

perimentally tested a number of suicide enzyme inactivators. Some of our data are collected in Table I to indicate the effectiveness of these compounds. We believe the effectiveness of so-called suicide inactivators depends upon two properties: (1) their ability to bind at the enzyme active site and (2) their ability to undergo enzyme-catalyzed conversion to reactivate species capable of reacting irreversibly with the active site.

That suicide inactivation occurs can best be demonstrated by identifying the structural changes which take place in both the enzyme and the inhibitor. However, the careful application of a number of kinetic criteria can be used to demonstrate with reasonable certainty that suicide inactivation has in fact occurred. All the

inhibitors we have described were activated, we believe, by one of the following enzymatically catalyzed processes: proton abstraction leading to carbanion formation, proton abstraction leading to isomerization, proton abstraction leading to elimination, or oxidation.

We hope the examples cited have illustrated the potential usefulness of suicide enzyme inactivators for a wide variety of studies, both *in vitro* and *in vivo*. We believe that the design of suicide inactivators may in the future provide one rational approach to the design of pharmacologically useful compounds.

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## Total Synthesis of Natural Products by Retro Mass Spectral Synthesis

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The structure of natural compounds can be determined by the systematic use of chemical reactions and spectroscopic methods.<sup>1</sup> In contrast, one can not establish a definite method for synthesis of natural products, although there is a long history in synthetic organic chemistry. Biogenetic-type synthesis<sup>2</sup> is one effective route for the synthesis of natural products, such as morphine, and sometimes photolytic reactions can be applied to the total synthesis of complicated natural products.<sup>3,4</sup> Recently, Corey<sup>5</sup> developed a method of computer-assisted synthetic analysis that allows the automatic processing of a target molecule in the antithetic (retrosynthetic) direction.

The mass spectrum of an organic compound usually provides two types of information: one is a knowledge of the molecular weight and formula based on the molecular ion, and the second is a determination of the molecular structure on the ground of its fragmentation pattern. Since fragmentation is a chemical process that results in bond breaking, fragmentation of a compound in the mass spectrum is sometimes closely similar to chemical degradation reactions. For example, cyclohexene produces butadiene ion radical and ethylene in its fragmentation, a process which is also observed in chemical reaction. On the other hand, cyclohexenes can be obtained from butadienes and ethylene derivatives by a Diels–Alder reaction. These facts indicate that

some mass spectral fragmentations parallel chemical degradation processes and therefore also parallel retroprocesses of synthetic reactions of organic compounds. In this Account, we will discuss *retro mass spectral synthesis* as an effective method of analysis for designing synthetic approaches. This analysis is based on fragmentation processes in the mass spectrometer.

### Retro Mass Spectral Synthesis

In the mass spectra<sup>6</sup> of a series of 1-monosubstituted 1,2,3,4-tetrahydro-2-methylisoquinolines (1), fragment ions (2 and 3) formed by loss of the C-1 substituent or C-1 hydrogen are observed, in addition to an  $M^+ - 43$  ion (4) derived by a retro-Diels–Alder reaction of 1.

Reduction of 1-substituted 3,4-dihydroisoquinolines (2) is the most common method for the synthesis<sup>7,8</sup> of 1-monosubstituted 1,2,3,4-tetrahydroisoquinoline derivatives (1). Another method is an alkylation of 1-unsubstituted 3,4-dihydroisoquinolines (3) with alkyl anions, derived from Grignard reagents.

On comparison of these syntheses with the mass spectra of isoquinolines, the reduction method corresponds to a retrograde of the formation of the 3,4-

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(1) S. Sasaki, "Determination of Organic Structures by Physical Method", Academic Press, New York, N.Y., 1973, pp 284–321.

(2) T. Kametani and K. Fukumoto, *Synthesis*, 657 (1972); *Bioorg. Chem.*, 3, 420 (1974).

(3) P. G. Sammes, *Q. Rev., Chem. Soc.*, 24, 37 (1970).

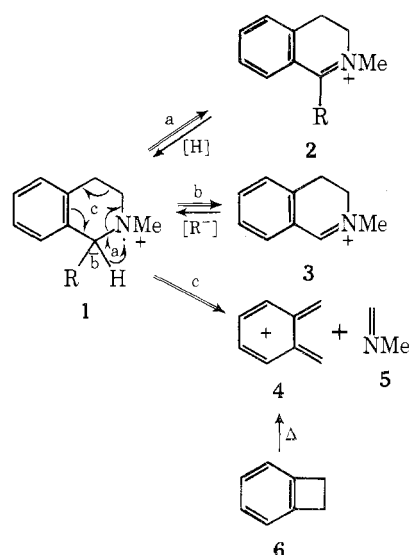
(4) T. Kametani and K. Fukumoto, *Acc. Chem. Res.*, 5, 212 (1972).

(5) E. J. Corey, *Pure Appl. Chem.*, 14, 19 (1967); E. J. Corey, W. J. Howe, and D. A. Pensak, *J. Am. Chem. Soc.*, 96, 7724 (1974); E. J. Corey, *Q. Rev., Chem. Soc.*, 25, 455 (1971).

(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. 1, Holden-Day, San Francisco, Calif., 1964.

(7) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1974.

(8) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology", Academic Press, New York, N.Y., 1972.

