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

HYDROBORATION OF ISONEOPINE, NEOPINE, NEOPINONE AND THEBAINE

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Abstract—Hydroboration of isoneopine gave (−)-3-methoxy-6β,8α-dihydroxy-4,5α-epoxy-N-methylisomorphinan (II) in good yield, while hydroboration of neopine gave very low yields of two dihydroxy derivatives isomeric with II. Neopinone gave II and neopine. Hydroboration of thebaine, a cyclic diene system, was also examined.

IN AN earlier paper,[1] the synthesis of (−)-3-methoxy-8α-hydroxy-4,5α-epoxy-N-methylisomorphinan (*trans*-8α-hydroxydihydrodeoxycodeine; VIII) by the hydroboration of Δ^8-deoxycodeine was described. It was hoped that extension of this reaction to Δ^8-morphine structures bearing a substituent on the C-ring would provide

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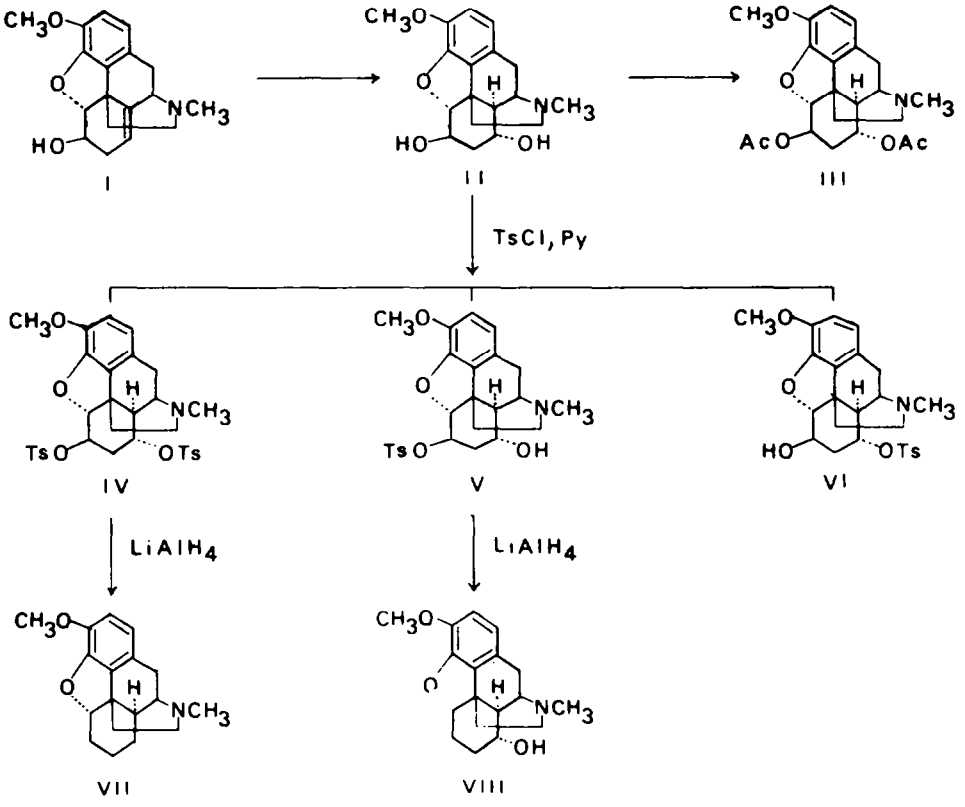
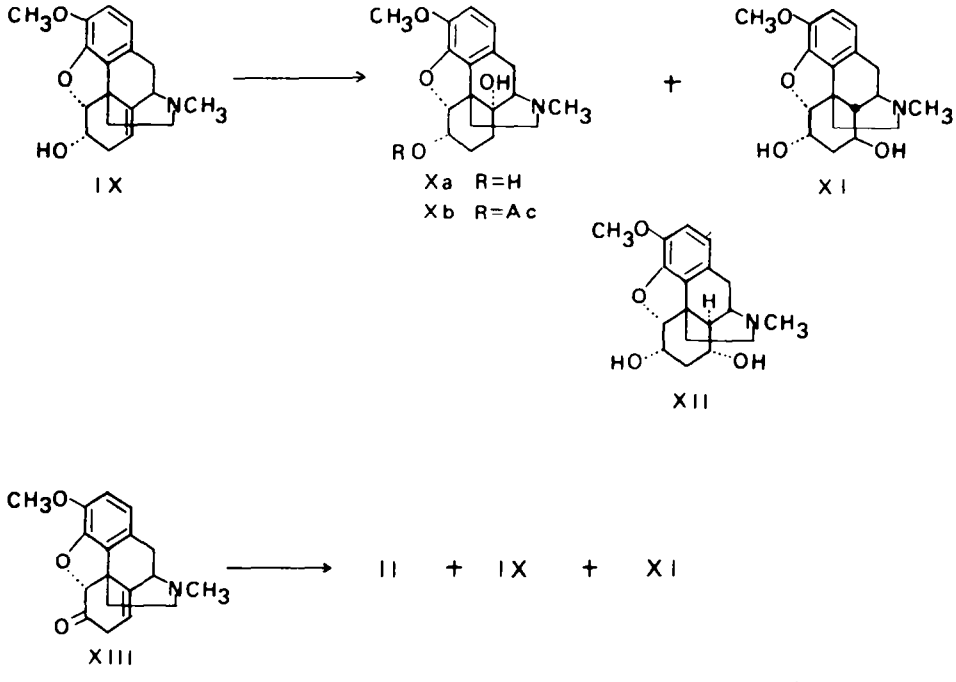


a number of B/C *trans*-fused morphine derivatives with pronounced pharmacological activity. Further, it was hoped that *trans*-morphine itself could be obtained if the substituent on the C-ring was appropriate. This work was initiated with the hydroboration of isoneopine, neopine and neopinone.

