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Studies on Morphine Alkaloids. V.[1] Reaction Mechanism of the Reduction of 14β-Bromocodeinone with Sodium Borohydride

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Sodium borohydride reduction of 14β-bromocodeinone was reexamined using deuterated reagents, and the position deuterated and deuterium contents of labeled products were measured by nuclear magnetic resonance and mass spectrometer to confirm the reaction routes and quantitative relationship of each of these routes, and reaction mechanisms were proposed.

Reduction of 14-bromocodeinone (I) with sodium borohydride was first reported by Conroy[3] who carried out the reduction of I in aqueous methanol and found the formation of neopine (III) *via* 14-bromocodeine (II), and proposed the two routes as its formation mechanism. Later, Okuda, *et al.*[4] reexamined this reaction and found the formation of three products besides III. They determined the structure of these compounds as isoneopine (IV), indolinocodeine (V), and 9α-methoxyindolinocodeine (VI),[5] and newly proposed the formation mechanism for these compounds.

In order to confirm these routes, the reaction was carried out with sodium borodeuteride to check the position deuterated and an attempt was also made to calculate the quantitative relationship of each of these routes by measurement of the deuterium content of labeled compounds.

1) Proposed Mechanisms for Sodium Borohydride Reduction of 14-Bromocodeinone

The assumed reaction mechanisms proposed to date are illustrated in Chart 1.

Since there is a formation of IV, which differs in steric configuration at C_6, besides III, it would be possible to consider a mechanism, such as 1,4-elimination depicted in Chart 1, of the primary formation of a C_6-ketone which undergoes reduction to form III and IV. On the other hand, III could also have been formed by the SN_2' type reaction, and the products formed by these two routes may be present as a mixture. As for the formation of V and VI, both would be formed with the aziridinium ion as an intermediate, as indicated in Chart 1, followed by α-side attack of reagent at C_9 position.

2) Reduction of 14-Bromocodeine (II) with Sodium Borodeuteride

As has been shown above, reduction of I with sodium borohydride is known to form III to VI through II and, therefore, II is used as the starting material for reduction with sodium borodeuteride in order to confirm the position at which the hydride ion attacks.

14-bromocodeine, which was obtained by reduction of I with sodium borohydride was further treated with sodium borodeuteride. The products thereby obtained were separated

1) Part IV: S. Okuda, K. Abe, and M. Onda, *Chem. Pharm. Bull.* (Tokyo), **16**, 1124 (1968).
2) Location: *a*) *5-9-1, Shirokane, Minato-ku, Tokyo*; *b*) *Yayoi-cho, Bunkyo-ku, Tokyo.*
3) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).
4) S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1092 (1965).
5) S. Okuda, K. Abe, S. Yamaguchi, and T. Ibuka, *Chem. Pharm. Bull.* (Tokyo), **16**, 370 (1968).