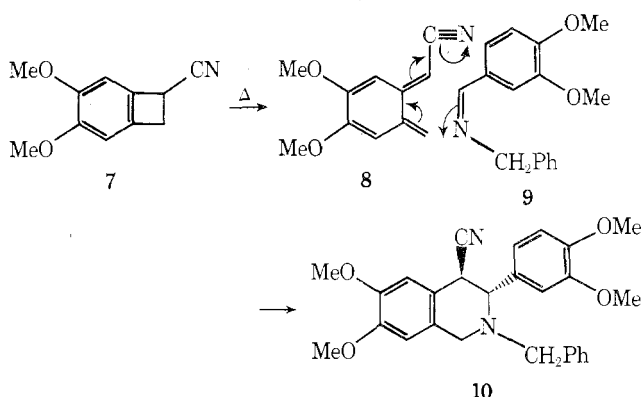


→ means mass spectral fragmentation process

→ indicates chemical reaction

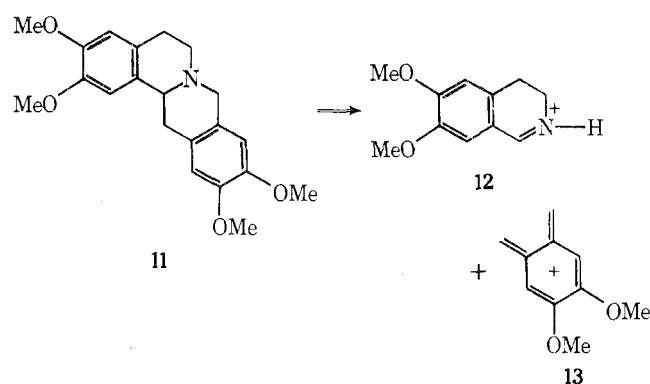
dihydroisoquinolinium ion **2** from the molecular ion **1** and the alkylation method to a retrograde of the formation of ion **3** from **1** in its mass spectrum. These phenomena suggest that the fragment processes in the mass spectrometer provide an effective way for retrosynthesis and might also be a useful synthetic route to target compounds.

We therefore examined a synthesis of 1,2,3,4-tetrahydroisoquinoline from the compounds which correspond to an ion **4** and fragment **5** formed by retro-Diels-Alder reaction of the molecular ion **1**. It is well known that a benzocyclobutene (**6**) can generate a reactive *o*-quinodimethane by heating.<sup>9</sup> We selected the benzocyclobutene **7** as a chemical equivalent to ion **4**. A reaction of **7** with Schiff base **9**, the synthon corresponding to ion **5**, at 150–160 °C without solvent afforded, in 45% yield, the 1,2,3,4-tetrahydroisoquinoline **10** in both regio- and stereospecific manner by a cycloaddition of the *o*-quinodimethane **8** to the Schiff base.<sup>10</sup> Thus, we succeeded in a developing a new synthesis of 1,2,3,4-tetrahydroisoquinolines by applying retro mass spectral synthetic analysis.



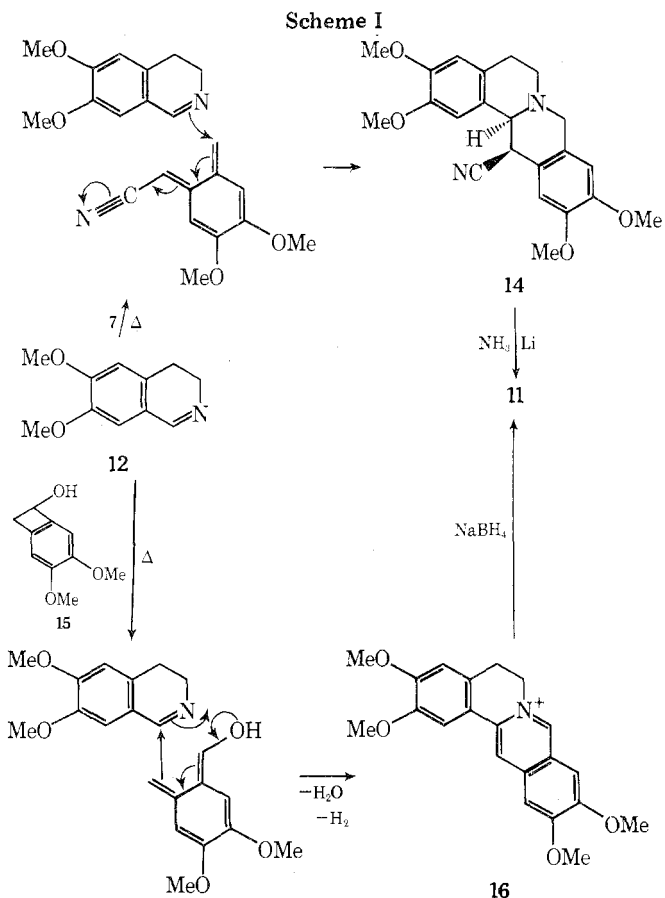
### Protoberberine Alkaloids

The mass spectrum<sup>6</sup> of xylopinine (**11**) shows an ion (**13**) having an *o*-quinodimethane system together with a 3,4-dihydroisoquinolinium ion (**12**). This fragment



process suggests that a combination of synthons corresponding to the two ions **12** and **13** would give xylopinine (**11**) by retro mass spectral synthesis. On the basis of this consideration, a total synthesis of **11** by use of 1-cyano- and 1-hydroxybenzocyclobutenes was examined as shown in Scheme I.

Heating an equimolar amount of 1-cyanobenzocyclobutene (**7**) and the 3,4-dihydroisoquinoline **12** at 150–160 °C gave, in 80–88% yield, 13-cyanoprotoberberine (**14**).<sup>11</sup> Reductive decyanation with lithium and liquid ammonia in the presence of isopropyl alcohol afforded xylopinine (**11**) in 84.6% yield.<sup>12</sup> Similarly, a mixture of the benzocyclobutenol **15** and **12** in benzene was heated to give the expected protoberberine (**16**) in 52% yield, which was reduced with sodium borohydride to afford xylopinine (**11**).<sup>13</sup>



(11) T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *J. Org. Chem.*, **39**, 447 (1974).

(12) T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 737 (1975).

