
(Experimental Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd.**)

Morphine, with its unique pentacyclic structure and pain-relieving activity forced many research workers to synthesize numerous derivatives in the purpose of obtaining physiologically more acceptable compounds, and efforts made by these researchers have shed a light on the structure-activity relationship of morphine derivatives. However, the cis-decalin type junction† of B and C-rings of the morphine structure remained common among those derivatives which have been evaluated for the physiological activity. It became now attractive for us to change this stereochemical feature to a trans-decalin type since morphine-like structures containing such a system seemed to be of interest in the light of Gates' observation‡ of a strong analgesic activity in certain isomorphinian (trans junction of B and C-rings) derivatives, and of the fact reported by May and coworkers that in the benzomorphan series, trans-5,9-dialkyl derivatives usually exceed the corresponding cis dialkyl derivatives in physiological activity.§ In a recent paper which described a ring-closure of the dibromo derivative of trans-dihydrothebainone to trans-1-bromodihydrocodeinone, Gates and Shepard appeared to express their interest in B/C trans-fused morphine derivatives.¶

Preceeding papers§§ presented by us described the stereospecific nature of the hydroboration of 9-methylethenobenzomorphan. This preliminary study strongly suggested the possibility of transferring this unique reaction to the 6-14 morphine structure. This proved to be the case and the present paper describes the synthesis of a hitherto unknown B/C trans-fused morphine structure, (—)-3-hydroxy-4,6α-oxy-N-methylisomorphinian§§ (II).

6-Desoxycodeine§§ (I), the most simple 6-14 morphine structure, was chosen as a starting material in the present study. Diborane was introduced into a tetrahydrofuran solution of I under a nitrogen atmosphere and the mixture was allowed to stand at room temperature for two hours as in the usual case. Subsequent oxidation of the mixture with alkaline hydrogen peroxide afforded a crystalline product, m.p. 156-157° in 67% yield. Infrared spectrum of this compound showed B-H bands at 2260 cm⁻¹ and 2360 cm⁻¹ indicating the nitrogen-co-ordinated character of the borane molecule. ASSIGNMENT of the structure (II) to this compound was confirmed when this was reconverted to the starting compound (I) by heating with acetic acid in

---

** 3073, Shimotoda, Toda-machi, Kita-adachi, Saitama (市田根市, 武田根町).
† Conventionally it may be called as trans-dihydrooxymorphine (cf. Gates' proposal of the prefix "trans" for B/C trans-fused morphine structures. Reference 4). (—) shows simply the sign of rotation.
dioxane. The formation of the amine-borane (II) was utterly justified with our earlier finding that 9-methylenebenzomorphan gave the similar borane adduct by reaction with diborane in a limited molecular ratio, and clearly indicates that the borane molecule first co-ordinate to the nitrogen as in the previous case. However, that the sterical environment of the α-side in this case is more retardatory to the second borane molecule approaching to the double bond than that in the benzomorphan was conspicuous by the fact that II was the only product of this reaction. The reaction time was therefore extended to the period of 115 hours at room temperature (27°C), after that the reaction mixture was oxidized by the usual method. Chromatographic separation of the product gave two hydroxy compounds, m.p. 142-144°C and m.p. 148-152°C, in 63 and 2.9% yield respectively. Our earlier paper on the hydroboration of
9-methylenebenzomorphan revealed the concomitant formation of a very small amount of a hydroxy compound, and isomeric nature of this with the major hydroboration product has been already established. The present result therefore seemed normal and the minor product was likely to be dihydropseudoocodeine (IV). An authentic sample of IV was prepared from codeine by the known method to prove the identity. The major product was hence assigned of the B/C trans structure, (−)-3-methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphan (trans-8α-hydroxy-dihydrodesoxycodine) (II). In addition to these two hydroxy derivatives there was isolated a very small amount of compound which was shown to be a desoxy compound by its infrared spectrum and analyzed for the molecular formula of (−)-3-methoxy-4,5α-oxy-N-methylisomorphan (trans-dihydrodesoxycodine) (VII). The structure of this compound was later confirmed by comparison with VII derived from III as shown in the chart. A possible protonolysis during the treatment of the oxidation

product, which may have been accompanied by a small amount of unchanged alkylborane, with acetic acid in boiling dioxane (see experimental part) was considered to be responsible for the formation of $\text{VII}$.

