[Chem. Pharm. Bull. 23(6)1271—1275(1975)]

UDC 547.978.1.04 : 547.32.04

8,13a-Propanoberbines. III.[1] Reaction of Acetoneberberine Type Enamine with Alkyl Halide[2]

Shunsuke Naruto, Haruki Nishimura, and Hidehiko Kaneko

Research Laboratories, Dainippon Pharmaceutical Co., Ltd.[3]

(Received November 11, 1974)

The reaction of acetoneberberine(I) with methyl iodide was found to give 8, 13a-(2′-oxopropano)-13, 13-dimethylberbine derivative (IV) and 8, 13a-(2′-oxopropano)-13-methylberbine derivative(V) as side products together with the expected 13-methylberberinium(II) and berberinium iodide(III). Analogous reaction of I with allyl bromide gave rise to 8, 13a-(2′-oxopropano)-13, 13-diallylberbine derivative(XI). The structures of products were deduced from chemical and spectral data.

Although it has been well known that the reaction of acetoneberberine (I) with alkyl halide affords 13-alkylberberinium and berberinium halides,[4] other products of this reaction has not yet been reported. In the present paper, we wish to describe the further investigation on the alkylation of acetoneberberine type enamine with alkyl halide.

Methylation of I with excess methyl iodide[4] gave two major products, 13-methylberberinium iodide (II, X=I) and berberinium iodide (III, X=I), and two novel 8,13a-propanoberbine derivatives, compound IV and V. The nuclear magnetic resonance (NMR) spectra of IV and V exhibited the signals of one methylenedioxy, two methoxyl and four aromatic protons. Furthermore a signal corresponding to C-8 proton of I appeared at δ 4.6—4.7 as double-doublet in both compounds. Their ultraviolet (UV) spectra exhibiting the absorption maximum at 288 nm (log ε, 3.8) indicated the presence of berbine structure.

Compound IV was analyzed for $C_{25}H_{27}O_5N$. Its NMR spectrum exhibited two tertiary methyl signals at δ 0.93 and 1.53. The infrared (IR) absorption of IV at 1695 cm^{-1} suggested the presence of ketone. Reduction of IV with sodium borohydride yielded only an alcohol (VI) which afforded an acetate (VII). In the NMR spectrum, acetyl signal of VII showed a high field shift appearing at δ 1.53. As was discussed in the previous papers[1,5] in this series, the high field shift of about 0.5 ppm of acetyl signal has been playing an important role in the structural elucidation of 8,13a-(2′-acetoxypropano)berbine derivatives, VIII and IX, in which the acetyl group was located on ring D having an anisotropic effect as a result of stereoselective reduction of 2′-carbonyl group. Thus it was suggested that the acetate VII was 8,13a-(2′-acetoxypropano)berbine derivative. On the other hand, a stable hydrochloride of IV was obtained, whereas 13-monosubstituted 8,13a-(2′-oxopropano)berbine derivative did not afford a stable hydrochloride, but was decomposed to give acetone and 13-substituted berberinium chloride by hydrochloric acid.[1,5] Therefore, two tertiary methyl signals in the NMR spectrum of IV was assigned as 13,13-dimethyl group. The relative configuration and the further confirmation of the position of tertiary methyl group at C-13 of IV were clarified from Nuclear Overhauser Effect (NOE) studies. Molecular model study of IV showed that irradiation of equatorial methyl proton at C-13 should increase in the area of the protons at C-1 and C-12.

1) Part II: S. Naruto, H. Nishimura, and H. Kaneko, *Tetrahedron Letters*, **1972**, 2127.
2) A part of this work was presented at the 16th Symposium on the Chemistry of Natural Products, Oct., 1972, Osaka.
3) Location: *33—94, Enoki-cho, Suita, Osaka.*
4) M. Freund and P. Walbaum, *Ann.*, **409**, 266 (1915); T. Takemoto and Y. Kondo, *Yakugaku Zasshi*, **82**, 1408 (1962).
5) J. Iwasa and S. Naruto, *Yakugaku Zasshi*, **86**, 534 (1966).

