To a solution of 1.1 g of the about N-oxide in 6.6 ml of $CHCl_3$ was added 1.3 g of tosyl chloride with occasional shaking, and the mixture was heated under reflux on a water bath for 10 min. After cooling, the reaction mixture was made basic with 10% Na_2CO_3 aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried on Na_2SO_4, and distilled to give the crude solid, whose recrystallization from MeOH gave 520 mg (2.3%) of 7-methylcarbostyril (VII) as colorless needles, mp 190—198° (lit.,[7] mp 198°). *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.43; H, 5.69; N, 8.79. Found: C, 75.49; H, 5.96; N, 8.88. IR cm^{-1} (KBr): ν_{NH} 3390, $\nu_{C=O}$ 1660 (amide).

Catalytic Hydrogenation of 7-Methylcarbostyril (VII)——A mixture of 200 mg of 7-methylcarbostyril (VII) and 20 ml of EtOH was hydrogenated in the presence of 200 mg of 40% Pd-C in a current of H_2, a calculated amount of H_2 being absorbed within 30 hr. Filtration of the catalyst and evaporation of the filtrate gave the solid, which was recrystallized from ether to give 192 mg (95%) of 3,4-dihydro-7-methylcarbostyril (Vb) as colorless needles, mp 160—161°. This compound was identical with the sample formed in case of Chichibabin reaction of IV from the points of admixed melting point test and infrared spectral comparison.

Friedel-Crafts Reaction of N-(*m*-Tolyl)-β-chloropropionamide (VIII)——To 5.8 g of VIII heated at 100° was added portionwise with stirring 12 g of $AlCl_3$ within 5 min. After the addition the mixture was stirred at 100° for 3 hr and the resultant mixture was decomposed with water and extracted with ether. The extract was treated as usual and distilled to give 2.98 g (63.42%) of 3,4-dihydro-7-methylcarbostyril (Vb) as colorless needles, mp 160—161°, whose IR spectrum was identical with that of the above sample (Vb).

Friedel-Crafts Reaction of N-(*p*-Tolyl)-β-chloropropionamide (IX)——To 6.25 g of fused substance (IX) at 140° was added in small protions with stirring 13 g of $AlCl_3$ within 5 min. After the addition the stirring was continued for 2 hr. The reaction mixture was decomposed with water, treated as usual and extracted with ether. The extract was washed with water, dried on Na_2SO_4, and distilled to afford the solid whose recrystallization from ether gave 2.84 g (50.7%) of Vb as colorless needles, mp 159.5—160.5°. The IR spectrum of this compound was identical with that of the above sample.

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Studies on Morphine Alkaloids. III.[1] Indolinocodeine. II. 9α-Methoxyindolinocodeine

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In a previous paper,[1] we reported that on sodium borohydride reduction of 14β-bromocodeinone (I) in aqueous methanol solution, neopine (III), isoneopine (IV), and indolinocodeine (VIa) are produced *via* 14β-bromocodeine (II), the first reduction product, and discussed the mechanisms of this rather complicated reaction. The present studies deal with the isolation and characterization of 9α-methoxyindolinocodeine (VII), the fourth product of the above reaction.

This product is most nonpolar and eluted first from sillica gel column with pure benzene to furnish colourless needles, mp 139—140° (from methanol), $[\alpha]_D^{20}=+146°$ ($c=1.21$ in EtOH),

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1) Part II: S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1092 (1965).

