NATURAL and SYNTHETIC ORGANIC MEDICINAL COMPOUNDS

O. LeROY SALERNI

NATURAL and SYNTHETIC ORGANIC MEDICINAL COMPOUNDS

O. LeROY SALERNI, Ph.D.
School of Pharmacy, Butler University,
Indianapolis, Indiana

Illustrated by Michael Carpenter

The C. V. Mosby Company
Saint Louis 1976

Copyright © 1976 by The C. V. Mosby Company

All rights reserved. No part of this book may be reproduced in any manner without written permission of the publisher.

Printed in the United States of America

Distributed in Great Britain by Henry Kimpton, London

Library of Congress Cataloging in Publication Data

Salerni, O LeRoy
Natural and synthetic organic medicinal compounds.

Bibliography: p.
Includes index.
1. Chemistry, Medical and pharmaceutical.
2. Drugs. I. Title. [DNLM: 1. Chemistry, Pharmaceutical. QV744 S163n]
RS403.S28 615'.3 75-29249
ISBN 0-8016-4303-1

GW/M/M 9 8 7 6 5 4 3 2 1

To

CAROLE LYNN

and

ORESTE MARCELLUS

PREFACE

This text is an outgrowth of a two-semester lecture course in medicinal chemistry presented at the School of Pharmacy at Butler University. The extensive literature covering such a multidisciplinary subject staggers the imagination. Consequently, the student will appreciate the clear and compact manner in which the important considerations of organic medicinal agents are presented. Unquestionably, the book is about drugs. It concerns the mode and site of action of drugs and their use, nomenclature, and synthesis. Acidity, basicity, hydrogen bonding, chelation, and tautomeric considerations are included. Structure-activity relationships are outlined whenever applicable. Physiological processes are briefly reviewed when deemed necessary to enhance understanding of drug action. This is particularly important for those students who have not yet had physiology or are taking physiology and medicinal chemistry courses concurrently. Important combinations of drugs that are frequently prescribed by physicians are also mentioned.

Although the book is primarily designed for pharmacy students enrolled in medicinal chemistry, it is anticipated that students of other health-related professions will profitably employ the text as a reference or for review.

I would like to thank the following individuals for their assistance in the preparation of this manuscript: Dean Karl L. Kaufman, for his encouragement; Dr. James E. Berger, who provided the originals for the drawings and numerous helpful discussions; and Mrs. Joan Ragozzino, for her tireless and superlative efforts in typing the manuscript. Joan symbolizes many of the finer qualities of America's youth that bode well for the future.

O. LeRoy Salerni

此为试读,需要完整PDF请访问: www.ertongbook.com

NATURAL and SYNTHETIC ORGANIC MEDICINAL COMPOUNDS

CONTENTS

Appendix

chapter 1

AGENTS AFFECTING THE CENTRAL NERVOUS SYSTEM

DEPRESSANT DRUGS

SEDATIVES AND HYPNOTICS

sedative Central nervous system depressant that decreases excitability but does not induce sleep.

hypnotic Central nervous system depressant that produces sleep; used to induce sleep when natural sleep is impossible.

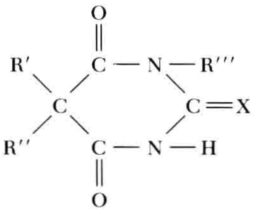
Since their introduction in 1903, the barbiturates have become the most widely used sedative-hypnotic drugs. Prior to the advent of the barbiturates, ethanol, opium, inorganic bromides, chloral hydrate, and paraldehyde were used.

Barbiturates

Barbiturates are used for sedation and convulsions (that is, antiepileptics), to induce general anesthesia, and for insomnia (hypnotic doses*).

Half of the people in the United States suffer from insomnia at some time. Prior to the enactment of the Controlled Substances Act of 1970, approximately 200 tons of barbiturates were consumed yearly in this country. The mode of action of these drugs is dimly understood. The phenomenon of sleep must await further explanation.

Barbiturates interrupt impulses from the reticular arousal system (at the brain stem) to the cerebral cortex, or they may act on the cortex directly. In any event, the cortex is lulled. (See Fig. 1-2.)



R' = Alkyl or aryl group
R'' = Alkyl group
R''' = Alkyl group or hydrogen
X = Oxygen, sulfur

When X = sulfur, ultra-short acting barbiturates (thiopental and thiamylal) are obtained (p. 5).