Reaction of isoneopine (I)[2] with excess diborane for an extended period and subsequent oxidation with alkaline hydrogen peroxide gave an 89% yield of (−)-3-methoxy-6β,8α-dihydroxy-4,5α-epoxy-N-methylisomorphinan (II) which was acetylated to the diacetoxy derivative III. Reaction of II with an excess of *p*-toluenesulphonyl chloride gave the ditosylate IV in 82% yield together with two monotosylates. V, m.p. 141–143°, and VI, m.p. 111–114° in 5·6 and 0·6% yields respectively. LAH reduction of the ditosylate IV afforded (−)-3-methoxy-4,5α-epoxy-N-methylisomorphinan (*trans*-dihydrodeoxycodeine; VII) in 34% yield* and identical with an authentic specimen.[1] A similar reduction of the monotosylate V gave VIII, identical with the hydroboration product of Δ^8-deoxycodeine. These results show that the hydroboration product of isoneopine is II and the two monotosylates, m.p. 141–143° and m.p. 111–114°, are the 6β-tosyloxy-8α-hydroxy and 6β-hydroxy-8α-tosyloxy derivatives, respectively.

Neopine (IX), a 6-hydroxy epimer of isoneopine, resisted hydroboration because of inaccessibility to the double bond from the side of the aromatic ring.† The starting

CHART 2



* The crude reduction product contained an olefinic derivative. Hydrogenation of the mixture gave a homogeneous product. This suggests that the LAH reduction is accompanied by elimination leading either to the Δ^6 or Δ^7 derivative.

† The 6α-hydroxy group nearly overhangs the α-side of the double bond when the C-ring takes a half-chair conformation. cf. S. Okuda, S. Yamaguchi, Y. Kawazoe and K. Tsuda, *Chem. Pharm. Bull. Tokyo* **12**, 104 (1964).

material and very low yields of two dihydroxy derivatives were isolated. These two compounds, m.p. 196–198° and m.p. 209–211°, are both isomeric with II and on account of the limited availability only the NMR spectral data could provide information on the possible structure.

The dihydroxy derivative, m.p. 209–211°, shows a signal attributable to 9α-H as a doublet at 7·03 τ (J = 6 c/s) indicating the absence of 14-H.* Acetylation of this derivative afforded a monoacetoxy derivative whose NMR spectrum shows signals of 5β-H at 5·55 τ (d, J = 6 c/s) and 6β-H(AcO—C<u>H</u>) at 4·4 τ (mult). The absence of any other signal due to C<u>H</u>—O suggests that the remaining OH group is attached to a quarternary carbon (14-C) and accordingly, the 6α-acetoxy-14-hydroxy structure (Xb) was assigned. The m.p. of 14-hydroxydihydrocodeine (B/C *cis*)[3] is 140–141°, but our compound melted at 209–211°. Consequently, the dihydroxy derivative has the 6α.14α-dihydroxy structure (Xa; B/C *trans*).

The NMR spectrum (CF_3COOD) of the second dihydroxy derivative, m.p. 196–198°, shows three protons attributable to C<u>H</u>—O (5·1 τ, 1H, d, J = 6 c/s; 5·3–5·6 τ, 2H, mult). Acetylation gave a diacetoxy derivative. 8-Hydroxydihydrocodeine (B/C *cis*; XI), m.p. 207°, synthesized by Findley and Small[4] should be identical with the second dihydroxy derivative. The sterical relationship between the 8-OH group and 14-hydrogen should be *cis* since the hydroboration proceeds with *cis*-addition of the borane molecule to the double bond.[5]† In previous work with Δ^8-deoxycodeine it was shown that 8-hydroxydihydrodeoxycodeine (B/C *cis*) is produced as a minor product.[1] Therefore, the formation of 8-hydroxydihydrocodeine (XI) by the hydroboration of neopine was not unusual. However the formation of Xa is contrary to ordinary hydroboration in that it occurred without formation of the normal anti-Markownikoff type product XII.

Hydroboration of neopinone (XIII) afforded the dihydroxy derivative II and neopine (IX) in 18 and 20% yields respectively together with a very small amount of a compound, m.p. 196–198°. The latter was identical with the dihydroxy derivative XI. Therefore, in the reaction of neopinone with diborane, the CO group was first reduced[6] to two 6-OH derivatives, isoneopine (I) and neopine (IX), and subsequently I underwent further reaction with diborane to give the dihydroxy derivative II in a manner similar to that observed in the hydroboration of isoneopine, while IX remained virtually unaffected giving only a small amount of XI.

The LAH reduction of 3-methoxy-8α-tosyloxy-4,5α-epoxy-N-methylisomorphinan[1] revealed that the reaction is accompanied by formation of a small amount of the parent 8α-OH derivative.[7] When the ditosylate IV was heated with LAH, V was isolated in 13% yield together with unchanged starting material (56% recovery). Investigation of the reaction under a variety of conditions did not produce a higher yield of V. Reaction of the dihydroxy derivative II with a limited amount of *p*-toluenesulfonyl chloride (1·0–1·8 moles) yielded only a small amount of V, nearly all the starting material being recovered.