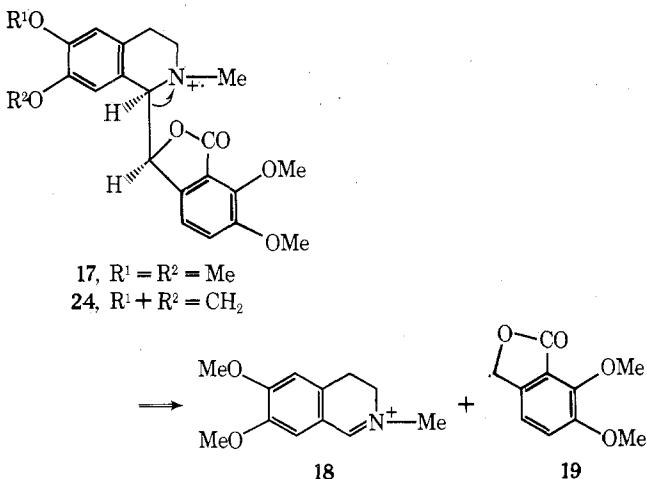
(13) T. Kametani, Y. Kato, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1712 (1974).

(9) I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

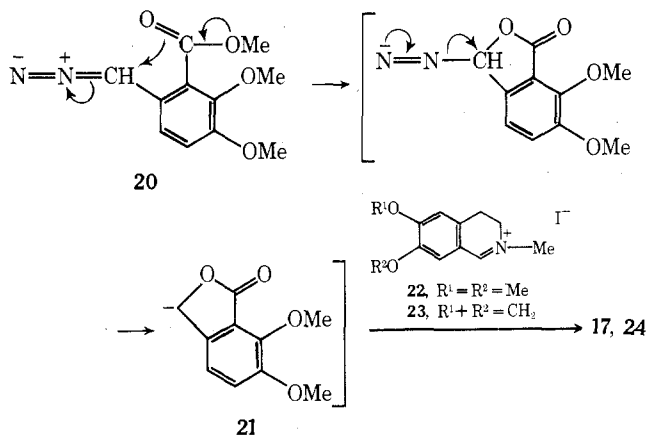
(10) T. Kametani, T. Takahashi, K. Ogasawara, and K. Fukumoto, *Tetrahedron*, **30**, 1047 (1974).

### Phthalideisoquinoline Alkaloids

The base peak of cordrastine (17) occurs at  $m/e$  204, which is assigned to ion 18. This fact reveals the partner ion of 18 to be the phthalide radical 19.<sup>8</sup>



In cases of retro mass spectral synthesis of this type of alkaloid, methyl 6-diazomethyl-2,3-dimethoxybenzoate (20) was used as a chemical equivalent to the phthalide radical 19, because the 6-diazomethyl compound generated easily a reactive ion (21) which has a similar structure to that of 19. Treatment of the 6-diazomethyl compound 20 with 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (22) in methanol-chloroform solution at room temperature for 2 days gave, in 10% yield, cordrastine (17), stereoselectively. Similarly, hydrastine (24) was obtained from the 6,7-methylenedioxyisoquinoline 23 and the 6-diazomethyl derivative 20.<sup>14</sup>

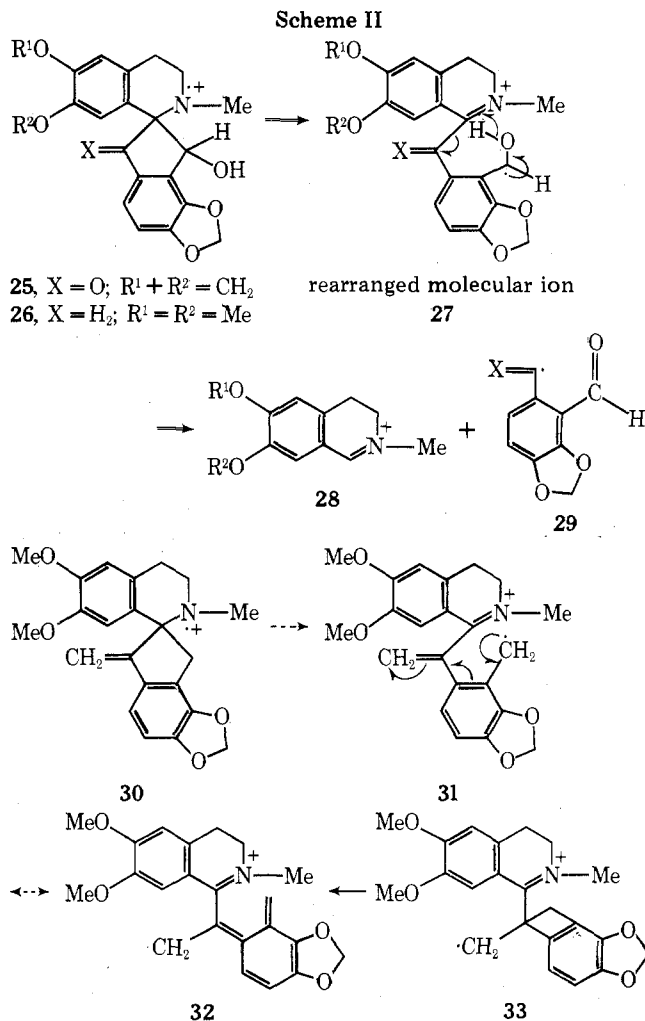


### Spirobenzylisoquinoline Alkaloids

Although a facile pathway for fragmentation of ochotensimine (30) could not be observed, the mass spectra of sibiricine (25) and fumaricine (26) show a common fragmentation pattern, as shown in Scheme II.<sup>7,8,15</sup> A rearranged molecular ion (27) is suggested in the formation of ions 28 and 29. When this fragmentation process is applied to the synthesis of ochotensimine (30), the rearranged molecular ion could be shown as 31, which would be equivalent to the *o*-quinodimethane 32 or the benzocyclobutene ion 33.