---

*The hypnotic dose is generally two to three times the sedative dose.

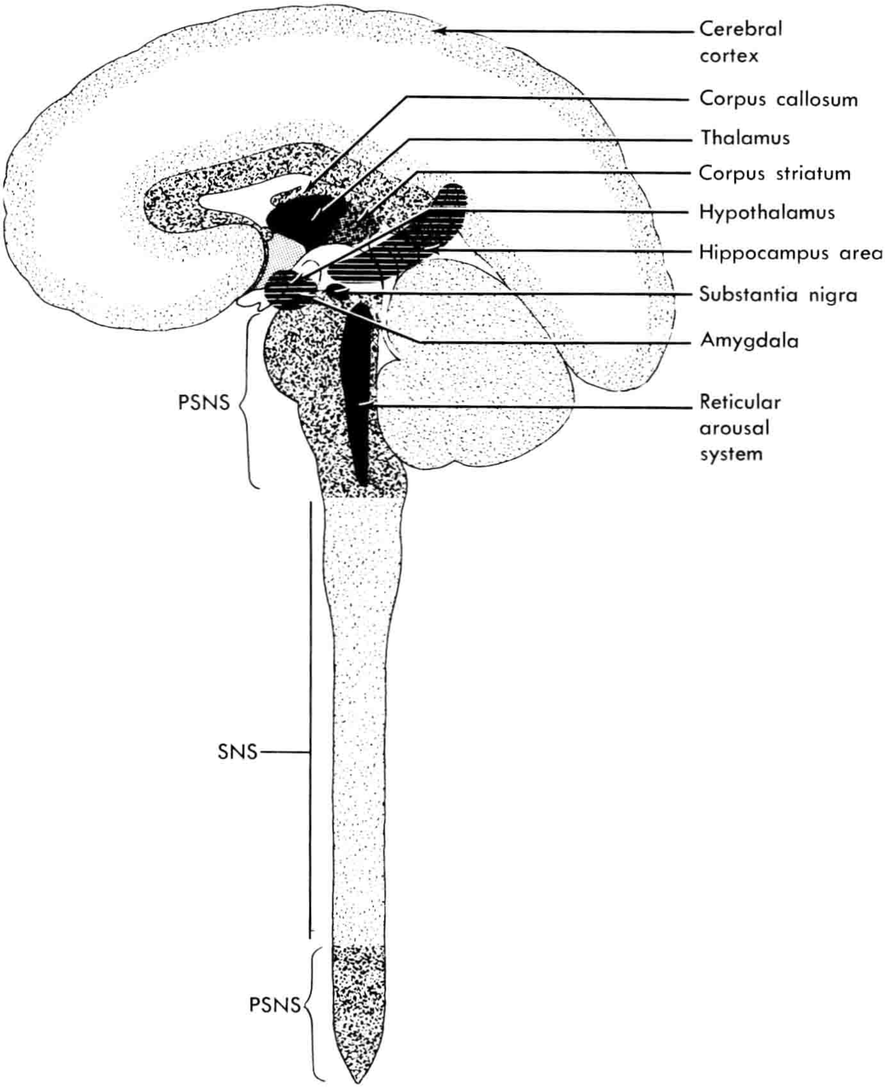
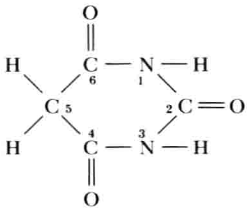


FIG. 1-1. Key to cross section of brain and spinal column.

Structure-activity relationships

All barbiturates are derivatives of barbituric acid.