The $8\alpha$-hydroxy derivative ($\text{III}$) gave the acetate ($\text{Va}$) on treatment with acetic anhydride, and the benzoate ($\text{Vb}$) and the toluene-$p$-sulfonate ($\text{Vc}$) by reaction with benzoyl chloride and $p$-toluenesulfonyl chloride in the presence of pyridine respectively. The rotation difference between the benzoate ($\text{Vb}$) and the carbinol ($\text{III}$) ([M]$_{\text{benzoate}}$ = $-108.7\degree$) indicated that the absolute configuration at carbon-8 should assume $R$-configuration, and that the secondary hydroxy group accordingly the $\alpha$-configuration. On the other hand, the benzoate ($\text{VI}$) of $\text{N}$ was more dextrorotatory than the parent carbinol ([M]$_{\text{benzoate}}$ = $+206.9\degree$) indicating $S$-configuration (hence $\beta$-configuration of the secondary hydroxy group) in accordance with the established stereochemistry of $\text{N}$.$^{19}$ Cis-hydration of the olefin by the hydroboration has been well known$^{14}$ and the $\alpha$-configuration of the hydroxy group of $\text{III}$ might accordingly serve for the assignment of $\alpha$-configuration to 14-hydrogen, i.e. the B/C $trans$ structure to $\text{III}$. Treatment of the tosylate ($\text{Vc}$) with lithium aluminum hydride in boiling di-$n$-butyl ether gave the non-phenolic compound, ($-$)-3-methoxy-4,5$\alpha$-oxy-$N$-methylisomorphinan ($\text{VI}$) in 71% yield. $\text{VII}$ gave the 3-hydroxy derivative ($\text{VIII}$) by heating with 48% hydrobromic acid in 66% yield. $\text{VIII}$ was reconverted to the parent methoxy derivative in nearly quantitative yield by reaction with diazomethane.

Although our earlier studies on the hydroboration mechanism of 9-methylene-benzomorphan well justify the present assignment of the B/C $trans$ structure ($\text{III}$) to the hydroboration product, additional studies on $\text{III}$ were thought desirable for verification of the structure. The hydroxy compound ($\text{III}$), upon treatment with potassium tert-butoxide and benzophenone in benzene$^{20}$ gave a ketonic compound, m.p. 112–114°, in 6.9% yield. Starting carbinol ($\text{III}$) was recovered (70%) unchanged by this oxidation in accordance with the less-susceptibility of dihydrosedecodeine and dihydroisocodeine$^{22}$ to the oxidation.$^{19}$ The product was proved identical with dihydropsedecodeinone$^{23}$ ($\text{X}$) by melting point and infrared spectral comparison. Alkaline nature of the reaction medium may have caused the epimerization at carbon-14 of the intermediate B/C $trans$ 8-oxo compound ($\text{XI}$).

This oxidation of $\text{III}$ to the 8-oxo compound ($\text{X}$), despite the somewhat unexpected epimerization at carbon-14 during the reaction, clearly indicates the presence of 8-hydroxy group in $\text{III}$ which was shown already different from the known 8-hydroxy derivatives, $\text{V}$ and its isomer, dihydroalloedecodeine,$^{19}$ and accordingly that $\text{III}$ had the basic pentacyclic system of morphine only differing in the configuration of 14-hydrogen.

The tosylate ($\text{Vc}$) was treated with 2,4,6-collidine under an elimination condition.$^{17}$ Chromatography of the reaction product afforded two olefins in 43% and 50% yield.

---

*14 The hydroxy group is $trans$ to the $\alpha$-substituent, namely to the 9, 14 carbon-carbon bond in dihydropsedecodeine and to the carbon-oxygen bond at carbon 5 in dihydroisocodeine.
*15 The authors are grateful to Dr. L. J. Sargent, Laboratory of Chemistry, National Institutes of Health, U.S.A. for providing the sample.

One of the two proved to be identical with α-desoxycodine (I) and the other was assigned of the α' structure, (+)-3-methoxy-4,5α-oxy-α'-N-methylisomorphinan (trans-α'-desoxodydrocodeine) (Ⅲ) by inspection of the nuclear magnetic resonance spectrum (two olefinic protons at 3.7~4.2). Hydrogenation of Ⅲ over Adam's catalyst gave the dihydro derivative which was identical in every respect with Ⅳ obtained by lithium aluminium hydride treatment of Ⅳ. Similar hydrogenation of I afforded the B/C cis isomer of Ⅳ, dihydrodesoxycodineβ (Ⅲ).