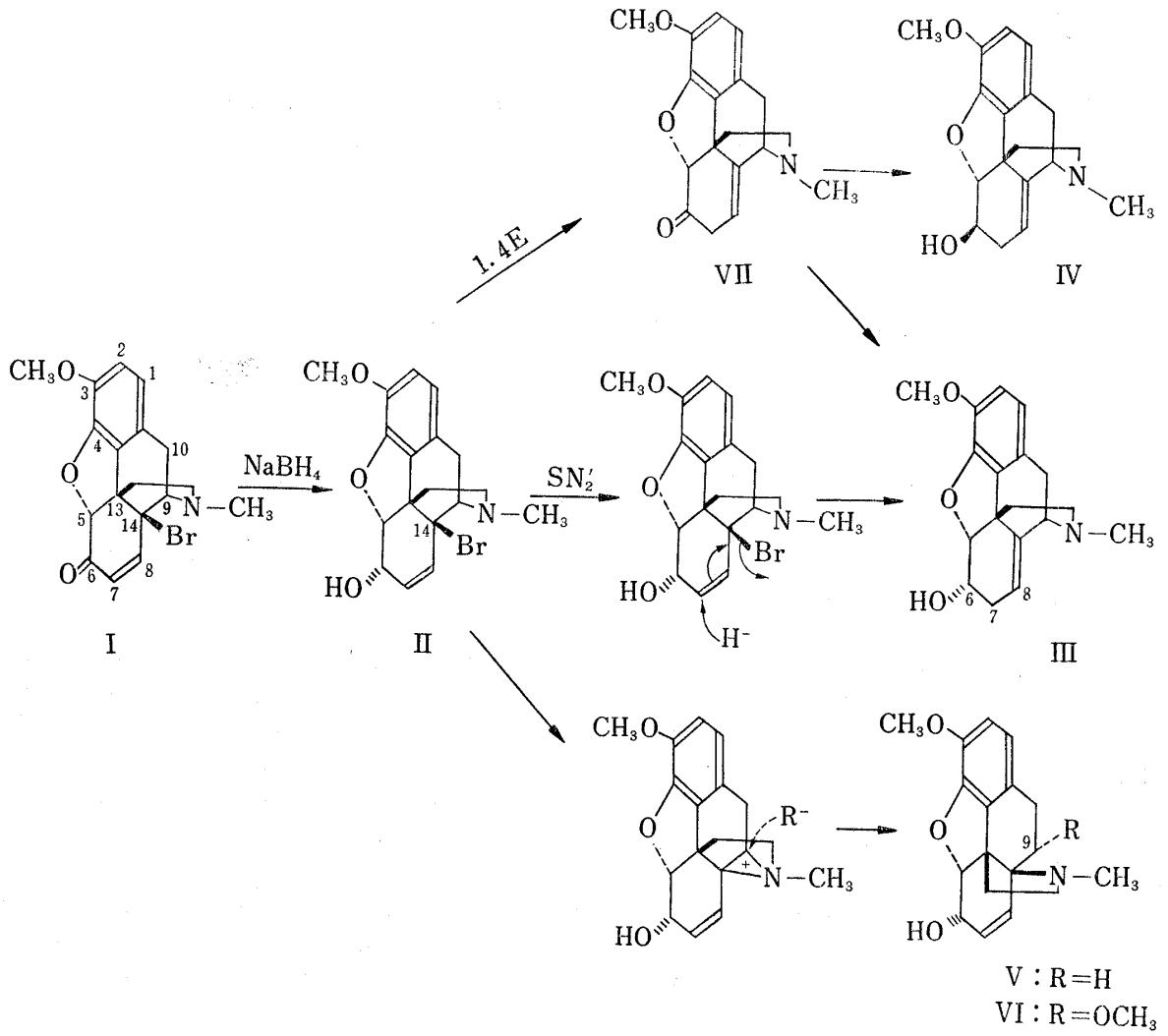

Chart 1

by column chromatography and the above-mentioned four compounds were obtained as white crystals in respective yield of 50% (III), 10% (IV), 30% (V), and 0.3% (VI).

These reaction products were submitted to nuclear magnetic resonance (NMR) and mass spectral analyses. However, since VI is a minor product of this reaction and its formation mechanism may be assumed to differ from that of the others, having no direct bearing on this reduction, VI was excluded from this analysis, and discussions will hereafter be confined to the three products.

i) NMR Spectra: Comparison of the NMR spectra of the deuterated products and non-deuterated compounds (III to V) is shown in Fig. 1 and Fig. 2.

In neopine, the triplet signal for C_8–H has changed to a doublet indicating that one of the hydrogen atoms at C_7 had been deuterated. Its coupling constant ($J_{7,8}$=6.0 cps) suggested that C_7–D takes a β-configuration. As for isoneopine, the disappearance of the signal for $C_{6\alpha}$–H at around δ 3.7 and the change of the singal at $C_{5\beta}$–H at δ 4.46 from a doublet to a singlet indicated deuteration of the hydrogen atom at $C_{6\alpha}$. The same comparison of the NMR spectra of two kinds of indolinocodeine showed that the signal (A) of V (Fig. 2) that has appeared at δ 1.00 had disappeared in the labeled compound and this signal does not appear around this region in the NMR spectrum of VI. The dihedral angle of C_9–H and C_{10}–H obtained from the Dreiding model and the coupling constants calculated according to the Karplus equation came out as shown in Fig. 2. From these data, the signal (A) was assigned to $C_{9\alpha}$–H, and it has become clear that this position had been deuterated in this reaction.

