[Chem. Pharm. Bull. 18(8)1569—1575(1970)]

UDC 547.94.07 : 615.322.011.5

Synthesis of B/C *trans*-Fused Morphine Structures. IV.[1] Synthesis of B/C *trans*-Isomorphine

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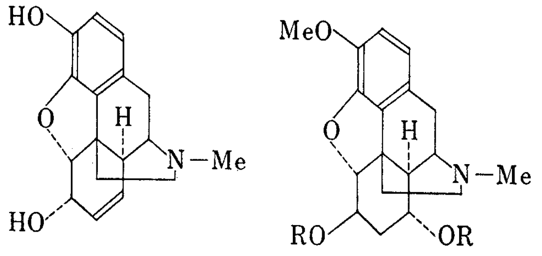
(Received February 9, 1970)

Acetylation and subsequent oxidation of the organoborane intermediate obtained from hydroboration of isoneopine (III) gave (−)-3-methoxy-6β-acetoxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (IV). Hydroboration of isoneopine-(N-*n*-butyl)-carbamate (XIV) gave the 6β-(N-*n*-butyl)-carbamoyloxy-8α-hydroxy derivative (XV). (−)-3-Methoxy-6β-hydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (XIII, B/C *trans*-isocodeine) was synthesized from either IV or XV *via* elimination of the respective 8α-tosyloxy derivatives (VI and XVI). XIII was also obtained by solvolysis of (+)-3-methoxy-6α-tosyloxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (XIX). Demethylation of XIII gave the title compound (XXII).

In the foregoing paper[1] of this series, the synthesis of B/C *trans*-morphine (I) by the hydroboration of isoneopine-O-tosylate was described. In the continuance of our studies on the B/C *trans*-fused morphine derivatives for pharmacological evaluation, we have prepared (−)-3,6β-dihydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (XXII), 6-OH epimer of *trans*-morphine and called hereafter *trans*-isomorphine.

Synthesis of (−)-3-methoxy-6β,8α-dihydroxy-4,5α-epoxy-N-methylisomorphinan (IIa) from isoneopine (III) and unsuccessful elimination reaction of the di-*p*-toluenesulfonyl derivative (IIb) to the Δ^7 structure were described previously.[3]

Accordingly, protecting of the 6-OH group of III prior to introduction of the 8-OH group was necessary.



I

IIa : R=H
IIb : R=Ts
Ts=Tosyl

Chart 1

Acetylation of the organoborane intermediate obtained from III and subsequent hydrogen peroxide oxidation afforded (−)-3-methoxy-6β-acetoxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (IV) in 75% yield. Small amount of the diacetoxy derivative (V)[3] and the dihydroxy derivative (IIa) were also obtained in this reaction.[4] Acetylation of IV gave the diacetate (V) and hydrolysis of IV gave IIa. Reaction of IV with *p*-toluensulfonyl chloride gave the O-tosylate (VI), which was different from the 6β-tosyloxy-8α-acetoxy derivative (VIII) prepared from the known 6β-tosyloxy-8α-hydroxy derivative (VII).[1]

Careful lithium aluminum hydride reduction of VI gave the known 6β-hydroxy-8α-tosyloxy derivative (IX).[3] These results confirm the location of acetoxy group of IV on carbon 6.

Elimination of VI with collidine gave two isomeric olefins. One was identified with isoneopine-O-acetate (XI) and the other was assigned the Δ^7 structure (X). Inspection of

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[1] Part III: H. Kugita, M. Takeda and H. Inoue, *Tetrahedron*, **25**, 1851 (1969).
[2] Location: *2-2-50 Kawagishi, Toda, Saitama.*
[3] M. Takeda, H. Inoue and H. Kugita, *Tetrahedron*, **25**, 1839 (1969).