Barbituric acid

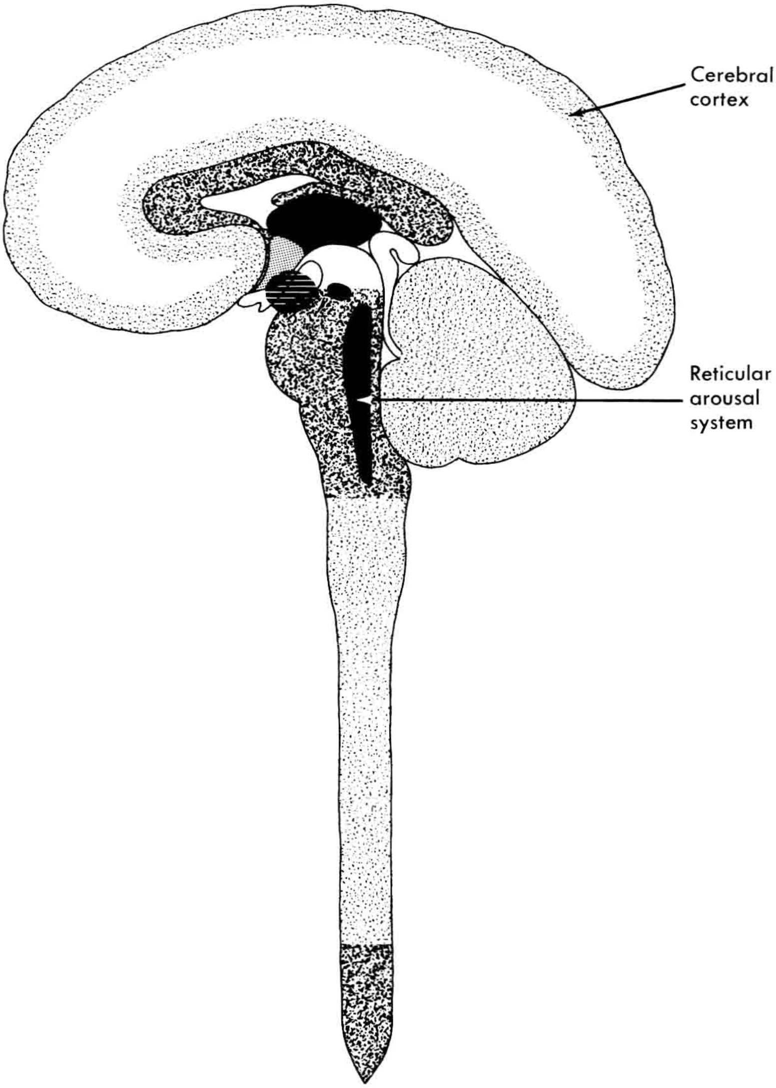


FIG. 1-2. Cross section of brain and spinal cord showing sites of action of barbiturates.

1. Barbituric acid is not active. *Both* hydrogens at C_5 must be replaced to yield activity. For example, two small groups (that is, CH_3) at C_5 yield a compound that is not active. Activity appears when two ethyl groups are present at C_5 (barbital).
2. Increasing the length of the chain to six carbons at the 5 position of barbituric acid enhances the biological activity.
3. Branching a carbon chain at C_5 gives briefer effects.
4. An unsaturated chain at C_5 gives briefer effects.
5. Insertion of alkyl groups at the 1 and 3 positions may impart convulsant effects.

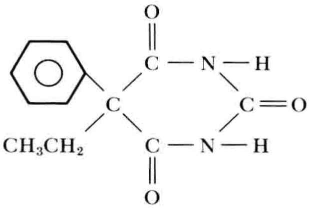
此为试读,需要完整PDF请访问: www.ertongbook.com

6. Replacing oxygen with sulfur at the 2 position produces ultra-short effects (thiobarbiturate).

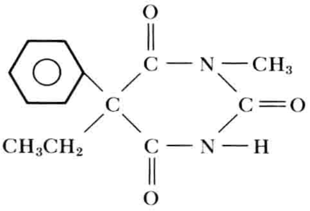
Classification

Long acting barbiturates

Onset of action: 30 minutes to 1 hour
Duration of action: 6 or more hours



Phenobarbital (Luminal)
5-Ethyl-5-phenylbarbituric acid

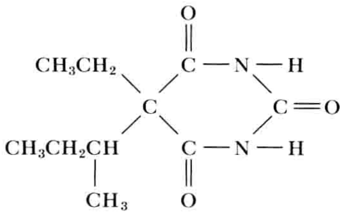


Mephobarbital (Mebaral)
1-Methyl-5-ethyl-5-phenylbarbituric acid

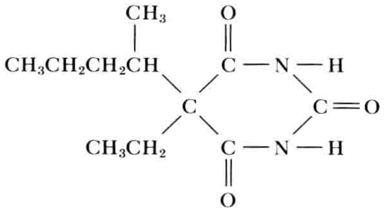
The student should remember that 3-methyl-5-ethyl-5-phenylbarbituric acid is not correct nomenclature since the substituents should have the lowest possible numbers.

