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Studies on the Morphine Alkaloids and Its Related Compounds. XVI.[1] Synthesis of 14-Hydroxy-allopseudocodeine 8-Ethers and Its Derivatives

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Synthesis and the results of pharmacological tests of 14-hydroxy-dihydro-allopseudocodeine 8-ethers (VIII) were described. The potent local anaesthetic activity of the 8α-ethers and the contrary relationship between analgetic activity and local anaesthetic activity with the change of alkyl chain on ether group were observed in guinea pigs.

The 6-ethers of morphine and codeine were obtained by a long way starting from N-oxide to avoid a quaternization of tertiary amino group at the 17-position and offered to examine pharmacological effects of the ether group.[3] Some of 8-ethers of pseudocodeine can be prepared by $S_{N2'}$-reaction on 6β-chloro-codide (so-called 'α-chloro-codide')[4] but no 8α-ethers of morphine and codeine were prepared. On the other hand, the corresponding ethers of 14-hydroxy-morphine derivatives have not been known. On the basis of consideration described in the Part XV of this series,[1] we have devised a synthetic method of 14-hydroxy-allopseudocodeine 8-ethers in order to investigate pharmacological activity of the 8α-substituted group of 14-hydroxy-morphines, and actually succeeded in developing the useful method. Interestingly, it was found that the some of these compounds are almost lacking in the analgetic activity in mice but shows potent local anaesthetic activity in guinea pigs. Such the anaesthetic activity have not been found among the morphine derivatives.

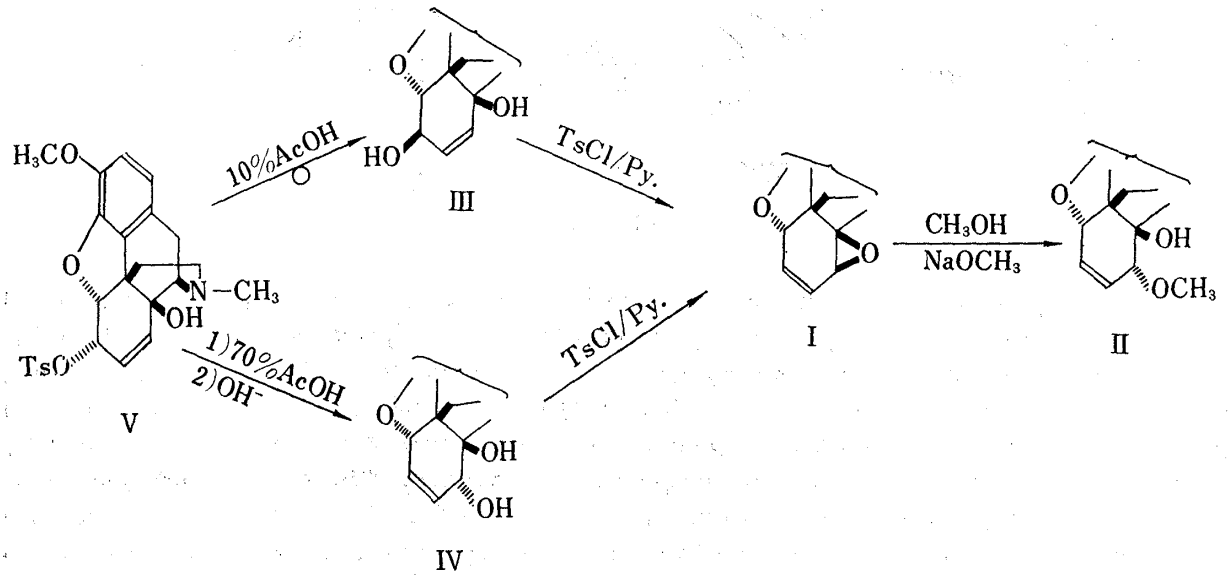


Chart 1

1) Part XV: I. Seki, *Chem. Pharm. Bull.* (Tokyo), **17**, 1549 (1969).
2) Location: *1-Chome Hiromachi, Shinagawa-ku, Tokyo.*
3) C. Mannich, *Arch. Pharm.*, **254**, 349 (1916); B.F. Faris and L. Small, *J. Org. Chem.*, **1**, 194 (1936).
4) L. Knorr and W. Hartmann, *Ber.*, **45**, 1354 (1912).