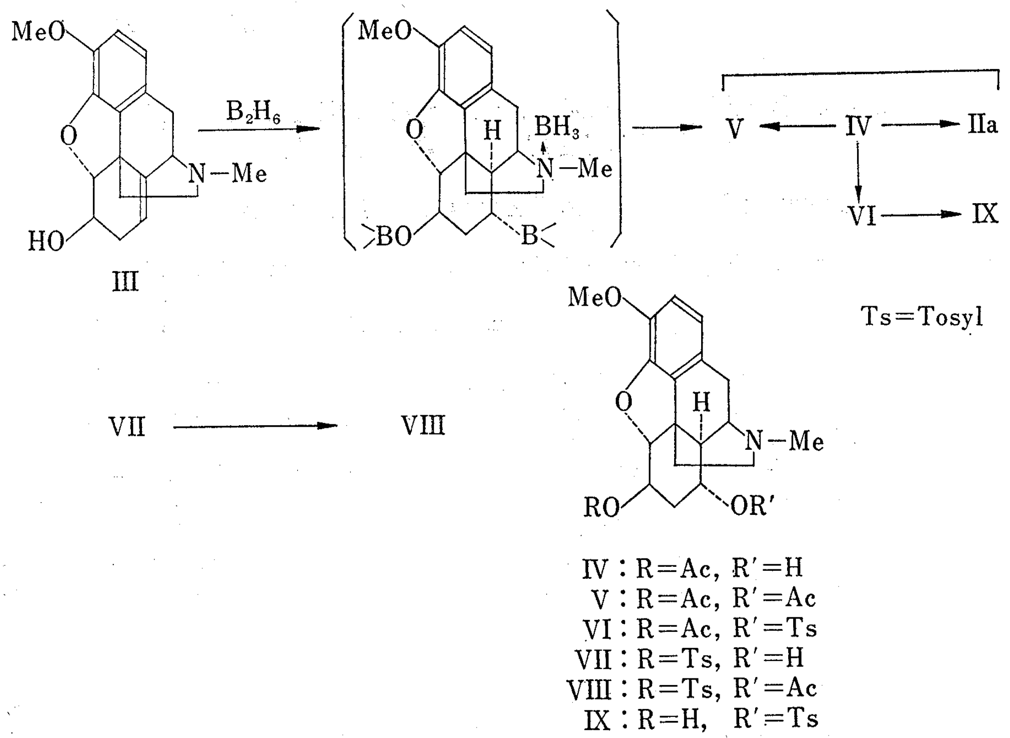


Chart 2

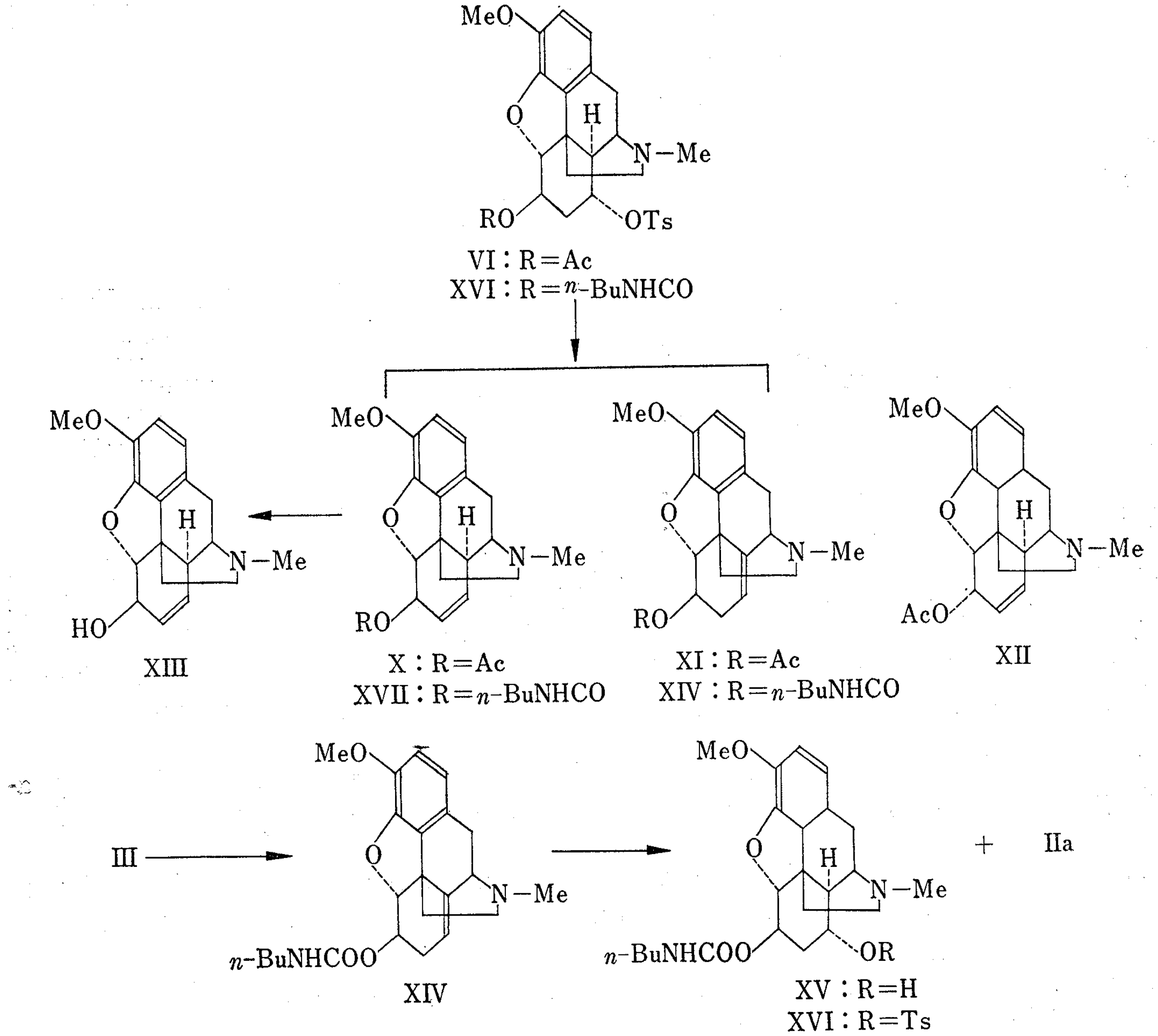
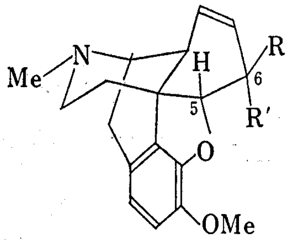


