[Chem. Pharm. Bull. 13(9)1092~1103(1965)] UDC 615.783.1.-011

143. Shigenobu Okuda,*1 Sadao Yamaguchi,*2 and Kyosuke Tsuda*1 : Studies on Morphine Alkaloids. II.*3 Indolinocodeine. I.*4 A New Skeletal Rearrangement of 14-Bromocodeine.

(*Institute of Applied Microbiology, University of Tokyo*1 and *Research Laboratories, Sankyo Co., Ltd.*2)

Sodium borohydride reduction of 14-bromocodeinone (I) was reported to give first 14-bromocodeine (II) which could be further reduced into neopine (III) with the same reagent.[1] It was suggested that the course of reaction from II to III might be formulated either as a direct S_N2' attack of complex hydride ion upon C_7 or more probably, as a base catalyzed 1,4-elimination of hydrogen bromide yielding neopinone enol (IV), which was reduced after ketonization.

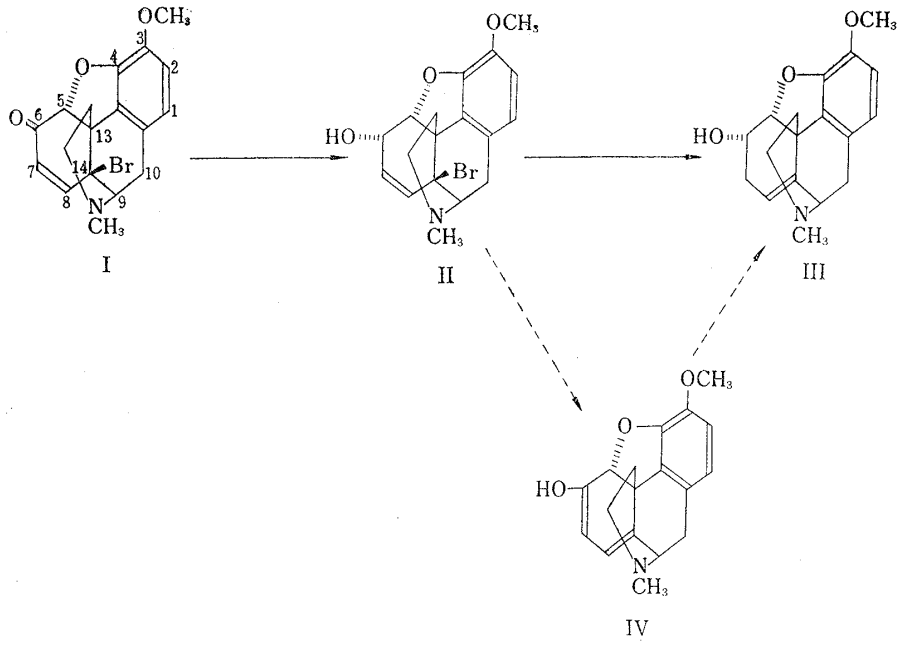


Chart 1.

In the course of substrate preparation for microbial transformation studies,[2] sodium borohydride reduction of I and II were carried out as described in literature[1] and in both cases three products, compound A ($Rf_{(7.0)}$: 0.85), B ($Rf_{(7.0)}$: 0.65), and C ($Rf_{(7.0)}$: 0.30), were detected with Büchi's paper partition chromatography (P.P.C.)[3] Silica gel chromatography of reaction mixture served for the isolation of the above three substances, compound A (eluted with ether), B (eluted with 9:1 ether-acetone) and C (eluted with acetone) in 30, 10, and 50% yield, respectively.

*1 Mukogaoka-yayoicho, Bunkyo-ku, Tokyo (奥田重信, 津田恭介).
*2 1-Chome, Hiromachi, Shinagawa-ku, Tokyo (山口定男).
*3 Part I. S. Okuda, S. Yamaguchi, Y. Kawazoe, K. Tsuda : This Bulletin, **12**, 104 (1964).
*4 Preliminary communications of this work appeared in J. Org. Chem., **27**, 4121 (1962) and "The 7th Symposium on the Chemistry of Natural Products, Japan" (Fukuoka, Oct., 1963), Symposium Abstract, p. 72 (1963).

1) H. Conroy : J. Am. Chem. Soc., **77**, 5960 (1955).
2) M. Yamada, K. Iizuka, S. Okuda, T. Asai, K. Tsuda : This Bulletin, **10**, 981 (1962).
3) J. Büchi, R.Huber, H. Schumacher : Bull. Narcot., **1960**, April~June, 25.

Both the hydrochloride and hydrobromide of compound A are sparingly soluble in ethanol, acetone, aqueous ethanol or aqueous acetone. The hydrobromide of compound C is sparingly soluble in water, ethanol or acetone, but the hydrochloride is easily soluble in water or aqueous ethanol. On the other hand, the corresponding salts of compound B are not crystalline and easily soluble in the above solvents. Therefore isolation of these three products was also effected by utilization of solubility differences of the salts as shown in Fig. 1.

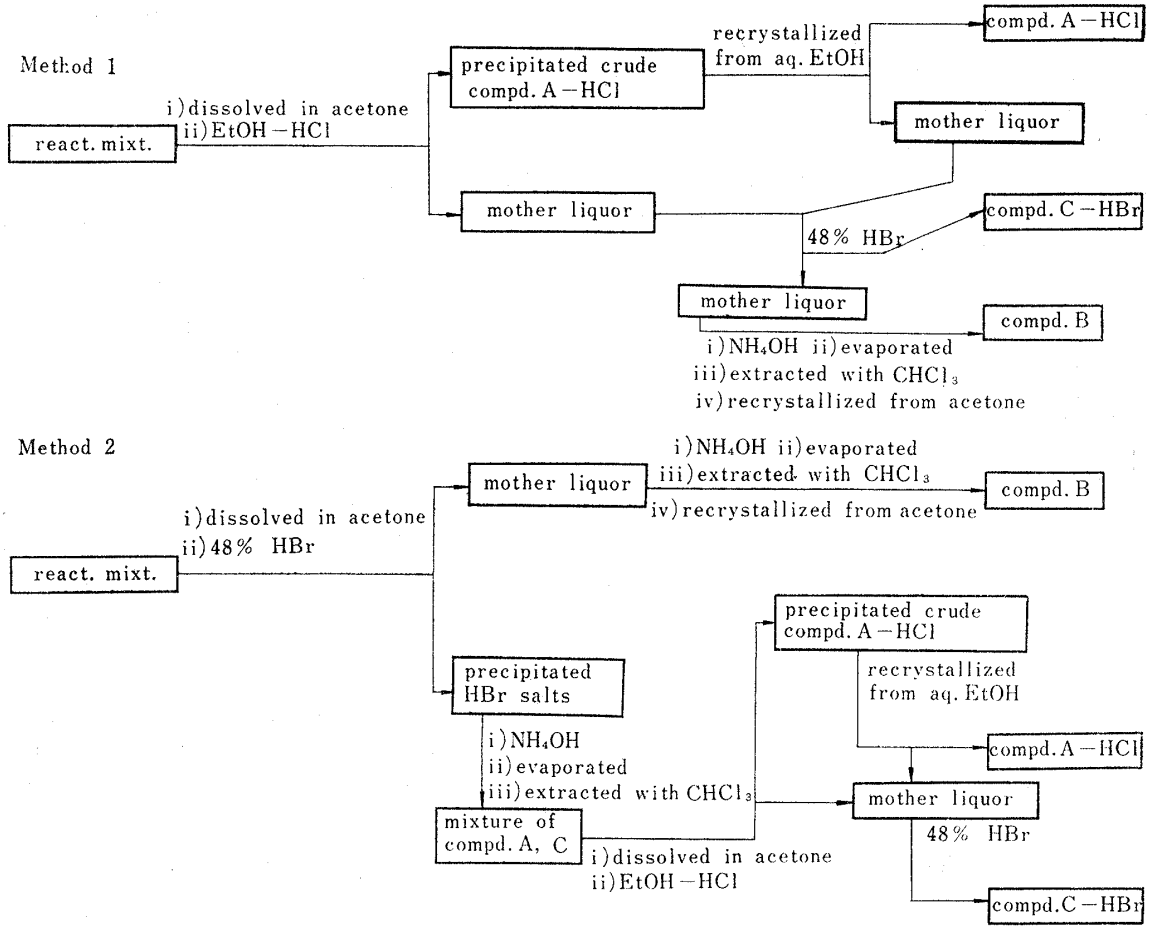
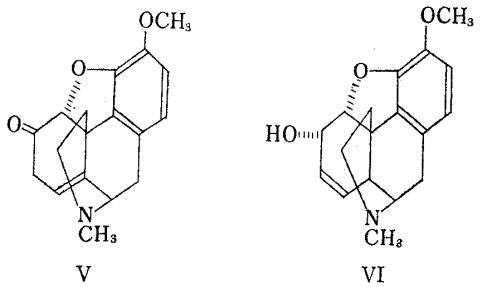


