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60. Isao Seki : Studies on the Morphine Alkaloids and Its Related Compounds. XIII.[*1] On the Nucleophilic Substitution Reactions of the 14-Hydroxylated Morphine Alkaloids.

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Although the detailed discussion on the nucleophilic substitution reaction (called SN-reaction) in the series of the 14-unsubstituted morphine compounds (called 14-H series) have been described,[1] the acetolysis of 14-hydroxycodeine 6α-tosylate (I)[*3,2], is the only cases which have been reported for the series of the 14-hydroxylated morphines (called 14-OH series). In a previous paper of this series,[3] it was reported that in the SN-reaction of I with pyrrolidine the configuration at the 6-position was retained to give the 6α-pyrrolidinyl derivative (Ⅷ) and the result was attributed to steric effects of the 14β-hydroxyl group. In this paper, steric effects of the 14β-hydroxyl group on SN-reactions in the 14-OH series will be described.

(I) Reaction of I with Halogeno-anions

Lithium chloride reacted with I in boiling acetone to give a chloro-compound. The reaction required more than 24 hours. However, the reaction of I with lithium bromide and sodium iodide was complete within 5～8 hours and 1～2 hours, respectively, to afford the corresponding halo-compound. The yields of the halo-compounds were rather low (25～30%) as compared with the 14-H series in which the reaction proceeded almost quantitatively within 3～4 hours.

(1) On the substituent position of halogen atoms : It had been shown that catalytic hydrogenation of the Δ^6-morphine compounds results in hydrogenolysis of the 4,5-ether ring to afford phenolic compounds as the main product ("abnormal hydrogenation") while Δ^7-morphines are hydrogenated simply to give only non-phenolic compounds ("normal hydrogenation").[4] The chloro-compound rapidly absorbed two molar equivalents of hydrogen to give a non-phenolic compound, 14-hydroxy-dihydrodeoxycodeine (Ⅳ), in a good yield. On the other hand, the bromo and iodo-compounds

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[*1] Part XII : Yakugaku Zasshi, 85, 359 (1965).

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[*3] Composition of the acetolysis product of I was found by the alumina column chromatography to be : I with 10% acetic acid → XIV+XV (1:4); I with 70% acetic acid → XIV+XV (1:1).

1) *a*) G. Stork : "The Alkaloids," **2**, 176, 180 (1952); *Ibid.*, **6**, 226 (1960). Academic Press, New York.
b) G. Stork, F.H. Clark : J. Am. Chem. Soc., **78**, 4619 (1956).

2) A.C. Currie, *et al.* : J. Chem. Soc., **1960**, 773.

3) I. Seki : Yakugaku Zasshi, **84**, 631 (1964).

4) R.E. Lutz, L.F. Small : J. Am. Chem. Soc., **54**, 4715 (1932).

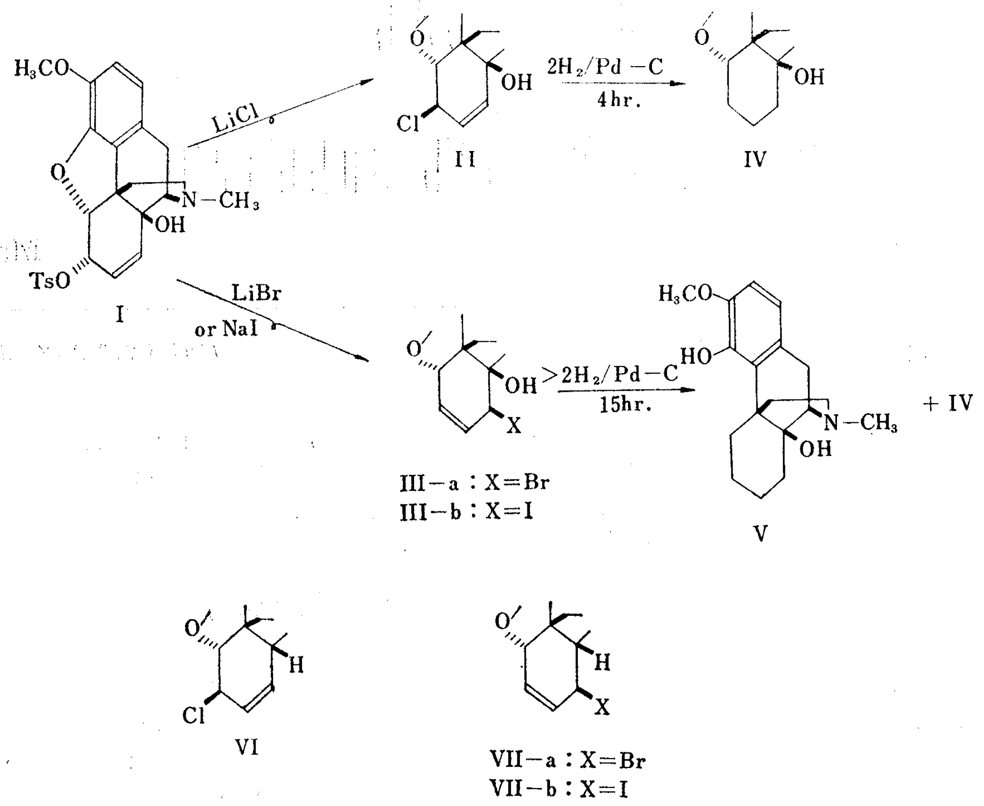

Chart 1.

slowly absorbed more than two moles of hydrogen to give a phenolic compound, 14-hydroxytetrahydrodeoxycodeine (V), as a main product, accompanying Ⅳ.