Chart 3

nuclear magnetic resonance (NMR) spectrum revealed the isomeric nature of X to the C_6-epimer, *trans*-codeine-O-acetate (XII).[1]

Difference of the chemical shifts of 6-acetoxy Me (X, 7.86 τ; XII, 8.25 τ) due to a diamagnetic anisotropy effect of aromatic ring, and the larger coupling constant of 5β-H of X ($J_{6\alpha}=8$ cps) than that of XII ($J_{6\beta}=5.5$ cps) were in good agreement with the structures shown in Fig. 1.

Hydrolysis of X gave (−)-3-methoxy-6β-hydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (*trans*-isocodeine, XIII).



X : R=OAc, R'=H
XII : R=H, R'=OAc

Fig. 1

XIII ($[\alpha]^{20}_D$ −40°) was more levorotatory than *trans*-codeine ($[\alpha]^{20}_D$ +61°) in consistent with the Mills' rule.[6]

Carbamoyl group was considered to be another protective group of III.[7] Reaction of III with *n*-butylisocyanate gave isoneopine-(N-*n*-butyl)-carbamate (XIV) in a quantitative yield. Hydroboration and subsequent oxidation of XIV gave the 6β-carbamoyloxy-8α-hydroxy derivative (XV) and the dihydroxy derivative (IIa) in 12.3 and 48.3% yields, respectively. Therefore, significant amount of carbamoyloxy group was reduced with diborane in the present reaction.[8] The O-tosylate (XVI) prepared from XV was converted to *trans*-isocodeine (XIII) ultimately by the same sequence of reactions as described previously (Chart 3).