![Fig. 1. Nuclear Magnetic Resonance Spectrum of Ⅳ (B/C trans) in Deuterochloroform](image1)

![Fig. 2. Nuclear Magnetic Resonance Spectrum of Ⅴ (B/C cis) in Deuterochloroform](image2)

### Table I.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical shift (τ)</th>
<th>1,2H</th>
<th>3-OMe</th>
<th>5β-H</th>
<th>7-H</th>
<th>8-H</th>
<th>9α-H</th>
<th>10β-H</th>
<th>N-CH₃</th>
<th>etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VII</td>
<td>3.37 6.16 5.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIII</td>
<td>3.32 6.16 5.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3.40 6.20 ca.5.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Va</td>
<td>3.38 6.17 5.64</td>
<td>4.6 ca.6.8</td>
<td>6.77 7.68</td>
<td>7.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XII</td>
<td>3.31 6.14 5.56 ca.4.2 ca.3.7</td>
<td>6.55 6.70 7.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All spectra were determined at 60 Mc. in CDCl₃ solutions (10~15%) containing tetramethylsilane as an internal standard using a JNM-C-60 spectrometer (Japan Electric Optical Laboratory Co. Ltd.).
This sequence of reactions outlined above unequivocally leads to the conclusion that Vc had the pentacyclic structure only differing from the morphine structure in configuration of 14-hydrogen, and the B/C trans character of the hydroboration product (Ill) and its desoxy derivative (IV) was thus ascertained. Finally the isomeric nature of VI to the known XIll was examined by the nuclear magnetic resonance spectroscopy.

As shown in Fig. 1 the spectrum of VI had a close similarity to that of XIll in the field lower than the r value 8. However, a major divergence was observed in the region of 8~9 r where signals of the saturated methylene appear. A mountainous character of signals centering at 8.3 r constitutes a sharp contrast to the broad wave of the signal of XIll. This spectral feature of VI appeared characteristic of all other B/C trans series compounds and geometry of the C-ring relative to the benzene ring was thought to be the cause. In the cis compound, protons on the C-ring are located in various geometrical positions relative to the benzene ring, probably thus causing the wide-spread manner of the chemical shifts. Whereas in the trans compound, the protons are located in directions which make approximately a coplane with the benzene ring, resulting in the concentration of the chemical shifts. This geometrical effect of the C-ring was also witnessed in the spectrum of the A~48 derivative (VII). VII showed signals attributable to the 7,8-protons at a lower field (0.6~0.7 p.p.m.) compared to the B/C cis isomer, desoxycodeine–E,18 while lacking the mountainous signals characteristic of the trans compound. Comparison of the nuclear magnetic resonance spectra of the trans and cis compounds revealed also a difference in the chemical shift of 10β-proton. In the trans series the signal assignable to 10β-proton always shifted to a lower field (about 0.15 p.p.m.) than that of the cis isomer. Yamaguchi, et al., in their study of the nuclear magnetic resonance spectra of morphine derivatives reasoned a magnetic anisotropy effect of the tertiary amine nitrogen for the downward shift of 10β-proton.19 The difference of the chemical shift of 10β-proton between the morphine and the trans type morphine compounds might have been caused by unknown factors which may be ascribed to the geometrical difference of the C-ring.

This unique reaction of the A~48 morphine structure now confirmed to produce the B/C trans morphine system provides a new way to hitherto yet unpublished derivatives. Synthesis of B/C trans morphine structures bearing various substituents on the C-ring is now going on in this laboratory applying this hydroboration reaction to properly substituted A~48 morphine structures. Results will be published in a later communication.

Experimental

A'-Desoxycodeine–borane (II)—BF3-ether (4.86 g.) was added to a boiling mixture of NaBH4 (0.98 g.) and tetrahydrofuran (THF) (43 ml.) over a period of 1.5 hr. and the generated B3H6 was introduced into a solution of I (1.07 g.) in THF (35 ml.) at 26~27° under N2 stream. After completion of the B3H6 introduction the mixture was kept at 26~27° for 2 hr., then decomposed with H2O (1 ml.) and added with 3N NaOH (4.27 ml.) and 33% H2O2 (1.45 ml.) gradually. The mixture was stirred at room temperature for 20 hr., diluted with H2O and extracted with ether. Evaporation of the dried extracts and recrystallization of the residue from benzene–petr. ether gave II (650 mg.), colorless needles, m.p. 156~156.5° (decomp.). [α]25° +14.1°(c=1.1, benzene). IR cm⁻¹: ν3–H 2260, 2360. Anal. Calcd. for C16H20ONB : N, 4.71. Found : N, 4.87.