(1) Chemistry

Previously, the one of authors reported that the methanolysis of 8β,14β-epoxy-codide (I) which is derived from 14-hydroxy-codeine 6-tosylate (V) *via* 14-hydroxy-isocodeine (III) or 14-hydroxy-allopseudocodeine (IV) gives 14-hydroxy-allopseudocodeine 8-methyl ether (II) in a good yield.[1] This method, however, can not be available for the preparation of 14-hydroxy-8α-ethers because of a low yields of the epoxide (I).

As described in the preceding paper, the *cis*-displacement of acetoxy group from 6α-position to 8α-position in the acetolysis of 6α-tosylate (V) would occurred *via* thel epoxide (I).[1] Consequently, it may be considered that in the alcoholysis of 6α-tosylate (V) the 8α-ethers should also be afforded. On a separation of methanolysis product of 6α-tosylate (V) using alumina column chromatography, the main product eluated with benzene (53% yield) was identical with the methanolysis product (II) of epoxide (I), while the minor product eluated with chloroform (8% yield) can be supposed to be a 6β-methyl ether (VI) from the observation of nuclear magnetic resonance (NMR) spectra of 5β-proton (4.8 ppm, singlet).[5] From these results it is concluded that the methanolysis of 6α-tosylate (V) proceeds mainly in accordance with the *cis*-displacement as was expected.

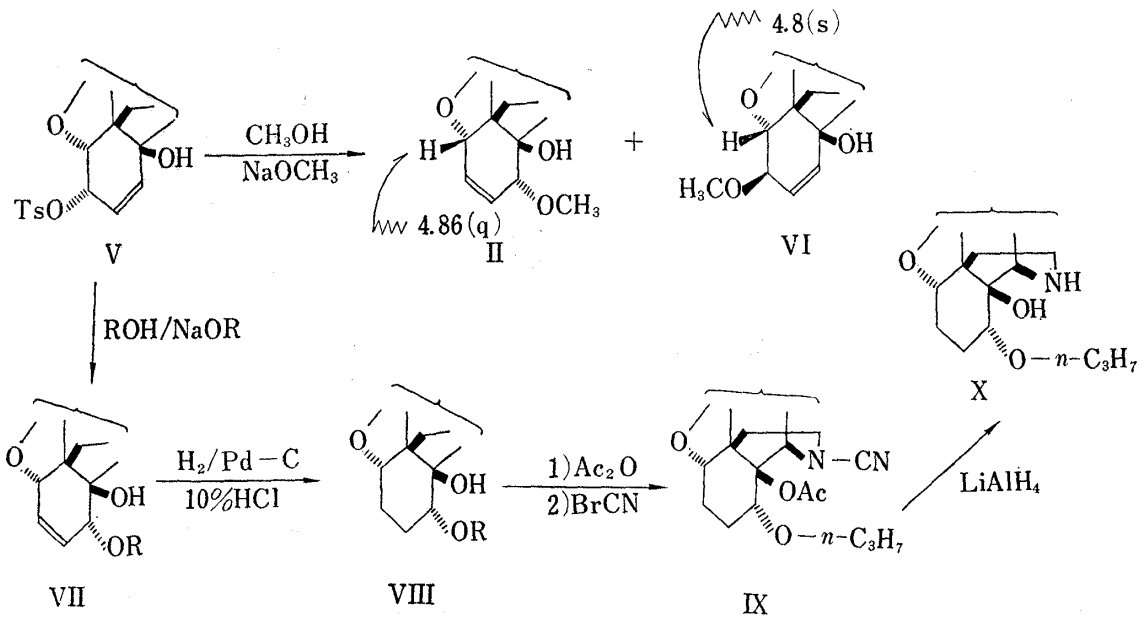
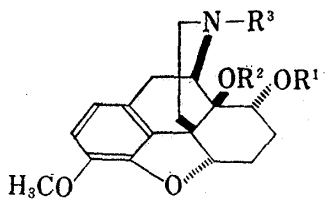


