Synthetic Studies of Heterocyclic Compounds III

—Synthesis of Benz [*d*] indeno [1, 2-*b*] azepines—

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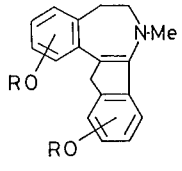
Abstract

Synthetic reactions to afford new tetracyclic compounds, benz [*d*] indeno [1, 2-*b*] azepines, are described, together with the studies of the synthetic approaches to these ring systems in our laboratories.

Introduction

It is in 1970 that the title compound appeared first in the literature[1]. Since then, many synthetic routes have been extensively studied, and these compounds have been substantiated to play central roles in the synthesis of the alkaloids which has been developed due to biogenetic[2] or pharmacological[3] interests. The first scheme shows isoquinoline alkaloids, such as rhoeadine **2**, spirobenzylisoquinoline **3**, phthalide isoquinoline **4** and protopine **5**, which have been derived from benzindenoazepine **1**.



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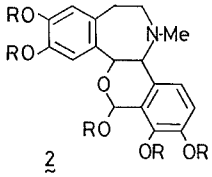

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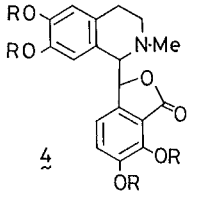

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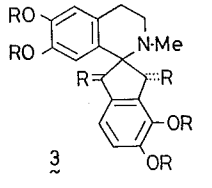

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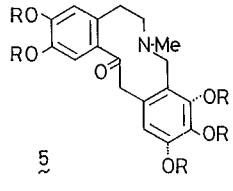

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Discussion

First synthesis was accomplished by intramolecular rearrangement reaction of spirobenzyl isoquinoline **8** of the type **3** by Irie et al. in 1970[1]. A Pictet-Spengler cyclization of 3, 4-dihydroxyphenethylamine and 4, 5-alkoxyindane-1, 2-dione **6**, followed by treatment with the chloroformate and triethylamine, gave the urethane

