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Studies on Morphine Alkaloids. VI.[1] Indolinocodeine. IV.[2] Conversion of Indolinocodeine Series Compounds into Morphine Series Compounds

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Solvolysis of indolinocodeine derivatives (III and IV) was carried out under the conditions employed for conversion of morphine series compounds into indolinocodeine series compounds to attempt their conversion to morphine type skeleton, and VI was obtained from III. An assumed mechanism through an aziridinium intermediate was proposed.

In previous papers of this series,[2,4] we reported the synthesis of indolinocodeine derivatives, in which the C_9–N bond in morphine series compounds had undergone rearrangement to C_{14}, and showed that this rearrangement reaction occurred under solvolytic conditions, and an assumed reaction mechanism was proposed in which an aziridine–type quaternary immonium cation was formed as an intermediate.

In the present work, solvolysis of indolinocodeine series compounds was carried out under similar conditions to attempt their conversion into morphine series compounds, and it was found that the double bond in the C-ring of these compounds participated to a great extent in these reactions.

Some examples have been reported[5] on the internal displacement of the leaving group by the lone pair electrons of the nitrogen, due to neighboring group participation of the tertiary nitrogen atom, subsequent formation of a cyclic ammonium compound as an intermediate, and followed by ring opening to form a rearranged product. This reaction has recently been used by Mokotoff and Sargent[6] for the rearrangement of morphine series compounds. This reaction occurs most easily when the leaving group and the nitrogen are in 1,2-*trans*-diaxial position. Therefore, an attempt was made to carry out this reaction on compounds with a substituent in the $C_{9\alpha}$–position, which has the same relation to the C_{14}–N bond as the foregoing.

The starting material used for this reaction, 9α-acetoxyindolinocodeine (I), which was synthesized by the method already reported,[2] was treated with phosphorus pentachloride in chloroform by which C_6-chloro derivative (II), mp 125—126°, was formed quantitatively. Configuration of chlorine in C_6 was determined from the nuclear magnetic resonance (NMR) spectrum of II, which showed the proton signals of C_5 and C_6 at δ 4.42 (doublet, J=8.5 cps) and 4.11 (multiplet), respectively. From the dihedral angle between C_5- and C_6-protons measured with the Dreiding model of II, it becomes possible to estimate the values of this coupling constant. The values thus obtained were $J_{5\beta,6\alpha}$=8.0—8.5 and $J_{5\beta,6\beta}$=4.0—5.0, and

1) Part V: K. Abe, M. Onda, and S. Okuda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1847 (1969).
2) Part III: S. Okuda, K. Abe, and M. Onda, *Chem. Pharm. Bull.* (Tokyo), **16**, 1124 (1968).
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4) S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1092 (1965).
5) J.D. Horbson and W.D. Riddell, *Chem. Commun.*, **1968**, 1180; J.W. Huffman and T. Kamiya, *Tetrahedron Letters*, **1966**, 1857; R.C. Fuson and C.L. Zirkle, *J. Am. Chem. Soc.*, **70**, 2760, (1948).
6) M. Mokotoff and L.J. Sargent, *J. Org. Chem.*, **33**, 3551, 3556 (1968).

the coupling constant in II ($J_{5\beta,6}$=8.5) corresponds to the above $J_{5\beta,6\alpha}$, so that the chlorine at C_6 in II would be in β-configuration.

II was catalytically reduced over palladium charcoal under atmospheric hydrogen pressure. After an absorption of hydrogen had almost ceased in 8 hr, the hydrogenated product, whose thin-layer chromatography (TLC)[7] showed no starting material, was followed by hydrolysis with methanolic potassium hydroxide. The reaction products thus obtained showed two spots in TLC (*Rf* 0.3, and 0.5), which was separated by column chromatography over alumina into III and IV in a respective yield of 45 and 40%.

