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# Studies on the Syntheses of Heterocyclic Compounds. DXIX.[1] A Total Synthesis of (±)-Discretine by Thermolysis

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In the course of their remarkable synthesis of a model compound for an ochotensine alkaloid, Shamma and Jones proposed "the protoberberine progenitor biogenesis" and they proved it did work *in vitro* experiment.[3]

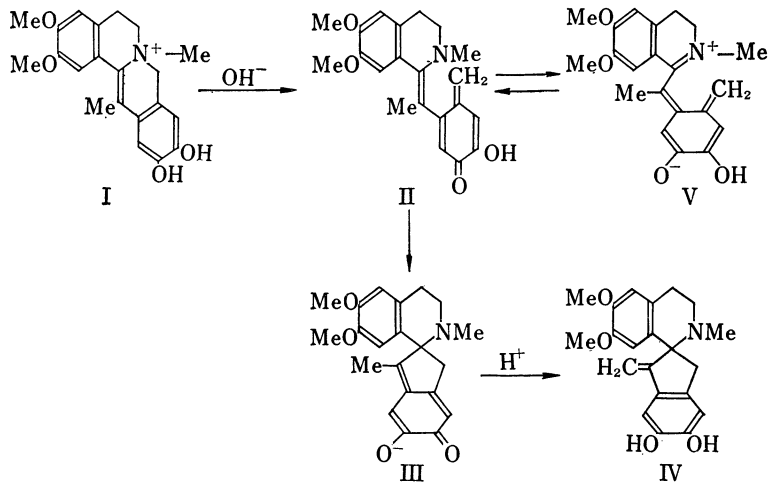


Chart 1

Considering their proposed mechanism (I→II→III→IV), we were interested in the intermediate (II), since it is electronically equivalent to the *o*-quinodimethane structure (V), the system of which seemed to be easily available from the recently developed Oppolzer's method.[4] Oppolzer has shown that thermolysis of the benzocyclobutenes (VI) afforded the corresponding tricyclic compounds (VIII) possibly *via* the *o*-quinodimethane intermediates (VII).

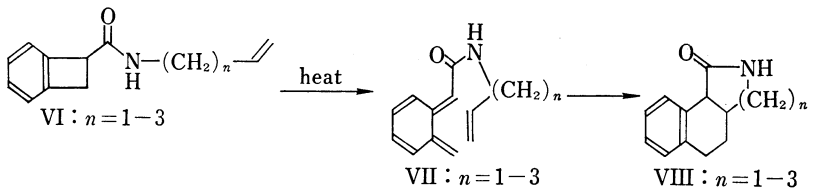


Chart 2

1) Part DXVIII: T. Kametani and K. Ogasawara, *Chem. Pharm. Bull.* (Tokyo), **21**, 893 (1973).
2) Location: *Aobayama, Sendai.*
3) M. Shamma and C.D. Jones, *J. Am. Chem. Soc.*, **91**, 4009 (1969); **92**, 4943 (1970).
4) W. Oppolzer, *J. Am. Chem. Soc.*, **93**, 3833, 3834, 3836 (1971).

Recently, we have presumed the thermolytical formation of ochotensine and (±)-xylopinine.[5] Namely, a quinodimethane (X), which would be formed by thermolysis of a substituted 1-benzocyclobutenylisoquinolinium salt (IX, R=Me), finally would collapse to a spirobenzylisoquinoline (XII) *via* an intermediate (XI). Furthermore, when the above thermal condition is applied to a benzocyclobutenylisoquinoline (IX, R=H), a dihydroprotoberberine (XIII) would be formed from an *o*-quinodimethane (X, R=H) through the intramolecular Diels–Alder type reaction.

Among the above two types of compounds, (±)-xylopinine as a protoberberine was synthesized successfully from the benzocyclobutenylisoquinoline (IX, R=H) based on the above hypothesis.[5] In a similar manner we have examined the total synthesis of (±)-domesticine, the details of which will here be described.