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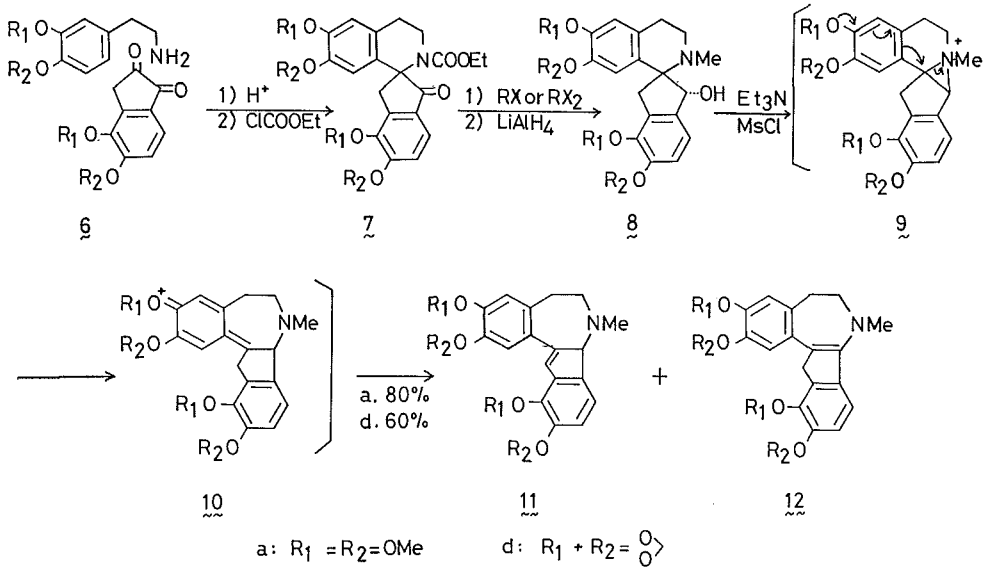
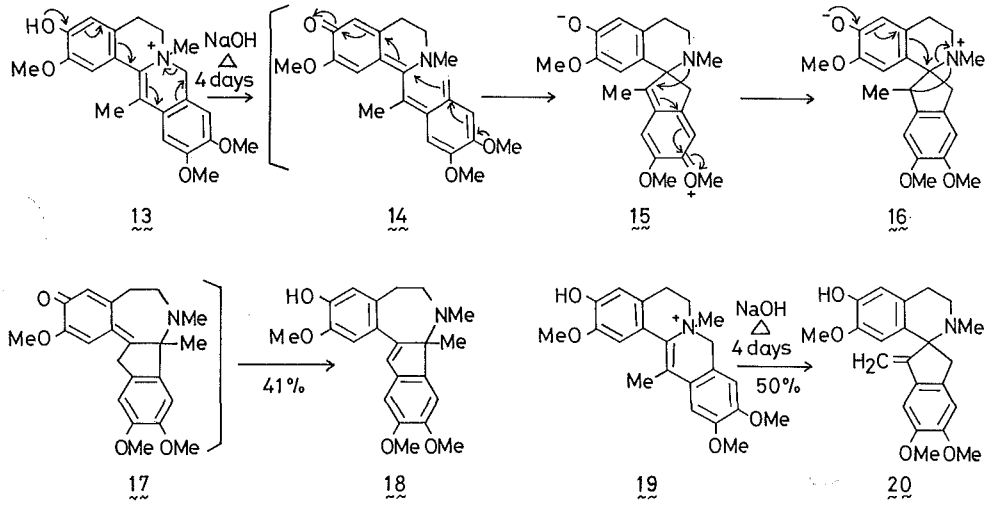
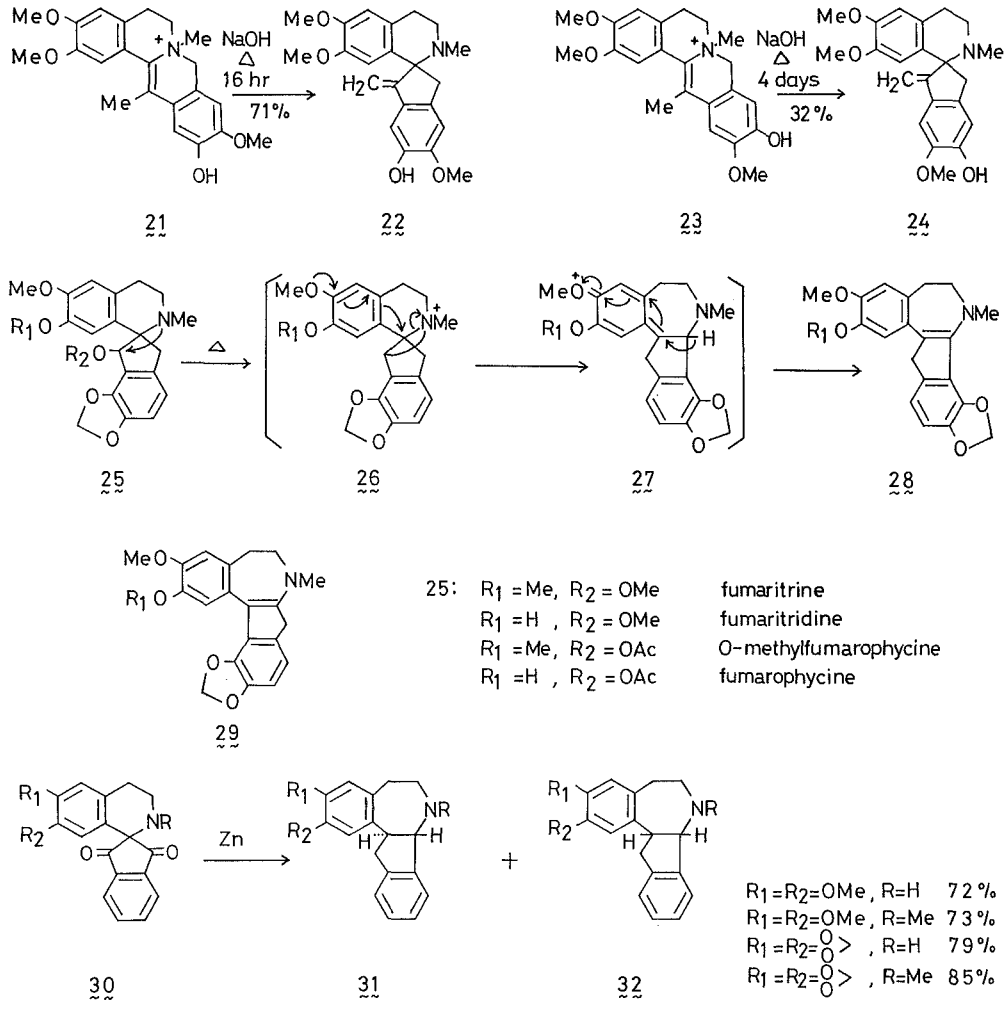
7, which was converted to the hydroxyspirobenzylisoquinoline **8 a, b** by alkylation of phenolic hydroxy groups and reduction with lithium aluminum hydride. **8 a, b** was treated with methanesulfonyl chloride and triethylamine to give two types of benzindenoazepines in a ratio of 10 : 1 for **11 a** and **12 a** (2 : 1 for **11 d** and **12 d**). Further conversion of **11 a, d** led to the synthesis of the rhoeadine alkaloids **2**[1,4].