Chart 2

According to the above conclusion the 14-hydroxy-8α-phenyl-ether (VII: R=C_6H_5) and the homologues of 14-hydroxy-8α-methyl-ether (VII: R=alkyl) were easily obtained by the phenolysis and the alcoholysis of 6α-tosylate (V) or reaction product of V with lithium chloride, respectively. A catalytic reduction in 10% hydrochloric acid of these 8α-ethers (VI, VII) gave the corresponding dihydro-compounds (VIII) in a yield of 50—80% accompanied by a small amount of 4-phenolic dihydro-compound. 14-Hydroxy-dihydro-allopseudonorcodeine 8-*n*-propyl ether (X) was prepared from the acetate of VIII (R=*n*-C_3H_7) by reaction with cyanogen bromide followed by the reductive removal of the cyano group with lithium aluminum hydride. On a reduction of 14-acetoxy-N-cyano-compound (IX) with metal hydride in tetrahydrofuran, the decomposition due to the cleavage of 4,5-ether ring under refluxing and the by-production of the original N-methyl-compound (VIII: R=*n*-C_3H_7) in a yield of 35% at room temperature were observed beside the main reaction.

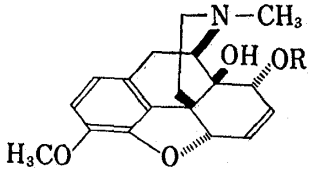
5) I. Seki, *Yakugaku Zasshi*, **84**, 631 (1964).

TABLE I.



R^1	R^2	R^3	Yield (%)	mp °C (recryst. solv.)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
CH_3	H	CH_3	47	152—154 (MeOH)[c]	$C_{19}H_{25}O_4N$	68.86	7.60	4.23	—	68.26	7.56	4.12	—
C_2H_5	H	CH_3	57	103—106 (EtOH)[d]	$C_{20}H_{27}O_4N$	69.54	7.88	4.06	—	69.47	7.94	4.07	—
n-C_3H_7	H	CH_3	64.3	228—230 (acetone)[a]	$C_{21}H_{30}O_4NCl \cdot 1/2H_2O$	62.28	7.72	3.46	8.77	62.44	7.79	3.35	8.71
n-C_4H_9	H	CH_3	30	238—240 (acetone)[a]	$C_{22}H_{32}O_4NCl \cdot 1/2H_2O$	63.06	7.94	3.34	8.47	63.59	7.96	3.27	8.66
n-C_5H_{11}	H	CH_3	30	229—231 (acetone)[a]	$C_{23}H_{34}O_4NCl \cdot 1/2H_2O$	63.79	8.15	3.24	8.20	64.44	8.12	3.25	8.37
i-C_3H_7	H	CH_3	62.5	amorphous powder[a]	$C_{21}H_{30}O_4NCl \cdot 1/2H_2O$	62.28	7.72	3.46	8.76	61.82	7.65	3.51	8.36
C_6H_5	H	CH_3	65.8	188—189 (EtOH)	$C_{24}H_{27}O_4N$	73.26	6.92	3.56	—	72.80	6.93	3.83	—
n-C_3H_7	Ac	CH_3	94.8	amorphous powder[a]	$C_{23}H_{32}O_4NCl \cdot H_2O$	61.58	7.52	3.07	7.78	61.37	7.49	3.24	7.38
n-C_3H_7	H	H	59.7	223—228[e] (acetone)[a]	$C_{20}H_{28}O_4NCl$	62.90	7.39	3.67	9.29	62.63	7.21	3.81	8.88
Ac	H	CH_3	53.5	154—156 (lit.[b] 154—156)	—	—	—	—	—	—	—	—	—

a) hydrochloride *b*) A.C. Currie, *et al.*: *J. Chem. Soc.*, 773 (1960) *c*) $[\alpha]_D^{21}$ −121.1° (c=2.05, $CHCl_3$) *d*) $[\alpha]_D^{21}$ −125.5° (c=2.07, $CHCl_3$) *e*) base: mp 109—111°C (from n-hexane) *Anal.* Calcd. for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.32; H, 8.00; N. 4.06.



