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182. Hiroshi Kugita and Mikio Takeda : Synthesis of a B/C *trans*-fused Morphine Structure.*1

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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[1] 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[2] of a strong analgesic activity in certain isomorphinan (*trans* juncture 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.[3] 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.[4]

Preceeding papers[5~7] presented by us described the stereospecific nature of the hydroboration of 9-methylenebenzomorphan. This preliminary study strongly suggested the possibility of transferring this unique reaction to the Δ^{8-14} 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-4,5α-oxy-N-methylisomorphinan*3 (Ⅷ).

Δ^{8}-Desoxycodeine[8] (Ⅰ), the most simple Δ^{8-14} 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.[5] 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.[9] 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

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*3 Conventionally it may be called as *trans*-dihydrodeoxymorphine (cf. Gates' proposal of the prefix "*trans*" for B/C *trans*-fused morphine structures. Reference 4). (−) shows simply the sign of rotation.

1) H.L. Holmes, G. Stork : "The Alkaloids," Vol. Ⅱ, 179 (1952), Academic Press Inc., New York.
2) M. Gates, W.G. Webb : J. Am. Chem. Soc., **80**, 1186 (1958).
3) C.F. Chignell, J.H. Ager, E.L. May : J. Med. Chem., 8, 235 (1965), and preceeding Papers.
4) M. Gates, M.S. Shepard : J. Am. Chem. Soc., **84**, 4125 (1962).
5) H. Kugita, M. Takeda : This Bulletin, **12**, 1163 (1964).
6) *Idem* : *Ibid.*, **12**, 1166 (1964).
7) *Idem* : *Ibid.*, **12**, 1172 (1964).
8) H. Rapoport, R.M. Bonner : J. Am. Chem. Soc., **73**, 2872 (1951).
9) B. Rice, R.J. Galiano, W.J. Lehmann : J. Phys. Chem., **61**, 1222 (1957); H.C. Brown : "Hydroboration," 179 (1962), W.A. Benjamin, Inc., New York.

dioxane.[6] 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 pervious 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°), after that the reaction mixture was oxidized by the usual method. Chromatographic separation of the product gave two hydroxy compounds, m.p. 142~144° and m.p. 148~152°, in 63 and 2.9% yield respectively. Our earlier paper on the hydroboration of