Fig. 1.

Compound C was a main product and, as expected, proved to be neopine (Ⅲ) by comparison with authentic specimen prepared by sodium borohydride reduction of neopinone (Ⅴ) according to Conroy's description.[1]



Ⅴ Ⅵ

Chart 2.

Although both empirical formula of compound A and B are same as that of codeine (Ⅵ), *viz.* $C_{18}H_{21}O_3N$, these corresponded neither to Ⅵ nor to any other codeine isomer of known structure. On the other hand, two reduction products of 14-bromocodeinone (Ⅰ) with unknown structures were reported and those are ketone compounds resulting from treatment with sodium hydrosulfite[4] and a lithium

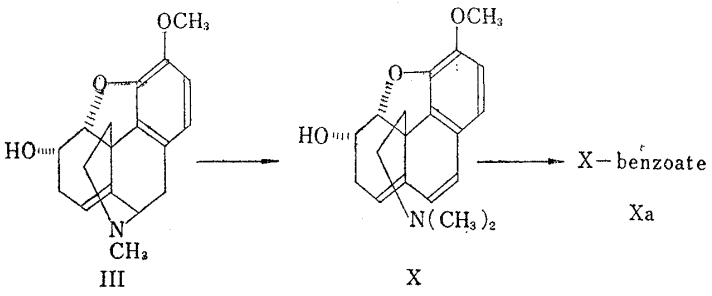
4) E. Speyer, H. Rosenfeld : Ber., 58, 1117 (1925).

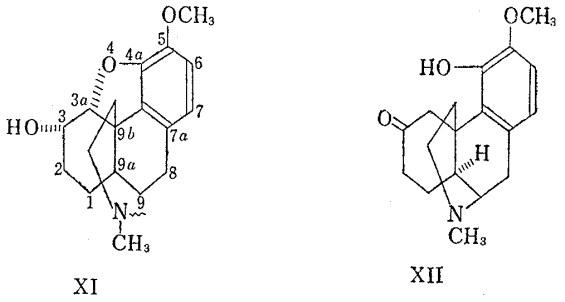
aluminum hydride[5] reduction compound with probably C_4-C_5 ether bridge opened. However neither of them was identical with compound A or B.

1) Structure Elucidation of Compound A

Compound A, m.p. 129~131°, $[\alpha]_D^{20}$ +23.7° (chloroform), $C_{18}H_{21}O_3N$, gave a monohydrochloride, m.p. 249~254°, and monohydrobromide, m.p. 262~266°.

a) Allylic alcohol system : Compound A exhibited OH-absorption (3600 cm^{-1}) in infrared spectrum (chloroform) and gave a monoacetate, m.p. 66°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1740 (acetyl), on heating with acetic anhydride at 80~85° for 8 hr. Catalytic hydrogenation of compound A with platinum dioxide afforded a dihydro derivative (Ⅶ) after one mole-equivalent hydrogen was absorbed. Rapoport[6] reported that allylic alcohol oxidation with silver carbonate was successfully applied to codeine (Ⅵ) yielding codeinone. Treatment of compound A with freshly prepared silver carbonate in hot benzene afforded a 60% yield of the corresponding α,β-unsaturated ketone (Ⅷ), m.p. 125~126°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1700 (α,β-unsaturated ketone). This proved the presence of allylic alcohol moiety in compound A.





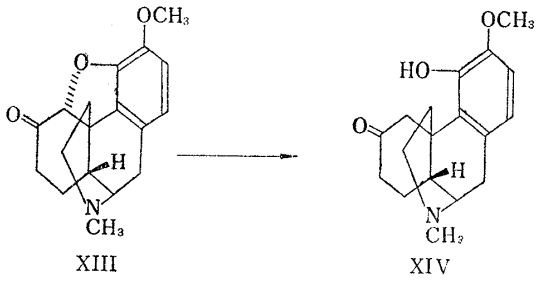


Chart 3.

b) 5-Methoxy-9*b*-(2-methylaminoethyl)-3,3*a*,8,9,9*a*,9*b*-hexahydrophenanthro[4,5-*bcd*]furan-3-ol skeleton: Methiodide (Ⅸ) of compound A, m.p. 236~238°, was dissolved in 20% ethanollic potassium hydroxide and heated for one hr. to effect Hofmann degradation. The resulting methine base was purified through silica gel column chromatography and converted into a benzoate, m.p. 154~156°, which was identified with authentic β-codeimethine benzoate (Xa)[7] prepared by Hofmann degradation of neopine (Ⅲ).

As described above, an allylic alcohol grouping exists in compound A. Therefore it is clearly shown that this compound possess a 5-methoxy-9*b*-(2-methylaminoethyl)-3,3*a*,8,9,9*a*,9*b*-hexahydrophenanthro[4,5-*bcd*]furan-3-ol skeleton (Ⅺ)*5 and should be an isomer of codeine (Ⅵ), regarding the connection of the methylaminoethyl nitrogen or B/C ring juncture.

To confirm whether or not compound A is a B/C ring juncture

*5 During Hofmann degradation, Δ^7-double bond shift occured yielding a diene conjugated with ring A. A similar alternation was observed in the conversions from α- or γ-codeimethine to β- or δ-codeimethine (cf. Knorr, *et al.* : Ber., **35**, 3009, 3010, (1902). Pschorr, *et al.* : Ber., **39**, 19 (1906).

