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Stereospecific Synthesis of Codeine 7,8-Oxide and Codeinone 7,8-Oxide[1]

Codeinone (**1**) was oxidized to codeinone 7,8-oxide (**2**) by hydrogen peroxide. Stereospecific reduction of **2** by sodium borohydride afforded codeine 7,8-oxide (**3**). The configuration of **3** was confirmed by X-ray analysis.

Keywords——codeine; codeinone; codeine 7,8-oxide; codeinone 7,8-oxide; stereospecific epoxydation; stereospecific reduction; X-ray analysis; ^{13}C-NMR

The oxidative metabolism of morphine alkaloids has been well investigated. For example, morphine is metabolized by the following oxidative pathways:[2] (A) N-oxidation to morphine N-oxide;[2a,b] (B) oxidation of 6-hydroxy group to morphinones[2c,d] and (C) oxidation of aromatic ring to 1- or 2-hydroxy morphine[2b] and morphine 2,3-quinone.[2e] However, the oxidative metabolites of Δ7, 8 double bond have not been reported yet. Recently, Yeh *et al.* suggested that the formation of morphine 7,8-oxide is one of the possible pathways to β- or γ-isomorphine.[2b] Nevertheless, several attempts to synthesize the 7,8-epoxy compounds were unsuccessful.[2b,3] Direct oxidation of codeine or morphine with peracids or peroxides does not give 7,8-oxide for its facile formation of N-oxide[4] and less reactivity of Δ7, 8 bond.[5]

During the course of study, we examined the oxidation of codeinone (**1**). It was quantitatively oxidized to the N-oxide with peracids. However, we have now found that codeinone 7,8-oxide (**2**) was afforded from **1** with other more polar oxidative products on treatment with hydrogen peroxide in mild condition. That is, to a solution of **1** (297 mg) in 20 ml of methyl alcohol was slowly added 4 ml of 3% hydrogen peroxide and 4 ml of 0.1 N sodium hydroxide at 0°. After stirring for 10 min, the reaction mixture was immediately extracted with methylene chloride. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 320 mg of solid residue, which was chromatographed on aluminium oxide (32 g). Elution with methylene chloride–methanol (99 : 1) gave crystals which were recrystallized from ether to afford **2** (88 mg, 28.1% yield) as colorless needles, mp 199—200°. The ^{1}H-nuclear magnetic resonance (NMR) spectrum of **2** showed a three proton singlet (N–CH_3) at δ 2.4, which denied the N-oxide formation.[6] On the other side, an increase of aliphatic

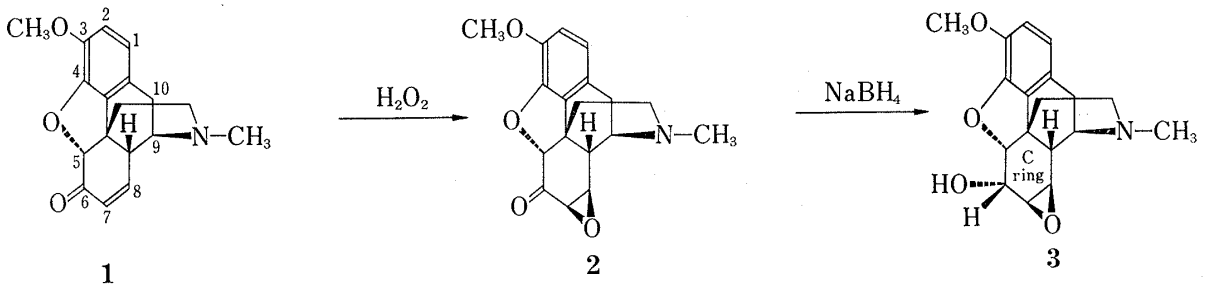

Chart 1

1) This forms part I of the series "Chemical Studies on Drug Metabolism."
2) *a*) J.D. Phillipson, W. El-Dabbas, and J.W. Gorrod, "Biological Oxidation of Nitrogen," ed. by J.W. Gorrod, Elsevier/North-Holland Biomedical Press, Amsterdam, 1978, p. 125; *b*) S.Y. Yeh, H.A. Krebs, and C.W. Gorodetzky, *J. Pharm. Sci.*, **68**, 133 (1979); *c*) S.Y. Yeh, C.W. Gorodetzky, and H.A. Krebs, *ibid.*, **66**, 1288 (1977); *d*) A. Klutch, *Drug Metab. Dispos.*, **2**, 23 (1974); *e*) A.L. Misra, N.L. Vadlamani, R.B. Pontani, and S.J. Mulé, *Biochem. Pharmacol.*, **22**, 2129 (1973).
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5) T. Itoh, K. Jitsukawa, K. Kaneda, and S. Teranishi, *J. Am. Chem. Soc.*, **101**, 159 (1979).
6) The peak of N-CH_3 protons of codeinone N-oxide is at δ 3.5 ppm.

