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SYNTHESIS OF B/C *TRANS*-FUSED MORPHINE STRUCTURES—III[1]

SYNTHESIS OF B/C *TRANS*-MORPHINE[2]

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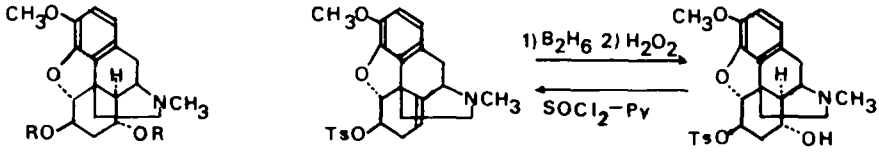
Abstract—Synthesis of B/C *trans*-morphine starting from isoneopine-O-tosylate is described.

MORPHINE, important on account of its physiological effect, possesses the *cis*-decaline type junction of B and C rings.[3] As the benzomorphan derivatives with *trans*-5,9-dialkyls and the isomorphinans are superior analgesics when compared with the respective *cis*-5,9-disubstituted benzomorphans and morphinans, we considered that the B/C *trans* isomer of natural morphine would exhibit profound physiological activity. In this connection the synthesis of B/C *trans*-morphine derivatives was initiated. It was found that the hydroboration of 2,5-dimethyl-9-methylenebenzomorphan affords selectively the 9β-hydroxymethyl derivative,[4] and consequently *trans*-8α-hydroxydihydrodeoxycodeine was synthesized by hydroboration of Δ^8-deoxycodeine.[5,6] This new approach to the *trans*-morphine structure indicated that *trans*-morphine itself could be synthesized from the appropriately substituted Δ^8-morphine derivative. Following on the exploratory work in the preceding paper, the present article gives a detailed account of this synthesis.[2]

Synthesis of (−)-3-methoxy-6β,8α-dihydroxy-4,5α-epoxy-N-methylisomorphinan (Ia) and unsuccessful elimination of the di-*p*-toluenesulfonyl derivative (Ib) to the Δ^7 derivative were described previously. Owing to the almost similar environments around the two OH groups, it was necessary to block the 6-OH group prior to introduction of the 8-OH group. When isoneopine-O-tosylate (II)[1] was hydroborated (−)-3-methoxy-6β-tosyloxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (III) was obtained in 74·6% yield. Dehydration of III with thionyl chloride in pyridine gave the Δ^8 derivative II as the only isolable product.

Reaction of III with various inorganic salts in boiling dimethylformamide gave



Ia R=H
Ib R=Ts

II

III

CHART 1

a mixture of products in all cases, the proportion of which varied according to the reagent and reaction time. Thus, heating III in dimethylformamide with potassium acetate[7] for 6 hr afforded (−)-3-methoxy-6α-acetoxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (IV), (−)-3-methoxy-6α,8α-dihydroxy-4,5α-epoxy-N-methylisomorphinan (V) and (−)-3-methoxy-8α-hydroxy-4,5α-epoxy-Δ^6-N-methylisomorphinan (VI) in 3 l., 19·4 and 17·4% yields respectively. Spectral and analytical data of these products were in accordance with the assigned structures. Hydrolysis of IV with alkali gave the dihydroxy derivative V. Acetylation of IV and V gave the same diacetoxy derivative VII, which was different from the known 6β,8α-diacetoxy derivative (VIII).[1]

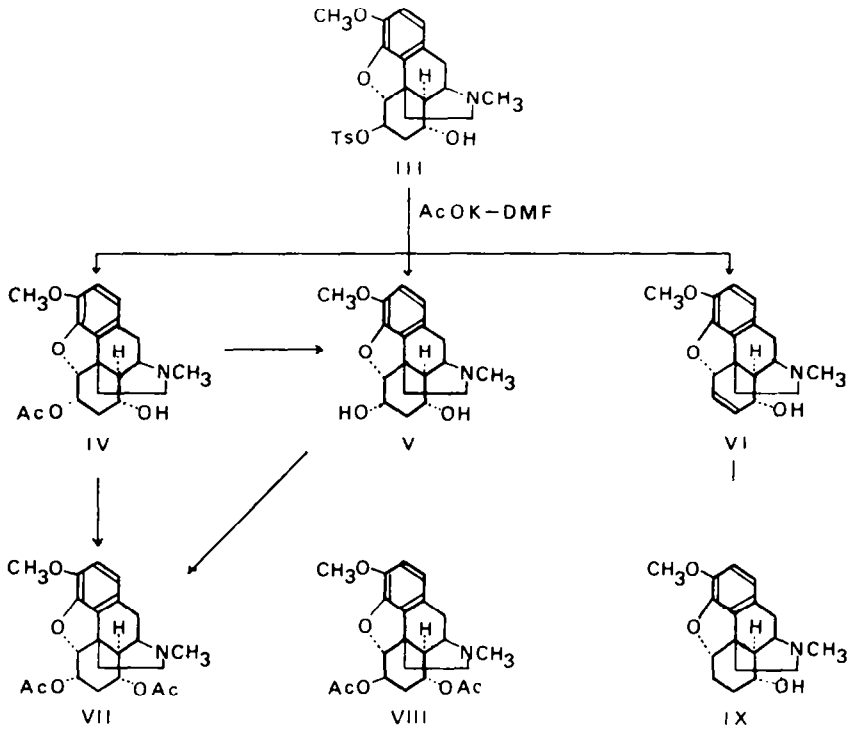
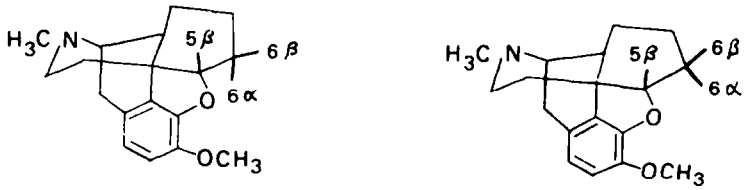