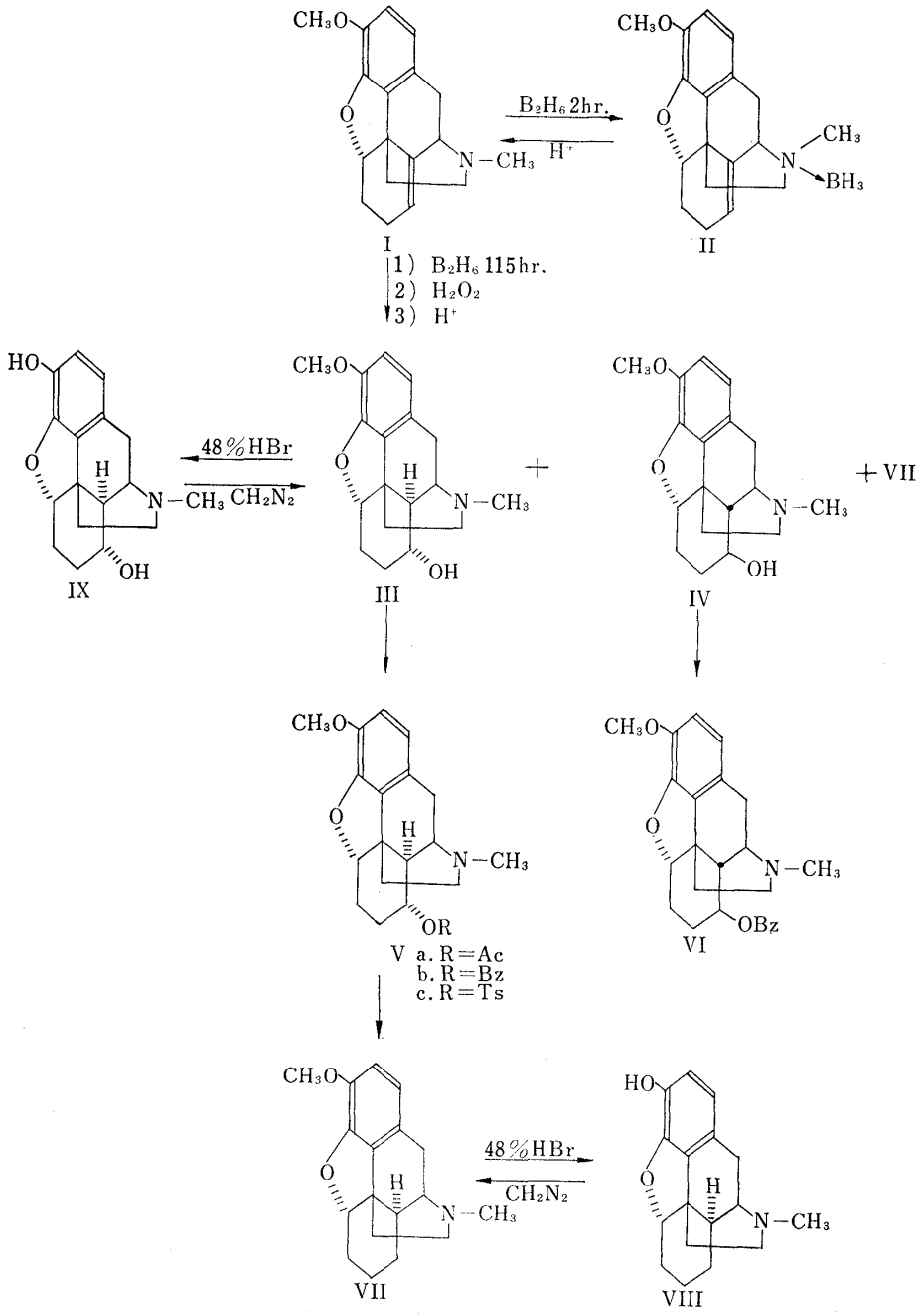


Chart 1.

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.[7] The present result therefore seemed normal and the minor product was likely to be dihydropseudocodeine (Ⅳ). An authentic sample of Ⅳ was prepared from codeine by the known method[10] to prove the identity. The major product was hence assigned of the B/C *trans* structure, (−)-3-methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan (*trans*-8α-hydroxy-dihydrodesoxycodeine) (Ⅲ). In addition to these two hydroxy derivatives there was isolated a very small

