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Studies on the Morphine Alkaloids and Its Related Compounds. XV.[1] Isolations of 8β,14β-Epoxy-codide and 14-Hydroxy-dihydropseudocodeine from Some Nucleophilic Substitution Reaction Products of Tosylate of 14-Hydroxy-codeine or Its Isomers[2]

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As the results of further investigation on nucleophilic substitution reactions of 14-hydroxy-codeine 6-tosylate (VIII) and its isomers which are performed to examine the effects of 14β-hydroxyl group on these reactions comparing with the known results in 14β-hydrogen-morphine alkaloids, a new epoxide in morphines, 8β,14β-epoxy-codide (III), which formed probably by internal SN-reaction with neighbouring group participation of the 14β-hydroxyl group to the 8-position in intermediates in the reactions, and a vicinal-*cis*-diol, 14-hydroxy-dihydropseudocodeine (XIV), were isolated.

In a previous paper of this series[4] some nucleophilic substitution reactions (called SN-reaction) of 14-hydroxy-codeine 6-tosylate (VIII) have been reported. As the results of further investigation on SN-reactions of VIII and its isomers which are performed to examine the effects of 14β-hydroxyl group on these reactions comparing with the known results in 14β-hydrogen-morphine alkaloids,[5] a new epoxide in the morphine alkaloids, 8β,14β-epoxy-codide (III), and a vicinal-*cis*-diol, 14-hydroxy-dihydropseudocodeine (XIV), were isolated. It is the purpose of this paper to report on isolation of these compounds and to propose on effects of 14β-hydroxyl group to formation of these.

(I) Isolation and Structural Observation of 8β,14β-Epoxy-codide (III)

Treatment of 14-hydroxy-allopseudocodeine (I) with tosyl chloride in pyridine at −5—0° for 48 hours gave only a crystalline product having melting point 132—133° in about 30% yield, and the reaction of 14-hydroxy-isocodeine (II) with tosyl chloride under same conditions mentioned above proceeded rapidly (0.5—1 hours) to give a same product in about 30% yield accompanied by large amounts of resinous substance.

In infrared (IR) spectrum of this product (Fig. 1), no absorption bands due to νO-H and νS-O anticipated were shown but the characteristic absorption bands at 1020, 926, 909

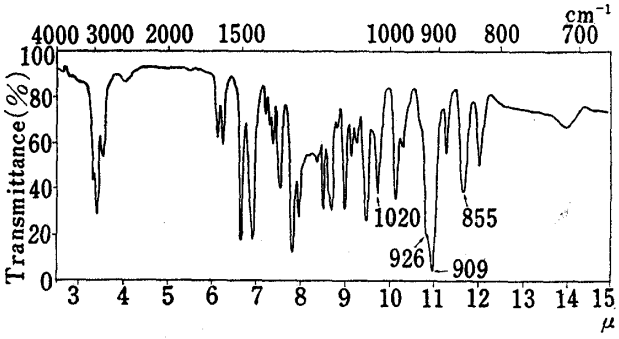

Fig. 1. The IR-spectrum of 8β,14β-Epoxy-codide (III) in $CHCl_3$

1) Part XIV: I. Seki, *Chem. Pharm. Bull.* (Tokyo), **14**, 453 (1966).
2) This work was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.
3) Location: *1-Chome Hiromachi, Shinagawa-ku, Tokyo.*
4) I. Seki, *Chem. Pharm. Bull.* (Tokyo), **14**, 445 (1966).
5) G. Stork, in "The Alkaloids," Vol. 2, ed. by R.H.F. Manske, Academic Press, N.Y., 1952, p. 176; G. Stork, F. H. Clarke, *J. Am. Chem. Soc.*, **78**, 4619 (1956).
6) L.J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1960, p. 118.

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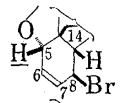
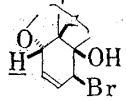
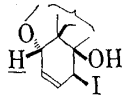
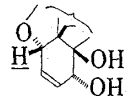
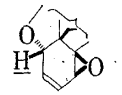
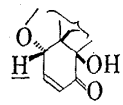
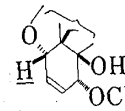
(very strong), and 855 cm^{-1} which seems due to an epoxy group[6] were observed. Therefore, it is considered that this product is not the expected tosylate but an epoxy compound[7].