CHART 2

Molecular models show that the saturated ring C in the B/C *trans*-fused morphine structure can take either a boat or skew boat form. The NMR spectrum of the 6β-acetoxy derivative (VIII) shows a doublet at 5·6 τ (J = 10 c/s) attributable to 5β-H. The large coupling constant could be explained by the *trans*-diaxial relationship between the 5β-H and 6α-H, only possible under the boat conformation.* On the other hand, the 6α-acetoxy derivative (VII) shows a doublet of 5β-H at 5·6 τ with a J-value of 4·5 c/s indicating that 6-H assumes a β-configuration, hence the 6-acetoxy group has the α-configuration. Also an upward shift of the 6-acetoxy Me of VII

* Relationship between the coupling constant of 5α-H and conformation of the C-ring has been discussed in the natural morphine series.[8]



Ring C: boat form Ring C: skew boat form

FIG. 1

(8·24 τ) compared with that of VIII (7·9 τ) is due to a diamagnetic anisotropy effect of the aromatic ring.

Hydrogenation of the third product (VI) gave (−)-3-methoxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (IX).[6] The NMR spectrum of VI shows two olefinic protons at 4·1 τ in accordance with the Δ^6 structure.

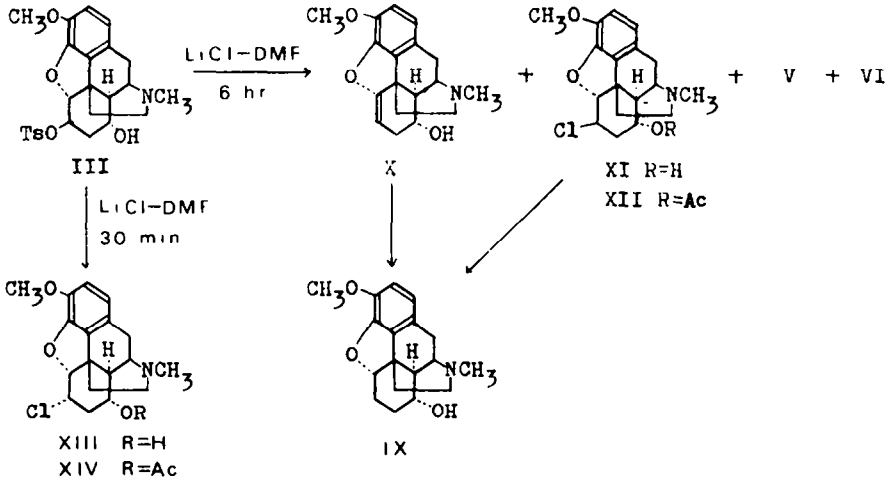


CHART 3

When III was heated with lithium chloride[9] for 6 hr olefinic and chlorinated derivatives were obtained in addition to V and VI. The olefinic derivative with the molecular formula, $C_{18}H_{21}O_3N$, proved to be a double bond isomer of VI and afforded IX by catalytic hydrogenation. Assignment of the Δ^5 structure X was based on spectral data; in the IR spectrum, the 1700 cm^{-1} absorption is due to an enol ether, and in the NMR spectrum a quartet (1H) centered at 5·0 τ is due to the β-proton of cyclic enol ether[10] and a multiplet at 5·3 τ assignable to 8β-H is observed without any other signals in the 3·5–6·0 τ region. The chlorinated derivative also gave IX on reduction with LAH and the 6β-chloro-8α-hydroxy structure (XI) assigned to it was based on the NMR spectrum of the 8-acetoxy derivative [a doublet (1H) at 5·6 τ with a *J*-value of 10·5 c/s].

When III was heated with lithium chloride for 30 min, another chlorinated derivative, $C_{18}H_{22}O_3NCl$ an isomer of XI, was isolated in 27% yield together with 34% recovery of the starting material. A comparison of the NMR spectrum of the acetoxy derivative XIV of the isomer with that of XII shows the 6-H signal at a lower field

(ca 0·3 ppm). In XII the 6-H signal suffers an upward shift due to the diamagnetic anisotropy effect of the aromatic ring and/or C—C bonds of the C-ring. From this observation the 6α-chloro-8α-hydroxy structure (XIII) was assigned to the chloro derivative.

These results suggest that the elimination of III with lithium chloride proceeds mainly via the substitution product XIII, which on further reaction affords the olefinic derivatives VI and X by *trans*-elimination.* Contrary to the reaction with lithium chloride, the elimination with potassium acetate (III → VI) was assumed to proceed competitively with the substitution (III → IV).† Reaction of III with sodium iodide was similar to that with lithium chloride. Reaction with lithium carbonate, however, mainly yielded the substitution product V. The results are summarized in Table 1.