Intermediate acting barbiturates

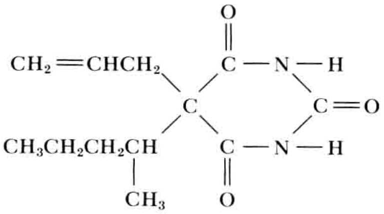
Onset of action: 15 to 30 minutes
Duration of action: 2 to 6 hours



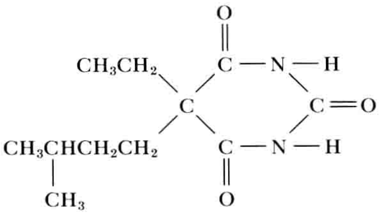
Butabarbital (Butisol)
5-Ethyl-5-*sec*-butylbarbituric acid



Pentobarbital (Nembutal)
5-(1-Methylbutyl)-5-ethylbarbituric acid



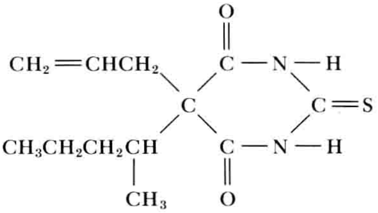
Secobarbital (Seconal)
5-Allyl-5-(1-methylbutyl)barbituric acid



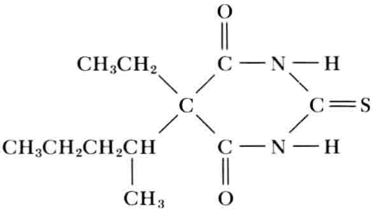
Amobarbital (Amytal)
5-Ethyl-5-(isopentyl)barbituric acid

Ultra-short acting barbiturates

Onset of action: Several seconds if given intravenously
Duration of action: Not specified



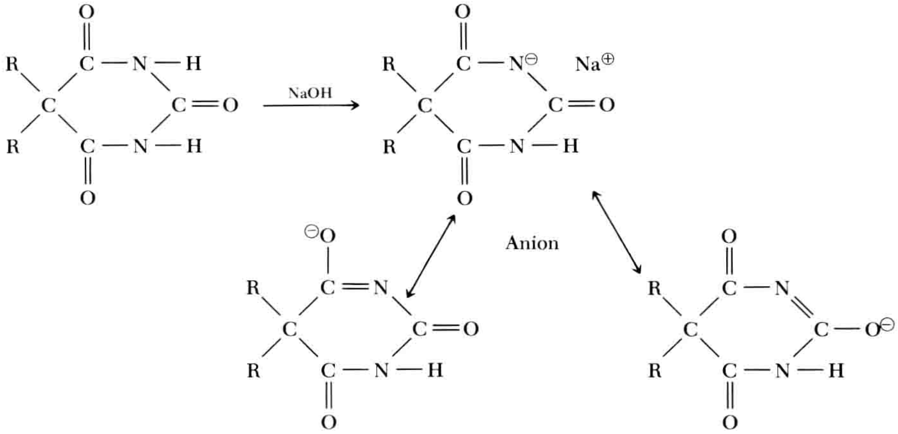
Thiamylal (Surital)
5-Allyl-5-(1-methylbutyl)-2-thiobarbituric acid



Thiopental (Pentothal)
5-Ethyl-5-(1-methylbutyl)-2-thiobarbituric acid

COMBINATIONS: Tuinal = Seconal + Amytal
Fiorinal = Butalbital (Sandoptal) + APC (analgesic sedative)