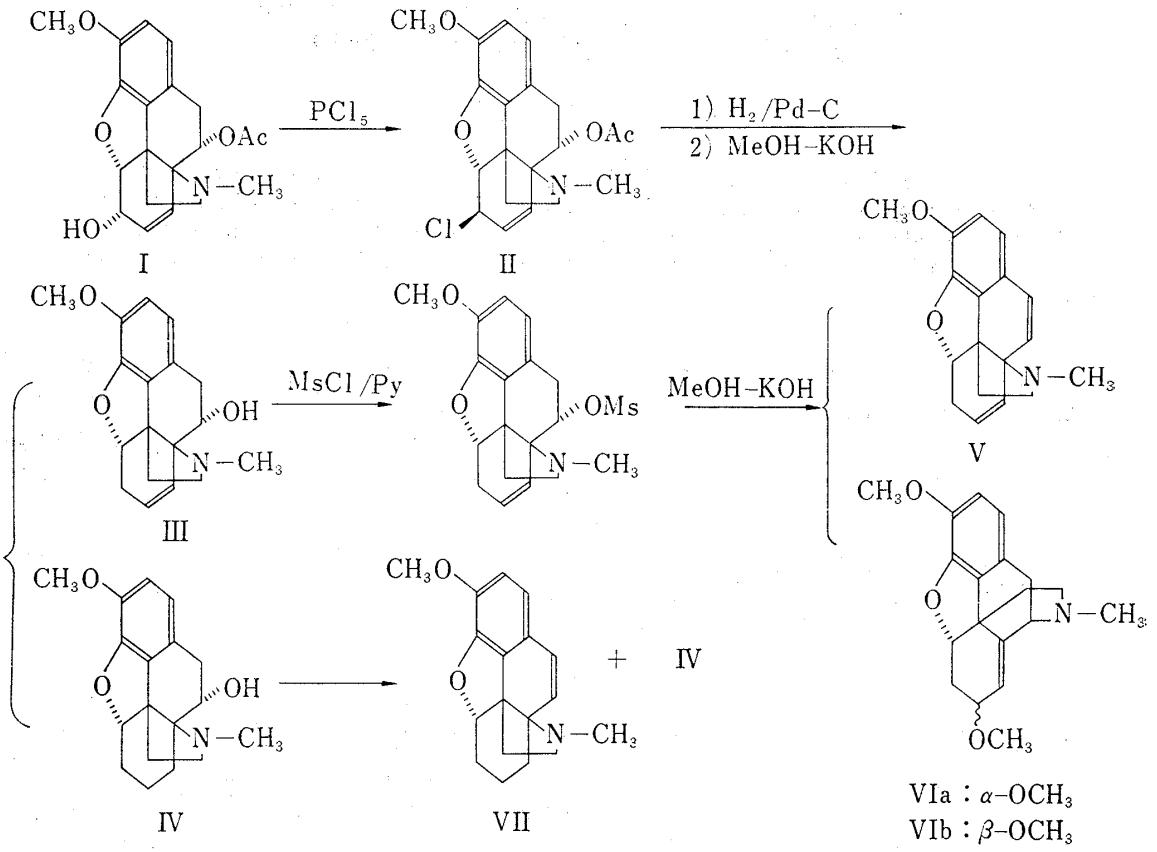

Chart 1

III: $C_{18}H_{21}O_3N$, colorless needles, mp 137—138°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (–OH), 1605 (C=C double bond); The NMR spectrum of III showed signals at δ 6.71 (2H, s, aromatic C_1- and C_2–H), 5.81—6.21 (2H, AB-quartet, olefinic C_7– and C_8–H), 4.5 (1H, q, J=9.6, 6.6 cps, $C_{5\beta}$–H), *ca.* 3.82 (1H, $C_{9\beta}$–H), 3.85 (O–CH_3), and 2.43 (N–CH_3). IV: $C_{18}H_{23}O_3N$, colorless needles, mp 121—122°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (–OH). NMR: δ 6.63 (2H, C_1–, C_2–H), 4.60 (broad q, J=6.8, 10.0, $C_{5\beta}$–H), 4.31 (1H, q, J=7.0, 10.3, $C_{9\beta}$–H), 3.85 (O–CH_3), 2.55 (N–CH_3).