The mother liquor was partitioned with ether and 10% HCl, and the ethereal layer was dried and evaporated to give an additional amount of II (100 mg.; total yield, 67%), m.p. 152~155°. The acid layer

*8 Melting points are uncorrected.
was basified with NH₄OH, extracted with ether, dried and evaporated. The residue was converted to the oxalate and recrystallized from EtOH to give I-oxalate (350 mg, 24.4%), mp. 211-213°C (decomp.).

A mixture of II (170 mg), AcOH (2.5 ml) and dioxane (5 ml) was refluxed for 40 min., concentrated under reduced pressure, basified with NH₄OH and extracted with ether. The extracts were dried and evaporated, the residue was converted to the oxalate and recrystallized from EtOH to give I-oxalate (200 mg, 93.5%), mp. 214-216°C (decomp.). This was identified with an authentic sample of I-oxalate by IR spectral comparison.

(+)3-Methoxy-8a-hydroxy-4,5a-oxo-N-methylisomorphinan (trans-8a-Hydroxydihydrodesoxycodeine) (III)—B₂H₆ generated by the reaction of BF₃·ether (46.8 g) and NaBH₄ (9.4 g) in THF (400 ml) in a similar manner to that described before was introduced into a solution of I (9.65 g) in THF (200 ml) at 25-28°C under N₂ stream. The flask was flushed with N₂ stopped, and allowed to stand at 27°C for 115 hr. The mixture was decomposed with H₂O (5 ml) under cooling, added with 3N NaOH (45.7 ml), 55% H₂O₂ (21 ml) and H₂O (80 ml) at 20-25°C, stirred at room temperature for 40 hr., diluted with H₂O, extracted with ether, dried and evaporated. The residue was refluxed with AcOH (100 ml) and dioxane (200 ml) for 40 min., concentrated under reduced pressure, basified with NH₄OH and extracted with CHCl₃. Evaporation of the dried extract gave a syrup which was converted to the hydrochloride and recrystallized from aceto-CHCl₃ to give III·HCl (monohydrate) (6.8 g), colorless needles, m.p. 252-259°C (decomp.), [α]D +56.7° (c=0.6, EtOH). IR cm⁻¹: νOH 3300, 3450. Anal. Calcd. for C₁₄H₁₄N₂O₂·HCl·H₂O: C, 60.75; H, 7.36; N, 3.94. Found: C, 60.82; H, 7.05; N, 3.82.

Free base recovered from the hydrochloride was recrystallized from benzene-petr. ether as colorless rods, m.p. 142-144°C, [α]D +108.3° (c=0.46, benzene). IR cm⁻¹: νOH 3150. Anal. Calcd. for C₁₄H₁₁ON: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.69; H, 7.59; N, 4.36.

Mother liquor of the recrystallization of the hydrochloride was concentrated, the residue was dissolved in H₂O, basified with NH₄OH, extracted with CHCl₃, dried and evaporated. The residue was dissolved in benzene-petr. ether (9:1) and chromatographed over Al₂O₃. The column was eluted with benzene-petr. ether (95:5), the eluate was evaporated and the residue was recrystallized from hexane to give (•–)3-methoxy-4,5a-oxo-N-methylisomorphinan (trans-dihydrodesoxycodeine) (IV) (70 mg, 0.7%), colorless prisms, m.p. 96-98°C, [α]D +57.0° (c=0.33, hexane). Anal. Calcd. for C₁₄H₁₄O₂N: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.89; H, 8.00; N, 4.71.

Next eluate with ether-MeOH (99:1) was converted to the hydrochloride giving an additional amount of III·HCl (860 mg, total yield, 63%), m.p. 250-253°C (decomp.). Further elution with ether-MeOH (99:4) and recrystallization from benzene-petr. ether gave dihydropseudocodeine (V) (300 mg, 2.9%), m.p. 148-151°C, [α]D +40.1° (c=0.41, benzene). This was identified with the authentic sample(30) by the mixed melting point and IR spectral comparison. Finally the column was eluted with benzene-ether (9:1) and the eluate was converted to the oxalate and recrystallized from EtOH to give I-oxalate (350 mg, 2.8%), m.p. 209-213°C (decomp.).

