TOTAL SYNTHESIS OF CERTAIN ISOQUINOLINE AND INDOLE ALKALOIDS BY THERMOLYSIS

Tetsuji Kametani* and Keiichiro Fukumoto

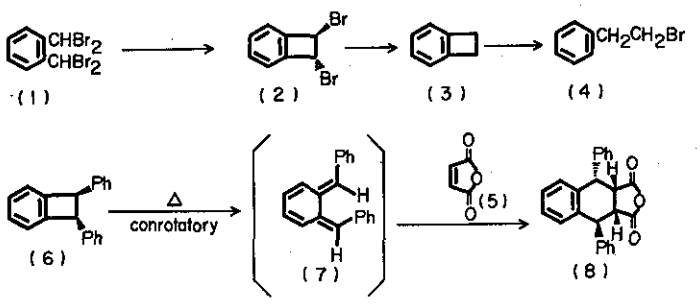
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan

The total syntheses of some isoquinoline and indole alkaloids were achieved by inter- and intramolecular cycloaddition of o-quinodimethanes by thermolysis.

The benzocyclobutenes have a long history in organic chemistry and also in physical organic chemistry. The first synthesis of the benzocyclobutene ring system was reported by Finkelstein[2] who prepared 1,2-dibromobenzocyclobutene (2) in 1910 by the reaction of α,α',β,β'-tetrabromo-o-xylene (1) with sodium iodide in boiling alcohol. However, due to the instability of the benzocyclobutenes, the field of benzocyclobutene chemistry lay dormant for 50 years until Cava and Napier[3] (Chart 1) synthesized the parent benzocyclobutene (3) by treatment of the dibromo intermediate (2) with sodium iodide followed by catalytic dehalogenation with palladium-on-charcoal and moreover indicated the reactivity of the benzocyclobutene ring system by the conversion of benzocyclobutene (3) with hydrobromic acid into phenethyl bromide (4). Soon thereafter, Jensen and Coleman carried out a thermolysis of 1,2-diphenylbenzocyclobutene (6) in the presence of the dienophile, maleic anhydride (5), obtained the tetralin derivatives (8) and suggested the o-quinodimethane (7) as the intermediate. In 1964, Huisgen and Seidel[5] proved that this type of reaction proceeded stereo-

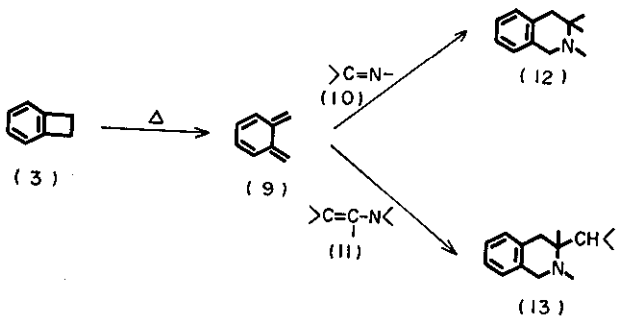
selectively, and in 1970, Woodward and Hoffmann[6] proposed that thermolytic ring opening occurs in a conrotatory manner.

Chart 1



The benzocyclobutene derivatives give on heating the reactive o-quinodimethanes (9) which can easily react stereoselectively and regioselectively with olefins to afford tetralin derivatives, and therefore are potential starting materials in synthetic organic chemistry, especially in the synthesis of natural products. In this connection, we examined the thermolysis of benzocyclobutenes (3) in the presence of the imines (10) or enamines (11) as the dienophiles in order to prepare isoquinolines

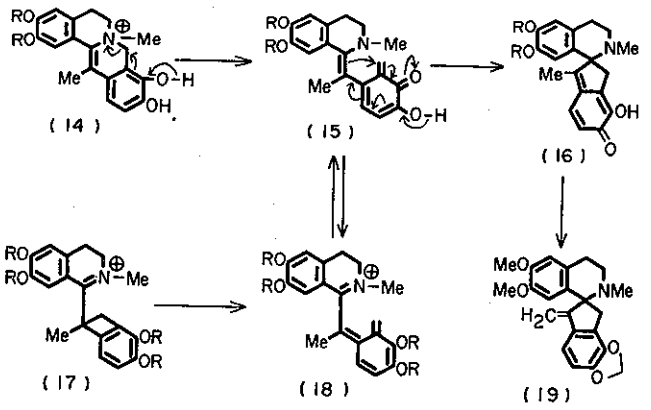
Chart 2



of the type 12 and 13 and these developed a new method for the total synthesis of isoquinoline and related alkaloids.

In 1969, Shamma and Jones.[7] proposed that the spirobenzylisoquinoline alkaloids, such as ochotensimine (19), could be biosynthesized from the protoberberine type compounds (14). In basic medium, this salt (14) could cleave to the o-quinonoid intermediate (15) which by an electrocyclic process due to a Michael condensation would form the spirane (16), followed by a tautomeric shift to yield the diphenol which could readily lead to ochotensimine (19) in the plant. Based on this hypothesis, we considered the o-quinonoid intermediate (15), electronically equivalent to the o-quinodimethane structure (18) which would seem to be easily available by thermolysis of the 1-benzocyclobutenyl-3,4-dihydro-2-methylisoquinolines (17). Thus, if the 1-benzocyclobutenyl-3,4-dihydroisoquinolines (17) were subjected to thermolysis, the o-quinodimethanes (18) which would be generated tautomerize to o-quinonoids (15) and then convert to the protoberberine (14) and/or ochotensine type compounds (19).

