Notes

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Tadashi Sasaki and Ken Kanematsu*1 : Studies on Morphine-like Compounds. Ⅳ.*1 Oxidation of N-Methylmorphinan and Related Compounds.

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Interest in the metabolic fate of morphine (Ⅰ) and morphine-like compounds in the addict compared to the non-addict has led to investigation of the various morphine-related compounds which appears to be reasonable for consideration as potential metabolites. Rapoport and Stevenson[1] described hydroxylated morphine derivatives to be the most interesting for that purpose. It has also been known[2] that codeine (Ⅲ) and dihydrocodeine (Ⅴ) are oxidized with chromic acid in very dilute sulfuric acid to give the corresponding hydroxylated products in very low yields.

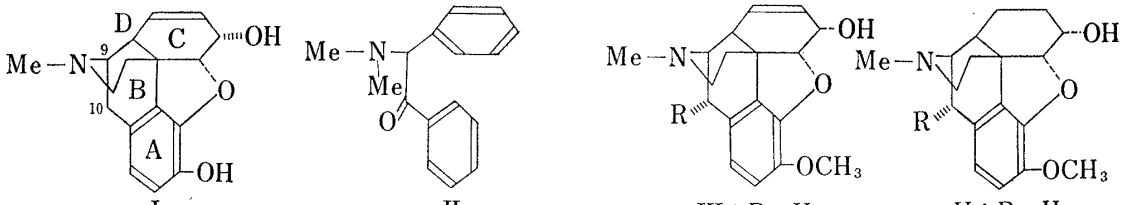

Chart 1.

In the previous paper,[3] the syntheses of several compounds possessing so-called A-C and A-B-C rings in the morphine skeleton as partially oxidized structures were reported and among these compounds, (±)-2-dimethylamino-2-phenylacetophenone (Ⅱ) showed potent analgesic activity. In the present paper, the preparation of some 10-oxo-compounds with more closely related structures to the morphine skeleton is described.

The first attempt was made to improve the low yields by the Rapoport and Stevenson method.[1] Namely, codeine (Ⅲ) and dihydrocodeine (Ⅴ) were oxidized with chromic acid

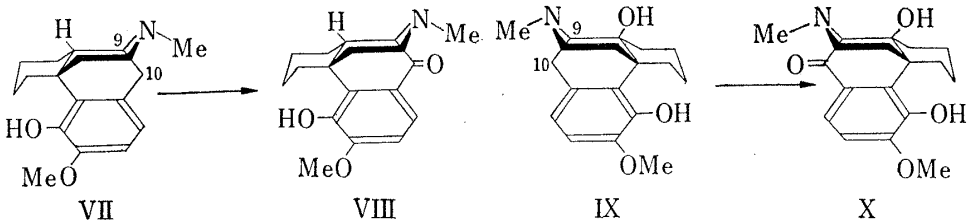

Chart 2.

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*2 Part Ⅲ: T. Sasaki, K. Kanematsu, S. Ohse: Yakugaku Zasshi, **84**, 977 (1964).

1) H. Rapoport, G. N. Stevenson: J. Am. Chem. Soc., **76**, 1769 (1954).

2) H. L. Holmes, G. Stork: "The Morphine Alkaloids" in "The Alkaloids," edited by R. H. Manske, H. L. Holmes, Vol. 2, p. 41 (1952), Academic Press.

3) T. Sasaki, K. Kanematsu, K. Minamoto, H. Fujimura: This Bulletin, **12**, 191 (1964).

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or sodium bichromate in dilute sulfuric acid under carefully controlled conditions. The appreciable amounts of III and V remained always unchanged, but the separation of the product from each starting material was efficiently achieved by chromatography on alumina. As shown in Table I which assembles these results, the above-mentioned attempt was unsuccessful.

Table I.