(+)-3-Methoxy-8a-hydroxy-4,5a-oxo-N-methylisomorphinan 8-Acetate (trans-8a-Hydroxydihydrodesoxycodeine 8-Acetate) (Va) Hydrochloride—A mixture of II (120 mg), Ac₂O (2.5 ml) and pyridine (2.5 ml) was heated on a steam bath for 2.5 hr. The mixture was concentrated under reduced pressure, basified with NH₄OH, extracted with ether, dried and evaporated. The residue was converted to the hydrochloride and recrystallized from aceto-CHCl₃ ether to give Va·HCl (110 mg, 73%), colorless needles, m.p. 244-245°C (decomp.). [α]D +26.3° (c=0.86, EtOH). IR cm⁻¹: νC=O 1740. Anal. Calcd. for C₁₄H₁₂O₃N·HCl: C, 63.23; H, 6.90; N, 3.69. Found: C, 62.83; H, 7.01; N, 3.67.

(–)-3-Methoxy-8a-hydroxy-4,5a-oxo-N-methylisomorphinan 8-Benzate (trans-8a-Hydroxydihydrodesoxycodeine 8-Benzate) (Vb)—BzCl (120 mg) was added to III (210 mg) in pyridine (5 ml) under cooling, the mixture was allowed to stand at room temperature overnight, concentrated under reduced pressure, basified with NH₄OH, extracted with ether, dried and evaporated. The residue in benzene was chromatographed over Al₂O₃ and eluted with benzene-ether (1:1). Evaporation of the solvent and recrystallization of the residue from ether-hexane gave Vb (190 mg, 67%), colorless needles, m.p. 141-149°C, [α]D +107.5° (c=0.41, benzene). IR cm⁻¹: νC=O 1715. Anal. Calcd. for C₁₄H₁₄O₃N·Bz: C, 74.34; H, 6.48; N, 3.83.

Dihydropseudocodeine 8-Benzate (Vd)—V (100 mg) was treated with BzCl (150 mg) in pyridine (4 ml) in the same manner as described above. The crude product was chromatographed over Al₂O₃ and eluted with benzene-ether (1:1) to give Vd (100 mg, 74%), colorless oil (homogeneous as shown by TLC). [α]D +21.2° (c=0.44, benzene). IR cm⁻¹: νC=O 1715. The picrate of the oil was recrystallized from EtOH-acetone in yellow needles, m.p. 153-156°C. Anal. Calcd. for C₁₆H₁₁O₃N·C₂H₅O₉: C, 58.87; H, 4.77; N, 8.83. Found: C, 58.57; H, 4.46; N, 8.42. Methiodide: Colorless plates (from aqueous EtOH), m.p. 217-219°C (decomp.). Anal. Calcd. for C₁₆H₁₂O₃N·CH₃I: C, 57.04; H, 5.52; N, 2.56. Found: C, 57.41; H, 5.33; N, 2.45.

(–)-3-Methoxy-8a-hydroxy-4,5a-oxo-N-methylisomorphinan 8-p-Toluene sulfonate (trans-8a-Hydroxydihydrodesoxycodeine 8-p-Toluene sulfonate) (Ve)—TsCl (780 mg) was added to III (1.01 g) in pyridine (6 ml) under cooling, the mixture was kept in a refrigerator for 3 days, poured into ice water, basified with NH₄OH and filtered. Recrystallization from hexane gave Ve (1.02 g, 70%), colorless prisms, m.p. 70°C.
126–128°. [α]D20 = −34.3° (c=0.35, benzene). Anal. Calcd. for C25H34O5NS: C, 65.91; H, 6.42; N, 3.08; S, 7.04. Found: C, 66.28; H, 6.39; N, 2.95; S, 7.03. II (220 mg, 22%) was recovered from the aqueous phase through extraction with CHCl3. m.p. 139–141°.

(−)-3-Methoxy-4,5a-oxo-N-methylisomorphinan (trans-Dihydroxyscodeine) (VII) — LiAlH4 (70 mg) was added to a stirred suspension of Vc (550 mg) in n-dibutyl ether (30 ml) and THF (1.5 ml) at 100° under N2 atmosphere, the mixture was stirred at the same temperature for 3 hr., cooled, added with H2O (0.4 ml) and filtered from an inorganic material. The filtrate was extracted with 5% HCl, basified with NH4OH, extracted with ether, dried and evaporated. The residue was converted to the hydrochloride and recrystallized from acetone to give VII·HCl (280 mg, 71%), colorless rods, m.p. 234–235° (decomp.). [α]D20 = −47.7° (c=0.51, EtOH). Anal. Calcd. for C23H24O2N·HCl: C, 67.17; H, 7.52; N, 4.55. Found: C, 67.77; H, 7.44; N, 4.81.