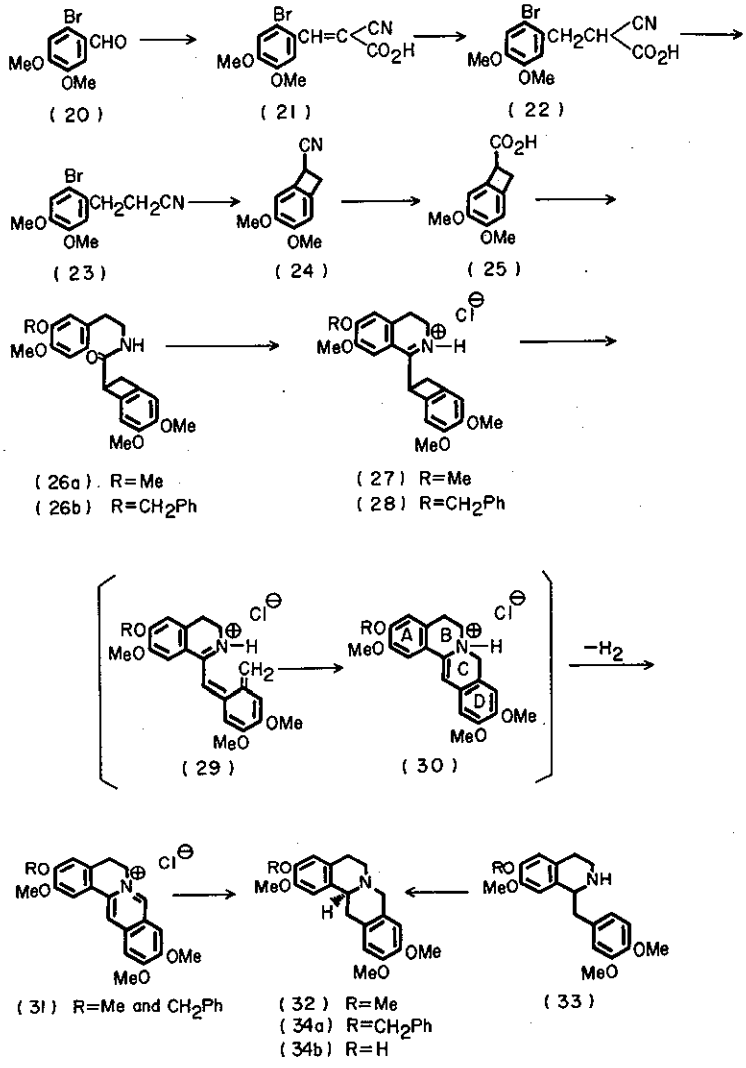
Chart 3



In order to explore the thermolysis of the 1-benzocyclobutenyl-3,4-dihydroisoquinolines, the latter was synthesized as follows:[8] 6-Bromoveratraldehyde (20), obtained from veratraldehyde, was condensed with cyanoacetic acid in the presence of ammonium acetate and pyridine in boiling benzene and the resulting cinnamic acid (21) was reduced with sodium borohydride in saturated aqueous sodium bicarbonate solution to the corresponding hydrocinnamic acid (22) in 95 % yield. Decarboxylation of (22) at 170° in dimethylacetamide or hexamethylphosphoramide afforded, in 95 % and 85 % yield, respectively, the phenylpropiononitrile (23). Treatment of (23) with 4 molar equivalents of sodium amide in liquid ammonia gave the benzocyclobutene derivative (24) in 74 % yield possibly via the benzyne reaction.

Hydrolysis of the nitrile (24) with potassium hydroxide yielded the corresponding carboxylic acid (25) in 91 % yield, followed by condensation with homoveratrylamine or 3-benzyloxy-4-methoxyphenethylamine in the presence of dicyclohexylcarbodiimide in dichloromethane to give the expected amides (26a) and (26b) in 83% and 78 % yield, respectively. Bischler-Napieralski reaction of these amides (26) with phosphoryl chloride in boiling benzene afforded the starting 3,4-dihydroisoquinoline hydrochlorides (27) and (28) in 98 % and 78 % yield, respectively[8,9] which were subjected to thermolysis in bromobenzene at 150 - 170° for 20 min in a current of nitrogen to furnish, presumably by cyclization of the o-quinodimethane (29) to the unstable dihydroprotoberberine (30) followed by dehydrogenation, the protoberberines (31) in 90 % and 78 % yield, respectively. Catalytic reduction of these protoberberines (31) gave (±)-xylopinine (32) and (±)-discretine (34a), in good yield which were identical with authentic samples prepared by the Pictet-Spengler reaction from the 1-benzyl-1,2,3,4-tetrahydroisoquinolines (33).[8,9]

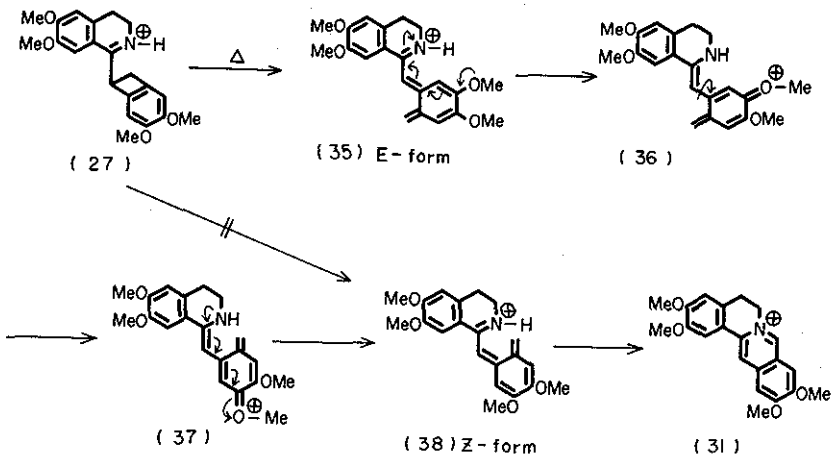
Chart 4



In the above thermolysis the same result was obtained when dichlorobenzene was used as a solvent although none of the expected protoberberines was isolated when

the free base (27) was heated at 150 - 170° in bromobenzene under a current of nitrogen. The different behavior of the free bases and the hydrochlorides in thermolysis might be due to the orientation of the benzocyclobutene ring cleavage product. During the thermolytic ring cleavage of (27), the more stable E-form of the o-quinodimethane (35) preferentially formed over the unstable Z - form (38), tautomerizes due to the activated $>C=\overset{+}{N}H-$ group to give the o-quinodimethane (38) via intermediates (36) and (37) followed by cyclization to the protoberberine (31). In contrast, the free base of (35) lacks the activating group and therefore cannot tautomerize to the Z - form corresponding to (38).

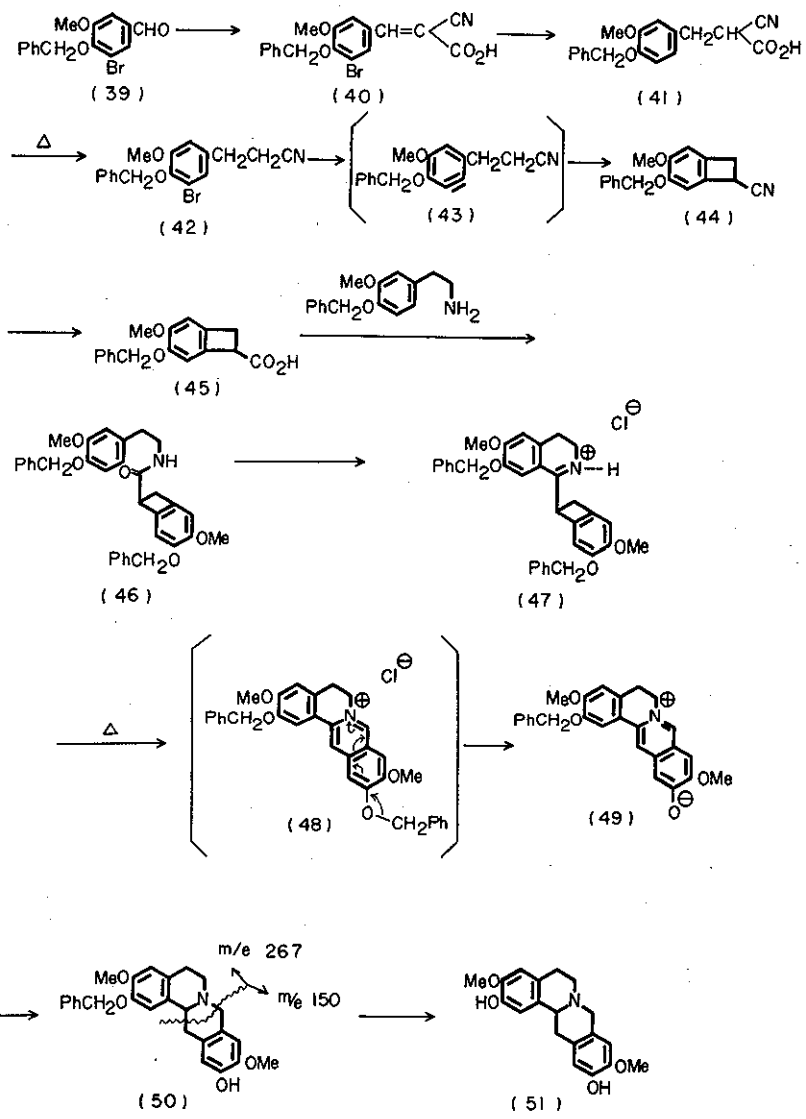
Chart 5



The same synthetic sequence was applied to the total synthesis of the protoberberine alkaloid, coreximine (51).[10] Thus, Knoevenagel reaction of 4-benzyloxy-3-bromo-5-methoxybenzaldehyde (39) with cyanoacetic acid followed by sodium borohydride reduction of the resulting cinnamic acid (40) gave the hydrocinnamic acid (41), which was heated in dimethylacetamide to afford the phenylpropiononitrile (42).

