Notes

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Synthesis of Sinomenine and Isosinomenine from Sinomeninone

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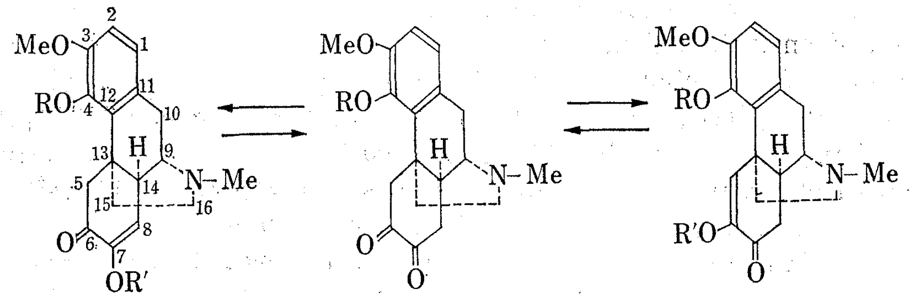
In 1958 Sasaki reported isolation of a new alkaloid,[2] mp 210—212°, $C_{19}H_{23}O_4N$, from the extracts of the root of *Sinomenium acutum* Rhed. et Wils. and gave this compound the name "isosinomenine." However continuing research revealed that this base had the formula of $C_{20}H_{25}O_4N$ instead of $C_{19}H_{23}O_4N$ and an ethoxyl group besides a methoxyl group, unlike sinomenine, which contains two methoxyl groups. As a result of this work the structure of the compound, mp 210—212°, was represented as (I) or (II) and the name "isosinomenine" was cancelled.[3] This report is concerned with establishment of the structure of this compound and with synthesis of sinomenine derivatives from sinomeninone (III).[4]



I : R=H, R'=Et
IV : R=H, R'=Me
VII : R=Me, R'=Et
IX : R=Me, R'=Me
XI : R=H, R'=n-C_3H_7
XIII : R=H, R'=iso-C_3H_7

III : R=H
VI : R=Me

II : R=H, R'=Et
V : R=H, R'=Me
VIII : R=Me, R'=Et
X : R=Me, R'=Me
XII : R=H, R'=n-C_3H_7
XIV : R=H, R'=iso-C_3H_7

Chart 1

The nuclear magnetic resonance (NMR) spectra of sinomenine (IV) and the base, mp 210—212° (II), in deuteriochloroform were reexamined.[5] Sinomenine shows a signal (doublet) due to a C_8–vinyl proton at 4.50 τ, two proton signals due to C_5–methylene at 5.63 τ and 7.57 τ and two methoxyl signals at 6.27τ and 6.55 τ, whereas the base, mp 210—212°, shows a sharp signal due to a C_5–vinyl proton at 3.23τ, a methoxyl signal at 6.17τ and a triplet methyl signal at 8.63τ. These facts suggest that the structure of the compound, mp 210—212°, is II. As stated before this compound was isolated from the mother liquors of sinomenine hydrochloride which was prepared by treating the crude base with HCl–alcohol. It was considered that the hydrolysis of sinomenine to sinomeninone followed by enol ethylation might give this compound. Goto, *et al.* reported that sinomeninone (III) was converted to methylsinomenine

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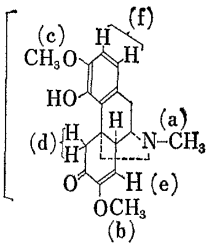
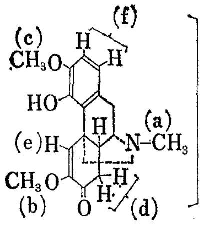
1) Location: *Sagisukami, Fukushima-ku, Osaka.*
2) Y. Sasaki and S. Ueda, *Yakugaku, Zasshi*, **78**, 44 (1958).
3) Y. Sasaki and K. Okabe, *Yakugaku Zasshi*, **83**, 418 (1963).
4) K. Goto and I. Yamamoto, *Proc. Japan Academy*, **34**, 619 (1958).
5) Y. Sasaki, the 4th Symposium on the Chemistry of Natural Products, Kyoto (1960), Symposium papers p. 17.

