CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 19, No. 1 January 1971

Regular Articles

[Chem. Pharm. Bull. 19(1) 1—5 (1971)]

UDC 547.94.07.09 : 615.234.011.5.076.9

Studies on the Morphine Alkaloids and Its Related Compounds. XX.[1] Syntheses and Pharmacology of Some Demethylated Compounds Related to the 14-Hydroxy-dihydro-6β-thebainol 4-Methyl Ether (Oxymethebanol), A New Potent Antitussive

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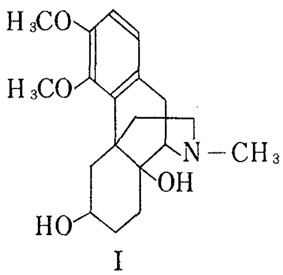
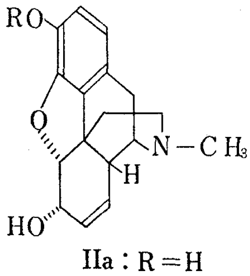
(Received September 3, 1969)

Syntheses and pharmacology of some demethylated compounds related to 14-hydroxy-dihydro-6β-thebainol 4-methyl ether (oxymethebanol), a new potent antitussive, were presented with interest to the structure-antitussive activity relationship on the 6-hydroxyl group in the morphinans. It was suggested that the β(equatorial)-configuration in 6-hydroxyl group is one of essential factors for an appearance of strong antitussive action of the 3,4,6,14-tetrahydroxy-morphinan 3,4-diethers.

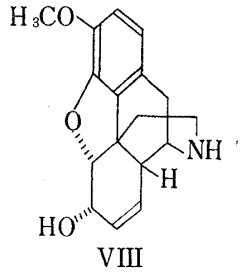
The pharmacology of 14-hydroxy-dihydro-6β-thebainol 4-methyl ether (oxymethebanol; I), a new potent antitussive, has been reported recently.[3] The metabolism and the distribution of I have also been studied using small animals.[4] In this paper, we wish to describe the syntheses and the pharmacology of some demethylated compounds related to I with interest to the structure–antitussive activity relationship on the configuration of 6-hydroxyl group in the morphinans.



