MEDICINAL CHEMISTRY

F. F. BLICKE

R. H. COX

Editors

VOLUME IV

Medicinal Chemistry

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A SERIES OF REVIEWS PREPARED
UNDER THE AUSPICES OF THE
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VOLUME IV

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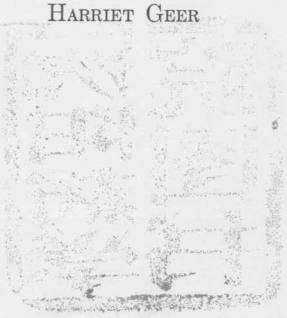


Preface to the Series

Chemists and pharmacologists concerned with the synthesis and evaluation of new compounds have long realized the need for a publication that would provide comprehensive and systematic summaries of available data on the biological properties of substances already studied. The correlation of structure and activity in such summaries stimulates the visualization of new molecular structures and leads to the synthesis and testing of new compounds.

The Division of Medicinal Chemistry of the American Chemical Society, at its business meeting in Chicago on September 11, 1946, decided to initiate plans for a series of books that would present reviews in the field of medicinal chemistry. This project was to be under the general supervision of an editorial board chosen from the membership of the division and in harmony with the rules of the national society.

After plans for the new publication had matured so that a definite proposal could be made, including discussion with prospective publishers, the board of directors of the American Chemical Society was asked for permission to proceed with the publication under the specific auspices of the Division of Medicinal Chemistry and the general guidance of the committee on publications of the society. Approval was granted by the board on April 19, 1948. It is a pleasure to express our indebtedness to the directors of the society for this expression of confidence and to Mr. Alden H. Emery, Dr. W. A. Hamor, and Mr. Arthur B. Hanson of the American Chemical Society, who have been most cooperative in advice on matters of general policy and contractual arrangements.

A chief objective of MEDICINAL CHEMISTRY is to include in each chapter references to all the compounds that have been tested for a particular type of pharmacological activity. Where it is necessary to limit one chapter to a segment of the field because of lack of space, a division is made, based on a chemical classification. It is expected that the additional areas will be treated in later volumes. The compounds are presented mostly in tabular form according to chemical groups or series. Associated with this comprehensive survey of compounds are discussions of the relationships between chemical structure

and pharmacological action. Many references are given to groups of compounds, particularly in the patent literature, which have been claimed to have pharmacological activity even if data to sustain this statement have not been published. Each chapter also contains brief discussions of methods of synthesis and pharmacological test procedures which aid the reader in judging the status of work in a given area. It is not feasible, within the space limitations, to give a comprehensive treatment of organic or analytical chemistry problems or, on the other hand, of the detailed pharmacology of single compounds. The interests of the chemist and pharmacologist, who are searching for new and useful molecular structures, seem best served by concentration on the comparison of the "screening" results. These preliminary data are employed in making decisions as to what compounds receive intensive study.

Those concerned with this publication will be pleased to have suggestions with regard to improvements for future volumes and comments on subject matter suitable for review. Suggestions from the members of the Division of Medicinal Chemistry are particularly solicited because this is a publication of their division.

Contents

BARBITURIC ACID HYPNOTICS

WILBUR J. DORAN
Eli Lilly and Company, Indianapolis

SCOPE OF THIS REVIEW

In the preparation of this review, the literature search included the references found under the heading *Barbituric Acid** in *Chemical Abstracts* (1907 through 1956) and in *Chemische Zentralblatt* (1897 through 1944, with the exception of the years 1940 and 1943). In addition, Microfilm No. 1720 of the War Department Army Medical Library, which described over two hundred barbituric acid derivatives tested at the I.-G. Farbenindustrie plant at Elberfeld, Germany, was reviewed.

An attempt has been made to include in this review all barbituric acid derivatives disclosed in the above-mentioned literature. Pharmacological data have been given wherever possible, but they were not available for many of the barbituric acids listed.

For ready reference, each barbituric acid derivative has been listed in one or more of the tables of this monograph. Compounds have been arranged and tabulated systematically according to their molecular structure (see explanation of Tabular Classification, p. 48), in order to facilitate the location of data on a particular compound and also to make possible the ready comparison of such data with those on other barbituric acid derivatives of closely related structure.

Further assistance in locating reference in this review to a particular compound has been provided by inclusion of a formula index (refer to key to index, p. 269).