From the foregoing data, III was found to be the compound formed by dechlorination under the reduction condition and IV, that formed by further reduction of the double bond. In the above reaction, III is further reduced to IV on addition of more catalyst and the reaction time is prolonged.

Tosylation of III with tosyl chloride in pyridine failed to give the tosylate and III was recovered completely. Mesylation of III with mesyl chloride in pyridine afforded a mesylate (*Rf* 0.7 on TLC[7]) after 10 hr. This mesylate was so labile that it was not purified further at this step but was used immediately for the following reaction.

7) Silica gel plates (0.25 mm); solvent, $CHCl_3$: MeOH=9:1.

A mixture of this mesylate in 10% methanolic potassium hydroxide was refluxed on a water bath for 30 min, by which the mesylate disappeared completely and two products (*Rf* 0.5 and 0.37 on TLC) were obtained. These products were separated by alumina column chromatography into V and VI in a respective yield of 25 and 30%. V; $C_{18}H_{19}O_2N$, oxalate, colorless needles, mp 204—205°. NMR spectrum of V was shown in Fig. 1.

Besides the C_7– and C_8–H at δ 5.71, olefinic protons of AB-quartet (J=10 cps) appeared at 6.42 and 5.72, and the signal of $C_{9\beta}$–H at around 3.8 in the NMR spectrum of III had disappeared in this spectrum. These data show that mesyl group at C_9 had liberated in this reaction with introduction of a double bond at C_9 and C_{10}, taking the structure shown in Fig. 1.

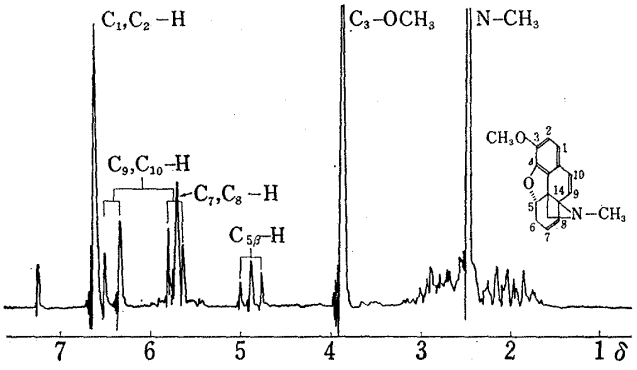

Fig. 1. NMR Spectrum of V

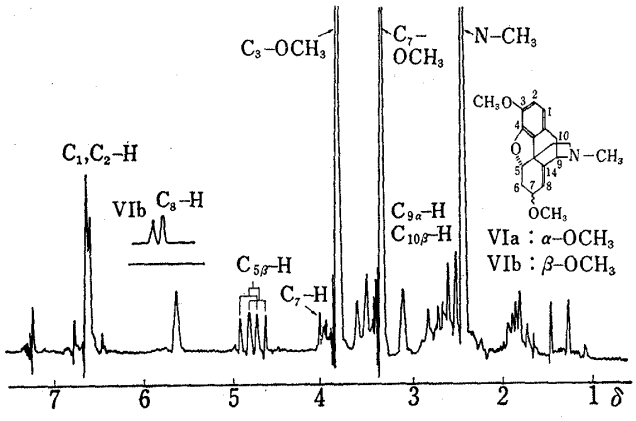

Fig. 2. NMR spectra of VIa and VIb (superimposed)

From the results of thin-layer[8] and gas-liquid[9] chromatography, VI was found to be a mixture of two substances (VIa, VIb), and the ratio of VIa to VIb in this mixture was assumed as about 3:1 on the observation of gas-liquid chromatogram. These two compounds seemed to be isomers from their IR and NMR spectra, but further separation and purification of VI through alumina or silica gel column chromatography failed to effect this separation, and derivation of this mixture to crystalline salts was also unsuccessful. Therefore, preparative thin-layer chromatography was carried out using alumina plate (0.5 mm) with chloroform containing 1% of methanol. VIa was thereby obtained as colorless needles, mp 156—157°, $C_{19}H_{23}O_3N$, and VIb, $C_{19}H_{23}O_3N$, oxalate, colorless needles, mp 224—226°.