This prediction was confirmed experimentally since there were observable NOE of 12% at C-1 and 11% at C-12 protons when the methyl protons at δ 1.53 was irradiated. Therefore the other methyl signal at δ 0.93 could be assigned to axial methyl protons at C-13. These assignments of axial and equatorial methyl signals at C-13 were in fair agreement with those established on the methyl group of corydaline and meso-corydaline.[6] The carbon framework of IV was also deduced on the basis of the fact that each of IV and VI exhibited an intense peak at *m/e* 189 corresponding to the characteristic fragment (X) of 8,13a-propanoberbines

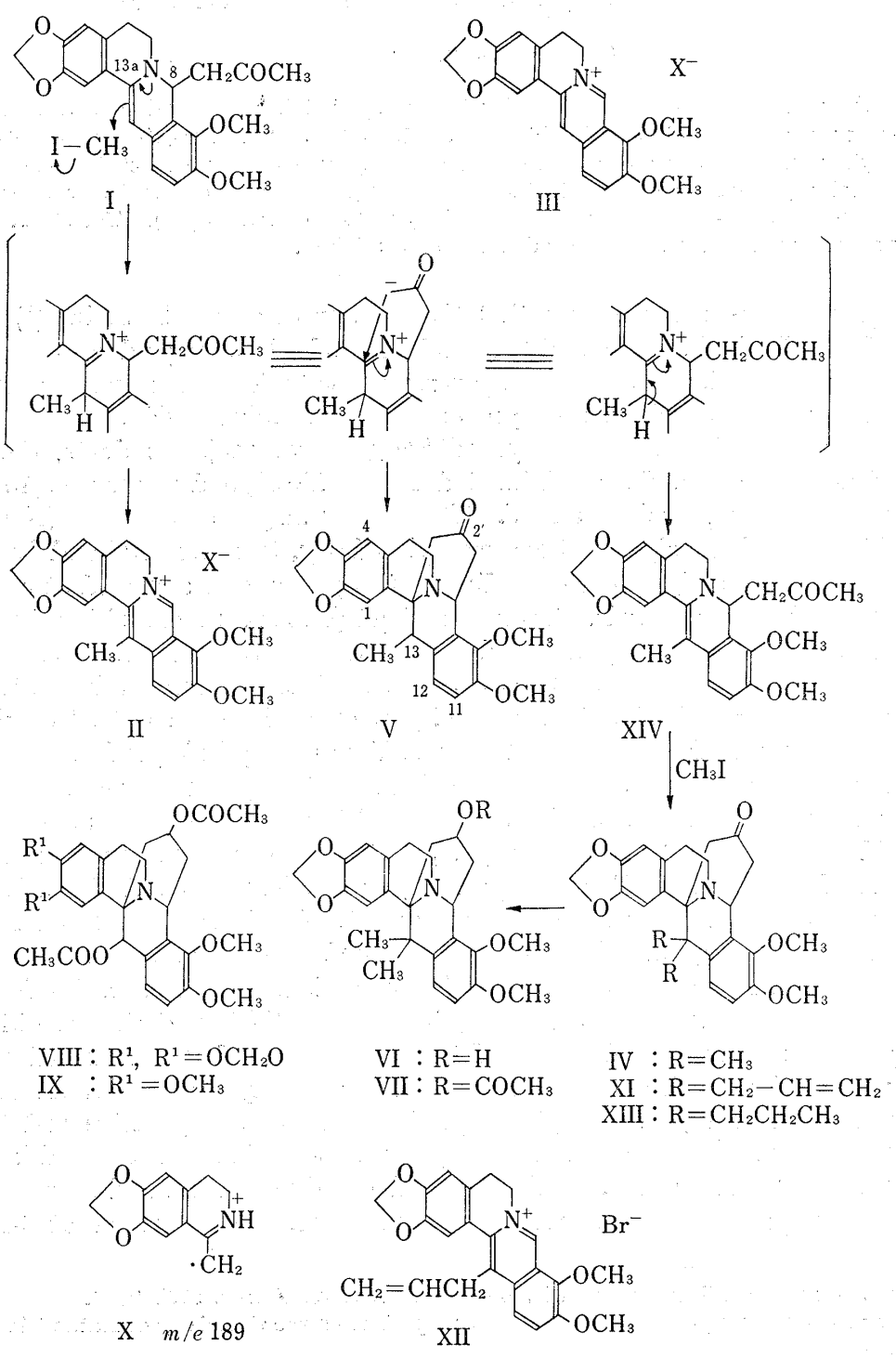

Chart 1

6) S. Naruto and H. Kaneko, *Yakugaku Zasshi*, **92**, 1017 (1972).

in their mass spectra.[7] Considering with the reaction mechanism shown in Chart 1, it seems most reasonable to conclude that IV is 8,13a-(2′-oxopropano)-13,13-dimethyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine (IV).