5) F. Krausz, T. Rull : Bull. soc. chim. France, **1960**, 2148.
6) H. Rapoport, H. N. Reist : J. Am. Chem. Soc., **77**, 490 (1955).
7) L. Small : J. Org. Chem., **12**, 359 (1947).

isomer of Ⅵ, the comparison between *trans*-dihydrothebainone (Ⅻ)[8] and a corresponding C_4-C_5 ether bridge opened derivative*[6] from compound A was attempted. Schöpf, *et al.*[9] reported that on heating with zinc dust and ammonium chloride in ethanol, a facile reductive ether bridge opening of dihydrocodeinone (XIII) took place affording *cis*-dihydrothebainone (XIV). Oppenauer oxidation of dihydro derivative (Ⅶ) of compound A afforded a saturated ketone (XV), which was treated as in the case of XIII. As expected, reductive ether ring opening gave rise to a dihydro phenolic ketone (XVI), m.p. 196~198°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3580 (phenol-OH), 1709 (saturated C=O), $C_{18}H_{23}O_3N$, $[\alpha]_D^{20}$ +18.0° (ethanol). However the physical constants of this compound were unambiguously different from those reported of *trans*-dihydrothebainone (Ⅻ) or *cis*-dihydrothebainone (XIV).[7,8] Accordingly, compound A is not an isomer of codeine (Ⅵ) with respect to the B/C ring juncture but should be an isomer involving the position of attachment of iminoethano nitrogen.

c) Assignment of indolinocodeine structure to compound A : To confirm the point of attachment of iminoethano bridge in compound A, nuclear magnetic resonance spectra of this series were compared with those of morphine series.[2] As shown in Fig. 2, the

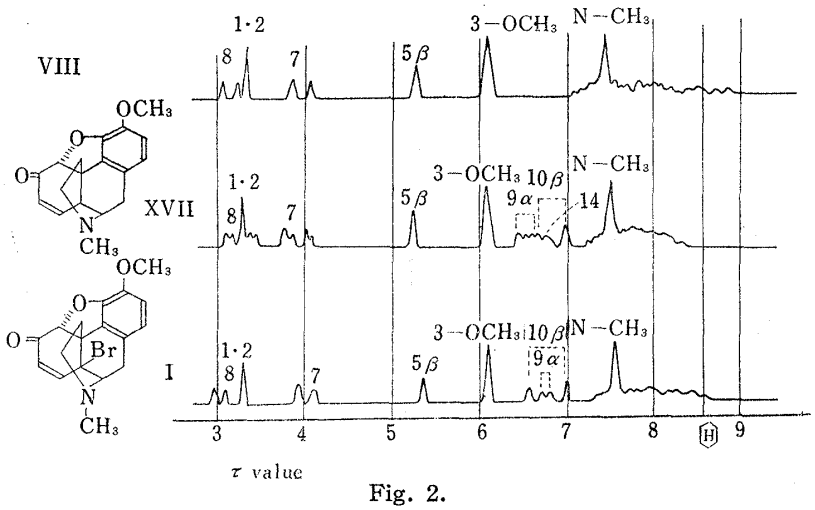


Fig. 2.

double bond protons of α,β-unsaturated ketone exhibited ABX-type in codeinone (XVII). On the other hand, the signals of corresponding protons in 14-bromocodeinone (I) and the α,β-unsaturated ketone (Ⅷ) derived from compound A were both AB-type. This fact definitely indicates the absence of a hydrogen at C_{14}-position in Ⅷ, *viz.* the existence of a C_{14}-C_{13} iminoethano bridge. Therefore we concluded that compound A is represented by formula XVIII, in which a hydroindole structure is comprised instead of hydroisoquinoline skeleton in the case of morphine series. According to IUPAC nomenclature, XVIII is (3*S*:3*aR*:9*aS*:9*bR*)-5-methoxy-10-methyl-3,3*a*,8,9-tetrahydro-9*a*,9*b*-iminoethanophenanthro[4,5-*bcd*]furan-3-ol. We propose indolinocodeine*[7] as a conventional name of XVIII because of its partial hydroindole structure.

Structure (XVIII) is further supported by the significant differences in nuclear magnetic resonance absorption patterns between indolinocodeine and morphine series. In the spectra of the latter series, signals of $C_{9\alpha}$ and $C_{10\beta}$ appear in a region between the absorptions of methoxyl and N-methyl. In contrast with the above case, those in

*6 Hereafter numbering similar to morphine is employed for compound A (XVIII) and derivatives.
*7 Hereafter a conventional name similar to morphine alkaloid is temporally proposed for this series derivative employing a prefix "indolino."
8) L. Small, G. L. Browning : J. Org. Chem., 3, 618 (1939).
9) C. Schöpf, T. Pfeifer : Ann., 483, 157 (1930).

indolinocodeine derivatives do not appear in this area but are notably shifted upfield. This interesting difference can be rationalized as follows. Since protons at $C_{10\beta}$ in morphine derivatives are deshielded by a magnetic anisotropy of nitrogen[10] and those on $C_{9\alpha}$ by an electrostatic effect of nitrogen, these signals are observed in that region. However these effects do not operate in indolinocodeine series because a position of attachment of iminoethano nitrogen is shifted from $C_{9\beta}$ to $C_{14\beta}$.

The chemical reactions, carried out for confirmation of the structure of indolinocodeine (XVIII), are illustrated in Chart 4.

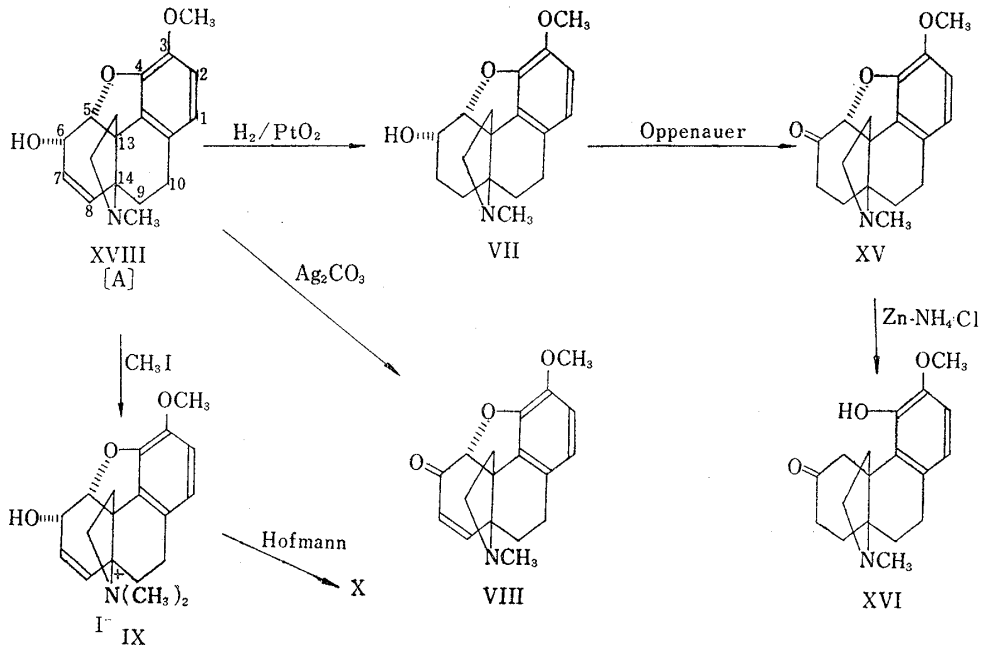


Chart 4.