Treatment of 42 with sodium amide in liquid ammonia gave the benzocyclobutene (44) by cine-substitution which indicated that this reaction proceeded via the benzyne

Chart 6



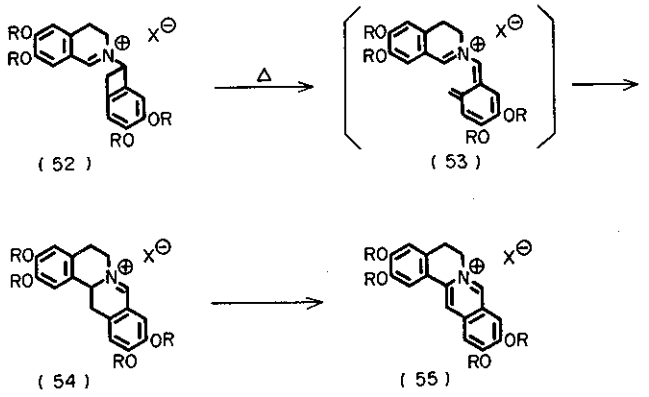
intermediate (43). Hydrolysis of the nitrile (44) furnished the corresponding carboxylic acid (45) which was condensed with 4-benzyloxy-3-methoxyphenethylamine in the presence of dicyclohexylcarbodiimide to give the amide (46) which was cyclized by a Bischler-Napieralski reaction to yield the 1-benzocyclobutenyl-3,4-dihydroisoquinoline hydrochloride (47). Thermolysis of (47) then gave the phenolic protoberberine (49) whose reduction with sodium borohydride afforded the tetrahydroprotoberberine (50) with the phenolic hydroxyl group assigned to ring D based on the reaction mechanism of debenzylation as shown for intermediate (48). This suggestion was partially supported by mass spectrometry which showed fragment ions at m/e 267 and m/e 150. Confirmation for this assignment was obtained by an alternative synthesis of the 11-hydroxytetrahydroprotoberberine (50) via standard methods involving Mannich reaction of appropriately 1-substituted benzyltetrahydroisoquinolines.

Finally, debenzylation of the phenolic protoberberine (50) with ethanolic hydrochloric acid afforded (±)-coreximine (51) identical with authentic coreximine by ir spectral comparison.[10]

The above protoberberine alkaloid synthesis, based on thermolysis of suitable benzocyclobutene, proved more convenient than the standard Mannich reaction with regard to the number of synthetic steps as well as yields.

In addition, we were also interested in determining whether thermolysis of 2-(1-benzocyclobutenyl)-3,4-dihydroisoquinolinium salt (52) would form the o-quinodimethane derivative (53) followed by rearrangement to give the dihydroprotoberberine (54) or protoberberine (55).

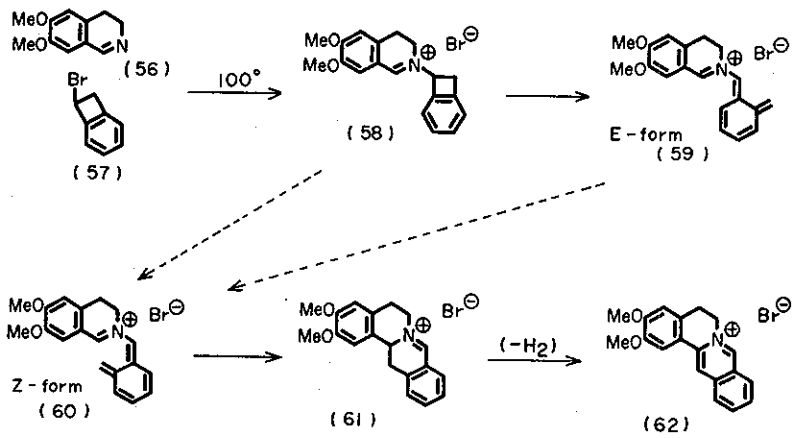
Chart 7



In this connection 1-bromobenzocyclobutene (57) was heated with 3,4-dihydro-6,7-dimethoxyisoquinoline (56) without solvent on a water bath for 20 hr to give, surprisingly, the desired protoberberinium salt (62), but not the corresponding 2-(1-benzocyclobutenyl)-3,4-dihydroisoquinoline (58). The structure was easily proved by comparison with an authentic sample prepared by a known method.[11]

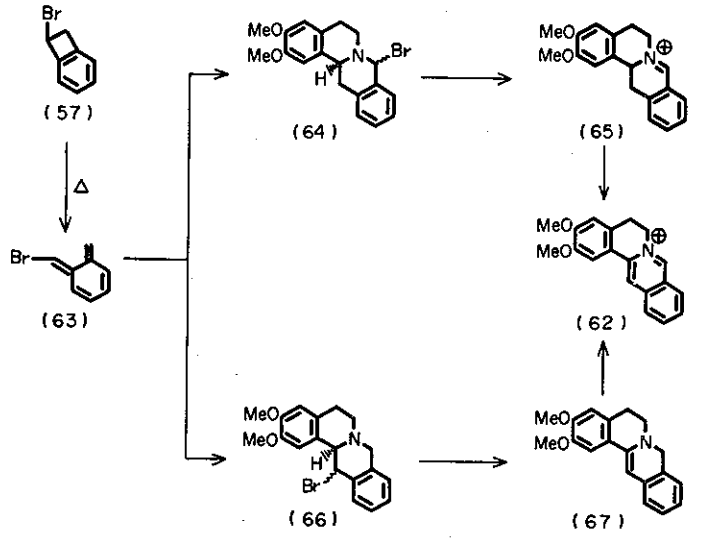
This reaction can be explained by the transformation of quaternary salt (58), obtained from the 3,4-dihydroisoquinoline (56) and bromobenzocyclobutene (57), into protoberberine (62), via the unstable dihydroprotoberberine (61) formed by cyclization of o-quinodimethane (60) having the Z-form. However, the direction of ring opening is preferable to the stable E-form (59) which could not be cyclized to the protoberberine, than to the unstable Z-form (60). Moreover, 1-bromobenzocyclobutene (57) could not react with the 3,4-dihydroisoquinoline (56) under the reaction condition in which the 3,4-dihydroisoquinoline (56) forms the corresponding quaternary salts with the usual halides.

Chart 8



Therefore, it is reasonable to postulate that the benzocyclobutene (57) is

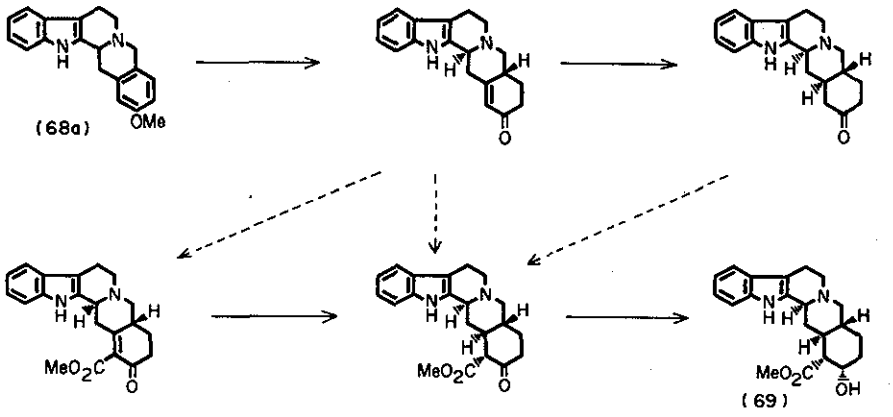
Chart 9



thermally converted into the o-quinodimethane (63) which then reacts with the 3,4-dihydroisoquinoline to form the 8- or 13-bromotetrahydroprotoberberine (64 or 66) followed by transformation into the protoberberine (62) via the corresponding dihydroprotoberberine (65 or 67). Thus, this transformation demonstrates a facile and simple entry into the synthesis of certain protoberberine type compounds.

