Notes

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Studies on Morphine Alkaloids. IV.[1] Indolinocodeine. III. Preparation of 9α-Substituted Indolinocodeine[2,3]

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In a previous paper,[5] it was reported that on treatment of 14β-bromocodeine (I) with sodium borohydride in aqueous methanol, 9α-methoxyindolinocodeine (IV) was produced in a very small yield by the competitive attack of methoxide anion towards the immonium cation (II), from which indolinocodeine (III) was derived by the attack of borohydride. In this paper, we wish to report some solvolytic reactions of I, which have been examined in order to improve the yield of IV and also to obtain other 9α-substituted indolinocodeine derivatives.

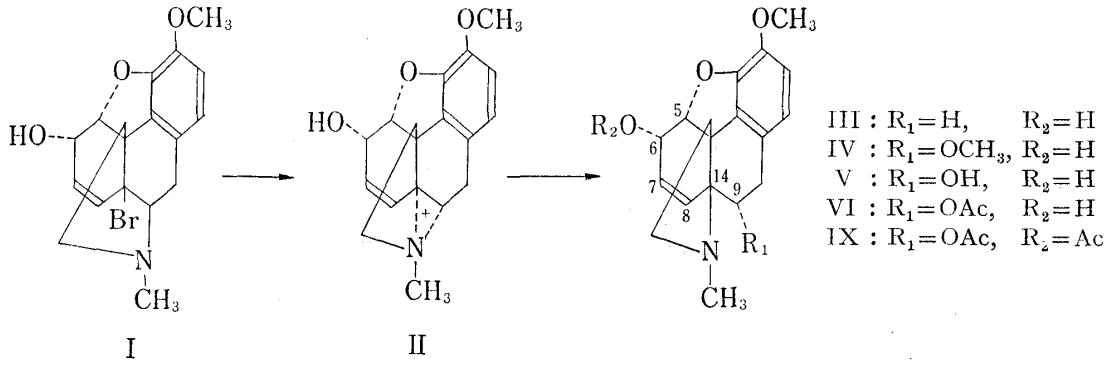

Chart 1

I. Methanolysis of 14β-Bromocodeine (I)

The preliminary examinations to find out the most appropriate conditions to produce IV were carried out by utilizing thin-layer chromatography (TLC).[6] Solvolysis with sodium hydroxide, sodium bicarbonate, and sodium methoxide in methanol always gave rise to three main products (*Rf*: 0.75, 0.50, 0.40.) in various ratios depending on the reagents and conditions. Furthermore, treatment with only methanol at room temperature or under refluxing also furnished similar results. Finally, it was found that methanolysis of I with a mixture of methanol and tetrahydrofuran (THF)[7] at room temperature was the most appropriate procedure to obtain 9α-methoxyindolinocodeine (IV), and in this case the yield was improved till over 20%.

1) Part III: S. Okuda, K. Abe, S. Yamaguchi, and T. Ibuka, *Chem. Pharm. Bull.* (Tokyo), **16**, 370 (1968).
2) This paper also constitutes part I of a series entitled "Solvolytic Reaction of 14β-Bromocodeine."
3) A part of this work was presented at the Annual Meeting of the Pharmaceutical Society of Japan, Sendai, October 1966.
4) Location: *a*) *Yayoi-cho, Bunkyo-ku, Tokyo*; *b*) *Shiba-shirokane, Minato-ku, Tokyo.*
5) S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1092 (1965).
6) Silica gel (Kiesel gel G nach Stahl, Merck) was used as TLC adsorbent. Solvent system.$CHCl_3$–MeOH (9:1).
7) THF was used for increasing the solubility of I in this solution.

The first product, *Rf* 0.75, which was identified as 9α-methoxyindolinocodeine, and the second, *Rf* 0.50, were easily purified by silica gel column chromatography. However, the third product, *Rf* 0.40, could not be purified because of difficulties for separation from the minor impurities.

The compound, *Rf* 0.50, was easily crystallized from the eluates of column chromatogram to afford colourless needles, mp 69—70° (from methanol), $C_{19}H_{23}O_4N \cdot CH_3OH$, in 40% yield. The structure of this compound has been assigned as 7-methoxyneopine (VIII) mainly from the comparison of NMR spectra of VIII and neopine (VII), which are summarized in Table I.