Partial elimination of IV with an equimolar amount of collidine gave an olefinic derivative (21%), identical with isoneopine-O-tosylate (XIV) obtained by the reaction

* Signal of 9α-H usually appears as a quartet when C-14 is unsubstituted. Coupling constant with 14-H is about 3 c/s in most cases.

† B/C *trans* isomer of 8-hydroxydihydrocodeine XII was synthesized in later work by another route and was different from XI.

CHART 3

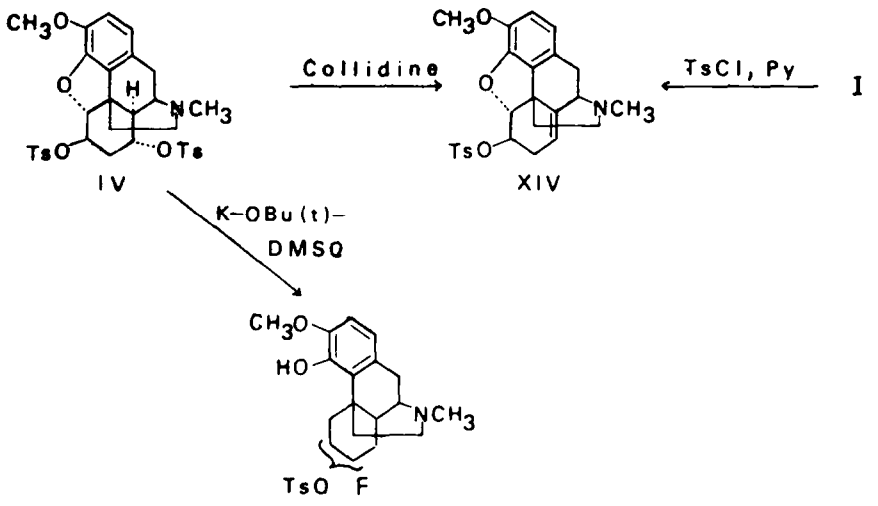
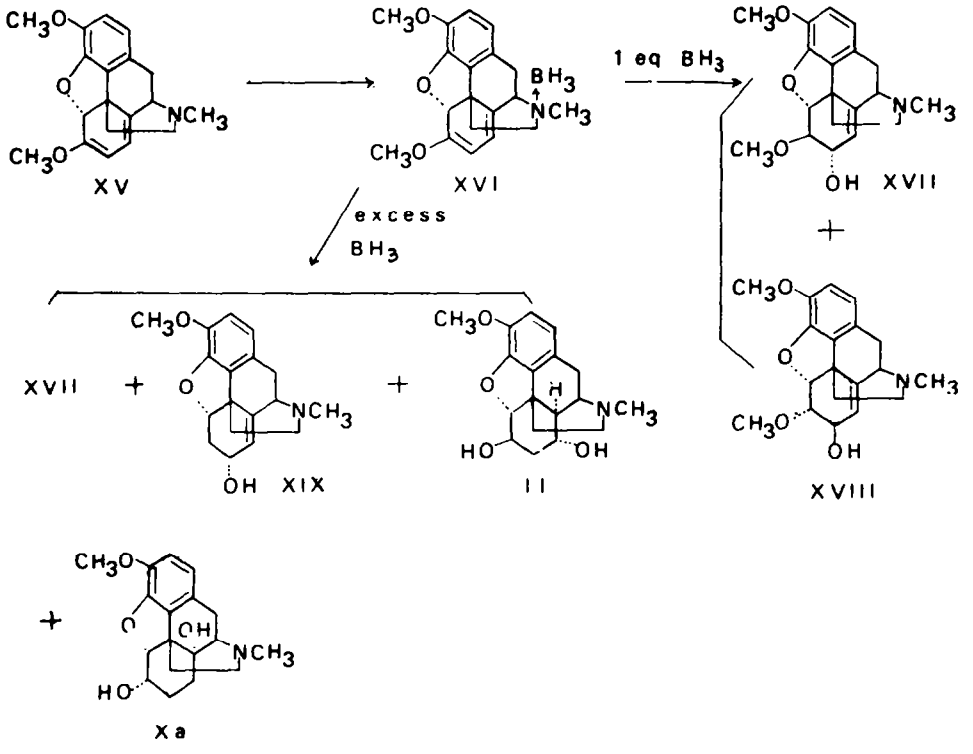