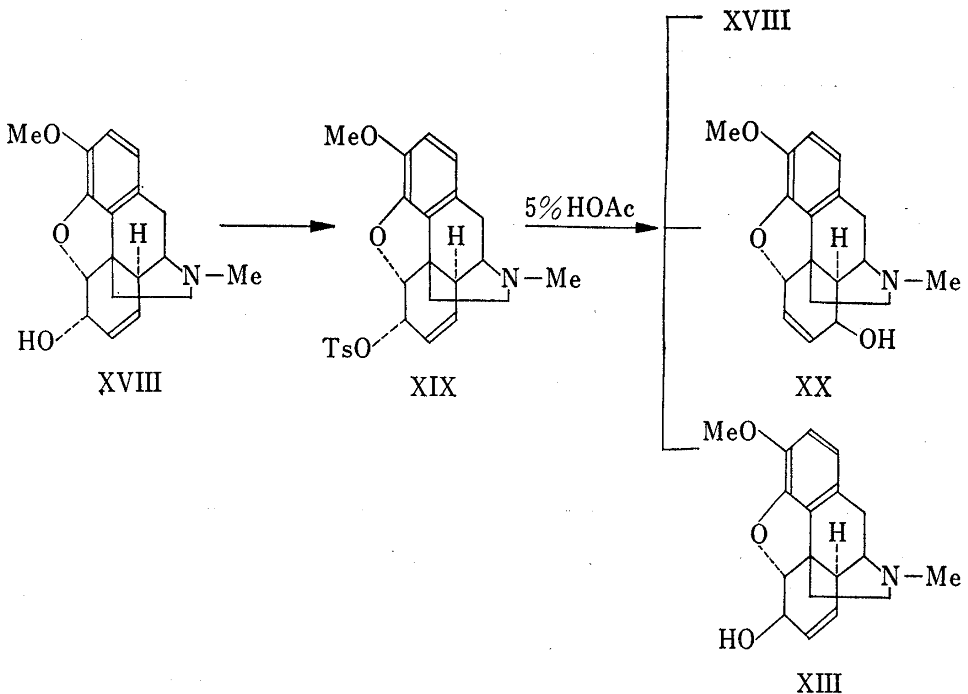


Chart 4

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[4] Conversion of organoborane to acetoxy group on treatment with acetic anhydride–acetic acid has been reported.[5]

[5] K. Bailey and T.G. Halsall, *J. Chem. Soc.* (*C*), **1968**, 679.

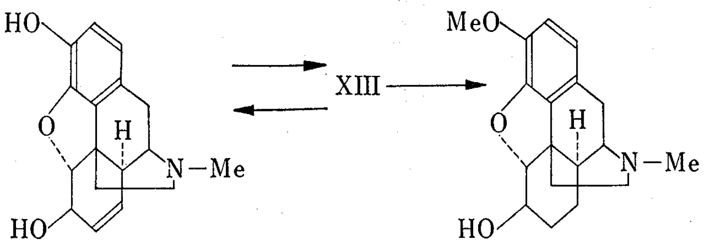
[6] J.A. Mills, *J. Chem. Soc.*, **1952**, 4976; K.W. Bentley and H.M.E. Cardwell, *J. Chem. Soc.*, **1955**, 3252.

[7] D.N. Butler and A.H. Soloway, *J. Am. Chem. Soc.*, **88**, 484 (1966); W.V. Curran and R.B. Angier, *J. Org. Chem.*, **31**, 3867 (1966).

[8] Carbamoyloxy group of XIV was proved to be stable in the alkaline hydrogen peroxide oxidation condition as well as on the heating with acetic acid.

Finally, nucleophilic substitution of *trans*-codeine-O-tosylate (XIX) was studied as an alternative route to XIII.

XIX was prepared from *trans*-codeine (XVIII) in 26.4% yield with 53% recovery of starting material.[9]



XXII XXI

Chart 5

Heating of XIX with 5% acetic acid gave *trans*-isocodeine (XIII) in 14.4% yield. The 8β-OH derivative (XX)[1] and XVIII were also isolated in 40.2% and 6.8% yields respectively. Formation of the main product (XX) might be rationalized by the pseudo-axial attack of OH$^-$ ion upon C_8 position of allylic cation.[10]

Hydrogenation of XIII gave the dihydro derivative (XXI).

Demethylation of XIII with diphenylphosphine anion[14] gave (—)-3,6β-dihydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (*trans*-isomorphine XXII) in 61% yield. Rodionov[15] reaction of XXII regenerated XIII. Pharmacological data of *trans*-isomorphine derivatives will be presented in a later communication.