Table I

	 Sinomenine IV	 Isosinomenine V
a) $N-C\underline{H}_3$	7.62(s)	7.62(s)
b) $OC\underline{H}_3$ (enol)	6.55(s)	6.48(s)
c) $OC\underline{H}_3$ (arom)	6.27(s)	6.15(s)
d) $-C\underline{H}_2-\underset{\overset{\|}{O}}{C}-$	5.63(d) 7.57(d)	
e) $-C\underline{H}=C\langle_{OMe}$	4.50(d)	3.25(s)
f) Arom-$\underline{H}$	3.43	3.30

(IX) by the action of dimethylsulfate in only 2.5% yield.[4] Then several attempts were made for the purpose of enol alkylation.

The ethylation of methylsinomeninone (VI) was carried out using ethyl *p*-toluenesulfonate to afford a base (VIII), mp 144—145°, $[\alpha]_D$ +89.4° and oily base (VII), $[\alpha]_D$ −11.5°, in 12% and 29% yields, respectively. The former was undepressed on admixture with a sample, mp 144—145°, prepared from Sasaki's base (II) by Rodinov's method.[6,7]

Now the question remained whether Sasaki's base was obtained from the natural product or not. Since the thin layer chromatogram of the crude extracts did not show a spot corresponding to Sasaki's base, it was assumed that this compound was obtained by the action of HCl–alcohol. Then an attempt was made to prepare a compound corresponding to Sasaki's sample from sinomeninone (III). Treatment with HCl–alcohol gave two isomeric compounds, mp 141—142°, (I), $[\alpha]_D$ −46.5° and mp 212—213°, (II), $[\alpha]_D$ +92.4°, in yields of 45% and 17%, respectively. The latter was identical in every respect with Sasaki's base. Similar treatment of sinomeninone (III) with HCl–MeOH gave two compounds, sinomenine (IV), mp 160—161°, $[\alpha]_D$ −70.7° and the base, (V), mp 196—197°, $[\alpha]_D$ +94.7°, in 45.2% and 14.5% yields, respectively. The ultraviolet (UV) spectrum of the latter is similar to that of compound (II). These facts show that the struc-

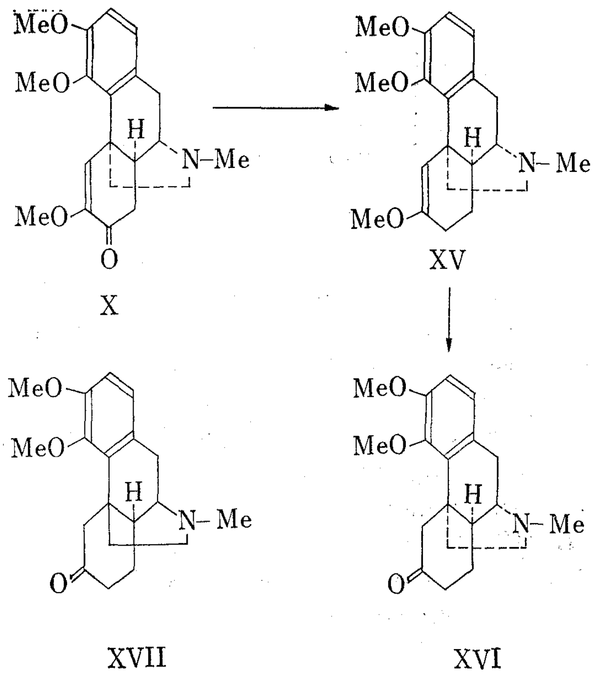


Chart 2

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[6] W. Rodinov, *Bull. Soc. Chim.*, **39**, 305 (1926).
[7] K. Okabe, *Yakugaku Zasshi*, **82**, 1500 (1962).

ture of Sasaki's base belongs to the (II) system. Thus, the authors would like to suggest that the name "isosinomenine" be reassigned to the base, mp 196—197° (V). Furthermore methylation of methylsinomeninone (VI) was studied. Treatment with Rodinov's reagent gave methylsinomenine (IX), mp 174—175°, $[\alpha]_D$ $-44°$ and methylisosinomenine (X), mp 141—142°, $[\alpha]_D$ $+88°$, in yields of 28% and 25%, respectively.

