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8,13a-Propanoberbines. V.[1] Michael Type Condensation of Acetoneberberine Type Enamine[2]

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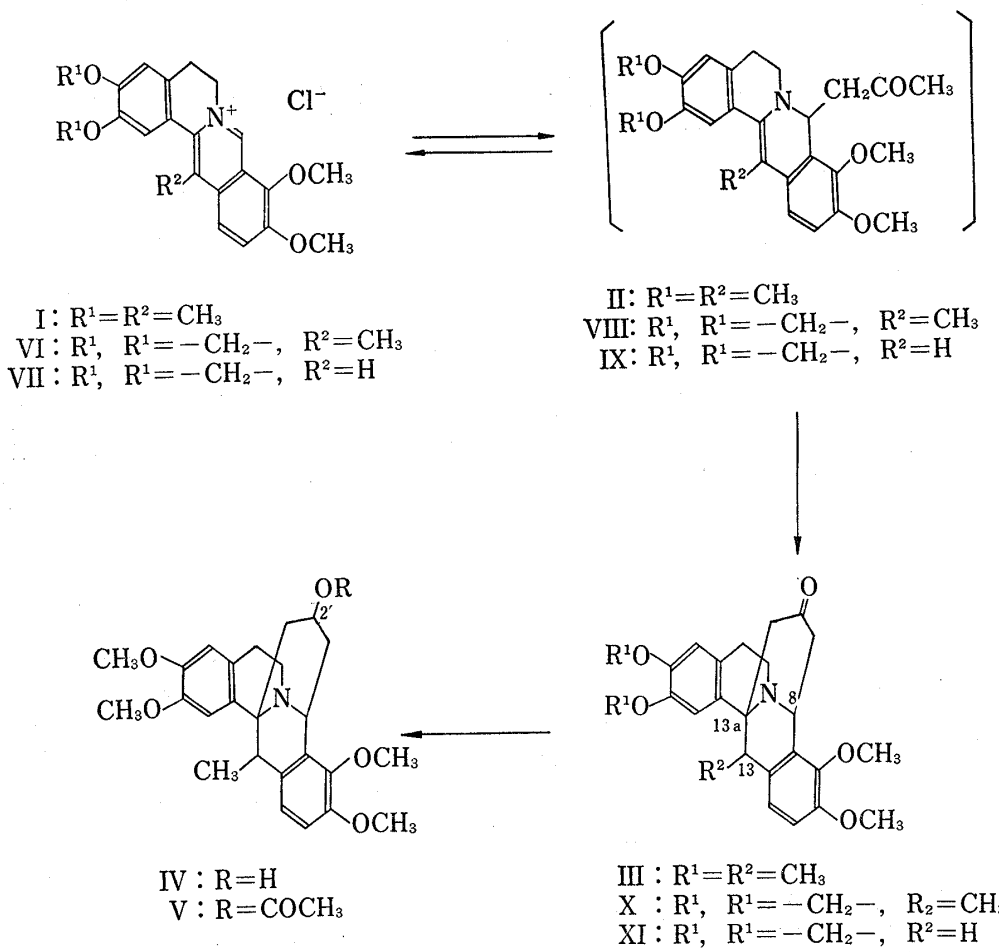
It has been found that the crude acetone adducts of quaternary protoberberinium salts, dehydrocorydalinium chloride (I), 13-methylberberinium chloride (VI) and berberinium chloride (VII), were contaminated with about a few per cent of 8,13a-propanoberbine derivatives, III, X and XI, respectively, as a result of intramolecular Michael condensation of each acetone adduct. The presence of these compounds was deduced from the direct isolation or from the product analysis of the reaction using a crude acetone adduct as a starting material.

In the course of a study on derivatives of dehydrocorydaline as antipeptic ulcer agents, we became interested in the formation of 8,13a-propanoberbine (PB) derivatives from acetoneberberine type enamines. In the previous papers of this series, we reported that acetoneberberine type enamine reacted with potassium permanganate to give 13-hydroxy-8,13a-PB derivatives in fair yield[1,4] whereas alkylation with alkyl halide afforded 13-alkyl-8,13a-PB derivatives as side products.[5] The present paper deals with a formation of 8,13a-PB derivatives from acetoneberberine type enamines on intramolecular Michael condensation.

In a process of a purification of dehydrocorydalinium chloride (I) *via* acetone adduct (II), a new PB derivative (III) was obtained as a side product. A crude acetonedehydrocorydaline (II) deposited by an addition of sodium hydroxide into an aqueous acetone solution of I was used without further purification because it was known that yields of recrystallization of acetone adducts were very poor.[5] Treatment of the crude II with 3% hydrochloric acid at 60—70° for 5 min gave I and a hydrochloride of PB derivative (III) in 95—98% and 2—5% yield, respectively. Compound III was analyzed for $C_{25}H_{29}O_5N$ and its infrared (IR) spectrum exhibited carbonyl bands at 1700 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of III revealed the presence of one secondary methyl and four methoxyl groups along with C_8-proton appeared at δ 4.76 as double-doublet. Reduction of III with sodium borohydride ($NaBH_4$) yielded an alcohol (IV) which afforded an acetate (V) on usual acetylation. In the NMR spectrum of V, an acetyl signal appeared at δ 1.45. As was discussed in the previous papers,[1,4,5] the high field shift of about 0.5 ppm of an acetyl signal was a characteristic of 8,13a-(2′-acetoxypropano)berbine derivatives. On the other hand, a treatment of V with refluxing methanolic hydrochloric acid[4] yielded acetone and I. Therefore, the formulation III for this compound became unequivocal. The presence of III in the crude precipitates of II was detected by means of thin-layer chromatography (TLC). Thus, it is assumed that III was formed from II by intramolecular Michael condensation in alkaline medium.