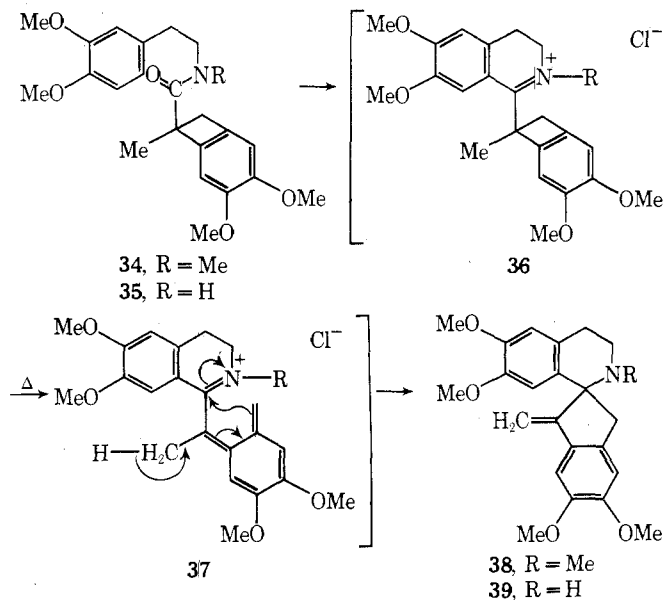
(14) T. Kametani, T. Honda, H. Inoue, and K. Fukumoto, *Heterocycles*, 3, 1091 (1975).

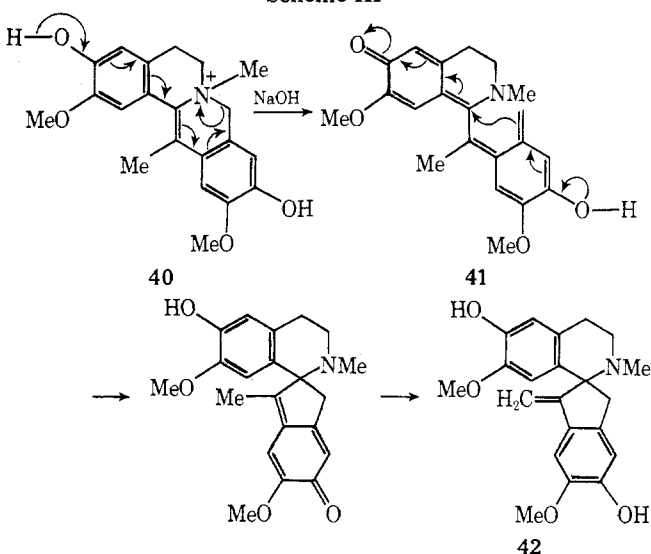
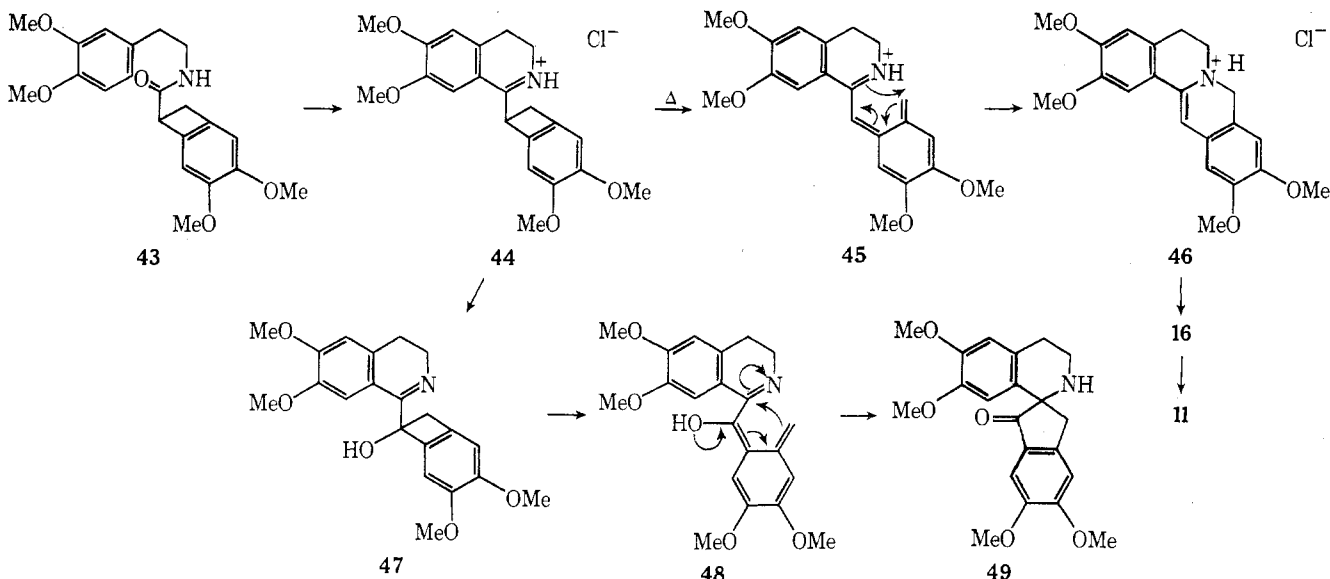
(15) C. K. Yu, J. K. Saunderson, D. B. McLean, and R. H. F. Manske, *Can. J. Chem.*, 49, 3021 (1971).



On the basis of this consideration, a retro mass spectral synthesis of spirobenzylisoquinoline was investigated from a 1-benzocyclobutenyl-3,4-dihydro-2-methylisoquinoline.

Bischler-Napieralski reaction of the *N*-phenethylbenzocyclobutene-1-carboxamide 34 with phosphoryl chloride in boiling benzene did not yield the expected 3,4-dihydro-2-methylisoquinolinium salt 36, but afforded the spirobenzylisoquinoline 38 in 14% yield. It





is probable that the 3,4-dihydroisoquinolinium salt **36** was initially formed and this rearranged thermally via *o*-quinodimethane **37** to yield the ochotensimine-type compound **38**.<sup>16</sup>

Similarly, the *de-N*-methylamide **35** gave, in 45% yield, the spirobenzylisoquinoline **39**, which was methylated by Eschweiler-Clarke reaction to the ochotensimine-type compound **38**.<sup>17</sup>

Shamma reported a synthesis of the ochotensimine-type compounds (**42**) via the quinodimethane intermediates (**41**) from the phenolic 7,8-dihydro-13-methylprotoberberines (**40**), as shown in Scheme III.<sup>18</sup>

On the other hand, Bischler-Napieralski reaction of the amide **43** having no *C*-methyl group on a cyclobutene ring afforded the 3,4-dihydroisoquinoline hydrochloride **44** in 98% yield. This was subjected to thermolysis in bromobenzene at 150–170 °C to furnish, presumably by cyclization of the *o*-quinodimethane **45** to the unstable dihydroprotoberberine **46** followed by dehydrogenation, protoberberine (**16**), in 90% yield.