Shamma et al. demonstrated the rearrangement of 3-hydroxyprotoberberine by heating in sodium hydroxide solution to benzindenoazepine **18**, proposing the reaction mechanism (**13**→**18**) on the basis of other related reactions (**19**→**20**, **21**→**22** and **23**→**24**)[5,6]. Accordingly, they suggested the mechanism *via* the aziridinium salt **9** to the Irie's scheme and also the structure **28** instead of **29** proposed by

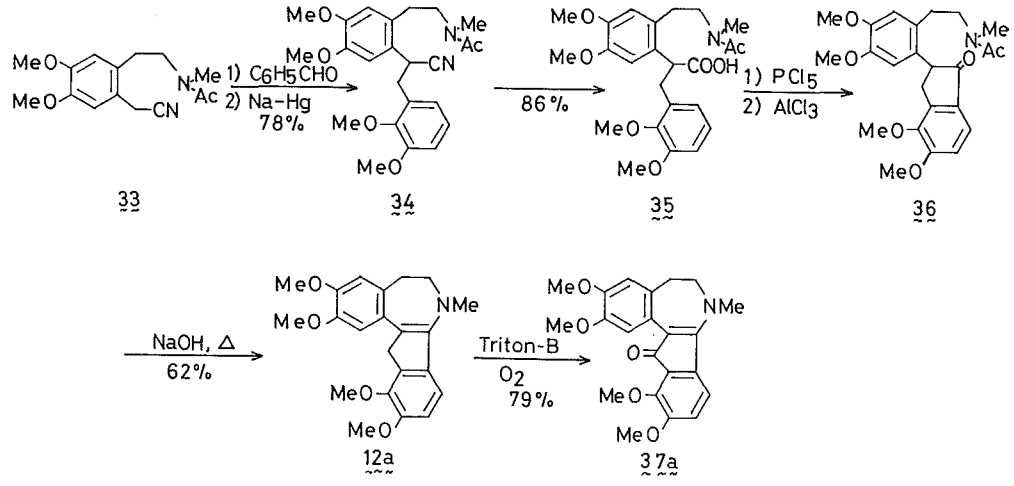


Mollov[7,8] who attempted the pyrolysis of **25** to benzindenoazepine ring system. Rearrangement of spirobenzylisoquinoline was also achieved by Kametani's group[9]. They found that the treatment of the compound **30** of the type **3** with zinc in boiling acetic acid for 1.5 hr gave a mixture of the *cis*- and *trans*-indanoazepines **31** and **32** in a ratio of 1 : 3.