The above observations could most reasonably be explained as a result that the chloro-compound underwent the normal hydrogenation as well as dehalogenation to give Ⅳ, while the bromo- and iodo-compound yielded V as a main product by the abnormal hydrogenation followed by dehalogenation. Furthermore, the chloro-compound showed a strong absorption band at 10.7μ in the infrared spectrum like in the case of Δ^7-chloro-codide (*i.e.* Ⅵ),[1b] and the bromo- and iodo-compounds showed a strong absorption at 11.2μ as in the case of Δ^6-halo-codides (*i.e.* Ⅶ)[1b] Therefore, it is suggested that the double bond of the chloro-compound must be located at the 7-position, while the double bond of the bromo- and iodo-compounds must be at the 6-position. Consequently, it is concluded that the chlorine substitution occurs at the 6-position when 14-hydroxycodeine 6α-tosylate (I) was treated with lithium chloride but bromine and iodine anions attack the 8-position on treatment of I with lithium bromide and sodium iodide, respectively.

(2) On the configuration of the halo-compounds : In nuclear magnetic resonance (NMR) spectrum of the 6-chloro-compound, the signal at 4.99 τ due to 5β-H was a singlet and no coupling with 6-H was observed just as in the case of the 6β-chloro-codide (so-called "α-chloro-codide", Ⅵ).[5] Therefore, the configuration of the chlorine atom in the 6-chloro-compound must be β as shown in Ⅱ.

In NMR spectra of the 8-bromo- and 8-iodo-compounds, the signals at 5.45 τ (quartet, J=6 c.p.s.) and 5.25 τ (quartet, J=6 c.p.s.) due to 8-H were observed, respectively. The difference (0.2τ) arises from the different inductive power of the halogens.[6] From

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[5] T. Rüll : Bull. soc. chim. France, **1963**, 586; S. Okuda, *et al.* : This Bulletin, **12**, 104 (1964).

[6] L. M. Jackmann : "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," p. 54 (1959). Pergamon Press, London.

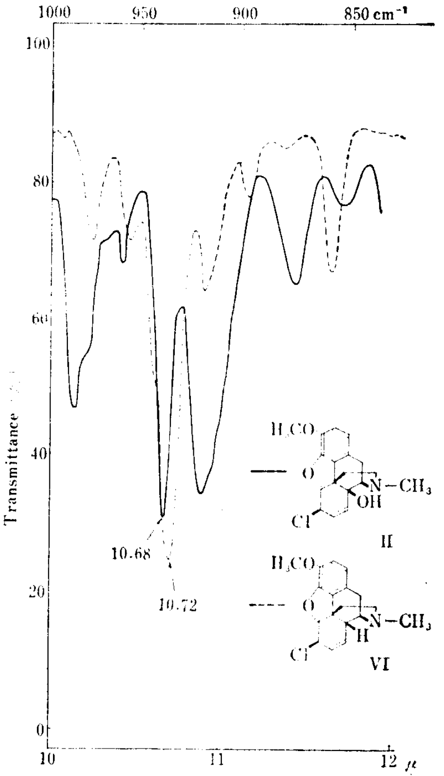

Fig. 1. Infrared Spectra of 6β-chloro-derivatives in 10～12 μ (in $CHCl_3$)

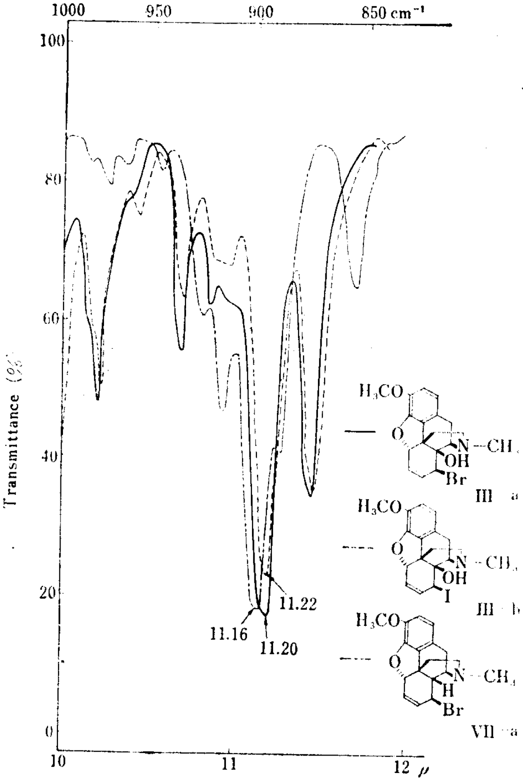

Fig. 2. Infrared Spectra of 8β-halogeno-derivatives in 10～12 μ (in $CHCl_3$)