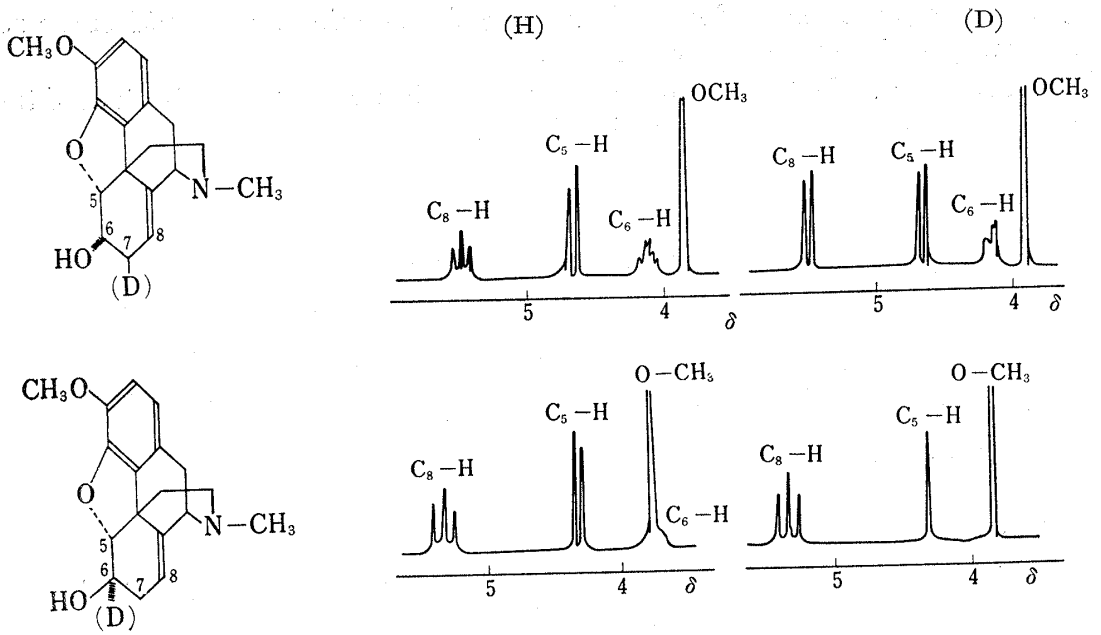

Fig. 1. Comparison of NMR Spectra of III and IV with that of Deuterated Compounds