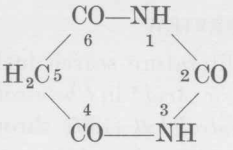
Trade and generic names, and molecular structures, of the barbituric acid derivatives of therapeutic importance are given in the Addenda, pp. 44–47.

Collective reference has been made in the bibliography of this review to other reviews on barbituric acids which have appeared in the literature.[5]

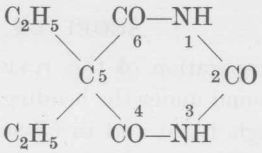
* A number of explanations have been offered regarding the derivation of the common name "barbituric acid" for malonylurea (2,4,6-triketohexahydropyrimidine).[1–4] One of the more interesting explanations is that attributed to Theodore Swarts, a colleague of von Baeyer who was present when *barbituric acid* was first prepared from *uric acid* on St. *Barbara's* Day.[1]

HISTORICAL DEVELOPMENT

Although the preparation of barbituric acid (malonylurea) was reported by von Baeyer[6] in 1864, it was the subsequent discovery of the hypnotic properties of 5,5-diethylbarbituric acid (barbital or Veronal) by Fischer and von Mering[7, 8] in 1903 that led to the extensive development of the barbituric acid class of drugs. Since that time more than two thousand "barbiturates"* have been prepared, although only twenty or so have achieved appreciable therapeutic importance.



Barbituric acid



Barbital (5,5-diethylbarbituric acid)

Barbituric acid derivatives are most frequently employed as sedatives and hypnotics, and as such are administered at relatively low dosage levels. However, they can also be employed intravenously to effect surgical anesthesia. Since the pharmacological end-point is so much more definite in anesthesia than it is in hypnosis, most activity data in the literature based upon animal experimentation are expressed in terms of anesthetic dosage.[9]

von Baeyer's[6] original synthesis of barbituric acid involved bromination of hydurilic acid [5,5′-bis(barbituric acid)] and reduction of the 5,5-dibromobarbituric acid so formed with sodium amalgam. Structural determination was subsequently carried out by Mulder[10] in 1873.

Conrad and Guthzeit[11] first synthesized barbital (5,5-diethylbarbituric acid) in 1882 by heating the silver salt of barbituric acid with ethyl iodide. Fischer and von Mering[7] subsequently prepared barbital (and christened it "Veronal"†) by condensing diethylmalonic acid with urea in the presence of phosphorus oxychloride. This condensation method was first used by Grimaux[12] in his synthesis of barbituric acid.

After the discovery of the hypnotic properties of barbital by Fischer and von Mering in 1903, Fischer and Dilthey[13] prepared a number of dialkylbarbituric acids by condensation of diethyl dialkylmalonates with urea, using sodium ethylate as the condensation agent.

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* The term "barbiturate," in general usage, is not restricted to salts of barbituric acid, but rather is used to designate mono- and polysubstituted barbituric acids and their salts.

† It is said[1] that von Mering so named 5,5-diethylbarbituric acid as a tribute to the beautiful city of Verona.

The second barbiturate of therapeutic usefulness was 5-ethyl-5-phenylbarbituric acid (phenobarbital or Luminal). A United States patent was granted for this compound in 1912.[13a]

Most of the early German patent literature on barbituric acid derivatives is concerned with various processes for the preparation of barbital and phenobarbital. Both of these compounds demonstrate a relatively prolonged pharmacological action (see Table 1) and hence are classified as "long-acting" barbiturates. Phenobarbital (together with its N-alkyl derivatives) is unique among members of the barbiturate series in that it shows a selective depressant action on the motor cortex and hence has long been used for the control of epilepsy.

Early work on substituted barbituric acids in the United States resulted in the development of 5-butyl-5-ethylbarbituric acid (butethal or Neonal) in 1922.[14] The effective dose of butethal in animals is one quarter that of barbital, and the duration of anesthetic action is about one third that of barbital (Table 1).

5-*iso*-Amyl-5-ethylbarbituric acid (amobarbital or Amytal) was described in 1923.[15] It is effective at the same dosage level as butethal, but its duration of anesthetic action is less than half that of butethal and about one seventh that of barbital (Table 1).