Elimination of the 7-oxo group of methylisosinomenine gave, in high yield, an oily non-ketonic compound, which showed an absorption band due to enol methylether at 1680 cm^{-1}. Hydrolysis of this compound gave a ketonic base, mp 147—148°. Comparison of the infrared (IR) spectra indicated that this compound (XVI) was an enanthiomer of dihydrothebainone methyl ether (XVII). In connection with these studies several sinomenine and isosinomenine derivatives were synthesized from sinomeninone by the action of HCl in the presence of the corresponding alcohols as shown in the following table. It is of interest to note that the sinomenine derivatives show dextro rotation, whereas the isosinomenine derivatives levo rotation.

Table II

Compouud	Rotation ($CHCl_3$)	Compound	Rotation ($CHCl_3$)
(I)	$[\alpha]_D^{28}$ $-46.5°$	(II)	$[\alpha]_D^{26}$ $+92.4°$
(IV) Sinomenine	$[\alpha]_D^{26}$ $-70.7°$	(V) Isosinomenine	$[\alpha]_D^{27}$ $+94.7°$
(VII)	$[\alpha]_D^{26}$ $-11.5°$	(VIII)	$[\alpha]_D^{28}$ $+89.4°$
(IX) Methylsinomenine	$[\alpha]_D^{22}$ $-44.0°$	(X) Methylisosinomenine	$[\alpha]_D^{27}$ $+88.0°$
(XI)	$[\alpha]_D^{26}$ $-58.3°$	(XII)	$[\alpha]_D^{26}$ $+95.8°$
(XIII)	$[\alpha]_D^{26}$ $-83.2°$[a]	(XIV)	$[\alpha]_D^{26}$ $+70.8°$

a) Measured as hydrochloride in EtOH.

Considering the above mentioned experimental evidence, it is concluded that the so-called "isosinomenine" (mp 210—212°) must be converted from sinomeninone (III), which was the hydrolysis product of natural sinomenine.

Experimental

All melting points were uncorrected. Optical rotations, unless otherwise stated, were measured in $CHCl_3$ and UV spectra in EtOH. The IR spectra were obtained with a Nihon Bunko DS-201 in $CHCl_3$ soln, and NMR spectra were obtained with a Varian A-60 high resolution spectrometer using deuteriochloroform as a solvent. The line positions are given in τ values using tetramethylsilane as internal reference.

Enol Ethylation of Methylsinomeninone (VI)——A solution of sodium ethylate (prepared from 0.13 g Na) and ethyl *p*-toluenesulfonate (1.65 g) in ethanol was added to a solution of methylsinomeninone (1.1 g) in ethanol (15 ml) and the mixture was refluxed for 1 hr. The precipitated salt was filtered off and the filtrate was evaporated under reduced pressure. The residue was extracted with benzene, and the organic layer washed with 10% aq. NaOH soln and then with water to remove the starting material.

The benzene soln was extracted with 1% HCl to remove neutral and acidic substances.

The acidic soln was made alkaline with aq. Na_2CO_3 and extracted with benzene. The benzene soln was washed with water, dried, and evaporated *in vacuo* to give an oily substance, $[\alpha]_D^{26}$ $-11.5°$ ($c=1.026$), which did not crystallize on standing. Attempts to crystallize the hydrochloride failed giving an oily product, treatment of which with aq. KI soln gave the hydroiodide of 3,4-dimethoxy-7-ethoxy-6-oxo-N-methyl-Δ^7-morphinan (VII) in 29% yield as crystals (350 mg), mp 92—95°.

