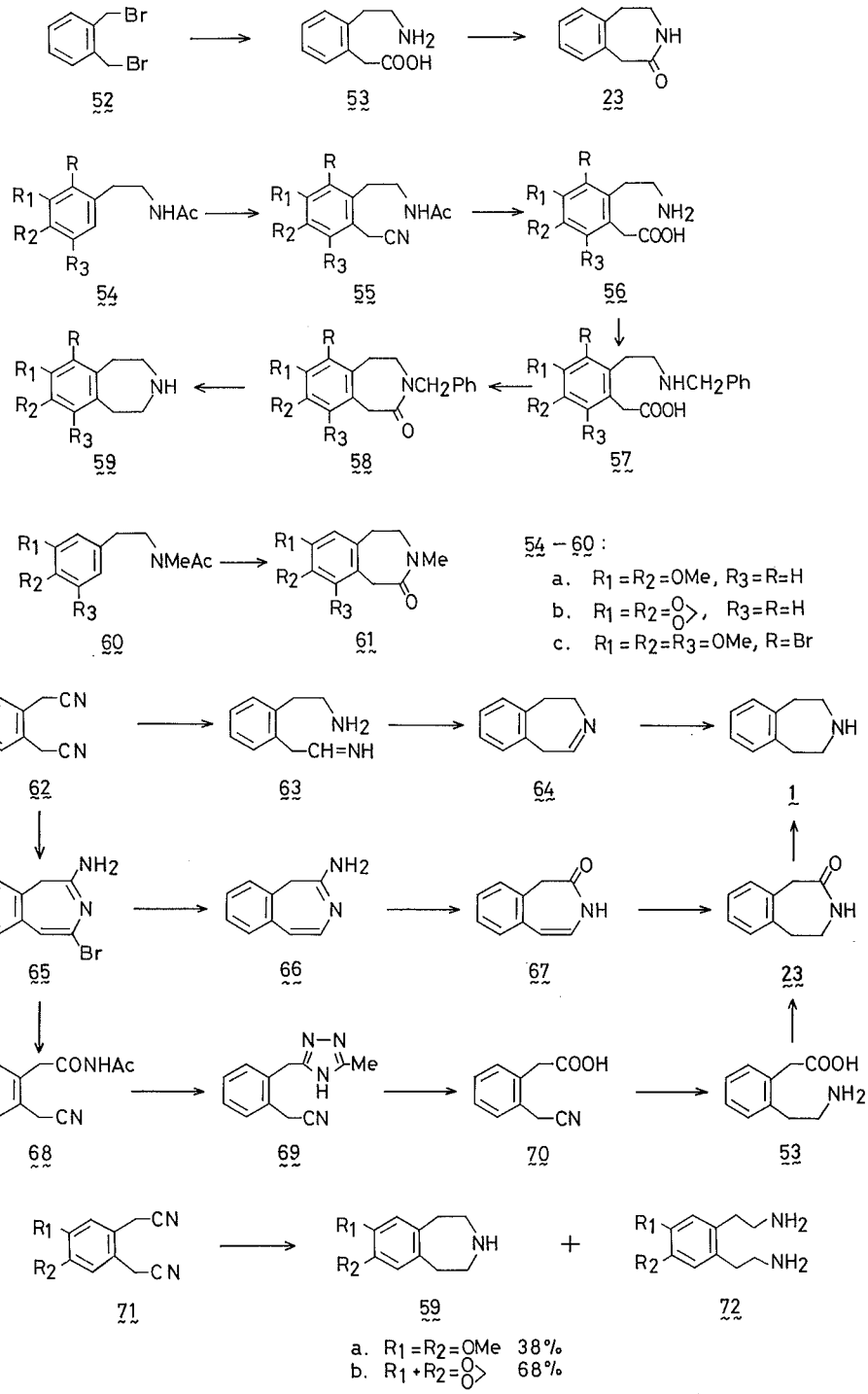


Type 3. ring closure, C_2–N

In 1925, von Broun[29] reported the formation of the compound **23** by dehydrative cyclization of the amino acid **53**. Starting from xylene dibromide **52**, this method is also applicable to aromatic alkoxy substituted benzazepines. Brossi[30] reported the conversion of N-phenethylacetamide **54** to benzylnitrile **55** by chloromethylation with formalin and hydrogen chloride and further treatment with sodium cyanide.