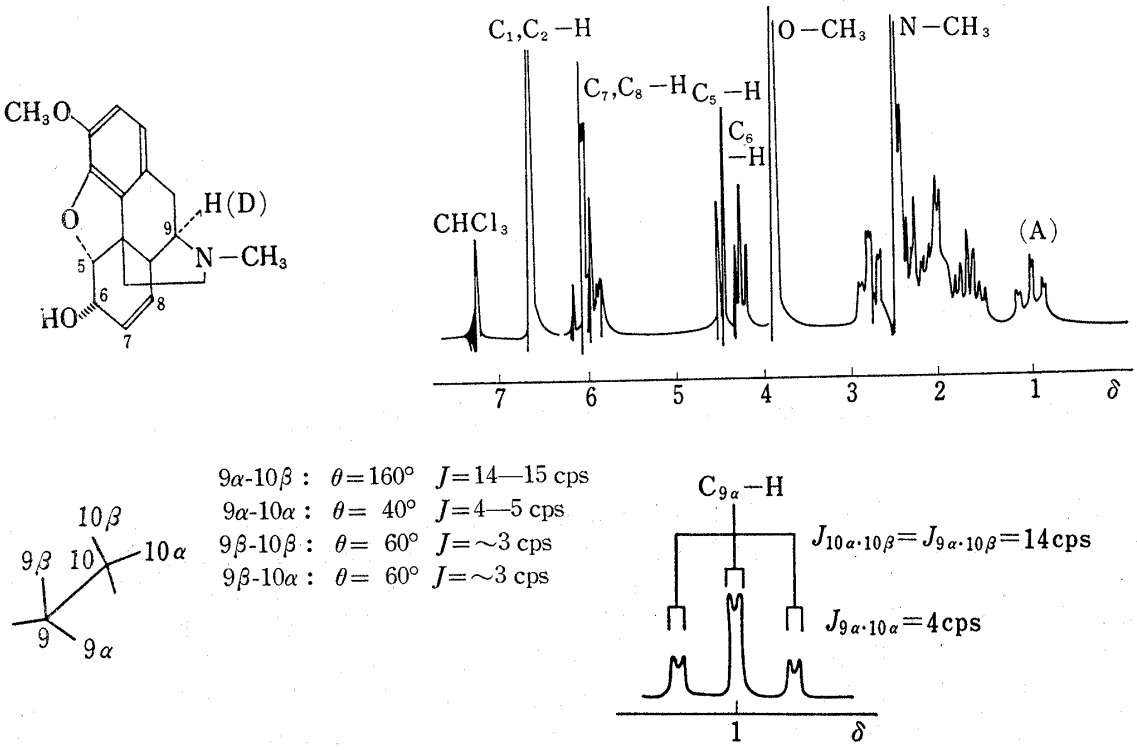

Fig. 2. NMR Spectra of Indolinocodeine

ii) Mass Spectra: The mass spectra of the foregoing three compounds were measured and deuterium content was calculated for each. It was thereby found that all these compounds were deuterated approximately quantitatively.

3) Reduction of I with Sodium Borodeuteride

Reduction of I in aqueous methanol with sodium borodeuteride at 0°, gave the deuterated 14-bromocodeine. Comparison of its NMR spectrum with that of II showed the disappearance of the hydrogen signal at C_6 and the change of C_5–H from a doublet to a singlet, indicating that $C_{6\beta}$ position had been deuterated. This product was further treated with sodium boro-

hydride, and separation of the products as in the foregoing experiment afforded four compounds which were analyzed in the same way as above.

i) NMR Spectra: NMR spectra of the three products are compared with that of the corresponding non-deuterated compounds in Fig. 3.