Subatance (g.)	$1N$ H_2SO_4 (ml.)	CrO_3 (g.)	$10N$ H_2SO_4 (ml.)	Reaction Temp. (°C)	Reaction Time (hr.)	Product (%)	
III 1.5	250	0.44	22	5	6	27	
III 1.5	250	0.40	20	10	6.5	27	
III 1.5	250	0.40	20	20	6	23	IV[a]
III 1.5	100	0.40	20	30	7	19	
III 1.5	100	0.40	20	40	7	10	
V 0.5	200	0.30	20	5	6	15	
V 0.5	200	0.30	20	10	6	15	
V 0.5	200	0.30	20	30	6	15	VI[b]
V 0.5	200	0.30	20	40	6	13	

a) m.p. 205~207° (lit.[1] 205~206°) *b*) m.p. 208~209° (lit.[1] 202~203°)

Secondly, (+)-demethoxydesoxydihydrosinomenine (VII) and (−)-14-hydroxytetrahydrodesoxycodeine (IX) were oxidized with sodium bichromate or chromic acid in glacial acetic acid. Since these compounds lack a reactive group such as double bond in the ring C of the morphine skeleton, oxidation of these compounds might occur at the C_{10} position. After the following discussion on their spectroscopic data, the oxidation products of VII and IX were concluded to be 10-oxo-demethoxydesoxydihydrosinomenine (VIII) and 14-hydroxy-10-oxo-tetrahydrodesoxycodeine (X), respectively. The infrared spectra of VIII and X showed both sharp absorption at 1670 cm^{-1} which might be assignable either to a carbonyl conjugated with an aromatic ring or to a N-formyl group possibly resulted from oxidation of a N-methyl group. Their ultraviolet absorption spectra showed maxima at 241 mμ (log ε 4.21), 289 (4.10), and 315 (3.96) in VIII and at 245 mμ (log ε 4.23), 289 (4.07) and 312 (3.70) in X, as shown in Fig. 1. Rapoport and Stevenson[1] reported that 10-oxo-tetrahydro-N-methylmorphimethine had three ultraviolet absorption maxima at 244 mμ, 284 and 323, and these positions and intensities are typical for methoxy and hydroxy aromatic ketones.[4] From these facts the last bands at 315 mμ (VIII) and 312 mμ (X) could be assignable to a conjugation between an aromatic ring and a ketone, since it is absent in 10-hydroxycodeine. The nuclear magnetic resonance spectra of these compounds in deuterochloroform solution showed the existence of an N-methyl group (3H, singlet at 7.6 τ). Furthermore, VIII and X showed characteristic signals in the regions of 6.7~7.3 τ and 2.3~3.5 τ, and the general patterns were simpler than those of codeine (III). Recently, Okuda, *et al.*[5] reported that the signals of $C_{9\alpha}$- and $C_{10\beta}$-protons of III appeared in 6.6~7.3 τ region and their coupling constants, $J_{9\alpha,10\alpha}$, $J_{9\alpha,10\beta}$, $J_{9\alpha,14\beta}$, $J_{10\alpha,10\beta}$ were about 5, 0, 3 and 18 c.p.s., respectively. On the basis of this, the chemical shifts of the C_9-protons in VIII and X might be assignable as given in Table II which is the summary of the NMR data of compounds III, IV, V, VI, VIII and X. About the behavior of the aromatic protons at 2.24 τ (1H, doublet, J, 8.5 c.p.s.) in both VIII and X, it is probable that anisotropy of a conjugated carbonyl group is sufficient to account for the low-field displacement of one of two protons in a AB-type compound. Tomita, *et al.*[6] reported that the aromatic

4) R. F. Patterson, H. Hibbert: J. Am. Chem. Soc., **65**, 1862 (1943).
5) S. Okuda, S. Yamaguchi, Y. Kawazoe, K. Tsuda: This Bulletin, **12**, 104 (1964).

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protons of deoxomethaphanine-B appeared at 2.37 τ (1H, doublet, J=8.5 c.p.s.) and 3.17 τ (1H, doublet, J=8.5 c.p.s.). From the above evidence, the structures of Ⅷ and Ⅹ were determined to be the 10-oxo compounds. It is also of interest to compare the patterns of Ⅷ and Ⅹ with those of 10-*trans*-hydroxylated compounds such as Ⅳ and Ⅵ in Table Ⅱ; the absorption patterns of Ⅳ and Ⅵ in 6.7~7.3 τ region are much simpler than those of codeine (Ⅲ) and Ⅳ showed a doublet (J=3.3 c.p.s.) at 6.62 τ and Ⅵ exhibited a doublet (J=2.8 c.p.s.) at 6.90 τ, coupled with C_{14}-proton.