Another product (V) was analyzed for $C_{24}H_{25}O_5N$ and exhibited the IR absorption at 1695 cm^{-1}. Its NMR spectrum showed the secondary methyl signal at δ 1.42 as doublet (J=7 Hz). And its mass spectrum exhibited a peak of fragment ion X at *m/e* 189. Treatment of V with ethanolic hydrochloric acid yielded acetone and 13-methylberberinium chloride (II, X=Cl). Thus the formulation V for this compound became unequivocal.

The analogous reaction of I with excess allyl bromide afforded 13,13-diallylpropanoberbine derivative (XI) besides 13-allylberberinium bromide (XII)[6] and berberinium bromide (III, X=Br). Compound XI was isolated as its hydrobromide from the reaction mixture and yielded a tetrahydro-derivative (XIII) on catalytic reduction.

Table I. Effect of Alkali on Yield (%) of 8,13a-Propanoberbines

Added alkali	Mole ratio[a] alkali[b]	0 none	0.1 NaOH	0.1 Et_3N	0.3 Et_3N	0.3 NaOH	0.5 Et_3N	1.0 Et_3N
Yield(%) of	IV	3	5	5	6		7	8
8,13a-propanoberbine	IX	4				10		

a) Mole ratio to acetoneberberine (I), and 2.8 mol equivalent of alkyl halide to 1 mole equivalent of I was used.
b) Et_3N: triethylamine

From the fact that 13-methylacetoneberberine (XIV) prepared from II gave compound IV on methylation with methyl iodide, the tentative reaction mechanism similar to the thermal annelation of enamine with methyl vinyl ketone[8] is proposed as shown in Chart 1. According to this mechanism, the excess of alkyl halide and the alkaline medium are favorable for the formation of 8,13a-propanoberbine derivatives. In practice, the yields of IV and XI increased in general with addition of sodium hydroxide or triethylamine in the presence of excess methyl or allyl halide in the reaction medium as shown in Table I.

Experimental

All the melting points are uncorrected. NMR spectra were obtained in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on Varian A-60 or Varian HA-100 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.

Reaction of Acetoneberberine(I) with Methyl Iodide——A mixture of I(40 g), CH_3I(18 ml), and $CHCl_3$ (160 ml) was heated in an autoclave at 100° for 1 hr. The solvent was evaporated and the residue was refluxed with CH_2Cl_2(1 liter). From an insoluble part in hot CH_2Cl_2 berberinium iodide(III, X=I) was obtained in 35% yield. A soluble part was concentrated to dryness and the residue was recrystallized from MeOH to give 13-methylberberinium iodide(II, X=I) in 45% yield. The mother liquor of II was concentrated to dryness. The residue was chromatographed on silica gel and eluted successively with $CHCl_3$, 1% and 5% MeOH–$CHCl_3$. First, the fraction eluted with $CHCl_3$ was combined and recrystallized from CH_2Cl_2–MeOH to give IV(yield, 3.5%), colorless prisms, mp 214—215°. *Anal.* Calcd. for $C_{25}H_{27}O_5N$: C, 71.24; H, 6.45; N, 3.32. Found: C, 71.21; H, 6.39; N, 3.11. IR: 1695 cm^{-1}. UV: λ_{max} 288 nm(log ε, 3.78). NMR(δ): 0.93 (s, 3H, C_{13}–CH_3), 1.53(s, 3H, C_{13}–CH_3), 3.83(s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 4.75(double-doublet, 1H, J=2 and 5 Hz, C_8–H), 5.95(s, 2H, OCH_2O), 6.61—6.98(4H, aromatic proton). HCl salt: mp 278—280°(decomp.). *Anal.* Calcd. for $C_{25}H_{27}O_5N \cdot HCl \cdot 1/2H_2O$: C, 64.30; H, 6.26; N, 3.00; Cl, 7.59. Found: C, 64.22; H, 6.59; N, 2.74; Cl, 6.97. Secondly, the fraction eluted with 1% MeOH–$CHCl_3$ was purified by recrystallization from CH_2Cl_2–MeOH to give 8.13a-(2′-oxopropano)-13-methyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine(V)(0.01%), colorless plates, mp 228—230°. *Anal.* Calcd. for $C_{24}H_{25}O_5N$: C, 70.74; H, 6.18; N, 3.44. Found: C, 70.64; H, 6.29; N, 3.39. IR: 1695 cm^{-1}. UV: λ_{max} 288 nm(log ε, 3.77). NMR (δ):

7) The mass spectral analyses of 8, 13a-propanoberbines will be reported elsewhere.
8) R.V. Stevens and M.P. Wentland, *J. Am. Chem. Soc.*, **90**, 5580 (1968).

