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SYNTHESIS OF B/C TRANS-MORPHINE

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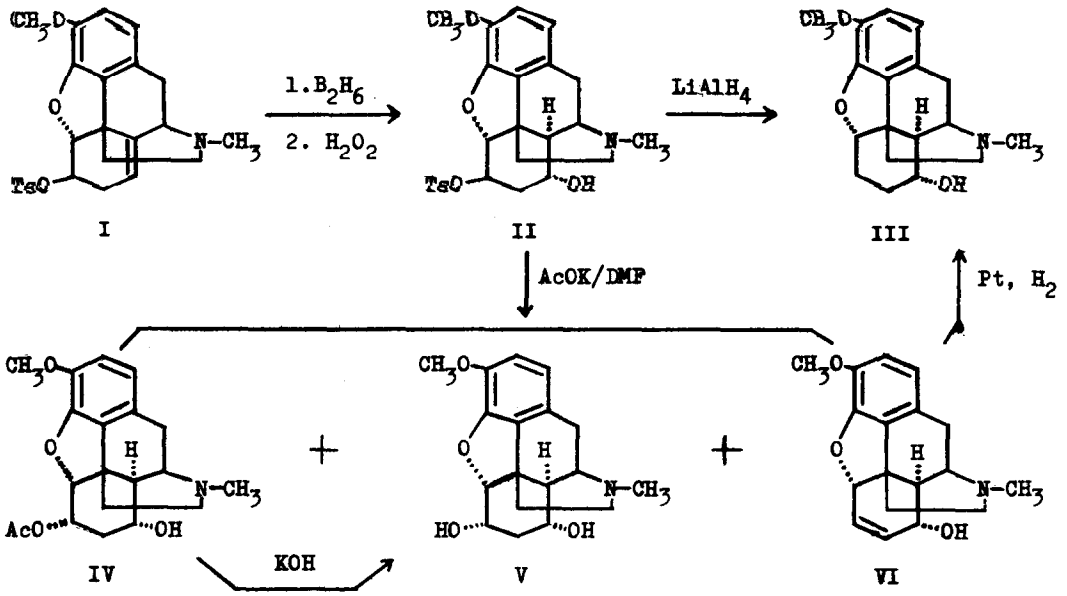
In a previous paper, we described the synthesis of a B/C trans morphine structure (III) by the hydroboration of Δ^8-dihydrodesoxycodeine.[1] This reaction was extended to some Δ^8-derivatives bearing a substituent on the C-ring in the hope of obtaining various compounds of the B/C trans system for pharmacological evaluation. This communication concerns with the synthesis of trans-codeine and -morphine.*

Reaction of isoneopine (prepared in two steps from thebaine[2]) and toluene-p-sulfonyl chloride in pyridine gave tosylisoneopine (I), $C_{25}H_{27}NO_5S$**, m.p. 186-8°. Hydroboration of I in tetrahydrofuran and subsequent alkaline oxidation gave trans-6β-tosyloxy-8α-hydroxydihydrodesoxycodeine (II), $C_{25}H_{29}NO_6S$, m.p. 141-2° (benzene), in 74.6% yield with a recovery of I (15%). Reduction of II with lithium aluminum hydride gave the 8α-hydroxy derivative (III), identical with the authentic compound. Boiling of II with potassium acetate in aqueous dimethylformamide gave a mixture which was chromatograghed on alumina to give the trans-6α-acetoxy-8α-hydroxy derivative (IV), $C_{20}H_{25}NO_5$, m.p. 161.5-2.5° (AcOEt-hexane), IR(Nujol) ν_{OH} 3200 cm^{-1}, ν_{CO} 1740 cm^{-1}, trans-6α,8α-dihydroxy derivative (V), $C_{18}H_{23}NO_4$, m.p. 144.5-5.5° (AcOEt), IR(Nujol) ν_{OH} 3380 cm^{-1}, and trans-8α-hydroxy-Δ^6-derivative (VI), $C_{18}H_{21}NO_3$, m.p. 159-160.5° (AcOEt), IR (Nujol) ν_{OH} 3200 cm^{-1}, in 31, 19.4 and 17.4 % yield respectively. Hydrogenation

* All the compounds having the B/C trans structure described herein will be called with the prefix trans in accordance with the Dr. Gates' naming appeared in J. Am. Chem. Soc. 84, 4125 (1962).