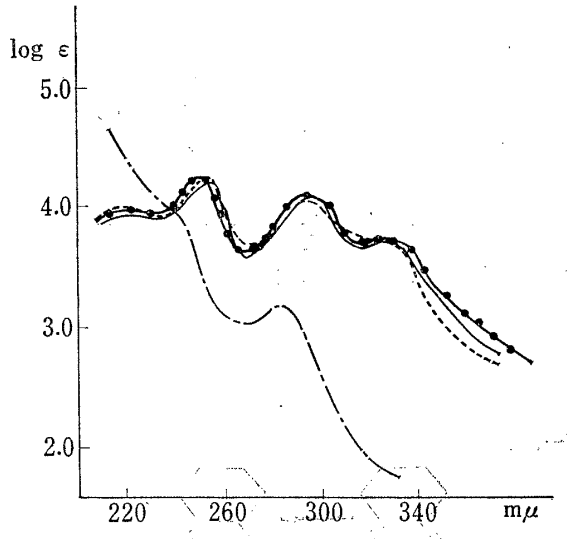

Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

------ Dihydrodesoxycodeine
——— 10-oxo-tetrahydro-N-methylmorphimethine
-------- VIII -●-●-●- X

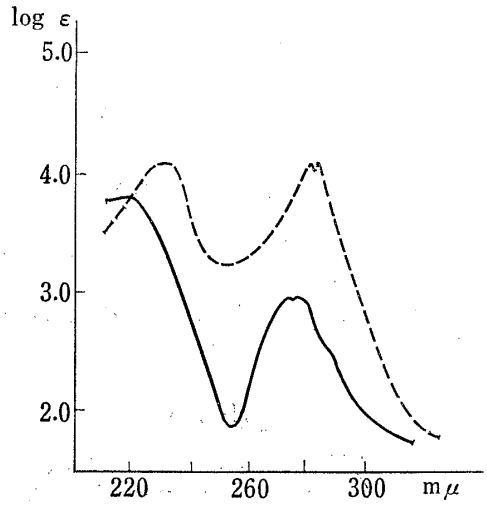

Fig. 2. Ultraviolet Absorption Spectra (in EtOH)

-------- XII
——— XIV

Table Ⅱ.

	Region in 2.0~3.5 τ (J c.p.s.)		Region in 6.5~7.3 τ (J c.p.s.)	
			C_9-H	C_{10}-H
Ⅲ	3.03	3.36	6.62 ($J_{10\alpha}$ 5.6) (J_{14} 3.2)	6.93 ($J_{10\alpha}$ 18.4)
Ⅳ	3.13	3.20	6.62 (J_{14} 3.3)	
Ⅴ	3.32	3.35	6.95 ($J_{10\alpha}$ 5.8) (J_{14} 2.6)	7.01 ($J_{10\alpha}$ 18.1)
Ⅵ	3.05	3.10	6.90 (J_{14} 2.8)	
Ⅷ	2.24 (doublet) (J 8.5)	3.13 (doublet) (J 8.5)	7.03 (J_{14} 3.0)	
Ⅸ	3.19	3.35	7.09 ($J_{10\alpha}$ 5.0) (J_{14} 2.0)	7.00 ($J_{10\alpha}$ 18.0)
Ⅹ	2.24 (doublet) (J 8.5)	2.08 (doublet) (J 8.5)	7.15	

Similar treatment of (+)-3-methoxy-N-methylmorphinan (Ⅺ) with sodium bichromate or chromic acid gave the oxidation product (Ⅻ) in a good yield. Its infrared spectrum showed a sharp absorption at 1670 cm^{-1} owing to a conjugated carbonyl group. Its ultraviolet absorption spectrum had two maxima at 232 mμ (log ε 4.70) and 287 mμ (4.14), distinctly different from those of Ⅷ and Ⅹ. As shown in Fig. 2, the spectrum of Ⅻ resembles that of 6-methoxy-1-tetralone (XIV), indicating a characteristic absorption

6) M. Tomita, T. Ibuka, Y. Inubushi, K. Takeda: This Bulletin, **13**, 695, 704 (1965).