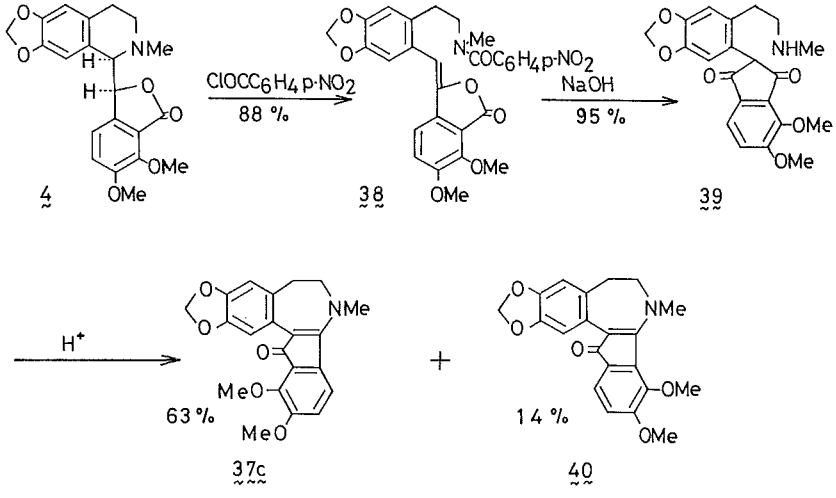
Orito et al. obtained benzindenoazepine **37** by first general synthetic method[10], not starting with alkaloids. Condensation of benzyl nitrile **33** with benzaldehyde, followed by reduction with sodium amalgam, gave α, β-diphenylpropionitrile **34**. Treatment of **34** with ethanolic hydrochloride and saponification of the resultant ethyl ester led to the formation of the acid **35**.

This acid was then subjected to intramolecular cyclization to give indanone **36**, the basic hydrolysis of which led to spontanious enamine formation to the tetramethoxybenz [*d*] indeno [1, 2-*b*] azepine **12 a**. In addition, the air oxidation of **12 a**



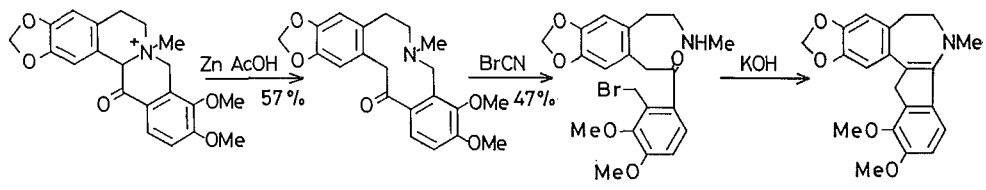
in the presence of Triton-B was carried out to afford 12-oxo derivative **37 a** in good yield, which turned into the synthetic precursor to the rhoeadine **2**[9] and phthalide isoquinoline alkaloids **4**[11]. Moreover, these benzindenoazepines **12 a** and **37 a** were converted to spirobenzyl isoquinoline alkaloids **3**[12].

MacLean reported the conversion of phthalide isoquinoline alkaloids **4** into the above 13-oxo derivatives[13]. The β-hydrastine **4** was treated with *p*-nitrophenyl chloroformate in the presence of a base to give **38**, which rearranged on interaction with sodium methoxide to the indane-1, 3-dione **39**, Basic hydrolysis and the following acid treatment led to the formation of two isomeric 12-oxoazepines **37 c** and **40**.



Another transformation reaction of isoquinoline alkaloid had been reported by Rodrigo et al[14].

Reductive ring opening reaction of 13-ketotetrahydropalmatine methosalt **41** with zinc in acetic acid produced the dibenzazecin-13-one **42**, which ring system

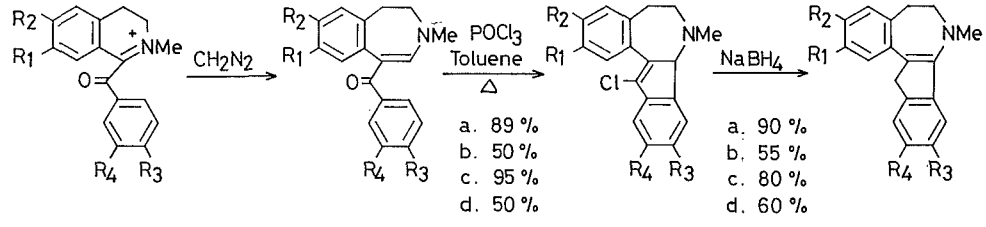


41 42 43 12c

was further opened by the von Braun reaction to give the keto-bromide **43**. This compound was in turn ring-closed to the enamine **12 c** by base treatment.

Second approach in the common route has been undertaken by Kametani's group[15,16,17], consisting of ring expansion of 2, 3-dihydroisoquinoline methiodide **44** with diazomethane to afford the 3 H-3-benzazepine **45**, which cyclized to 12-chlorobenzindenoazepine **46** by treatment with phosphoryl chloride in boiling toluene.

Treatment of **46** with sodium borohydride caused the dechlorination to lead to benzindenoazepines **47**. **46 a** has been derived into the analogue of phthalide isoquinoline alkaloid **4**[18].