** Satisfactory analyses were obtained for all the compounds described herein with the chemical formula.

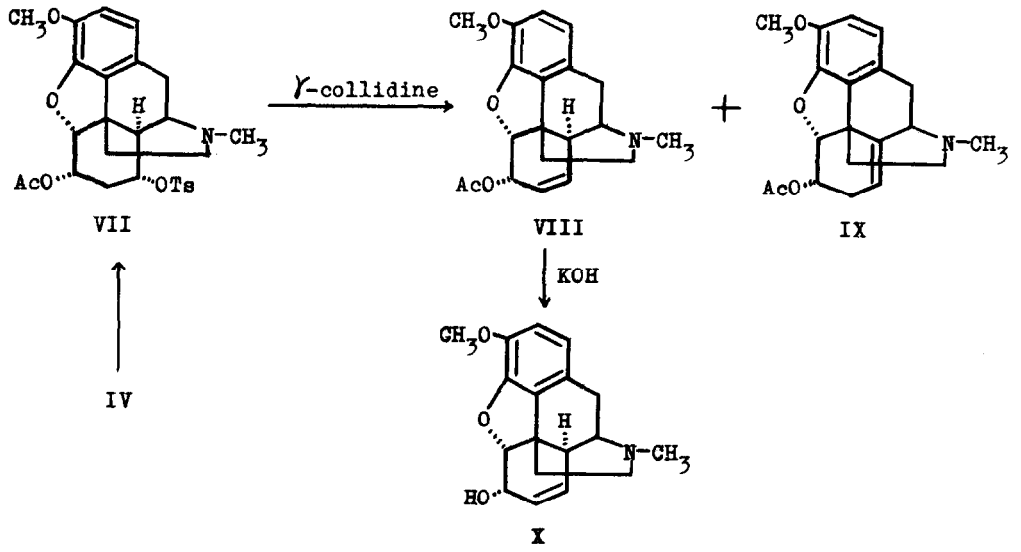


of VI with PtO_2 in acetic acid gave III. Heating of IV under the reaction condition described above (AcOK/aq.DMF) gave V in 22% yield with a recovery of IV (74%). Hydrolysis of IV with 4% KOH-ethanol also gave V. Acetylation of both IV and V with Ac_2O-pyridine gave an identical diacetate, $C_{22}H_{27}NO_6$, m.p. 140-1.5°. NMR spectra*** of IV, V, VI and the diacetate were in agreement with the assigned structure.****

The 6α-acetoxy-8α-hydroxy derivative (IV), on reaction with toluene-p-sulfonyl chloride in pyridine gave the 8α-tosyloxy derivative(VII) in 92% yield, $C_{27}H_{31}NO_7S$, m.p. 162-3°. Heating of VII in γ-collidine under reflux gave two double bond isomers, trans-acetylcodeine(VIII) (41.5%), $C_{20}H_{23}NO_4$, m.p. 91.5-93° (hexane); IR(Nujol) ν_{CO} 1740 cm^{-1}; NMR 7-H (4.0τ, heptet), 8-H (3.43τ, quartet), 5β-H (5.36τ, doublet), 6β-H (4.36τ, quartet), and neopine acetate (41%) (IX); methiodide, m.p. 255-8° (Lit.[3] 256-7°). This result was in parallel with an

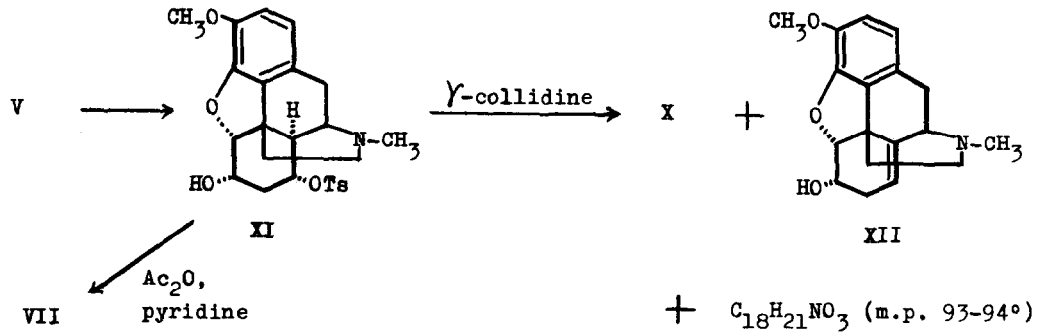
*** NMR spectra were taken on a JNM-C-60 spectrometer (Japan Electron Optics Laboratory Co.) in $CDCl_3$(10-15%) with TMS as an internal standard.

**** Signal of 5-H of the diacetoxy derivative, centered at 5.6τ, has J(5-H, 6-H) =4.5c.p.s.. This shows that 6-H is cis to 5-H, hence that 6-AcO is trans to 5-H. α-Configuration of 6-AcO of IV as well as 6-OH of V is accordingly obvious.