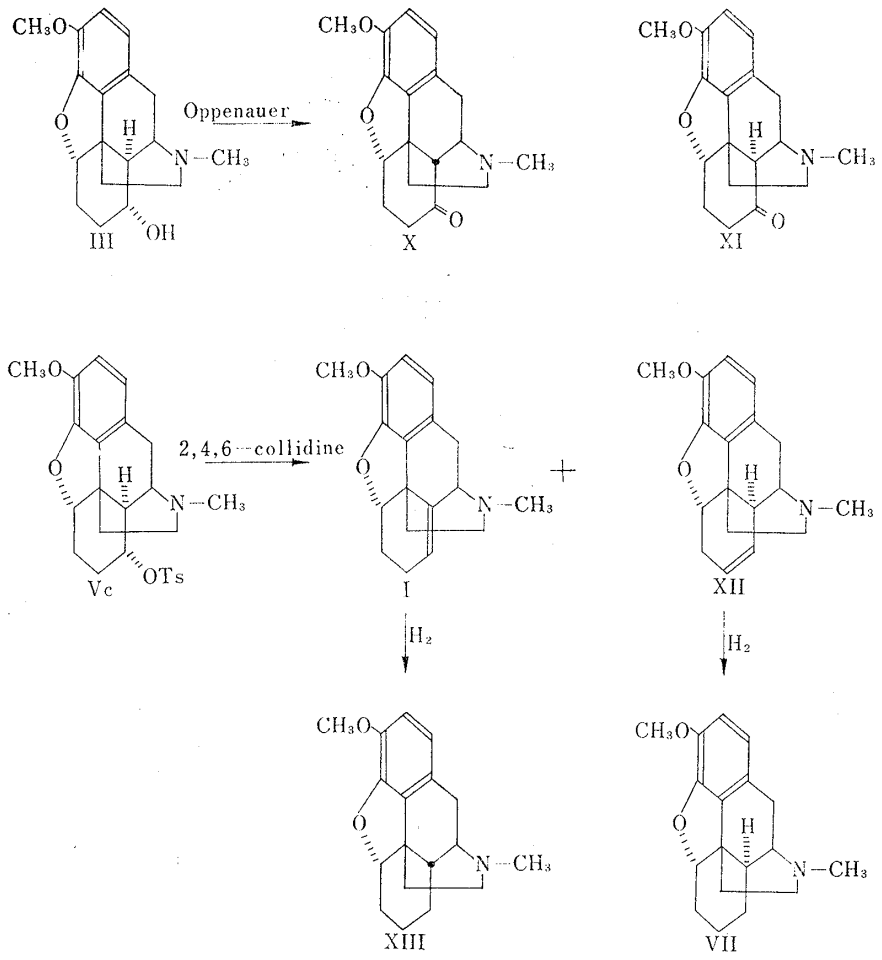


Chart 2.

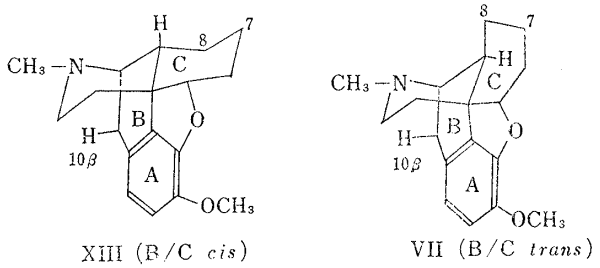


Chart 3.

amount of compound which was shown to be a desoxy compound by its infrared spectrum and analized for the molecular formula of (−)-3-methoxy-4,5α-oxy-N-methylisomorphinan (*trans*-dihydrodesoxycodeine) (Ⅶ). The structure of this compound was later confirmed by comparison with Ⅶ derived from Ⅲ as shown in the chart. A possible protonolysis[11] during the treatment of the oxidation

10) R.E. Lutz, L.F. Small : J. Am. Chem. Soc., **54**, 4715 (1932).
11) H.C. Brown : "Hydroboration," 62 (1962), W.A. Benjamin, Inc., New York.

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 Ⅶ.

The 8α-hydroxy derivative (Ⅲ) gave the acetate (Va) on treatment with acetic anhydride, and the benzoate (Vb) and the toluene-*p*-sulfonate (Vc) by reaction with benzoyl chloride and *p*-toluenesulfonyl chloride in the presence of pyridine respectively. The rotation difference between the benzoate (Vb) and the carbinol (Ⅲ) ([M]benzoate-[M]carbinol= −108.7) indicated that the absolute configuration at carbon-8 should assume *R*-configuration,[12] and that the secondary hydroxy group accordingly the α-configuration. On the other hand, the benzoate (Ⅵ) of Ⅳ was more dextrorotatory than the parent carbinol ([M]benzoate-[M]carbinol= +206.9) indicating *S*-configuration (hence β-configuration of the secondary hydroxy group) in accordance with the established stereochemistry of Ⅳ.[13] *Cis*-hydration of the olefin by the hydroboration has been well known[14] and the α-configuration of the hydroxy group of Ⅲ might accordingly serve for the assignment of α-configuration to 14-hydrogen, *i.e.* the B/C *trans* structure to Ⅲ. Treatment of the tosylate (Vc) with lithium aluminum hydride in boiling di-*n*-butyl ether gave the non-phenolic compound, (−)-3-methoxy-4,5α-oxy-N-methylisomorphinan (Ⅶ) in 71% yield. Ⅶ gave the 3-hydroxy derivative (Ⅷ) by heating with 48% hydrobromic acid in 66% yield. 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-methylenebenzomorphan well justify the present assignment of the B/C *trans* structure (Ⅲ) to the hydroboration product, additional studies on Ⅲ were thought desirable for verification of the structure. The hydroxy compound (Ⅲ), upon treatment with potassium *tert*-butoxide and benzophenone in benzene[15] gave a ketonic compound, m.p. 112~114°, in 6.9% yield. Starting carbinol (Ⅲ) was recovered (70%) unchanged by this oxidation in accordance with the less-susceptibility of dihydropseudocodeine and dihydroisocodeine*[4] to the oxidation.[15] The product was proved identical with dihydropseudocodeinone*[5] (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 (Ⅺ).