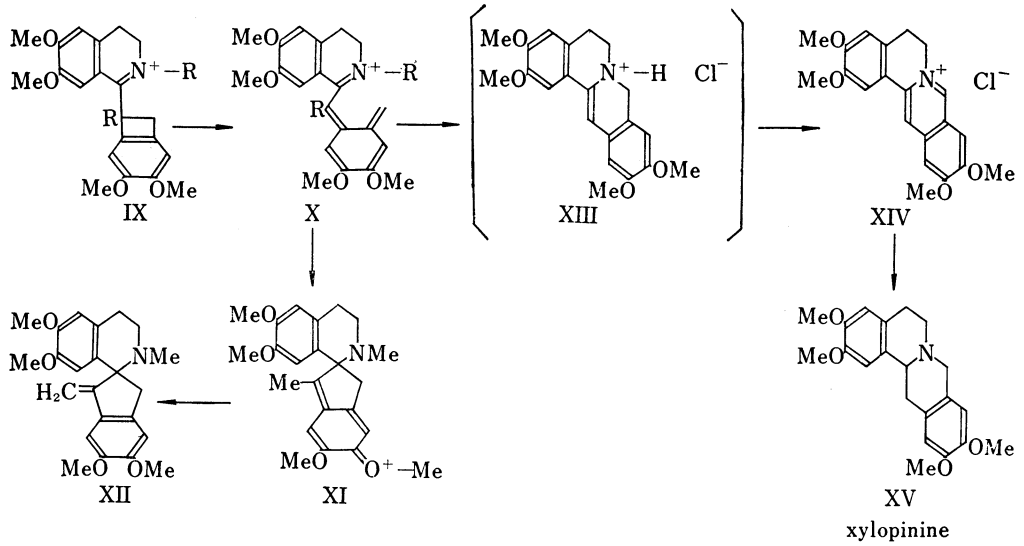


Chart 3

The synthesis of the key intermediate, 1-benzocyclobutenyl-3,4-dihydroisoquinoline (XXIII), was carried out as follows. Condensation of 4,5-dimethoxybenzocyclobutenyl-1-carboxylic acid (XXI) (XVI→XVII→XVIII→XIX→XX→XXI)[6] with 3-benzyloxy-4-methoxyphenethylamine in methylene chloride in the presence of dicyclohexylcarbodiimide to give the amide (XXII), the Bischler–Napieralski reaction of which in benzene in the presence of phosphoryl chloride gave rise to the expected 1-benzocyclobutenylisoquinoline hydrochloride (XXIII) in 78.3% yield.

As we reported previously,[6] the free base of IX (R=H) was heated at 160°—170° in bromobenzene in a current of nitrogen, but none of the expected dihydroprotoberberine (XIII) had not been isolated. The thermolysis of the hydrochloride of IX (R=H) was then carried out under the same condition as above to separate the compound (XIV) rapidly as yellow crystals.

Similarly, thermolysis of XXIII in bromobenzene at 160—170° gave no dihydroprotoberberine but the protoberberinium chloride (XXV).[7]

5) T. Kametani, K. Ogasawara, and T. Takahashi, *Chem. Commun.*, **1972**, 675.
6) T. Kametani, T. Takahashi, and K. Ogasawara, *Tetrahedron*, **29**, 73 (1973).
7) In case of the previous paper[6] the dehydrogenation might be occurred due to a rather thermolysis than disproportionation, since a tetrahydroberberine derivative (XV), a counterpart of the dehydrogenated product (XIV), was only recognized on thin-layer chromatography (TLC) of the mother liquor.

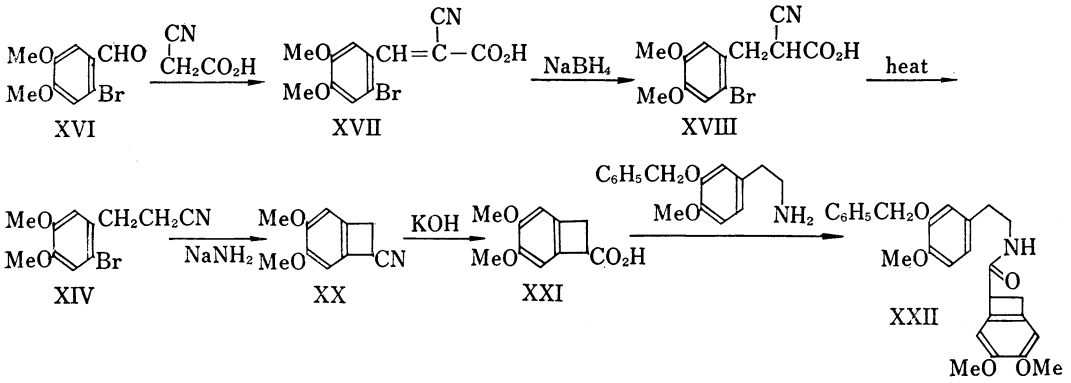

Chart 4

Examination of the nuclear magnetic resonance (NMR) spectrum (in $CF_3CO_2H$) of the above thermolyzed product revealed that it was not the dihydroprotoberberine hydrochloride, but the dehydrogenated protoberberinium chloride (XXV) described in experimental.