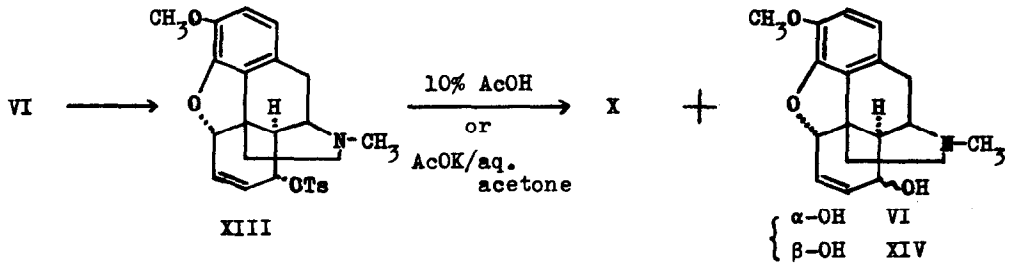
analogous case reported previously[1]. VIII, on heating with KOH in ethanol gave trans-codeine(X) in quantitative yield, $C_{18}H_{21}NO_3$, m.p. 98-102° (Et_2O), $[\alpha]_D^{25}$= +61°(c=0.4 $CHCl_3$); IR(Nujol) ν_{OH} 3200 cm^{-1}; NMR 5β-H(5.6τ, doublet, $J_{6\beta}$=5), 6β-H (5.35τ, quartet, $J_{5\beta}$=5, J_7=6), 7-H(4τ, heptet, $J_{6\beta}$=6, J_8=9, J_{14}=3), 8-H(3.42τ, quartet, J_7=9, J_{14}=3); hydrobromide, $C_{18}H_{22}NO_3Br$, m.p. 233-5°(EtOH).

Inspection of the molecular model of the 6,8-dihydroxy derivative(V) revealed a steric congestion around the 6α-hydroxy group larger than that around the 8α-hydroxy group. When V was tosylated with one mole of toluene-p-sulfonyl chloride in a usual manner only the 8α-tosyloxy derivative(XI) was obtained, $C_{25}H_{29}NO_6S$, m.p. 150-2°(EtOH); IR(Nujol) ν_{OH} 3480 cm^{-1}, ν_{SO_2} 1175, 1360 cm^{-1}.



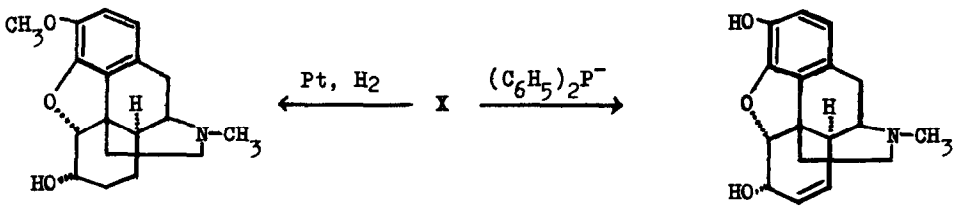
Acetylation of XI with Ac_2O-pyridine gave VII. Heating of XI in γ-collidine under reflux gave X in 39.6%, neopine(XII) in 42%; hydrobromide, m.p. 277-9°[4], and an unknown compound, $C_{18}H_{21}NO_3$, m.p. 93-4°, in 17% yield respectively.

SN_2, reaction has been known in morphine chemistry to occur when backside approach was hindered by steric crowding[5]. The 8α-tosyloxy derivative(XIII), m.p. 173-6°(benzene), prepared from VI in a usual manner, was heated with 10% acetic acid under reflux to give X in 8.9% yield, concomitantly obtained were VI(4.1%) and the 8β-hydroxy derivative(XIV)(35%), $C_{18}H_{21}NO_3$, 130-1°(AcOEt-hexane)*****; hydrochloride, m.p. 252-4°(EtOH-Et_2O). Heating of XIII with AcOK-aq. acetone also gave the three products in a comparable yield respectively.



XIII

Trans-codeine(X) gave the dihydro derivative(XV) on catalytic hydrogenation with PtO_2; hydrochloride, $C_{18}H_{24}NO_3Cl$, m.p. 246-8°, IR(Nujol) ν_{OH} 3400 cm^{-1}.



XV XVI

***** A strong band due to an intramolecular OH--N was observed at 3255 cm^{-1} with no sign of free OH (0.07 mole and 0.035 mole conc. in CCl_4), while the 8α-hydroxy derivative showed a band only at 3634 cm^{-1}(free OH).

Demethylation of X was effected with diphenylphosphide ion[6] to give trans-morphine(XVI), $C_{17}H_{19}NO_3 \cdot CH_3OH$, m.p. 108-9°($CH_3OH$), $[\alpha]_D^{20}$ = +80 (c=0.13 $CHCl_3$); NMR 5β-H(5.7τ, doublet, $J_{6\beta}$=5), 6β-H(ca. 5.5τ), 7-H(4.1τ, heptet, J_8=9, J_6=6, J_{14}=3), 8-H(3.5τ, quartet, J_7=9, J_{14}=3), solvated CH_3OH(6.6τ, 3H singlet); picrate, $C_{23}H_{22}N_4O_{10}$, m.p. 217-220°(EtOH-acetone). Demethylation with pyridine hydrochloride gave a trace of XVI.

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