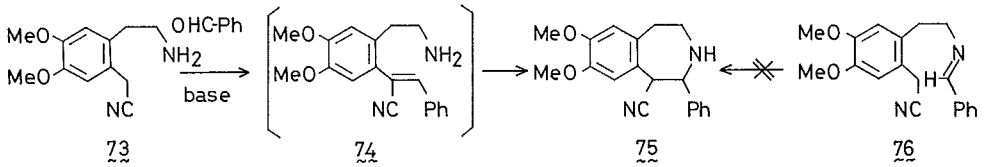
Hydrolysis and N-benzylation, followed by thermal cyclization of the products **57**, afforded N-benzyl-3-benzazepinone **58**, whose reduction yielded alkoxy substituted benzazepine **59**. Trimethoxy derivative **56 c** was subjected to direct cyclization without benzylation to give **59 c** on the further reduction. Orito[31] started from N-methylamides **60** and readily prepared N-methylbenzazepin-2-ones **61 a, b, c**.

It has been known that hydrogenolysis of o-dicyanomethyl benzene **62** gives the 1, 2, 4, 5-tetrahydro-3 H-3-benzazepine **1**[32]. On the other hand, treatment of **62** with hydrogen bromide affords the benzazepine **65**, which was further derived into benzazepin-2-one **23** or the aforementioned amino acid **53**[33]. These


Br
Br
NH2
COOH
NH
O
52
53
23
R
R1
R2
R3
NHAc
CN
NH2
COOH
54
55
56
NHCH2Ph
NCH2Ph
NH
59
58
57
NMeAc
NMe
60
61
54 – 60 :
a. R1 = R2 = OMe, R3 = R = H
b. R1 = R2 = O, O, R3 = R = H
c. R1 = R2 = R3 = OMe, R = Br
CN
CN
NH2
CH=NH
N
NH
62
63
64
1
NH2
N
Br
O
NH
65
66
67
23
CONHAc
CN
N–N
N
H
Me
COOH
NH2
68
69
70
53
CN
CN
NH
NH2
NH2
71
59
72
+
a. R1 = R2 = OMe 38%
b. R1 + R2 = O, O 68%

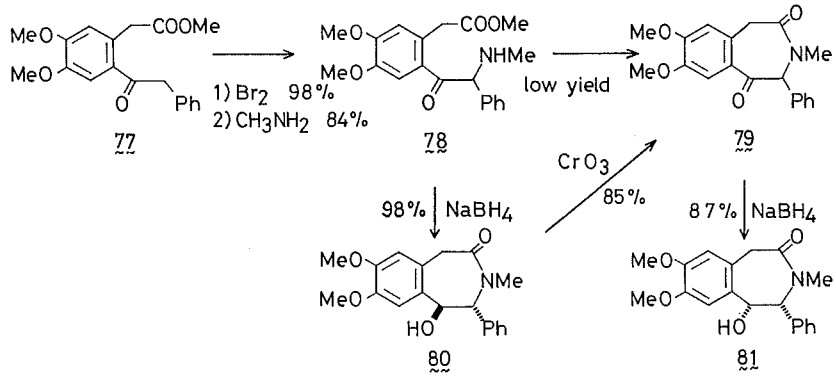
reaction sequences received attention in the synthesis of the corresponding aromatic alkoxy benzazepines[34], in which 7, 8-dimethoxy- and 7, 8-methylendioxy-benzazepine **59 a, b** were formed by the hydrogenolysis of the o-dicyanomethyl-benzenes **71**, accompanied with the diamines **72**.

Aminonitrile **73** was condensed with benzaldehyde under basic conditions to give 1-cyano-2-phenyl-benzazepine **75**[34]. Reaction mechanisms have been explained to be Michael type addition reaction of amino group to cinnamonitrile function in **74**, since **76** did not cyclize to **75** under the same basic conditions as for **73** to **75** or the acid treatment.