R	Yield (%)	mp °C	Formula	Analysis (%) Calcd. C	H	N	Cl	Found. C	H	N	Cl
C_2H_5	78.8	245—250 (decomp.)[a]	$C_{20}H_{26}O_4NCl$	63.20	6.91	3.69	9.35	63.00	6.88	3.70	9.32
n-C_3H_7	78.3	213—215 (decomp.)[a]	$C_{21}H_{28}O_4NCl$	64.03	7.16	3.56	9.00	63.74	7.23	3.53	8.84
C_6H_5	74.3	amorphous powder[a]	$C_{24}H_{26}O_4NCl \cdot 1/2H_2O$	65.97	6.23	3.21	8.11	65.34	6.37	3.50	7.86

a) hydrochloride

(2) Pharmacology

The pharmacological activity of the 8α-ethers as shown in Table I were tested. The analgetic activity of the 14-hydroxy-dihydro-8α-ethers (VIII: R=alkyl, phenyl) was measured by Haffner's pressure stimulation method[6] and by writhing syndrome method with acetic acid[7] using mice. The respiratory depressed effect on cat, and potentiation activity of thiopental anaesthesia in mice were very weak comparing with those of the parent 8α-alcohol (VIII: R =H) but the acute toxicity was rather high to some extent. However, interestingly, the potent local anaesthetic activity of the 8α-ethers as lidocaine was observed in guinea pigs. Furthermore, the contrary relationship between analgetic activity and local anaesthetic activity in the 14-hydroxy-dihydro-allopseudocodeine (VIII: R=H) and its 8-ethers (VIII: R=alkyl, phenyl) was observed. From the result measured by Chance and Lobstein's corneal reflex test in guinea pigs[8] the relationship between local anaesthetic activity and the chemical structure of 14-hydroxy-8α-ethers can be concluded as follows: (1) the etherification of 8α-hydroxyl group results appearance of the local anaesthetic action accompanying with decrease of the analgetic activity. (2) Although the intensity of local anaesthetic activity increases with the number of carbon atom in alkoxy group the *n*-propyl ether (VIII: R=*n*-C_3H_7) shows the strongest and prolonged activity (effectively over 30 min at 0.5% concentration and within 10 min at 0.1% concentration), and in the isopropyl ether (VIII: R=iso-C_3H_7) the central depressed activity still remained in some extent. (3) The activity of phenyl ether (VIII: R=C_6H_5) is weaker than that of alkyl ethers (VIII: R=alkyl). (4) The introduction of 8α-acetoxy group in place of 8α-ether group results decrease of the activity. (5) The activity of 6,7-unsaturated 8α-ether (VII) is weaker than that of 6,7-saturated one (VIII). (6) Demethylation of tertiary amino group at the 17-position such as a conversion of VIII (R=*n*-C_3H_7) to X and acetylation of the 14-hydroxyl group in the dihydro-8α-ether (VIII) give rise to lack of the activity.

Experimental[9]

Methanolysis of 14-Hydroxy-codeine 6-Tosylate (V)——To a solution of Na (1.4 g) in absolute MeOH (150 ml) was added 14-hydroxy-codeine 6-tosylate (V; 5 g), and it was refluxed for 5 hours. After the removal of MeOH with distillation, the residue was dissolved in benzene and washed with water. The benzene solution was dried over Na_2SO_4, and evaporated to dryness *in vacuo*. Pale yellowish residue was chromatographed on active Al_2O_3 (36 g). The benzene eluate was collected to give 2.65 g of 14-hydroxy-allopseudocodeine 8-methyl ether (II). mp 105—107° (alone and mixed with the sample obtained by preceding work[1]). Then, $CHCl_3$ eluate was collected to give 0.45 g of 14-hydroxy-isocodeine 6-methyl ether (VI). mp 110—112° (from ether). NMR: 4.8 ppm. (1H, singlet, 5β-H). $[\alpha]_D^{21}$ −25.9° ($CHCl_3$, c=2.05). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.11; H, 7.14; N, 4.23.