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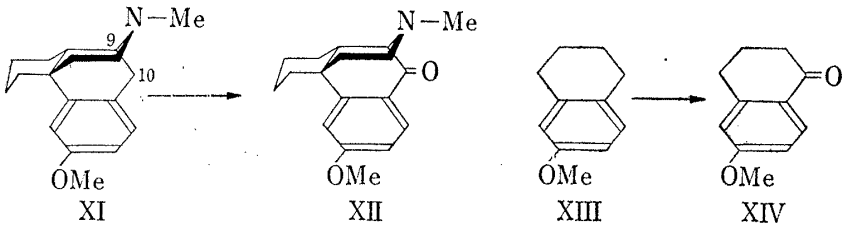
curve of *para*-substituted tetralone type chromophore. The NMR spectral data of XII are shown in Table III in comparison with those of 6-methoxytetraline (XIII), 6-methoxy-1-tetralone (XIV) and 3-methoxy-N-methylmorphinan (IX). It can be seen from this table that in these carbonyl compounds the characteristic absorption of aromatic protons in the above-mentioned 2.0~3.5 τ region shifts regularly to the lower field. On the basis of the above results and from the analytical values of XII it can be concluded that XII is 3-methoxy-10-oxo-N-methylmorphinan and a carbonyl group was newly introduced at the 10-position of the morphine skeleton.

Table III.

	Region in 2.0~3.5 τ (J c.p.s.)		Region in 6.5~7.3 τ (J c.p.s.)	
			C_9–H	C_{10}–H
XI	2.90~3.40 (multiplet)		7.09 ($J_{10\beta}$ 5.7) (J_{14} 2.6)	6.97 ($J_{10\beta}$ 18.6)
XII	1.99 (doublet) (J 9.0)	3.06~3.21 (multiplet)	6.90 (J_{14} 2.8)	
XIII	3.04~3.43 (multiplet)			
XIV	1.89 (doublet) (J 8.5)	3.12~3.30 (multiplet)		



XI XII XIII XIV

Chart 3.

Experimental*3

Oxidation of Codeine (III) and Dihydrocodeine (V) with Chromic Acid——The general procedures are as follows: a solution of chromic acid in 10*N* sulfuric acid was added to a cooled base solution with gentle stirring. The reaction mixture was stirred at the reaction temperature for the reaction time as indicated in Table I. Surplus oxidant was decomposed by addition of sodium sulfite and sodium carbonate and the reaction mixture was extracted with chloroform. After removal of the solvent under reduced pressure, the residue was recrystallized from acetone to give a 10-hydroxylated product mixed with the starting material, which was purified by column chromatography on alumina using 85% chloroform-benzene mixture as an eluent. Yields of the products under several conditions are summarized in Table I.

Oxidation of (−)-Demethoxydesoxydihydrosinomenine (VII)——A solution of 0.4 g. of sodium bichromate in 10 ml. of AcOH and 5 ml. of H_2O was added during 1 hr. at 10° to a stirred solution of 0.9 g. of VII in 10 ml. of AcOH. Temperature was raised to 25~30° and the mixture was stirred for further 6 hr. at this temperature. After the reaction mixture was kept overnight, 10 ml. of EtOH was added to this solution and the solvents were removed. The oily residue was dissolved in 10% aq. Na_2CO_3 (50 ml.) and the solution was extracted with chloroform. Removal of the solvent from the chloroform layer gave VIII as pale yellow prisms after recrystallization from MeOH, m.p. 217°. Yield 75%. *Anal.* Calcd. for $C_{18}H_{23}O_3N$: N, 4.56. Found: N, 4.64. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. UV λ_{max}^{EtOH} mμ (log ε): 241 (4.21), 289 (4.10), 315 (3.69). $[\alpha]_D^{23}$ −112° (c=1.0, MeOH). NMR τ ($CDCl_3$): 6.00 (3H, $OC\underline{H}_3$), 7.67 (3H, N-$C\underline{H}_3$).