In nuclear magnetic resonance (NMR) spectrum of one, the 5β-proton give rise to quartet (J=3.5 cps) centered at 5.21τ which shows the couplings of the 5β-proton with the each proton of the double bond of C-ring located at 6- and 7-positions like in the case of other Δ^6-morphines (Table I). The presence of allylic ether group in the structure is proved also by a formation of phenolic compound (VII) with catalytic hydrogenolysis.[8]

Table I. NMR-spectra of $H_{5\beta}$ in the Δ^6-Morphine Alkaloids

Compound		τ-value[a]	Type[b]	J (cps)
		4.98	q	5
	(IX)	4.96	q	5
		4.95	q	5.5
	(I)	5.08	q	3.6
	(III)	5.21	q	3.5
		4.85	q	4.3
	(I-a)	5.14	q	4

a) at the center *b*) q=quartet *c*) instrument: Varian A-60 at 60 Mc solvent $CDCl_3$

The mechanistic and steric considerations on formation of epoxide in the above reactions suggested that an epoxy group should be located between the 8β- and 14β-positions and it was confirmed by the solvolysis of this compound. Thus, when this compound is treated with 10% acetic acid for one hour at 70° or for 24 hours at room temperature, 14-hydroxy-allo-pseudocodeine 8-acetate (IV) was obtained quantitatively. Also, treatment of one with the mixture of 30% potassium hydroxide solution and methanol gave a mixed product of 14-hydroxyallopseudocodeine (I; in 10% yield) and its methyl ether (Ia; in 52% yield).

In a view of the above observations one might concluded that this compound is 8β,14β-epoxy-codide which is represented with formula III, and the elemental analysis of this has agreed with the formula. The fact that the tosylation of 8α-alcohol (I) or 6β-alcohol (II) gave unexpectedly the epoxide (III) as a main product can reasonably be explained by internal SN-reaction which is driven with the neighbouring group participation of 14β-hydroxyl group to the 8-position in intermediate tosylates (V and VI) as shown in Chart 1.[9]

7) It has been reported that the 14β-hydroxyl group did not reacted with tosyl chloride (I. Seki, *Ann. Sankyo Res. Lab.*, **13**, 67 (1961)).
8) L. Small and F.L. Cohen, *J. Am. Chem. Soc.*, **53**, 2214 (1931).
9) B. Capon, *Quart. Rev.* (London), **18**, 56 (1964).

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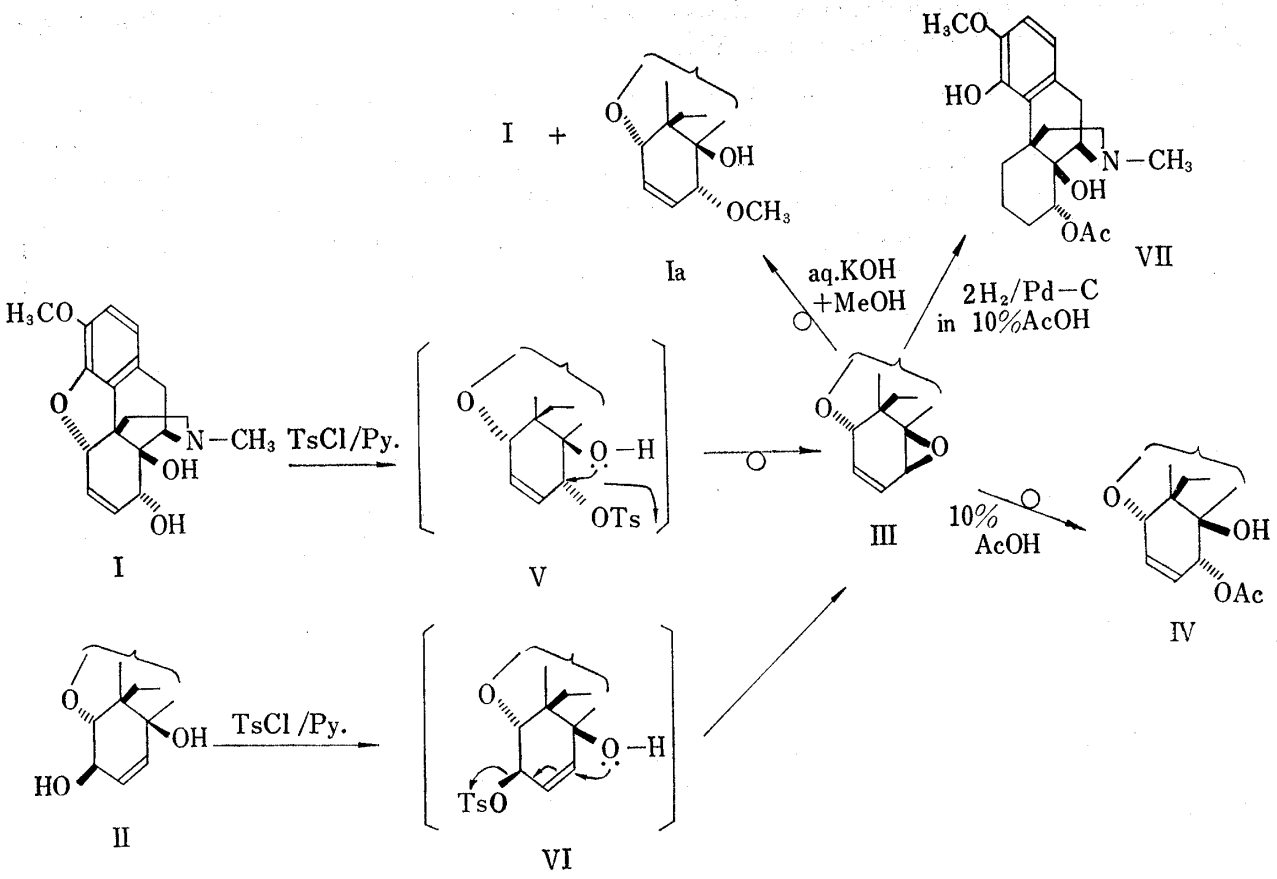