the above spectral data, the configuration of these 8-halogen groups cannot be established since the NMR spectra of 8-substituted morphine compounds have not been investigated well. On the other hand, it is evident that the reaction course with bromine and iodine anions is quite similar to that with chlorine anion except that the former is accompanied by *cis*-rearrangement from the 6β- to 8β-position,[1] and the SN_2-displacement of chlorine proceeded just as in the case of the 14-H series as mentioned above. Therefore, it is reasonable to suggest the 8β-configuration for the bromide and iodide as shown in III.

From these argumentations, one could conclude that the reaction of I with smaller anions, such as halogeno-ions, than the pyrrolidinyl anion would proceed by way of the SN_2-mechanism like in the case of the 14-H series,[1] and that the reaction with bromo- or iodo-anion followed the $SN_{2'}$-type since these anions are susceptible to allylic rearrangement.[1] However, the reaction time required for the case of chloro-anion was longer than that in the case of the 14-H series probably due to steric hindrance of the 14-hydroxyl group to the 6β-side. The low yields of these halo-compounds (II, III) are due to complicated factors, such as susceptibility of the 14-hydroxyl group to halogeno-anions in the case of II, and instability of the halohydrin under reaction conditions in the case of III.

(II) The Reaction of the Halo-compounds (II, III) with Pyrrolidine

As previously discussed,[3] the attack by pyrrolidinyl anion from the 6β-side is sterically hindered by the 14β-hydroxyl group so as to afford the 6α-pyrrolidinyl compound (VIII). Therefore, the author became interested in the fate of steric effects of the 14-hydroxyl group on the $SN_{2'}$-reaction involving by 8β- and 6-positions as the reaction termini.

Reactions of the 8β-halo-compounds (III) with pyrrolidine in boiling benzene smoothly proceeded to give 14-hydroxy-6α-pyrrolidinyl-codide (VIII) in good yield. Thus, the result indicated that in this reaction the large pyrrolidinyl anion attack the 6-position from α-side because steric hindrance of the 14-hydroxyl group to the 6β-side is so great.

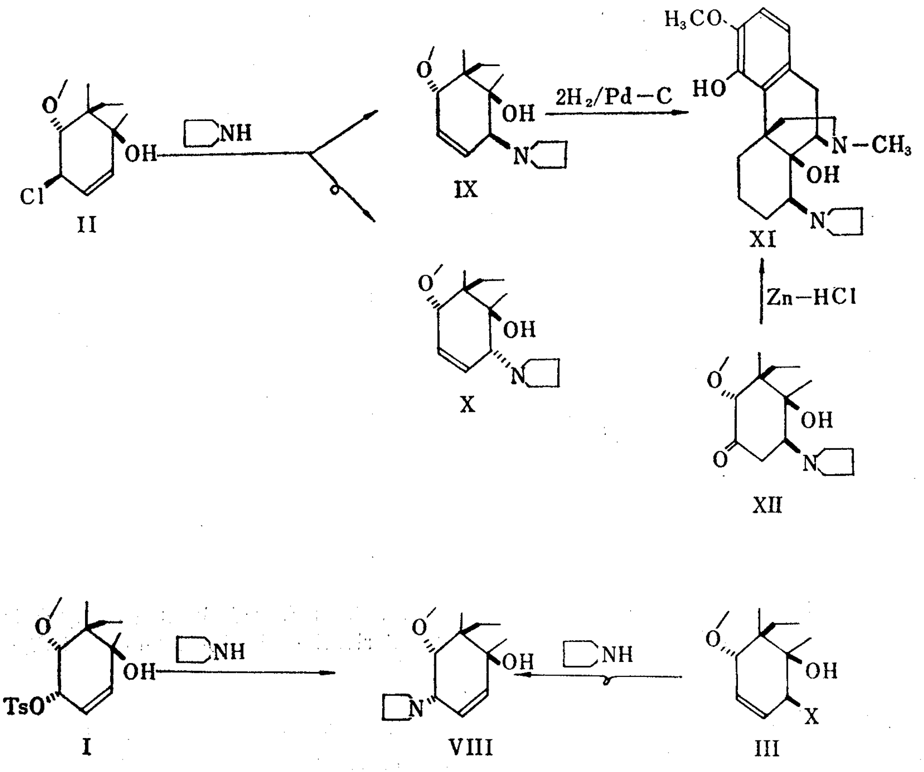

Chart 2.