It was found that the crude acetone adducts of quaternary protoberberinium salts, 13-methylberberinium chloride (VI) and berberinium chloride (VII), were contaminated with about a few per cent of similar Michael condensation products, X and XI, respectively. Direct

1) Part IV: S. Naruto, H. Nishimura and H. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **23**, 1276 (1975).
2) Presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July, 1970 and at the 16th Sympodium on the Chemistry of Natural Products, Osaka, Oct., 1972.
3) Location: *33-94, Enoki-cho, Suita, Osaka.*
4) J. Iwasa and S. Naruto, *Yakugaku Zasshi*, **86**, 534 (1966).
5) S. Naruto, H. Nishimura and H. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **23**, 1271 (1975).



I: $R^1=R^2=CH_3$
VI: R^1, $R^1=-CH_2-$, $R^2=CH_3$
VII: R^1, $R^1=-CH_2-$, $R^2=H$

II: $R^1=R^2=CH_3$
VIII: R^1, $R^1=-CH_2-$, $R^2=CH_3$
IX: R^1, $R^1=-CH_2-$, $R^2=H$

IV: R=H
V: R=COCH₃

III: $R^1=R^2=CH_3$
X: R^1, $R^1=-CH_2-$, $R_2=CH_3$
XI: R^1, $R^1=-CH_2-$, $R^2=H$

Chart 1

isolation of these two by-products was unsuccessful under the acidic condition as described above. However, the existence of these were deduced experimentally from the results of the following reactions using the crude acetone adduct as a starting material.

Firstly, on oxidation of a crude acetone adduct (VIII)[5] of 13-methylberberinium chloride (VI) with potassium permanganate, an intact PB derivative (X) was isolated in about 1% yield from the reaction mixture and identified with an authentic sample which was prepared by a methylation of acetoneberberine (IX).[5] The existence of X in the starting material was also detected by means of TLC.

Secondly, the presence of a PB derivative (XI) in the crude acetoneberberine (IX) was deduced from an isolation of its Hofmann degradation product (XV) as the following manner. An aqueous acetone solution of berberinium chloride (VII) was added sodium hydroxide to afford crude precipitates of acetoneberberine (IX) which was contaminated with about 1% of water, about 0.8% of sodium hydroxide and a few per cent of PB derivative (XI). Methylation of this acetone adduct with an excess methyl iodide gave rise to a complex mixture from which the following compounds were isolated; 13-methylberberinium iodide (VI, Cl=I), berberinium iodide (VII, Cl=I), 13,13-dimethyl-PB derivative (XII),[5] 13-methyl-PB derivative (X),[5] 13-methyl-13-hydroxy-PB derivative (XIII),[1] a hemiketal of XIII (XIV)[1] and a Hofmann degradation product (XV). These products except a compound XV were identified with each authentic sample[1,5] by usual direct comparisons. The structural elucidation of XV is discussed below.

Compound XV was assigned to the molecular formula $C_{25}H_{27}O_5N\cdot CH_3I$ on the bases of analytical and mass spectral data. Its NMR spectrum (Fig. 1) exhibited three vinyl protons,

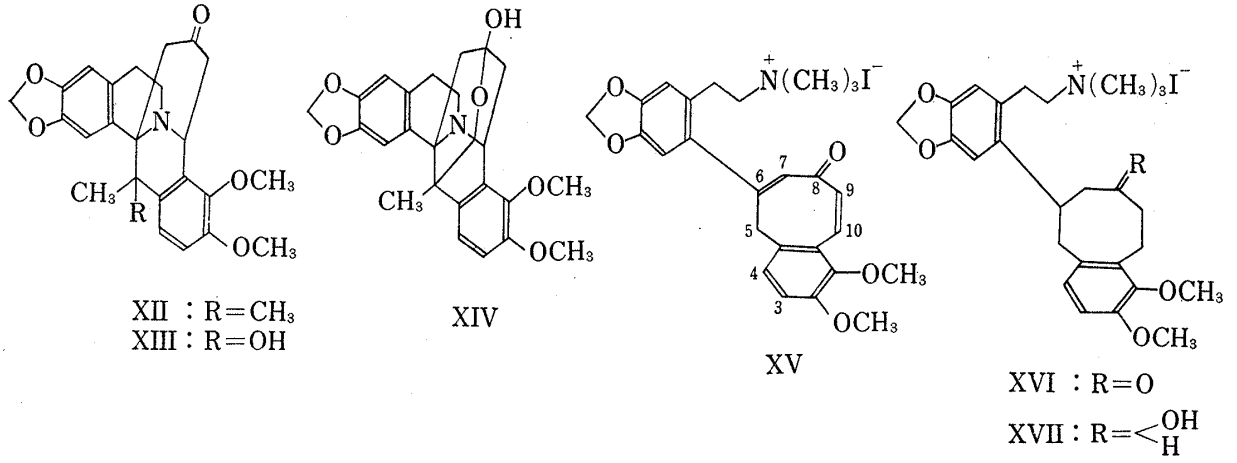
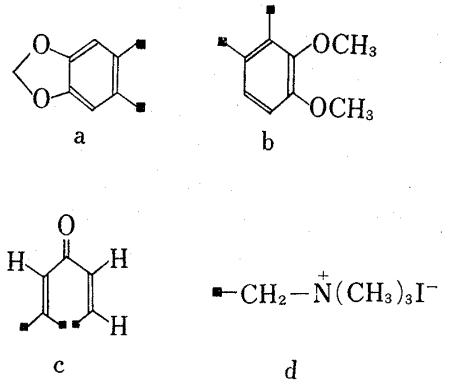