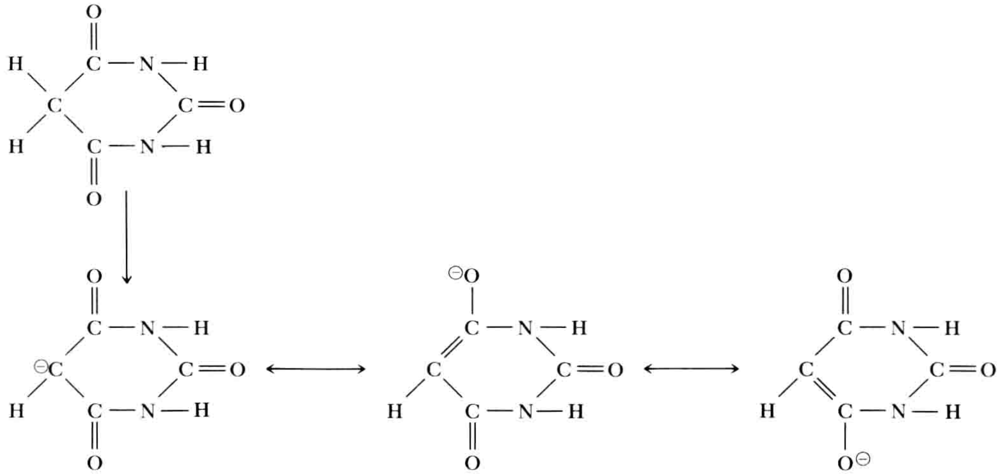
Acidity of 5,5-disubstituted barbituric acids



(Anion is resonance stabilized.)

Acidity of barbituric acid

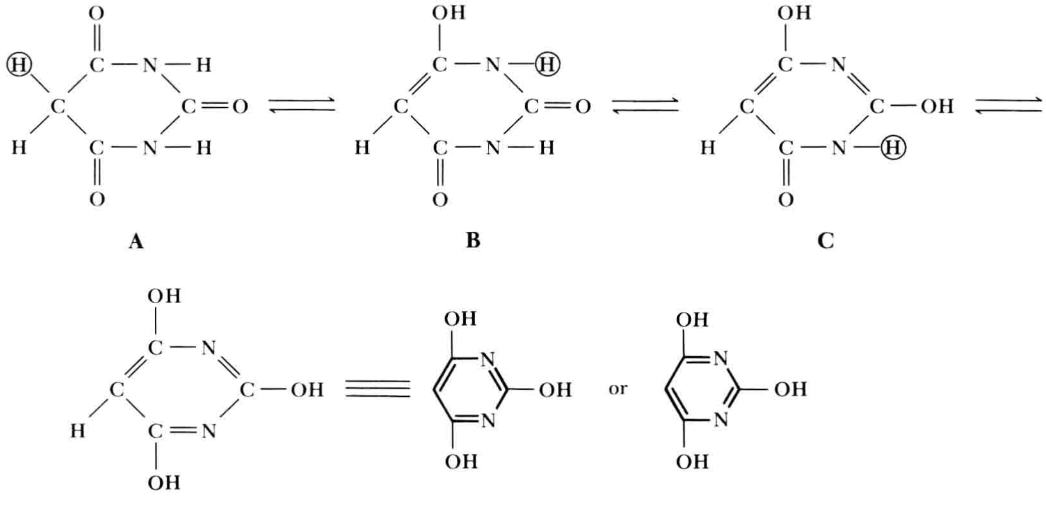
As depicted with the 5,5-disubstituted barbituric acids, the protons on the nitrogens are acidic. Also, the hydrogens on C_5 are acidic. Removal of a proton gives an anion (carbanion) that is resonance stabilized.



Tautomerism

Tautomerism, of course, involves proton migration. In the following examples, A to D are tautomeric structures. E and F represent resonance forms, or hybrids.