The reaction of 14-hydroxy-6β-chloro-codide (II) with pyrrolidine gave two pyrrolidinyl-compounds. The main product (IX) was established to be the 8β-pyrrolidinyl derivative since on catalytic reduction it absorbed two molar equivalents of hydrogen to give a phenolic diamine, 14-hydroxy-8β-pyrrolidinyltetrahydrodeoxycodeine (XI), which was identical with a sample prepared by reduction of 14-hydroxy-8β-pyrrolidinyldihydrocodeinone (XII) with zinc powder and hydrochloric acid.3,7) Consequently, it is apparent that the reaction of II with pyrrolidine proceeds in the type of the $SN_{2'}$-reaction without inversion just in the case of the 14-H series.

(III) The Acetolysis of Halo-compounds (II, III)

When the chloro-compound (II) was heated in boiling 10% acetic acid for 3~4 hours, 14-hydroxyallopseudocodeine 8-acetate (XIII) was obtained in 45% yield. From the result of the formation of XIII from I, Currie, *et al.* assumed that the $SN_{2'}$-reaction proceeded without inversion.*4,4) However, the formation of XIII from II is different from the above example since the SN_2'-reaction is followed by inversion. Furthermore, the same 1,2-*trans*-diol (XIV) was obtained from both 6α (axial)- and 6β (equatorial)-compounds (I and II). It has been considered that a conformation of the

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*4 In the 14-H series, the acetolysis of codeine tosylate was studied by the author and found to afford isocodeine (6β-alcohol) as a main product accompanying a very small amount of pseudocodeine (8β-alcohol). And the acetolysis of isocodeine tosylate gave a mixture of isocodeine and pseudocodeine (1:1).

7) I. Seki: Yakugaku Zasshi, 84, 626 (1964).

14β,8α-diol (XIV, diaxial) is preferred to that of the 14β,8β-diol (axial-equatorial) because of steric repulsion between the two vicinal hydroxyl groups.

Treatment of the 8β-halo-compounds (Ⅲ) with boiling 10% acetic acid gave 14-hydroxyisocodeine (XV). In this case, however, a remarkable amount of the starting material was recovered even after heating for 24 hours.

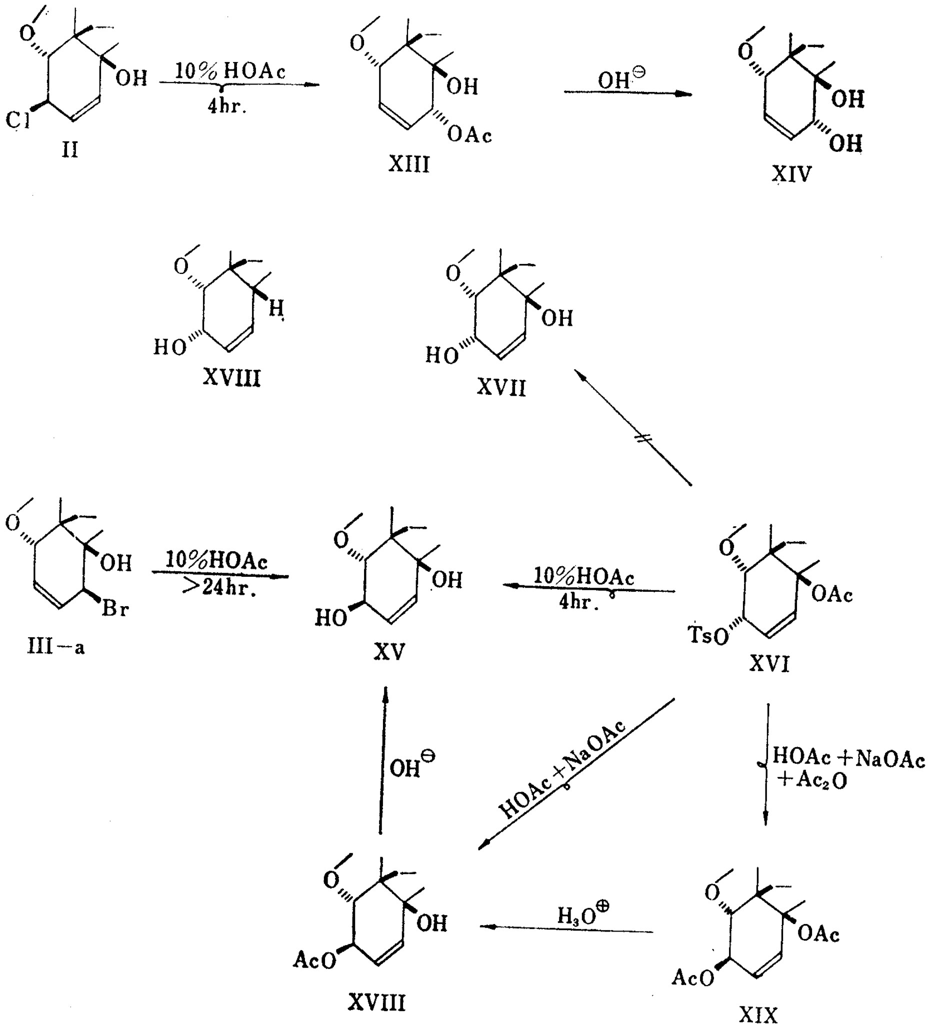

Chart 3.