Chart 2

one of them appeared at δ 5.95 as singlet and other two AB type quartet protons at δ 7.43 and 6.52 (J=14 Hz), along with two methoxyl, one methylenedioxy, four aromatic and trimethylammonium protons. The mass spectrum of XV showed a M-58 M–CH_2=$N(CH_3)_2$ ion peak at m/e 363 indicating the existence of CH_2–$N^+(CH_3)_3I^-$ group. These data suggested the presence of the following partial structures (a, b, c and d) in accordance with the IR and ultraviolet (UV) spectral data; $\nu_{C=O}$ 1636 cm^{-1}, $\nu_{C=C}$ 1617 and 1587 cm^{-1} (see also Fig. 2), λ_{max} 219 nm (log ε, 4.64) and 297 nm (log ε, 4.12). In order to elucidate the structure around a conjugated carbonyl group of a partial structure c, catalytic and $NaBH_4$ reductions were



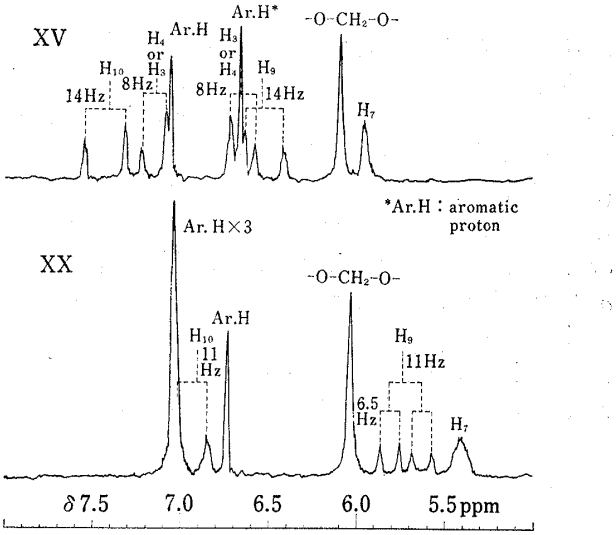


Fig. 1. NMR Spectra (Low Field Region) of XV and XX (in DMSO-d_6) (60 MHz)

attempted. Compound XV was recovered unchanged by catalytic reduction on palladium charcoal, but it was reduced on platinic oxide to give tetrahydroketone (XVI) as major product and tetrahydroalcohol (XVII) as minor. In the low field region of the NMR spectra, both XVI and XVII showed no longer the signal corresponding to vinyl proton and exhibited four aromatic protons. The UV spectra of XVI and XVII had absorption maxima at 287 nm (log ε, 3.74) and 287 nm (log ε, 3.76), respectively. On the IR spectra, XVI showed the bands at 1688 cm^{-1} (Fig. 2) attributable to a carbonyl group, but XVII showed hydroxyl absorption bands at 3350 cm^{-1} and no carbonyl band. These facts indicated that two double bonds of the partial structure c in XV were reduced to give a tetrahydroketone (XVI) and that the conjugated carbonyl group of XV was further reduced catalytically to afford a tetra-