Barbituric acid

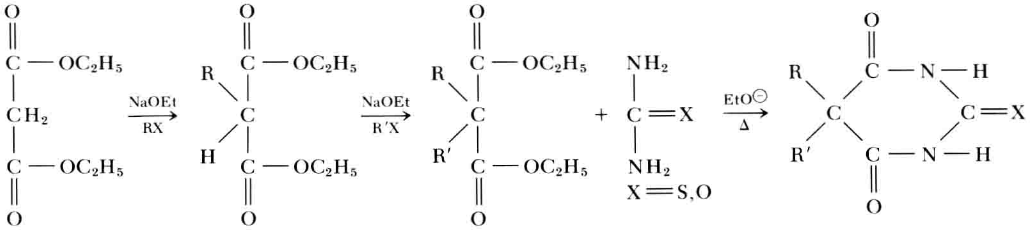


A **B** **C**

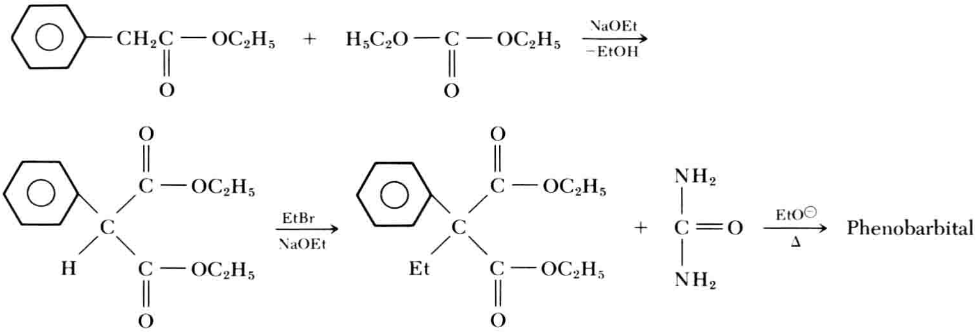
D **E** **F**

Synthesis studies

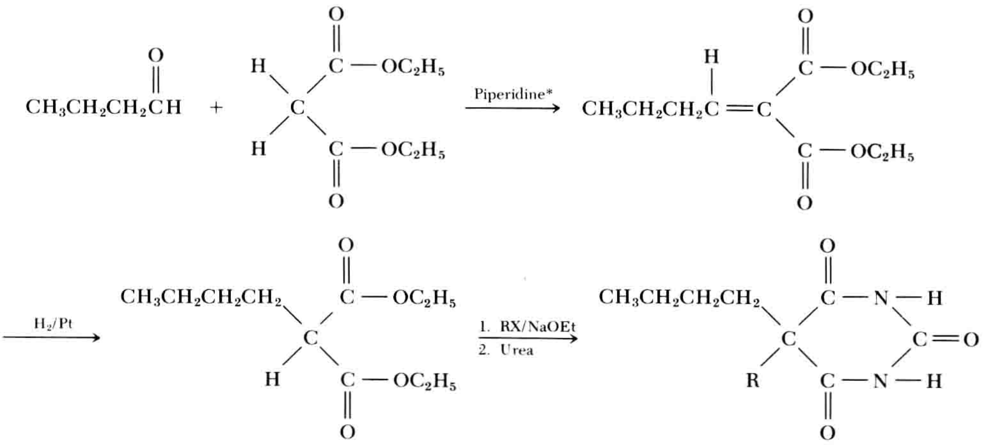
Alkyl barbituric acids



Aryl barbituric acids. It is not possible to introduce aryl groups into diethyl malonate by alkylation. The synthesis of phenobarbital takes this principle into account.



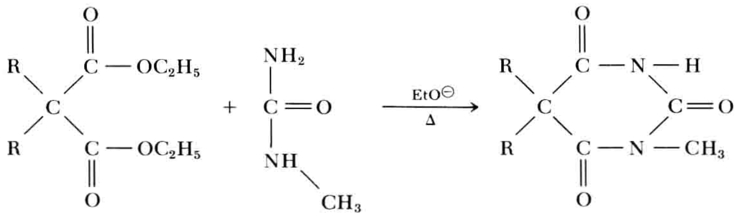
Alternate route to alkyl barbituric acids



---

*This reaction is an example of the *Knoevenagel condensation.*

N-Substituted dialkyl barbituric acids



Barbiturates and enzyme induction

Barbiturates can increase the activity of various enzymes in the liver that degrade many drugs, including diphenylhydantoin, warfarin, and aminopyrine. It may be necessary to increase the dosage of these drugs to obtain the desired therapeutic effect. Discontinuation of the barbiturate may then convert a satisfactory therapeutic dose into an overdose.

Barbiturate abuse

tolerance Decreased effects after repeated doses; increasing the dose regains the original effect.

psychic dependence Psychological craving but no physical craving or need to increase dosage.

physical dependence Psychological and physical craving and need to increase dosage.

Drug dependence may occur when doses far in excess of those prescribed for medicinal purposes are used. Chronic use of barbiturates may produce an intoxicated state much like that seen with alcohol.