This oxidation of Ⅲ to the 8-oxo compound (X), despite the somewhat unexpected epimerization at carbon-14 during the reaction, clearly indicates the presence of 8-hydroxy group in Ⅲ which was shown already different from the known 8-hydroxy derivatives, Ⅳ and its isomer, dihydroallopseudocodeine,[16] and accordingly that Ⅲ had the basic pentacyclic system of morphine only differing in the configuration of 14-hydrogen.

The tosylate (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.

*4 The hydroxy group is *trans* to the α-substituent, namely to the 9, 14 carbon-carbon bond in dihydropseudocodeine and to the carbon-oxygen bond at carbon 5 in dihydroisocodeine.

*5 The authors are grateful to Dr. L. J. Sargent, Laboratory of Chemistry, National Institutes of Health, U. S. A. for providing the sample.

12) J. H. Brewster : Tetrahedron, **13**, 106 (1961).
13) H. L. Holmes, G. Stork : "The Alkaloids," Vol. Ⅱ, 178 (1952), Academic Press Inc., New York : K. W. Bentley, H. M. E. Cardwell : J. Chem. Soc., **1955**, 3252; D. Elad, D. Ginsburg : J. Am. Chem. Soc., **78**, 3691 (1956).
14) H. C. Brown : "Hydroboration," 123 (1962), W. A. Benjamin, Inc., New York.
15) H. Rapoport, R. Naumann, E. R. Bissell, R. M. Bonner : J. Org. Chem., **15**, 1103 (1950).
16) R. E. Lutz, L. F. Small : J. Am. Chem. Soc., **56**, 2466 (1934).
17) M. Gates, G. Tschudi : *Ibid.*, **78**, 1380 (1956).

One of the two proved to be identical with Δ^8-desoxycodeine (I) and the other was assigned of the Δ^7 structure, (+)-3-methoxy-4,5α-oxy-Δ^7-N-methylisomorphinan (*trans*-Δ^7-desoxydihydrocodeine) (XII) by inspection of the nuclear magnetic resonance spectrum (two olefinic protons at 3.7~4.2 τ). Hydrogenation of XII over Adam's catalyst gave the dihydro derivative which was identical in every respect with VII obtained by lithium aluminium hydride treatment of Vc. Similar hydrogenation of I afforded the B/C *cis* isomer of VII, dihydrodesoxycodeine[8] (XIII).

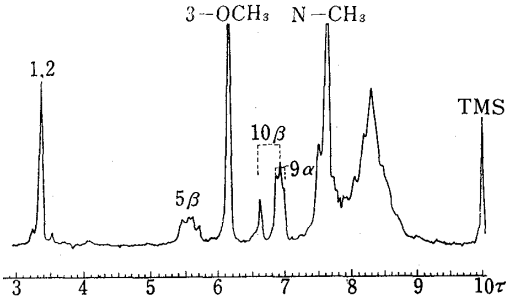


Fig. 1. Nuclear Magnetic Resonance Spectrum of VII (B/C *trans*) in Deuterochloroform