(IV) Discussion

It has been shown that steric hindrance of the 14β-hydroxyl group operates greatly on the SN-reactions at the 6-position. Reactions of I with small anions, such as halogeno-anions or acetate-anion, is normal and affected only by the steric hindrance to be 6α-side due to the morphine skeleton rather than that of the 14β-hydroxyl group. Thus, in the case where small anions are involved, the reaction proceeds according either to SN_2- (*e.g.* I→Ⅱ) or to $\mathrm{SN}_{2'}$- (*e.g.* 1→Ⅲ, Ⅲ→XV) type as in the case of the 14-H series which gives the 6β-compound,[1] but the reaction rates are very small.

On the other hand, bulky anions such as pyrrolidinyl anion cannot attack the 6β-position because of steric hindrance of the 14β-hydroxyl group. Therefore, in this case the substitution proceeds rather smoothly to afford the 6α-compound in good yield as shown in I→Ⅷ, Ⅲ→Ⅷ.

(V) The Acetolysis of 14-Acetoxycodeine 6-tosylate (XVI)

Hitherto, the 6α-alcohols (XVII, XVIII) have not been found in the acetolysis product of the 6β-chloro- or 8β-halo-compounds (II, III, VI, VII) in both 14-H and 14-OH series because the back-side attack is sterically impossible.[1] However, when a reagent of an adequate size (*e.g.* pyrrolidinyl anion) was used, it was possible to obtain the 6α-compound in the 14-OH series as mentioned above. Then, the acetolysis of 14-acetoxycodeine 6-tosylate (XVI) was investigated in expectation that the 6α-alcohol (XVII) would be the main product.[8]

The acetolysis of XVI in 10% acetic acid or glacial acetic acid with sodium acetate, however, gave only 14-hydroxyisocodeine (XV) or its 6-acetate (XVIII) as a crystalline product. Consequently, it was assumed that the reaction proceeded analogous to the normal S_N2-reaction (*e.g.* I→XV) because the 14-acetoxy group was easily converted to a hydroxyl group at an early stage of the reaction under these conditions. In a mixture of glacial acetic acid and acetic anhydride, the 14-acetoxy group was not changed to a hydroxyl group and one obtained 14-acetoxyisocodeine 6-acetate (XIX) either in the presence or in the absence of sodium acetate. Thus, in this case it can be assumed that the 6α-side attack by acetate anion on the cation XVI-α does not occur (*i.e.* XVI-a→XVI-b) and migration of the 14β-acetoxy group to the 6β-position proceeds because of the higher stability of the tertiary cation XVI-c as compared with the secondary cation XVI-a.

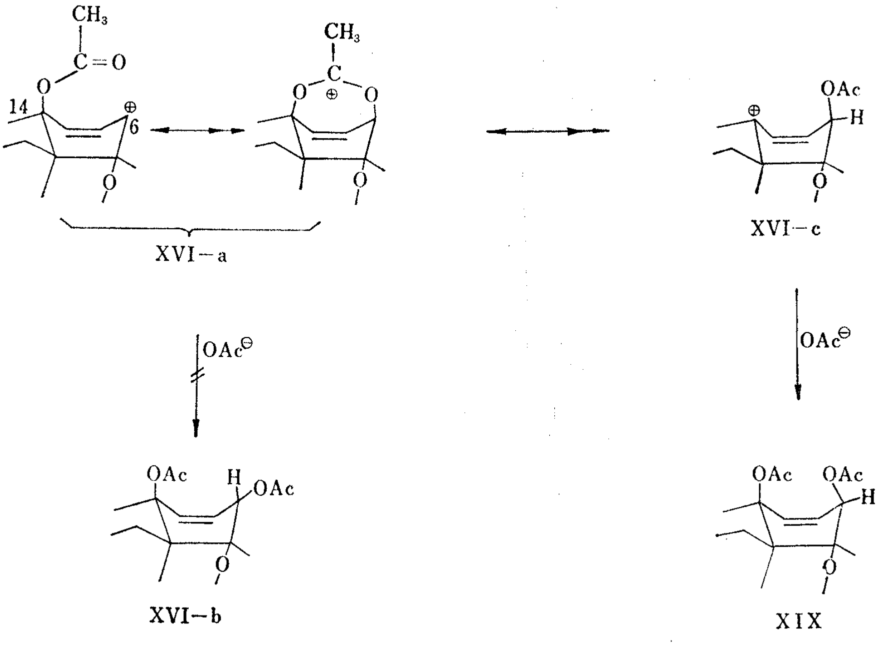

Chart 4.