The above example illustrates a new synthetic method for the benzoquinolizidine system based on electrocyclic reaction of 1-benzocyclobutenyl-3,4-dihydroisoquinolines by thermolysis. This method could also be similarly applied to the synthesis of the yohimbane system (68) which would be a useful key intermediate for the synthesis of yohimbine (69).

Chart 10



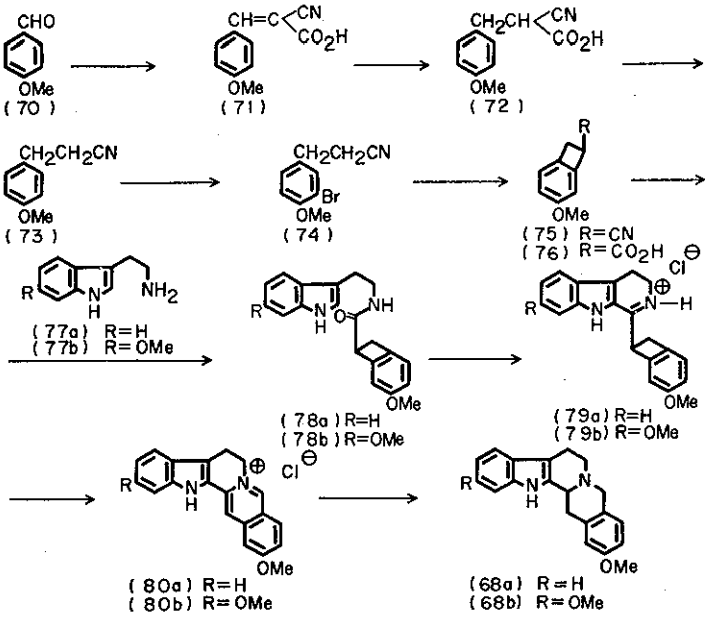
For example, 5-methoxybenzocyclobutene-1-carboxylic acid (76), as a key intermediate, was synthesized in the usual way as follows; Knövenagel reaction of p-anisaldehyde (70) with cyanoacetic acid gave the cinnamic acid (71) which on sodium borohydride reduction afforded the hydrocinnamic acid (72), followed by decarboxylation at 150° in dimethylacetamide and bromination of the resulting nitrile (73) with

bromine in the presence of sodium acetate in acetic acid to give 3-bromo-4-methoxyphenylpropiononitrile (74). Treatment of (74) with sodium amide in liquid ammonia gave the benzocyclobutene (75) via a benzyne intermediate which was hydrolyzed with ethanolic potassium hydroxide to the corresponding carboxylic acid (76).[12]

Condensation of tryptamine (77a) with the carboxylic acid (76) in the presence of dicyclohexylcarbodiimide gave the amide (78a) which was converted by a Bischler-Napieralski reaction with phosphoryl chloride to the 3,4-dihydro-β-carboline hydrochloride (79a). Thermolysis of (79a) at 155° in bromobenzene for 30 min in a current of nitrogen gave the expected decadehydroyohimbane (80a) in 70 % yield which was reduced with sodium borohydride to give the hexadehydroyohimbane (68a) followed by conversion into yohimbone and allo-yohimbone.[12]

The structures of the decadehydroyohimbane (80a) and the hexadehydroyohimbane

Chart II

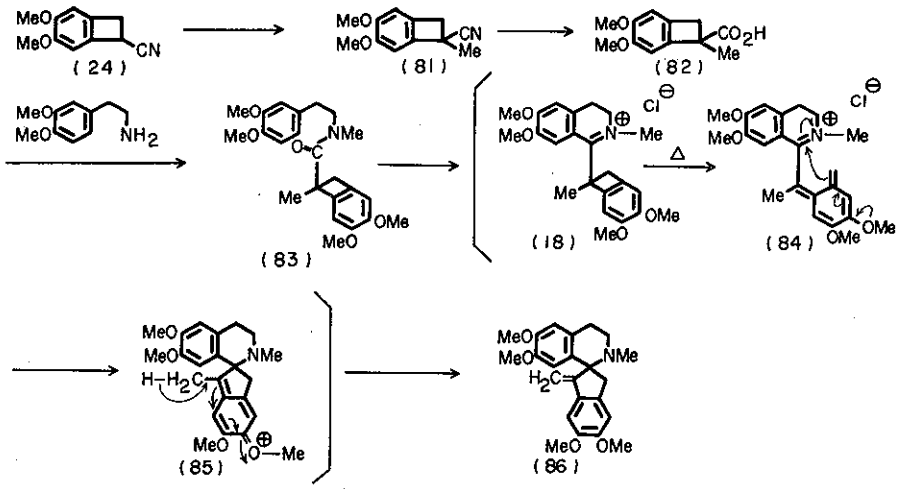


(68a) were proved by comparison with authentic samples synthesized by standard method.[12]

Similarly, using 6-methoxytryptamine (77b) as a starting material, the decadehydroyohimbane (80b) and hexadehydroyohimbane (68b) derivatives, both key compounds for the synthesis of reserpine,[13] were obtained.

Treatment of the known cyanobenzocyclobutene (24) with methyl iodide in the presence of sodium amide for 30 hr afforded 1-cyano-1-methylbenzocyclobutene (81) in 41 % yield. Hydrolysis of this with ethanolic potassium hydroxide provided the acid (82) in 82 % yield which was condensed with N-methylhomoveratrylamine in the presence of dicyclohexylcarbodiimide at room temperature to give the amide (83) in 52 % yield. Bischler-Napieralski reaction of the amide (83) with 2 molar equivalents of phosphoryl chloride in boiling benzene for 22 hr did not yield the expected 3,4-dihydro-2-methylisoquinolinium salt (18) but afforded the spirobenzylisoquinoline (86) in 14 % yield, accompanied by 35 % of the starting amide.

Chart 12

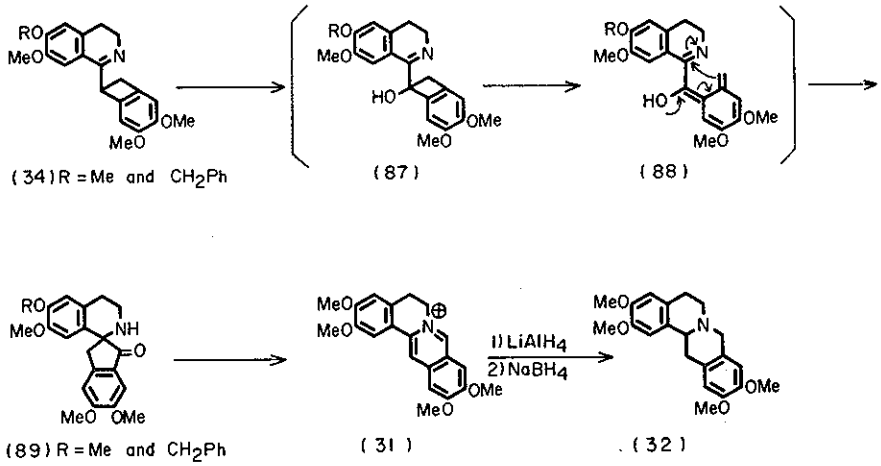


It is probable that the 3,4-dihydroisoquinolinium salt (18) was initially formed and this rearranged thermally via o-quinodimethane (84) and the spiro compound (85) to yield the ochotensine-type compound (86).[14]

This finding provides a more direct route to the ochotensine-type alkaloids than the stepwise procedure heretofore reported, and this transformation also represents a convenient entry into the synthesis of the spirobenzylisoquinoline alkaloids.