2) Structure Elucidation of Compound B

Compound B, m.p. 155~156°, $[\alpha]_D^{20}$ −7.5° (chloroform), $C_{18}H_{21}O_3N$, exhibited OH-absorption (3600 cm^{-1}) in infrared spectrum (chloroform) and gave a monoacetate. Catalytic hydrogenation of this compound with platinum dioxide in 5% hydrochloric acid afforded dihydro derivative, which was identical to dihydroisocodeine (XIX) prepared *via* epimerization of dihydrocodeine (XX) on heating with aluminum isopropoxide.[11]

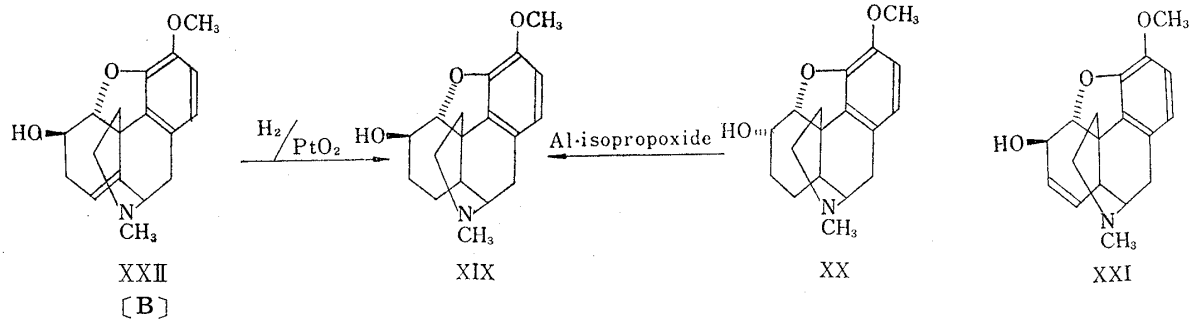


Chart 5.

10) S. Yamaguchi, S. Okuda, N. Nakagawa : This Bulletin, **11**, 1465 (1963).
11) M. M. Baizer, A. Loter, K. S. Ellner, D. R. Satrianan : J. Org. Chem., **16**, 530 (1951).

Compound B differed from isocodeine (XXI) and should be an isomer of isocodeine regarding the double bond position. Consequently compound B is XXII and named isoneopine*[8] since this is a 6β-OH isomer of neopine.

The nuclear magnetic resonance patterns of isoneopine (XXII) and monoacetate are quite similar to those of III and its corresponding acetate respectively, except the absorptions of C_6-H and C_6-OAc.*[9] This also supported the above structure assignment of isoneopine (XXII).

3) Reaction Mechanisms

Although Conroy[1] reported that sodium borohydride reduction of 14-bromocodeinone (I) gave rise to only neopine (III) probably by a base catalized 1,4-elimination or S_N2' reaction of 14-bromocodeine (II), it was demonstrated as mentioned above that in this reaction isoneopine (XXII) and indolinocodeine (XVIII) were also produced besides the main product neopine (III).

To obtain information regarding the reaction mechanism, variation of products depending on changes of reaction conditions was examined. Summing up a number of experimental data, the following results were observed.

1) A significant change in yields of three products was not observed in experiments utilizing aqueous methanol or ethanol as solvent. However, in the case of reaction in absolute methanol or ethanol, compound D*[10] was obtained besides neopine (III) and isoneopine (XXII) but no trace of indolinocodeine (XVII) was detected. When a solvent, immiscible with water, such as chloroform or benzene, was used, this reaction did not proceed.

2) When the pH of reaction mixture was maintained below 9.0 or over 11.5, indolinocodeine (XVIII) was not produced. In the latter case neopine (III) and isoneopine (XXII) were obtained, and in the former case compound D was also detected in addition to the above two.

3) If lithium aluminum hydride was used instead of sodium borohydride, neopine (III) and isoneopine (XXII) were only the products. This is probably due to absence of water under this conditions.

4) Reaction temperature or period did not significantly affect yields of products.

5) Addition of zinc or lead acetate also did not significantly influence this reaction.

6) It was reconfirmed that sodium borohydride reductions of 14-bromocodeinone (I) and 14-bromocodeine (II) gave rise to the same results.

Consequently the following conclusions regarding reduction products were reached. 1) indolinocodeine (XVIII) is produced only in presence of water and at a pH between 9~11.5, 2) both neopine (III) and isoneopine (XXII) are obtained in all cases.

Discussion

Sodium borohydride reduction of 14-bromocodeine (II) afforded the same products as in the case of reduction of 14-bromocodeinone (I). This fact indicates that II is the first reaction intermediate which is reduced into three products by subsequent reactions. Conroy[1] also pointed out II as an intermediate but nothing was further mentioned regarding this compound. We examined purity of II utilizing p.p.c. and realized that this was sufficiently pure for further investigation. It is well known that the

*[8] This nomenclature is similar to the case of codeine and isocodeine.

*[9] cf. Part I : This Bulletin, **12**, 104 (1964).

*[10] Compound D showed $Rf_{(7.0)}$ 0.75. Although purification of this compound was not accomplished, this seemed to be a C_4-C_5 ether bridge opened derivative because of its blue green color with ferric chloride.

sodium borohydride reduction of codeinone,[12] 1-bromocodeinone,[12] or 14-hydroxycodeinone[13] always proceeds stereospecifically yielding only 6α-OH derivative but never 6β-OH isomers. Therefore $C_{6\alpha}$-OH orientation in II is reasonably assigned. An S_N2' attack of hydride ion on II produces only neopine (III) and 1,4-elimination affords an enol (IV) of neopinone which after ketonization, is reduced to the alcoholic derivative. If, as Conroy reported,[1] the sodium borohydride reduction of neopinone (V) also proceeds affording only neopine (III), isoneopine (XXII) should not be produced from II. However we found that sodium borohydride treatment of neopinone (V) afforded approximately the same amounts of both neopine (III) and isoneopine (XXII), and rationalized the above inconsistency as follows : 1,4-elimination of bromine in II followed by ketonization and then nonstereospecific reduction yielded both 6α-OH (III) and 6β-OH (XXII) derivative. If in the reaction in question, 1,4-elimination procedure is a main path for III and XXII, the yields of these two should be roughly equal. Actually the yield ratio of III and XXII is about 5:1. Consequently S_N2' reaction, which gives only II, might play some important part in production of III.

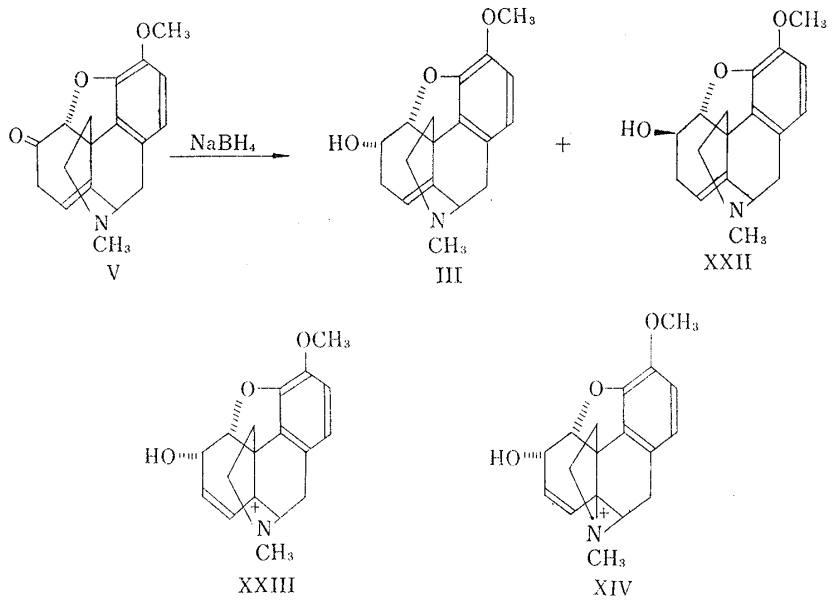


Chart 6.