Anal. Calcd. for $C_{21}H_{27}O_4N \cdot HI \cdot \frac{1}{2}H_2O$: C, 51.02; H, 5.91; N, 2.83; I, 25.67; MeO, 12.56; EtO, 9.12. Found: C, 50.91; H, 6.16; N, 2.77; I, 25.28; MeO, 11.81; EtO, 8.57.[8]

The mother solution from the hydroiodide was made alkaline with dil. NaOH and extracted with benzene. The solvent was distilled off and the residue crystallized from ether to afford 140 mg (11.7%) of 3,4-dimeth-

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[8] Measured by Dr. J. Fukuda (Osaka University).

xy-6-ethoxy-7-oxo-N-methyl-Δ^5-morphinan (VIII), mp 144—145°, $[\alpha]_D^{28}$ +89.4° (c=1.089). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; MeO, 17.36; EtO, 12.60. Found: C, 70.68; H, 7.65; MeO, 16.92; EtO, 12.28.8) The picrate was prepared in ether and crystallized from EtOH, mp 195—196°. *Anal.* Calcd. for $C_{21}H_{27}O_4N \cdot C_6H_3O_7N_3$: C, 55.29; H, 5.16; N, 9.55. Found: C, 55.30; H, 5.36; N, 9.87.

Methylation of the Base mp 210—212° (So-called Isosinomenine) by Rodinov's Method——The so-called "isosinomenine" (0.25 g) was dissolved in toluene (15 ml) and Rodinov's reagent (1.25 mmole) was added dropwise to the above soln. During the successive 40 min refluxing, the color of the soln became yellow from light red. The organic solvent was evaporated under reduced pressure and dimethylaniline was removed by steam distillation. The remaining alkaline soln was extracted with benzene to give 220 mg. nonphenolic base, which was crystallized from ether, mp 144—145°. IR ν_{max} cm^{-1}: 1687 (C=O conj.), 1617 (-C=C-). The infrared spectrum in $CHCl_3$ soln was undistinguishable from that of 3,4-dimethoxy-6-ethoxy-7-oxo-N-methyl-Δ^5-morphinan (VIII) derived from methylsinomeninone by the above-mentioned method. *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 71.00; H, 7.72; N, 3.90. The picrate was prepared in and recrystallized from EtOH, mp 195—196°. *Anal.* Calcd. for $C_{21}H_{27}O_4N \cdot C_6H_3O_7N_3$: C, 55.29; H, 5.16; N, 9.55. Found: C, 55.32; H, 5.35; N, 9.73.

Enol Ethylation of Sinomeninone (III)——A solution of sinomeninone (3.2 g) in 10 g ethanol was saturated with dry HCl gas for 2 hr at room temperature. The solvent was distilled off under reduced pressure, the residue was made alkaline with aqueous K_2CO_3 soln and extracted with $CHCl_3$. The $CHCl_3$ soln was chromatographed on Al_2O_3 (90 g).

Fraction A: The product (1.2 g) eluted with chloroform was crystallized from ether to yield 571 mg (16.6%) 3-methoxy-4-hydroxy-6-ethoxy-7-oxo-N-methyl-Δ^5-morphinan (II), mp 212—213°. $[\alpha]_D^{26}$ +92.4° (c=1.06). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.27;H, 7.46; N, 4.02. The picrate was crystallized from EtOH, mp 135—140° (sintered at 120°). *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 52.88; H, 5.21; N, 9.49. Found: C, 53.28; H, 5.21; N, 9.50. This base and its picrate showed no melting point depression on admixture with respective samples of the so-called "isosinomenine."

Fraction B: The procut eluted with methanol was crystallized from ether to afford 3-methoxy-4-hydroxy-6-oxo-7-ethoxy-N-methyl-Δ^7-morphinan (I), mp 141—142°, 1.55 g (45.1%). $[\alpha]_D^{23}$ −46.5° (c=1.074). IR ν_{max} cm^{-1}: 3580 (OH), 1690 (C=O conj.), 1618 (-C=C-). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.08. Found: C, 70.08; H, 7.24; N, 3.90. Attempts to crystallize the picrate failed giving an oily substance.

Enol Methylation of Sinomeninone (Preparation of Sinomenine (IV) and Isosinomenine (V))——A stream of dry hydrogen chloride gas was passed through a solution of sinomeninone (3.2 g) in methanol (10 g) for 2 hr. The solution was evaporated *in vacuo*, and the residue was taken into a small amount of water under cooling. The solution was made alkaline with 10% aq. Na_2CO_3 and extracted with $CHCl_3$.