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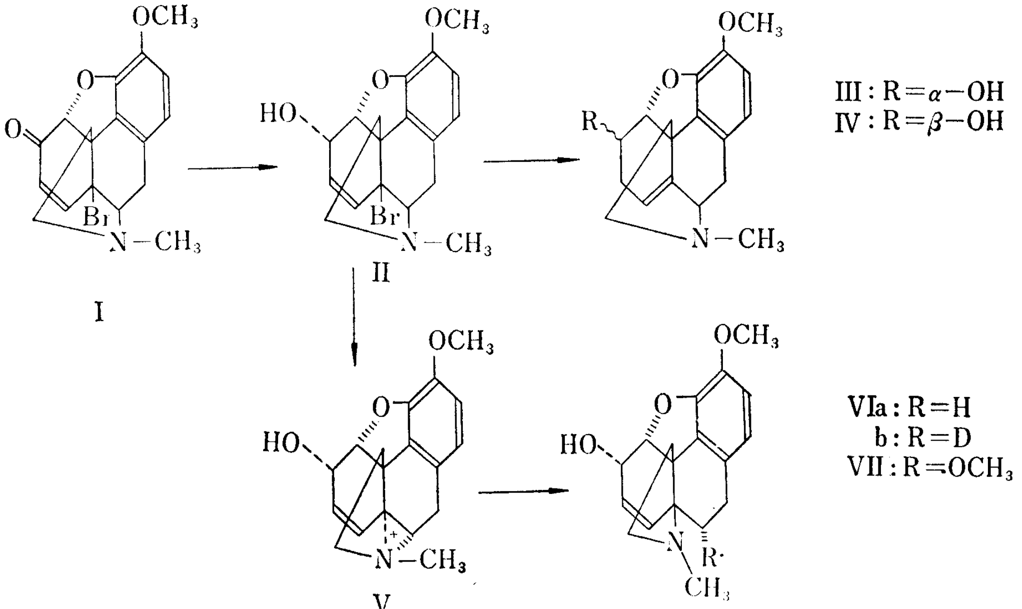

Chart 1

in 0.4% yield. The molecular formula, $C_{19}H_{23}O_4N$, derived from the microanalytical and mass spectral data, suggests that this may be one of the methoxyl derivatives of III, IV, or VI. Infrared (IR) spectrum, 3400 cm^{-1}, invariable with the change of concentration (1%—0.1%), exhibits an intramolecular hydrogen bonding, which is also observed in nuclear magnetic resonance (NMR) spectra. The structure of this compound has been elucidated mainly from the investigation of NMR spectra and then on the basis of reaction mechanisms as follows.

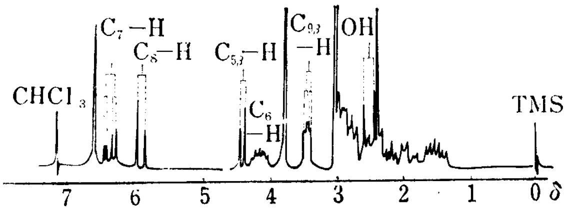

Fig. 1. NMR Spectrum of 9α-Methoxyindolinocodeine (VII)

The NMR spectrum of this compound is shown in Fig. 1. The complicated signal at δ 4.17 was analyzed utilizing spin-spin decoupling technique and replacement of active hydrogen with deuterium, and assigned as that of $C_{6\beta}$-H ($J_{5\beta}=4.5$, $J_7=6.1$, $J_{OH}=10.6$). The spin-spin coupling with hydroxyl hydrogen indicates the fixation of this active hydrogen by intramolecular hydrogen bonding. The signals due to C_7- and C_8-H appear at δ 6.41 ($J_{6\beta}=6.1$, $J_8=10.0$) and δ 6.00 ($J_7=10.0$) respectively. The absence of C_{14}-H, which can be concluded from the sharp doublet signal of C_8-H, demonstrates the possibility that this compound should be one of the three, 14β- (VIIIa), 14α-methoxycodeine (VIIIb), and methoxyindolinocodeine.

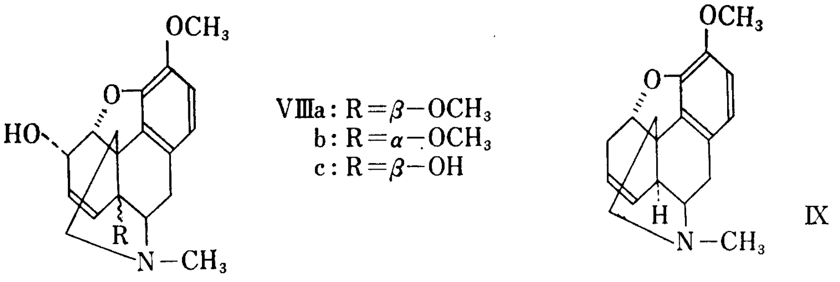

Chart 2

If this is 14β-methoxycodeine (VIIIa), two doublets due to 9α- and 10β-H should be observed at the region between δ 3.8—3.0.[3] A quartet at δ 3.52 ($J=3.0$ and 2.0) of this compound corresponds to only one hydrogen and J-values are quite inconsistent with the expected values of 9α- and 10β-H of VIIIa, which might be quite similar to those of 14β-hydroxycodeine (VIIIc) ($J_{9\alpha,10\alpha}=5.8$, $J_{10\alpha,10\beta}=18$). Furthermore VIIIa should not possess an intramoelcular hydrogen bonding, and consequently this product can not be VIIIa.