Table I. NMR Spectra of B/C *trans*-Isomorphine Derivatives

Compound	Chemical shift (τ)									
	1,2-H	3-OMe	5β-H	6-H	7-H	8-H	9α-H	10β-H	N-Me	Others
X	3.39	6.19	5.56 $J_{6\alpha}=8$	4.80	4.48	3.74	6.58 $J_{10\alpha}=6$ $J_{14}=3$	6.76 $J_{10\alpha}=18$	7.62	6β-OAc 7.86
XIII	3.33	6.15	5.70	5.70	4.20	3.70	6.53 $J_{10\alpha}=6$ $J_{14}=3$	6.73 $J_{10\alpha}=18$	7.60	
XIV	3.34	6.16	5.45 $J_{6\alpha}=8$	5.40		4.53 (q)	6.42 $J_{10\alpha}=6$	6.75 $J_{10\alpha}=18$	7.59	
XV	3.34	6.15	5.72 $J_{6\alpha}=10$	4.9—5.3		4.9—5.3		6.75 $J_{10\alpha}=18$	7.67	
XXI	3.38	6.16	5.78 $J_{6\alpha}=9$	6.10			6.95	6.78 $J_{10\alpha}=18$	7.67	
XXII·HCl	3.26		5.60	5.60	4.0	3.60	6.0		6.86	

All spectra were measured at 60 Mc in $CDCl_3$ except for XXII (D_2O) containing tetramethylsilane as internal standard. The authers thank Dr. K. Kotera and Mr. N. Takeda for measurement of the spectra and useful discussion.

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9) Low yield was apparently due to the sterical crowding around the 6α-OH group.[1]

10) The pronounced tendency of cyclohexenyl cation to pick up nucleophiles in pseude-axial manner has been reported.[11,12] In S_N2' reaction (another possible mechanistic pathway in solvolysis of allylic tosylate), the entering group should come in *cis* to the departing group.[13] Formation of such a product (8α-hydroxy-Δ^6 derivative) was not detected in the present reaction.

11) H. Goering, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **21** 109 (1960).

12) H.W. Whitlock, Jr, and G.L. Smith, *J. Am. Chem. Soc.*, **89**, 3600 (1967).

13) G. Stork and W.N. White, *J. Am. Chem. Soc.*, **78**, 4609 (1956); G. Stork and F.H. Clarke, *ibid.*, 4619 (1956).

14) F.G. Mann and M.J. Pragnell, *J. Chem. Soc.*, **1965**, 4120.

15) K.W. Bentley, "The Chemistry of the Morphine Alkaloids," Oxford at the Clarendon Press London, 1954, p. 60.

Experimental[16]

(−)-3-Methoxy-6β-acetoxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (IV)——B_2H_6 (from 42.5 g BF_3–ether and 8.5 g $NaBH_4$) was introduced into a solution of III (8.5 g) in THF (130 ml) at 25°, and the mixture was allowed to stand at room temperature for 160 hr under N_2 and evaporated under reduced pressure to give a residue.

Ac_2O (30 ml) and AcOH (30 ml) was added to the residue in THF (50 ml) at 10° and heated at 80—90° for 9 hr. The mixture was poured into ice–water, and basified with 20% NaOH (pH 9), and treated with $CHCl_3$ (30 ml) and 30% H_2O_2 (10 ml) under vigorous stirring. The mixture was stirred at 0° for 5 min, extracted with $CHCl_3$, the $CHCl_3$ extract was dried and evaporated. The residue was recrystallized from AcOEt–*n*-hexane to give IV (6.8 g), colourless pillars, mp 158—159°. $[\alpha]_D^{20}$ −123° (c=0.354, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3470, 1693. *Anal.* Calcd. for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01; N, 3.90. Found: C, 67.15; H, 7.12; N, 3.82.

The mother liquor (AcOEt–*n*-hexane) was evaporated and the residue was chromatographed over Al_2O_3 and eluted with benzene to give V, (125 mg, 1.1%), mp 169—172°, identical with the authentic specimen.[3] The next elution with benzene–ether (1:1)–ether gave additional IV (0.85 g, total yield 75%). Following elution with ether–MeOH (8:2) gave IIa hemihydrate (400 mg, 4.3%), mp 100—105°.

Acetylation of IV——A mixture of IV (25 mg), Ac_2O (0.3 ml) and pyridine (0.3 ml) was heated on a steam bath for 1 hr and worked up in the usual manner to give V (27 mg), mp 165—170° (from ligroin).

Hydrolysis of IV——IV (20 mg) and 5% KOH–EtOH (0.4 ml) was heated on a steam bath for 1 hr and evaporated in reduced pressure to give IIa hemihydrate (15 mg), mp 103—105°.