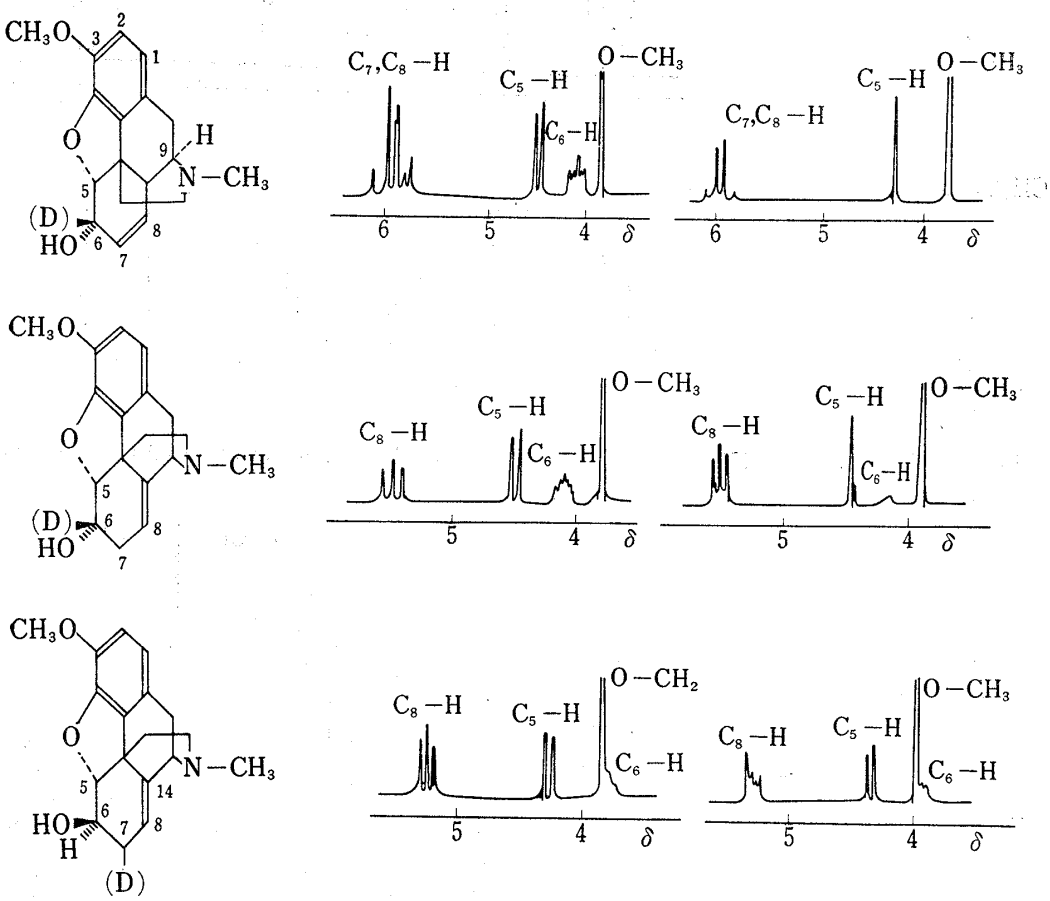

Fig. 3. Comparison of NMR Spectra of the Deuterated and Non-deuterated Compounds

It is seen from this Chart that in indolinocodeine, C_6 position had been deuterated, but there is no change in the signal for C_9–H. In neopine, the doublet signal for $C_{5\beta}$–H has changed approximately to a singlet and a weak absorption signal appears at the position for C_6–H. Its area intensity indicates that about 20% of the compound has a hydrogen at C_6. In the spectra of isoneopine, there is no change in the signal for C_5–H and there is no decrease in the area intensity of C_6–H. These evidences indicate that the C_6 position is not deuterated, or in other words, the deuterium atom at C_6 has been completely replaced by a hydrogen atom. However, the signal for C_8–H has changed from a triplet to a somewhat distorted form, indicating that some change has taken place at C_7-position, and a part of C_7–H must have been deuterated.

ii) Mass Spectra: The mass spectra of these compounds were measured and deuterium content of the compounds was calculated from the peaks around the molecular ion, using the corresponding compounds (III to V) as standard.[6] The contents so calculated were 90% in indolinocodeine, 85% in neopine, and 45% in isoneopine. If the deuterium content of

6) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, 1962 Chapter 5; H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 1, Holden-Day, Inc., San Francisco, 1964, p. 34.

indolinocodeine is taken as standard for this reaction,[7] it is shown that in the formation of neopine, C_6 position hardly takes part but about one-tenth of it is replaced by hydrogen, and that about one-half of deuterium is lost from isoneopine during the reaction.

4) Discussions on the Reaction Mechanism

The foregoing experimental results will be summarized as follows. For the formation of indolinocodeine, a mechanism has already been presented for the formation of an aziridinium ion as an intermediate and an α-side attack of the hydride at C_9. The present series of experiments has shown that reduction of I with sodium borodeuteride and borohydride has left deuterium at C_6, while the reduction of II with sodium borodeuteride resulted in the introduction of deuterium at $C_{9\alpha}$. These facts are not inconsistent with the above mechanism. In the ring-opening of this aziridine-type intermediate, attack of methoxy ion in the solvent instead of hydride ion is possible, and 9α-methoxyindolinocodeine (VI) is considered to have been formed by such a mechanism.

As for neopine and isoneopine, it was found that the reduction of C_6-D compound of II with sodium borohydride resulted in complete disappearance of deuterium from C_6 position, as evidenced by NMR spectrum, and reduction of the C_6-H compound with sodium borodeuteride resulted in approximately quantitative introduction of deuterium into C_6 position. These evidences support the assumed mechanism that isoneopine is formed through an intermediate with C_6-ketone, which is further reduced to form IV. However, about one-half the quantity of deuterium in the reduction product of C_6-D compound, as indicated by the mass spectral data, is actually present in C_7 and not in C_6, from the NMR spectrum of the product. As shown in Chart 2, this can be explained by assuming that deuterium in C_6 transferred to C_7 through 1,2-shift.