Experimental[*5]

Preparation of 14-Hydroxy-halo-codides (II, III)——To a solution of I (0.01 mole) in acetone (200 ml.) was added LiCl, LiBr, or NaI (each 0.04 moles), and it was refluxed for the required time (Table I). After concentration to one-third, it was poured into water (500 ml.), and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The crystalline residue

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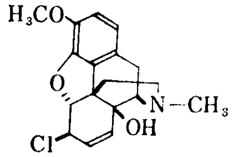
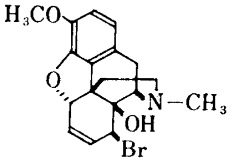
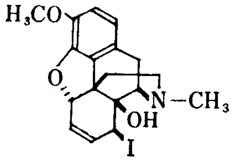
[*5] All melting points were uncorrected. The active Al_2O_3 used was the Merck "nach Brockmann" without pre-treatment. The NMR spectra were measured in $CDCl_3$ with a Varian A-60 spectrometer at 60 Mc. using Me_4Si as an internal standard.

8) B. Capon: Quart. Revs., 18, 68 (1964).

was extracted with ether. The ether solution was evaporated to dryness. The residue was recrystallized from EtOH to give the halo-compounds (II, III) (Table I).

Table I. 14-Hydroxy-halogeno-codides

Compound	Reaction time (hrs.)	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) C%	H%	N%	X%
	24	35	143~146[a]	$C_{18}H_{20}O_3NCl$	64.75/64.75	6.04/6.04	4.20/4.29	10.65/10.99
	8	24	159~162	$C_{18}H_{20}O_3NBr$	57.15/57.13	5.33/5.49	3.71/3.78	21.13/20.99
	2	30	150~152[b]	$C_{18}H_{20}O_3NI$	50.75/51.35	4.73/4.62	3.29/3.44	29.85/29.67

a) Bath pre-heat 130~135° b) Bath pre-heat 140~145°

Catalytic Reduction of Halo-compounds (II, III) in Acidic Medium——A mixture of II or III (each 0.003 moles), 5% Pd-C (1 g.), and 10% AcOH (30 ml.) was shaken in a H_2 atmosphere at room temperature and normal pressure. The chloro-compound (II) absorbed 2 molar equivalents of H_2 for 4 hr., while the bromo- and iodo-compounds (III-a and III-b) absorbed about 2.8 moles of H_2 for 15 hr. After filtration, the filtrate was made alkaline with NH_4OH to pH 9.0, and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue obtained from II was triturated with a small amount of MeOH in an ice bath to give 14-hydroxydihydrodeoxycodeine (IV), m.p. 115~116°(alone and mixed with an authentic sample[9]), yield 66.5%. The residue obtained from III was triturated with MeOH, and filtered. The insoluble crystals, m.p. 111~115°(yield 33%), were identical with IV by an admixture melting point and comparison of the IR spectrum with an authentic sample.[9] The more soluble crystals were recrystallized from ether to give 14-hydroxytetrahydrodeoxycodeine (V), m.p. 135~138°(alone and mixed with an authentic sample[10]), yield 67%.

Reaction of Halo-compounds (II, III) with Pyrrolidine——1) To a solution of chloro-compound (II; 3 g.) in benzene (90 ml.) was added pyrrolidine (6 ml.), and it was refluxed for 24 hr. After cooling, the mixture was washed with 5% KOH (20 ml.) and then with water (30 ml.), dried over Na_2SO_4 and evaporated to dryness. The solution of this residue (halogen free; 3 g.) in ether (30 ml.) was allowed to stand for three days in a chilled box. A small amount of crystals were collected by filtration; m.p. 158~164°. NMR : 5.71 τ (1-H, multiplet, J=25 c.p.s.). The crystals are assumed to be the 8α-pyrrolidinyl compound (X) since further examination was impossible because of a very small amount of the sample. The filtrate was evaporated to give an oily 8β-pyrrolidinyl compound (IX). NMR : 5.5 τ (1-H, doublet, J=5.5 c.p.s.). A mixture of this oily compound (2.5 g.), 5% Pd-C (0.5 g.), and 10% AcOH (50 ml.) was shaken in the H_2 atmosphere at the room temperature and normal pressure. It absorbed 2 molar equivalents of H_2 for 24 hr. After filtration, the filtrate was made alkaline with NH_4OH to pH 9.0, and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue (2 g.) was recrystallized from ether to give 14-hydroxy-8β-pyrrolidinyl-tetrahydrodeoxycodeine (XI), m.p. 185~190°(alone and mixed with a sample derived by reduction of XII). $FeCl_3$ reaction : green. *Anal.* Calcd. for $C_{22}H_{32}O_3N_2$: C, 70.93; H, 8.66; N, 7.52. Found : C, 71.00; H, 8.19; N, 7.47.