In respect to the formation of indolinocodeine (XVIII) the following scheme is proposed. An S_N1 type bromine elimination of II gives rise to a C_{14} cation (XXIII) which is converted into a cyclic ammonium cation (XXIV) involving participation of the nitrogen lone pair.*[11] Then reductive cleavage between N-C_9 of this cyclic cation*[12] by a complex hydride ion yields indolinocodeine (XVIII). Under the absence of water or below pH 9, S_N1 reaction was completely suppressed and indolinocodeine (XVIII) was not produced. On the other hand, when the basicity of reaction mixture is increased, 1,4-elimination might be accelerated suppressing the formation indolinocodeine (XVIII) in inverse ratio. The reaction scheme of sodium borohydride reduction of 14-bromocodeine (II) is summerized below.

*[11] Since lone pair of iminoethano nitrogen and a vacant orbital in a C_{14} cation (XXIII) is located in 1,3-diaxial relation, a facile formation of cyclic cation (XXIV) is expected.

*[12] Since the backside of N-C_9 is less hindered than that of N-C_{14}, a complex hydride ion attack stereospecifically occurs from the former resulting in N-C_9 bond cleavage.

12) M. Gates : J. Am. Chem. Soc., **75**, 4340 (1953).

13) *a*) L. J. Sargent, L. H. Schwartzman, L. Small : J. Org. Chem., **23**, 1247 (1958). *b*) A. C. Currie, J. Gillon, G. T. Newbold, F. S. Spring : J. Chem. Soc., **1960**, 773.

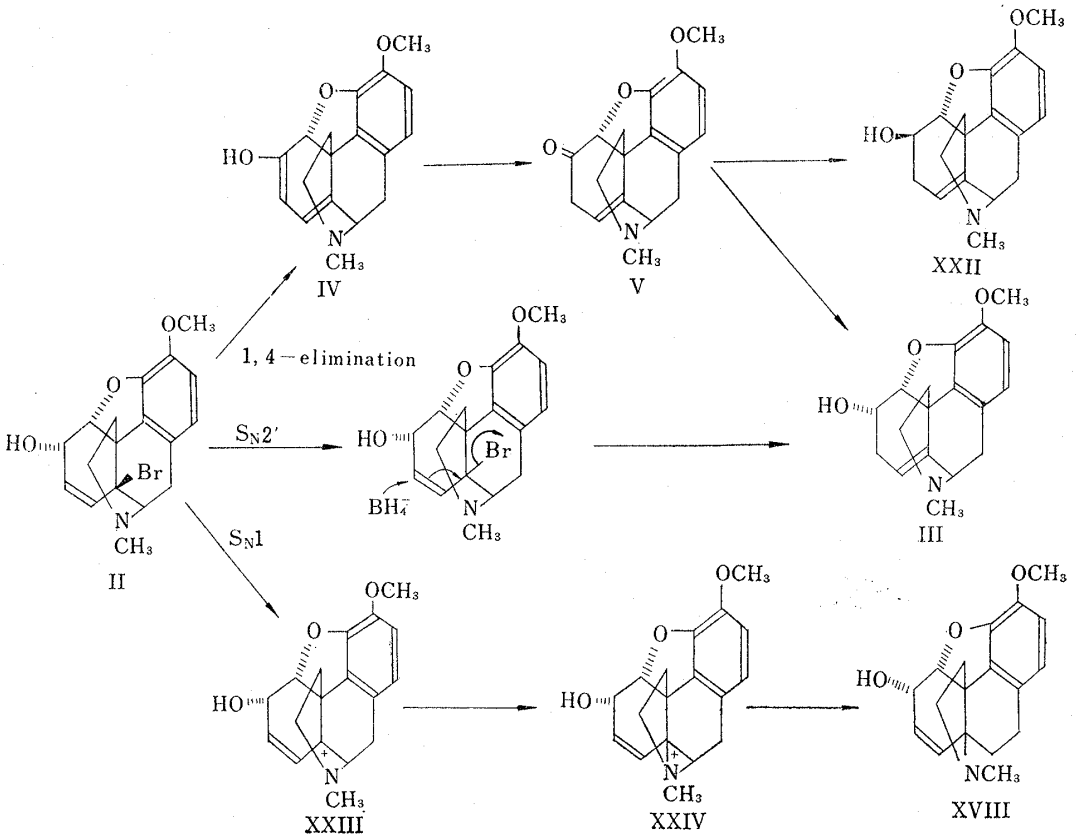


Chart 7.

Experimental*13

14-Bromocodeinone (I)——This was prepared according to the description of Conroy.[1] To a suspension of 218 g. (0.7 mol.) of thebaine in 700 ml. of acetone-H_2O (2:1), stirred mechanically, was added a solution of 130 g. (0.7 mol. × 1.04) of N-bromosuccinimide, m.p. 173°, in 1400 ml. of acetone-H_2O (2:1) over a period of 15 min. The temperature was maintained at 15~18° by external cooling during the addition, and for additional 10 min. To the reaction mixture was added 1750 ml. of H_2O over a period of 30 min. with stirring, at which point 14-bromocodeinone began to crystallize. Stirring was continued for 1 hr. at 20°, and then for another 2 hr. at 0~5°. The product was sucked dry and washed with 500 ml. of H_2O. The yield, after drying at 60°, was 179 g. For the purpose of purification this crude product was dissolved in acetone under warming and insoluble material was removed by filtration after adding a small amount of active charcoal. To the filtrate was added a small amount of EtOH and after cooling to 0°, 75 g. of pure 14-bromocodeinone separated as a yellowish silky needles, IR ν_{max} cm^{-1}: 1679 (C=O). Concentration of mother liquids gave a second crop of 41 g. When the sample is inserted in a melting-point apparatus heated to 157°, it melts immediately, but if inserted at 154° or below, it dose not melt even if the temperature is raised above 200°.

Sodium Borohydride Reduction of 14-Bromocodeinone (I)——To a stirring suspension of 50 g. of I in 500 ml. of MeOH was added 100 ml. of 15% H_2O solution of $NaBH_4$ dropwise over a period of 20 min. at 0~5°, after stirring during 20 min. at 0°, a further 250 ml. of 15% H_2O solution of $NaBH_4$ was added

*13 All melting points are uncorrected. Procedure A of Büchi's paper partition chromatography was employed with Toyo Roshi paper No. 51-A treated with Kolthoff buffer solution, isobutanol-toluene (1:1) mixture saturated with water as mobil phase. Either ascending or descending development was used at 20±2°. For detection of alkaloides, ultraviolet light or Dragendorff reagent was utilized. As Rf values are variable owing to pH of buffer solution, the pH value is stated in ( ) to the right side of Rf. Buffer solutions of (pH : 4.5, 5.6, 6.3, 7.0 and 7.7) were employed. Infrared spectra were taken in chloroform solutions unless otherwise specified. NMR spectra were determined at 60 megacycles/second with a Varian Associates D. P. 60. High Resolution NMR Spectrometer. The compounds were examined in a 2~10% solutions in chloroform. The chemical shifts are given in τ values calibrated using cyclohexane as an internal standard (τ cyclohexane = 8.564).

for 10 min. After stirring at 40° during 2 hr., 50 ml. of 10% $NaBH_4$ solution was added, and most of MeOH in the reaction mixture was evaporated *in vacuo*. The bases were extracted thoroughly with $CHCl_3$, washed with H_2O, dried over Na_2SO_4, evaporated to dryness to yield 37 g. (93%) of a colorless glass whose p.p.c. showed three spots, $Rf_{(7.0)}$: 0.85 (A), 0.65 (B), 0.30 (C). Five grams of the product was chromatographed on 150 g. of silica gel. First, elution with 2 L. of ether afforded 1.41 g. (28%) of A (indolinocodeine), second with 1 L. of ether-acetone (9:1) 0.32 g. (6%) of B (isoneopine), with a further 1 L., 0.38 g. (7%) of mixture of B and C (neopine), and lastly with acetone 2.30 g. (46%) of C (neopine).