TABLE 1. SOLVOLYSIS OF III IN DMF

Reagent	Time	Product %						
		IV	V	VI	X	XI	XIII	III (recovered)
AcOK	6 hr	31	19·4	17·4				
LiCl	6 hr		4·7	22·3	29	11		
LiCl	30 min						29	34
NaI	6 hr		9	20	22			
Li_2CO_3	6 hr		50		1			11

Now that the appropriate intermediates IV and V were available, efforts were made to introduce the C-7 double bond with retention of the hydroxy or acetoxy group at the 6-position. Reaction of IV with *p*-toluenesulphonyl chloride gave the O-tosylate (XV), which in turn was heated with collidine to give two isomeric olefins. One was identical with neopine-O-acetate (XVI)[11] and the other was assigned the Δ^7 structure (XVII) after inspection of the NMR spectrum which shows the presence of two olefinic protons. This result confirms earlier findings in the 6-deoxy series.[6] Hydrolysis of XVII gave (+)-3-methoxy-6α-hydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (*trans*-codeine; XVIII) in quantitative yield. Hydrogenation of XVIII gave the dihydro derivative XIX, which was also obtained in small amount by LAH reduction of XV.

As the molecular model indicates (Fig. 1), the 6α-substituent of the B/C *trans* structure stretches near over the benzene ring, and therefore the 6α-OH group of the 6α,8α-dihydroxy derivative (V) was expected to suffer steric hindrance. Reaction of V with an equimolar amount of *p*-toluenesulphonyl chloride gave the 8α-tosyloxy derivative (XX) in 79% yield. Acetylation of XX gave the 6α-acetoxy derivative which was identical with XV obtained previously from IV. Elimination of XX with collidine gave neopine (XXI) and *trans*-codeine (XVIII) in 39·6 and 42% yields respectively.

* Two mechanisms have been proposed for the elimination of steroidal α-halo ketones with lithium chloride. One is the *cis*-elimination involving the six-membered transition state, and the other is that involves displacement of the halogen with inversion as the first step. R. P. Holysz, *J. Am. Chem. Soc.* **75**, 4432 (1953).

† Heating of IV with potassium acetate in DMF gave the dihydroxy derivative V in 22% yield with 74%recovery of IV.

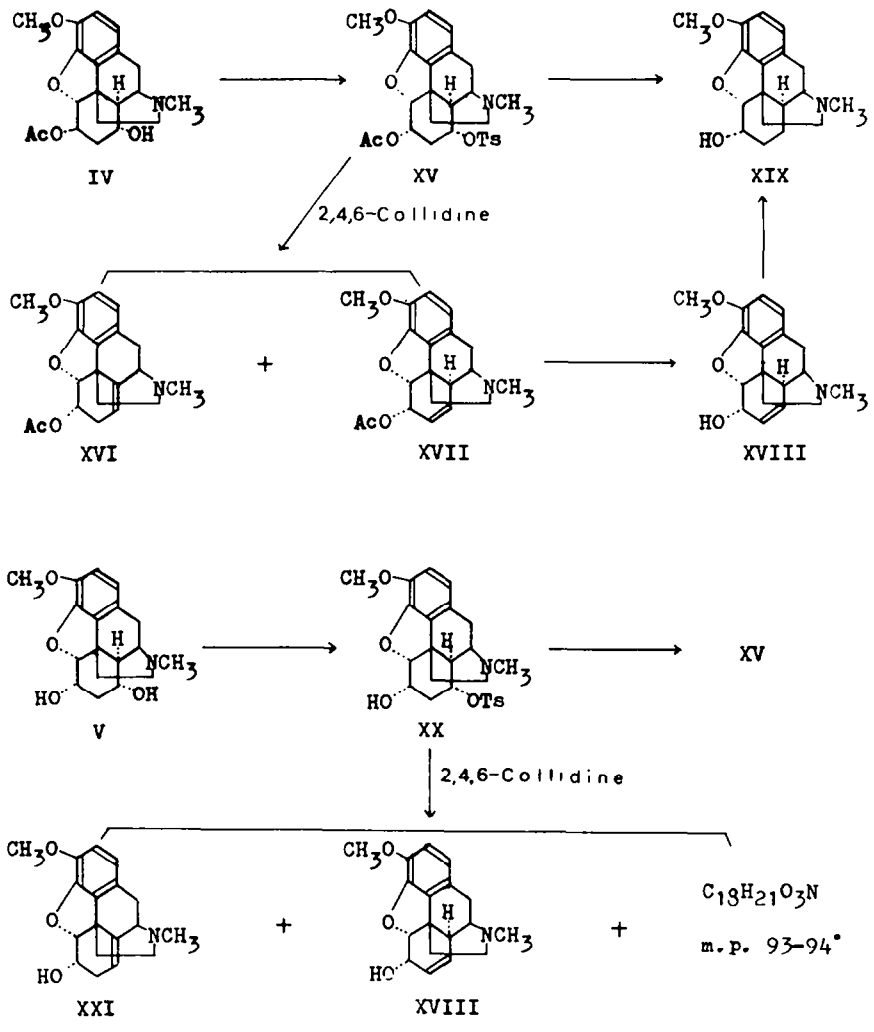


CHART 4

In addition to these olefinic derivatives this reaction produced another isomeric but nonolefinic derivative, $C_{18}H_{21}O_3N$, in 17% yield. Since such an isomer was not formed by the elimination of the 6α-acetoxy-8α-tosyloxy derivative (XV), participation of the 6α-hydroxy group in the present reaction is obvious. The structure of this isomer has not been ascertained.*

Nucleophilic substitution of the 8α-tosyloxy derivative (XXII) prepared from VI was another alternative for the synthesis of XVIII.[12] Heating of XXII with 10% acetic acid gave XVIII in 8·9% yield. The 8β-OH derivative (XXIII)† and the 8α-OH

* Signals (2H) due to CH—O at 5·4–5·7 τ and the 9α-H singal (d) in the NMR spectrum, coupled with the absence of OH band in the IR spectrum, may support a 6α,14α-epoxy structure.