The different behavior of the free base and the hydrochloride in the thermal condition might be due to the orientation of the benzocyclobutene ring cleavage. During the thermolytic ring cleavage, a more stabilized *o*-quinodimethane (XXVIII) formed at first, as in the case of Oppolzer's experiment[4] and then only the hydrochloride, which possessed an activated group, $>C=\overset{+}{N}H$, tautomerized to the required *o*-quinodimethane (XXIV) to give the protoberberinium chloride (XXV). Thus the electrocyclization would have occurred in the following steps (XXIII→XXVIII→XXIV→XXV).

Finally catalytic hydrogenation of the protoberberinium chloride (XXV) in the presence of platinum oxide afforded (±)-discretine (XXVII) hydrochloride. Comparison of the infrared

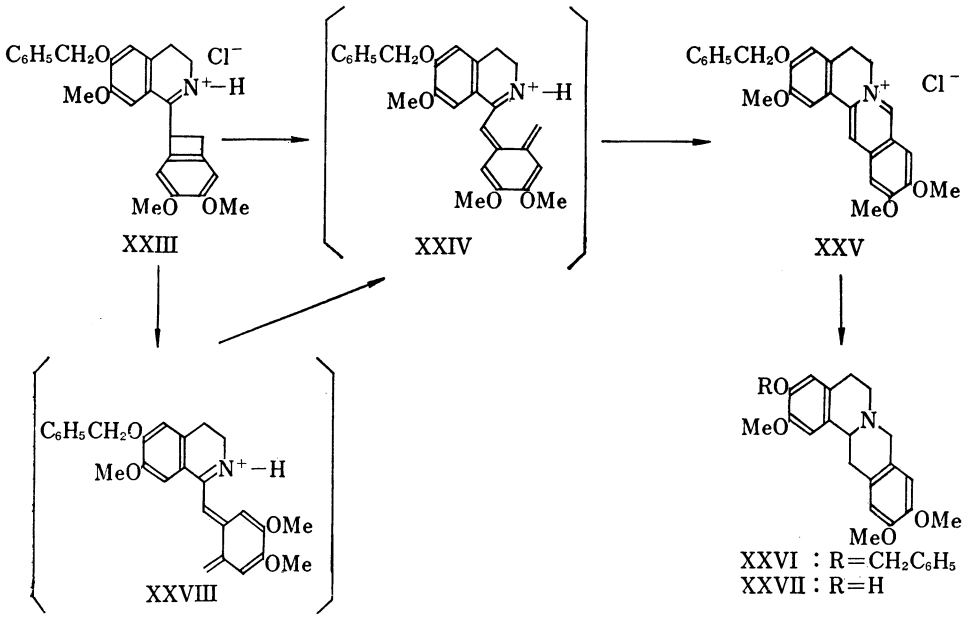

Chart 5

(IR), NMR and mass spectra and TLC behavior of both hydrochloride and free base confirmed the identity with those of the authentic sample.[8] The mixed melting point test of the free base with an authentic specimen showed no depression. On the other hand, sodium borohydride reduction of XXV gave (±)-*O*-benzyldiscretine (XXVI), which was also identical with an authentic sample.[8]

This thermolytic method for protoberberine alkaloids would be suitable for the synthesis of 9,10-oxygenated protoberberines, which could not be easily obtained by the conventional Mannich cyclization,[9] if the corresponding 5,6-oxygenated cyanobenzocyclobutenes might be synthesized through the benzyne reaction.

## Experimental[10]

**N-(3-Benzyloxy-4-methoxyphenethyl)-4,5-dimethoxybenzocyclobutene-1-carboxamide (XXII)**——A mixture of 7.7 g of 3-benzyloxy-4-methoxyphenethylamine, 6.3 g of 4,5-dimethoxybenzocyclobutene-1-carboxylic aicd (XXI),[6] 6.8 g of dicyclohexylcarbodiimide, and 150 ml of methylene chloride was stirred for 2 hr at room temperature, and the material separated was removed by filtration. The filtrate was diluted with 200 ml of methylene chloride, washed with 2% hydrochloric acid, 5% sodium hydrogen carbonate, and water, dried over $Na_2SO_4$, and evaporated *in vacuo* to give 10.4 g (78.4%) of the amide (XXII) as hygroscopic colorless needles, mp 123—124° (from benzene). *Anal.* Calcd. for $C_{27}H_{29}O_5N \cdot 0.25H_2O$: C, 71.74; H, 6.57. Found: C, 71.80; H, 6.86. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1640 (CONH). NMR (in $CDCl_3$) $\delta$ (ppm): 2.68 (2H, t, $J$=6.5 Hz, $ArCH_2$-$CH_2NH$), 3.10—3.62 (4H, m, $ArCH_2CH_2NH$ and methylene protons in benzocyclobutenyl group), 3.74, 3.78, 3.81 (3Heach, each s, $3\times OCH_3$), 3.99 (1H, d, d, $J$=5.5 and 2.5 Hz, methine in benzocyclobutenyl group), 5.04 (2H, s, $C_6H_5CH_2O$), 5.51—5.76 br (1H, NH), 6.47—6.75 br (4H, aromatic ptorons), and 7.80 (5H, s, $C_6H_5CH_2O$).