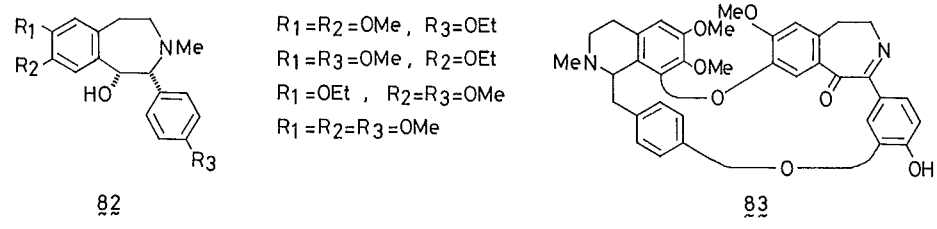


73 **74** **75** **76**

Inubushi et al[35]. reported the synthesis of *trans*- and *cis*-isomers of 7, 8-dimethoxy-N-methyl-2-phenyl-1, 2, 4, 5-tetrahydro-3 H-3-benzazepin-1-ols (**80, 81**), in which the amino ester **78** was obtained by bromination and amination of the keto ester **77**. The thermal treatment of **78** provided poor yield of the benzazepine **79**, but sodium borohydride reduction in ethanol gave trans 1-ol **81**, in good yield. On the other hand, ketone **79**, which was also obtained by oxidation of **80** was reduced with sodium borohydride to give the cis 1-ol **81**. Similar reactions by the same group afforded the stereospecific synthesis of some other derivatives **82** in use for the structure determination of the bisbenzylisoquinoline alkaloid **83**[36,37].



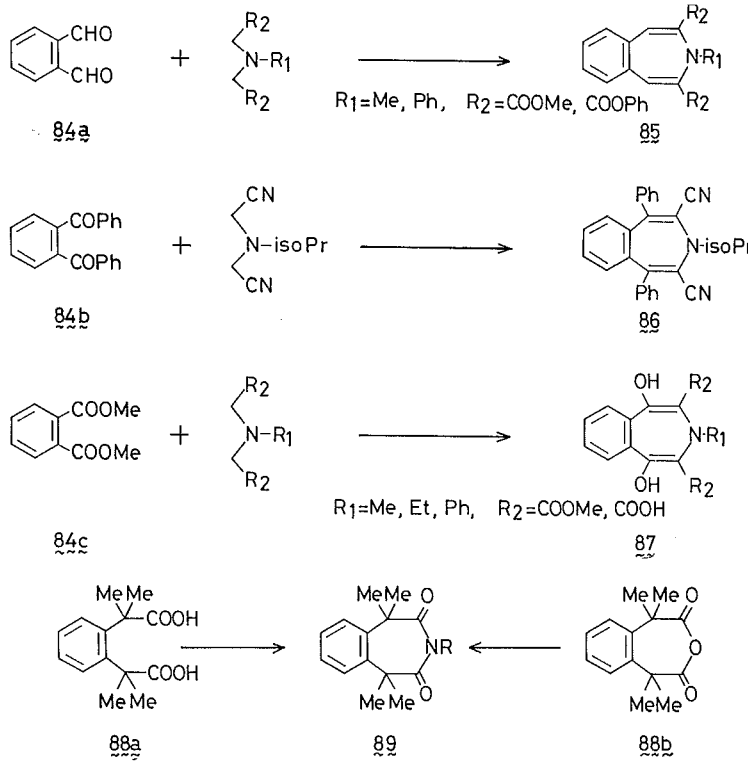
77 **78** **79** **80** **81**



82 **83**

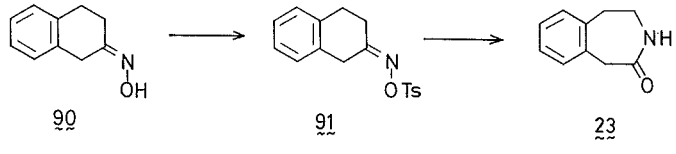
Type 4. ring closure, C_1-C_2 and C_4-C_5

Aldol like condensation of phthalaldehyde **84 a** with imino diacetic acid esters catalyzed with sodium or potassium methoxide[38,39] or potassium *t*-butoxide[40] gave low yields of benzazepine **85**. Diketone **84 b**[41] or dimethylphthalate **84 c**[42] has also been known to give benzazepine **86** or **87** in low yield. The phthalic acid **88 a** or its anhydride **88 b** was heated with conc. ammonia or N, N-dimethylethylenediamine to gave the cyclic imide **89**[43].