The solvent was removed and the crude base chromatographed on alumina. The product (1.02 g) eluted with $CHCl_3$ was crystallized from $CHCl_3$-ether to yield 477 mg (14.5%) of isosinomenine (3,6-dimethoxy-4-hydroxy-7-oxo-N-methyl-Δ^5-morphinan)(V), mp 196—197°, $[\alpha]_D^{27}$ +94.7° (c=1.108). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25; MeO, 18.84. Found: C, 69.02; H, 7.17; N, 4.21; MeO, 18.94. UV λ_{max} mμ (log ε): 237 (3.90), 267 (3.95); λ_{min} mμ (log ε): 249 (3.81). IR ν_{max} cm^{-1}: 1685 (C=O conj.), 1623 (-C=C-), 3580 (OH). The picrate, prepared in and recrystallized from alcohol, mp 224—225° (decomp.). *Anal.* Calcd. for $C_{19}H_{23}O_4N \cdot C_6H_3O_7N_3$: C, 53.76; H, 4.69; N, 10.03. Found: C, 53.87; H, 4.82; N, 9.90. The hydrochloride: mp 236—238° (decomp.) (from EtOH), $[\alpha]_D^{26}$ +53.5° (c=1.031, EtOH). *Anal.* Calcd. for $C_{19}H_{23}O_4N \cdot HCl \cdot H_2O$: C, 59.45; H, 6.83; N, 3.65; Cl, 9.24; H_2O, 4.69. Found: C, 59.48; H, 6.90; N, 3.74; Cl, 9.14; H_2O, 4.58. Elution with methanol gave 1.8 g of crude base, which was crystallized from ether to give 1.48 g (45.2%) of sinomenine, mp 160—161°. No melting point depression was observed on admixture with an authentic sample and identity was also demonstrated by comparison of the infrared spectra. The picrate prepared in and recrystallized from EtOH: mp 181—183°. *Anal.* Calcd. for $C_{19}H_{23}O_4N \cdot C_6H_3O_7N_3 \cdot \frac{1}{2}H_2O$: C, 52.91; H, 4.80; N, 9.87. Found: C, 53.02; H, 4.98; N, 9.88.

Enol Methylation of Methylsinomeninone (VI) by Rodinov's Method——A solution of 1.0 g of methylsinomeninone in toluene (35 ml) was treated with Rodinov's reagent (0.05 mole) for 2 hr.

After removal of the dimethylaniline by steam distillation, the basic product was extracted with benzene and the organic layer was evaporated. The residue was treated with aqueous dil. HCl to separate the less soluble salt of methylsinomenine.

Thus obtained hydrochloride (308 mg) was suspended in a small amount of water, made alkaline with aq. Na_2CO_3 soln and extracted with benzene. The benzene solution was evaporated and the residue crystallized from benzene to give rhombic crystals, mp 174—175°, $[\alpha]_D^{26}$ −44° (c=1.060) 287 mg (27.6%). UV λ_{max} mμ (log ε): 246 (3.66), 265 (3.77). On admixture with an authentic sample of methylsinomenine no melting point depression was observed, and the infrared spectra of both compounds were superimposable. After separation of the above mentioned hydrochloride, the mother solution was made alkaline with dil. Na_2CO_3 and extracted with benzene. The solvent was removed and the residue was crystallized from ether to yield 264 mg of methylisosinomenine (X) (25.4%), mp 141—142°, $[\alpha]_D^{27}$ +88.0° (c=1.029). UV λ_{max} mμ (log ε): 232 (3.95), 266 (3.93); λ_{min} mμ (log ε): 225 (3.93), 246 (3.73). IR ν_{max} cm^{-1}: 1687 (C=O conj.), 1622 (-C=C-), 1605 (Arom). *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.95; H, 7.33; N, 4.08; MeO, 27.11. Found:

C, 69.83; H, 7.38; N, 4.03; MeO, 27.18. The picrate was crystallized from EtOH, mp 183—185°. *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot C_6H_3O_7N_3$: C, 54.54; H, 4.93; N, 9.79. Found: C, 54.68; H, 5.04; N, 9.89.