(16) T. Kametani, T. Takahashi, and K. Ogasawara, *Tetrahedron Lett.*, 4847 (1972); *J. Chem. Soc., Perkin Trans. 1*, 1464 (1973).

(17) T. Kametani, Y. Hirai, H. Nemoto, and K. Fukumoto, *J. Heterocycl. Chem.*, **12**, 185 (1975).

(18) M. Shamma and C. D. Jones, *J. Am. Chem. Soc.*, **91**, 4009 (1969); **92**, 4943 (1970); M. Shamma and J. F. Nugent, *Tetrahedron Lett.*, 2625 (1970); *Chem. Commun.*, 1642 (1971); *Tetrahedron*, **29**, 1265 (1973).

Catalytic reduction of **16** gave (±)-xylopinine (**11**) in good yield.<sup>19</sup> By the same method, discretine<sup>20</sup> and coreximine were synthesized.<sup>21</sup>

The different chemical behavior in the above two types of amides (**34** and **43**) must arise from hyperconjugation and the steric effect of the methyl group.

Interestingly, the hydrochlorides of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline **44** are stable at room temperature, but the free bases of these compounds are unstable in air. A chloroform solution of the free base **44** on standing at room temperature was transformed into the ketospirobenzylisoquinoline **49** by air oxidation to the benzocyclobutenol **47**, followed by ring opening to *o*-quinodimethane **48** and then an electrocyclic process.<sup>22</sup>

### Olivacine

The mass spectrum of olivacine (**55**) shows no characteristic ions except its molecular ion. However, the dihydropyridocarbazole **50**<sup>23</sup> reveals two ions (**52** and **53**) formed by a ring opening of ring C. This suggests that dihydroolivacine (**51**) would generate an indole (**52**) and *o*-quinodimethane-pyridine analogous ions (**54**) in its mass fragment process. Therefore, olivacine synthesis from indole (**52**) and the dibromomethylpyridine **57**, which is a chemical equivalent to the *o*-quinodimethane-pyridine analog **54**, has been examined.

Refluxing 4-(1-hydroxyethyl)-3-methoxymethyl-2-methylpyridine (**56**) in 47% hydrobromic acid gave the corresponding dibromide (**57**), which was condensed with indole by heating to afford, in one step, olivacine in 30% yield.<sup>24</sup> By the same method, many pyridocarbazoles were synthesized from indole.<sup>23–25</sup>

(19) T. Kametani, K. Ogasawara, and T. Takahashi, *J. Chem. Soc., Chem. Commun.*, 675 (1972); *Tetrahedron*, **29**, 73 (1973).

(20) T. Kametani, Y. Hirai, F. Satoh, K. Ogasawara, and K. Fukumoto, *Chem. Pharm. Bull.*, **21**, 907 (1973).

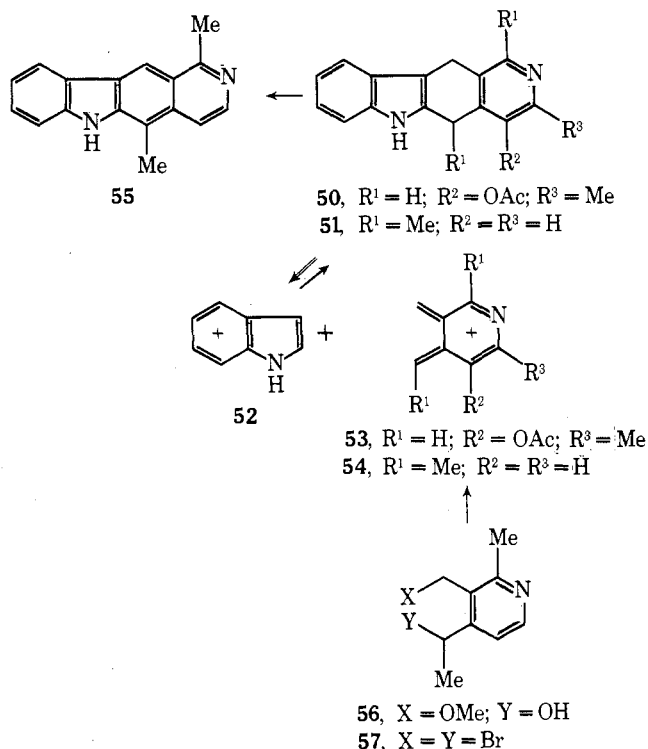
(21) T. Kametani, M. Takemura, K. Ogasawara, and K. Fukumoto, *J. Heterocycl. Chem.*, **11**, 179 (1974).

(22) T. Kametani, Y. Hirai, H. Takeda, M. Kajiwara, T. Takahashi, F. Satoh, and K. Fukumoto, *Heterocycles*, **2**, 339 (1974); T. Kametani, H. Takeda, Y. Hirai, F. Satoh, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 2141 (1974).

(23) T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *Heterocycles*, **2**, 171 (1974); *Tetrahedron*, **30**, 3713 (1974).

(24) T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, *Heterocycles*, **3**, 401 (1975).

(25) T. Kametani, T. Suzuki, K. Takahashi, Y. Ichikawa, and K. Fukumoto, *Heterocycles*, **2**, 9 (1974); *J. Chem. Soc., Perkin Trans. 1*, 413 (1975).