CHART 4

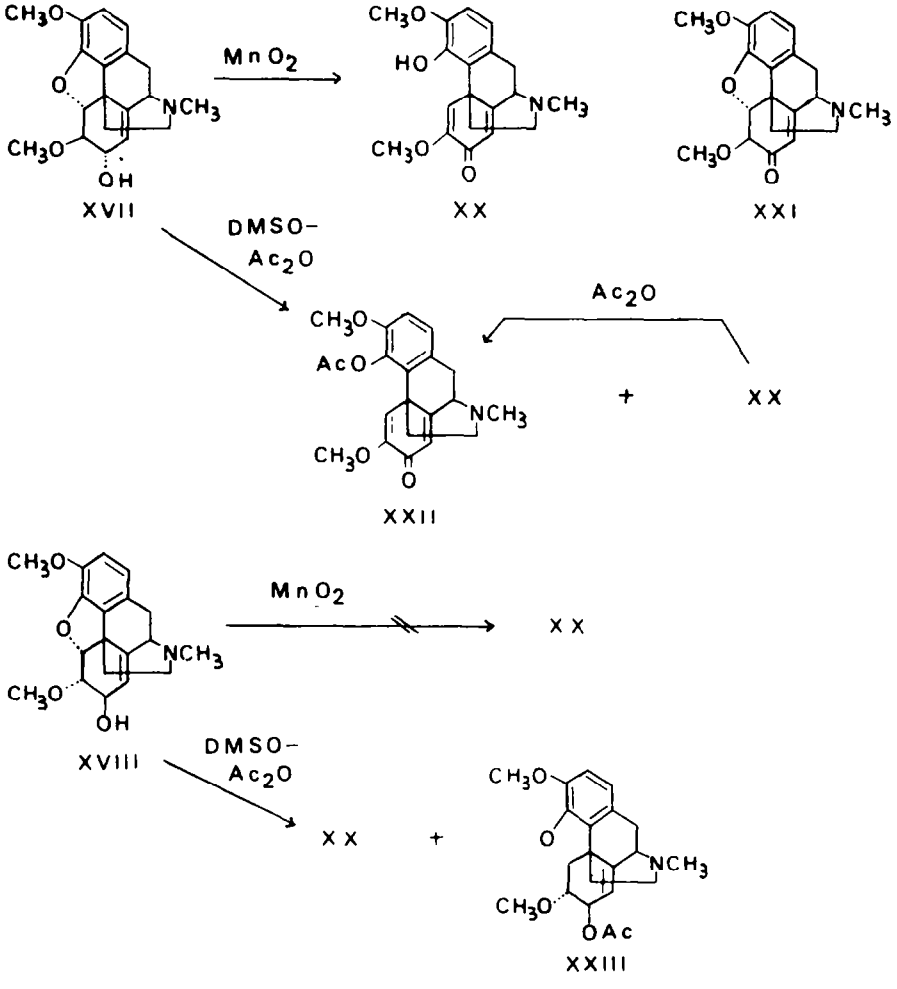


of I with *p*-toluenesulfonyl chloride. Heating of IV with excess collidine gave XIV in 30% yield.

Reaction of IV with potassium t-butoxide[8] gave a phenolic olefinic monotosyloxy derivative, the structure of which was not elucidated.

Although the reaction of diborane with the diene structure could be complex, hydroboration of thebaine could possibly lead to the formation of the B/C *trans* structure of morphine. Since in a Δ^8-morphine derivative the initial addition of the borane molecule occurs at the nitrogen giving the amine–borane,[1] thebaine–borane (XVI) (prepared by the reaction of XV with an equivalent amount of pyridine–borane or diborane) was used for the hydroboration. Reaction of XVI with one molar equivalent of borane followed by oxidation (Expl. 1) gave 7α-hydroxyisoneopine methylether (XVII) and 7β-hydroxyneopine methylether (XVIII) in 45·7 and 8·1% yields respectively. Small amounts of isoneopine and a phenolic compound were also

CHART 5



isolated. Oxidation of XVII with manganese dioxide produced salutaridine (XX),* identical with authentic sample.† Oxidation of XVII with DMSO and acetic anhydride[11] also gave salutaridine (31%) together with salutaridine-O-acetate (XXII), identical with the sample obtained by acetylation of XX.

Similar oxidation of XVIII with manganese dioxide failed to give XX. Oxidation with DMSO and acetic anhydride, however, afforded XX (17%) together with 7β-acetoxyneopine methylether (XXIII). These results confirm the isomeric nature of XVII and XVIII. Since XVII and XVIII were main products, addition of borane to XVI is predominantly from the α-side at C-7 due to the presence of steric factors.

Elimination of alkylated boranes with an adjacent alkoxy group has been reported to occur during hydroboration.[12] In the present case such an elimination should give an unsubstituted diene system. The presence of excess borane would result in a series of reactions which ultimately should give the dihydroxy derivative as visualized in the following scheme.