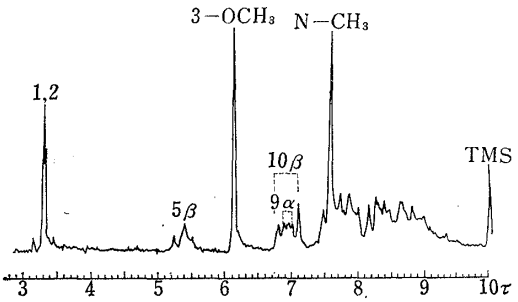
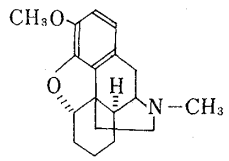
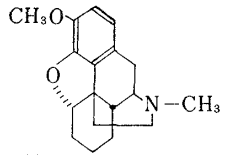
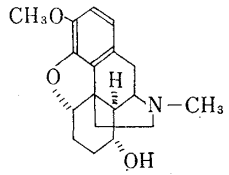
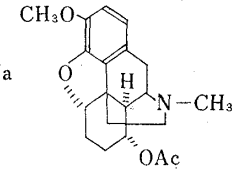
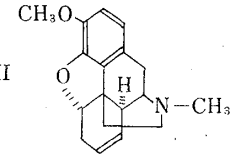


Fig. 2. Nuclear Magnetic Resonance Spectrum of XIII (B/C *cis*) in Deuterochloroform

TABLE I.

Compound	Chemical shift (τ) 1,2H	3-OMe	5β-H	7-H	8-H	9α-H	10β-H	N-CH3	etc.
VII 	3.37	6.16	5.58			ca. 6.95	6.78 $J_{10\alpha}=18$	7.67	
XIII 	3.32	6.16	5.41			6.96	6.95 $J_{10\alpha}=18$	7.61	
III 	3.40	6.20	ca. 5.7		ca. 5.7	ca. 6.6	6.75 $J_{10\alpha}=18$	7.67	
Va 	3.38	6.17	5.64		4.6	ca. 6.8	6.77 $J_{10\alpha}=18$	7.68	8α-OAc 7.97
XII 	3.31	6.14	5.56	ca. 4.2	ca. 3.7	6.55	6.70 $J_{10\alpha}=18$	7.57	

All spectra were determined at 60 Mc. in $CDCl_3$ 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 (Ⅲ) and its desoxy derivative (Ⅶ) was thus ascertained. Finally the isomeric nature of Ⅶ to the known XIII was examined by the nuclear magnetic resonance spectroscopy.

As shown in Fig. 1 the spectrum of Ⅶ had a close similarity to that of XIII in the field lower than the τ value 8. However, a major divergence was observed in the region of 8~9 τ where signals of the saturated methylene appear. A mountainous character of signals centering at 8.3 τ constitutes a sharp contrast to the broad wave of the signal of XIII. This spectral feature of Ⅶ 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 Δ^{7-8} derivative (XII). XII 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 Δ^{8-14} 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 Δ^{8-14} morphine structures. Results will be published in a later communication.

Experimental*6

Δ^{8}-Desoxycodeine-borane (II)——BF_3·ether (4.86 g.) was added to a boiling mixture of $NaBH_4$ (0.98 g.) and tetrahydrofuran (THF) (43 ml.) over a period of 1.5 hr. and the generated B_2H_6 was introduced into a solution of I (1.07 g.) in THF (35 ml.) at 26~27° under N_2 stream. After completion of the B_2H_6 introduction the mixture was kept at 26~27° for 2 hr., then decomposed with H_2O (1 ml.) and added with 3*N* NaOH (4.27 ml.) and 33% H_2O_2 (1.45 ml.) gradually. The mixture was stirred at room temperature for 20 hr., diluted with H_2O 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.). $[\alpha]_D^{28}$ +14.1°(c=1.1, benzene). IR cm^{-1} : ν_{B-H} 2260, 2360. *Anal.* Calcd. for $C_{18}H_{24}ONB$: 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

*6 Melting points are uncorrected.

18) S. Okuda, S. Yamaguchi, Y. Kawazoe, K. Tsuda : This Bulletin, **12**, 104 (1964).