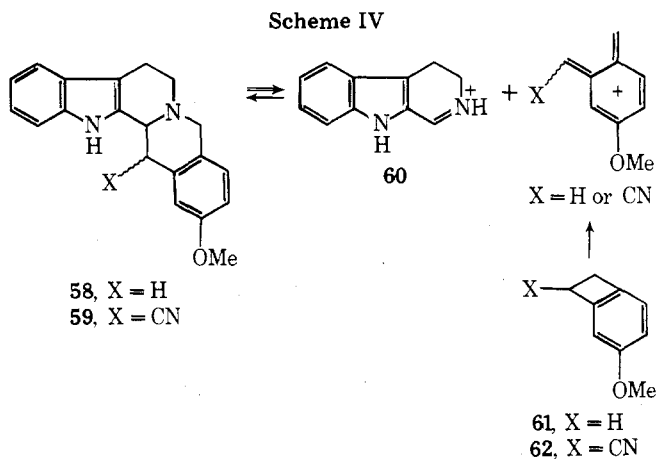


### Yohimbine

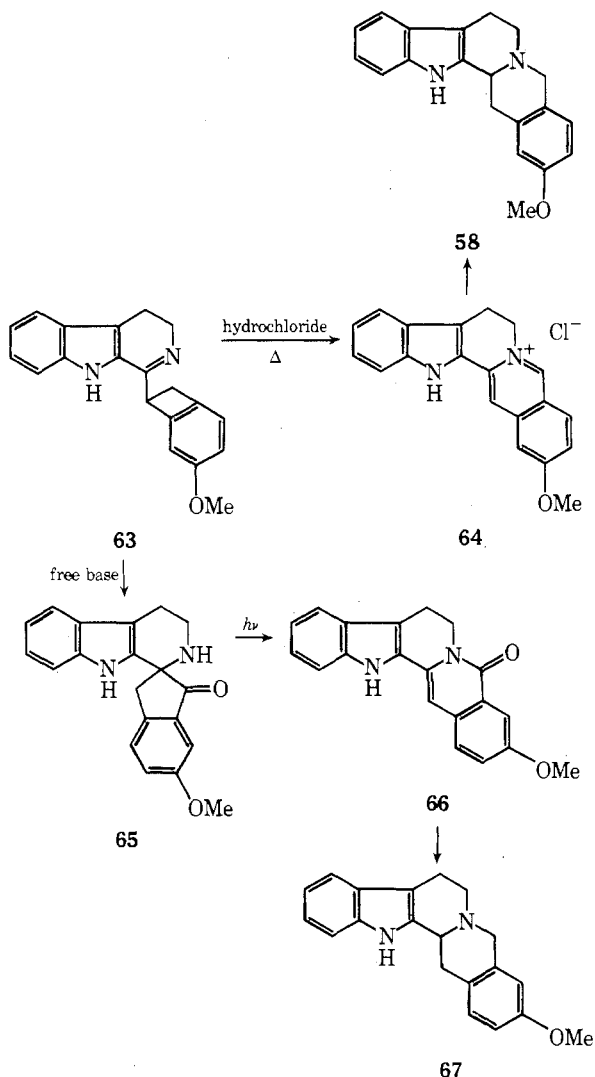
The main fragmentation pathway for the 15,16,17,18,19,20-hexadehydroyohimbane **58**<sup>26</sup> is shown in Scheme IV, and indicates strongly that **58** would be obtained from a mixture of 3,4-dihydro- $\beta$ -carboline (**60**) and methoxybenzocyclobutene **61** by retro mass spectral synthesis.

An intermolecular cycloaddition of 1-cyanobenzocyclobutene **62** to 3,4-dihydro- $\beta$ -carboline (**60**) was effected at 140–150 °C without solvent to give regioselectively the 14-cyanohexadehydroyohimbane **59** in 85% yield. This was decyanated by treatment with metallic lithium and liquid ammonia in the presence of isopropyl alcohol to afford, in 65% yield, the hexadehydroyohimbane **58**.<sup>12,16</sup>

Since it is well known that the *o*-quinodimethanes react intramolecularly with olefins to give tetralin derivatives, we attempted the synthesis of the yohimbane system by an intramolecular reaction of *o*-quinodimethanes with imines. Thermolysis of the 3,4-dihydro- $\beta$ -carboline hydrochloride **63** at 155 °C in bromo-



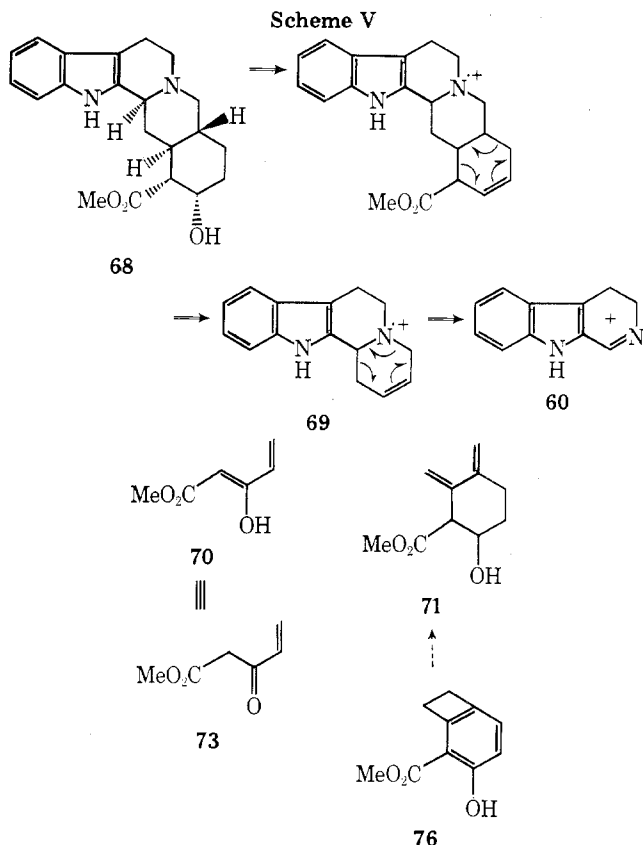
benzene gave the expected decadehydroyohimbane (**64**) (70% yield) which was reduced with sodium borohydride to give hexadehydroyohimbane **58**.<sup>26</sup>