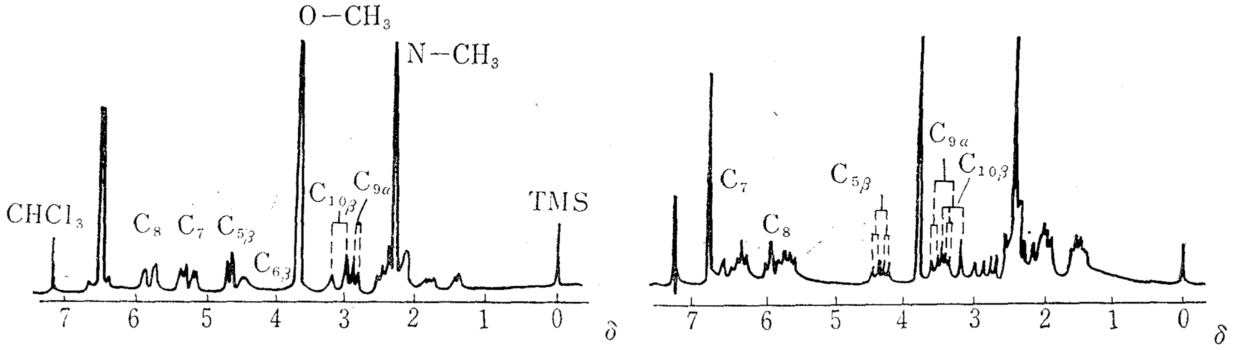

Fig. 2. NMR Spectra of VIIIc and IX

To determine the possibility of 14α-methoxycodeine (VIIIb), the NMR spectrum of *trans*-Δ^7-desoxydihydrocodeine (IX),[4] in which B/C ring juncture is not *cis* but *trans*, was measured for comparison.[5] In this case the signals of 9α- and 10β-H appear at 3.40 ($J_{10\alpha}=6.50$, $J_{14\alpha}=3.0$, $J_{10\beta}=0$), and 3.26 ($J_{10\alpha}=17.5$, $J_{9\beta}=0$) respectively. Accordingly, the signals of these hydrogens in question of VIIIb should be observed as two doublets with approximately the same J-values as those of IX and then the above possibility is now eliminated.

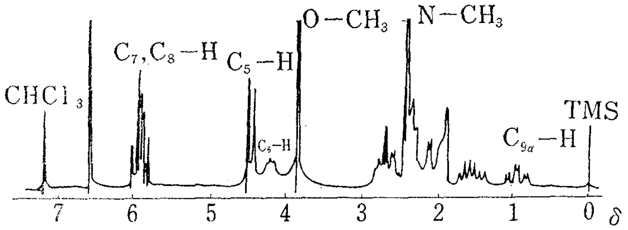

Fig. 3. NMR Spectrum of Indolinocodeine (VIa)

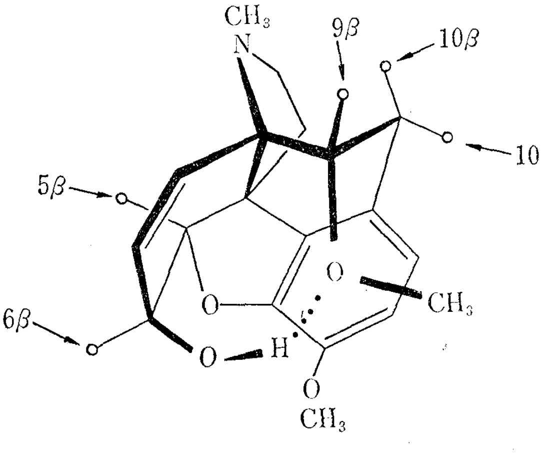

Chart 3

Finally, the compound, mp 139—140°, is most probably 9α-methoxyindolinocodeine (VII), since this may be produced by the attack of methoxide anion at 9α-position of immonium cation (V) instead of borohydride ion in the formation of indolinocodeine (VIa).