Type 5. Beckmann rearrangement

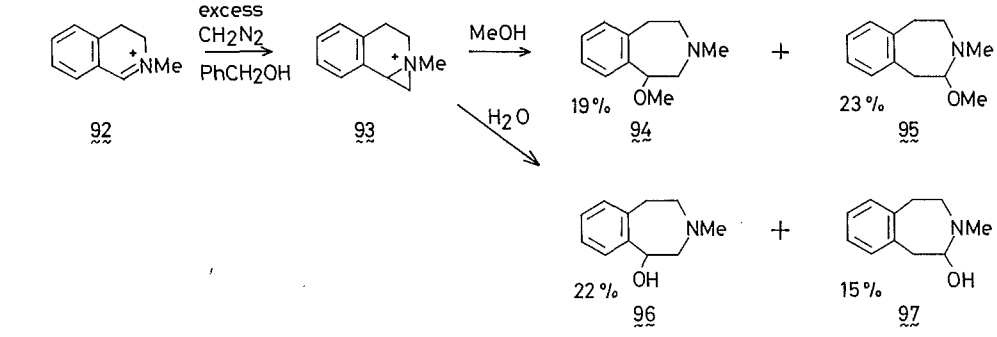
β-Tetralone oxime **90** was converted to the azepinone **23** by Beckmann rearrangement reaction of its tosylate **91**[44]. However, any isolation of aromatic alkoxy substituted benzazepinone in this method has not yet been reported.

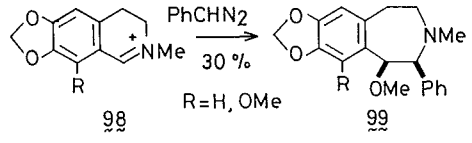


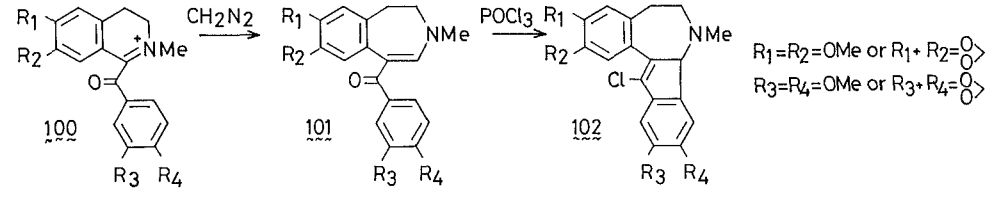
Type 6. ring expansion of isoquinoline nucleous

The reactions of 3, 4-dihydro-2-methyl-isoquinolinium salt and diazoalkane have been extensively studied.

Sniekus[21] reported the salt **92** gave the aziridinium salt **93**, which was converted to the azepine **94**, **95** in methanol and the azepine **96**, **97** in boiling water. Interaction of the salt **98** with phenyldiazomethane gave the 1-methoxy-2-phenylbenzazepines **99**[45]. Kametani[46~48] converted 1-benzoyl-3, 4-dihydroisoquinoline methiodides **100** into 5-benzoyl-1, 2-dihydro-3 H-3-benzazepines **101**, which was cyclized to benzindenoazepine **102** by treatment of phosphoryl chloride in boiling toluene. Tetramethoxy derivative of **102** was transformed to the phthalide isoquinoline alkaloid analogue[49].