Table I. Nuclear Magnetic Resonance Spectral Data of VII and VIII

	$C_{5\beta}$–H	$C_{6\beta}$–H	C_7–H	C_8–H	$C_{9\alpha}$–H	$C_{10\beta}$–H	C_3–OCH_3	O–CH_3
VII	4.64(d) J_6=4.6	4.22(m)	—	5.46(t) J_7=3.8	3.57(d) J_{10}=6.1	3.27(d) J_{10}=18	3.86(s)	—
VIII	4.75(d) J_6=4.5	4.28(m)	3.85	5.80(d) J_7=6.0	3.5 (d) J_{10}=6	3.2 (d) J_{10}=18	3.85(s)	3.43(s)

The molecular formula, derived from microanalytical and mass spectral data, indicates that this compound is one of the structural isomer of 9α-methoxyindolinocodeine (IV). However, as shown in Table I, the signals due to 9α- and 10β-H, which are characteristic to morphine type skeleton,[8] are quite similar to those of neopine (VII). Therefore, this compound does not belong to indolinocodeine type. The doublet at δ 5.8 (J=6) due to only one proton on double bond indicates that this compound has a partial structure >C=C(H)–C(H)–. The coupling constant between 5β- and 6β-H is in good agreement with that of VII, but this 6β-H couples with only one of 7α- or 7β-H in addition to 5β-H. These facts strongly suggest that this compound should be 7-methoxyneopine (VIII).

If VIII is produced *via* SN_2' type reaction, the configuration of 7-methoxyl may be presumed to be β. However, nuclear magnetic resonance (NMR) studies on the relationship between J-value and dihedral angle of the vicinal hydrogens or infra red (IR) spectral investigation on intramolecular hydrogen bonding could not afford the definite conclusion

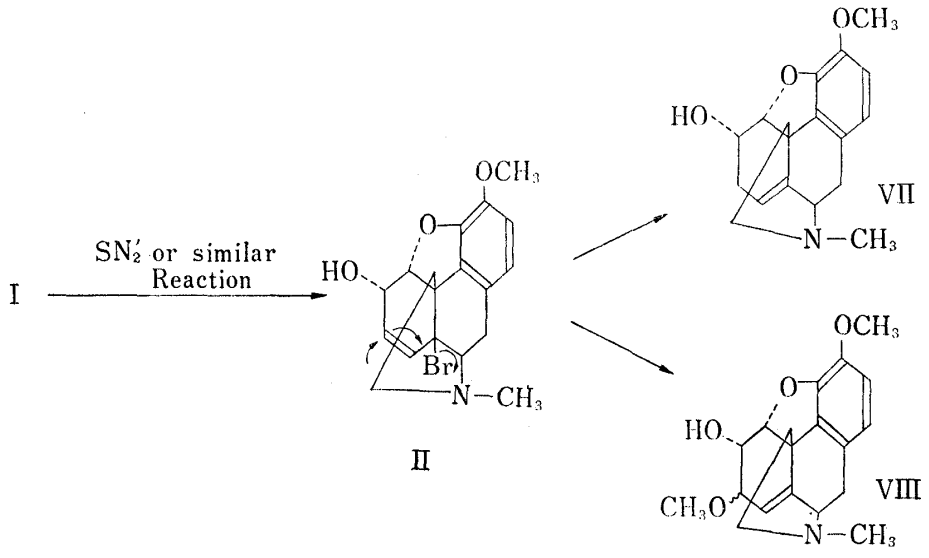

Chart 2

8) S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), 11, 1465 (1963).

of this problem. Further approaches to clarify this and to elucidate the structure of the third, the most polar product, are now under investigation.

II. Hydrolysis and Acetolysis of 14β-Bromocodein (I)

To obtain 9α-hydroxy- (V) and 9α-acetoxy-indolinocodeine (VI), hydrolysis and acetolysis of I were carried out. As expected, treatment of I with aqueous tetrahydrofuran[7] or with saturated potassium acetate in acetic acid or in methanol afforded V and VI in 30% and 50% yield respectively.