**6-Benzyloxy-3,4-dihydro-7-methoxy-1-(4,5-dimethoxybenzocyclobutenyl)isoquinoline (XXIII)**——A mixture of 0.91 g of the amide (XXII), 30 ml of dry benzene, and 0.9 g of phosphoryl chloride was refluxed for 2 hr and the reaction mixture was cooled to precipitate 0.685 g (78.4%) of the 3,4-dihydroisoquinoline (XXIII) hydrochloride as yellow needles, mp 185—187° (from ethanol). *Anal.* Calcd. for $C_{27}H_{27}O_4N \cdot HCl \cdot H_2O$: C, 67.00; H, 6.20; N, 2.89. Found: C, 66.94; H, 6.40; N, 2.53. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1640 ($\overset{+}{\rangle}C=\overset{+}{N}H$). NMR (in $CF_3CO_2H$) $\delta$ (ppm): 3.05—3.55 (4H, m, $CH_2$ at C-3 position and $CH_2$ due to cyclobutenyl group), 3.96 (6H, s, $2\times OCH_3$), 4.03 (3H, s, $OCH_3$), 5.32 (2H, s, $C_6H_5CH_2O$), 6.95—7.18 br (4H, aromatic protons), and 7.42 (5H, s, $C_6H_5CH_2O$).

**3-Benzyloxy-2,10,11-trimethoxyprotoberberinium Chloride (XXV)**——A suspension of 0.2 g of the 3,4-dihydroisoquinoline (XXIII) hydrochloride in 10 ml of bromobenzene was heated at 160—170° for 20 min in a current of nitrogen and cooled to give 0.156 g (78.1%) of the protoberberinium chloride (XXV) as hygroscopic yellow neeldes, mp 230—235° (decomp.) (from methanol). *Anal.* Calcd. for $C_{27}H_{26}O_4NCl \cdot 1.25H_2O$: C, 66.66; H, 5.90; N, 2.85. Found: C, 66.36; H, 5.45; N, 3.01. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1640 ($\rangle C=N^+$). NMR (in $CF_3CO_2H$) $\delta$ (ppm): 4.11, 4.18, 4.22 (3Heach, each s, $3\times OCH_3$), 5.28 (2H, s, $C_6H_5CH_2O$), 7.04—7.28 br (4H, 1-H, 4-H, 9-H, and 12-H), 7.42 (5H, s, $C_6H_5CH_2O$), 8.40 (1H, s, 13-H), and 9.08 (1H, s, 8-H).

**(±)-O-Benzyldiscretine (XXVI)**——To a stirred solution of 50 mg of the protoberberinium chloride (XXV) in 20 ml of methanol was added in portions 50 mg of sodium borohydride under ice-cooling, and the mixture was stirred for 30 min. After refluxing for 30 min, the methanol was distilled off, and the residue was decomposed with 20 ml of water and extracted with chloroform. The extract was washed with water, dried over $Na_2SO_4$, and evaporated to give 36.8 mg (74%) of (±)-O-benzyldiscretine (XXVI) as yellowish brown needles, mp 168—171° (from methanol), the spectral data of which were identical with those of the authentic specimen.[9]

**(±)-Discretine (XXVII)**——A mixture of 100 mg of the protoberberinium chloride (XXV), 100 mg of Adams' catalyst and 20 ml of methanol was shaken in a current of hydrogen at room temperature and atmospheric pressure. After absorption of a calculated amount of hydrogen, the catalyst was filtered off and the filtrate was evaporated *in vacuo* to give a solid, the recrystallization of which from methanol afforded 65.6 mg (78%) of (±)-discretine (XXVII) as a pale yellow powder. The IR ($CHCl_3$) and NMR spectra of this were

8) T. Kametani, Y. Takeshita, and S. Takano, *J. C. S. Perkin I*, **1972**, 2834.