1.42(d, J=7 Hz, 3H, C_{13}–CH_3), 3.83(s, 3H, OCH_3), 3.90(s, 3H, OCH_3), 4.60(d—d, J=2 and 5.5 Hz, 1H, C_8–H), 5.93(s, 2H, OCH_2O), 6.60—7.00(4H, aromatic proton). Compound V(300 mg) was decomposed by treatment with 3% HCl–EtOH(200 ml) according to the manner described previously[5] to give acetone-2,4-DNP and 13-methylberberinium chloride(II, X–Cl)(280 mg), mp 195—200°(decomp.). *Anal.* Calcd. for $C_{21}H_{20}O_4NCl \cdot H_2O$: C, 62.46; H, 5.49; N, 3.46; Cl, 8.78. Found: C, 62.47; H, 5.35; N, 3.42; Cl, 8.87. Finally, the fraction eluted with 5% MeOH–$CHCl_3$ gave an additional amount of II(X=I).

8,13a-(2′-Hydroxypropano)-13,13-dimethyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine (VI)——To a solution of IV (270 mg) in $CHCl_3$–MeOH was added $NaBH_4$ (200 mg). The mixture was stirred at room temperature for 1 hr. The solvent was evaporated and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried over K_2CO_3. The solvent was removed and the residue was recrystallized from MeOH to give VI(237 mg), colorless prisms, mp 182—184°. *Anal.* Calcd. for $C_{25}H_{29}O_5N$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.73; H, 6.76; N, 3.31. IR: 3475 cm^{-1}. NMR(δ): 0.93(s, 3H, C_{13}–CH_3), 1.58(s, 3H, C_{13}–CH_3), 1.20(d, J=9 Hz, 1H, OH), 3.85(s, 3H, OCH_3), 3.93(s, 3H, OCH_3), 4.33(d—d, J=2 and 6 Hz, 1H, C_8–H), 5.93(s, 2H, OCH_2O), 6.55—7.05(4H, aromatic proton).

8,13a-(2′-Acetoxypropano)-13,13-dimethyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine (VII)——A mixture of VI (130 mg), pyridine (2 ml) and acetic anhydride (1 ml) was left standing overnight at room temperature. The reaction mixture was evaporated to dryness. The residue was recrystallized from EtOH to give VII, mp 182—184°. *Anal.* Calcd. for $C_{27}H_{31}O_6N$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.39; H, 6.75; N, 2.88. IR: 1720 cm^{-1}. NMR(δ): 0.93(s, 3H, C_{13}–CH_3), 1.53(s, 3H, C_{13}–CH_3), 1.53(s, 3H, $COCH_3$), 3.84(s, 3H, OCH_3), 3.90(s, 3H, OCH_3), 5.93(s, 2H, OCH_2O), 6.05—7.01(4H, aromatic proton).

8,13a-(Oxopropano)-13,13-diallyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine (XI)——A mixture of I (40 g), allyl bromide (27 ml) and $CHCl_3$ (160 ml) was heated in an autoclave at 110° for 1 hr. The reaction mixture was concentrated to dryness and the residue was treated with CH_2Cl_2 (1 liter). From an insoluble part in CH_2Cl_2, berberinium bromide(III, X=Br) was obtained. A soluble part was evaporated to give a residue to which EtOH(400 ml) and 10% HBr aq. (40 ml) were added, and the mixture was warmed. After cooling, resulting crystals were collected and recrystallized from MeOH to give XI–HBr salt(2 g), colorless prisms, mp 250—252°(decomp.). *Anal.* Calcd. for $C_{29}H_{31}O_5N \cdot HBr$: C, 62.81; H, 5.82; N, 2.53; Br, 14.41. Found: C, 63.03; H, 6.03; N, 2.60; Br, 14.36. XI–HBr salt was dissolved in a mixture of pyridine and 10% Na_2CO_3, and the mixture was poured into an ice water with stirring. Resulting precipitates were 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 acetone to yield XI, colorless prisms, mp 186—187°. *Anal.* Calcd. for $C_{29}H_{31}O_5N$: C, 73.55; H, 6.60; N, 2.96. Found: C, 73.78; H, 6.57; N, 2.84. IR: 1695 cm^{-1}. NMR (δ): 3.83 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 4.7—5.4 (m, 7H, vinyl protons and C_8–H), 5.97 (s, 2H, OCH_2O), 6.59—6.78 (4H, aromatic proton). 13-Allylberberinium bromide(XII) was obtained from the mother liquor of XI–HBr salt as described previously.[6]