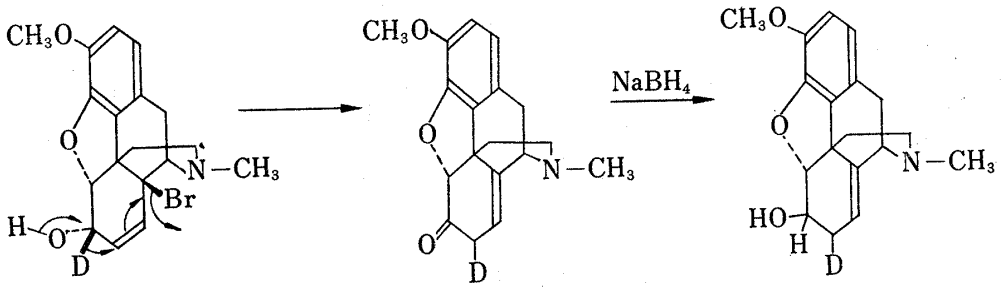

Chart 2

It has become clear from this evidence that in the formation of isoneopine, 1,4-elimination route and deuterium shift route occur at the same time in approximately the same ratio. It is already known that in the reduction of neopinone (VII) with sodium borohydride, approximately equal amounts of neopine (III) and isoneopine (IV) are formed. In this reaction, the formation of isoneopine is accompanied by the formation of the corresponding amount of neopine. With consideration on the yield of products from the present reduction, it may be assumed that about 10% of neopine has been formed through the ketonic intermediate, and about one-half of this reaction is occupied by the route of deuterium shift, as in the case of isoneopine. The remainder is formed through the SN_2' type reaction route in which C_6-H

7) Quantitative determination of deuterium in the sodium borodeuteride used as the reagent was made by mass spectrum[8] and the value of 96.8% was obtained. A small amount of 14-bromocodeinone (I) was found to be present as an impurity in 14-bromocodeine (II) used as the starting material because II is so labile that its complete purification is impossible. IR spectral determination of I present in II, after its preparation by the standard procedure and purification, showed the amount to be *ca.* 5%. From these facts, this deuterium content of indolinocodeine was used as a standard in the deuteration in this reaction.

8) G.G. Swain, *J. Am. Chem. Soc.*, 82, 5949 (1960); T. Frund, *J. Inorg. & Nuclear Chem.*, 9, 246 (1959).

does not take part at all. These considerations can explain the above-mentioned mass and NMR data without inconsistence.

The foregoing evidences are summarized and illustrated in Chart 3.