Chart 1

(2) Isolation of the Epoxide (III) from Other SN-reaction Products

As the internal SN-reaction is considered on mechanism in the above reactions, formation of III should be expected also in the related SN-reactions reported previously.[4] Actually, III was isolatedf rom ether-soluble fraction of the product obtained by reaction of 14-hydroxy-codeine 6-tosylate (VIII) with lithium chloride or lithium bromide in 19% and 7% yield, respectively. In these cases, the internal SN-reactions on the 6β-bromide (IX′), which is not captured because of susceptibility of the bromine anion in an allylic rearrangement to the 8β-bromide (IX),[5] and the 6β-chloride (X) can also be suppose as shown in Chart 2.

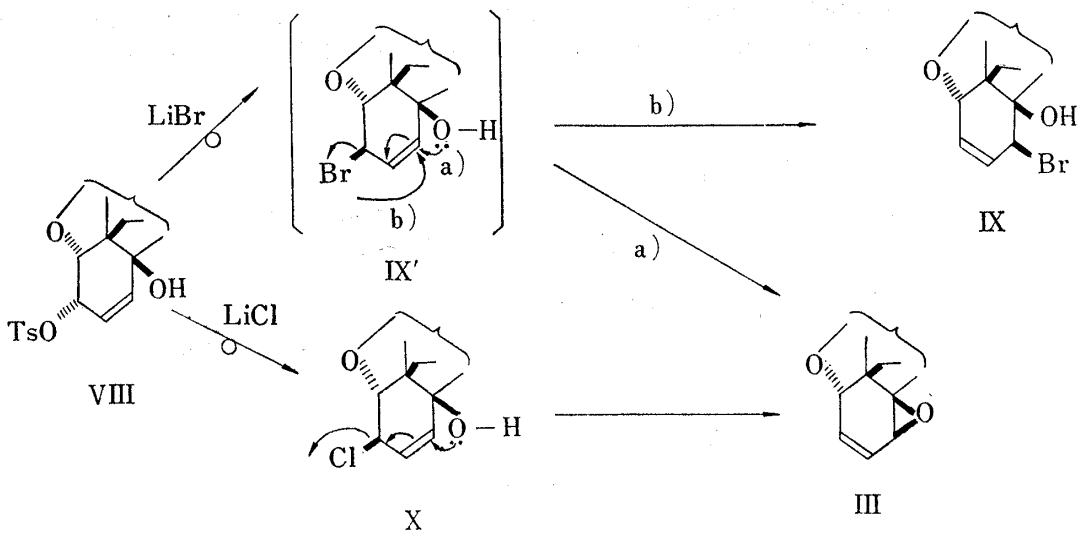

Chart 2

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(3) Discussion on the Perplexed Acetolysis of VIII and X, and Isolation of the Dihydro-8β,14β-diol (XIV) from Acetolysis Product of VIII

On the basis of the consideration on a formation mechanism of the epoxide (III) in some SN-reactions of tosylate of 14-hydroxy-codeine or its isomers mentioned above, the facts reported previously that acetolyses of the 6α-tosylate (VIII)[4,10] and the 6β-chloride (X)[4] gave the same 8α-acetate (IV) as a main product could most reasonably be explained by supposition of the course containing double inversion which occurred first at the 6-position and then the 8-position from VIII and the course containing one inversion at the 8-position from X *via* the epoxide (III) as shown in Chart 3.

