

# **Chemical Stability of Pharmaceuticals**

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**A Handbook for Pharmacists**

**Second Edition**

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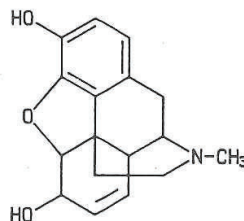
## Morphine

### GENERAL

#### Names

Morphine; 7,8-didehydro-4,5 $\alpha$ -epoxy-17-methylmorphinan-3,6 $\alpha$ -diol.

#### Structure



$C_{17}H_{19}NO_3$

mol. wt. 285.33

#### Forms Available

Free base (morphine); morphine hydrobromide,  $C_{17}H_{19}NO_3 \cdot HBr \cdot 2H_2O$ ; morphine hydrochloride,  $C_{17}H_{19}NO_3 \cdot HCl \cdot 3H_2O$ ; morphine methylbromide,  $C_{18}H_{22}NO_3Br$ ; morphine sulfate,  $(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ ; morphine N-oxide,  $C_{17}H_{19}NO_4$ ; morphine dinicotinate,  $C_{29}H_{25}N_3O_5$ .

#### Physical Properties

Melting point 254 to 256°C (decomposition); it has a metastable phase with melting point 197°C. Solubility: 1 g of morphine dissolves in about 5.0 L of water at 25°C; 1 g in 1075 mL of boiling water; 1 g in 210 mL of ethanol at 25°C; 1 g in 1220 mL of chloroform; 1 g in about 6.5 L of ether; freely soluble in alkaline solutions and acidic solutions. Most morphine salts are soluble to the extent of 1 g in 15 to 20 mL of water at 25°C and are freely soluble in boiling water. A saturated aqueous solution of morphine

is basic to litmus (1).  $pK_a = 9.51$  at  $25^\circ\text{C}$  for the phenolic group (2);  $pK_a = 8.31$  at  $25^\circ\text{C}$  for the amino group (2).

#### Stability Summary

Although morphine contains many functional groups that undergo reaction under certain conditions, the functional group primarily responsible for its instability in aqueous solutions is the phenolic moiety. This group readily undergoes oxidation, the major products being pseudomorphine (I) and morphine N-oxide (II). Aqueous morphine solutions exhibit a strong dependence of stability on pH and also on the presence of oxygen. The pH-rate profile shows that solutions of morphine are relatively stable at low pH values, but degradation proceeds at a much higher rate in neutral or basic media. Degradation is often accompanied by the appearance of a yellow or brown color in the solution.

#### DRUG KINETICS

##### Reactions

Oxidation is the most important reaction contributing to the degradation of aqueous morphine solutions. The oxidation of morphine is promoted by oxygen (3-6), sunlight (3), UV radiation (7), organic impurities (3,8), certain fungi (9), and iron (10). The major products of the oxidation are pseudomorphine (I) (oxydimorphine) and morphine N-oxide (II), which are formed in a ratio of 9:1, respectively. A trace of a base, believed to be methylamine (3), is also formed.

The kinetics of the degradation are dependent on both the amount of oxygen and the particular morphine species present (3). The overall reactions can be written



where M and  ${}^+HM$  represent the neutral and protonated forms of morphine, respectively. The parameters  $k_M$

cy-17-methylmorphinan-

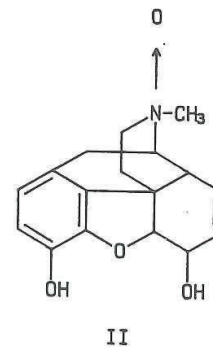
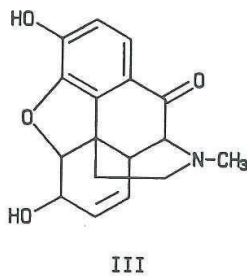
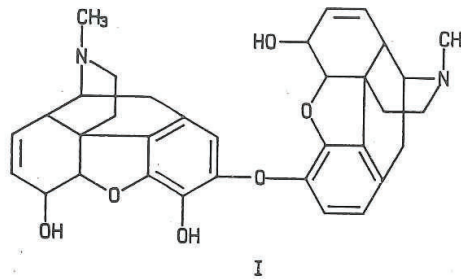
$C_{17}H_{19}NO_3$

$CH_3$  mol. wt. 285.33

phine hydrobromide, perchloride,  $C_{17}H_{19}NO_3 \cdot$  ide,  $C_{18}H_{22}NO_3Br$ ; morphine  $S_2O_4 \cdot 5H_2O$ ; morphine N-otate,  $C_{29}H_{25}N_3O_5$ .

composition); it has a point  $197^\circ\text{C}$ . Solubility in about 5.0 L of boiling water; 1 g in 1220 mL of chloroform; freely soluble in solutions. Most morphine extent of 1 g in 15 to freely soluble in boiling solution of morphine

and  $k_{+HM}$  are second-order rate constants for the oxygen-catalyzed degradation of M and  ${}^+HM$ , respectively. These rate constants become pseudo first order when a large excess of oxygen is maintained.



#### pH-Rate Profile

Figure 1 shows a plot of  $\log k$  vs. pH for the oxidation of aqueous morphine solutions at 95°C in the presence of excess oxygen (3). The curve is satisfactorily described by the equation

$$\text{rate} = \left[ k_1' \left( \frac{K_a}{K_a + [H^+]} \right) + k_2' \left( \frac{H^+}{K_a + [H^+]} \right) \right] [M]_t \quad (3)$$

where  $k_1'$  and  $k_2'$  are pseudo-first-order rate constants for the initial oxidation reactions of M and  ${}^+HM$  to

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