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Synthesis and Analgesic Activity of Morphine-7,8-oxide and Heroin-7,8-oxide[1,2]

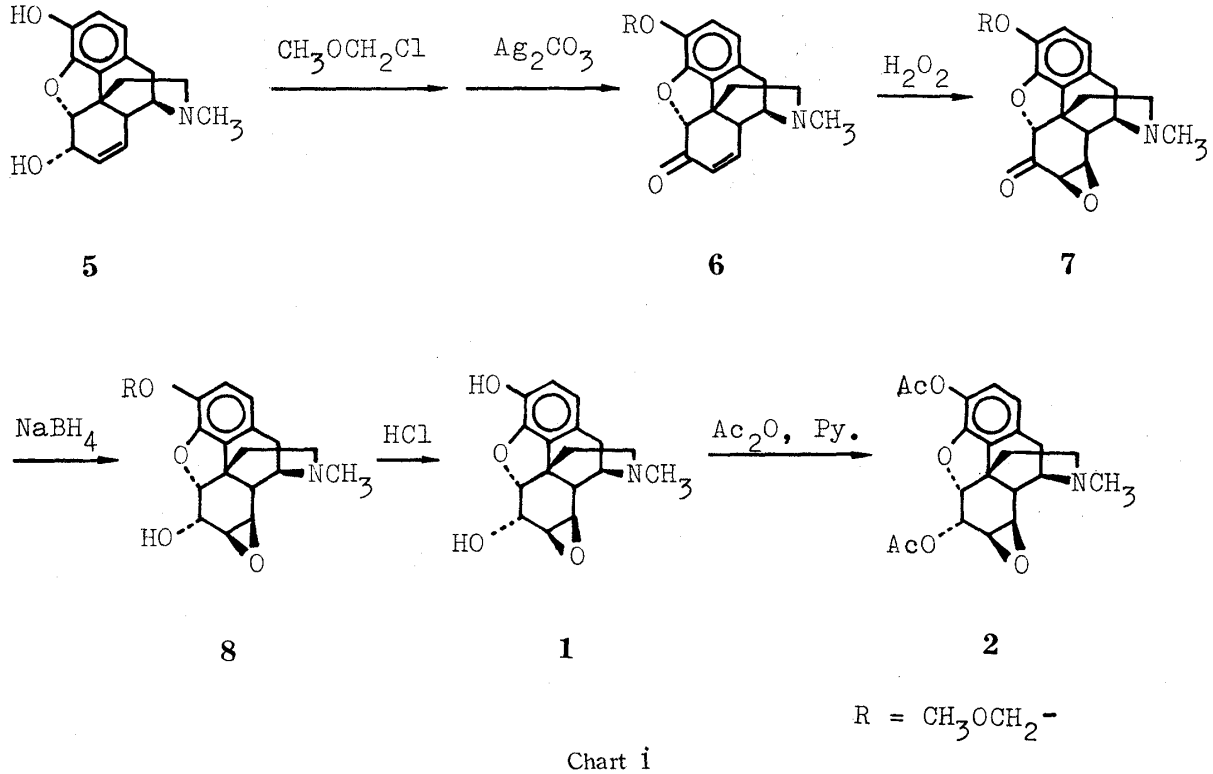
Morphine-7,8-oxide (**1**) was synthesized from 3-methoxymethylmorphinone-7,8-oxide which was obtained by the oxidation of 3-methoxymethylmorphinone with H_2O_2. Heroin-7,8-oxide (**2**) was also synthesized from **1**.

The analgesic activity of 7,8-epoxides (**1**, **2** and codeine-7,8-oxide) was determined by the method of pressure stimuli on the rat tail. **2** was the most analgesic among all of them. In comparison with each of their parent compound (morphine, heroin and codeine), the introduction of the 7,8-epoxy moiety into morphine skeleton resulted in some increase in their analgesic activity.

Keywords——morphine alkaloid; epoxidation; morphine-7,8-oxide; heroin-7,8-oxide; codeine-7,8-oxide; analgesic activity; structure-activity relationship

As previously reported,[3] codeine-7,8-oxide (**3**) was identified as a new metabolite of codeine (**4**). This finding encouraged us to study the chemical and pharmacological properties of 7,8-epoxides of morphine alkaloids. In this paper, we wish to report the synthesis of morphine-7,8-oxide (**1**) and heroin-7,8-oxide (**2**), and their analgesic activity including that of **3**.

Several attempts were made to synthesize **1** from morphine (**5**) directly, but these met with failure.[4] Then we attempted the epoxidation of a protected morphinone, 3-methoxymethylmorphinone (**6**),[5] in accordance with the synthesis of **3** from codeinone.[6] 3-Methoxy-



5 **6** **7**

8 **1** **2**

R = CH_3OCH_2-

Chart I

1) This forms part IV of a series entitled "Chemical Studies on Drug Metabolism." Part III: T. Ohta, N. Miyata, and M. Hirobe, *Chem. Pharm. Bull.*, submitted for publication.
2) A part of this work was presented at the 12th Symposium on Drug Metabolism and Action, Kanazawa, October 1980.
3) K. Uba, N. Miyata, K. Watanabe, and M. Hirobe, *Chem. Pharm. Bull.*, **28**, 356 (1980).
4) S.Y. Yeh, H.A. Krebs, and C.W. Gorodetzky, *J. Pharm. Sci.*, **68**, 133 (1979).
5) H. Rapoport, D.R. Baker, and H.N. Reist, *J. Org. Chem.*, **22**, 1489 (1957).
6) K. Uba, N. Miyata, K. Watanabe, and M. Hirobe, *Chem. Pharm. Bull.*, **27**, 2257 (1979).