The NMR data can be completely rationalized by this structure VII as follows. The chemical shifts and J-values of C$_{5\beta}$-H (δ 4.43, $J_{6\beta}=4.5$) and C$_{6\beta}$-H (δ 4.17) are quite similar to those of VIa (C$_{5\beta}$-H: 4.50, C$_{6\beta}$-H: 4.30, $J_{5\beta,6\beta}=4.4$), but this $J_{5\beta,6\beta}$ is different from that of codeine type derivatives ($J=6$—7)[6] and of *trans*-desoxycodeine (IX) ($J=6.8$). This may be attributed to the conformational differences of ring C,[6] and the above facts indicate that compound VII has a conformation of ring C in indolinocodeine type.

The signal of C$_{9\alpha}$-H in VIa appears at δ 1.00 as sextet ($J_{9\beta}=J_{10\beta}=14$, $J_{10\alpha}=4$), which disappears in the NMR spectrum of VIb prepared by the reduction of II with sodium borodeu-

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[3] S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1465 (1963).
[4] H. Kugita and M. Takeda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1422 (1965).
[5] This NMR chart was kindly supplied by Dr. H. Kugita.
[6] S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 104 (1964).

teride. Contrary to this, the compound in question does not possess this signal but a characteristic quartet at 3.52, which is now assigned as that of $C_{9\beta}$–H. The coupling constants between 9β–10α (J=3.0), and 9β–10β (J=2.0) are in good agreement with the expected values of the corresponding dihedral angles, measured by Dreiding Model of VII. Furthermore, the structure VII can explain the presence of an intramolecular hydrogen bonding between 6α–hydroxyl and 9α–methoxyl, as shown in Chart 3.

Therefore, this very minor fourth product is concluded to be 9α–methoxyindolinocodeine (VII), and the further investigations to improve the yield under the appropriate solvolytic conditions are now in progress.

Experimental

Melting points were uncorrected. NMR spectra were measured on a Varian Associates HR–100 spectrometer, operating at 100 Mc, and examined in a 5—10% solution in deuteriochloroform using tetramethylsilane as an internal reference. The chemical shifts were given in ppm values and coupling constants (J) in cps. IR spectra were recorded on Perkin Elmer Model 521–grating photospectrometer.

Sodium Borohydride Reduction of 14β-Bromocodeinone (I)——This was carried out according to the description previously reported in part II of this series,1) and from 10.0 g of starting material, there obtained 7.2 g of colourless oily substance, which contains four products on thin–layer chromatography (TLC).7) The *Rf*–values of them were (A): 0.90, (B): 0.85, (C): 0.50, (D): 0.25, and (B), (C), (D) were found to be indolinocodeine (VIa), neopine (III), and isoneopine (IV) respectively. This reaction products mixture was chromatographed on 400 g of sillica gel column.

a) The first fractions eluted with pure benzene afforded 32 mg (0.4%) of 9α–methoxyindolinocodeine (VII), which was recrystallized from methanol to give colourless needles, mp 139—140°, $[\alpha]_D^{20}=+146°$ (c=1.21, EtOH). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.54; H, 7.23; N, 4.37. Mass spectral data: *m/e* 329:M^+ (base peak), *m/e* 314: $(M-CH_3)^+$, *m/e* 298: $(M-OCH_3)^+$.

b) The next fractions eluted with benzene–ether (1:5) and with pure ether gave 2.3 g (30%) of indolinocodeine (VIa). Recrystallization from methanol–water afforded colourless needles, mp 103—104°,8) $[\alpha]_D^{20}$ +150° (c=1.1, EtOH), +149.5° (c=0.8, $CHCl_3$).8) *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.21; H, 7.07; O, 16.03; N, 4.68. Found: C, 72.04; H, 7.12; O, 16.03; N, 4.75. IR and NMR data unambiguously showed that this compound was VIa.

c) The elutions with ether and ether–ethyl acetate afforded neopine (III), mp 127°, and isoneopine (IV), mp 155—156°, in 50 and 10% yield respectively.

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7) TLC was performed on alumina plates (0.25 mm), using $CHCl_3$ containing 1% of methanol as a developing solvent.

8) Since the specimen with the physical constants previously reported, mp 129—130°, $[\alpha]_D$ +23.7° (c=1.1, $CHCl_3$), has not been obtained through repeated experiments, mp and $[\alpha]_D$ of VIa are now corrected to be these values. This compound also shows mp 63—65.5° ($C_{18}H_{21}O_3N\cdot C_6H_{14}$) after recrystallization from n–hexane (a private communication from Dr. Y.K. Sawa, Shionogi & Co., Ltd.).