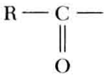
Barbiturates are very commonly prescribed and many people feel they are safe to take as they choose. Although the oral use of barbiturates is considered more socially acceptable than the intravenous use of narcotics, barbiturate withdrawal is a more serious medical problem. Convulsions and delirium tremens may occur on withdrawal from barbiturates.

Barbiturate poisoning is a leading cause of accidental death and the main method of suicide, accounting for 20% of all suicides.

SLANG TERMS: Barbiturates = Goofballs, downers
Nembutal = Yellow jackets
Seconal = Red devils
Tuinal = Tooies, double trouble

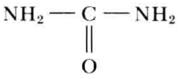
Nonbarbiturate sedatives and hypnotics

Ureides: acyl derivatives of urea



$R-C(=O)-$

Acyl



$NH_2-C(=O)-NH_2$

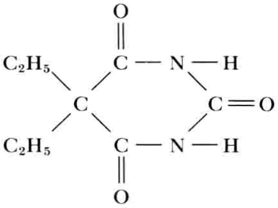
Urea

$R-C(=O)-N(H)-C(=O)-NH_2$

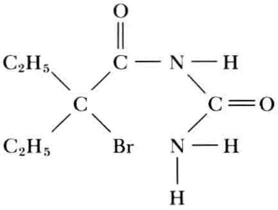
Ureide

NOTE: A barbiturate is a cyclic diureide formed by the diacylation of urea by a malonic acid.

The structural similarity between barbiturates and ureides is depicted at the top of the facing page.

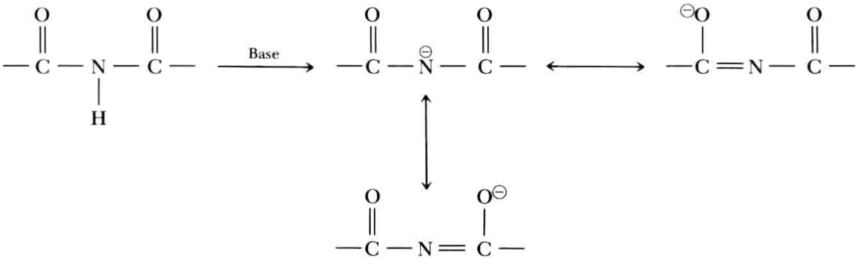


Barbital
5,5-Diethylbarbituric acid

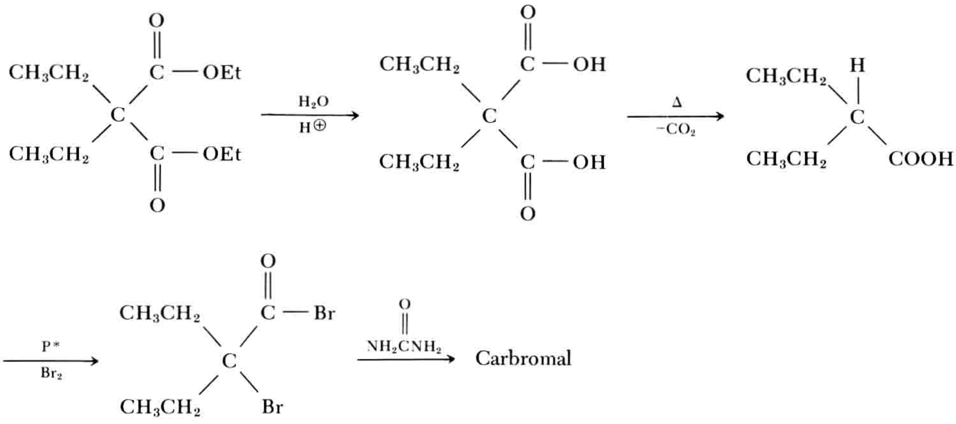


Carbromal
2-Bromo-2-ethylbutyrylurea

All ureides have a $-\underset{\displaystyle \text{H}}{\underset{|}{\text{N}}}-$ (imide) function flanked by two carbonyl groups resulting in an acidic proton.



Synthesis of carbromal



Carbromal is ranked as a less potent hypnotic than the barbiturates.

COMBINATION: Carbrital = Pentobarbital + Carbromal

---

*The reaction of a carboxylic acid with phosphorus and bromine is the *Hell-Volhard-Zelinsky* reaction.

此为试读,需要完整PDF请访问: www.ertongbook.com