19) S. Yamaguchi, S. Okuda, N. Nakagawa : This Bulletin, **11**, 1465 (1963).

was basified with NH_4OH, 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%), m.p. 211~213°(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 NH_4OH 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%), m.p. 214~216°(decomp.). This was identified with an authentic sample of I-oxalate by IR spectral comparison.

(−)-3-Methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan(*trans*-8α-Hydroxydihydrodesoxycodeine) (III)——B_2H_6 generated by the reaction of BF_3-ether (46.8 g.) and $NaBH_4$ (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° under N_2 stream. The flask was flushed with N_2, stoppered, and allowed to stand at 27° for 115 hr. The mixture was decomposed with H_2O (8 ml.) under cooling, added with 3*N* NaOH (43.7 ml.), 33% H_2O_2 (21 ml.) and H_2O (80 ml.) at 20~25°, stirred at room temperature for 40 hr., diluted with H_2O, 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 NH_4OH and extracted with $CHCl_3$. Evaporation of the dried extract gave a syrup which was converted to the hydrochloride and recrystallized from acetone-EtOH to give III·HCl (monohydrate) (6.8 g.), colorless needles, m.p. 252~255°(decomp.). $[\alpha]_D^{26}$ −56.7°(c=0.6, EtOH). IR cm^{-1} : ν_{OH} 3300, 3450. *Anal.* Calcd. for $C_{18}H_{23}O_3N \cdot HCl \cdot H_2O$: 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°. $[\alpha]_D^{26}$ −108.3°(c=0.46, benzene). IR cm^{-1} : ν_{OH} 3150. *Anal.* Calcd. for $C_{18}H_{23}ON$: 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 H_2O, basified with NH_4OH, extracted with $CHCl_3$, dried and evaporated. The residue was dissolved in benzene-petr. ether (9:1) and chromatographed over Al_2O_3. 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-4,5α-oxy-N-methylisomonphinan (*trans*-dihydrodesoxycodeine) (VII) (70 mg., 0.7%), colorless prisms, m.p. 96~98°. $[\alpha]_D^{26}$ −57.0°(c=0.33, hexane). *Anal.* Calcd. for $C_{18}H_{23}O_2N$: 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°(decomp.). Further elution with ether —MeOH (96:4) and recrystallization from benzene-petr. ether gave dihydropseudocodeine (IV) (300 mg., 2.9%). m.p. 148~151°. $[\alpha]_D^{26}$ −40.1°(c=0.41, benzene). This was identified with the authentic sample[10] 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°(decomp.).

(+)-3-Methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan 8-Acetate (*trans*-8α-Hydroxydihydrodesoxycodeine 8-Acetate) (Va) Hydrochloride——A mixture of III (120 mg.), Ac_2O (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 NH_4OH, extracted with ether, dried and evaporated. The residue was converted to the hydrochloride and recrystallized from acetone-EtOH-ether to give Va·HCl (110 mg., 73%), colorless needles, m.p. 244~246°(decomp.). $[\alpha]_D^{26}$ +26.5°(c=0.86, EtOH). IR cm^{-1} : $\nu_{C=O}$ 1740. *Anal.* Calcd. for $C_{20}H_{25}O_4N \cdot HCl$: C, 63.23, H, 6.90; N, 3.69. Found : C, 62.83; H, 7.01; N, 3.67.

(−)-3-Methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan 8-Benzoate (*trans*-8α-Hydroxydihydrodesoxycodeine 8-Benzoate) (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 NH_4OH, extracted with ether, dried and evaporated. The residue in benzene was chromatographed over Al_2O_3 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. 141~143°. $[\alpha]_D^{26}$ −107.3° (c=0.41, benzene). IR cm^{-1} : $\nu_{C=O}$ 1715. *Anal.* Calcd. for $C_{25}H_{27}O_4N$: C, 74.05; H, 6.71; N, 3.47. Found : C, 74.34; H, 6.48; N, 3.83.