I



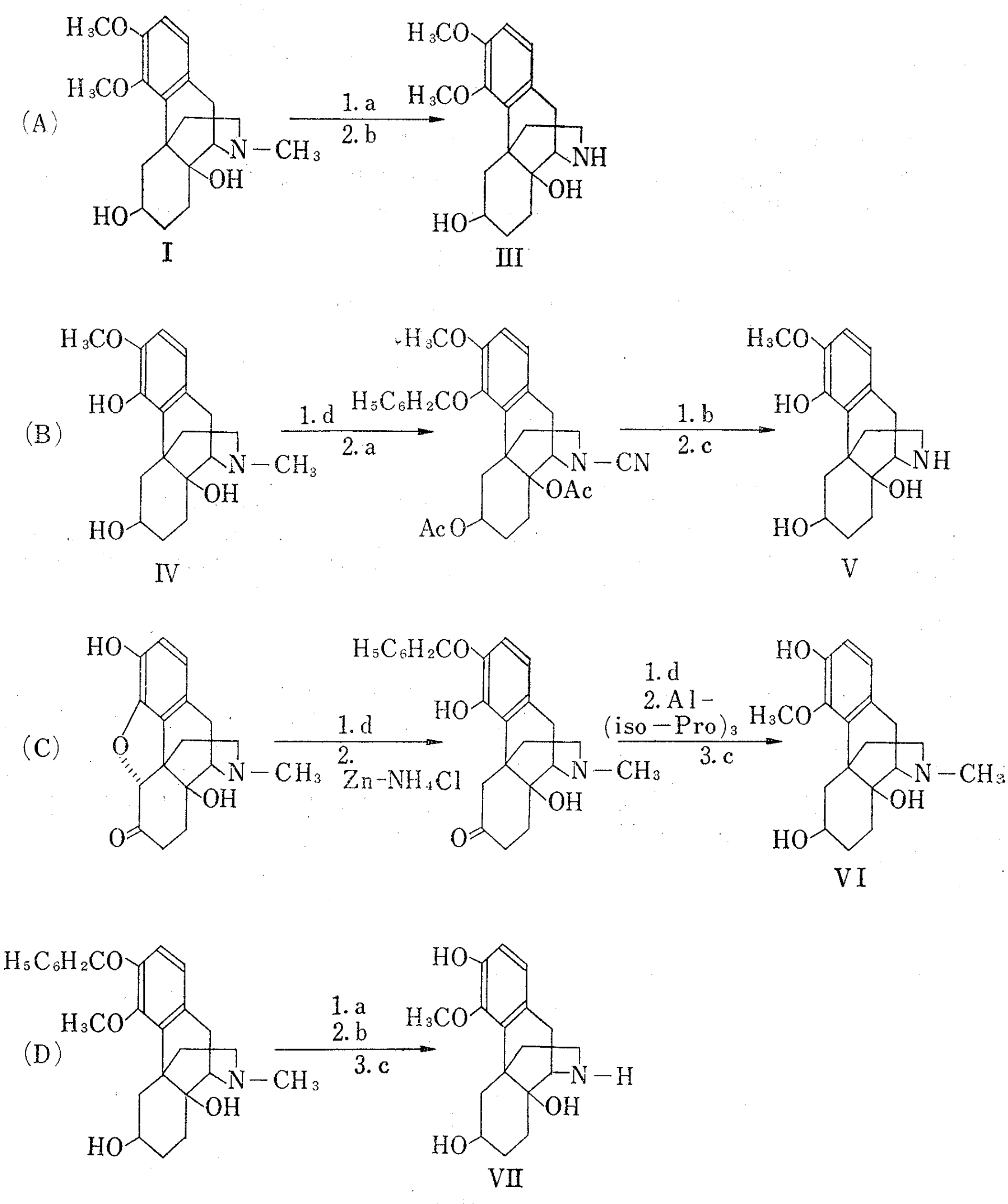
IIa : R=H
IIb : R=CH3



VIII

1) Part XIX: I. Seki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1269 (1970).
2) Location: *1-Chome Hiromachi, Shinagawa-ku, Tokyo.*
3) H. Takagi, S. Kobayashi, S. Kumakura, M. Mori, H. Koike, T. Kamioka, K. Hasegawa, and T. Ohshima, *Nippon Yakurigaku Zasshi*, **65**, 120 (1969); S. Kobayashi, K. Hasegawa, M. Mori, and H. Takagi, *Arzneimittel-Forsch.*, **20**, 43 (1970).
4) H. Shindo, T. Komai, E. Nakajima, H. Murata, A. Yasumura, and I. Seki, *Yakugaku Zasshi*, **90**, 36 (1970).

The demethylated compounds (Table I) were readily synthesized according to the course joined with the known methods[5,6] as illustrated in Chart 1. In the synthesis it was observed that the 4-hydroxy-N-nor-bases (V) are more soluble in water than the 3-hydroxy-N-nor-bases (VI, VII). Among these compounds, it has been reported that 3- and/or 17-demethylated compounds (III, VI, VII) were found in the metabolite of I, while formation of 4-demethylated compounds (IV, V) were not confirmed.[4] It is of interest to consider that phenolic properties of 4-hydroxyl group is much weaker than that of 3-hydroxyl group.[6] So far an

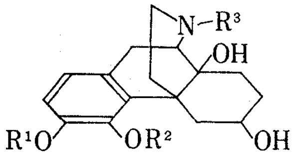


a : 1. Ac_2O, 2. BrCN in $CHCl_3$
b : $LiAlH_4$ in THF or KOH in $HOCH_2CH_2OH$
c : H_2/Pd-C in 10%AcOH
d : $C_6H_5N^+(CH_3)_2CH_2C_6H_5 \cdot OH^-$ or $C_6H_5N^+(CH_3)_3 \cdot OH^-$ in *n*-PrOH

Chart 1

5) I. Seki, *Ann. Sankyo Res. Lab.*, **12**, 56 (1960).
6) I. Seki, *Yakugaku Zasshi*, **84**, 615 (1964).