The hydrochlorides of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (34) are stable at room temperature but the free bases of these compounds are unstable in air. A chloroform solution of the free base (34) on standing at room temperature for 2 or 3 days was transformed, in good yield, into the ketospirobenzylisoquinolines (89). The mechanism of this reaction could be explained by air oxidation of the benzocyclobutenes (34) to the benzocyclobutenols (87), followed by ring opening to o-quinodimethanes (88) and then electrocyclic reaction as

Chart 13

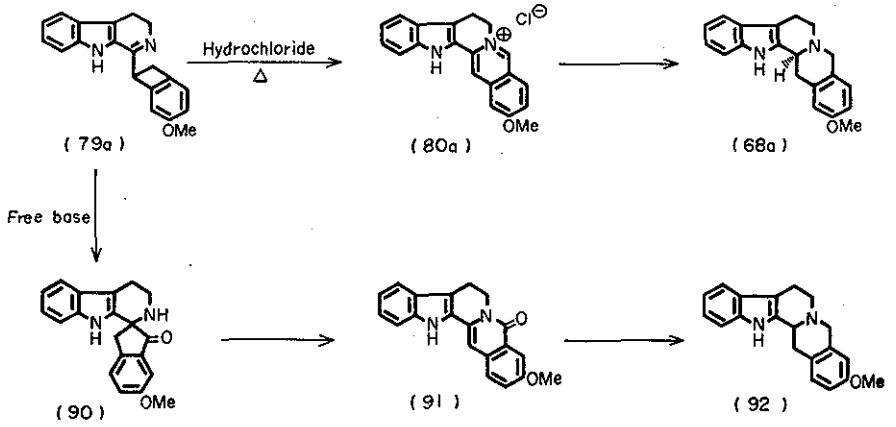


shown in Chart 13.[15] One of the ketospirobenzylisoquinoline (89) was converted to xylopinine (32) by Irie and co-workers;[16] thus the photolysis of the tetramethoxy compound (89) gave the protoberberine (31) whose reduction by the usual method afforded xylopinine (32).

In addition, we synthesized two kinds of hexadehydroyohimbanes (68a and 92), differing only in the position of the methoxyl substituent by utilizing the different reactivity of the free base and the hydrochloride. Thus, the hydrochloride of 79a was heated at 155° to form the decadehydroyohimbane (80a) which was easily converted into the 17-methoxyyohimbane (68a). On the other hand, the free base (79a) rearranged on standing in chloroform at room temperature for 3 days to the ketospirobenzyl-β-carboline (90), followed by irradiation in dry tetrahydrofuran at room temperature for 3 hr to give the lactam (91) which has already been converted into the 18-methoxyyohimbane (92).[15]

It is interesting that the same starting material (79a) gives the two yohimbanes (68a and 92) which are position isomers.

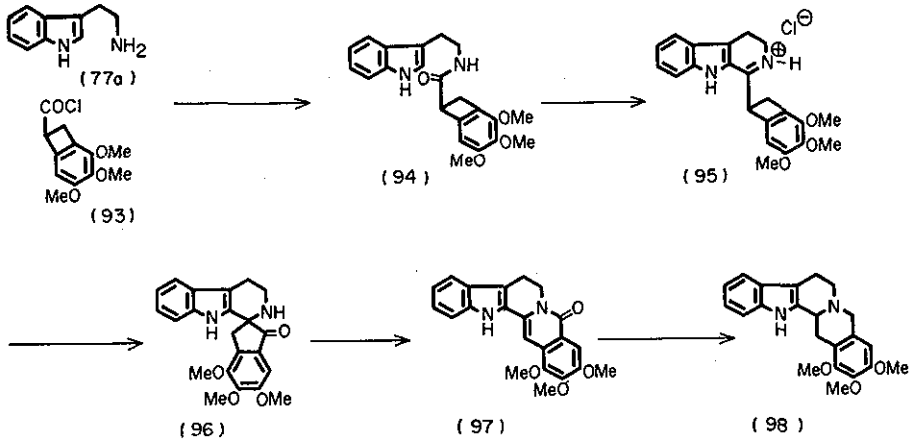
Chart 14



Similarly, the hexadehydroyohimbane (98) was synthesized as follows: Schotten-Baumann reaction of tryptamine (77a) with the acid chloride (93) gave the amide (94), which was cyclodehydrated with phosphoryl chloride to afford the 3,4-dihydro-β-carboline, characterized as its hydrochloride (95). The free base of 95 was rearranged to the spiro-compound (96) and photolyzed to give the lactam (97) followed by reduction to furnish the hexadehydroyohimbane (98).[15]

Thus, we have demonstrated the utility of a new method for the synthesis of the protoberberine alkaloids and yohimbane ring system which is based on thermolysis of the 1-benzocyclobutenyl-3,4-dihydroisoquinolines and 1-benzocyclobutenyl-3,4-dihydro-β-carbolines via the corresponding o-quinodimethanes. This method is also a useful reaction for the synthesis of the benzoquinolizidine ring system which has pharmacological activity.[17]

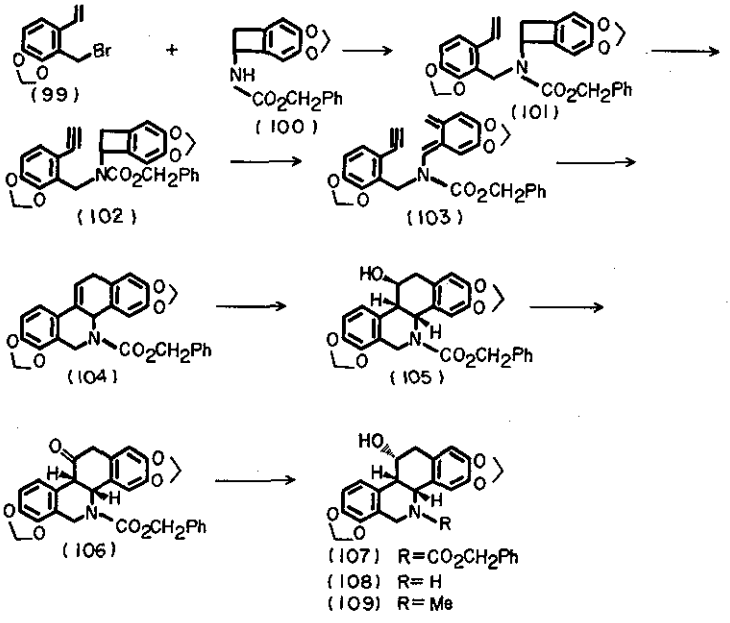
Chart 15



Oppolzer and Keller[18] have evolved the synthesis of chelidonine (109) based on the thermolysis of a benzocyclobutene and intramolecular cycloaddition of the

resulting o-quinodimethane. The condensation of urethan (100) with benzylic bromide (99) gave the olefin (101), which was converted into the acetylenic urethan (102) by bromination, followed by dehydrobromination in the presence of potassium butoxide and 1,5-diazobicyclo[5.4.0]undecene-6 (DBU). Thermolysis of 102 led to the formation of the benzophenanthridine (104) through the o-quinodimethane (103). Hydroboration then afforded the secondary alcohol (105), which was transformed to the epimeric alcohol (107) via the ketone (106). Hydrogenolysis of the benzyloxycarbonyl group then produced norchelidonine (108) which on methylation gave chelidonine (109).