protons at δ 3.2(m) with a disappearance of olefin proton peaks (C_7–H and C_8–H) at δ 6.0(q) and δ 6.6(m) indicated the oxidation of Δ7, 8 double bond. The ^{13}C-NMR spectrum data (in $CDCl_3$: δ 56.1, 57.4 and 57.7 for C_7, C_8 and C_9),[7] the mass spectrum (MS) data (*m/e*: 313 (M^+), 297 (M^+-16)) and elemental analysis (EA) (*Anal.* Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.72; H, 6.08; N, 4.56) supported **2**. Selective reduction of the carbonyl group of **2** (313 mg) in methanol (56 ml) was accomplished by the use of sodium borohydride (110 mg) for 15 min at 0°, and the reaction products were extracted with methylene chloride. The organic layer was washed with water and dried over Na_2SO_4. Removal of the solvent gave crystals, which were recrystallized from ether to give codeine 7,8-oxide (**3**) (135 mg), colorless needles, mp 189—190° in 42.7% yield. The ^{13}C-NMR spectrum (in $CDCl_3$) of **3** showed the C_6 peak at δ 71.0. Furthermore, the infrared spectrum (IR ν_{max}^{KBr} cm^{-1}: 3550 –OH) and the ^{1}H-NMR (in $CDCl_3$: δ 4.1 (1H, m, C_6–H), δ 4.7 (1H, d, C_5–H)) supported the reduction of carbonyl group. Additionally, the molecular ion peak at *m/e* 315 and EA (*Anal.* Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.59; H, 6.71; N, 4.42) suggested the retention of oxirane ring. To clarify the configuration of **3**, an X-ray diffraction study was performed. The data of X-ray analysis (Fig. 1) indicated that the C ring takes a half boat conformation[8] and that C_6 hydroxy group and oxirane ring take α and β configuration respectively. The conformation of the C ring and the configuration of the C_6 hydroxy group coinsided with those of codeine. From these results, it is obvious that the epoxydation of codeinone proceeds from the less hindered β side of **1** and the reduction of carbonyl group of **2** also proceeds from the β side. We suppose, the oxirane ring is not reduced with hydride since metal hydride can not attack from α side of oxirane due to the steric hindrance of **2**.[9] These epoxides are fairly stable to acids and bases, but in strong acid media (pH=1) **3** was slowly decomposed to the triol. The biological activities and metabolism of these epoxides will be reported in subsequent papers.

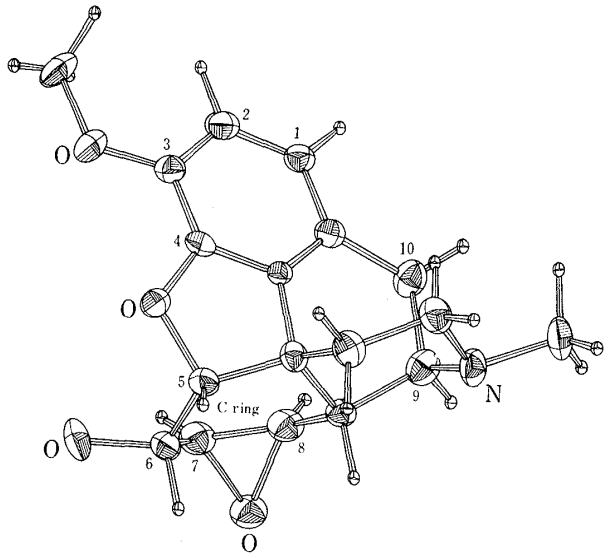

Fig. 1. Structure of Codeine 7,8-Oxide

Hydrogen atom of C_6 hydroxy group does not appear by this analysis and C_{10} α-hydrogen is behind the C_{10} carbon atom in this figure.

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