SCHEME

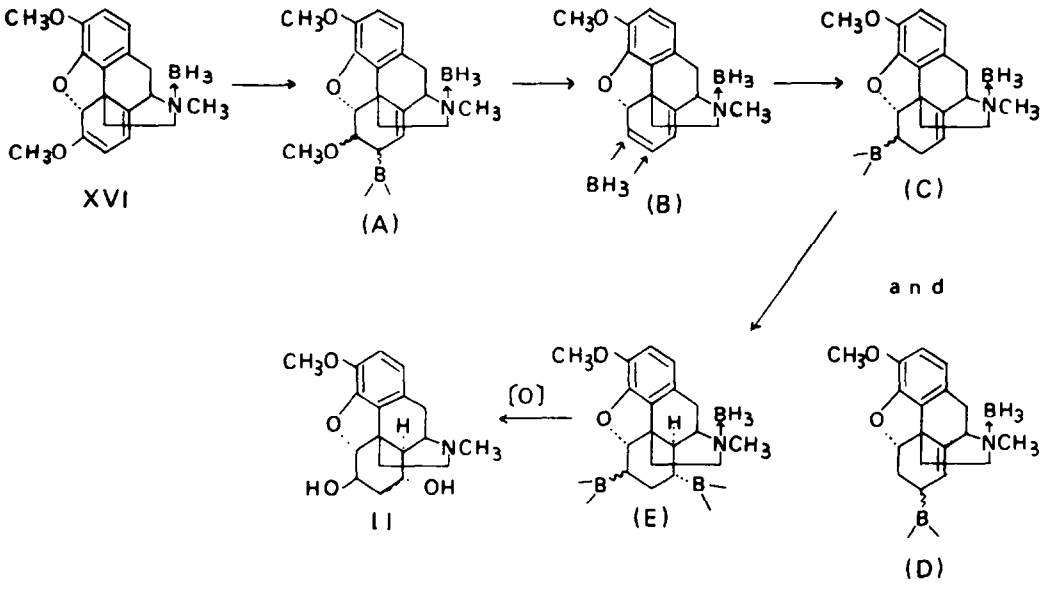


TABLE 1

Expl.	BH_3	Reaction time	Product (isolated)
1	1 eq.	45 hr	XVII (45·7%), XVIII (8·1%) XVII + XVIII (8·6%), I (< 1%)
2	excess (3 eq.)	180 hr	XVII (4·72%), XIX (7·03%) XVII + XIX (14%)
3	excess (ca. 7–8 eq.)	18 hr	XIX (10·1%), II (3·4%), Xa (4·6%)

* Cyclization of salutaridine (XX) to XXI, which was once proposed for an alternative pathway of biosynthesis of thebaine, does not occur by chemical procedures.[10]

† The sample was kindly supplied by Prof. D. H. R. Barton.

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-Me	others
III	3·25	6·10	5·60 $J_{6\alpha} = 10$	4·2–5·0		4·2–5·0	6·74 $J_{10\alpha} = 6$ $J_{14} = 2$	6·70 $J_{10\alpha} = 18$	7·65	6β-OAc 7·90 8α-OAc 7·94
Xa	3·36	6·22	ca. 5·65 (2H)				7·03 $J_{10\alpha} = 6$	6·93 $J_{10\alpha} = 18$	7·66	
Xb	3·33	6·20	5·55 $J_{6\beta} = 5·5$	4·4 (m)			7·03 $J_{10\alpha} = 6$	6·90 $J_{10\alpha} = 18$	7·65	6α-OAc 8·10
XVII	3·37	6·15	5·40 $J_{6\alpha} = 8·5$	7·0 $J_{5\beta} = 8$ $J_{7\beta} = 8$	5·75 $J_{6\alpha} = 8$ $J_{8} = 1·5$	4·56 $J_{7\beta} = 1·5$	6·45 $J_{10\alpha} = 6$	6·78 $J_{10\alpha} = 18$	7·60	6β-OMe 6·40
XVIII	3·45	6·19	5·04 $J_{6\beta} = 4$	6·25 (t) $J_{5\beta} = 4$ $J_{7\alpha} = 4$	5·85 $J_{6\beta} = 4$ $J_{8} = 5$	4·28 $J_{7\alpha} = 5$	6·45 $J_{10\alpha} = 6$	6·77 $J_{10\alpha} = 18$	7·60	6α-OMe 6·77
XIX	3·38	6·19	5·35 $J_{6\alpha} = 11$ $J_{6\beta} = 6$		5·78 (q)	4·48 $J_{7\beta} = 0$	6·51 $J_{10\alpha} = 6$	6·80 $J_{10\alpha} = 18$	7·65	

* All spectra were measured at 60 Mc in $CDCl_3$ containing tetramethylsilane as internal standard. The authors thank Dr. K. Kotera and Mr. N. Takeda for measurements of the spectra and useful discussion.

Reaction of XVI with excess dibórane (three equivalents; Expl. 2) did not give the dihydroxy derivative II although the yield of XVII was greatly diminished. 7α-Hydroxy-Δ^8-dihydrodeoxycodeine (XIX;* 7%) was also isolated, a mixture of XVII and XIX being produced in about 14% yield.

Reaction of XVI with excess diborane for a limited period (18 hr;† Expl. 3) gave XIX as the main product in 10% yield. The dihydroxy derivative II and Xa were also isolated in 3·4 and 4·6% yields respectively.‡

Although inconsistent results obscure the course of hydroboration, elimination of the 6-alkylborane (A) appeared to take place when excess diborane was present. The poor yield of the dihydroxy derivative II and the decreased combined yield of the products suggests that side reactions occur in the course of transformation from the unsubstituted diene (B) to the possible intermediate E.

EXPERIMENTAL

All m.ps were determined in an open capillary tube and are uncorrected. IR spectra were measured in Nujol unless otherwise stated.

(−)-3-*Methoxy*-6β,8α-*dihydroxy*-4,5-*epoxy*-N-*methylisomorphinan* (II)

BF_3–Et_2O (150 g) was added to a boiling mixture of $NaBH_4$ (30 g) and THF (400 ml), and B_2H_6 was introduced into a soln of I (29·2 g) in THF (450 ml) at 20–26° under N_2. The soln was allowed to stand for 140 hr at 27°, decomposed with water and neutralized with 10% NaOH aq 33% H_2O_2 (15 ml) and 10% NaOH aq (50 ml) were added to the mixture, stirred at room temp for 20 hr, diluted with water, extracted with $CHCl_3$, dried and evaporated. The residue was refluxed with AcOH (80 ml) and dioxan (160 ml) for 30 min, concentrated under reduced press, basified with NH_4OH aq and filtered to give II (hemihydrate from AcOEt–H_2O; 27 g), m.p. 104–106°. $[\alpha]_D^{20}$ −108° (benzene); ν_{max} 3150–3250 cm^{-1}. (Found: C, 66·21; H, 7·48; N, 4·31. $C_{18}H_{23}O_4N \cdot \frac{1}{2}H_2O$ requires: C, 66·23; H, 7·41; N, 4·29%).