† A strong band due to an intramolecular H-bond (OH···N) is observed at 3255 cm^{-1} with no band of free OH in a diluted CCl_4 solution, while VI shows only a band of free OH at 3634 cm^{-1}.

TABLE 2. NMR SPECTRA OF B/C *trans*-MORPHINE DERIVATIVES

Compound	Chemical shift (τ)*									
	1,2-H	3-OMe	5β-H	6-H	7-H	8-H	9α-H	10β-H	$N\text{-}CH_3$	others
VII	3·26	6·10	5·6 $J_{6\beta} = 4·5$	ca. 4·5		ca. 4·5	6·73 $J_{10\alpha} = 6$ $J_{14\alpha} = 3$	6·72 $J_{10\alpha} = 18$	7·65	8α-AcO 7·95 6α-AcO 8·24
VIII	3·26	6·11	5·6 $J_{6\alpha} = 10$				6·75 $J_{10\alpha} = 6$ $J_{14\alpha} = 3$	6·7 $J_{10\alpha} = 18$	7·65	8α-AcO } 7·90 6β-AcO } 7·95
VI	3·42	6·13	5·4	equivalent 4·1		5·5	6·49 $J_{10\alpha} = 6$ $J_{14\alpha} = 3$	6·75 $J_{10\alpha} = 18$	7·65	
X	3·33	6·13		5·0 $J_7 = 3$ 4·5		ca. 5·3	6·57	6·75 $J_{10\alpha} = 18$	7·63	
XII	3·25	6·11	5·6 $J_{6\alpha} = 10$	ca. 5·8		ca. 4·5	6·77 $J_{10\alpha} = 6$ $J_{14\alpha} = 3$	6·74 $J_{10\alpha} = 18$	7·67	8α-AcO 7·94

XIV	3·30	6·12	ca. 5·5	ca. 5·5		ca. 4·5	6·79 $J_{10\alpha} = 6$ $J_{14\alpha} = 3$	6·75 $J_{10\alpha} = 18$	7·7	8α-AcO 7·95
XVII	3·35	6·15	5·56 $J_{6\beta} = 5$	4·36 $J_{5\beta} = 5$ $J_7 = 6$	4·0 $J_8 = 9$ $J_{6\beta} = 6$ $J_{14} = 3$	3·43 $J_7 = 9$ $J_{14} = 3$	6·6 $J_{10\alpha} = 6$ $J_{14} = 3$	6·75 $J_{10\alpha} = 18$	7·6	6α-AcO 8·25
XVIII	3·32	6·13	5·6 $J_{6\beta} = 5$	5·35 $J_{5\beta} = 5$ $J_7 = 6$	4·0 $J_8 = 9$ $J_{6\beta} = 6$	3·42 $J_7 = 9$ $J_{14} = 3$	6·6 $J_{10\alpha} = 6$ $J_{14} = 3$	6·75 $J_{10\alpha} = 18$	7·6	
XXV	3·5		5·7 $J_{6\beta} = 5$	ca. 5·5	4·1 $J_8 = 9$ $J_{6\beta} = 6$ $J_{14} = 3$	3·5 $J_7 = 9$ $J_{14} = 3$	ca. 6·6	6·77 $J_{10\alpha} = 18$	7·6	solvated CH_3OH 6·6

* All spectra were determined at 60 Mc in $CDCl_3$ (10–15%) containing tetramethylsirane as internal standard using a JNM-C-60 Spectrometer (Japan Electric Optical Lab. Co. Ltd.). The authors thank Dr. K. Kotera for measurement of the spectra and helpful discussion.

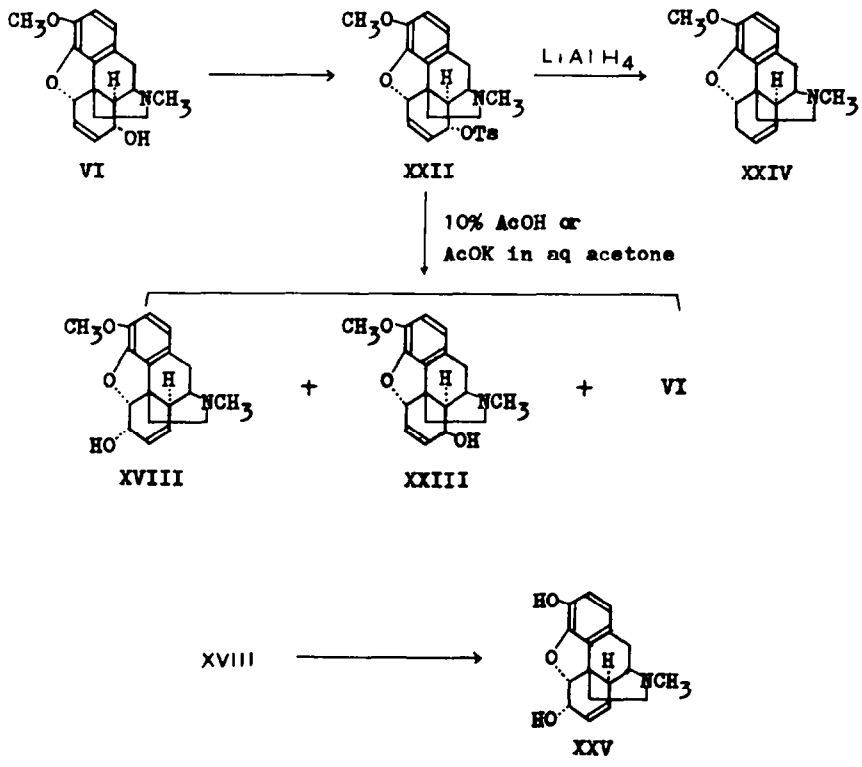


CHART 5

derivative (VI) were also isolated in 35 and 4% yields respectively. Solvolysis of XXII with potassium acetate in aqueous acetone also gave the three products in comparable yields. LAH reduction of XXII afforded a low yield of (+)-3-methoxy-4,5α-epoxy-Δ^7-N-methylisomorphinan (XXIV), identical with an authentic sample.[6]