9) T. Kametani and M. Ihara, *J. Chem. Soc.*, **1966**, 2010; T. Kametani and M. Ihara, *Yakugaku Zasshi*, **87**, 174 (1967); T. Kametani, I. Noguchi, S. Nakamura, and Y. Konno, *Yakugaku Zasshi*, **87**, 168 (1967).

10) IR spectra were measured with a Hitachi RPI-3 recording spectrophotometer, and NMR spectra with a Hitachi A-60 spectrometer with tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-7 spectrometer. Mps were determined with a Yanagimoto microapparatus (MPS-2).

superimposable upon those of natural discretine. Moreover, the spectral data, chromatographic behavior and mp of XXVII were identical with those of (±)-discretine[9] prepared by one of the present authors.

**Acknowledgement** We thank Professor F. Bernoulli, University of Basel, Basel, Switzerland, for a gift of natural discretine. We also thank Miss A. Sato, Miss C. Koyanagi, Miss A. Ujiie, Miss T. Yoshida, Miss C. Yoshida, Miss R. Kato, Miss F. Yoshinaka, and Mr. T. Ohuchi for microanalyses and spectral measurements.

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# Synthesis of 5-Chloro-7-iodo-8-quinolinol Sulfate

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In 1953, Haskins and Luttermoser[2] first suggested the existence of chinoform sulfate and glucuronide in the urine of rabbits administered 5-chloro-7-iodo-8-quinolinol (clioquinol or chinoform) (I), and later Liewendahl, *et al.*[3] demonstrated their existence in human urine after enzymic hydrolysis. However, all these results were obtained without authentic samples. For the ultimate identification of the metabolites and for further studies of the metabolism of I in relation to SMON (subacute myelo-optico-neuropathy),[4] we have tried to synthesize both metabolites. The glucuronide has already been synthesized in our laboratory.[5] The present paper deals with the synthesis of the sulfate (II).

After preliminary experiments for reaction condition, a system of chlorosulfonic acid N,N-dimethylaniline in benzene was finally employed. The reaction proceeded at room temperature. The resulting precipitate was neutralized with an alkaline solution under ice

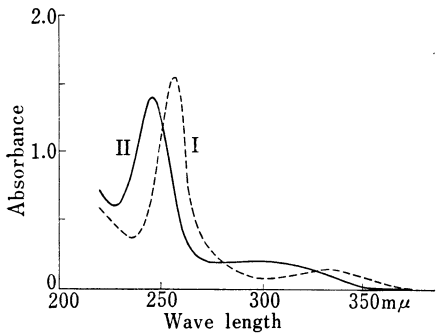


Fig. 1. UV Spectra of Chinoform(I) and Na Salt of Chinoform Sulfate(II)

I: $2.7\times10^{-5}$ M in EtOH
II: $2.6\times10^{-5}$ M in EtOH

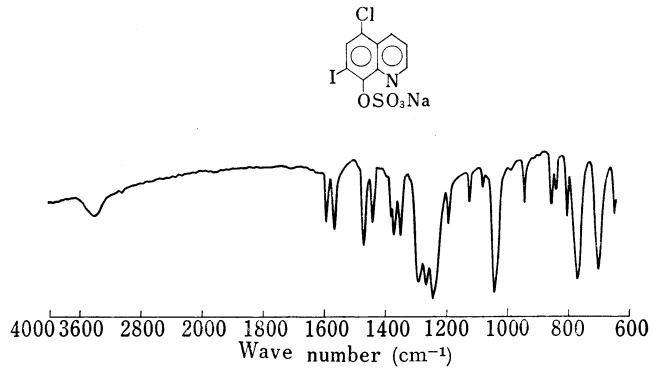


Fig. 2. IR Spectrum of Na Salt of Chinoform Sulfate(II) (KBr Tab.)

1) Location: *Hongo 7-3-1, Bunkyo-ku, Tokyo.*
2) W.T. Haskins and G.W. Luttermoser, *J. Pharmacol. Exptl. Therap.*, **109**, 201 (1953).
3) K. Liewendahl, V. Kivikangas, and B.-A. Lamberg, *Nucl. Med. (Stuttg.)*, **6**, 32 (1967).
4) T. Tsubaki, Y. Toyokura, and H. Tsukakoshi, *J. Japanese Soc. Internal Med.*, **53**, 779 (1964) (in Japanese).
5) I. Matsunaga and Z. Tamura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1056 (1971).