

Chemical Stability of Pharmaceuticals

A Handbook for Pharmacists

Second Edition

Kenneth A. Connors

School of Pharmacy, The University of Wisconsin

Gordon L. Amidon

College of Pharmacy, The University of Michigan

Valentino J. Stella

School of Pharmacy, The University of Kansas

A Wiley-Interscience Publication

JOHN WILEY & SONS

New York • Chichester • Brisbane • Toronto • Singapore

Copyright © 1986 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

Connors, Kenneth A. (Kenneth Antonio), 1932-
Chemical stability of pharmaceuticals.

"A Wiley-Interscience publication."

Includes bibliographies and index.

1. Drug stability. I. Amidon, Gordon L. II. Stella, Valentino J., 1946- . III. Title. [DNLM: 1. Drug Stability—handbooks. 2. Kinetics—handbooks. QV 735 C752c]

RS424.C66 1986 615'.18 85-31455
ISBN 0-471-87955-X

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

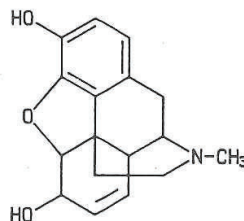
Morphine

GENERAL

Names

Morphine; 7,8-didehydro-4,5 α -epoxy-17-methylmorphinan-3,6 α -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°C for the phenolic group (2); $pK_a = 8.31$ at 25°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-

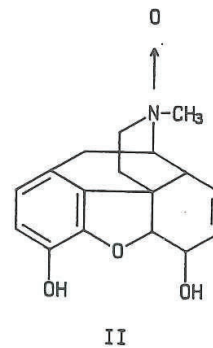
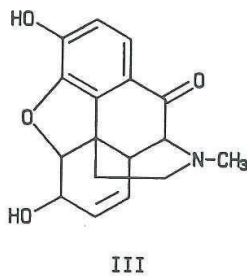
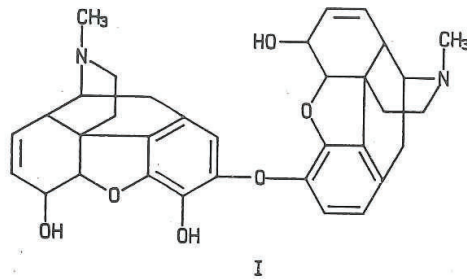
$C_{17}H_{19}NO_3$

CH_3 mol. wt. 285.33

phine hydrobromide, perchloride, $C_{17}H_{19}NO_3 \cdot$ ide, $C_{18}H_{22}NO_3Br$; morphine $SO_4 \cdot 5H_2O$; morphine N-otate, $C_{29}H_{25}N_3O_5$.

composition); it has a point 197°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

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.