(−)-3-Methoxy-6β-acetoxy-8α-tosyloxy-4,5α-epoxy-N-methylisomorphinan (VI)——TsCl (8.2 g) was added to a solution of IV (7.65 g) in pyridine (40 ml) under cooling. The mixture was kept in a refrigerator for 3 days, poured into ice–water, basified with NH_4OH and filtered to give the tosylate (VI), needles (9.5 g, 87%), mp 198—199° (from benzene). $[\alpha]_D^{20}$ −85.4° (c=0.30, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1736, 1360. *Anal.* Calcd. for $C_{27}H_{31}O_7NS$: C, 63.14; H, 6.08; N, 2.75. Found: C, 63.39; H, 6.14; N, 2.57.

$LiAlH_4$ Reduction of VI——$LiAlH_4$ (100 mg) was added to a solution of VI (100 mg) in THF (10 ml) under cooling. The mixture was stirred at 6—10° for 15 min, and worked up in an usual manner to give IX (70 mg, 76.5%), colourless prisms, mp 161—163° (from AcOEt–*n*-hexane), identical with an authentic sample.[17] Prolonged stirring (room temperature, 20 hr) of the reaction mixture gave IIa hemihydrate (48.8%), mp 103—105°, and the dihydroxy derivative (5.6%), mp 253—255° (from AcOEt), the structure of which has not been ascertained.

(−)-3-Methoxy-6β-tosyloxy-8α-acetoxy-4,5α-epoxy-N-methylisomorphinan (VIII)——VII (100 mg), Ac_2O (0.3 ml) and pyridine (0.4 ml) was heated on a steam bath for 20 min and worked up in the usual manner to give VIII (90 mg, 83%), colourless pillars, mp 194.5—195° (from AcOEt). $[\alpha]_D^{20}$ −176° (c=0.324, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1730. *Anal.* Calcd. for $C_{27}H_{31}O_7NS$: C, 63.14; H, 6.08; N, 2.75. Found: C, 63.21; H, 6.18; N, 2.55.

Treatment of VI with Collidine——A mixture of VI (9.5 g) and 2,4,6-collidine (55 ml) was refluxed for 1 hr under N_2 and worked up in the usual way. The crude product was crystallized from ether to give (−)-3-methoxy-6β-acetoxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (X) (2.52 g), colourless prisms (from benzene–*n*-hexane), mp 176—177°. $[\alpha]_D^{20}$ −29.3° (c=0.164, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1730. *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.63; H, 6.86; N, 4.09. The mother liquor (ether) was evaporated and the residue was chromatographed over Al_2O_3. Elution with benzene gave additional X (0.5 g, total yield 47.8%). Next elution with benzene–ether (9:1–1:1) gave isoneopine-O-acetate (XI) (1.63 g, 25.8%), colourless needles, mp 127—128° (from ligroin). $[\alpha]_D^{20}$ −33.9° (c=0.602, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1720. *Anal.*. Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.41; H, 6.89; N, 4.04. This was identified with the sample prepared through acetylation of III in the usual way.

Following elution with ether gave III (240 mg, 4.3%) and XIII (230 mg, 4.2%) respectively.

(−)-3-Methoxy-6β-hydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (*trans*-isocodeine, XIII)——A mixture of X (2.9 g), 5% KOH–EtOH (30 ml) and EtOH (30 ml) was refluxed for 10 min. The mixture was evaporated under reduced pressure to leave a residue which was taken up in water and extracted with $CHCl_3$, the $CHCl_3$ extract was dried and evaporated to give XIII (2.20 g, 86.5%), colourless needles, mp 160—161° (from AcOEt–*n*-hexane). $[\alpha]_D^{20}$ −40° (c=0.20, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3150. *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; N, 4.68. Found: C, 71.76; H, 7.14; N, 4.53. Hydrochloride; mp 254—257° (decomp.), colourless prisms (from EtOH). *Anal.* Calcd. for $C_{18}H_{22}O_3NCl$: C, 64.38; H, 6.61; N, 4.17. Found: C, 64.35; H, 6.76; N, 4.07.

Isoneopine-(N-*n*-butyl)-carbamate (XIV)——III (20.6 g), *n*-BuNCO (38 g), pyridine (7 ml) and CH_3CN (500 ml) was refluxed for 20 hr and evaporated under reduced pressure. The residue was taken up in ether,

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16) All melting points were determined in an open capillary tube and uncorrected.