Free base recovered from the hydrochloride was recrystallized from hexane, m.p. 96–98°. This was identical with VII previously obtained in the hydroboration of I in every respect.

(−)-3,8a-Dihydroxy-4,5a-oxo-N-methylisomorphinan (trans-8a-Hydroxydihydroxyscodeine) (IX) Hydrobromide — VII·HCl (560 mg) in 48% HBr (3 ml) was refluxed for 30 min., concentrated to dryness under reduced pressure, the residue was washed several times with ether, digested with acetone and filtered. Recrystallization from aqueous EtOH afforded K·HBr (350 mg, 62%), colorless needles, m.p. 268–271° (decomp.). [α]D20 = −59.1° (c=0.43, MeOH), IR cm⁻¹: νOH 3350. Anal. Calcd. for C23H25O2N·HBr: C, 55.44; H, 6.02; N, 3.80. Found: C, 55.34; H, 5.97; N, 3.81.

A solution of K (24 mg) in MeOH (2 ml) was treated with a large excess of CH3N2-ether, the mixture was allowed to stand at room temperature for 3 days, and evaporated. Recrystallization of the residue from ether gave the 3-methoxy derivative, m.p. 140–142°, which was identical with III in every respect.

(−)-3-Hydroxy-4,5a-oxo-N-methylisomorphinan (trans-Dihydroxyscodeine) (VIII) Hydrobromide — A mixture of VII (500 mg), 48% HBr (3 ml) and AcOH (3 ml) was refluxed for 30 min. The solution was evaporated to dryness under reduced pressure, was washed with ether, digested with acetone and filtered. Recrystallization from EtOH gave VII·HBr (405 mg, 66%), colorless needles, m.p. 282–284° (decomp.). [α]D20 = −46.9° (c=0.53, MeOH), IR cm⁻¹: νOH 3200. Anal. Calcd. for C23H24O2N·HBr: C, 57.96; H, 6.30; N, 3.98. Found: C, 57.72; H, 6.52; N, 4.01.

VII (23 mg) in MeOH (3 ml) was methylated with an excess of CH3N2 in the same way as described previously. 3-Methoxy derivative, m.p. 93–95°, which was identical with VII in every respect was obtained.

Oppenauer Oxidation of III — A mixture of tert-ButOK, freshly prepared from K (0.4 g),[13] II (1 g), benzophenone (6.2 g) and benzene (20 ml) was refluxed for 2.5 hr. under N2 atmosphere, and cooled. The mixture was extracted with 10% HCl, the acid layer was basified with NH4OH, extracted with CHCl3, dried and evaporated to give an oil, which was dissolved in benzene and chromatographed over Al2O3. The eluate with ether was evaporated and the residue was recrystallized from hexane to give dihydroseudocodeinone (X) (70 mg, 6.92%), m.p. 112–114°. Admixture with the authentic sample* did not depress the melting point. IR spectra of the two were superimposable. The starting material III (700 mg, 70%), m.p. 140–141°, was recovered from the eluate with ether–MeOH (98:2).

Elimination Reaction of Vc with 2,4,6-Collidine — A mixture of Vc (1.3 g) and 2,4,6-collidine (7 ml) was refluxed for 1 hr. under N2 atmosphere, diluted with benzene, washed with 5% Na2CO3, then water, and dried. The solution was distilled under reduced pressure in a water bath, and finally at 3 mm.Hg at a temperature below 100° to remove collidine completely. The oily residue was dissolved in benzene and chromatographed over Al2O3. Elution with benzene–petr. ether (9:1) and recrystallization from hexane gave (+)-3-methoxy-4,5a-oxo-5'-N-methylisomorphinan (trans-5'-dihydroxyscodeine) (XI) (400 mg, 50%), colorless rods, m.p. 93.5–95.5°. [α]D20 = +31° (c=0.31, EtOH). Anal. Calcd. for C23H23O2N·2H2O: C, 75.29; H, 7.47; N, 4.94. Found: C, 75.34; H, 7.11; N, 5.28. Further elution with benzene–ether (111) gave a colorless oil (homogeneous as shown by TLC) (360 mg, 43%), which was converted to the oxalate and recrystallized from EtOH to give 1-oxalate (425 mg), m.p. 215–216° (decomp.). Identity of the oxalate and 5'-desoxyscodeine oxalate was proved by IR spectral comparison. The hydrochloride, m.p. 233–235° (decomp.) (from acetone), was also identical with 5'-desoxyscodeine hydrochloride.