Table I.



No.	R^1	R^2	R^3	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
III	CH_3	CH_3	H	amorphous powder[a]	$C_{18}H_{26}O_4NCl \cdot 0.5H_2O$[a]	59.25	7.46	3.84	59.84	7.58	3.86
IV	CH_3	H	CH_3	203.5—204.5[b]							
V	CH_3	H	H	209 —211[c]	$C_{19}H_{27}O_6N \cdot 0.5H_2O$[c]	60.95	7.48	3.74	60.58	7.56	3.91
VI	H	CH_3	CH_3	225.5—226.5	$C_{18}H_{25}O_4N \cdot H_2O$	64.07	8.06	4.15	63.95	8.10	4.05
VII	H	CH_3	H	150 —160 (forming)[d]	$C_{17}H_{23}O_4N \cdot C_2H_5OH$	64.93	8.32	3.99	64.60	8.18	3.99

a) hydrochloride: *Anal.* Calcd. for Cl, 9.72. Found Cl, 9.90
b) known Compound, see I.Seki, *Yakugaku Zasshi*, **83**, 389 (1963).
c) acetate
d) decomp. at 210—250°

attempt on preparation of 6-glucuronide of I by Koenigs–Knorr method[7] was unsuccessful to obtain the sole product because of the more complexed reaction. Although the artificial preparation of 6-glucuronide of morphine (IIa) or codeine (IIb), which have 6α(quasi-axial)-hydroxyl group, have been reported recently,[8] no descriptions on the preparation of 6-glucuronide in dihydro-morphine alkaloids or morphinans were found. Consequently, it remained as future problems.

Pharmacology

For pharmacological characterization of the compounds III, V, VI and VII, analgetic effects, antitussive activities, effects on respiratory rate, potentiating actions of thiopental anesthesia, and acute toxicities were observed according to the methods described in experimental part. No respiratory depression of these compounds were observed in an intravenous dose of 3 mg/kg. Also, potentiating effects of thiopental anesthesia were not shown in a dose of 60 mg/kg. Acute toxicity (LD_{50}) of these compounds was over 300 mg/kg. No analgetic and antitussive activities of VII was shown in a dose of 30 mg/kg. On the other hand, it was shown that the compounds III, V, and VI still possess antitussive activity in spite of loss of analgetic activity in a dose of 30 mg/kg. However, in VI, 17-methylated compound, the Straub's tail reaction was shown in a dose of 300 mg/kg.

Among the compounds showing antitussive activity in a dose of 30 mg/kg, V, N-nor-14-hydroxy-dihydro-6β-thebainol, was selected for a detailed evaluation of antitussive activity comparing with those of codeine (IIb) and norcodeine (VIII). As shown in Table II, the antitussive activity of V was comparable with that of IIb and about 8 times as strong as that of VIII, while the analgetic activity and the acute toxicity of V were much weaker than those of IIb and VIII.

In a consideration of structure–activity relationship between codeine (IIb) and norcodeine (VIII) which are 6α-alcohol, as was expected from the studies carried out until now,[9] demethylation of the 17-position resulted in a marked decrease in the analgetic (ED_{50} 25 mg/kg→

7) P. Casparis, E. Kühni, and E. Leinzinger, *Pharm. Acta Helv.*, **24**, 145 (1949).
8) H. Yoshimura, K. Oguri, and H. Tsukamoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 2114 (1968).
9) O.J. Braenden, N.B. Eddy, and H. Halbach, *Bull. of the W.H.O.*, **13**, 937 (1955).