Indolinocodeine (A)——Compound A was recrystallized from H_2O-MeOH to give rods, m.p. 129~131°, $[\alpha]_D^{20}$ +23.7° (c=1.1, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07; N, 4.68. Found : C, 72.51; H, 7.10; N, 4.77. A-HCl : from H_2O-EtOH, a needles, m.p. 249~254°. *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot HCl$: C, 64.37; H, 6.60; N, 4.32. Found : C, 64.11; H, 6.67; N, 4.32. A-HBr : prepared by neutralizing with 48% HBr in EtOH gave rods, m.p. 262~266°. *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot HBr$: C, 56.85; H, 5.83; N, 3.68. Found : C, 56.50; H, 5.91; N, 3.68.

A-monoacetate (acetylindolinocodeine) : Acetylation of indolinocodeine was carried out with 5 ml. of acetic anhydride by heating at 80~85° for 8 hr. after addition of 5 ml. of absolute EtOH, the solution was allowed to stand overnight. Most of the organic solvent was evaporated *in vacuo*, and the resulting residue was dissolved in $CHCl_3$, and the solution was washed with 2% NH_4OH, dried over Na_2SO_4, and evaporated *in vacuo* to afford a gum which was crystallized from ether into cubes, m.p. 65~66°, IR ν_{max} cm^{-1} : 1740 (R-C-O-), $Rf_{(7.0)}$: 0.98.

Isoneopine (B)——Compound B was recrystallized from acetone to give rods, m.p. 155~156°, $[\alpha]_D^{20}$ −7.5° (c=1:0, $CHCl_3$). *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07; N, 4.68. Found : C, 72.01 : H, 7.00; N, 4.68. mol. wt. (micro Rast) : 273. The HCl, HBr, oxalic acid and tartaric acid salts could not be crystallized.

B-monoacetate (acetylisoneopine) : Heating of 2 g. of B, with 5 ml. of acetic anhydride at 80~85° for 3 hr., gave a gum, which was recrystallized from MeOH-ether to afford cubes, m.p. 121~122°, IR ν_{max} cm^{-1} : 1740 (R-C-O). *Anal.* Calcd. for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found : C, 70.32; H, 6.79; N, 4.23.

Neopine (C)——Compound C was treated with 48% HBr in EtOH to afford the crystalline C-HBr. Recrystallization from H_2O-EtOH gives cubes, m.p. 282~283°, undepressed upon admixture with authentic neopine hydrobromide, $[\alpha]_D^{20}$ +17.5°. IR spectra of the two samples in Nujol mulls were identical.

Separation of Reduction Products utilizing Solubility Differences of the Salts——1) A solution of 20 g. of reduction products in 50 ml. of acetone was neutralized with alcoholic hydrochloric acid. Crystalline A-HCl was added and the seeded mixture was allowed to stand at 0° for 1 day. The crystals were sucked dry and twice recrystallized from H_2O-EtOH to give 5.8 g. of A-HCl, m.p. 248~254° (single spot in p.p.c.). The recrystallization mother liquors were concentrated to give a second crop, 0.8 g., m.p. 230~245°, whose p.p.c. showed a trace of C besides A. The second mother liquor was combined with the filtrate and 10 ml. of 48% HBr was added. Standing at 0° for 1 day afforded crude C-HBr, which was twice recrystallized from H_2O to give 8.6 g. of crystals, m.p. 282~283° (single spot in p.p.c.). Concentration of mother liquors afforded 3.0 g. of a second crop, m.p. 280~283°. The combined mother liquors were made alkaline by addition of 10% NH_4OH, and most of the organic solvent was removed by distillation *in vacuo*. The organic base was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporatod *in vacuo* to leave 3.1 g. of a gum, whose p.p.c. showed 3 spots. Three times recrystallization from acetone gave 1.6 g. of B, m.p. 155~156° (single spot in p.p.c.).

2) A solution of 32 g. of reduction products in 100 ml. of acetone was neutralized first with 48% HBr. A mixture of C-HBr and A-HBr were separated from the solution. To the mother liquor was added H_2O, and the most part of acetone was evaporated. The resulting H_2O-solution was decolorized with active charcoal, made alkaline with NH_4OH, and the organic bases were extracted with $CHCl_3$. Concentration of the extract gave 5.0 g. of a gum whose p.p.c. showed 3 spots. Three recrystallizations from acetone gave 2.2 g. of B, m.p. 155~156° (single spot in p.p.c.). The previously separated mixture of crystalline hydrobromides was converted into free bases by addition of NH_4OH, which were combined with the above mother liquors. Removal of organic solvent by distillation left a gum. It was taken up into acetone and neutralized with alcoholic hydrochloric acid to separated crude A-HCl which was recrystallized from H_2O-EtOH, yielding 9.5 g., m.p. 248~254° (single spot in p.p.c.). From mother liquors 1.1 g. of a second crop was obtained. C-HBr was obtained from the filtrate by addition of 48% HBr as crystals, first crop 13.8 g., m.p. 282~283°, second crop 5.0 g.

Hofmann Degradation of Indolinocodeine (A)——To a solution of 500 mg. of A in 5 ml. of EtOH was added 1.5 ml. of CH_3I, and the mixture was refluxed for 1 hr. On cooling, A-CH_3I (K) separated yielding 510 mg., m.p. 236~238°, $[\alpha]_D^{20}$ +5.47° (c=1.0, H_2O). *Anal.* Calcd. for $C_{18}H_{21}O_3N \cdot CH_3I$: C, 51.71; H, 5.49; N, 3.81. Found : C, 51.71; H, 5.47; N, 3.46. A mixture of 400 mg. of A-CH_3I in 10 ml. of 20% KOH and 5 ml. of EtOH, was refluxed for 1 hr. After most of EtOH was evaporated *in vacuo*, the bases were thoroughly extracted with $CHCl_3$. Combined extracts were washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting residue was purified by chromatography on silica gel. Eluates with benzene-acetone (1:1) exhibited one spot in p.p.c., $Rf_{(5.6)}$: 0.36. This was taken to hot EtOH, neutralized

with benzoic acid and then cooled to give indolinocodeimethine benzoate as needles, m.p. 154~155°. *Anal.* Calcd. for $C_{26}H_{29}O_5N$: C, 71.70; H, 6.71; N, 3.22. Found : C, 71.46; H, 6.92; N, 3.26. This was identified as β-codeimethinebenzoate (Xa) prepared below by the comparison of melting point, mixed melting point and IR (Nujol).

β-Codeimethine Benzoate (Xa)——According to the method of Small,[7] neopine (Ⅲ) was derived to β-codeimethine (X), which was converted into a benzoate (Xa), m.p. 154~155° (ref. : m.p. 157°), by neutralization with benzoic acid.