NMR spectra of these compounds are shown in Fig. 2.

Comparison of these spectra with that of III indicates the decrease of one olefinic proton, presence of a double bond with a partial structure of $>\underset{H}{C}-\underset{H}{C}=C<$ from the manner of its coupling, new introduction of one methoxyl group, and the appearance of proton signals of $C_{9\alpha}$ and $C_{10\beta}$ at δ around 2.5—3.5. These facts show that VI no longer has the indolinocodeine type skeleton.[10]

These experimental evidences indicate that VI is 6-deoxy-7-methoxyneopine, formed by rearrangement of the C–N bond from C_{14} to C_9, and that VIa and VIb are stereoisomers with respect to the methoxyl group in C_7 position.

Configuration of Methoxyl Group in VI: In an earlier work of this series,[1] treatment of 14β-bromocodeine (VIII) with sodium borodeuteride gave the compound (X) in which

8) Alumina plate (0.25 mm); solvent, $CHCl_3$: MeOH=99:1.
9) Column, SE-30, 1.5%, column temp., 210°, or column, OV-17, 1.5%, column temp., 230°.
10) S. Yamaguchi, S. Okuda, and N. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).

deuterium was introduced into C_7 position of neopine (IX). It has also been found that methoxyl group is introduced during the methanolysis of VIII to form XI.[2)]

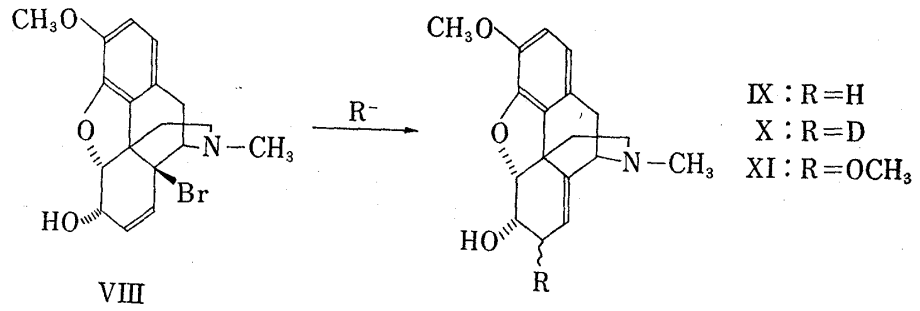

Chart 2

The NMR data of C_8–H in these compounds are compared with those of VI in Table I.

Table I. Comparison of NMR Data of C_8-H in VI, X, and XI

Compound	δ	$J_{7,8}$	Compound	δ	$J_{7,8}$
X	5.50	6.0	VIa	5.65	~1
XI	5.56	6.0	VIb	5.80	6.0

The Dreiding model of VI shows the dihedral angle of $C_{7\beta}$– and C_8–H to be *ca.* 85° and that of $C_{7\alpha}$– and C_8–H to be *ca.* 35°, from which the coupling constant, $J_{7\beta,8}=\sim 1$, $J_{7\alpha,8}=\sim 6$, will be calculated.

From the comparison of coupling constant indicated above, it is assumed that the methoxyl group at C_7 in VIa takes the α-configuration and that in X, XI, and VIb, β-configuration. The above assumption was also supported by the comparison of the IR spectrum of XI with that of IX as shown in Fig. 3.