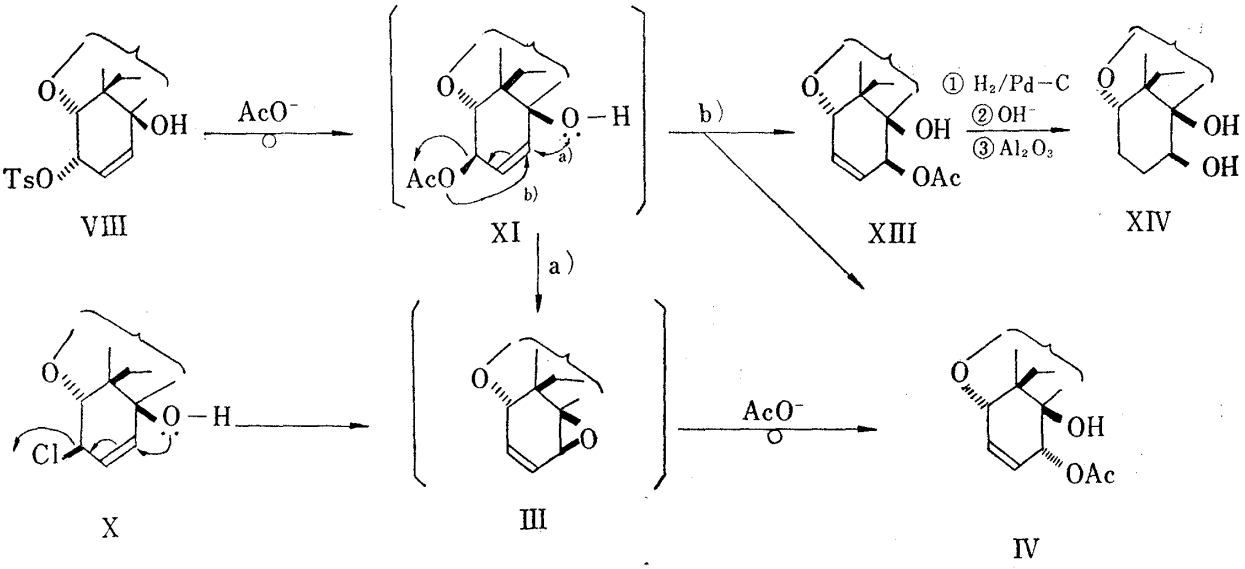

Chart 3

On the other hand, a formation of the 8β-acetate (XIII) by a competitive attack of the acetate anion at the 8-position should also be considered in the acetolysis. Although a separation of XIII itself from crude acetolysis mixture was unsuccessful, when the mixture reduced catalytically and then hydrolyzed with alkali, a dihydro-diol was isolated by chromatography on active alumina in 6% yield as the methanol eluate after removed the known epimer, 14-hydroxy-dihydroallopseudocodeine (XV),[4,10] with non-polar solvent such as benzene. In IR spectrum of the dihydro-diol, no absorption band at 3500—3700 cm^{-1} for 8-hydroxyl group was shown, while in diluted chloroform solution the absorption band at 3333 cm^{-1} for the 14β-hydroxyl group was much stronger and broadly than that of the epimer (XV) showing the band at 3636 cm^{-1} for the 8α-hydroxyl group. These spectral data indicated that in the di-

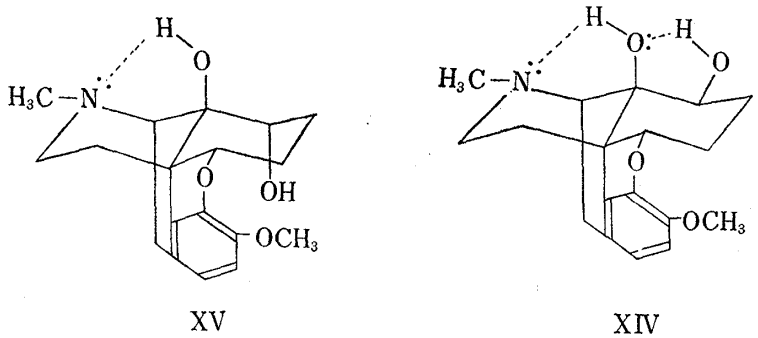

Fig. 2

10) A.C. Currie, J. Gillon, G.T. Newbold, and F.S. Spring, *J. Chem. Soc.*, **1960**, 773.