Anhydrous II was obtained on drying the hemihydrate at 100°; colourless needles (AcOEt–pet. ether), m.p. 185–187°; ν_{max} 3460 cm^{-1}. (Found: C, 68·01; H, 7·00; N, 4·82. $C_{18}H_{23}O_4N$ requires: C, 68·11; H, 7·30; N, 4·41%); hydrochloride: Colourless pillars (AcOEt–EtOH), m.p. 253–255° (dec); ν_{max} 3470, 3300 cm^{-1}. (Found: C, 61·00; H, 6·77; N, 3·60. $C_{18}H_{24}O_4NCl$ requires: C, 60·72; H, 6·80; N, 3·90%.

The aqueous phase was extracted with $CHCl_3$, dried and evaporated, the residue in benzene was chromatographed over Al_2O_3 and eluted with ether–MeOH (9:1) to give additional II (1·33 g, total yield 89%).

(−)-3-*Methoxy*-6β,8α-*diacetoxy*-4,5α-*epoxy*-N-*methylisomorphinan* (III). A mixture of II (200 mg), Ac_2O (4 ml) and pyridine (8 ml) was heated on a steam bath for 40 min, concentrated under reduced press, diluted with water, basified with NH_4OH aq and filtered to give colourless plates (from ligroin; 250 mg), m.p. 175–177°; $[\alpha]_D^{20}$ −182° (benzene); ν_{max} 1733, 1740 cm^{-1}. (Found: C, 65·83; H, 6·43; N, 3·45. $C_{22}H_{27}O_6N$ requires: C, 65·82; H, 6·78; N, 3·49%).

Tosylation of II. TsCl (25 g) was added to II (15 g) in pyridine (75 ml) under cooling, the mixture was kept in a refrigerator for 4 days, poured onto ice–water and filtered to give (−)-3-*methoxy*-6β,8α-*ditosyloxy*-4,5α-*epoxy*-N-*methylisomorphinan* (IV; from $CHCl_3$–EtOH; 21 g). m.p. 169–171, which was recrystallized from EtOH, m.p. 178–179°; $[\alpha]_D^{20}$ −109° (benzene). (Found: C, 61·60; H, 5·34; N, 2·16. $C_{32}H_{35}O_8NS_2$ requires: C, 61·40; H, 5·64; N, 2·24%). The aqueous phase was extracted with $CHCl_3$, dried, combined with the mother liquor of the recrystallized and evaporated. The residue was chromatographed over Al_2O_3 and eluted with benzene–ether (1:1) to give additional IV (550 mg, total yield 82%). Next eluate with ether–MeOH (99:1) gave (−)-3-*methoxy*-6β-*tosylate*-8α-*hydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (V; colourless prisms from benzene; 1·25 g, 5·6%), m.p. 141–143°;§ $[\alpha]_D^{20}$ −178° (benzene); ν_{max} 3380, 1170 cm^{-1}

* The structure of XIX was deduced from its NMR spectrum.

† Checking of an aliquort on TLC showed disappearance of XVI.

‡ XVII could not be isolated although the presence of it was suggested by TLC. Isolation of minor products by chromatography was time-consuming and sometimes ended to vain throughout this series of experiments.

§ In another run V was obtained as colourless needles m.p. 170–172°. IR spectra ($CHCl_3$) of both samples were superimposable.

(SO_2). (Found: C, 63·59; H, 5·92; N, 2·92. $C_{25}H_{29}O_6NS$ requires: C, 63·67; H, 6·20; H, 2·97%). The mother liquor (benzene) was evaporated, the residue was dissolved in $CHCl_3$, and purified by TLC* to give 3-*methoxy*-6β-*hydroxy*-8α-*tosyloxy*-4,5α-*epoxy*-N-*methylisomorphinan* (VI; from ether–pet. ether; 130 mg), m.p. 114–115°; ν_{max} 3320, 1175 cm^{-1} (SO_2). (Found: C, 64·69; H, 6·52; N, 2·41; S, 6·39. $C_{25}H_{29}O_6NS$ requires: C, 63·67; H, 6·20; N, 2·97; S, 6·81%).

LAH reduction of IV. LAH (150 mg) was added to a soln of IV (1 g) in di-n-butyl ether (30 ml) and THF (5 ml) at 100° under N_2, the mixture was stirred at the same temp for 3 hr and worked up in a usual way. The crude base was hydrogenated in AcOH with PtO_2 (H_2 6 ml) to give VII (170 mg), m.p. 94–96°.

LAH reduction of V. V (500 mg) was reduced as described above to give VIII–HCl (from EtOH–ether; 30 mg), m.p. 248–251° (dec).