methylmorphinone-7,8-oxide (**7**, mp 121.5—122.5°, colorless needles) was synthesized by the reaction of **6** with H_2O_2 in aqueous methanol containing NaOH in 81.0% yield. The keto epoxide **7** was selectively reduced with $NaBH_4$ in methanol to 3-methoxymethylmorphine-7,8-oxide (**8**, colorless oil) in 66.0% yield. Deprotection of the methoxymethyl group of **8** readily proceeded in 1 N HCl solution at 20° without oxirane ring cleavage. To liberate the free base, the reaction mixture was adjusted to pH 8.7 with 1 N NH_4OH. The crystalline precipitates of **1** were collected and recrystallized from methanol: yield 73.1%; colorless needles; mp 241—242° (dec); MS *m/e* 301 (M^+), 272 (M^+-CHO), 216 (base peak); ^{1}H-NMR ($CDCl_3$) δ 2.46 (3H, s, N–CH_3), 2.63—2.72 (1H, d-d, C_7–H), 3.52—3.69 (2H, q and q, C_6–H and C_8–H), 4.68 (1H, d, C_5–H); ^{13}C-NMR ($CDCl_3$) δ 72.2 (C_6), 53.0, 54.7 and 59.3 (C_7, C_8 and C_9); *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.49; H, 6.38; N, 4.63. Acetylation of **1** with acetic anhydride in pyridine afforded heroin-7,8-oxide (3,6-diacetylmorphine-7,8-oxide, **2**)in 62.9% yield: colorless amorphous; MS *m/e* 385 (M^+), 356 (M^+—CHO), 258 (base peak); ^{1}H-NMR ($CDCl_3$) δ 2.19 (3H, s, CH_3COO–C_3), 2.32 (3H, s, CH_3COO–C_6), 2.42 (3H, s, N–CH_3), 2.87 (1H, d-d, C_7–H), 3.63 (1H, d-d, C_8–H), 4.59 (1H, d-d, C_6–H), 4.82 (1H, d, C_5–H).[7]

The analgesic activity of 7,8-epoxides (**1**, **2** and **3**) was determined by the method of pressure stimuli on the base of a rat tail.[8,9] In Fig. 1, the log dose-response curves are plotted for three 7,8-epoxides and their parent compounds.

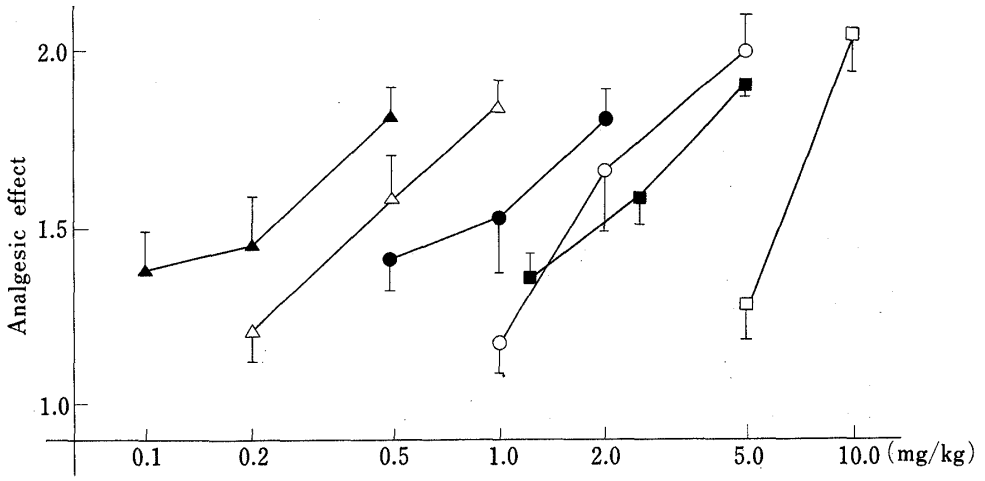


Fig. 1. log Dose-Response Curves of the Pain Threshold in the Rat

—▲— heroin-7,8-oxide (2), —△— heroin, —●— morphine-7,8-oxide (1), —○— morphine (5), —■— codeine-7,8-oxide (3), —□— codeine (4).

All the tested compounds dose-dependently exhibited their analagesic activity. **2** was the most analgesic among all of the tested compounds. When the analgesic potency of these compounds was compared by the dose which was calculated at 50% increase in pain threshold,

7) The configurations of the oxirane ring and the C_6 hydroxy group of these 7,8-epoxides (**1**, **2** and **3**) were confirmed as β and α respectively by their proton magnetic resonance spectra and X-ray crystal analysis of **3**.[6]

8) A.F. Green, P.A. Young, and E.I. Godfrey, *Brit. J. Pharmacol.*, **6**, 572 (1951).

9) Three doses of each compound (dissolved in propylene glycol) were injected intraperitoneally into groups of four male rats (180—230 g). The pain thresholds to pressure stimuli were determined before and after 15, 30, 60, 90, 120 and 180 minutes of treatment. The maximum pain threshold was attained at 15 minutes after injection in each case, then the degree of analgesia was calculated as the ratio of the threshold at 15 minutes after injection to that of the treatment before. The mean threshold for the control group which received injection of propylene glycol was never significantly different before and after treatment.

these epoxides possessed about two times as much analgesic potency as their parent compounds.

To clarify the interaction of these epoxides with opiate receptor, now we are studying further pharmacological properties.

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