Dihydropseudocodeine 8-Benzoate (VI)——IV (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 Al_2O_3 and eluted with benzene-ether (1:1) to give VI (100 mg., 74%), colorless oil (homogeneous as showh by TLC). $[\alpha]_D^{26}$ +21.2°(c=0.44, benzene). IR cm^{-1} : $\nu_{C=O}$ 1715. The picrate of the oil was recrystallized from EtOH-acetone in yellow needles, m.p. 153~156°. *Anal.* Calcd. for $C_{25}H_{27}O_4N \cdot C_6H_3O_7N_3$: C, 58.67; 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°(decomp.). *Anal.* Calcd. for $C_{25}H_{27}O_4N \cdot CH_3I$: C, 57.04; H, 5.52; N, 2.56. Found : C, 57.41; H, 5.33; N, 2.45.

(−)-3-Methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan 8-*p*-Toluenesulfonate (*trans*-8α-Hydroxydihydrodesoxycodeine 8-*p*-Toluenesulfonate) (Vc)——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 NH_4OH and filtered. Recrystallization from hexane gave Vc (1.02 g., 70%), colorless prisms, m.p.

126~128°. $[\alpha]_D^{26}$ −34.3° (c=0.35, benzene). *Anal.* Calcd. for $C_{25}H_{29}O_5NS$: 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. III (220 mg., 22%) was recovered from the aqueous phase through extraction with $CHCl_3$; m.p. 139~141°.

(−)-3-Methoxy-4,5α-oxy-N-methylisomorphinan (*trans*-Dihydrodesoxycodeine) (VII)——$LiAlH_4$ (70 mg.) was added to a stirred suspension of Vc (530 mg.) in *n*-dibuthylether (30 ml.) and THF (1.5 ml.) at 100° under N_2 atmosphere, the mixture was stirred at the same temperature for 3 hr., cooled, added with H_2O (0.4 ml.) and filtered from inorganic material. The filtrate was extracted with 5% HCl, basified with NH_4OH, 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. 234~236° (decomp.). $[\alpha]_D^{26}$ −47.7° (c=0.31, EtOH). *Anal.* Calcd. for $C_{18}H_{23}O_2N$·HCl: C, 67.17; H, 7.52; N, 4.35. 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.

(−)-3,8α-Dihydroxy-4,5α-oxy-N-methylisomorphinan (*trans*-8α-Hydroxydihydrodesoxymorphine) (IX) Hydrobromide——III·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 IX·HBr (350 mg., 62%), colorless needles, m.p. 268~271° (decomp.). $[\alpha]_D^{26}$ −59.1° (c=0.43, MeOH). IR cm^{-1}: ν_{OH} 3350. *Anal.* Calcd. for $C_{17}H_{21}O_3N$·HBr: C, 55.44; H, 6.02; N, 3.80. Found: C, 55.34; H, 5.97; N, 3.81.

A solution of IX (24 mg.) in MeOH (2 ml.) was treated with a large excess of CH_2N_2–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-4,5α-oxy-N-methylisomorphinan (*trans*-Dihydrodesoxymorphine) (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, the residue was washed with ether, digested with acetone and filtered. Recrystallization from EtOH gave VIII·HBr (405 mg., 66%), colorless needles, m.p. 282~284° (decomp.). $[\alpha]_D^{26}$ −46.9 (c=0.53, MeOH). IR cm^{-1}: ν_{OH} 3200. *Anal.* Calcd. for $C_{17}H_{21}O_2N$·HBr: C, 57.96; H, 6.30; N, 3.98. Found: C, 57.72; H, 6.29; N, 4.01.