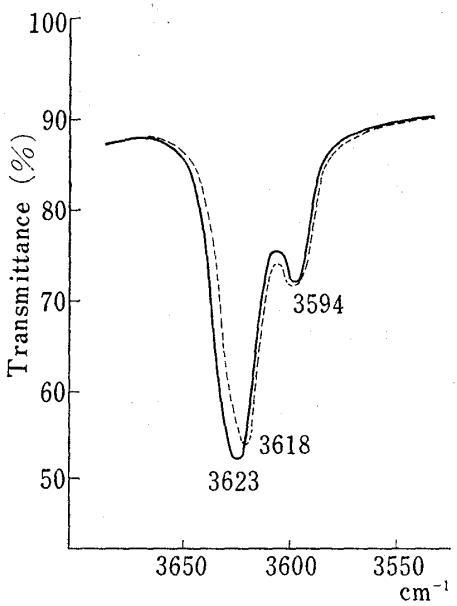

Fig. 3. IR spectra of IX and XI
0.002 mole/l in CCl_4
——: IX
——: XI

The IR spectrum of IX exhibits absorption for free OH at 3623 cm^{-1} and a weak intramolecular hydrogen bonded OH at 3594 cm^{-1}. The same absorptions appear in the IR spectrum of XI. If the C_7–OCH_3 in XI were to take the α-configuration, it would be in a *cis* position with respect to $C_{6\alpha}$–OH, and there would naturally be formed a stronger intramolecular hydrogen bonding than in IX. If C_7–OCH_3 takes a β-configuration, it would be in 1,2-*trans*-diaxial position with $C_{6\alpha}$–OH, and there would not be an intramolecular hydrogen bonding here. In the present case, the IR spectral pattern of XI is the same as that of IX, and from these spectral evidences, the C_7–OCH_3 in XI would be in β-configuration, so would be that in VIb from the comparison of $J_{7,8}$ in its NMR spectrum, and its isomer VIa would have the methoxyl group at C_7 in α-configuration.

The same reaction was carried out on IV which does not possess a double bond in the C-ring. Mesylation of IV in pyridine followed by treatment with methanolic potassium hydroxide afforded a colorless oily substance in an yield of 65%. Purification of this product

through alumina column chromatography gave a product (VII), $C_{18}H_{21}O_2N$; oxalate, colorless needles, mp 220—221°. The NMR spectrum showed signals at δ 6.68 (2H, aromatic C_1–, C_2–H), AB-quartet at 6.70 and 5.78 (J=10.0 cps, C_9– and C_{10}-olefinic H), 4.72 (1H, broad quartet, $C_{5\beta}$–H), 3.90 (–OCH_3), 2.42 (N–CH_3). These data indicate that VII is a compound corresponding to V from III, formed by introduction of a double bond into the B-ring. In the case of IV, VII is the main product (80% of the reaction product) and a small quantity of IV was recovered but there seemed no rearranged product like VI from III.

Reaction Mechanism: As described above, solvolysis of the mesylate of IV afforded VII, formed by elimination reaction, as the main product. However, the fact that a small quantity of IV, without a sign of the isomer with respect to OH at C_9, was also obtained seems to indicate that there is an another route through an aziridinium ion (XII) as an intermediate as shown in Chart 3.