Hydroboration of neopine (IX). B_2H_6 generated from BF_3–Et_2O (10 g) and $NaBH_4$ (2 g) in THF (30 ml) was introduced into a soln of IX (2·2 g) in THF (30 ml) at 23–27° and allowed to stand for 140 hr. The mixture was oxidized with 30% H_2O_2 (1 ml) and 10% NaOH (3 ml) and worked up in the same manner as described previously to give a mixture, which was converted to hydrobromides and recrystallized from EtOHaq to give IX–HBr (642 mg), m.p. 275–277° (dec). The crude base obtained from the mother liquor was chromatographed (Al_2O_3) and eluted with ether–MeOH (99:1) to give additional IX–HBr (80 mg, total recovery 27%). Next eluate (ether–MeOH 98:2) gave (−)-3-*methoxy*-6α,14-*dihydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (Xa; from benzene; 100 mg), m.p. 209–211°; $[\alpha]_D^{20}$ −110° (EtOH); ν_{max} 3340, 3270 cm^{-1}. (Found: C, 68·20; H, 7·00; N, 4·58. $C_{18}H_{23}O_4N$ requires: C, 68·11; H, 7·30; N, 4·41%).

Elution with ether–MeOH (1:1) gave 8-hydroxydihydrocodeine (XI) (hydrate from AcOEt; 120 mg), m.p. 196–198°. $[\alpha]_D^{20}$ −113° (EtOH); ν_{max} 3350, 3200–3250 cm^{-1}. (Found: C, 64·52; H, 7·30; N, 4·19. $C_{18}H_{23}O_4N \cdot H_2O$ requires: C, 64·46; H, 7·51; N, 4·18%). The *diacetate of* XI was prepared in a usual way; hydrochloride, m.p. 233–236° (dec) (acetone–AcOEt–ether). (Found: C, 59·34; H, 6·68; N, 3·09. $C_{22}H_{28}O_6NCl \cdot \frac{1}{2}H_2O$ requires: C, 59·12; H, 6·32; N, 3·13%).

Acetylation of Xa. Xa (100 mg) gave (−)-3-*methoxy*-6α-*acetoxy*-14-*hydroxy*-4,5α-*epoxy*-N-*methylisomorphinan* (Xb) by usual acetylation: picrate (170 mg), m.p. 169–170° (EtOH–acetone). (Found: C, 53·24; H, 4·75; N, 9·32. $C_{26}H_{28}O_{12}N_4$ requires: C, 53·06; H, 4·80; N, 9·52%). Free base: ν_{max} ($CHCl_3$) 3350 (OH), 1760 cm^{-1} (CO).

Hydroboration of neopinone (XIII). Reaction of XIII[13] (2 g) with diborane was carried out in the same manner as described previously. The crude base (1·6 g) in benzene was chromatographed over Al_2O_3, eluted with ether–MeOH (99:1) and converted to hydrobromide to give IX–HBr (510 mg, 20%), m.p. 274–276° (dec). Following eluate with ether–MeOH (9:1) gave II (hemihydrate 380 mg, 18%), m.p. 106–108°. Final elution with ether–MeOH (1:1) gave XI (60 mg), m.p. 196–198°.

Elimination of IV *with* 2,4,6-*collidine*

(a) A mixture of IV (2·08 g) and 2,4,6-collidine (9 ml) was refluxed for 2 hr under N_2, diluted with $CHCl_3$, washed with 5% Na_2CO_3, dried, and solvents were removed under reduced press. The residue was extracted with $CHCl_3$, dried and evaporated to give XIV (from benzene; 370 mg), m.p. 186–188°, which was identical with the product obtained by the tosylation of isoneopine. From the mother liquor (benzene) additional XIV (80 mg, total yield 30%) was obtained (Al_2O_3 chromatography).

(b) A mixture of IV (1·5 g), 2,4,6-collidine (300 mg) and toluene (15 ml) was refluxed for 48 hr. Chromatography on Al_2O_3 of the crude base gave recovered IV (730 mg, 49%), m.p. 178–179°, and XIV (230 mg, 21%), m.p. 185–187°.

Isoneopine-O-*tosylate* (XIV). TsCl (7·4 g) was added to a soln of I (8 g) in pyridine (30 ml) under cooling, the mixture was kept in a refrigerator for 3 days, poured onto ice–water, basified with NH_4OHaq and filtered; colourless pillars (from benzene; 10 g, 84%), m.p. 186–188°. $[\alpha]_D^{20}$ −112° (benzene); ν_{max} 1685 (C=C), 1175, 1350 cm^{-1} (SO_2). (Found: C, 66·41; H, 6·26; N, 3·26. $C_{25}H_{27}O_5NS$ requires: C, 66·19; H, 6·00; N, 3·09%).

Elimination of IV *with* t-BuOK

A soln of IV (6 g) in DMSO (20 ml) was added to a soln of t-BuOK (prepared from 0·37 g K) in DMSO (20 ml) at 20–25° under N_2 and stirred for 6 hr at room temp, poured onto ice–water and filtered to give recovered IV (from $CHCl_3$–EtOH; 2·6 g). The aqueous phase was extracted with $CHCl_3$, combined with the mother liquor of the recrystallized and evaporated. The residue in benzene was chromatographed

* Kiesel Gel nach Stahl, 2 × 200 × 200 mm, $CHCl_3$–MeOH (9:1).

on Al_2O_3 to give additional IV (0·3 g). Elution with benzene–ether (8:2) gave colourless plates (from benzene–pet. ether; 1·6 g), m.p. 100–101°; ν_{max} 1650, 1180 and 1380 cm^{-1} (SO_2); $FeCl_3$ test, green. Hydrobromide: m.p. 100–103° (acetone–ether).