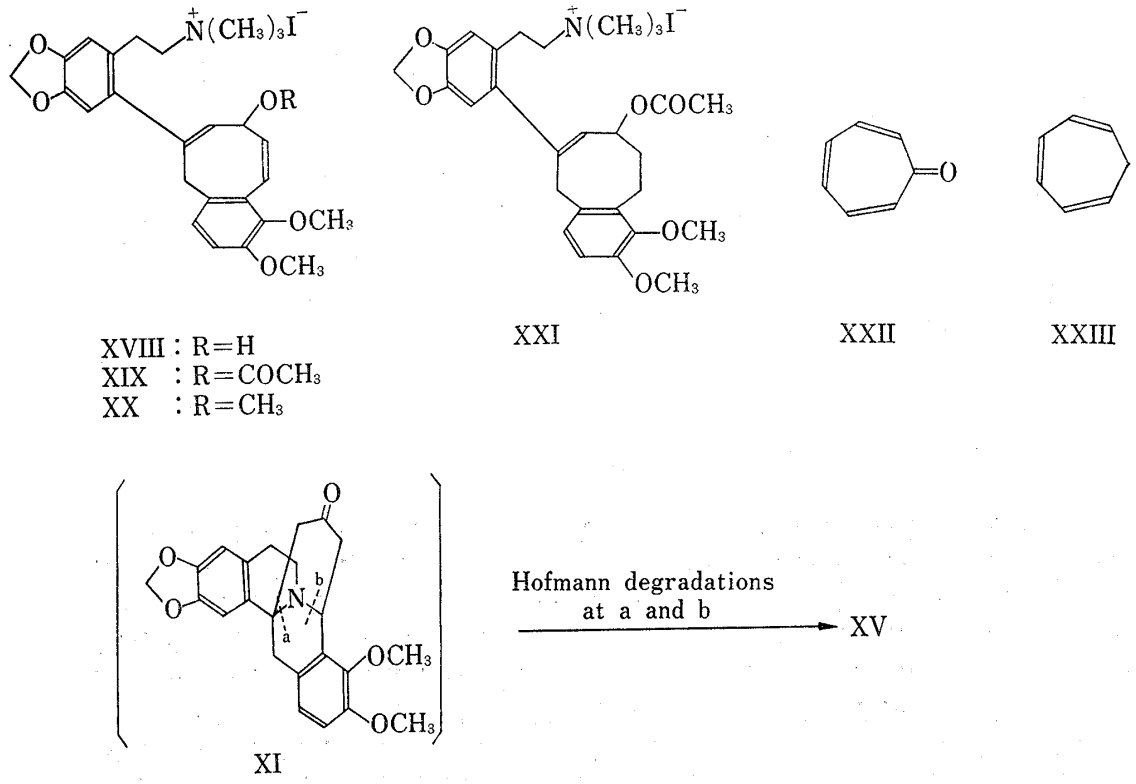


Chart 3

hydroalcohol (XVII). On reduction with $NaBH_4$, XV afforded an amorphous alcohol (XVIII) which was homogenious on TLC. Its IR and NMR spectral data suggested that the carbonyl group of XV was reduced to a secondary alcohol group. Acetylation of XVIII gave a crystalline monoacetate (XIX) whose UV spectrum showed an absorption maximum at 292 nm (log ε, 3.84). In an attempt to obtain a pure alcohol (XVIII), the amorphous product (XVIII) was treated with Amberlite IRA-405 (I^- form) in methanolic solution to give an unexpected crystalline methylether (XX). The spectral data of XX, *e.g.*, λ_{max} 293 nm (log ε, 3.81) and δ 3.20 (singlet of three protons of methoxyl group), were reconciled with a structure XX in which the hydroxyl group of XVIII was replaced by methoxyl group. It was confirmed that this substitution reaction was occurred at the step of the treatment with the ion exchange resin in methanol as illustrated below.

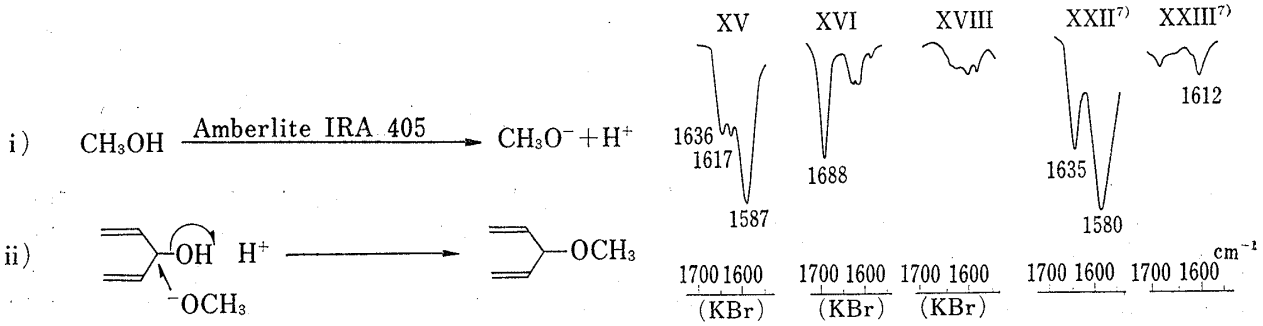


Fig. 2. IR Spectra (1600—1700 cm^{-1}) of XV, XVI, XVIII, XXII, and XXIII

When compound XV was reacted with a large excess of $NaBH_4$ followed by acetylation to obtain a dihydromonoacetate (XXI) whose NMR spectrum showed one vinyl proton appeared at δ 5.20. Its UV spectrum exhibited an absorption maximum at 286 nm (log ε,

3.75) as similar to those of XVI and XVII. These evidences indicated that both conjugated carbonyl group and disubstituted double bond in the partial structure c were reduced by $NaBH_4$.[6]