VIII (25 mg.) in MeOH (3 ml.) was methylated with an excess of CH_2N_2 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*-BuOK, freshly prepared from K (0.4 g.),[15] III (1 g.), benzophenone (6.2 g.) and benzene (20 ml.) was refluxed for 2.5 hr. under N_2 atmosphere, and cooled. The mixture was extracted with 10% HCl, the acid layer was basified with NH_4OH, extracted with $CHCl_3$, dried and evaporated to give an oil, which was dissolved in benzene and chromatographed over Al_2O_3. The eluate with ether was evaporated and the residue was recrystallized from hexane to give dihydropseudocodeinone (X) (70 mg., 6.9%), m.p. 112~114°. Admixture with the authentic sample*5 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 N_2 atmosphere, diluted with benzene, washed with 5% Na_2CO_3, then with 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 Al_2O_3. Elution with benzene–petr. ether (9:1) and recrystallization from hexane gave (+)-3-methoxy-4,5α-oxy-Δ^7-N-methylisomorphinan (*trans*-Δ^7-dihydrodesoxycodeine) (XII) (400 mg., 50%), colorless rods, m.p. 93.5~95°. $[\alpha]_D^{26}$ +31° (c=0.31, EtOH). *Anal.* Calcd. for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.94; H, 7.11; N, 5.28. Further elution with benzene–ether (1:1) gave a colorless oil (homogeneous as shown by TLC) (360 mg., 43%), which was converted to the oxalate and recrystallized from EtOH to give I-oxalate (425 mg.), m.p. 215~216° (decomp.). Identity of the oxalate and Δ^8-desoxycodeine oxalate was proved by IR spectral comparison. The hydrochloride, m.p. 233~235° (decomp.) (from acetone), was also identical with Δ^8-desoxycodeine hydrochloride.

Dihydrodesoxycodeine (XIII)——I (260 mg.) in AcOH (7 ml.) was hydrogenated over PtO_2 (35 mg.). One molar equivalent of hydrogen was absorbed in 12 hr. The solution was filtered and evaporated, the residue was basified with NH_4OH, extracted with ether, dried and evaporated. The residue was recrystallized from hexane to give XIII (230 mg., 89%), m.p. 105~107° (Lit.,[8] m.p. 106~107°).

Hydrogenation of XII——XII (85 mg.) in AcOH (10 ml.) was hydrogenated with PtO_2 (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 $LiAlH_4$ treatment of Vc by the mixed melting point and IR spectral comparison.

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Summary

Hydroboration of Δ^8-desoxycodeine (I) gave a B/C *trans*-fused morphine derivative, (−)-3-methoxy-8α-hydroxy-4,5α-oxy-N-methylisomorphinan (Ⅲ) along with two minor products, dihydropseudocodeine (Ⅳ) and Ⅵ. Ⅲ, by reaction with *p*-toluenesulfonylchloride gave the 8-*p*-toluenesulfonate (Ⅴc), which was treated with lithiun aluminum hydride to give (−)-3-methoxy-4,5α-oxy-N-methylisomorphinan (Ⅵ). Elimination reaction of Ⅴc with 2,4,6-collidine afforded two double-bond isomers, I and 3-methoxy-4,5α-oxy-Δ^7-N-methylisomorphinan (Ⅻ). I gave on hydrogenation the known dihydrodesoxycodeine (XIII). Hydrogenation of Ⅻ gave the B/C *trans* isomer, Ⅵ. Some additional studies were made on the hydroboration product (Ⅲ) and its derivatives to support the B/C *trans* pentacyclic structure.

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183. Itiro Yosioka and Takeatsu Kimura : Studies on the Constituents of Atractylodes. X.*1 Correlation of Hinesol and β-Vetivone.

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In the preceding communication,[1] the formula (Ia) was proposed as the structure of hinesol (I), a sesquiterpene alcohol isolated from *Atractylodes lancea* De Candoll.[2] Subsequently, Šorm, *et al.* revised the formula to Ib, and ascertained the absolute configuration of a methyl group on $C_{(6)}$ with an oxidative degradation.[3] On the other hand, the structure of β-vetivone (Ⅱ) was established by St. Pfau and Plattner,[4] and the relative configurations of Ⅱ and α-vetivone (Ⅲ) were proposed by Naves and Perottet,[5] 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 mμ (log ε 3.99) in ultraviolet, and 3500 (OH), 2730, 1685, 1626 (C=C-CHO), and 1418 cm^{-1} ($-CH_2-C=$) in infrared spectra. These data suggest that the oily substance contains mainly an α,β-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.

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