The structures of the compound V, mp 193—195°, $C_{18}H_{21}O_4N$, and VI, mp 135.5—136°, $C_{20}H_{23}O_5N$, were elucidated through the microanalytical and mass spectral data, and also by physicochemical data, especially by NMR spectra, which are summarized in Table II together with that of IV.

Table II. Nuclear Magnetic Resonance Spectral Data of IV, V, and VI

	$C_{5\beta}$–H	$C_{6\beta}$–H	C_7–H	C_8–H	$C_{9\beta}$–H	$C_{10\alpha}$–H	C_9–O–R
IV	4.43(d) J_6=4.5	4.17(m)	6.41(q) J_6=6.1 J_8=10.0	6.00(d) J_7=10.0	3.52(q) J_{10}=3.0 J_{10}=2.0	3.05 —	3.10 (R=C<u>H</u>$_3$)
V	4.48(d) J_6=4.7	4.30(m)	6.37(q) J_6=6.0 J_8=10	6.20(d) J_7=10	4.0	3.18(q) J_9=3.0 J_{10}=16	2.7 (R=<u>H</u>)
VI	4.5 (d) J_6=4.7	4.3 (m)	6.41(q) J_6=6.0 J_8=10	5.90(d) J_7=10	5.26(q) J_{10}=3.0 J_{10}=2.0	3.22(q) J_9=3.0 J_{10}=16	1.8 (R=CO<u>C</u>H$_3$)

The chemical shifts and J-values of the characteristic signals due to 5β-, 6β-, 7-, and 8-H of V and VI are quite similar to the corresponding signals of IV. In both cases, the quartets due to 9β-H are shifted to lower field due to the deshielding effect of 9α-O-functional groups, but the coupling constants of VI[9] ($J_{9\beta\text{-}10\alpha}$=3.0, $J_{9\beta\text{-}10\beta}$=2.0), are in complete accordance with those of IV. The signal at δ 3.2, which was not seen in the spectrum of indolinocodeine (III), was assigned as that of 10α-H by spin-spin decoupling technique, and coupling constants between 9β-10α (J=3.0), and 10β-10α (J=16) are in good agreement with the values expected from the corresponding dihedral angles, measured by Dreiding Model. Furthermore, the signals of acetyl methyl and hydroxyl hydrogen appear at δ 2.7 and δ 1.8 respectively in the spectrum of V and VI.

As shown in Fig. 1, the IR spectra of V and VI showed bands in the OH stretching region, which were invariable with the change of concentration. This is due to an intramolecular hydrogen bond between C_6–OH and C_9–OH or C_9–OAc group, and these facts also confirmed the orientation of C_9-substituted group to be α.

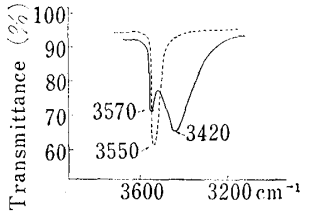

Fig. 1. IR Spectra of V and VI.
0.003 mole/liter in CCl_4
———: V, - - - - - - - - : VI

From these facts, the structure of the compound is concluded to be 9α-hydroxy- (V) and 9α-acetoxyindolinocodeine (VI). This is also confirmed by the fact that acetylations of V and VI with acetic anhydride afforded the same diacetate (IX).

The 9α-substituted indolinocodeines, (V) and (VI), are the main products of the above solvolytic reactions. However, several other minor products are also obtained in both cases and the investigations of these compounds are now in progress.

9) The coupling constants of 9β-H of V are not clear because of its overlapping on the signal of C_3–OCH_3.