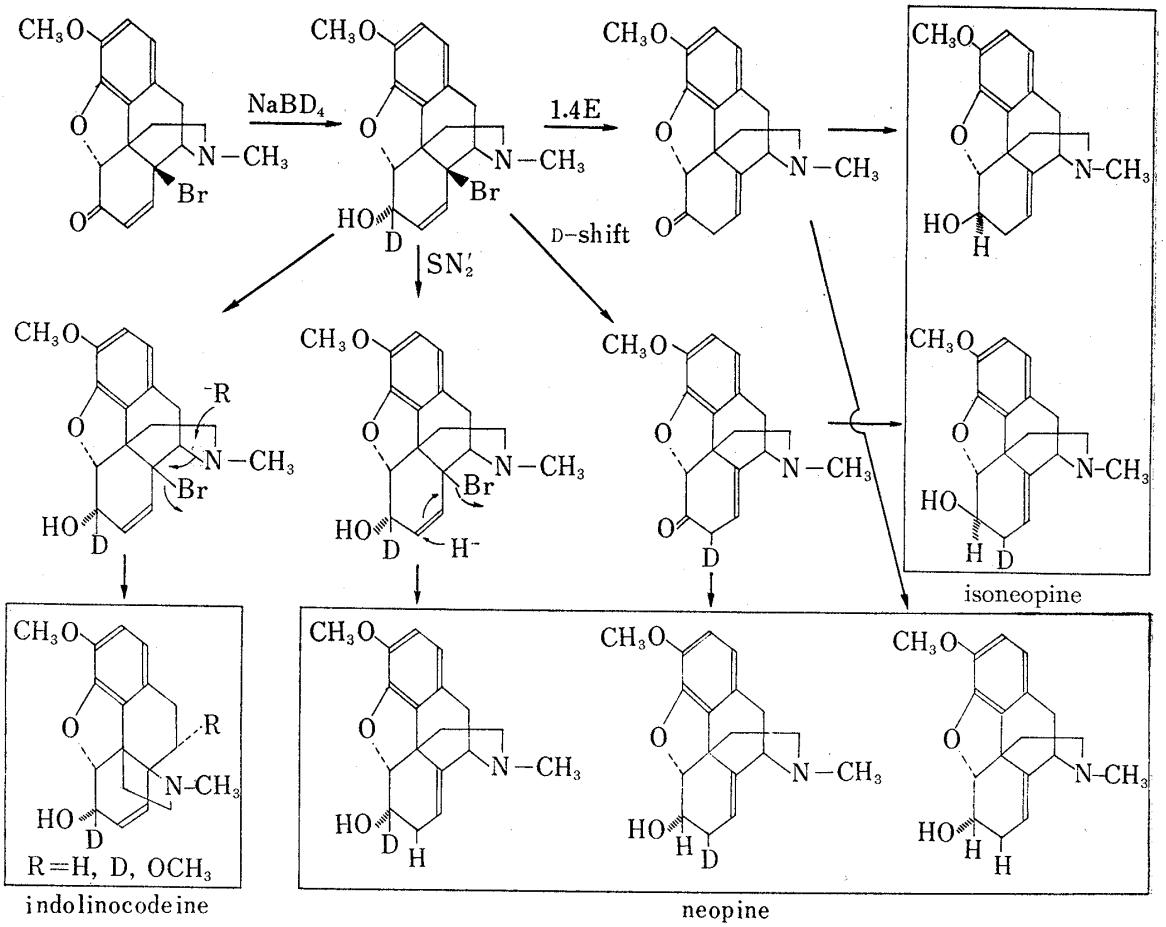

Chart 3

Experimental

Melting points were uncorrected. IR spectra were recorded on Japan Spectroscopic Co., Model DS-402 spectrophotometer, in chloroform solution or in nujol pastes. 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. Chemical shifts were given in δ values and coupling constants (J) in cps. Following abbreviations are used for the representation of NMR data: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. Mass spectra were recorded on Hitachi RMU-6D Mass Spectrometer, under following conditions, Ion Accel Volt, 1800V; Ionization Volt, 70—80 eV; Ion temp, 200—220°; and direct sample introduction system with vacuum lock.

Reduction with $NaBH_4$——Sodium borohydride reduction of I and/or II was carried out as reported in the preceding papers of this series.[1,4]

Reduction with $NaBD_4$——This reduction was carried out by means of the standard procedure as employed for reduction with $NaBH_4$. Identification and purity of the products were carefully checked by their physical constants (melting points, thin-layer and gas-liquid chromatographic data, IR, NMR, and mass spectra).

Reduction of 14-Bromocodeine (II) with $NaBD_4$——To a stirring suspension of 1 g of II in 10 ml of MeOH was added a solution of 1 g of $NaBD_4$ in 5 ml of H_2O at 0° over a period of 5 min, and the mixed solution was stirred at room temp. (20°) for 15 min, and then at 40° for 30 min. After 5 ml of H_2O was added, most of MeOH in the reaction mixture was evaporated *in vacuo*, and extracted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4, evaporated to dryness to yield 0.8 g of a colorless oily substance, which contains four products identical respectively to be III to VI by comparison with the authentic samples on TLC and GLC as listed below.

Compounds	TLC (*Rf*) S[a]	TLC (*Rf*) A[b]	GLC[c] RT[d]	GLC[c] RRT[e]
Neopine	0.3	0.5	16.8	1.13
Isoneopine	0.3	0.25	19.8	1.34
Indolinocodeine	0.6	0.7	11.8	0.80
9α–Methoxyindolinocodeine	0.8	0.85	22.0	1.84

a) silica gel plate, solvent system: $CHCl_3$:MeOH=9:1
b) alumina plate, solvent system: $CHCl_3$:MeOH=99:1
c) apparatus: Barber Colman Model 10, with argon ionization detector, column, 1% XE-60 (nitril silicon) on chromosorb W, temp.: column, 190°; cell, 230°; flash heater, 215°; carrier gas pressure: 2kg/cm²
d) retention time given in minutes
e) relative retention time using codeine (R_t=14.0) as standard

The reaction products were separated with silica gel (Merck) column chromatography.

a) The first fractions eluted with pure benzene was recrystallized from MeOH to give colorless needles, (3.7 mg; 0.3%), mp 139—140°, which was identical with an authentic sample of 9α-methoxyindolinocodeine (VI) by comparison of the IR and NMR spectra and mixed melting point test.