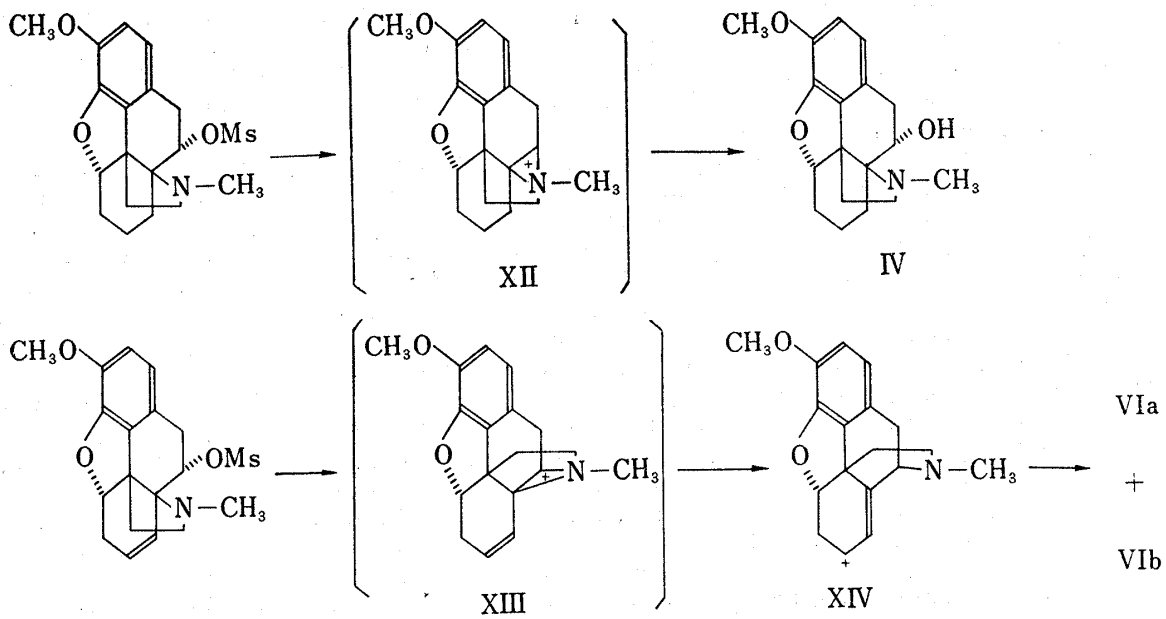

Chart 3

The elimination of mesyloxy group is participated by the lone pair electrons of the ring nitrogen to form the intermediate (XII), which is attacked from the α-side at C_9 by a base. If the formation of IV is an SN_1 type of reaction, the intermediate carbonium ion ($^+C_9$) should give rise to two isomers.

In the case of III with a double bond in the C-ring, V formed by elimination and VI formed by rearrangement were obtained.

Formation of VI shoud also take a pathway through an aziridinium ion intermediate (XIII) (Chart 3).

With this compounds having a double bond in ring C, in contrast to IV, it would be possible to consider a two competing mechanism, such as α-side attack of reagent to this cation as described in the case of IV, and the participation of the double bond followed by the rearrangement of C–N bond to form XIV whose carbonium ion ($^+C_7$) would be attacked by the methoxy anion to form VIa and VIb. As described above, in the solvolysis of the mesylate of III, there is no product like IV formed by the former process. This fact seems to indicate that the latter process would occur predominantly in this reaction.

Further investigations to clarify these reactions are now in progress.

Experimental

Melting points were uncorrected. IR spectra were recorded on Japan Spectroscopic Co. Model DS-403 spectrophotometer, in chloroform or in carbon tetrachloride solutions. NMR spectra were measured on a Hitachi H-60 spectrometer, examined in a 5—10% solution in deuteriochloroform using tetramethylsilane as an internal reference. Chemical shifts were given in δ values in ppm and coupling constants (J) in cps. Following abbreviations are used for the representation of NMR data: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. Mass spectra were determined on a Japan Electron Optics JMS-OlS Mass spectrometer with the direct sample inlet system; ionizing potential at 70 eV.

9α-Acetoxyindolinocodeine (I)——I was prepared according to the procedure previously reported,[2] and was obtained as colorless neeldes, mp 135—136°.

6-Desoxy-6β-chloro-9α-acetoxyindolinocodeine (II)——To a stirring suspension of PCl_5 (6 g) in $CHCl_3$ (15 ml) was added a solution of 9α-acetoxyindolinocodeine (I) (5 g) in $CHCl_3$ (20 ml) at 0—5° over a period of 30 min. After the reaction mixture was stirred at room temperature for 30 min, H_2O (30 ml) was added, made alkaline with 5% NH_4OH, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated *in vacuo* to leave a crystalline residue (5.2 g, 96%), which was easily recrystallized from *n*-hexane to afford colorless needles (4.3 g), mp 125—126°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1245 (–O–CO–CH_3), 940 (C–Cl); NMR δ 6.66 (2H, s, C_1, C_2-H), around 5.85 (2H, AB-q, C_7, C_8-H) 5.17 (1H, q, J=4.5, 3.0 cps, $C_{9\beta}$–H), 4.42 (1H, d, J=8.5, $C_{5\beta}$–H), 4.11 (1H, m, $C_{6\alpha}$–H), 3.90 (3H, s, C_3–OCH_3), 2.52 (N–CH_3), 1.73 (3H, –O–CO–CH_3). Mass spectrum: *m/e* 375 (M^+). *Anal.* Calcd. for $C_{20}H_{22}O_4NCl$: C, 63.95; H, 5.88; N, 3.73. Found: C, 63.58; H, 5.95; N, 3.91.