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9) I. Seki : Ann. Rept. Takamine Lab., **13**, 67 (1961).
10) *Idem* : *Ibid.*, **13**, 75 (1961).

2) To a solution of bromo- or iodo-compound (III-a or III-b; each 0.5 g.) in benzene (30 ml.) was added pyrrolidine (1 ml.), and it was refluxed for 24 hr. After cooling, the mixture was washed with 5% KOH (15 ml.) and then with water, dried over Na_2SO_4, and evaporated to dryness. The residue (halogen free; 0.5 g.) was repeatedly triturated with ether-H_2O to give crystalline needles, m.p. 104~118°. It was identical with 14-hydroxy-6*α*-pyrrolidinyl-codide (VIII) by an admixture melting point and comparison of the IR spectrum with an authentic sample.[3)]

Reduction of 14-Hydroxy-8*β*-pyrrolidinyl-dihydrocodeinone (XII) with Zinc Powder and Hydrochloric Acid——To a mixture of XII[7)] (3.5 g.) and zinc powder (20 g.) was added 35% HCl (50 ml.) for 5 min. After the vigorous foaming ceased, the supernatant was made alkaline with large excess of NH_4OH, and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, decolorized with charcoal and active Al_2O_3, and evaporated to dryness. The residue (1.3 g.) was dissolved in ether (30 ml.), and it was allowed to stand for 24 hr. in a chilled box. The crude crystals (0.1 g.) were collected by filtration, and recrystallized from ether to give pure crystals, m.p. 185~190°. $FeCl_3$ reaction: green. Brady reagent: negative. IR $\lambda_{max}^{CHCl_3}$ μ: 2.8 (4-OH), 2.9 (14-OH), 6.2+6.3 (4,5-opened). It was identical with 14-hydroxy-8*β*-pyrrolidinyl-tetrahydrodeoxycodeine (XI) by an admixture melting point and comparison of the IR spectrum with a sample which was prepared by a SN-reaction of II and pyrrolidine followed by catalytic reduction.

The Acetolysis of Halo-compounds (II, III)——1) A solution of chloro-compound (II; 0.5 g.) in 10% AcOH (25 ml.) was refluxed for 24 hr. After cooling, the solution was made alkaline with 30% KOH to pH 9.0, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue (halogen free; 0.45 g.) was dissolved in benzene, and chromatographed on active Al_2O_3 (11 g.). The benzene eluate was collected, and evaporated to give fine prisms (0.35 g.), m.p. 195~196° (MeOH). IR $\lambda_{max}^{CHCl_3}$ μ: 2.9 (14-OH), 5.8 (8-OAc). It was identical with 14-hydroxyallopseudocodeine 8-acetate (XIII) by an admixture melting point and comparison of the IR spectrum with an authentic sample.[2)] *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.01; H, 6.47; N, 4.01.

After the elution of XIII with benzene, the eluate with MeOH contained nothing.

2) A mixture of bromo-compound (III-a; 0.5 g.) and 10% AcOH (25 ml.) was refluxed for 24 hr. After cooling, the mixture was made alkaline with 30% KOH to pH 9.0, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue (Beilstein reaction: positive; 0.3 g.) was dissolved in benzene, and chromatographed on active Al_2O_3 (9 g.). The benzene eluate was collected, and evaporated to give the starting material (0.15 g.), m.p. 159~160° (alone and mixed with III-a). The benzene-ether (1:1) eluate contained nothing. And lastly, the MeOH-ether (3:7) eluate was collected, and evaporated to give 14-hydroxyisocodeine (XV; 0.15 g.), m.p. 149~153° (alone and mixed with an authentic sample[2)]). Beilstein reaction: negative. IR $\lambda_{max}^{CHCl_3}$ μ: 2.8~2.9 (broad, 6*β*-OH+14-OH). NMR: 5.15 τ (1-H, singlet). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.30; H, 6.68; N, 4.51.

14-Hydroxyallopseudocodeine (XIV)——A mixture of XIII (0.5 g.), MeOH (20 ml.), water (5 ml.), and KOH (1 g.) was warmed for one hour at 40~50°. After evaporation of the MeOH, the residue was extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was recrystallized from *n*-hexane-ether to give 14-hydroxyallopseudocodeine (XIV), m.p. 133~136° (alone and mixed with an authentic sample[2)]). IR $\lambda_{max}^{CHCl_3}$ μ: 2.8 (8*α*-OH), 2.9 (14-OH). NMR: 5.95 τ (1-H, multiplet, J=10 c.p.s.). *Anal.* Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.48; H, 6.71; N, 4.57.