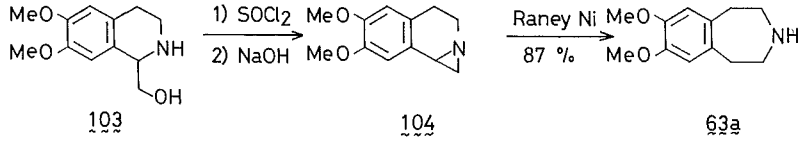
Examples of reductive ring expansion method using isoquinolines have been reported. Hydrogenation of **104** with Raney-Mickel in methanol underwent smoothly to give the benzazepine **59 a** in good yield[50]. 1-Benzoyl-3, 4-dihydro-or 1-benzoyl-1, 2, 3, 4-tetrahydro-2-alkyl isoquinolines **105** yielded the tetrahydrobenzazepines **106** by treatment with zinc and propionic acid[51]. Spiro isoquinolines **107** were also treated with zinc in boiling acetic acid to give benzazepines **108**, **109** in a ratio 1 : 3[52].

The aminoalcohol **110** of spirobenzylisoquinoline type compound as a result of treatment with mesyl chloride and triethylamine rearranges to the benzindenoazepine skeleton **112**, **113** *via* aziridinium intermediate **111**[53]. However, similar treatment of β-hydroxylaudanosine **114** gave 1-phenylazepine **115** in poor yield[54].

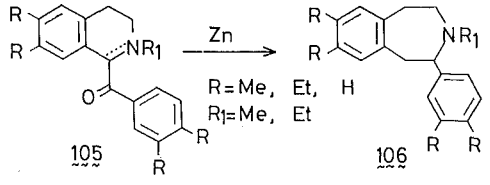
The stylene oxide **116** and the diol **117** were treated with acetic acid in the pres-

ence of *p*-toluenesulfonic acid to afford the same azepine **115** as described above[55].

Thus, the preparative methods to 3-benzazepine were briefly described, together with the results in our laboratories. The examples of the transformation reactions from the natural alkaloids to these azepine ring system were excluded in this article.



103 104 63a



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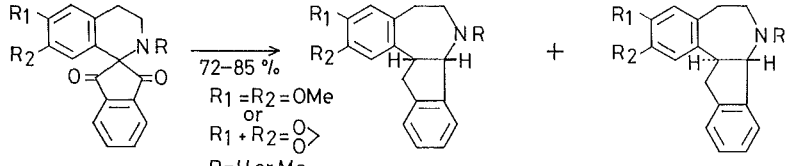

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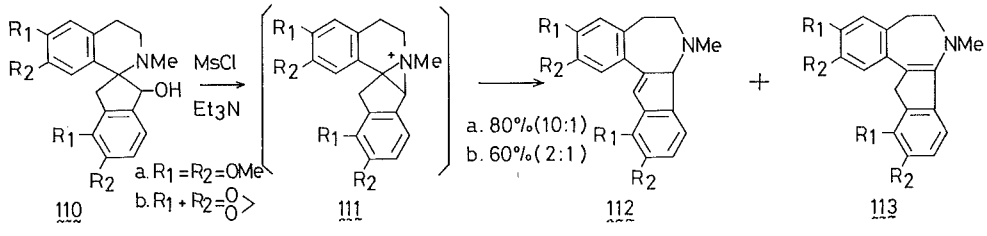

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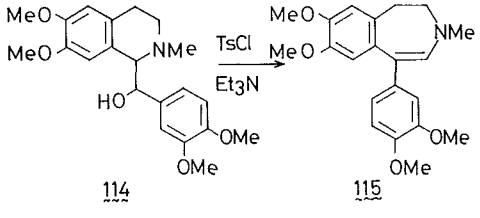

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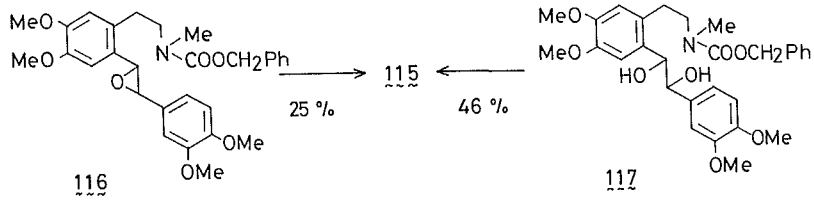

116 117

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