Following the procedure successfully used in the synthesis of morphine from codeine[13] XVIII was treated with pyridine hydroxhloride to give only a trace of *trans*-morphine[(+)-3,6α-dihydroxy-4,5α-epoxy-Δ^7-N-methylisomorphinan; XXV]. Recently, Mann[14] reported a mild demethylation of phenylmethyl ethers with diphenylphosphide ion. A modification of this method gave XXV in 16·3% yield.

trans-Morphine crystallized from methanol with one mole of MeOH, the NMR spectrum of which is in good agreement with the structure. The hydrochloride and picrate analysed correctly.

Contrary to our expectation, *trans*-morphine shows much less analgesic activity than that of natural morphine when tested by the hot plate method.* Acute toxicity was about twice that of morphine. Pharmacological data of *trans*-morphine derivatives will be presented in a later communication.

* Determination of the analgesic activity was made by Dr. G. Hayashi and others of our Department of Clinical Pharmacology.

EXPERIMENTAL

All m.ps were determined in an open capillary tube and are uncorrected. IR spectra were taken in Nujol, and optical rotations were measured in $CHCl_3$ inless otherwise stated.

(−)-3-*Methoxy*-6β-*tosyloxy*-8α-*hydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (III)

B_2H_6 (from 177 g BF_3–Et_2O and 34·5 g $NaBH_4$) was introduced into a suspension of II (65 g) in THF (580 ml) at 23–27° and allowed to stand at room temp for 140 hr. The mixture was decomposed with water, then oxidized with 30% H_2O_2 (34 ml) and 10% NaOH (115 ml), extracted with $CHCl_3$, dried and evaporated. The residue was refluxed with AcOH (200 ml) and dioxan (160 ml) for 40 min. concentrated under reduced press, basified with NH_4OH aq, extracted with $CHCl_3$, dried and evaporated. The residue was recrystallized from benzene to give III (44 g), m.p. 168–170°. Frok the filtrate (benzene) II (9·8 g), m.p. 179–185°, and III (6·5 g, total yield 74·6%) were obtained.

Dehydration of III

Compound III (800 mg) was added to a mixture of $SOCl_2$ (280 mg) and pyridine (8 ml) under cooling, allowed to stand at room temp for 72 hr, poured into water, basified with NH_4OH aq and extracted with $CHCl_3$. The crude base was chromatographed in benzene over Al_2O_3 and eluted with benzene–ether (1:1) to give II (120 mg, 16%), m.p. 176–180°. Following elution with ether–MeOH (98:2) gave recovered III (220 mg), m.p. 168–170°.

Solvolysis of III

(a) *With* AcOK. A mixture of III (50·5 g), AcOK (62 g), DMF (620 ml) and water (15·5 ml) was refluxed for 6 hr. The mixture was diluted with water, basified with NH_4OH aq, extracted with $CHCl_3$, dried and evaporated. The residue was chromatographed (Al_2O_3) and eluted with ether–MeOH (97:3). The first part of the eluate (1·5 l) gave (−)-3-*methoxy*-8α-*hydroxy*-4,5α-*epoxy*-Δ⁶-N-*methylisomorphinan* (VI) (from AcOEt; 5·58 g), m.p. 159–160·5°; $[\alpha]_D$ −89·7°; ν_{max} 3200 cm^{-1}. (Found: C, 72·23; H, 6·76; N, 4·49. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%). Hydrochlorides: colourless plates (from EtOH). m.p. 265–268° (dec); ν_{max} 3250 cm^{-1}. (Found: C, 64·40; H, 6·22; N, 4·41. $C_{18}H_{22}O_3NCl$ requires: C, 64·37; H, 6·60; N, 4·17%).

Next eluate (1·5 l) gave (−)-3-*methoxy*-6α-*acetoxy*-8α-*hydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (IV; 11·8 g), colourless needles (from AcOEt-n-hexane), m.p. 161·5–162·5°; $[\alpha]_D$ −94·8°; ν_{max} 3200, 1740 cm^{-1}. (Found: C, 67·19; H, 6·82; N, 4·03. $C_{20}H_{25}O_5N$ requires: C, 66·83; H, 7·01; N, 3·90%); hydrochloride: Colourless plates (from EtOH aq), m.p. 263–265° (dec); ν_{max} 3400, 1740 cm^{-1}. (Found: C, 60·24; H, 6·96; N, 3·48. $C_{20}H_{26}O_5NCl$ requires: C, 60·68; H, 6·62; N, 3·54%).

Following eluation with ether–MeOH (8:2) gave (−)-3-*methoxy*-6α,8α-*dihydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (V; 6·58 g), colourless plates (from AcOEt), m.p. 144·5–145·5°; $[\alpha]_D$ −103·1°; ν_{max} 3380 cm^{-1}. (Found: C, 68·09; H, 7·05; N, 4·76. $C_{18}H_{23}O_4N$ requires: C, 68·11; H, 7·30; N, 4·41%); hydrochloride: colourless pillars (from EtOH), m.p. 272–274° (dec); ν_{max} 3420, 3360 cm^{-1}. (Found: C, 58·67; H, 6·94; N, 3·97. $C_{18}H_{24}O_4NCl$ $\frac{1}{2}H_2O$ requires: C, 59·25; H, 6·91; N, 3·84%).