Chart 16

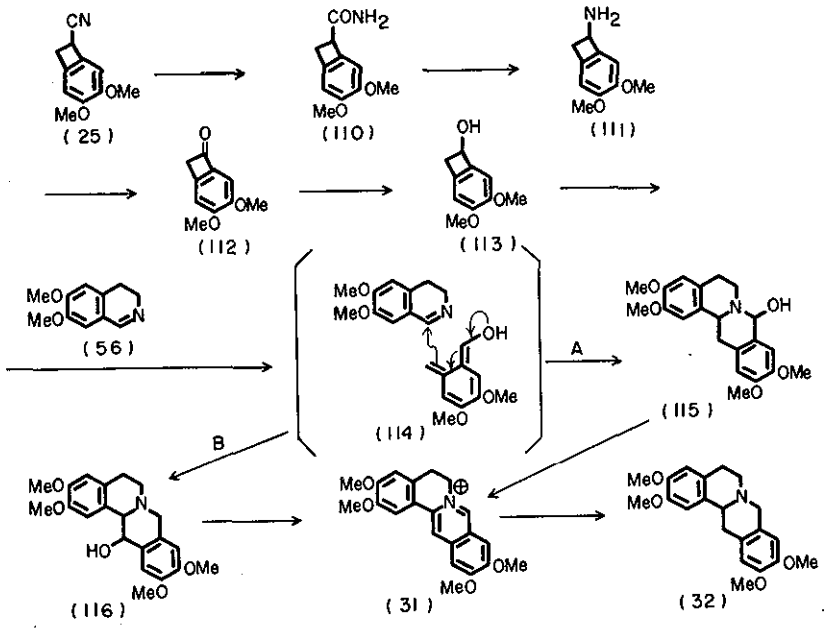


As previously mentioned, the o-quinodimethanes derived from the benzocyclobutene react intramolecularly with the imine system to give the benzoquinolizidine

derivatives by an electrocyclic reaction. This type of reaction has also been extended to the synthesis of the protoberberine alkaloids and the ochotensine-type compounds. Since it is well known that the o-quinodimethanes react intermolecularly with olefins to easily give the tetralin derivatives,[1] we attempted the synthesis of the protoberberine system by the intermolecular reaction of o-quinodimethanes with imines.

The starting benzocyclobutenol (113) was synthesized as follow. The treatment of the nitrile (25) with hydrogen peroxide and sodium hydroxide at 60° gave the amide (110) which was subjected to a Hofmann rearrangement with potassium hypobromite at 70° to furnish the amine (111). This amine was then oxidized with potassium permanganate at room temperature to afford the benzocyclobutene (112)[19] which on sodium borohydride reduction gave the desired benzocyclobutenol (113). This

Chart 17

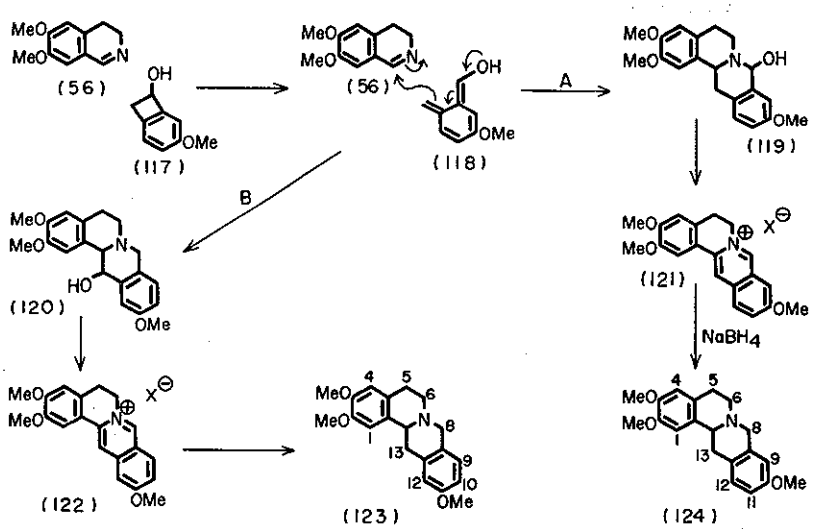


was condensed with 3,4-dihydro-6,7-dimethoxyisoquinoline (56) in benzene at 80° for 5 hr to give the protoberberine (31) in 52 % yield, identical with the thermal product from the 1-benzocyclobutenyl-3,4-dihydroisoquinoline derivative mentioned previously. Moreover, this quaternary (31) was converted into the protoberberine alkaloid xylopinine (32), in good yield, by reduction with sodium borohydride.

The mechanism of this reaction could be reasonably explained (route A) by a cycloaddition of the o-quinodimethane (114) to the isoquinoline (56) to give the 7,8,13,13a-tetrahydro-8-hydroxyprotoberberine (115) followed by dehydration and dehydrogenation to yield (31). Alternatively, it is possible to proceed by an another route via the second intermediate (116) as shown in route B. In order to clarify which is the preferred route, we examined the following reaction.

In the thermolysis of 5-methoxybenzocyclobutenol-1 (117) in the presence of the 3,4-dihydroisoquinoline (56), attack by the methylene carbon of o-quinodimethane (118) on the C_1-carbon in the isoquinoline (56) by route A would lead via (119) to

Chart 18



the 10-methoxyprotoberberines (121, 124) whereas attack by the methine carbon of intermediate (118) (route B) would generate (120) and result in the formation of the 11-methoxyprotoberberines (122, 123).

Experimentally, we found that treatment of 3,4-dihydroisoquinoline (56) and the benzocyclobutenol (117) at 80° for 5 hr formed a methoxyprotoberberine which was reduced with sodium borohydride to afford the 10-methoxyprotoberberine (124), in 20 % yield, identical by mp and spectral comparisons with an authentic sample.[19]

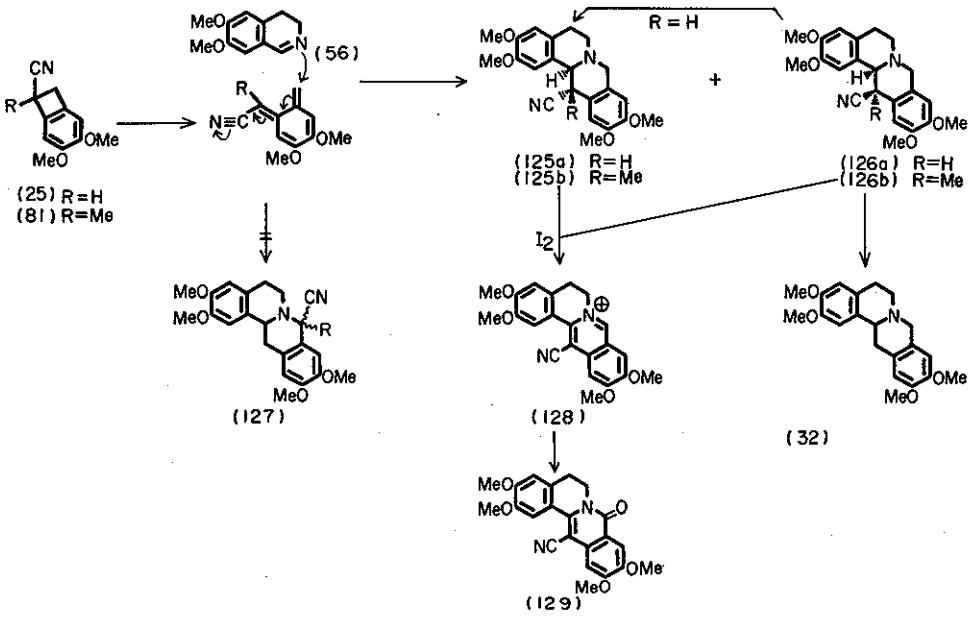
Thus, the reaction of the benzocyclobutenol with the 3,4-dihydroisoquinoline proceeds regioselectively via route A to form the 8-hydroxyprotoberberine (119).