The Acetolysis of 14-Acetoxycodeine 6-Tosylate (XVI)——1) A mixture of XVI (5.1 g.) and 10% AcOH (250 ml.) was refluxed for 4 hr. After cooling, the mixture was made alkaline with NH_4OH to pH 9.0, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The orange-red colored residue (3.15 g.) was dissolved in benzene, and chromatographed on active Al_2O_3 (60 g.). The benzene and benzene-ether (1:1) eluates contained nothing. Lastly, the MeOH-ether (3:7) eluate was collected, and evaporated to give the pale orange-red colored crystals (3 g.). IR $\lambda_{max}^{CHCl_3}$ μ: 2.8~2.9 (weak broad), 5.8 (medium). In order to hydrolysis of the acetate, a mixture of the crystals (3 g.), MeOH (50 ml.), water (10 ml.), and KOH (2.5 g.) was treated as described in the preparation of XIV to give 14-hydroxyisocodeine (XV), m.p. 149~150° (alone and mixed with an authentic sample[2)]), 2 g.

2) A mixture of XVI (2.9 g.), glacial AcOH (20 ml.), and NaOAc (2 g.) was refluxed for 4 hr. After cooling, the mixture was diluted with cold water (100 ml.), neutralized with Na_2CO_3 to pH 5.0, and washed with benzene. The aqueous layer was made alkaline with NH_4OH to pH 9.0, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to give orange-colored crystals, 1.9 g. IR $\lambda_{max}^{CHCl_3}$ μ: 2.8~2.9 (weak broad), 5.8 (medium). In order to hydrolysis of the acetate, a mixture of the crystals (1.9 g.), MeOH (50 ml.), water (10 ml.), and KOH (2.5 g.) was treated as described above except recrystallization, and chromatographed on active Al_2O_3 (30 g.). The MeOH-ether (3:7) eluate was collected, and evaporated to dryness. The residue was recrystallized from MeOH to give XV (0.85 g.), m.p. 152~153° (alone and mixed with an authentic sample[2)]).

3) A mixture of XVI (2.5 g.), glacial AcOH (20 ml.), Ac_2O (5 ml.), and NaOAc (2 g.) was refluxed for 2 hr. After cooling, the mixture was diluted with cold water (100 ml.), neutralized with Na_2CO_3 to pH 5.0, and washed with benzene. The aqueous layer was made alkaline with NH_4OH to pH 9.0, and extracted with

benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to give orange-red colored crystals (0.95 g.). IR $\lambda_{max}^{CHCl_3}$ μ: 5.8 (strong). In order to hydrolysis of the acetate, a mixture of the crystals (0.95 g.), MeOH (25 ml.), water (5 ml.), and KOH (1.25 g.) was treated as described above, and chromatographed on active Al_2O_3 (10 g.). The MeOH-ether (3:7) eluate was collected, and evaporated to dryness. The residue was recrystallized from MeOH to give XV (0.35 g.), m.p. 149~151°(alone and mixed with an authentic sample[2]).

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Summary

Preparation of 14-hydroxy-halo-codides (II, III), the reactions of II or III with pyrrolidine, and the acetolysis of II, III, or 14-acetoxycodeine 6-tosylate (XVI) were described with regard to steric effects of the 14β-hydroxyl group on these reactions.

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61. Isao Seki: Studies on the Morphine Alkaloids and Its Related Compounds. XIV.[*1] Preparation of 6-Amino-hydrophenanthrene Compounds from Hofmann Degradation Products of the Morphine Alkaloids.

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Although the Hofmann degradation reaction of the morphine alkaloids has been well studied,[1] chemical and pharmacological properties of these products and their various derivatives have been little investigated. 6-Amino-hydrophenanthrenes were prepared from the Hofmann degradation products of the 6-oxomorphine compounds in order to investigate the relationship between pharmacological activity and the position of basic groups in the morphine nucleus. In this paper, the author describes preparation of 6-amino-hydrophenanthrenes (XIV~XX).

6-Oxo-hydrophenanthrenes (I~XIII) were obtained from the 6-oxo-morphines according to the known Hofmann degradation reaction. (Scheme 1) The methine and dihydromethine bases of the 14-hydroxy-compounds (*e.g.* IX, X) formed the corresponding methiodide with much greater ease than the 14-hydroxymorphines (*e.g.* XI, X) as shown in Table I. Both 14-hydroxy-compounds have a hydrogen bond between the 14-hydroxyl group and a lone pair of the nitrogen atom at the 17-position.[2,3] In the methine bases the hydrogen bond forms a seven-membered ring but in the 14-hydroxymorphines a five-membered one. In the former compounds the hydrogen bond must

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[*1] Part XIII. I. Seki: This Bulletin, **14**, 445 (1966).

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[1] K.W. Bentley: "The Chemistry of the Morphine Alkaloids," Oxford (1954), the literature cited in this monograph.

[2] I. Seki: Ann. Rept. Takamine Lab., **13**, 67 (1961).

[3] *Idem*: Yakugaku Zasshi **85**, 359 (1965).