8,13a-(2′-Oxopropano)-13,13-dipropyl-2,3-methylenedioxy-9,10-dimethoxydibenzo[*a*,*g*]quinolizidine (XIII)——A solution of XI (0.5 g) in EtOH (30 ml) was shaken at room temperature in the presence of 5% Pd–C(0.6 g) under an atmospheric hydrogen pressure. After hydrogen absorption was ceased, the catalyst was filtered off and the filtrate was evaporated to give a residue. The residue was recrystallized from EtOH to give XIII, colorless prisms, mp 194—195°. *Anal.* Calcd. for $C_{29}H_{35}O_5N$: C, 72.93; H, 7.39; N, 2.93. Found: C, 72.79; H, 7.20; N, 3.01. NMR(δ): 0.62 (t, 3H, $CH_2CH_2\underline{CH_3}$), 0.98 (t, 3H, $CH_2CH_2\underline{CH_3}$), 3.84 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.71 (d—d, 1H, C_8–H), 5.97 (s, 2H, OCH_2O), 6.58—6.80 (4H, aromatic proton).

13-Methylacetoneberberine(XIV)——To a stirred mixture of II(X=I)(10 g), water (60 ml) and 50% NaOH aq. (40 ml) was added aqueous acetone solution(acetone 70 ml and water 400 ml) under cooling with ice bath. Resulting precipitates of the crude acetone adduct were collected, washed with ice water and dried *in vacuo* to give 7—8 g of XIV which was used for the following experiments without further purification. The analytical sample was obtained by several recrystallizations from acetone–ether to afford pale yellow prisms in very low yield. mp 148—150°. *Anal.* Calcd. for $C_{24}H_{25}O_5N$: C, 70.74; H, 6.18; N, 3.44. Found: C, 70.45; H, 5.89; N, 3.37. NMR(δ): 2.00 (s, 3H, $COCH_3$), 2.29 (s, 3H, C_{13}–CH_3), 3.86 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.27 (d—d, J=4.5 and 7 Hz, C_8–H), 5.95 (s, 2H, OCH_2O), 6.64—7.08 (4H, aromatic proton). IR: 1700 cm^{-1}.

Reaction of 13-Methylacetoneberberine(XIV) with Methyl Iodide——A mixture of XIV (4 g), CH_3I(5 ml) $CHCl_3$(16 ml) was heated in a sealed tube at 100° for 1 hr. The solvent was evaporated to give a residue which was treated with MeOH(40 ml). Resulting crystals of II(X=I)(2.7 g) were collected and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (20 g) column. The first $CHCl_3$ elute was collected and recrystallized from CH_2Cl_2–MeOH to give IV(55 mg), mp 214—215°, which was identical with a sample of IV described above in all respects.

Reaction of Acetoneberberine(I) with Alkyl Halide in the Presence of Alkali——a) A mixture of I(4.0 g), $CHCl_3$(16 ml), CH_3I(1.8 ml, 2.8 fold moles) and each alkali shown in Table I was heated in a sealed tube at 110° for 1 hr. In a reference experiment, no alkali was used in the reaction. Each reaction mixture was treated as described above to give a residue obtained from a mother liquor of II(X=I). Each residue was chromatographed on silica gel (10 g) and eluted with $CHCl_3$. The $CHCl_3$ elute was concentrated to give crys-

tals which were recrystallized from CH_2Cl_2–MeOH to afford colorless prisms(IV). Each per cent yield of IV shown in Table I was calculated on the basis of the weight of the pure crystals.

b) A mixture of I(4.0 g), $CHCl_3$(16 ml), allyl bromide(2.7 ml) and powdered NaOH(40 mg) was heated in a sealed tube at 110° for 1 hr. NaOH was not used in a reference experiment. The reaction mixture was treated as in the case of XI to give crystals of XI–HBr salt. Each per cent yield of XI was calculated on the basis of the weight of XI–HBr salt(Table I).

Acknowledgement We wish to thank Drs. H. Takamatsu and S. Minami, Directors of this laboratory, for their encouragements. Thanks are also obliged to Nichiden-Varian Co., Ltd. for NOE measurement, and to the members of Analytical Center of this laboratory for microanalyses and NMR measurements.