Dihydroxyscodeine (XIII) — I (280 mg) in AcOH (7 ml) was hydrogenated over PtO2 (35 mg). One molar equivalent of hydrogen was absorbed in 12 hr. The solution was filtered and evaporated, the residue was basified with NH4OH, extracted with ether, dried and evaporated. The residue was recrystallized from hexane to give XIII (230 mg, 89%), m.p. 105–107° (Lit.,[6] m.p. 106–107°).

Hydrogenation of XII — XII (85 mg) in AcOH (10 ml) was hydrogenated with PtO2 (20 mg). One molar equivalent of hydrogen was absorbed in 15 min. The filtered solution was worked up as usual to give VII (85 mg, quantitative), m.p. 95–97° (from hexane). This was identified with VII previously obtained by LiAlH4 treatment of Vc by the mixed melting point and IR spectral comparison.

The authors express their gratitude to Dr. N. Sugimoto, Director of the Osaka Research Laboratory and Dr. J. Iwao, Director of this Laboratory, for their interest and encouragement. The authors also
thank Dr. K. Koteru for measurement of NMR spectra and very helpful cooperation in interpreting the spectra, and Mrs. F. Hisamichi and Mr. T. Kono for microanalyses.

Summary

Hydroboration of $\Delta^5$-desoxycodeine (I) gave a B/C trans-fused morphine derivative, (−)-3-methoxy-8α-hydroxy-4,5α-oxo-N-methylisomorphinan (III) along with two minor products, dihydropseudocodeine (IV) and VII. III, by reaction with $p$-toluenesulfonylchloride gave the 8-$p$-toluenesulfonate (Vc), which was treated with lithium aluminum hydride to give (−)-3-methoxy-4,5α-oxo-N-methylisomorphinan (VII). Elimination reaction of Vc with 2,4,6-collidine afforded two double-bond isomers, I and 3-methoxy-4,5α-oxo-$\Delta^5$-N-methylisomorphinan (XII). I gave on hydrogenation the known dihydrodesoxycodeine (XIII). Hydrogenation of XII gave the B/C trans isomer, VII. Some additional studies were made on the hydroboration product (III) and its derivatives to support the B/C trans pentacyclic structure.

(Received June 4, 1965)

183. Itiro Yosioka and Takeatsu Kimura: Studies on the Constituents of Atractylodes. X. Correlation of Hinesol and $\beta$-Vetivone.

(Faculty of Pharmaceutical Sciences, Osaka University)

In the preceding communication, the formula (Ia) was proposed as the structure of hinesol (I), a sesquiterpene alcohol isolated from Atractylodes lancea De Candolle. Subsequently, Šorm, et al. revised the formula to Ib, and ascertained the absolute configuration of a methyl group on C(20) with an oxidative degradation. On the other hand, the structure of $\beta$-vetivone (II) was established by St. Pfau and Plattner, and the relative configurations of Ib and $\alpha$-vetivone (III) were proposed by Naves and Perrotet, as expressed by the formula (IIa) and (IIia). The experiments described below made the interrelation between I and II clear, and confirmed the structure of I. Furthermore, their absolute configurations were partially determined.

On oxidation of hinesol (I) with selenium dioxide in dioxane, a slightly yellow oil was obtained, which gave positive 2,4-dinitrophenylhydrazine-sulfuric acid test, and exhibited absorption maxima at 233.5 m$\mu$ (log ε 3.99) in ultraviolet, and 3500 (OH), 2730, 1685, 1626 (C-C-CHO), and 1418 cm$^{-1}$ (–CH$_3$–C=) in infrared spectra. These data suggest that the oily substance contains mainly an $\alpha$, $\beta$-unsaturated aldehyde as expressed by the formula (IV). So the formula (Ib) having a methyl group on the ethylenic linkage is preferred for I rather than Ia.

---

* Part X. This Bulletin, 12, 755 (1964).
5) Y.R. Naves, E. Perrotet: Ibid., 24, 3 (1941).