On the other hand, the presence of a dienone group on seven- or eight-membered ring in the compound XV was deduced from the IR spectral data shown in Fig. 2. The intensity and wave number of the bands of carbonyl and/or double bond of XV and the alcohol (XVIII) (or its acetate XIX) were very similar to those of the reported[7] troponoid derivatives, XXII and XXIII, respectively. In the NMR spectral analyses, the coupling constants of two vicinal vinyl protons (H_9 and H_{10}) of XVIII, XIX and XX (Fig. 1) were 11 Hz indicating the fact that these protons were *cis* on six-, seven- or eight-membered ring.[8] The abnormal large coupling constant (J=14 Hz) between these two protons of XV (Fig. 1) was probably explained by a neighboring C_8-carbonyl group. The vinyl proton (H_7) of XV appeared at δ 5.95 as broad singlet was shifted to higher field at about δ 5.4 with more broadening on reduction of C_8-carbonyl function (Fig. 1). Furthermore, a pair of doublet of AB type quartet appearing at higher field corresponding to C_9-proton was splited by an adjacent C_8-proton and recognized as double-doublet in the NMR spectra of XVIII, XIX and XX. In a case of XX, it is demonstrated through the first order analysis shown in Fig. 1. These facts were consistent with the partial structure c in which C_8-carbonyl group adjoined to a trisubstituted C_6-C_7-double bond and also conjugated with a disubstituted C_9-C_{10}-double bond.

On the basis of the above evidences considering with the fact that a small amount of sodium hydroxide and an excess of methyl iodide were presented in the methylation medium of the crude acetoneberberine, it seems most reasonable to conclude that the structure of compound XV is 5,8-dihydro-1,2-dimethoxy-8-oxo-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl)-benzocyclooctene methiodide (XV) corresponding to a Hofmann degradation product of the PB derivative (XI) as shown in Chart 3.

It has been well known that 13-substituted- and 13-unsubstituted-tetrahydroprotoberberine type alkaloids showed differing behaviour on Hofmann degradation, and that the Hofmann degradation products of 13-methyltetrahydroprotoberberines depended on the configuration at C-13 position.[9] Thus, it is assumed that 13-methyl PB derivative (III) afford a different product on Hofmann degradation. However, a Hofmann degradation of III gave a complex mixture which showed many spots on TLC. And none of them was isolated as a crystalline form. On the other hand, several attempts to isolate the intermediate XI from the crude acetoneberberine were unsuccessful. It may be considered that XI is very sensitive to an acidic condition because of having no 13-methyl group.

Experimental

All the melting points are uncorrected. NMR spectra were obtained in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) solution with tetramethylsilane as an internal standard on Varian A-60 spectrometer and IR spectra were taken in KBr disks with a Hitachi EPI-S2 spectrometer. All UV spectra were obtained in EtOH solution on Hitachi EPS-2U spectrometer. Mass Spectra were taken with a Hitachi RMU-6 spectrometer with a heated direct inlet system.

Isolation of 8,13a-(2′-Oxopropano)-13-methyl-2,3,9,10-tetramethoxydibenzo[*a*,*g*]quinolizidine (III)——To a solution of dehydrocorydalinium chloride (I) (10 g) in water (200 ml) was added acetone (2 ml) and NaOH (3 g) at 50—55° and the mixture was cooled at 4° for 24 hr. Resulting precipitates of a crude acetone adduct (II) were collected, washed with ice water and treated with 3% HCl aq. (50 ml) at 60—70° for 5 min. Result-

6) M.S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).
7) Y. Ikegami, "Sekigaisen Kyushu Supekutoru," Vol. 8, ed. by T. Shimanouchi, Y. Masuko and K. Nakanishi, Nankodo, Kyoto, 1959, p. 39.
8) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon Press, Oxford, 1969, p. 303.
9) P.W. Jeffs, "The Alkaloids, Chemistry and Physiology," Vol. IX, ed. by R.H.F. Manske, Academic Press, New York, 1967, p. 78.

ing yellowish white precipitates were collected, washed with hot water and recrystallized from a large amount of MeOH to give III-HCl salt (540 mg), colorless crystalline powder, mp 207—209° (decomp.). *Anal.* Calcd. for $C_{25}H_{29}O_5N \cdot HCl$: C, 65.28; H, 6.58; N, 3.04; Cl, 7.71. Found: C, 65.04; H, 7.10; N, 2.91; Cl, 7.84. The hot filtrate of 3% HCl aq. solution was cooled in ice bath to give yellow needles of I (9.5 g) which were collected by filtration. Several conditions for the formation of III-HCl salt are shown in Table I. In each experiment

Table I. Reaction Conditions for the Formation of Compound III Hydrochloride (III-HCl)