17) In the earlier report[3] IX was obtained as colourless needles, mp 114—116° from ether–pet. ether. On recrystallization from AcOEt–*n*-hexane, this was converted to prisms, mp 161—163°.

extracted with 10% HCl. The aqueous layer was basified with K_2CO_3 and extracted with ether which was dried and evaporated to give XIV as gum (28.5 g, 100%). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3430, 1710. *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59; N, 7.03. Found: C, 68.90; H, 7.74; N, 6.96. Picrate; mp 161—164° (fromMeOH). *Anal.* Calcd. for $C_{23}H_{30}O_4N_2 \cdot C_6H_3O_7N_3$: C, 55.49; H, 5.30; N, 11.16. Found: C, 55.38; H, 5.38; N, 11.03.

Hydroboration of XIV——B_2H_6 (from 100 g BF_3–ether and 19.9 g $NaBH_4$) was introduced into a solution of XIV (28 g) in THF (280 ml) at 5° under N_2 and allowed to stand at 5° for 144 hr, then at room temperature for 3 days. The mixture was decomposed with water, neutralized with 10% NaOH, oxidized with 30% H_2O_2 (14 ml) and 10% NaOH (20 ml) at 5—10° for 3 hr, diluted with water, extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated. The residue was heated with AcOH (140 ml) and dioxane (280 ml) on a steam bath for 1.5 hr, concentrated under reduced pressure, basified with NH_4OH, extracted with $CHCl_3$. The extract was dried and evaporated. The residue was crystallized from benzene to give dihydroxy derivative (IIa) (8.8 g), mp 180—182°.

The crude base obtained from the mother liquor (benzene) was chromatographed on Al_2O_3. XIV (1.23 g, 4.4%) was recovered from the eluate with benzene–ether (2:1). Elution with ether–MeOH (98:2) gave (−)-3-methoxy-6β-(N-*n*-butyl)-carbamoyloxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (XV) (3.59 g, 12.3%), colourless neeles, mp 166—167° (from benzene–*n*-hexane). $[\alpha]_D^{20}$ −141° (c=0.40, MeOH). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3320, 3260, 1680. *Anal.* Calcd. for $C_{23}H_{32}O_5N_2$: C, 66.32; H, 7.73; N, 6.73. Found: C, 66.51; H, 7.90; N, 6.63. Elution with ether–MeOH (95:5—9:1) gave additional IIa hemihydrate (2 g, total yield 48.3%), mp 104—106°.

(−)-3-Methoxy-6β-(N-*n*-butyl)-carbamoyloxy-8α-tosyloxy-4,5α-epoxy-N-methylisomorphinan (XVI)—— TsCl (3.4 g), XV (2.5 g) and pyridine (50 ml) was kept in a refrigerator for 4 days. Work-up in the usual way gave XVI (from benzene–*n*-hexane, 2.95 g, 89%), mp 161—162°. $[\alpha]_D^{20}$ −90.8° (c=0.207, MeOH). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3280, 1705, 1677, 1538, 1362, 1176. *Anal.* Calcd. for $C_{30}H_{38}O_7N_2S$: C, 63.13; H, 6.71; N, 4.91. Found: C, 63.25; H, 6.81; N, 4.68.

Treatment of XVI with Collidine——XVI (3.5 g) and 2,4,6-collidine (25 ml) was refluxed for 2.5 hr and worked up in the usual way. The crude base was chromatographed on Al_2O_3.

Elution with benzene–*n*-hexane (98:2) gave (−)-3-methoxy-6β-(N-*n*-butyl)-carbamoyloxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (XVII) (1.05 g, 42.9%), colourless prisms (from ether–*n*-hexane), mp 123.5—124.5°. $[\alpha]_D^{20}$ −100° (c=0.203, $CHCl_3$). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3420, 1715. *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.40; 7.65; N, 6.97. Picrate: mp 212—213° (decomp.), yellow needles (from EtOH–acetone). *Anal.* Calcd. for $C_{23}H_{30}O_4N_2$–$C_6H_3O_7N_3$: C, 55.49; H, 5.30; N, 11.16. Found: C, 55.66; H, 5.43; N, 10.90. The next eluate with ether–benzene (1:2) gave XIV (900 mg, 36.8%). picrate: mp 161—164°.

Hydrolysis of XVII——XVII (950 mg), 5% KOH–EtOH (20 ml) and EtOH (7 ml) was refluxed for 30 min. XIII (670 mg, 94.5%), mp 160—162° was obtained.