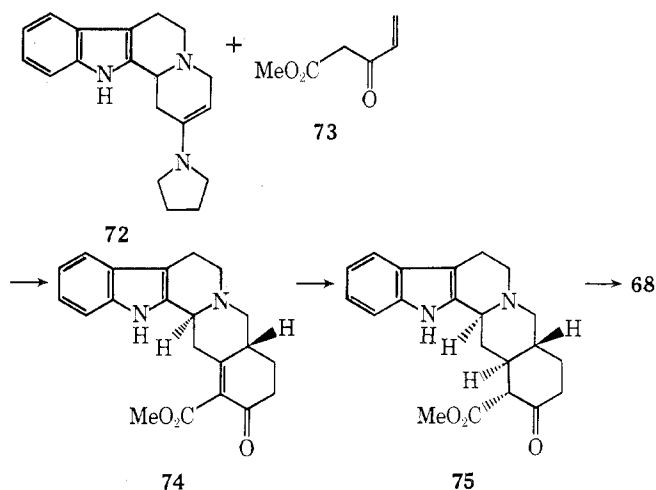
In addition, we synthesized the second hexadehydroyohimbane (**67**), differing from **58** only in the position of the methoxyl substituent, by utilizing the different reactivity of the free base and the hydrochloride. Thus, the free base **63** rearranged on standing in chloroform at room temperature to the ketospirobenzyl- $\beta$ -carboline **65**. On irradiation, **65** gives the lactam **66** which had already been converted into 18-methoxyyohimbane (**67**).<sup>12,22</sup>

On the basis of the above findings, we examined a total synthesis of yohimbine (**68**). A characteristic ion (**60**) in the mass spectrum of yohimbine would be derived from the ion (**69**) formed by a cleavage of ring E as shown in Scheme V. The partners of both ions **69** and **60** would be the hypothetical ions **70** and **71**, respectively, and therefore a retro mass spectral synthesis would employ the enamine **72** and methyl 3-oxo-4-pentenoate (**73**) or 3,4-dihydro- $\beta$ -carboline (**60**) and the benzocyclobutene **76**, which are all chemical equivalents or synthons to ions **60** and **69**-**71**.

Reaction of the pyrrolidine enamine (**72**) of indolo[2,3-*a*]quinolizin-2-one with methyl 3-oxo-4-pentenoate (**73**) gave 15,16-dehydroyohimbine (**74**) in 17.2% yield. A catalytic hydrogenation of **74** on 30% palladium on carbon gave ( $\pm$ )-yohimbine (**75**), which



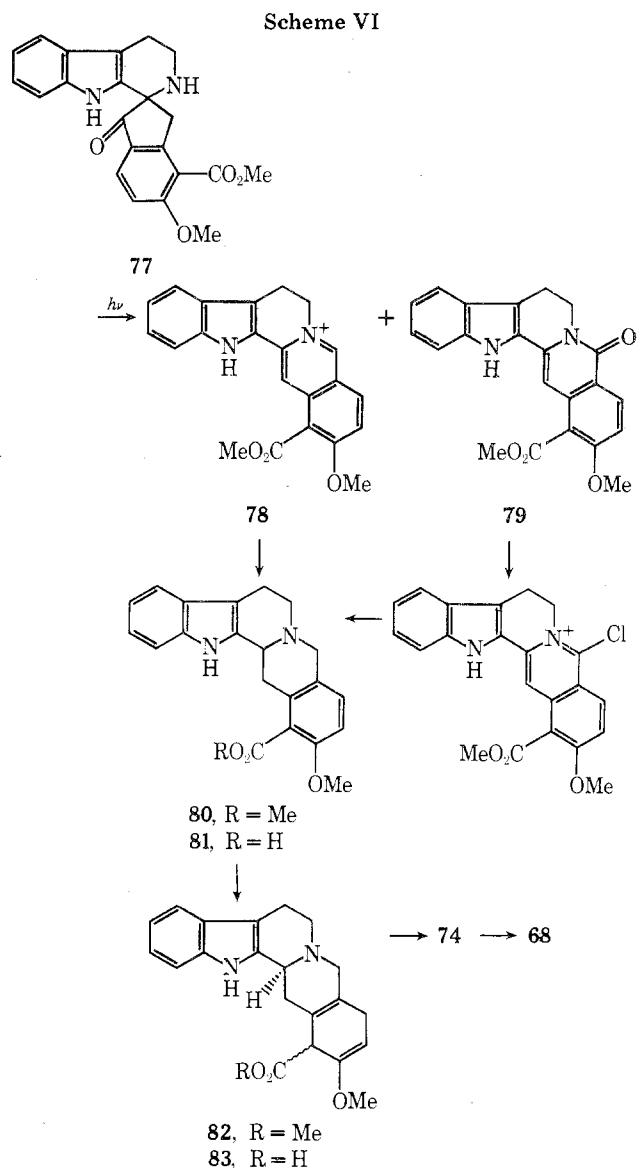
was converted into ( $\pm$ )-yohimbine (68) in addition to  $\beta$ -yohimbine by sodium borohydride reduction. Thus, a total synthesis of ( $\pm$ )-yohimbine (68) has been accomplished by a retro mass spectral route.<sup>27,28</sup>



The trial using 3,4-dihydro- $\beta$ -carboline (60) and benzocyclobutene 76 resulted in failure, but a modification gave a successful result as follows. The photolysis of the spirobenzyl- $\beta$ -carboline 77 yielded the decahydroyohimbane 78 and the decadehydroyohimbane-21-one 79. Reduction of both products gave *O*-methylhexadehydroyohimbine (80). Hydrolysis of this ester, followed by Birch reduction of the resulting carboxylic acid (81), afforded the enol ether 82, which was esterified with diazomethane to give the ester 83. Treatment of this product with diluted hydrochloric acid afforded dehydroyohimbine (74), which had

(27) T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Heterocycles*, **3**, 179 (1975).