Huang-Minlon Reduction of Methylisosinomenine (X)——A mixture of methylisosinomenine (685 mg) and 80% hydrazine hydrate (1.1 g) was heated at 110° for 1 hr. After cooling, 1.4 g of diethyleneglycol and 0.4 g of KOH pellets were added and the mixture was heated at 180° for 4 hr. The reaction mixture was poured into 10 ml of cold water and extracted with 50 ml of benzene. After removal of the solvent, there was obtained 680 mg of deoxomethylisosinomenine (XV) as a slightly yellow viscous oil, whose infrared spectrum shows no carbonyl band, but enol ether band at 1680 cm^{-1}.

Hydrolysis of Deoxomethylisosinomenine (XV)——Deoxomethylisosinomenine (XV) (300 mg) was hydrolyzed with 3 ml of 10% HCl on a steam bath for 5 min. The solution was made alkaline with aq. Na_2CO_3 soln, extracted with benzene, and the solvent was distilled off under reduced pressure. The residue was crystallized from ether to give 3,4–dimethoxy–6–oxo–N–methylmorphinan (XVI), mp 147—148°, $[\alpha]^{26}_{D}$ $+86.4°$ ($c=1.059$), 235 mg (82%). In the infrared spectrum, this compound showed a carbonyl absorption at 1710 cm^{-1}, and comparison of the spectra showed that this compound was the antipode of dihydrothebainone methyl ether derived from thebaine. *Anal.* Calcd. for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44; MeO, 19.68. Found: C, 72.21; H, 7.98; N, 4.55; MeO, 20.07.

3-Methoxy-4-hydroxy-6-propoxy-7-oxo-N-methyl-Δ^5-morphinan (XII) and 3-Methoxy-4-hydroxy-6-oxo-7-propoxy-N-methyl-Δ^7-morphinan (XI)——Dried HCl gas was passed through a soln of 3.7 g sinomeninone in 10 g *n*–PrOH as in the case of the enol methylation. The product was extracted with chloroform and chromatographed on neutral alumina (90 g). Elution with chloroform gave 1.27 g (35.4%) of 3–methoxy–4–hydroxy–6–propoxy–7–oxo–N–methyl–Δ^5–morphinan (XII) (isosinomenine form), recrystallization of which from ether gave the pure substance, mp 174—175°, $[\alpha]^{26}_{D}$ $+95.8°$ ($c=1.035$). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.62; H, 7.73; N, 4.34. Further elution with MeOH gave 1.5 g of crude oily base, which was crystallized from benzene to give 558 mg (15.7%) of 3–methoxy–4–hydroxy–6–oxo–7–propoxy–N–methyl–Δ^7–morphinan (XI), mp 128° (sinomenine form), $[\alpha]^{26}_{D}$ $-58.3°$ ($c=1.049$). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.40; H, 7.74; N, 4.03.

3-Methoxy-4-hydroxy-6-isopropoxy-7-oxo-N-methyl-Δ^5-morphinan (XIV) and 3-Methoxy-4-hydroxy-6-oxo-7-isopropoxy-N-methyl-Δ^7-morphinan (XIII)——Dried HCl gas was passed through a solution of sinomeninone (4.2 g) in isopropanol (12.6 g) for 1.5 hr and the mixture was worked up as in the preceeding experiment. Elution with chloroform yielded 1.14 g (31.8%) of 3–methoxy–4–hydroxy–6–isopropoxy–7–oxo–N–methyl–Δ^5–morphinan (isosinomenine form) (XIV). Recrystallization form ether gave pure material, mp 198—199°, $[\alpha]^{26}_{D}$ $+70.8°$ ($c=0.991$). *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.35; H, 7.78; N, 3.73. Elution with methanol gave 1.46 g (40.8%) of 3–methoxy–4–hydroxy–6–oxo–7–isopropoxy–N–methyl–Δ^7–morphinan (XIII) (sinomenine form) as a syrup. The hydrochloride, recrystallized from EtOH–ether, mp 190—192° (decomp.), $[\alpha]^{26}_{D}$ $-83.2°$ ($c=1.022$, EtOH). *Anal.* Calcd. for $C_{21}H_{27}O_4N \cdot HCl \cdot H_2O$: C, 61.23; H, 7.34; N, 3.40; Cl, 8.60. Found: C, 61.13; H, 7.56; N, 3.16; Cl, 8.92.

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