(+)-3-Methoxy-6α-tosyloxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (*trans*-codeine-O-tosylate: XIX)—— TsCl (4 g) was added to a solution of XVIII (5 g) in pyridine (15 ml) at 3—5°. The mixture was allowed to stand at −20° for 4 days, poured into ice–water, basified with NH_4OH and filtered to give XIX (2 g, 24.4%), colourless needles (from benzene), mp 133—135°. $[\alpha]_D^{20}$ +57.5° (c=0.145, $CHCl_3$). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1350, 1170. *Anal.* Calcd. for $C_{25}H_{27}O_5NS$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.14; H, 6.01; N, 3.06. From the filtrate (water), XVIII was recovered through extraction with $CHCl_3$. (picrate: 4.65 g, 52.7%, mp 235—237°).

Solvolysis of XIX——XIX (3.6 g) was heated in 5% AcOH (120 ml) on a steam bath for 1 hr, basified with NH_4OH, extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated. The residue in benzene was chromatographed on Al_2O_3. Elution with benznee–$CHCl_3$ (3:1) gave XX (950 mg, 40.2%), mp 130—131°, identical with an authentic specimen.[1] Following elution with benzene–$CHCl_3$ (3:1) gave XVIII. (picrate: 230 mg, 6.8%, mp 238—242°). The subsequent elution with $CHCl_3$ gave XIII (340 mg, 14.4%), mp 160—161°.

(−)-3-Methoxy-6β-hydroxy-4,5α-epoxy-N-methylisomorphinan (XXI)——XIII (100 mg) in EtOH (12 ml) was hydrogenated with PtO_2 (20 mg). The crude base was recrystallized from diisopropylether to give XXI (80 mg, 79.4%), colourless plates, mp 160—162°. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3500, 3160. *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.45; H, 7.83; N, 4.64. Hydrochloride: mp 239—241°, colourless needles (from EtOH–acetone). $[\alpha]_D^{20}$ −77° (c=0.13, MeOH). *Anal.* Calcd. for $C_{18}H_{24}O_3NCl$ $\frac{1}{2}H_2O$: C, 62.41; H, 7.56; N, 3.71. Found: C, 62.33; H, 7.27; N, 4.04.

(−)-3,6β-Dihydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan(*trans*-isomorphine: XXII) Hydrochloride—— Li (200 mg) was added to a solution of Ph_3P (1.7 g) in THF (30 ml) under N_2. The mixture was warmed to 35°, and then cooled to room temperature gradually during 30 min. To the resultant red solution of diphenylphosphine anion[18] was added XIII (1 g). The mixture was stirred at room temperature for 1 hr,

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18) This provided the convenient and practical method of generation of diphenylphosphine anion *in situ*. See: D. Wittenberg and H. Gilman, *J. Org. Chem.*, 23, 1063 (1958).

then refluxed for 1 hr, decomposed with moist ether, and evaporated under reduced pressure. The residue was partitioned in ether–water, the aquous layer was acidified with dil. HCl, basified with NH_4OH, concentrated under reduced pressure below 35°, extracted with $CHCl_3$–EtOH (4:1). The extract was dried and evaporated. The residue was crystallized from a small amount of ether to give XXII (500 mg), mp 230—233°. The mother liquor (ether) was evaporated and the residual gum was chromatographed over Al_2O_3. Elution with $CHCl_3$–MeOH (2:1) gave additional XXII (80 mg, total yield 61%). Hydrochloride: colourless plates or needles (from MeOH–ether), mp 312—314° (decomp.). $[\alpha]_D^{20}$ $-14.1°$ ($c=0.191$. MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3250, 3160. *Anal.* Calcd. for $C_{17}H_{20}O_3NCl$: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.32; H, 6.33; N, 4.23.

Methylation of XXII——Rodionov reagent (prepared from 5 mg Na, 70 mg trimethylphenylammonium tosylate and 0.31 ml MeOH) was added to the suspension of XXII (30 mg) in toluene (2 ml). After evaporation of MeOH, toluene (2 ml) was added and the mixture was refluxed for 3 hr. XIII (15 mg, 47.5%), mp 160—162°, was isolated in the usual manner.

Acknowledgement The authors thank Dr. N. Sugimoto, Mr. M. Yamazaki and Prof. Emeritus of Tokyo University, Dr. S. Sugasawa for their interest and helpful discussions.