Thebaine-borane (XVI). A mixture of XV (9·8 g), pyridine–borane (3·2 g) and benzene (75 ml) was heated in a sealed tube at 65–75° for 40 hr. The mixture was washed with 3% HCl, 5% $NaHCO_3$, water and dried. Evaporation of the solvent gave XVI (from benzene–pet. ether; 8·54 g), m.p. 192–195°; ν_{max} 2370, 2270 cm^{-1} (B—H).[14] Heating XVI (400 mg) with AcOH (1·2 ml) and dioxan (3·6 ml) for 1 hr gave XV (330 mg), m.p. 188–189°.

Hydroboration of XVI

(a) With 1 eq of BH_3 B_2H_6–THF (0·6M soln* 20·5 ml = 0·0123 mole) was added to a soln of XVI (8 g = 0·0246 mole) in THF at 5 ± 1° under N_2 and stirred at 20–25° for 45 hr. The mixture was oxidized in a usual manner and the crude product was extracted with $CHCl_3$. The extract was evaporated and benzene was added to the residue and filtered to give crystals (3·6 g), m.p. 205–210°; ν_{max} 2400, 3200 cm^{-1} (B—H). Evaporation of the filtrate gave viscous oil (4·8 g). The crystals were heated with AcOH–dioxan for 1 hr to give *7α-hydroxyisonepine methyl ether* (XVII; 2·78 g), m.p. 143–146°, recrystallized from AcOEt–n-hexane, colourless needles, m.p. 149–150°; $[\alpha]_D$ +2·4° (EtOH); ν_{max} 3440 cm^{-1}. (Found: C, 69·35; H, 6·79; N, 4·45. $C_{19}H_{23}O_4N$ requires: C, 69·27; H, 7·04; N, 4·25%).

The latter (oil) was likewise heated with AcOH–dioxan, the crude base (4·1 g) was chromatographed on Al_2O_3 to give additional XVII (1·3 g), m.p. 138–139° (total yield after recrystallized 3·7 g), and *7β-hydroxyneopine methyl ether* (XVIII)–HCl (from MeOH–ether; 660 mg), m.p. 260–261° (dec); ν_{max} 3300 cm^{-1}; $[\alpha]_D$ −58° (EtOH). (Found: C, 62·76; H, 6·75; N, 3·77. $C_{19}H_{24}O_4NCl$ requires: C, 62·38; H, 6·61; N, 3·83%). I (0·68%) and thebaine (XV; 0·66%) and a phenolic derivative† (0·86%), m.p. 108–110° (from AcOEt) were also isolated.

(b) With excess B_2H_6 (180 hr). Reaction of XVI (8 g) and B_2H_6 (3 eq BH_3) for 180 hr and subsequent oxidation gave the crude base (6·36 g). Chromatography on Al_2O_3 (eluted with ether–MeOH) gave *7α-hydroxy-Δ⁸-deoxycodeine* (XIX; 540 mg), m.p. 160–161° (from benzene); ν_{max} 3200 cm^{-1}; $[\alpha]_D$ +1·6° (EtOH). (Found: C, 71·90; H, 6·72; N, 4·81. $C_{18}H_{21}O_3N$ requires: C, 72·21; H, 7·07; N, 4·86%), and XVII (400 mg), m.p. 145–148°. A mixture of XVII and XIX (1·1 g) was additionally obtained.

(c) with excess B_2H_6 (18 hr). Reaction of XVI (6 g) and B_2H_6 (ca. 7 eq BH_3) and work-up in a similar manner gave the crude base (3·65 g), which was chromatographed on Al_2O_3 to give Xa (270 mg), m.p. m.p. 204–205°, XIX (560 mg), m.p. 150–151° and II (200 mg), m.p. 104–107°.

Oxidation of XVII

(a) Newly prepared MnO_2 (5 g) was added to a soln of XVII (500 mg) in $CHCl_3$ (25 ml), stirred at room temp for 20 hr, filtered and evaporated. The residue was dissolved in benzene, filtered and evaporated, AcOEt was added to the residue and filtered to give XX (180 mg), m.p. 194–195° (from AcOEt), which was identical with an authentic sample (m.p. 194–196°) (IR and mm.p.).

(b) A mixture of XVII (250 mg), Ac_2O (1·7 ml) and DMSO (2·5 ml) was alowed to stand at room temp for 18 hr, poured onto ice–water, basified with NH_4OH aq and extracted with $CHCl_3$, dried and evaporated to give XX (80 mg; from AcOEt), m.p. 189–193°. Chromatography (Al_2O_3) of the filtrate (AcOEt) gave additional XX (10 mg) and XXII (20 mg), m.p. 168–169° (lit.[10] m.p. 171°), which was identical with the sample prepared by acetylation of XX.

Oxidation of XVIII. XVIII (80 mg) was oxidized with Ac_2O (0·56 ml) and DMSO (0·8 ml) as described above. The crude base (80 mg) was purified by TLC (silica gel) to give XX (15 mg), m.p. 190–193°, and *7β-acetoxyneopine methyl ether* (XXIII) (oil 35 mg), ν_{max} (CCl_4) 1730 cm^{-1}. Picrate: Prisms, m.p. 197–199° (dec) (from acetone–EtOH). (Found: C, 54·28; H, 4·81; N, 9·22. $C_{27}H_{28}O_{12}N_4$ requires: C, 54·0; H, 4·70; N, 9·33%).

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