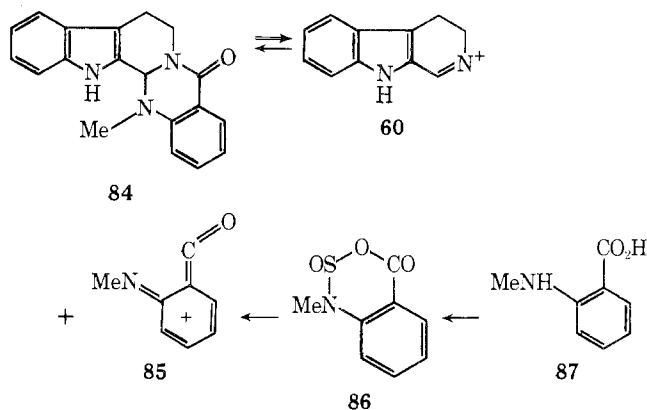
(28) T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Chem. Pharm. Bull.*, **23**, 2634 (1975).



already been converted into yohimbine (68) as shown in Scheme VI.<sup>28,29</sup>

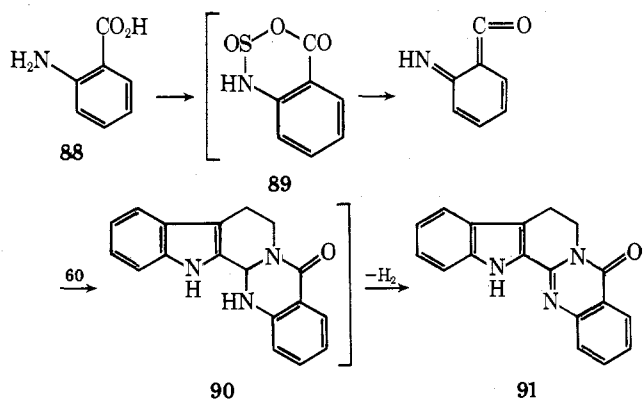
### Quinazolinocarboline Alkaloids

Evodiamine (84), a typical member of the quinazolinocarboline alkaloids, showed two characteristic ions, 60 and 85, by a retro-Diels-Alder reaction of ring D in its mass spectrum. This phenomenon indicates that evodiamine (84) could be synthesized from 3,4-dihydro- $\beta$ -carboline (60) and the iminoketene 85.



(29) T. Kametani, Y. Hirai, and K. Fukumoto, *Heterocycles*, **4**, 29 (1976).

Heating *N*-methylantranilic acid (87) with thionyl chloride gave an unstable sulfinamide anhydride (86), which was treated with 3,4-dihydro- $\beta$ -carboline (60) in dry benzene at room temperature to afford regioselectively evodiamine (84), in 65% yield. In this reaction, the sulfinamide anhydride 86 was converted into the iminoketene 85, which reacted regioselectively with 3,4-dihydro- $\beta$ -carboline (60) by cycloaddition pattern to form evodiamine.<sup>30</sup>



(30) T. Kametani, T. Higa, K. Fukumoto, and M. Koizumi, *Heterocycles*, 4, 23 (1976).

Rutecarpine (91) is also obtained in one step by the same way; thus a treatment of the sulfinamide anhydride 89, derived from anthranilic acid (88), with 60 gave, in 85% yield, rutecarpine (91), by a spontaneous dehydrogenation of the firstly formed product (90).<sup>30</sup>

Thus, one-step syntheses for evodiamine and rutecarpine have been accomplished by retro mass spectral methods.

In this Account, we have shown retro mass spectral analysis to provide a simple and effective synthetic approach to natural products having a complicated structure. Most of the important types of fragmentation in the mass spectrum are summarized as: (1) simple carbon-carbon bond cleavages; (2) cleavages involving heteroatoms; (3) retro-Diels-Alder types of concerted cleavages; and (4) rearrangements. We have discussed the power and generality of our method to syntheses of natural products which show fragmentation processes of types 1 and 3. Unfortunately, we have no successful results in retro mass spectral synthesis due to type 4 fragmentation. We have also found a new reaction of iminoketenes, generated in situ from anthranilic acids, with the imine system and have developed several new synthetic methods for some isoquinoline and indole alkaloids. We believe that retro mass spectral synthesis can be extended to the synthesis of tetracyclins, terpenes, and steroidal hormones in the future.

## Nuclear Reactions Revisited with Very Heavy Ions

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Intense excitement has been generated during the last decade by nuclear theorists who have predicted islands or regions of enhanced nuclear stability<sup>1</sup> for elements with *Z* values considerably larger than those now known (e.g., atomic numbers *Z* = 110 to 126). The calculations leading to the predicted properties of superheavy nuclei are based in part on experimental information about shape-dependent nuclear shells which account for the recently discovered two-humped fission barriers.<sup>2</sup> Although some effort has gone into various experimental searches for these new elements, no evidence for them has been found to date.<sup>1</sup> Reactions with heavy ions are possibly one mode of producing the superheavy elements and, hence, the development of heavy-ion science has been rapidly accelerated.

The search for superheavy elements was also one of the initial motivations for my interest in the various types of mechanisms involved in the interaction be-

tween two large complex nuclei. However, these reaction mechanisms are of great fundamental interest in themselves. In this Account I discuss the mechanisms of reactions between very heavy ions, with emphasis on the recently discovered strongly damped collision process. This new process has now been reported for reactions induced with heavy-ion projectiles from nitrogen to xenon.<sup>3-21</sup> In order to place this new reaction process

(1) For reviews of this subject and references, see *Phys. Scr.*, **10A**, 1 (1974); G. N. Flerov, "Reactions between Complex Nuclei", Vol. 2, North-Holland Publishing Co., Amsterdam, 1974, p 459.

(2) For references in this area, see R. Vandenbosch and J. R. Huizenga, "Nuclear Fission", Academic Press, New York, N.Y., 1973.

(3) A. G. Artukh, G. F. Gridnev, V. L. Mikheev, V. V. Volkov, and J. Wilczyński, *Nucl. Phys. A*, **211**, 299 (1973); **215**, 91 (1973).

(4) F. Hanappe, M. Lefort, C. Ngo, J. Peter, and B. Tamain, *Phys. Rev. Lett.*, **32**, 738 (1974).

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