Similarly, heating the 1-cyclobenzocyclobutene (25) with the 3,4-dihydroisoquinoline (56) at 150 - 160° gave in good yield the isomeric cyano-7,8,13,13a-tetrahydroberberines (125a and 126a). The latter isomer (126a) was converted by heating or by silica gel chromatography into (125a). Dehydrogenation of both products with iodine afforded the same cyanoprotoberberine (128). This indicated that the thermal products were a mixture of stereoisomers rather than position isomers (125a) or (126a) and (127). Treatment of the dehydrogenation product (128) with sodium hydroxide gave the lactam (129) which located the cyano group at the C-13 position. Thus, cycloaddition of the o-quinodimethane, derived from the cyanobenzocyclobutene (25), to the 3,4-dihydroisoquinoline (56) proceeded regioselectively to give a mixture of the 13-cyanotetrahydroprotoberberines (125a and 126a). The stereochemistry of both products could be easily determined by nmr spectral analysis. Based on the chemical shifts of the C_{13}-H and the C_{13a}-H and also of the coupling constants of both hydrogen, (125a) and (126a) could be assigned as trans and cis, respectively.

Moreover, 1-cyano-1-methylbenzocyclobutene (81) also gave two kinds of 13-cyano-methyltetrahydroprotoberberines (125b and 126b). However, in this case the conversion of one product into the other did not take place.[20]

Finally, decyanation of the 13-cyanotetrahydroprotoberberine (128) by a Birch-type reduction by use of lithium in liquid ammonia in the presence of isopropyl alcohol afforded xylopinine (32).[22]

Chart 19

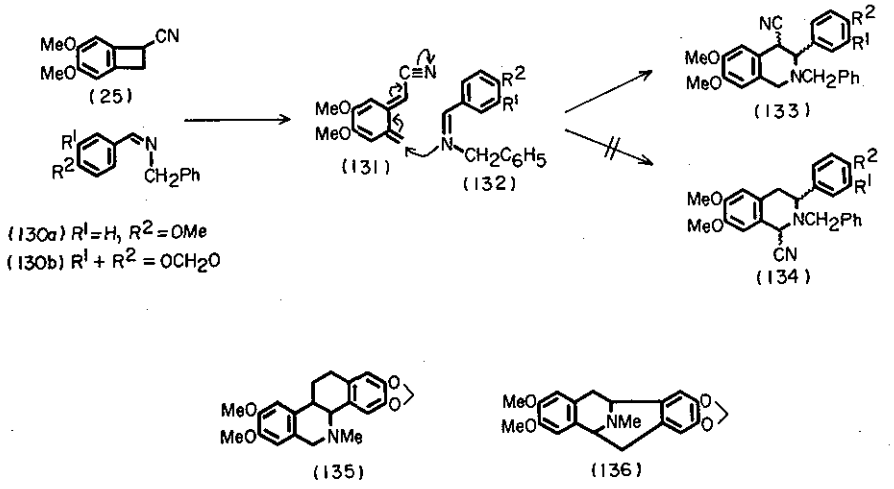


Since thermal intermolecular cycloaddition between benzocyclobutenes and 3,4-dihydroisoquinoline gave benzoquinolizidines, such as protoberberines, in good yield and in a highly regioselective manner, this suggested that an intermolecular reaction of the benzocyclobutene with the acyclic imine system could regioselectively give isoquinoline derivatives. Therefore, we examined a new regioselective cycloaddition for the synthesis of isoquinoline derivatives by extending the thermal intermolecular cycloaddition of benzocyclobutenes to the imine system.

In this conection, the Schiff bases (130) could react wtih the cyanocyclobutene (25) to give the 3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines (133) or 1,3-substituted isoquinolines (134). The former (133) would be an important starting material for the synthesis of benzophenanthridine alkaloids (135) while the latter (134) would be the intermediates leading to the pavine alkaloids (176).

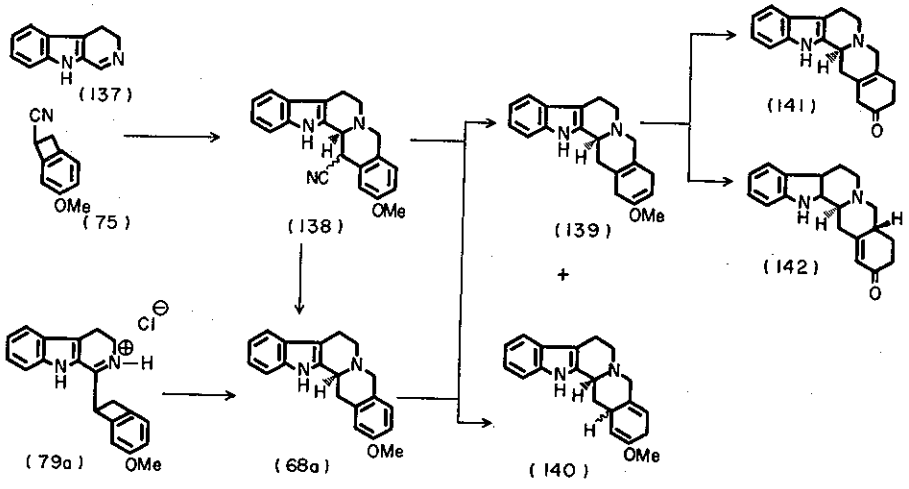
Experimentally, reaction of 1-cyanobenzocyclobutene (25) with Schiff bases (130) was carried out at 150 - 160° without solvent to give only the 3,4-disubstituted 1,2,3,4-tetrahydroisoquinolines whose structures were deduced from nmr spectral analysis which showed vicinal methine protons and a methylene having an AB type coupling pattern. Although the stereochemistry of the C-3 and C-4 positions was unclear, we assumed that the trans-configuration was the preferred one since epimerization at the C-4 position would be more thermodynamically. Finally, since the 3,4-disubstituted isoquinoline (133) was obtained as a single stereostructure, it may be concluded that the cycloaddition proceeded in both a regoselective and stereoselective manner.[21]

Chart 20



Similarly, an intermolecular cycloaddition of 1-cyanobenzocyclobutene (75) to 3,4-dihydro-β-carboline (137) was effected at 150 - 160° without solvent over 2 hr in a current of nitrogen to give regioselectively the 14-cyanohexadehydroyohimbane (138) in 85 % yield which was decyanated by treatment with metallic lithium and liquid ammonia in the presence of isopropyl alcohol to afford in 65 % yield the hexadehydroyohimbane (68a), identical with the product formed from the 1-benzocyclobutenyl-3,4-dihydro-β-carboline hydrochloride (79a) by thermal rearrangement followed by borohydride reduction. Birch reduction of the hexadehydroyohimbane (68a) with a lithium and liquid ammonia-isopropyl alcohol system gave the enol ether (139) as the major product, and in this reaction, the isomeric ether (140) as the minor product. The same ratio of (139) and (140) was obtained by reduction of 14-cyanoyohimbane (138) with a large excess of lithium in liquid ammonia and isopropyl alcohol.[22] Finally, treatment of the enol ether (139) with oxalic acid gave the dehydroyohimbone (141) in good yield while reaction with hydrochloric acid by Swan's method[23] afforded the dehydroyohimbone (142).