Dihydroindolinocodeine (VII)——A solution of 1.0 g. of A-HCl in 20 ml. of H_2O-EtOH easily hydrogenated at atmospheric pressure and room temperature over 0.1 g. of PtO_2 catalyst. After 3 hr. 1.0 mole-equivalent of hydrogen was absorbed and hydrogen uptake ceased. The solution was freed of catalyst by filtration, the filtrate was evaporated *in vacuo* to remove EtOH, and the residue was made alkaline with 5% NH_4OH. The organic base was extracted thoroughly with $CHCl_3$. Combined extracts were dried over Na_2SO_4, evaporated and pumped free off solvent to give 0.91 g. (quantitative yield) of a colrless glass whose p.p.c. showed only one spot, $Rf_{(7.0)}$: 0.78. This was coverted to Ⅶ-HCl by neutralizing with HCl in EtOH. Recrystallization from H_2O-EtOH afforded a needles, m.p. 257~259°, $[\alpha]_D^{20}$ −2.32° (c=1.0, H_2O). *Anal.* Calcd. for $C_{18}H_{23}O_3N \cdot HCl$: C, 64.00; H, 7.16; N, 4.15. Found : C, 63.95; H, 7.18; N, 4.28.

Ⅶ-monoacetate (acetyldihydroindolinocodeine): A mixture of 3 g. of Ⅶ in 5 ml. of acetic anhydride was heated at 80~85° for 3 hr. Then usual work up procedures were employed. The product was recrystallized from ether to give cubes, m.p. 93~95°, IR ν_{max} : cm^{-1} 1740 $\left(R-\overset{\overset{O}{\|}}{C}-O-\right)$, whose p.p.c. showed only one spot.

Indolinocodeinone (VIII)——To a solution of 0.3 g. of A in 7 ml. of dry benzene was added 1.5 g. of silver carbonate prepared by the method of Rapoport, *et al.*[6] The mixture was refluxed with mechanical stirring for 6 hr. and during this time silver carbonate gradually turned black. After cooling, the reaction mixture was freed from silver carbonate by filtration, the filtrate was evaporated *in vacuo* to afford a brown glass which was easily crystallized from MeOH. Recrystallization from MeOH gives 0.18 g. (61%) of rods, m.p. 125~126°, IR ν_{max} cm^{-1} : 1700 (α,β-unsatd. C=O), $[\alpha]_D^{20}$ +3.5° (c=1.0, $CHCl_3$), $Rf_{(6.3)}$: 0.80. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44; N, 4.71. Found : C, 72.61; H, 6.49; N, 4.71.

Dihydroindolinocodeinone (XV)——To a mixture of 5 ml. of *tert*-butanol, freshly distilled fron sodium, and 15 ml. of dry benzene was added 0.4 g. of potassium in small portions. After the potassium was dissolved, the excess of *tert*-butanol was removed by distillation as the benzene azeotrope with stirring. More benzene was added when necessary, to keep the potassium *tert*-butoxide in solution. A solution of 1.0 g. of Ⅶ and 6.0 g. of benzophenone in 8 ml. of dry benzene was added. The mixture was refluxed for 2 hr. in a nitrogen atmosphere. After cooling, the organic base was thoroughly extracted three times with 10 ml. portion of 10% HCl, and the combined H_2O-extracts were decolorized with small amounts of active charcoal. After the H_2O-solution was made basic with 25% NH_4OH, the organic base was thoroughly extracted with $CHCl_3$. Extracts were washed with H_2O, dried over Na_2SO_4, evaporated *in vacuo* and finally pumped out to give 0.32 g. (31%) of a gum, IR ν_{max} cm^{-1} : 1738 (C=O), whose p.p.c. showed only one spot, $Rf_{(7.0)}$: 0.95. This base and its hydrochloride, hydrobromide and perchloride could not be crystallized.

Dihydroindolinothebainone (XVI)——To a solution of 0.3 g. of XV in 20 ml. of 90% EtOH were added 0.4 g. of Zn powder and 0.4 g. of NH_4Cl, and was refluxed for 3 hr. with stirring. After cooling the reaction mixture was filtered, and the filtrate was distilled *in vacuo* to afford a crystalline residue which easily crystallized from MeOH. Recrystallization from MeOH gave 0.21 g. (70%) of needles, its p.p.c. shows only one spot $Rf_{(6.3)}$: 0.91, m.p. 196~198°, $[\alpha]_D^{20}$ +18° (c=0.5, EtOH), IR ν_{max} cm^{-1} : 3580 (phenol), 1709 (C=O). *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65. Found : C, 71.90; H, 7.87; N, 4.65. mol. wt. (micro Rast) : 290.

Hydrogenation of Isoneopine (B)——A solution of 0.5 g. of B in 10 ml. of 5% HCl was hydrogenated over 0.05 g. of PtO_2 catalyst at atmospheric pressure and room temperature. After 8 hr., 1.0 mole-equivalent of hydrogen was absorbed and hydrogen uptake ceased, the solution was freed from catalyst by filtration, made alkaline with 5% NH_4OH, and organic base was thoroughly extracted with benzene. Benzene extracts were dried over Na_2SO_4, evaporated *in vacuo* to afford 0.5 g. (quantitative yield) of a colorless glass whose p.p.c. showed only one spot, $Rf_{(7.0)}$: 0.53. Recrystallization from benzene gave rods, m.p. 200~202°, identical to dihydroisocodeine (XIX) prepared below by comparison of melting point, mixed melting point and IR.

Dihydroisocodeine (XIX)——According to the method of Baizer, *et al.*,[11] a solution of 5 g. of dihydrocodeine (XX) and 10 g. of freshly prepared Al-isopropoxide in dry toluene was refluxed for 24 hr. to give 3.15 g. of XIX. Recrystallization from benzene gave crystals melting at 200°, $Rf_{(7.0)}$: 0.53, $[\alpha]_D^{20}$ −134.1° (c=1.9, $CHCl_3$).

14-Bromocodeine (II)——According to the method of Conroy,[1] to a stirred suspension of 10 g. of 14-bromocodeinone (I) in 100 ml. of MeOH was added a solution of 3.0 g. of $NaBH_4$ in 20 ml. of H_2O with

cooling at 0~5° over a period of 10 min. After another 5 min. at 0°, the solid was removed by filtration, washed with 100 ml. of MeOH and with 100 ml. of acetone, dried *in vacuo* leaving 7.1 g. (70%) of II, needles, m.p. 150°, IR ν_{max} cm^{-1} : 3400 (-OH).

Neopinone (V)——According to the method of Conroy,[1] a solution of 5 g. of pure I in 20 ml. of $CHCl_3$ containing 2 ml. of MeOH was hydrogenated over 0.5 g. of 10% Pd-charcoal at atmospheric pressure and room temperature. After about 1 mole-equivalent of hydrogen was absorbed during 5 hr., the solution was freed from catalyst by filtration, and the filtrate was shaken with a cold solution of 1.7 g. of K_2CO_3 in 20 ml. of H_2O, washed three times with 30 ml. of ice-H_2O, dried over Na_2SO_4 and evaporated *in vacuo* below 40° leaving a residue. Recrystallization from anhydrous AcOEt afforded 2.8 g. of V, needles, m.p. 123~125°, IR ν_{max} cm^{-1} : 1733 (C=O).