14-Hydroxy-dihydro-allopseudocodeine 8-Ethers (VIII)——The main product obtained by the alcoholysis or phenolysis of 14-hydroxy-codeine 6-tosylate (V) in same manner as described for the methanolysis of V was catalytically reduced with hydrogen in 10% HCl. After completion of hydrogen absorption, the mixture was filtered. The filtrate was made alkaline to over pH 12.0 with 30% KOH and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from appropriate solvent, or converted to a crystallized hydrochloride by treatment with ethanolic hydrochloric acid in ethanol or acetone to give 14-hydroxy-dihydro-allopseudocodeine 8-ethers (VIII) as shown in Table I.

14-Hydroxy-dihydro-allopseudonorcodeine 8-*n*-Propyl Ether (X)——A mixture of 2.4 g of 14-hydroxy-dihydro-allopseudocodeine 8-*n*-propyl ether (VIII: R=*n*-C_3H_7) and 7.2 ml of Ac_2O was heated at 90° for one hour. After cooling, the mixture was poured into ice–water (100 ml), made alkaline with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4. To the $CHCl_3$ solu-

6) F. Haffner, *Deut. Med. Wochschr.*, **18**, 731 (1929).
7) B.A. Whittle, *Brit. J. Pharmacol.*, **22**, 246 (1964).
8) M.R.A. Chance and H. Lobstein, *J. Pharmacol. Exptl. Therap.*, **82**, 203 (1944).
9) 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.

tion was added 1.99 g (105 mole %) of 35% (by weight) BrCN–$CHCl_3$ solution, and it was refluxed for 5 hours in a draft chamber. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, washed with 5% AcOH then with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from acetone to give 2.35 g of N-cyano-14-hydroxy-dihydro-allopseudonorcodeine 8-*n*-propyl ether (IX). mp 163—165°. IR $\nu_{max}^{CHCl_3}$ μ: 4.48 (N-CN), 5.72 (Ac). *Anal.* Calcd. for $C_{23}H_{28}O_5N_2$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.01; H, 6.84; N, 6.93.

To a mixture of $LiAlH_4$ (1.56 g) and tetrahydrofuran (19.3 ml) was added the solution of the cyanamide (IX; 1.8 g) in tetrahydrofuran (19.3 ml) within one hour at room temperature under stirring. Then, the mixture was refluxed for 3 hours under stirring. After cooling on ice–bath, a mixture of water and $CHCl_3$ was added slowly to destroy a excess of $LiAlH_4$ at 0—5°. The mixture was filtered. The filtrate was poured into water (500 ml), and extracted with $CHCl_3$. The $CHCl_3$ sclution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was dissolved in 10% AcOH, and the insoluble matter was removed by washing with benzene. The aqueous layer was made alkaline with NH_4OH, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from *n*-hexane to give 0.4 g of 14-hydroxy-dihydro-allopseudonorcodeine 8-*n*-propyl ether (X). mp 109—111°. *Anal.* Calcd. for $C_{20}H_{27}O_4N$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.79; H, 8.07; N, 4.21.

n-Hexane mother liquor was evaporated to dryness *in vacuo*. The residue was chromatographed on active Al_2O_3 (9 g) and benzene eluate was collected to give 485 mg of 14-hydroxy-dihydro-allopseudocodeine 8-*n*-propyl ether (VIII: R=*n*-C_3H_7). This accorded with the product prepared by the propanolysis of V followed by catalytic reductcn in comparison with IR, NMR, and thin-layer chromatography.

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