(−)-3-*Methoxy*-6α,8α-diacetoxy-4,5α-epoxy-N-methylisomorphinan (VII) was prepared from IV and V by acetylation; colourless pillars (from ligroin), m.p. 140–141·5°; $[\alpha]_D$ −91·3°; ν_{max} 1740 cm^{-1}. (Found: C, 66·13; H, 6·48; N, 3·50. $C_{22}H_{27}O_6N$ requires: C, 65·82; H, 6·78; N, 3·49%).

(b) *With lithium chloride.* (1) A mixture of III (6 g), LiCl (2·7 g) and DMF (100 ml) was refluxed for 6 hr. The crude product was chromatographed in benzene over Al_2O_3 and eluted with ether–MeOH (98:2). The first eluate (80 ml) gave (−)-3-*methoxy*-6β-*chloro*-8α-*hydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (XI; from benzene; 450 mg), colourless pillars, m.p. 204–206°; $[\alpha]_D$ −154·4°; ν_{max} 3150 cm^{-1}. (Found: C, 64·86; H, 6·20; N, 3·90; Cl, 10·66. $C_{18}H_{22}O_3NCl$ requires: C, 64·37; H, 6·60; N, 4·17; Cl, 10·56%); hydrochloride: colourless plates (from EtOH), m.p. 271–273° (dec); ν_{max} 3360 cm^{-1}. The second eluate (120 ml) gave (−)-3-*methoxy*-8α-*hydroxy*-4,5α-*epoxy*-Δ⁵-N-*methylisomorphinan* (X; from AcOEt; 1·1 g), colourless plates, m.p. 159–161°; $[\alpha]_D$ −164·8°; ν_{max} 3160, 1700 cm^{-1}. (Found: C, 72·11; H, 6·82; N, 4·68. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%); hydrochloride: colourless plates (from EtOH), m.p. 251–253° (dec); ν_{max} 3200, 1710 cm^{-1}. Next eluate (250 ml) gave VI (955 mg hydrochloride), m.p. 262–266° (dec). Final elution with ether–MeOH (8:2) gave V (from AcOEt; 190 mg) m.p. 144–145°.

(2) A mixture of III (1·7 g), LiCl (0·8 g) and DMF (35 ml) was refluxed for 30 min. The crude base was dissolved into two portions by TLC (Kiesel Gel nach Stahl, 2 mm × 200 mm × 200 mm, developed with $CHCl_3$–MeOH 9:1). Portion of R_f 0·4 gave (−)-3-*methoxy*-6α-*chloro*-8α-*hydroxy*-4,5α-*epoxy*-N-*methyl*-

isomorphinan (XIII; from AcOEt–n-hexane; 350 mg), colourless pillars, m.p. 154–156°; $[\alpha]_D$ −83·3°; ν_{max} 3150 cm^{-1}. (Found: C, 64·44; H, 6·63; N, 4·36; Cl, 10·40. $C_{18}H_{22}O_3NCl$ requires: C, 64·37; H, 6·60; N, 4·17; Cl, 10·56%). The portion of R_f 0·6 gave III (580 mg), m.p. 168–171°.

(c) *With sodium iodide.* A mixture of III (1·5 g), NaI (0·6 g) and DMF (15 ml) was heated for 6 hr. The product was chromatographed (Al_2O_3) as previously described to give X (210 mg), m.p. 156–160°, VI (190 mg), m.p. 157–159°, and V (90 mg), m.p. 141–144°.

(d) *With lithium carbonate.* A mixture of III (1·8 g), $LiCO_3$ (0·8 g) and DMF (18 ml) was heated for 6 hr. Chromatography of the crude product gave X (12 mg), m.p. 158–160°, III (198 mg), m.p. 140–142°, and V (590 mg), m.p. 142–144°.

Hydrogenation of VI

A soln of VI–HCl (130 mg) in AcOH (25 ml) was hydrogenated with PtO_2 (30 mg) at room temp. The filtered soln was evaporated, basified with NH_4OHaq, extracted with $CHCl_3$, dried and evaporated. The residue was converted to hydrochloride and recrystallized from EtOH to give IX–HCl (115 mg, 83·5%), m.p. 245–248° (dec).

Hydrogenation of X

X (160 mg) was hydrogenated in MeOH (20 ml) with PtO_2 (35 mg). IX–HCl (from EtOH; 135 mg 75%), m.p. 245–247° (dec) was obtained.

LAH reduction of IX

LAH (95 mg) was added to a soln of XI (120 mg) in di-n-butyl ether (20 ml) and THF (5 ml) at 90° under N_2. The mixture was stirred at 90–100° for 5 hr and worked up as usual. The crude base in benzene was chromatographed (Al_2O_3, eluted with ether–MeOH 98:2), converted to hydrochloride and recrystallized from EtOH to give IX–HCl (38 mg, 30%), m.p. 245–248° (dec).

(−)-3-*Methoxy*-6β-*chloro*-8α-*acetoxy*-4,5α-*epoxy*-N-*methylisomorphinan* (XII)

A mixture of XI (130 mg), Ac_2O (4 ml) and pyridine (1·5 ml) was heated on a steam bath for 2 hr and worked up as usual to give colourless needles (from n-hexane; 132 mg 90%), m.p. 136·5–138°; $[\alpha]_D$ −148·5°; ν_{max} 1735 cm^{-1}. (Found: C, 63·55; H, 6·26; N, 4·0; Cl, 9·74. $C_{20}H_{24}O_4NCl$ requires: C, 63·57; H, 6·40; N, 3·71; Cl, 9·38%).