Dehydrocorydalinium chloride (I) (g)	Water (ml)	Acetone (ml)	NaOH			Yield of III-HCl (%)
			Amount (g)	Mole ratio[a)]	Concentration (%)	
10	200	2	1.5	1.5	0.75	4.3
10	200	2	3.0	3.0	1.5	5.4
2	200	2	1.0	5.0	0.5	2.5
5	400	4	15.0	30.0	3.75	1.8

a) mole ratio to dehydrocorydalinium chloride (I)

according to the procedure described above, resulting crystals of III-HCl salt which were insoluble in hot 3% HCl aq. were collected on glass filter and dried *in vacuo*. Experimental results are shown in Table I. Each per cent yield of III-HCl salt was calculated on the basis of the weight of each dried III-HCl salt. To a solution of III-HCl salt (5 g) in pyridine (150 ml) was added dropwise 10% NaOH to make pH 12. To this mixture was added water (1 liter) with stirring. Resulting precipitates were collected and recrystallized from $CHCl_3$–MeOH to give a free base III (4.1 g), colorless columns, mp 253—254°. *Anal.* Calcd. for $C_{25}H_{29}O_5N$: C, 70.90; H, 6.90; N, 3.31. Found: C, 71.03; H, 6.89; N, 3.30. NMR (δ in $CDCl_3$): 0.83 (d, J=7 Hz, 3H, C_{13}–CH_3), 3.82—3.91 (12H, OCH_3), 4.76 (d-d, J=2.5 and 5 Hz, C_8–H), 6.58—6.77 (4H, aromatic proton). III (300 mg) was decomposed by 3%HCl–EtOH (200 ml) according to the manner described previously[4] to give acetone-2,4-dinitrophenylhydrazone and I (280 mg).

8,13a-(2′-Hydroxypropano)-13-methyl-2,3,9,10-tetramethoxydibenzo[*a*,*g*]quinolizidine (IV)——To a solution of III (0.2 g) in $CHCl_3$–MeOH (1: 1) (30 ml) was added portionwise $NaBH_4$ (0.2 g) and the mixture left standing overnight at room tempearature. The solvent was evaporated to give a residue which was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over K_2CO_3 and evaporated to dryness. The residue was recrystallized from $CHCl_3$–MeOH to give IV, colorless columns, mp 198—200° or colorless prisms, mp 214—215° (dimorphous). *Anal.* Calcd. for $C_{25}H_{31}O_5N$: C, 70.56; H, 7.34; N, 3.29. Found: C, 70.55; H, 7.27; N, 3.35. NMR (δ in $CDCl_3$): 0.86 (d, J=7 Hz, 3H, C_{13}–CH_3), 3.87—3.94 (12H, OCH_3), 4.37 (m, 1H, C_8–H), 6.54—6.87 (4H, aromatic proton). IV-HCl salt, colorless prisms, mp 240—245° (decomp.) (MeOH). *Anal.* Calcd. for $C_{25}H_{31}O_5N \cdot HCl$: C, 64.99; H, 6.98; N, 3.03; Cl, 7.68. Found: C, 64.64; H, 6.91; N, 3.16; Cl, 8.08.

8,13a-(2′-Acetoxypropano)-13-methyl-2,3,9,10-tetramethoxydibenzo[*a*,*g*]quinolizidine (V)——A mixture of IV (135 mg), pyridine (2 ml) and acetic anhydride (2 ml) was allowed to stand for 18 hr at room temperature. The reaction mixture was evaporated to dryness. The residue was recrystallized from EtOH to give V, colorless needles, mp 162—163°. *Anal.* Calcd. for $C_{27}H_{33}O_6N$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.06; H, 7.37; N, 2.95. NMR (δ in $CDCl_3$): 0.87 (d, J=7 Hz, 3H, C_{13}–CH_3), 1.45 (s, 3H, $COCH_3$), 3.82—3.86 (12H, OCH_3), 4.32 (m, 1H, C_8–H), 5.02 (m, 1H, C_2'–H), 6.55—6.82 (4H, aromatic proton). V-HCl salt, colorless needles, mp 235—240° (decomp.) (MeOH). *Anal.* Calcd. for $C_{27}H_{33}O_6N \cdot HCl$: C, 64.34; H, 6.80; N, 2.78; Cl, 7.04. Found: C, 64.48; H, 6.75; N, 2.91; Cl, 7.48.

Isolation of 8,13a-(2′-Oxopropano)-13-methyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine (X)——To a solution of a crude 13-methylacetoneberberine[5] (VIII) (4 g) in acetone (200 ml) was quickly added with rapid stirring a 1.1% $KMnO_4$ aq. solution (200 ml). The reaction mixture was worked up as the reported procedure[1] to give 1-oxo-2-(2-acetyl-3-methyl-6,7-dimethoxy-1-indenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (yield 30%), XIV (4%) and XIII (1%). The mother liquors of XIII were evaporated to give a residue which showed two spots on TLC (Silica gel G, 5% MeOH–$CHCl_3$ as a solvent). The residue was purified by means of preparative TLC (Silica gel G, 5% MeOH–$CHCl_3$). A component of Rf 0.3 was obtained and identified with XIII. Another component of Rf 0.4 was obtained as colorless plates, mp 228—230°, after recrystallization from CH_2Cl_2–MeOH. The latter was identified with an authentic sample of X[5] by direct comparison, *e.g.*, mixed mp, TLC and IR.