Table II

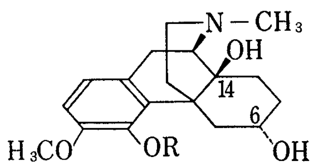
Compound	Antitussive ED_{50} *s.c.* in guinea pigs	Analgetic ED_{50} *s.c.* in mice	Acute toxicity LD_{50} *s.c.* in mice	Analgetic ED_{50}/Antitussive ED_{50}	LD_{50}/Antitussive ED_{50}
V	13 (6.2—27.3)[a]	610 (491—755)	780 (659— 938)	47.0	60
IV	33[b]	>100	178 (156— 204)[c]	>3.0	
Oxymethebanol (I)	0.44[b]	6 (4.2—8.6)	1150 (790—1660)	13.6	2613
Codeine (IIb)	11[b]	25 (18—35)	191 (178— 205)	2.3	17
Norcodeine (VIII)	100 (43.5—230)	245 (204—295)	*ca.* 600	2.5	*ca.* 6

a) Figures in parentheses are the 95% confidence limits.
b) ED_{50} was calculated according to the up-and-down method by K.A.Brownlee, *et al.*, *J. Am. Stat. Ass.*, **48**, 262 (1953).
c) *i. v.*

245 mg/kg) and the antitussive (ED_{50} 11 mg/kg→100 mg/kg) activities. However, in IV, which is 6β-alcohol, and its 17-demethylated compound V, an increase in the antitussive activity (ED_{50} 33 mg/kg→13 mg/kg) in spite of a lack in the analgetic activity (ED_{50}>100 mg/kg and 610 mg/kg, respectively) were shown unexpectedly. As reported previously,[10] in 14-hydroxy-dihydrothebainol 4-ethers it was observed that the 6β-alcohols such as I possess much stronger analgetic and antitussive activities than those of the 6α-epimers as shown in Table III. On the other hand, in codeine and dihydrocodeine isomers it was shown that the 6β- or 8β-alcohols has much stronger analgetic activity than the epimers,[11] but no comparative studies on antitussive activity were found.

From the facts described above, it can be suggested that the β(equatorial)-configuration in 6-hydroxyl group is one of essential factors for an appearance of strong antitussive action of the 3,4,6,14-tetrahydroxy-morphinan 3,4-diethers.

Table III. Comparison of Analgetic and Antitussive Activities in 14-Hydroxy-dihydrothebainol-4-ether Epimers



Configuration of 6-OH	R	Analgetic ED_{50} in mice, *s.c.*	Antitussive ED_{50} in guinea pig, *s.c.*
α	H	>100	>100
β	H	>100	33
α	Me	13	16
β	Me	6	0.44
α	Et	15	17.0
β	Et	6.4	5.0
α	Ph	88	80
β	Ph	18	8.2
α	CH_2Ph	23	7.1
β	CH_2Ph	3.5	3.5

10) I. Seki, H. Takagi, and S. Kobayashi, *Yakugaku Zasshi*, **84**, 280 (1964).
11) N.B. Eddy, *J. Pharmacol. Exptl. Therap.*, **45**, 361 (1932); **51**, 35 (1934).

Experimental[12]

Some crystallized intermediates obtained in the synthetic course as illustrated in Chart 1 were as follows.

(−)-6β,14β-Diacetoxy-3,4-dimethoxy-N-methylmorphinan——By acetylation of I with Ac_2O. mp 155—157°. *Anal.* Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.48; N, 3.36. Found: C, 66.17; H, 7.54; N, 3.34.

(−)-3-Methoxy-4,6β,14β-triacetoxy-N-methylmorphinan——By acetylation of IV with Ac_2O. mp 235—240°. *Anal.* Calcd. for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; N, 3.14. Found: C, 65.00; H, 7.02; N, 3.01.

(−)-3-Methoxy-4,6β,14β-triacetoxy-N-cyanomorphinan——By N-cyanation of the above triacetoxy compound with BrCN in $CHCl_3$.[5] mp 181—181.5°. *Anal.* Calcd for $C_{24}H_{28}O_7N_2$: C, 63.14; H, 6.18; N, 6.14. Found: C, 63.48; H, 6.15; N, 6.12.