Catalytic Reduction of II——A solution of II (4 g) in EtOH-THF[11] (3:1) (80 ml) was shaken with 10% Pd-C (300 mg) under a stream of hydrogen at room temperature for 8 hr. After removal of catalyst by filtration, the filtrate was concentrated under reduced pressure to give the oily substance (3.6 g). This residue was dissolved in 5% KOH–MeOH (10 ml) and heated on a water bath for 5 min. After concentration of the solvent *in vacuo*, the reaction mixture was diluted with H_2O (50 ml), and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* to give colorless oily residue (2.92 g, 91%), which shows two spots on TLC (*Rf* 0.3 and 0.5). This reaction products were separated with Alumina (Woelm, Activity grade III, 200 g) column chromatography.

i) The first fraction eluted with pure benzene afforded 6-deoxy-9α-hydroxy-7,8-dihydroindolinocodeine (IV), (1.17 g), *Rf*, 0.3, which was recrystallized from *n*-hexane–ether to give colorless plates, mp 121—122°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (–OH); NMR: δ 6.63 (2H, C_1, C_2–H), 4.60 (broad q, J=6.8, 10.0 cps, $C_{5\beta}$–H), 4.31 (1H, q, J=7.0, 10.3, $C_{9\beta}$–H) 3.85 (O–CH_3), 2.55 (N–CH_3). Mass spectrum: *m/e* 301 (M^+). *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.75; H, 7.85; N, 4.88.

ii) Next fractions eluted with benzene–AcOEt (5%—10%) afforded 6-deoxy-9α-hydroxyindolinocodeine (III) (1.47 g), *Rf* 0.5, which was recrystallized from ether–pet. ether to give colorless needles, mp 137—138°; IR $\nu_{max}^{CHCl_3}$: cm^{-1}: 3610 (–OH), 1605 (C=C double bond); NMR: δ 6.71 (2H, s, C_1, C_2–H), 5.81—6.21 (2H, AB–q, C_7, C_8–H), 4.5 (1H, q, J=9.6, 6.6 cps, $C_{5\beta}$–H), *ca.* 3.82 (1H, $C_{9\beta}$–H), 3.86 (O–CH_3), and 2.43 (N–CH_3). Mass spectrum: *m/e* 299 (M^+). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07; N, 4.68. Found. C, 72.22; H, 7.20; N, 4.91.

Solvolysis of III——To an ice-cooled solution of III (1 g) in dry pyridine (3 ml) was added a solution of mesyl chloride (0.3 ml) in dry pyridine (1 ml) with stirring and the reaction mixture was stirred for another 1 hr at 0°. After standing overnight at room temperature, the reaction mixture was poured into ice–water, made alkaline with 5% NH_4OH to give a pinkish syrup, which was extracted with AcOEt, washed with H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave the oily residue (600 mg), which showed one spot on TLC (*Rf* 0.7). This reaction product was not purified further but was immediately dissolved in 10% KOH–MeOH (10 ml), stirred for 1 hr at room temperature, and then refluxed on a water bath for 10 min. After most of MeOH was removed by evaporation, the residue was diluted with H_2O, and was extracted with $CHCl_3$, washed with H_2O. After usual work-up, and oily residue obtained, which showed mainly two spots on TLC (*Rf*, 0.37, 0.5), was chromatographed on alumina (Woelm, grade III, 50 g).

i) Fractions eluted with benzene and benzene–AcOEt (5%) afforded 6-deoxy-9,10-dehydroindolinocodeine (V) (143 mg) as colorless oily substance. Mass spectrum: *m/e* 281.1478 (M^+, $C_{18}H_{19}O_2N$; Calcd: 281.1415); UV λ_{max}^{EtOH} mμ (ε): 230 (14000), 273 (8900), 301 (3600). NMR; δ 6.60 (2H, s, C_1, C_2–H), 6.42, 5.72 (2H, AB–q, J=10.0 cps, C_9, C_{10}–H), 5.71 (2H, AB–q, J=1.0 cps, C_7, C_8–H), 4.89 (1H, t, J=7.2 cps, $C_{5\beta}$–H), 3.88 (OCH_3), 2.47 (N–CH_3). This oily substance was converted to oxalate by adding a solution of oxalic acid in acetone to a solution of V in ether. Recrystallization from acetone–ether gave a colorless rods, mp 204—205°. *Anal.* Calcd. for $C_{18}H_{19}O_2N$ $(COOH)_2$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.68; H, 5.79; N, 4.11.