Thin-Layer Chromatography of Crude Acetone Adducts (II and VII)——a) Precipitates of a crude acetone adduct (II) showed two spots (Rf 0.34 and 0.73) on TLC (on silica gel G, solvent: *n*-BuOH–AcOH–H_2O (4: 1: 5, v/v) use the top phase). One of them was a yellow spot of I (Rf 0.34) and another was a small spot of III (Rf 0.73) which was detected by a Dragendorff reagent.

b) On similar TLC condition, precipitates of a crude acetone adduct (VIII) also showed two spots (*Rf* 0.35 and 0.70). One of them was a yellow spot of VI (*Rf* 0.35) and another was a small spot of VIII (*Rf* 0.70). which was positive to a Dragendorff reagent.

Isolation of 5,8-Dihydro-1,2-dimethoxy-8-oxo-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl)-benzocyclooctene Methiodide (XV)——To a solution of berberinium chloride (VII) (400 g) in water (40 liter) was added with rapid stirring acetone (400 ml) and 50% NaOH (2 liter). The mixture was cooled with ice-water for 1.5 hr. Resulting precipitates of a crude acetone adduct (IX) were collected, washed with ice water and dried *in vacuo* at room temperature for 24 hr to give 360 g of a crude IX. Its water content was determined as 1% by Karl Fischer's method, and its NaOH content (0.8%) was determined back-titrimetrically by a dropwise addition of 0.1N NaOH into an acidic solution of IX. A mixture of the crude IX (300 g), $CHCl_3$ (1.2 liter) and methyl iodide (126 ml, 2.6 fold moles to IX) was heated in an autoclave at 100° for 1 hr. After cooling, the reaction mixture was evaporated and the residue was treated with CH_2Cl_2 (30 liter). As an insoluble part in hot CH_2Cl_2, yellow crystals of berberinium iodide (VII, Cl=I) (107 g, yield 30%) were obtained by filtration. The filtrate was concentrated to dryness. The residue was recrystallized from MeOH to give yellow crystals of 13-methylberberinium iodide (VI, Cl=I) (165 g, 45%). The methanolic mother liquor was evaporated to give a residue (19 g) which was treated by a hot $CHCl_3$ (400 ml). An insoluble part (11.6 g) in $CHCl_3$ was recrystallized from a large amount of MeOH to afford XV (9 g), colorless prisms, mp 239—241°. *Anal.* Calcd. for $C_{25}H_{27}O_5N \cdot CH_3I$: C, 55.42; H, 5.37; N, 2.49; I, 22.53. Found: C, 55.10; H, 5.51; N, 2.58; I, 22.40. NMR (δ in DMSO-d_6): 2.96 (s, 9H, $N^+(CH_3)_3$), 3.81 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), and also see Fig. 1. A small amount of berberinium iodide was obtained from the mother liquor of XV. A soluble part (7.2 g) in hot $CHCl_3$ was concentrated and the residue was chromatographed on silica gel (70 g) column. The column was eluted gradiently with 0—5% MeOH–$CHCl_3$. Each fraction was monitored by TLC on Silica gel G using 0.25% MeOH–$CHCl_3$ as a developing solvent. Compound XII (3.97 g, *Rf* 0.7), XIV (0.2 g, *Rf* 0.6), X (0.05 g, *Rf* 0.4), XIII (0.5 g, *Rf* 0.3) and 13-methylberberinium iodide (*Rf* 0.05) were isolated in this order after purification by recrystallization, and identified with each authentic sample by usual direct comparison, *e.g.* mixed mp, TLC and IR.

1,2-Dimethoxy-8-oxo-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl)benzocyclooctane Methiodide (XVI) and 1,2-Dimethoxy-8-hydroxy-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl)benzocyclooctane Methiodide (XVII)——A mixture of XV (1.4 g), MeOH (120 ml) and PtO_2 (150 mg) was shaked at room temperature under atmospheric hydrogen pressure for 7 hr and 150 ml of hydrogen was absorbed. The catalyst was filtered off. The filtrate was concentrated to a small volume and allowed to stand overnight at room temperature. Resulting crystals were collected to give XVII (100 mg), colorless prisms, mp 208—210°. *Anal.* Calcd. for $C_{25}H_{33}O_5N \cdot CH_3I$: C, 54.83; H, 6.37; N, 2.46. Found: C, 54.51; H, 6.47; N, 2.24. The mother liquor of XVII was concentrated to give a residue which was recrystallized from MeOH to afford XVI (1.2 g), colorless columns, mp 200—202°. *Anal.* Calcd. for $C_{25}H_{31}O_5N \cdot CH_3I$: C, 55.02; H, 6.04; N, 2.47; I, 22.36. Found: C, 54.89; H, 6.06; N, 2.38; I, 22.39. NMR (δ in DMSO-d_6): 3.17 (s, 9H, $N^+(CH_3)_3$), 3.76 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.02 (s, 2H, OCH_2O), 6.73—7.17 (4H, aromatic proton).