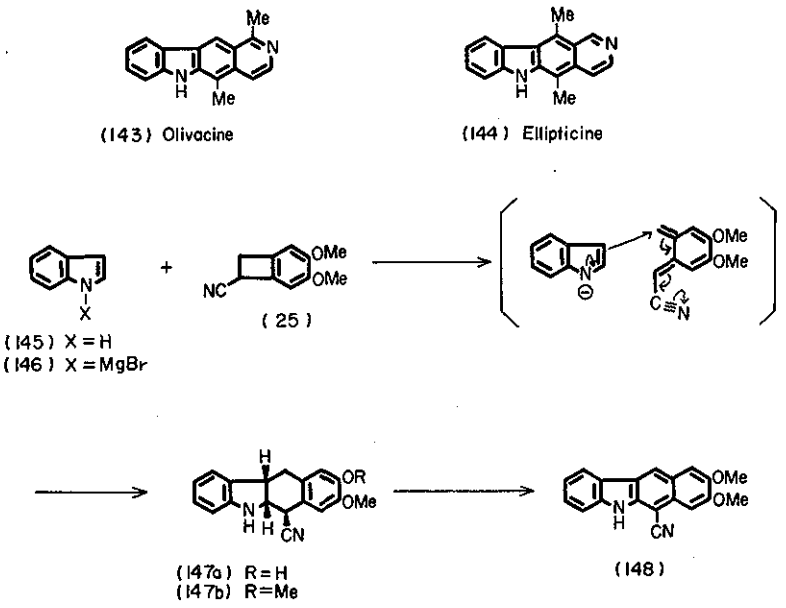
Chart 21



As a further extension of the electrocyclic reaction and intermolecular cycloaddition of o-quinodimethanes, derived from benzocyclobutenes, to the imines system, the possibility of obtaining a tetralin derivative by the reaction of an o-quinodimethane with indole, which is a type of enamine, was investigated. This was of particular interest if the expected cycloaddition product (147), which would result from indole (145) and the benzocyclobutene (25), would be an analog of olivacine (143) or ellipticine (144) which show antitumor activity.

However, since reaction of indole (145) with the cyanobenzocyclobutene (25) in boiling dichlorobenzene afforded only benzocyclobutene dimer, the more nucleophilic indolylmagnesium bromide (146) was fused with cyanobenzocyclobutene (25) at 160° for 10 min to give regioselectively and stereoselectively a mixture of 6-cyano-8,9-dimethoxytetrahydrobenzocarbazole (147b) in 83 % yield and its 9-hydroxy-compound (147a) in 5 % yield. While both compounds could be easily separated by

Chart 22

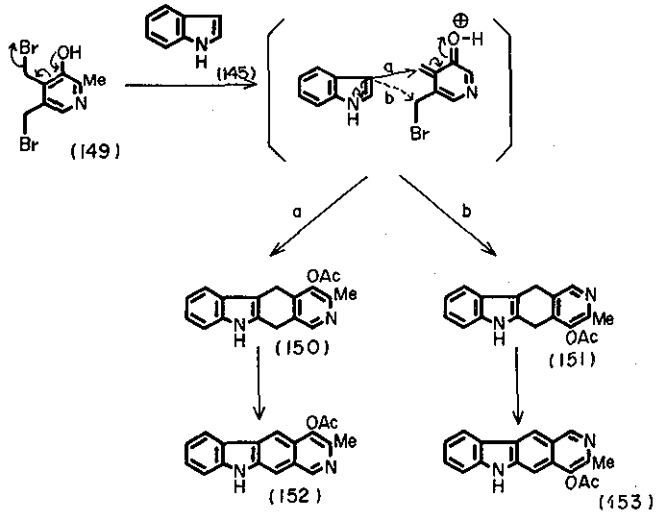


silica gel chromatography, the reaction mixture was treated, without purification, with diazomethane, followed by dehydrogenation on 30 % palladium-carbon in refluxing xylene to furnish 6-cyano-8,9-dimethoxybenzocarbazole (148) in 60 % yield. The structures of (147) and (148) were assigned by nmr and mass spectroscopic methods.[24]

Finally, in order to prepare the pyridocarbazole (153) which had the same ring system as ellipticine and olivacine, we investigated the reaction of pyridoxyl dibromide (149), obtained from pyridoxine and hydrobromic acid, with indole since it is known that o-di(halomethyl)benzene derivatives give o-quinodimethanes on treatment with sodium iodide.

Heating indole (145) and pyridoxyl dibromide (149) in dimethylformamide at 160°, followed by acetylation with acetic anhydride and pyridine, gave the expected isomeric pyridocarbazoles (150 and 151). While this reaction proceeded in the presence of sodium iodie, the yields of 150 and 151 were poor and many unidentified products were formed.

Chart 23



The structures of both products (150 and 151) were determined by uv spectral comparison of the dehydrogenated products (152 and 153) with the authentic 10H-pyrido[3,4-b]carbazole and olivacine. Dehydrogenation was carried out by using 30 % palladium-carbon in boiling xylene.[25]

In summary, we have found that heating benzocyclobutenes give the reactive o-quinodimethanes which react intermolecularly or intramolecularly with imines or enamines in a regioselective or stereoselective manner to give a variety of heterocyclic compounds. Specifically, we have shown that this type of reaction is an effective method for the total synthesis of natural products such as isoquinoline and indole alkaloids.

ACKNOWLEDGEMENT We thank Dr. Sidney Teitel, Hoffmann-La Roche Inc., Nutley, New Jersey, and Dr. Frank F. Ebetino, Norwich Pharmacal Company, Division of Morton-Norwich Products, Inc., Norwich, New York, for their kind suggestion and also Miss Reiko Kato and Miss Reiko Suenaga for their kind help in the preparation of this manuscript.

REFERENCES

1 I. L. Klundt, Chem. Rev., 1970, 70, 471.

2 H. Finkelstein, Ber., 1910, 43, 1528.

3 M. P. Cava and D. P. Napier, J. Amer. Chem. Soc., 1956, 78, 500.

4 F. R. Jensen and W. E. Coleman, J. Amer. Chem. Soc., 1958, 80, 4169.

5 R. Huisgen and H. Seidel, Tetrahedron Letters, 1964, 3381.

6 R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, GmbH, Weinheim/Bergstr., 1970.

7 M. Shamma and C. D. Jones, J. Amer. Chem. Soc., 1969, 91, 4009; 1970, 92, 4943.

8 T. Kametani, K. Ogasawara, and T. Takahashi, Chem. Comm., 1972, 675; Tetrahedron, 1973, 29, 73.

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

10 T. Kametani, M. Takemura, K. Ogasawara, and K. Fukumoto, J. Heterocyclic Chem., 1974, 11, 179.

11 T. Kametani, T. Kato, and K. Fukumoto, Tetrahedron, 1974, 30, 1043.

12 T. Kametani, M. Kajiwara, and K. Fukumoto, Chem. and Ind., 1973, 1165; Tetrahedron, 1974, 30, 1053.

13 T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, Anales de Quim., in press.

14 T. Kametani, T. Takahashi, and K. Ogasawara, Tetrahedron Letters, 1972, 4847; J. Chem. Soc. Perkin I, 1973, 1464.

15 T. Kametani, Y. Hirai, H. Takeda, M. Kajiwara, T. Takahashi, F. Satoh, and K. Fukumoto, Heterocycles, 1974, 2, 339; J. Chem. Soc. Perkin I, in press.

16 H. Irie, K. Akagi, S. Tani, K. Yabusaki, and H. Yamane, Chem. and Pharm. Bull. (Japan), 1973, 21, 855.

17 T. Kametani, K. Nyu, S. Ikeda, and R. Iwaki, J. Pharm. Soc. Japan, 1973, 93, 899.

18 W. Oppolzer and K. Keller, J. Amer. Chem. Soc., 1971, 93, 3836.

19 T. Kametani, T. Kato, and K. Fukumoto, J. Chem. Soc. Perkin I, in press.

20 T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, J. Org. Chem., 1974, 39, 447.

21 T. Kametani, T. Takahashi, K. Ogasawara, and K. Fukumoto, Tetrahedron, 1974, 30, 1047.

22 T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, to be published.

23 G. A. Swan, J. Chem. Soc., 1950, 1534.

24 T. Kametani, T. Suzuki, K. Takahashi, and K. Fukumoto, Heterocycles, 1974, 2, 9; Tetrahedron, 1974, 30, 2207.

25 T. Kametani, Y. Ichikawa, T. Suzuki, and K. Fukumoto, Heterocycles, 1974, 2, 171; Tetrahedron, in press.

Received, 30th August, 1974