11) THF (tetrahydrofuran) was used for increasing the solubility of II in this solution.

ii) Next fraction eluted with benzene–AcOEt (1:1) afforded 6-deoxy-7-methoxyneopine (VI) (243 mg) as colorless oily substance, which was submitted to preparative thin-layer chromatography on alumina plates (0.5 mm), using $CHCl_3$ containing 1% of MeOH as solvent. The adsorbents of the zones corresponding to *Rf* values 0.45 and 0.24 were collected and eluted with $CHCl_3$, respectively. The former eluate (135 mg) was crystallized from acetone–ether to give VIa (65 mg) as a colorless fine needles, mp 156—157°. Mass spectrum: *m/e* 313.1689 (M^+; $C_{19}H_{23}O_3N$, calcd: 313.1678). GLC; RT, 6.7. NMR: 6.65 (2H, C_1, C_2–H), 5.68 (1H, almost s, C_8–H), 4.80 (1H, q, J=6.0, 11.0 cps, $C_{5\beta}$–H), around 3.95 (1H, $C_{7\beta}$–H), 3.58 (1H, d, J=6.0, $C_{9\alpha}$–H), 3.27 (1H, d, J=18, $C_{10\beta}$–H), 3.87 (C_3–OCH_3), 3.36 (C_7–OCH_3), 2.45 (N–CH_3).

The latter eluate gave 6-deoxy-7β-methoxyneopine (VIb) (40 mg) as colorless oily substance, oxalate; colorless prisms, mp 224—226°. GLC: RT, 7.0. Mass spectrum: *m/e* 313.1728 (M^+; $C_{19}H_{23}O_3N$, calcd; 313.1678), NMR: 6.65 (C_1, C_2–H), 5.85 (1H, d, J=6.0, C_8–H), 4.80 (q, $C_{5\beta}$–H), 3.95 (1H, m, $C_{7\alpha}$–H), 3.58 (d, $C_{9\alpha}$–H), 3.27 (d, $C_{10\beta}$–H), 3.87 (C_3–OCH_3), 3.36 (C_7–OCH_3), 2.45 (N–CH_3).

Solvolysis of IV——This reaction was carried out by means of the method as employed for solvolysis of III described above. IV (500 mg) was subjected to the mesylation to afford the mesylate (300 mg), *Rf*, 0.75, as colorless oily substance, which was further treated with 10% KOH–MeOH and gave the reaction products (250 mg). Alumina column chromatography of this crude products gave IV and VII as follows.

i) The first fraction eluted with pure benzene afforded *cis*-3-methoxy-N-methyl-4-5R-oxo-4b,5,6,8a-tetrahydro-4bR-8aS-iminoethanophenanthrene (6-deoxy-9,10-dehydro-7,8-dihydroindolinocodeine) (VII) (100 mg) as colorless oily substance. Mass spectrum: *m/e* 283.1510 (M^+, $C_{18}H_{21}O_2N$; calcd, 283.1572), UV λ_{max}^{EtOH} mμ (ε): 230 (7000), 283 (5000), 304 (2900). NMR: δ 6.68 (2H, s, C_1, C_2–H), 6.70, 5.78 (2H, AB–q, J=10.0 cps, C_9, C_{10}–H), 4.72 (1H, q, J=6.6, 3.0, $C_{5\beta}$–H), 3.90 (C_3–OCH_3), 2.42 (N–CH_3).

ii) Next fraction eluted with benzene–AcOEt (5:1) was recrystallized from *n*-hexane–ether to give colorless needles, mp 121—122°, which was identical with an authentic sample of IV by comparison of the IR, NMR and mass spectra and by mixed melting point test.

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