Experimental[10]

Methanolysis of 14β-Bromocodeine (I)——To a solution of I (1 g) dissolved in tetrahydrofuran (15 ml) was added abs. MeOH (15 ml) and the solution was stirred overnight at room temperature. After concentration of solvent *in vacuo*, the reaciton mixture was diluted with H_2O, made alkaline with NH_4OH–H_2O, and then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to give red oily substance (*ca.* 800 mg). The resulted reaction products were chromatographed on silica gel (Merck) column (100 g).

a) The first fraction eluted with pure benzene was recrystallized from MeOH to give colourless needles, (250 mg), mp 139—140°, which was identical with an authentic sample of 9α-methoxyindolinocodeine (IV) by comparison of the IR and NMR spectra and by mixed melting point test.

b) The next fraction eluted with benzene–ether (1:1) afforded 420 mg of 7-methoxyneopine (VIII), which was recrystallized from MeOH to give colourless needles (300 mg) mp 69—70°, $[\alpha]_D^{20} = +116°$ ($c=0.90$ in $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580 (-OH). *Anal.* Calcd. for $C_{19}H_{23}O_4N \cdot CH_3OH$: C, 66.46; H, 7.53; N, 3.83. Found: C, 66.38; H, 7.57; N, 3.84.

c) The fractions eluted with ether, and then with ethyl acetate, MeOH afforded 150 mg of oily material, the main component of which (*Rf* 0.35) was not purified.

9α-Hydroxyindolinocodeine (V)——14β-Bromocodeine (I) (1 g) was dissolved in tetrahydrofuran (15 ml) and H_2O (10 ml) and the mixed solution was allowed to stand at room temperature overnight. After evaporation of organic solvent *in vacuo*, the reaction mixture was made alkaline with NH_4OH–H_2O and extracted with $CHCl_3$, washed with H_2O, dried over anhyd. Na_2SO_4. After evaporation of solvent, oily residue obtained (850 mg) was dissolved in $CHCl_3$ and chromatographed on 100 g of silica gel (Davison Chemical Company, No. 923, 100—200 mesh). The first eluate with $CHCl_3$ gave a small amount of coloured residue, which was not investigated further. The eluate with ethyl acetate (250 mg) was recrystallized from aqueous acetone to afford colourless prisms (200 mg), mp 193—195°, $[\alpha]_D^{20} = +159°$ ($c=1.04$ in EtOH). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; O, 20.29; N, 4.44. Found: C, 68.71; H, 6.61; O, 20.87; N, 4.13. IR: $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570, 3420 (-OH).

9α-Acetoxyindolinocodeine (VI)——A solution of 14β-bromocodeine (I) (1 g) in saturated KOAc in MeOH (20 ml) was refluxed for 1 hr. After evaporation of MeOH, the reaction mixture was diluted with H_2O, made alkaline with NH_4OH–H_2O, and then extracted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4. Silica gel column chromatography of the crude products from benzene–ethyl acetate and recrystallization from ether–pet. ether gave 460 mg of VI, mp 135.5—136°. $[\alpha]_D^{24} = +132°$ ($c=1.00$ in EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550 (OH), 1755, 1227 ($OCOCH_3$). *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.06; H, 6.51; N, 4.40.

6α,9α-Diacetoxyindolinocodeine (IX)——A) 100 mg of 9α-acetoxyindolinocodeine (VI) was heated with 1 ml of acetic anhydride at 70—80° for 3 hr. After addition of H_2O, the solution was made alkaline with NH_4OH–H_2O, and extracted with $CHCl_3$. The rdesulted oily residue was treated with picric acid in EtOH to afford the crystalline IX-picrate, which was recrystallized from EtOH–H_2O, mp 118—120°. IR ν_{max} cm^{-1}: 1750 ($OCOCH_3$), TLC: Rf[6] = 0.90. NMR (δ-value) 1.55, 1.70; ($OCOCH_3$), 5.25; (9β-H), 5.45; (6β-H). *Anal.* Calcd. for $C_{22}H_{25}O_6N \cdot C_6H_3O_7N_3 \cdot H_2O$: C, 52.01; H, 4.68; N, 8.67. Found: C, 52.03; H, 4.42; N, 8.82.

B) Acetylation of 9α-hydroxyindolinocodeine (V) was carried out with the same procedure described above and also gave a diacetate. Melting points of its picrate and the spectral data (IR and NMR) of this was identical with that of diacetate IX.

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10) Melting points were uncorrected. IR spectra were recorded on Japan Spectroscopic Co. Model DS-402 IR-spectrophotometer. NMR spectra were determined on a Hitachi H-60 spectrometer, using deuterated chloroform as solvent and tetramethylsilane as internal reference. Chemical shifts are reported in δ values and coupling constants (J) in cps.