Sodium Borohydride Reduction of Neopinone (V)——To a solution of 2.0 g. of V in 30 ml. of MeOH was added 5 ml. of 15% $NaBH_4$ H_2O-solution with stirring over a period of 10 min. After standing for 20 min., 2 ml. of 10% NaOH was added, and most of MeOH was removed by evaporation *in vacuo*. The organic base was thoroughly extracted with $CHCl_3$. Combined extracts were washed with H_2O, dried over Na_2SO_4, evaporated *in vacuo* and pumped free of solvent to afford 1.88 g. (93%) of colorless glass whose p.p.c. showed two spots, $Rf_{(7.0)}$: 0.65 (isoneopine, XXII), 0.30 (neopine, III). Dissolving the glass into 5 ml. of acetone and neutralizing with 48% HBr separated III-HBr, 1.22 g. (48%), which was recrystallized from H_2O-EtOH to give crystals, m.p. 282~283°. To the mother liquors was added H_2O, and organic solvent was evaporated *in vacuo*. After the H_2O-solution was decolorized with active charcoal and made alkaline with 25% NH_4OH, the organic base was thoroughly extracted with $CHCl_3$. Combined extracts were washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to give a colorless glass. Crystallization from acetone afforded 0.91 g. (41%) of XXII as prisms, m.p. 155~156°. Evaporation of mother liquors gave 0.06 g. of a gum whose p.p.c. showed 2 spots (XXII and III).

Table I.

No.	Starting material	Reagent	Temp. (°C), Time	p.p.c. A	B	C	D	Remarks
1	I (10 g.) MeOH, 100 ml.	NBH (3 g.) H_2O, 20 ml.	0, 10 min.	30%	15%	55%		standard for comparison
		NBH (10 g.) H_2O, 50 ml.	40, 90 min.	+	+	+	−	
2	I (0.5 g.) MeOH, 5 ml.	NBH (0.6 g.) MeOH, 5 ml.	25, 90 min.	−	+	+	+	anhydrous condition
3	II (0.5 g.) EtOH, 5 ml.	NBH (0.6 g.) H_2O, 5 ml.	25, 30 min.	+	+	+	−	
4	I (0.5 g.) $CHCl_3$, 8 ml.	NBH (0.6 g.)	25, 3 hr.	−	−	−	−	quantitative recovery of starting material
5	II (0.5 g.) THF, 5 ml.	LAH (0.8 g.) THF, 5 ml.	25, 1 hr.	−	+	+	±	LAH as the reagent
6	I (0.5 g.) MeOH, 5% KOH	NBH (0.6 g.) 5% KOH, 4 ml.	25, 30 min.	−	++	+	−	pH, 11.5~13
7	I (0.5 g.) MeOH, pH, 5-buffer sol.	NBH (1.6 g.) H_2O, 5 ml.	25, 1 hr.	−	+	+	+	pH, 6.5~9.0
8	I (0.5 g.) MeOH, pH, 5-buffer sol.	NBH (1.2 g.) H_2O, 5 ml.	25, 1 hr.	+	+	+	±	pH, 6.5~10.0
9	I (0.5 g.) MeOH, pH, 5-buffer sol.	NBH (1.2 g.) 5 ml.	25, 1 hr.	+	+	+	−	pH, 7.0~10.8
10	I (0.5 g.) aq. MeOH PbOAc	NBH (1.0 g.) H_2O, 5 ml.	25, 1 hr.	+	+	+	−	PbOAc or ZnOAc was added.
11	I (0.5 g.) aq. EtOH, 5 ml.	NBH (0.6 g.) aq. EtOH	60, 30 min.	±	+	+	−	temp. was rised to 60°
12	II (0.5 g.) aq. MeOH	NBH (0.6 g.) aq. MeOH	0, 2 days	+	+	+	−	time. prolonged
13	I (0.5 g.) MeOH	NBH (0.6 g.) H_2O	25, 1 hr.	+	+	+	−	starting material was added to the solution of reagent.

abbreviations: A; Indolinocodeine, B; Isoneopine, C; Neopine, D; cf. 10
NBH; $NaBH_4$, LAH; $LiAlH_4$, THF; Tetrahydrofuran
+; positive, −; negative, ++; strong positive, ±; slightly positive

Examination of Reaction Condition——Reaction conditions varying reaction temperature, reaction period, reagent, solvent, addition procedure of reagent, pH of reaction mixture, addition of heavy metal ion etc., were examined. General procedure was as follows : Reducing reagent was added to a magnetically stirred mixture, 0.5 g. of 14-bromocodeinone (I) or 14-bromocodeine (II) and 5 ml. of solvent, in a 20 ml. flask. After completing a reaction, the organic solvent was distilled off *in vacuo* and then the residue extracted with $CHCl_3$. $CHCl_3$ extract was used as a sample for qualitative determination, comparing p.p.c. pattern of the extract with that of a standard sample from the reaction mixture obtained under Conroy's conditions.[1] Experimental data was tabulated below. The pH of the reaction mixture was hardly maintained constant since pH increases as aq. $NaBH_4$ solution is added. The pH values at first and last point were described. Glass electrode pH meter, manufactured by Toa Denpa Kogyo, and Kolthoff buffer solution was utilized in these experiments.

The authors are indebted to Dr. Y. Kawazoe, National Cancer Center, for the measurement of NMR spectra and his kind discussion. They are also grateful to Mr. J. Nakahira, Sankyo Co., Ltd., for the supply of (−)-thebaine and to Misses H. Yamanouchi and K. Tohata, Institute of Applied Microbiology, University of Tokyo, for microanalyses and IR spectra.

Summary

Neopine (III), isoneopine (XXII) and indolinocodeine (XVII) were isolated from the sodium borohydride reduction mixture of 14-bromocodeinone (I) or 14-bromocodeine (II). The structures of new compounds, XVII and XXII, were elucidated. Hydroindole structure is comprised in XVII instead of hydroisoquinoline skeleton in codeine. The reaction mechanisms for production of the above three compounds were also discussed.

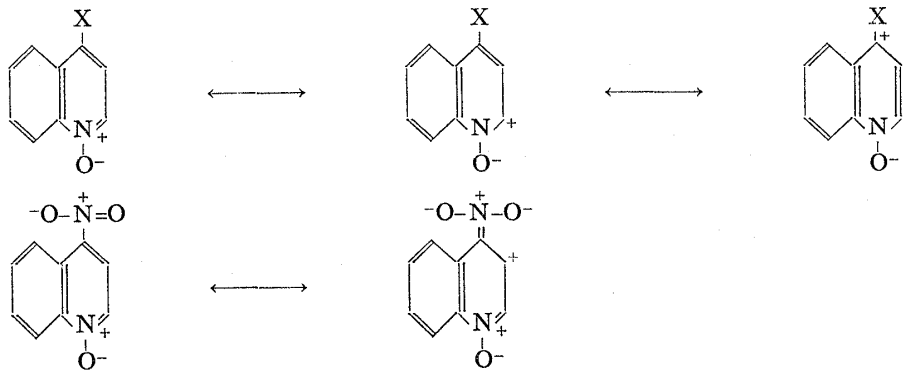
(Received February 3, 1965)

[Chem. Pharm. Bull. 13(9)1103~1107(1965)] UDC 615.771.7 : 547.831.1.07

144. Yutaka Kawazoe and Misako Tachibana : Studies on Chemical Carcinogens. I. Reduction of 4-Substituted Quinoline N-Oxides with Sodium Borohydride.*1

(*National Cancer Center Research Institute**2)

It is well known that quinoline N-oxides substituted by an electron withdrawing group at 4 position (*i.e.*, nitro, halogeno, methylsulfonyl) are very reactive toward nucleophilic reagents. In case where the substituent is nitro group, nitro nitrogen and 3-carbon may also be reactive to nucleophiles. This may be illustrated by resonance canonical formulae as follows :



*1 This paper also constitutes Part II of a series entitled "Studies on Hydrogen Exchange." Part I : This Bulletin, **11**, 1384 (1964).

*2 Tsukiji, Chuo-ku, Tokyo (川添 豊, 橘 美佐子).