NII-Electronic Library Service

hydro-diol intramolecular hydrogen bond between the 14β-hydroxyl group and the 8β-one as shown in Fig. 2 is present. Consequently, this dihydro-diol should be 14-hydroxy-dihydro-pseudocodeine which is represented with formula XV, and the elemental analysis of this has agreed with that of the formula.

As the results presented in the preceding[4] and this papers one might thought that on the SN-reactions of tosylate of 14-hydroxy-codeine or its isomers the 14β-hydroxyl group have some effects such as the steric hindrance to the 6-position and the neighbouring group participation to the 8-position.

Experimental[11]

8β,14β-Epoxy-codide (III)——1) From 14-hydroxy-allopseudocodeine (I). A mixture of I (3.15 g), dried pyridine (10 ml), and tosyl chloride (2.7 g) was allowed to stand for 48 hours in a chilled box. A red-coloured mixture was poured into cold water (500 ml). It was made alkaline with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*.[12] The residue was extracted with ether. The ether solution was decoloured with the mixture of charcoal and active alumina, and evaporated to dryness *in vacuo*. The crystalline residue was recrystallized from EtOH to give 0.96 g (30.4%) of 8β,14β-epoxy-codide(III), mp 132—133°. $[\alpha]_D^{20.5}$ +248.4° (c=2.02). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1020, 926, 909, 855 (C–O). NMR: 5.21 τ (1H, quartet, J=3.5 cps). *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.56; H, 6.42; N, 4.67.

2) From 14-hydroxy-isocodeine (II). A mixture of I (12.6 g), dried pyridine (25 ml), and tosyl chloride (7.1 g) was stirred at −5—0° for one hour. A red-coloured mixture was treated as described in method (1) to give III (3.6 g; 29.3%). mp 132—133° (alone and mixed with a sample obtained by method (1)).

3) From the reaction product of 14-hydroxy-codeine 6-tosylate (VIII) with lithium bromide. The benzene extract obtained by the reaction of VIII (20 g) with lithium bromide (15 g) in acetone (500 ml) as described in a previous paper[4] was washed with ether. The ether solution was decoloured with charcoal and active alumina, and concentrated to one-third, and allowed to stand for 24 hours in a chilled box. The crystals were collected by filtration to give the mixed crystal of 14-hydroxy-8β-bromo-codide (IX) and III (bromine content: 56% of theoretical), mp 139—141° (EtOH). The filtrate was concentrated to one-third, seeded with III, and allowed to stand for 24 hours in a chilled box. The crystals were collected by filtration to give the crude III (1.4 g), mp 120—127°. Beilstein reaction:negative. The crude III was purified by crystallization from EtOH. mp 132—133° (alone and mixed with a sample obtained by method (1) or (2)).

4) From the reaction product of 14-hydroxy-codeine 6-tosylate (VIII) with lithium chloride. A mixture of VIII (40 g), lithium chloride (16 g), and acetone (1500 ml) was refluxed for 24 hours, and it was concentrated to one-third. The concentrated solution was poured into ice water (2000 ml) and it was extracted with $CHCl_3$. The $CHCl_3$ extract was extracted with ether (300 ml). The ether solution was decoloured with charcoal, concentrated to one-third, and allowed to stand for 24 hours in a chilled box. The crystals were collected by filtration, and washed with ether to give 14-hydroxy-6β-chloro-codide (X; 10.5 g) mp 143—146° (bath pre-heated at 133°). The ethereal filtrate and washings were mixed, and evaporated to dryness *in vacuo*. The residue was chromatographed on active alumina (200 g). The n-hexane–benzene (3:2) eluate containing X and small amount of III was removed, and the $CHCl_3$ eluate was collected, and evaporated to dryness *in vacuo*. The obtained crude III (7.65 g; 19.1%; mp 127—131°) was purified by recrystallization from EtOH. mp 130—131° (alone and mixed with samples obtained by methods 1—3). The IR spectrum was in good agreement with that of III.