5,8-Dihydro-1,2-dimethoxy-8-hydroxy-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl) benzocyclooctene Methiodide (XVIII)——To a solution of XV (1 g) in MeOH (100 ml) was added portionwise $NaBH_4$ (0.1 g) with stirring at room temperature. After 30 min, the reaction mixture was concentrated to dryness. To the residue was added water and dil. HCl to make pH 4—5. The acidic solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and concentrated to give an amorphous powder of XVIII (910 mg) which was homogenious on TLC (Silica gel G, *n*-BuOH–AcOH–H_2O (4: 1: 5)). NMR (δ in DMSO-d_6): 3.15 (s, 9H, $N^+(CH_3)_3$), 3.72 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.5 (m, 1H, C_8–H), 5.25 (d, J=5 Hz, 1H, C_8–OH), 5.43 (bs, 1H, C_7–H), 5.74 (d-d, J=5 and 11 Hz, C_9–H), 6.74 (d, J=11 Hz, 1H, C_{10}–H), 6.05 (s, 2H, OCH_2O), 6.73—7.04 (4H, aromatic proton).

5,8-Dihydro-1,2-dimethoxy-8-acetoxy-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl) benzocyclooctene Methiodide (XIX)——A mixture of XVIII (910 mg), pyridine (5 ml) and acetic anhydride (3 ml) was allowed to stand overnight at room temperature. Resulting colorless needles in the reaction mixture were collected and washed with EtOH and ether to give pure XIX (0.4 g), mp 193—195° (decomp.). *Anal.* Calcd. for $C_{27}H_{31}O_6N \cdot CH_3I$: C, 55.30; H, 5.64; N, 2.31. Found: C, 55.17; H, 5.81; N, 2.25. NMR (δ in DMSO-d_6): 2.03 (s, 3H, $COCH_3$), 3.15 (s, 9H, $N^+(CH_3)_3$), 3.72 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.43 (bs, 1H, C_7–H), 5.60 (m, 1H, C_8–H), 5.82 (d-d, J=6.5 and 11 Hz, 1H, C_9–H), 6.89 (d, J=11 Hz, 1H, C_{10}–H), 6.03 (s, 2H, OCH_2O), 6.72—7.08 (4H, aromatic proton).

5,8-Dihydro-1,2,8-trimethoxy-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl) benzocyclooctene Methiodide (XX)——To a solution of XV (1 g) in MeOH (100 ml) was added portionwise $NaBH_4$ (0.2 g) with stirring at room temperature. After 1 hr, the reaction mixture was concentrated to give a residue to which was added water, dil. HCl and a small amount of KI. The acidic aq. solution was extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated to give a residue which was dissolved in MeOH and passed through a column of Amberlite IRA-402 (I^- form, 20 g). The elute was concentrated to give a residue (1 g) which was chromatographed on silica gel (14 g) column. The fraction eluted with 5%MeOH–$CHCl_3$ was collected and concentrated to give a residue. To a solution of the residue in water was added a small amount of KI. The

mixture was allowed to stand for a few days. Colorless needles were deposited and collected to give XX (0.3 g), mp 158—160°. *Anal.* Calcd. for $C_{26}H_{31}O_5N \cdot CH_3I \cdot H_2O$: C, 54.28; H, 6.07; N, 2.34. Found: C, 54.24; H, 6.45; N, 2.44. NMR (δ in DMSO-d_6): 3.15 (s, 9H, $N^+(CH_3)_3$), 3.20 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), and also see Fig. 1.

5,8,9,10-Tetrahydro-1,2-dimethoxy-8-acetoxy-6-(2-dimethylaminoethyl-4,5-methylenedioxyphenyl-1-yl)-benzocyclooctene Methiodide (XXI)——To a solution of XV (1 g) in EtOH (170 ml) was added portionwise $NaBH_4$ (0.5 g) with stirring at room temperature. After 2 hr, the solvent was evaporated to give a residue to which was added dil. HCl. The acidic solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3 and concentrated to give an amorphous residue which was acetylated with a mixture of pyridine (5 ml) and acetic anhydride (3 ml) at room temperature. After 16 hr, the reaction mixture was concentrated to give a residue to which was added dil. HCl. The acidic solution was extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated to afford a residue (770 mg) which was purified by a chromatography on silica gel (10 g) column. The fraction eluted with 5% MeOH–$CHCl_3$ was collected and evaporated to remove the solvent. The residue was dissolved in water. Precipitates were deposited from the aq. solution on addition of a small amount of KI, collected and recrystallized from $CHCl_3$–EtOH to give XXI (0.3 g), colorless prisms, mp 242—244°. *Anal.* Calcd. for $C_{27}H_{33}O_6N \cdot CH_3I \cdot 1/2H_2O$: C, 54.38; H, 6.04; N, 2.27. Found: C, 54.11; H, 5.89; N, 2.23. NMR (δ in DMSO-d_6): 1.97 (s, 3H, $COCH_3$), 3.16 (s, 9H, $N^+(CH_3)_3$), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.20 (bs, 1H, C_7–H), 5.20 (m, 1H, C_8–H), 6.05 (s, 2H, OCH_2O), 6.71—7.03 (4H, aromatic proton).

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