b) The next fractions eluted with benzene–ether (1:1) and with pure ether gave 245 mg (30%) of 9α-*d*-indolinocodeine, which was recrystallized from *n*-hexane to give colorless needles, mp 103—105°, HBr salt; mp 263—265°, HCl salt; mp 253—255°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (–OH), Mass: *m/e* 300 (M^+, 100%), 301 (31.0%), 299 (16.0%), NMR: δ 6.60 (2H, s, aromatic C_1, C_2–H), around 6.00 (2H, sextet, olefinic C_7, C_8–H), 4.48 (1H, d, J=5.4, C_5–H), 4.23 (1H, t, J=5.4, C_6–H), 3.75 (3H, s, C_3–OCH_3), 2.43 (3H, s, N–CH_3).

c) The elution with ethyl acetate afforded a mixture of neopine and isoneopine, which was re-chromatographed on alumina (Woelm, activity grade III) column to give 420 mg of 7β-*d*-neopine from the eluate of benzene–ethyl acetate (1:1), and 80 mg of 6α-*d*-isoneopine from ethyl acetate.

i) 7β-*d*-Neopine: recrystallized from *n*-hexane to give colourless plates; mp 127°, HBr salt; mp; darkened at 250° and decomp. at 280°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (–OH), Mass: *m/e* 300 (M^+, 100%), 301 (35.1%), 299 (14.0%). NMR: δ 6.57 (2H, AB-q, J=8.2, C_1, C_2–H), 5.40 (1H, d, J=6.0, C_8–H), 4.57 (1H, d, J=5.0, C_5–H), 4.18 (1H, broad q, C_6–H), 3.82 (3H, s, C_3–OCH_3), 2.40 (3H, s, N–CH_3).

ii) 6α-*d*-Isoneopine: Recrystallized from acetone to give colorless plates mp 155—156°, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (–OH), Mass: *m/e* 300 (M^+, 100%), 301 (23.8%), 299 (20.0%). NMR: 6.57 (2H, AB-q, C_1, C_2–H), 5.41 (1H, t, J=6.5, C_8–H), 4.42 (1H, s, C_5–H), 3.82 (C_3–OCH_3), 2.27 (N–CH_3)

Reduction of 14-Bromocodeinone (I) with $NaBD_4$——To a stirring suspension of 1 g of I (finely powdered) in 10 ml of MeOH was added dropwise a solution of 0.5 g of $NaBD_4$ in 2 ml of H_2O over a period of 10 min, while the temperature was maintained at −5°—0° by external cooling. After the solution was stirred at 0° for another 20 min, the precipitate was collected by filtration, washed well with H_2O, and then with MeOH, dried *in vacuo* to give 850 mg (84%) of 6β-*d*-14-bromocodeine as pale yellow fine needles, mp 156° (decomp.), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (–OH), NMR: 6.64 (2H, AB-q, J=8.0, aromatic C_1, C_2–H), 5.85 (2H, s, olefinic C_7, C_8–H), 4.90 (1H, s, C_5–H), 3.85 (3H, C_3–OCH_3), 2.50 (3H, N–CH_3).

Reduction of 6β-*d*-14-Bromocodeine with $NaBH_4$——The product obtained above was further treated with $NaBH_4$ by means of the method as employed for reduction described above, and separation of the products as in the foregoing experiment afforded the corresponding labeled compounds.

i) 6β-*d*-Indolinocodeine: Mass: 300 (M^+, 100%), 301 (22.6%), 299 (25.0%). NMR: 5.90 (2H, AB-q, olefinic C_7, C_8–H), 4.48 (1H, s, C_5–H), 1.00 (1H, t-d, J=14, 4 cps. $C_{9\alpha}$–H).

ii) 6β-*d*-Neopine: Contains about 20% of neopine (III) from NMR and Mass spectra. Mass: *m/e* 300 (M^+, 100%), 301 (31.0%) 299 (28.0%). NMR: 5.45 (1H, t, J=4.5, C_8–H), 4.60 (1H, s, C_5–H) 4.16 (0.2H from area intensity, m, C_6–H).

iii) 7-*d*-Isoneopine: Mass: *m/e* 300 (M^+, 100%), 299 (95.2%), 301 (23.8%). NMR: 5.81 (1H, distorted doublet, C_8–H), 4.42 (1H, d, J=5.5, C_5–H), 3.63 (1H, m, C_6–H).

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