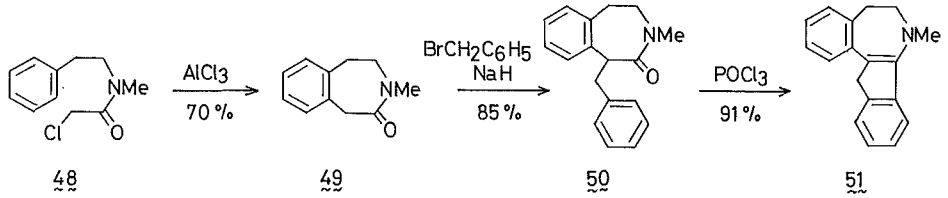


44 45 46 47

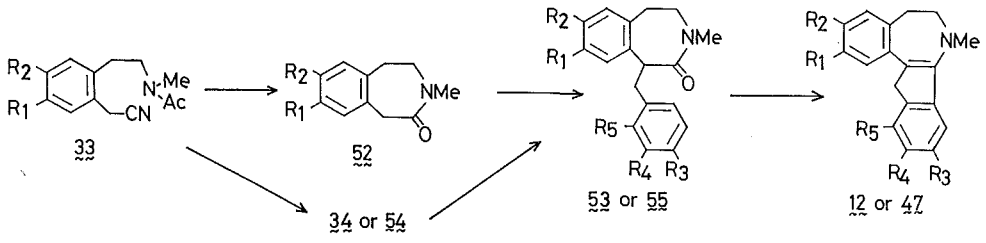
a: $R_1=R_2=R_3=R_4=OMe$ c: $R_1+R_2=\overset{O}{O}>$, $R_3=R_4=OMe$

b: $R_1=R_2=OMe$ $R_3+R_4=\overset{O}{O}>$ d: $R_1+R_2=R_3+R_4=\overset{O}{O}>$

Recently, we realized another simple approach to the construction of benzindenoazepine skeleton[19,20]. Friedel-Crafts cyclization of chloroacetamide **48** and successive treatment of the product, seven-membered lactam **49**, with benzyl bromide and sodium hydride yielded benzylbenzazepine **50**, whose cyclization with phosphoryl chloride produced 5, 6, 7, 12-tetrahydro-7-methyl-benz [*d*] indeno [1, 2-*b*] azepine **51**. Application of this reaction sequence starting from the aforementioned nitrile **33** led to an alternative method (**33**→**52**→**53**→**12**→**37** and **33**→**34**→**53**) to aromatic alkoxy substituted benzindenoazepines **12** and its 12-oxo derivatives **37**[21]. Similarly,



48 49 50 51



	33 → 52 → 53 → 12 → 37				33 → 34 → 53	
a $R_1=R_2=OMe$ $R_3=H$ $R_4=R_5=OMe$	81 %	84 %	83 %	79 %	88 %	85 %
b $R_1=R_2=OMe$ $R_3=H$ $R_4+R_5=O_2$		77	86	75	88	76
c $R_1+R_2=O_2$ $R_3=H$ $R_4=R_5=OMe$	88	87	78	76	93	74
d $R_1+R_2=O_2$ $R_3=H$ $R_4+R_5=O_2$		89	51	58	90	89
e $R_1=R_2=OMe$ $R_3=R_4=R_5=H$		86	92		85	88
	52 → 53 → 47				33 → 54 → 55	
a $R_1=R_2=R_3=R_4=OMe$ $R_5=H$		79 %	76 %		79 %	83 %
b $R_1=R_2=OMe$ $R_3+R_4=O_2$ $R_5=H$		85	72		80	86
c $R_1+R_2=O_2$ $R_3=R_4=OMe$ $R_5=H$		80	71		78	82
d $R_1+R_2=R_3+R_4=O_2$ $R_5=H$		83	69		81	90

known benzazepinones **47 a, b, c, d** were efficiently synthesized in these methods (**33**→**52**→**53**→**47** and **33**→**54**→**55**) [**54**: regio isomer (R_5=H) of **34**]. In addition, the photooxygenative ring enlargement reaction of **48** and further elaboration of dibenzazecinedione products resulted in the first total synthesis of pseudo type of the protopine alkaloids in a common route[22].

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