Oxidation of (−)-14-Hydroxytetrahydrodesoxycodeine (IX)——A solution of 0.4 g. of sodium bichromate in 10 ml. of AcOH and 5 ml. of H_2O was added during 1.5 hr. at 5° to a stirred solution of 1.0 g. of IX in

*3 All melting points are uncorrected. Microanalyses were carried out with a Yanagimoto C. H. N. Corder MT-1 type. Infrared spectra were taken on a Nippon-Bunko IR-S type spectrophotometer. All NMR spectra were determined with a Varian A-60 NMR spectrometer, operating at 60 Mc. with high resolution and all compounds were examined in 5~10% deuterochloroform solutions. The chemical shifts are given in τ values calibrated from tetramethylsilane as an internal standard.

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10 ml. of AcOH. Temperature was raised to 30° and the mixture was stirred for more 7 hr. The reaction mixture was worked up as above and the crude product was recrystallized from EtOH to give X as colorless prisms, m.p. 169~170°. Yield 70%. *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31. Found: C, 67.80; H, 7.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. UV λ_{max}^{EtOH} mμ (log ε): 245 (4.23), 289 (4.07), 312 (3.70). $[\alpha]_D^{25.5}$ +49.6° (c=1.04, MeOH). NMR τ ($CDCl_3$): 6.00 (3H, OCH_3), 7.65 (3H, N-CH_3).

Oxidation of (−)-3-Methoxy-N-methylmorphinan (XI)——A solution of 0.9 g. of chromic acid or 1.4 g. of sodium bichromate in 10 ml. of AcOH and 6 ml. of H_2O was added during 30 minutes at 10° to a stirred solution of 1.2 g. of XI in 10 ml. of AcOH. Temperature was raised to 30°. The mixture was stirred for further 7 hr. and worked up as above to give XII as pale yellow prisms from MeOH, m.p. 192~194°. Yield 80%. *Anal.* Calcd. for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12. Found: C, 75.81; H, 8.19. UV λ_{max}^{EtOH} mμ (log ε): 232 (4.07), 287 (4.14). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. $[\alpha]_D^{23}$ −98.6°(c=1.13, EtOH). NMR τ ($CDCl_3$): 6.22 (3H, OCH_3), 7.59 (3H, N-CH_3).

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Ryuichi Kato and Akira Takanaka*1: Lack of Chronic Morphine Effect on the Induction of Drug-Metabolizing Enzymes of Liver Microsomes by Phenobarbital in Female Rats.

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It has been shown that administration of phenobarbital and various drugs stimulate the activities of drug-metabolizing enzymes of liver microsomes.[1]

On the other hand, some investigators reported that repeated administration of morphine reduced the activities of the drug-metabolizing enzymes in male rate.[2,3] Moreover, Remmer demonstrated that chronic administration of morphine reduced the activities of the drug-metabolizing enzymes in male rats, but it stimulated the activities of the enzymes in female rats.[4]

Furthermore, Kato and Gillette showed that single injection of morphine reduced the activities of drug-metabolizing enzymes of liver microsomes in male rats, but it did not alter the activities in female rats.[5,6]

Okui and co-worker recently made an interesting observation that chronic administration of morphine for one month almost completely abolished the stimulatory effect of phenobarbital on the drug-metabolizing enzymes of male rats.[7,8] Injection of morphine for 4 days did not reduce the effect of phenobarbital, but it was progressively reduced according to the duration of morphine administration.

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4) H. Remmer: "Enzymes and Drug Action," Ciba foundation Symposium, ed. by J. L. Mongar and A. V. S. de Reuck, p. 276 (1962). Little, Brown and Co., Boston.
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6) *Idem*: J. Pharmacol., **150**, 285 (1965).
7) S. Okui, K. Minegishi: Eisei Kagaku, **11**, 143 (1965).
8) Y. Kuroiwa, K. Minegishi, S. Okui: This Bulletin, **13**, 731 (1965).

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