(−)-3-Benzyloxy-6β,14β-dihydroxy-4-methoxy-N-methylmorphinan——By benzylation of the corresponding 3-hydroxy-compound with benzyldimethylphenylammonium hydroxide in *n*-PrOH.[6] mp 157.5—158.5°. *Anal.* Calcd. for $C_{25}H_{31}O_4N$: C, 73.32; H, 7.62; N, 3.42. Found: C, 73.24; H, 7.68; N, 3.52.

(−)-3-Benzyloxy-6β,14β-diacetoxy-4-methoxy-N-methylmorphinan——By acetylation of the above dihydroxy-compound with Ac_2O. mp 139.5—140°. *Anal.* Calcd. for $C_{29}H_{35}O_6N$: C, 70.56; H, 7.15; N, 2.84. Found: C, 70.15; H, 7.29; N, 2.93.

(−)-3-Benzyloxy-6β,14β-dihydroxy-4-methoxymorphinan——From the above diacetoxy-compound by N-cyanation with BrCN in $CHCl_3$ followed by decyanation of the N-cyano-compound with KOH in ethylene glycol at 120—140°. mp 207—208°. *Anal.* Calcd. for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39; N, 3.54. Found: C, 72.61; H, 7.42; N, 3.68.

Pharmacological Assay——(1) Analgetic Effects: Analgetic effects of these compounds examined were carried out by using the Haffner's tail pinch method.[13] The compounds were administered subcutaneously to mice of the ddY strain, weighing 18 to 24 g. The analgetic potency was expressed as the ED_{50} calculated by the method of Litchfield–Wilcoxon.[14]

(2) Antitussive Activity: Antitussive activity was tested by the method of Takagi, *et al.*[15] in guinea pigs, Hartely strain, weighing 250 to 300 g. Animals were anesthetized by an intraperitoneal dose of 15 mg/kg of sodium pentobarbital and fixed in a dorsal position. The trachea was exposed and a small incision was made at a distance of 1.5 cm from the clavicle. A stimulating hair was inserted into the incision at deep as 3 cm. The stimuli were applied two times before and 15, 30, 45, 60 min after the subcutaneous administration of the compound. If no coughing occurred in 2 or more out of 4 trials after the administration, the dose was estimated as effective. Fifty percent of antitussive dose (ED_{50}) was calculated by the method of Litchfield–Wilcoxon.[14]

(3) Effects on Respiratory Rate: Respiratory rate was measured in cats waighing 2 to 3 kg. The cats were anesthetized by intraperitoneal administration of sodium pentobrabital in a dose of 35 mg/kg and fixed on their backs. Respiration was recorded on a kymograph through a T-shaped cannula introduced into the trachea and connected to Marey's tambour. The test compounds were administered through a polyethylene tube into the femoral vein.

(4) Potentiation of Thiopental Anesthesia: The ddY strain mice, weighing 18 to 25 g, were used in a group of 5 mice. The compounds were administered intraperitoneally, and after 30 min 30 mg/kg of sodium thiopental was injected intravenously. The duration of loss of the righting reflex was measured and the rate of increase in the treated group over the control group was determined.

(5) Acute Toxicity was determined in ddY strain mice, weighing 18 to 24 g. Five to ten mice were used per dose. The compounds were administered subcutaneously or intraperitoneally. Mortality was recorded one week later. LD_{50} was calculated by the method of Litchfield–wilcoxon.[14]

Acknowledgement The autors are grateful to Dr. G. Sunagawa, Director, and Dr. I. Iwai, Assistant Director, of this laboratories for their advice and encouragement throughout this work. Thanks are also due to Mrs. M. Kitami and K. Kamoshida for their experimental assistance and to the members of analytical and physical measuring section in this laboratories for the micro-analysis and spectral measuring.

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12) All melting points were uncorrected.
13) F. Haffner, *Deut. Med. Wochenschr.*, **18**, 731 (1929).
14) J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
15) K. Takagi, H. Fukuda, and K. Yano, *Yakugaku Zasshi*, **80**, 1497 (1960).