(−)-3-*Methoxy*-6α-*chloro*-8α-*acetoxy*-4,5α-*epoxy*-N-*methylisomorphinan* (XIV)

XIII was acetylated as described above to give XIV in a quantitative yield; colourless cubes (from ligroin), m.p. 133–135°; $[\alpha]_D$ −88·9°; ν_{max} 1735 cm^{-1}. (Found: C, 63·49; H, 6·19; N, 3·82; Cl, 9·63. $C_{20}H_{24}O_4NCl$ requires: C, 63·57; H, 6·40; N, 3·71; Cl, 9·38%).

(−)-3-*Methoxy*-6α-*acetoxy*-8α-*tosyloxy*-4,5α-*epoxy*-N-*methylisomorphinan* (XV)

TsCl (2·5 g) was added to a soln of IV (3·6 g) in pyridine (15 ml) under cooling. The mixture was kept in a refrigerator for 3 days, poured onto ice–water, basified with NH_4OHaq and filtered to give colourless plates (from $CHCl_3$–EtOH; 4·6 g, 90%), m.p. 162–163°; $[\alpha]_D$ −40·6°; ν_{max} 1740, 1370, 1175 cm^{-1}. (Found: C, 63·02; H, 5·88; N, 2·91. $C_{27}H_{31}O_7NS$ requires: C, 63·15; H, 6·08; N, 2·73%).

Elimination of XV

A mixture of XV (1·54 g) and 2,4,6-collidine (7 ml) was refluxed for 2 hr in N_2, diluted with benzene, washed with 1% Na_2CO_3, with water and dried. The solvent was removed under reduced press, the residue was dissolved in benzene, chromatographed on Al_2O_3 and eluted with benzene–ether (9:1). First eluate (400 ml) gave (+)-3-*methoxy*-6α-*acetoxy*-4,5α-*epoxy*-Δ^7-N-*methylisomorphinan* (XVII; from n-hexane; 425 mg 41·5%), colourless pillars, m.p. 91·5–93°; $[\alpha]_D$ +184·7°; ν_{max} 1740 cm^{-1}. (Found: C, 70·35; H, 6·71; N, 4·22. $C_{20}H_{23}O_4N$ requires: C, 70·36; H, 6·79; N, 4·10%). Next eluate (400 ml) gave XVI (410 mg, 41%), colourless oil. Methiodide: m.p. 255–258° (dec).[11]

(+)-3-*Methoxy*-6α-*hydroxy*-4,5α-*epoxy*-Δ^7-N-*methylisomorphinan* (trans-*codeine*; XVIII)

A mixture of XVII (200 mg) and 3% KOH–EtOH (8 ml) was heated for 1·5 hr. The mixture was concentrated under reduced press, water was added, extracted with $CHCl_3$, dried and evaporated. The residue was recrystallized from ether to give colourless needles (175 mg), m.p. 98–102°; $[\alpha]_D$ +61°; ν_{max} 3200 cm^{-1}.

(Found: C, 71·82; H, 6·79; N, 4·92. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%); hydrobromide: colourless needles (from EtOH), m.p. 233–235° (dec); ν_{max} 3400 cm^{-1}. (Found: C, 56·90; H, 5·86; N, 3·88. $C_{18}H_{22}O_3NBr$ requires: C, 56·85; H, 5·83; N, 3·68%); picrate: pillars (from acetone), m.p. 244–245° (dec).

(−)-3-*Methoxy*-6α-*hydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (XIX)

(a) A soln of XVIII (200 mg) in EtOH (20 ml) was hydrogenated with PtO_2 (40 mg). The crude base was converted to hydrochloride and recrystallized from EtOH to give XIX–HCl (hemihydrate; 180 mg 80%), colourless needles, m.p. 246–248° (dec); $[\alpha]_D$ −55° (EtOH); ν_{max} 3400 cm^{-1}. (Found: C, 61·68; H, 7·02; N, 4·22. $C_{18}H_{24}O_3NCl \cdot \frac{1}{2}H_2O$ requires: C, 62·33; H, 7·27; N, 4·04%).

(b) LAH (460 mg) was added to a mixture of XV (1·54 g), di-n-butyl ether (80 ml) and THF (4 ml) at 95° under N_2, stirred at 95–100° for 3 hr and worked up as usual. The crude base (chromatographed on Al_2O_3 and eluted with ether–benzene) was hydrogenated in AcOH with PtO_2, and converted to the picrate, m.p. 215–238°. The base recovered from the picrate gave XIX–HCl (90 mg), m.p. 246–248° (dec).

(−)-3-*Methoxy*-6α-*hydroxy*-8α-*tosyloxy*-4,5α-*epoxy*-N-*methylisomorphinan* (XX)

TsCl (7·35 g) was added to a soln of V (11·1 g) in pyridine (75 ml), kept in a refrigerator for 3 days and worked up as usual to give colourless needles (from EtOH; 13·1 g 79%), m.p. 150–152°; $[\alpha]_D$ −35·4°; ν_{max} 3480, 1360, 1175 cm^{-1}. (Found: C, 63·78; H, 6·10; N, 2·55. $C_{25}H_{29}O_6NS$ requires: C, 63·67; H, 6·20; N, 2·97%). V (1·3 g) was recovered from the mother liquor (EtOH).

Acetylation of XX with Ac_2O and pyridine gave XV (53·5%), m.p. 159–161°.