Acetolysis of 8β,14β-Epoxy-codide (III)——A solution of III (0.3 g) in 10% acetic acid (2 ml) was allowed to stand for one hour at 70° or 24 hours at room temperature. Then, it was made alkaline with NH_4OH, and extracted with benzene. The benzene extract (0.355 g; mp 185—190°) was recrystallized from MeOH tc give 14-hydroxy-allopseudocodeine 8-acetate (V), mp 196—197° (alone and mixed with an authentic sample[4]). The IR spectrum was in good agreement with that of V.

Methanolysis of 8β,14β-Epoxy-codide (III)——A mixture of III (600 mg), MeOH (5 ml), and 30% KOH (1.5 ml) was refluxed for 5 hours. After removal of MeOH with evaporation, the residue was extracted with benzene. The benzene extract was chromatographed on active alumina (15 g). The n-hexane–benzene (3:2) eluate (150 ml) was collected and evaporated to dryness *in vacuo*. The residue was recrystallized

11) All melting points were uncorrected. The active alumina used was the Merck "nach Brockmann" without pre-treatment. The NMR spectra were measured by a Varian A-60 at 60 Mc in $CDCl_3$ and used Me_4Si as internal standard. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer model 141 automatic polarimeter.

12) On the treatment of extracted solution same procedures were used in following experiments.

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from EtOH to give 14-hydroxy-allopseudocodeien 8-methyl ether (Ia; 311 mg). mp 106—107°. $[\alpha]_D^{20.5}$ −123.2° (c=2.01). NMR: 6.83 τ (3H, singlet), 5.14 τ (1H, quartet, J=4 cps). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C 69.14; H 7.14; N, 4.12.

Then, the $CHCl_3$ eluate was collected and evaporated to dryness *in vacuo*. The residue was recrystallized from ether to give 14-hydroxy-allopseudocodeine (I; 60 mg). mp 129—131° (alone and mixed with an authentic sample[4,10]).

14-Hydroxy-tetrahydroallopseudocodeine and 14-Hydroxy-dihydropseudocodeine (XIV)——A mixture of crude acetolysis product obtained from VIII or X (67.3 g), 10% acetic acid (600 ml), and 5% Pd-C (10 g) was shaken in hydrogen atmosphere under normal temperature and pressure. After completion of hydrogen absorption, the mixture was filtered, and the filtrate was made alkaline with NH_4OH, and extracted with benzene. The benzene extract (65.6 g) was dissolved in a mixture of MeOH (350 ml), water (150 ml), and 30% KOH (50 ml), and it was heated for 30 min at 50—60°. After removal of MeOH with distillation, it was extracted with benzene. The benzene extract (63 g) was chromatographed on active alumina (100 g).

The benzene eluate was collected and evaporated to dryness *in vacuo*. The residue (57.4 g) was repeatedly recrystallized from EtOH to give 14-hydroxy-dihydroallopseudocodeine (XV; 8.5 g). mp 176—178° (alone and mixed with an authentic sample[4,10]). The ethanolic mother liqours were collected and evaporated to dryness *in vacuo*. The residue was dissolved in 70% MeOH, and it was made strong alkaline with 30% KOH and refluxed for 3 hours. After removal of MeOH with distillation, it was extracted with benzene. The benzene extract (11.1 g) decoloured with active alumina (20 g) was recrystallized from EtOH to give 14-hydroxy-tetrahydroallopseudocodeine (700 mg). mp 170—171°. $[\alpha]_D^{21.5}$ +35.5° (c=2.06). $FeCl_3$ reaction: green. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571, 3333 (O–H), 1613, 1587 (C=C). *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.71; H, 7.91; N, 4.58.

Then, the MeOH eluate was collected and evaporated to dryness *in vacuo*. The residue (6 g) was chromatographed on active alumina (100 g). The benzene eluate was collected and evaporated to give 14-hydroxy-dihydroallopseudocodeine (XV; 1.8 g). mp 176—178° (alone and mixed with an authentic sample[4,10]). Then, the MeOH eluate was collected and evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 14-hydroxy-dihydropseudocodeine (XIV; 4.1 g). mp 171—172°. $[\alpha]_D^{21.5}$ −131.7° (c=2.02). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3333 (O–H). NMR: 5.47 τ (1H, triplet, J=8 cps). *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.96; H, 7.31; N, 4.55.

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