Elimination of XX

A mixture of XX (13·1 g) and 2,4,6-collidine (60 ml) was refluxed for 2·5 hr under N_2 and worked up in a usual way. The crude product was chromatographed (Al_2O_3) and eluted with benzene to give colourless pillars (from n-hexane; 1·4 g), m.p. 93–94°; $[\alpha]_D$ −113·8°; NMR: 5·5 τ (1H, d, J = 5·0), 5·62 τ (1H, s), 6·7 τ (1H, d, J = 6), 6·76 τ (1H, d, J = 17).

Elution with benzene–ether (1 : 1) gave XVIII (from ether; 3·27 g, 39·6%), m.p. 97–100°. Final elution with ether–MeOH (9 : 1) gave neopine (hydrobromide; 4·4 g, 42%), m.p. 277–279° (dec).

(−)-3-*Methoxy*-8α-*tosyloxy*-4,5α-*epoxy*-Δ⁶-N-*methylisomorphinan* (XXII)

Reaction of VI (5 g) with TsCl (4·5 g) in pyridine (15 ml) in a usual way gave XXII (from benzene; 4·47 g, 60%), colourless plates, m.p. 173–174°; $[\alpha]_D$ −35·1°; ν_{max} 1360, 1175 cm^{-1}. (Found: C, 66·32; H, 5·68; N, 2·79. $C_{25}H_{27}O_5NS$ requires: C, 66·21; H, 6·00; N, 3·09%).

Solvolysis of XXII

(a) XXII (1·3 g) in AcOH (50 ml) was refluxed for 4 hr, basified with NH_4OH aq, extracted with $CHCl_3$, dried and evaporated. The crude base was chromatographed (Al_2O_3) and eluted with benzene–ether (1 : 1, 150 ml) to give (−)-3-*methoxy*-8β-*hydroxy*-4,5α-*epoxy*-Δ⁶-N-*methylisomorphinan* (XXIII; from AcOEt-n-hexane; 300 mg), colourless pillars, m.p. 130–131°; $[\alpha]_D$ −24·4°; ν_{max} 3280 cm^{-1}; ν_{max} (CCl_4; 0·035 mmole/ml) 3255 cm^{-1} (intramol OH···N).* (Found: C, 72·47; H, 7·05; N, 4·78. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·68%); hydrochloride: colourless needles (from EtOH–ether), m.p. 252–254° (dec). The second portion of eluate (150 ml) gave XVIII (picrate, from acetone; 135 mg), m.p. 244–245° (dec). Final elution with ether gave VI (35 mg), m.p. 157–160°.

(b) A mixture of XXII (1·4 g), AcOK (0·9 g), acetone (60 ml) and water (20 ml) was refluxed for 20 hr, solvents were removed, the residue was basified with NH_4OH aq and extracted with $CHCl_3$. The crude base was warmed with ether and filtered to give recovered XXII (365 mg), m.p. 169–171°. The filtrate was evaporated and the residue was chromatographed (Al_2O_3) to give XXIII (300 mg), XVIII–picrate (165 mg) and VI (35 mg).

Reduction of XXII *with LAH*

ALH (170 mg) was added to a soln of XXI (1·36 g) in di-n-butyl ether (35 ml) and THF (1·5 ml) at 100° under N_2. The mixture was stirred at 95–100° for 3 hr and worked up in a usual manner. The crude base was chromatographed on Al_2O_3 and eluted with benzene–ether (8 : 2) to give XXIV (from n-hexane; 220 mg), m.p. 88–92°.

* Hitachi EPI-G2 Grating Infrared Spectrometer.

(+)-3,6α-*Dihydroxy*-4,5α-*epoxy*-Δ^7-N-*methylisomorphinan* (trans-*morphine*; XXV)

A soln of diphenylphosphine (1·08 g) in THF (30 ml) was added to a soln of n-BuLi (prepared from 262 mg Li and 2·06 g n-BuBr) in ether (40 ml) at 0° under N_2. XVIII (1·5 g) in THF (15 ml) was added to the mixture at the same temp, stirred at room temp for 30 min, ether was distilled and the mixture was heated for 1 hr at 60°. Solvents were removed under reduced press, water was added, extracted with $CHCl_3$, and the aqueous phase was acidified with con HCl aq, basified with NH_4OH aq and filtered. The filtrate was extracted with $CHCl_3$–EtOH (4:1), dried and evaporated. Chromatography (silica gel) of the residue (eluted with MeOH) gave XXV–MeOH adduct (from MeOH; 212 mg), colourless plates, m.p. 108–109°; $[\alpha]_D$ +80°; ν_{max} 3200 cm^{-1}. (Found: C, 68·39; H, 7·26, N, 4·28. $C_{17}H_{19}O_3N$ CH_3OH requires: C, 68·12; H, 7·31; N, 4·41%); hydrochloride: colourless needles (from EtOH), m.p. 263–265° (dec); ν_{max} 3180, 3350 cm^{-1}. (Found: C, 61·62; H, 6·87; N, 3·80. $C_{17}H_{20}O_3Cl \cdot \frac{1}{2}H_2O$ requires: C, 61·72; H, 6·40; N, 4·24%). Picrate: pillars (from EtOH–acetone), m.p. 217–220° (dec). (Found: C, 53·88; H, 4·42; N, 10·78. $C_{17}H_{19}O_3N \cdot C_6H_3O_6N_3$ requires: C, 53·70; H, 4·31; N, 10·89%). The picrate crystallized in another instance as needles m.p. 140–145° (dec). IR spectra of both samples were superimposable.

From the mother liquor (MeOH) XXV (hydrochloride; 40 mg) was obtained (total yield, 16·3%).

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