A further increase in effectiveness was found when a secondary amyl group was substituted for the primary *iso*-amyl group of amobarbital. 5-Ethyl-5-(1-methylbutyl)barbituric acid[16] (pentobarbital) has an anesthetic dose about two thirds that of amobarbital and a slightly shorter duration of action (Table 1).

Substitution of the allyl group for the ethyl radical of pentobarbital gives secobarbital (Seconal; 5-allyl-5-[1-methylbutyl]barbituric acid),[17] which has about the same anesthetic dose as pentobarbital but has a shorter duration of action (Table 1).

Although 5,5-dialkylbarbituric acids will produce anesthesia at higher dosage levels, they are not ordinarily used for surgical anesthesia, since barbiturates with a shorter duration of action are much more satisfactory for this purpose. 1,5,5-Trisubstituted barbituric acids have been found in most cases to be shorter acting than the corresponding parent 5,5-disubstituted acids, but many of the 1,5,5-trisubstituted compounds produce undesirable side effects. 5-(1-Cyclohexen-1-yl)-1,5-dimethylbarbituric acid (hexobarbital or Evipal), a trisubstituted compound[18] described in 1936, has been used in recent years for anesthetic purposes. While its anesthetic dose is more than twice those of pentobarbital and secobarbital, its duration of anesthetic action is approximately half those of pentobarbital and secobarbital (Table 1).

Before 1935 only a very few 5,5-dialkyl-2-thiobarbituric acids had

TABLE 1

ANESTHETIC ACTION OF SOME 5-R-5-R′-BARBITURIC ACIDS

	Compound[b]	5-R	5-R′	Intraperitoneal (IP) Injection of the Sodium Salt in Rats[a] MAD,[c] mg./kg.	MLD,[d] mg./kg.	Therapeutic Index (MLD/MAD)	Duration of Action,[e,f] min.
1	Phenobarbital	C_2H_5	C_6H_5	150	250	1.66	1660
2	Probarbital	C_2H_5	*iso*-C_3H_7	170	220	1.37	1520
3	Barbital	C_2H_5	C_2H_5	340	480	1.41	1400
4	Diallylbarbituric Acid	$CH_2{=}CHCH_2{-}$	$CH_2{=}CHCH_2{-}$	90	130	1.55	880
5	Aprobarbital	$CH_2{=}CHCH_2{-}$	*iso*-C_3H_7	100	160	1.60	720
6	Butethal	C_2H_5	C_4H_9	80	170	2.25	450
7	Cyclobarbital	C_2H_5	$CH_2(CH_2)_3CH{=}C{-}$	120	270	2.25	252
8	Amobarbital	C_2H_5	*iso*-C_5H_{11}	80	180	2.25	200
9	Pentobarbital	C_2H_5	$C_3H_7CH(CH_3){-}$	50	120	2.40	180
10	Secobarbital	$CH_2{=}CHCH_2{-}$	$C_3H_7CH(CH_3){-}$	45	110	2.44	150
11	Hexobarbital[g]	CH_3	$CH_2(CH_2)_3CH{=}C{-}$	110	270	2.45	81

[a] Pharmacological data furnished by E. E. Swanson of Eli Lilly and Company.

[b] For trade names see Addendum II, p. 45.

[c] Minimum Anesthetic Dose. For further discussion see section "Pharmacological Testing."

[d] Minimum Lethal Dose. For further discussion see section "Pharmacological Testing."

[e] Compounds listed in order of decreasing duration of action.

[f] For a more general classification of common barbiturates of commerce according to duration of action (i.e., long, medium, short, and ultra-short) refer to Table 8, p. 31.

[g] Also has a 1-methyl substituent.

been prepared, and they were used merely as intermediates[19] in the preparation of the corresponding 5,5-dialkylbarbituric acids (by replacement of the 2-thio group with oxygen).[20, 21] However, in 1935 and 1936 certain 2-thiobarbituric acids were reported to give anesthesia of short duration when administered intravenously as their sodium salts,[22, 23] and several of these compounds were found to be sufficiently free from undesirable side effects for clinical introduction. 5,5-Dialkyl-2-thiobarbituric acids now used clinically as intravenous anesthetics include: thiopental (Pentothal), 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid;[22, 24] thialbarbitone (Kemithal), 5-allyl-5-(2-cyclohexen-1-yl)-2-thiobarbituric acid;[25] Thionarcon, 5-butylmercaptomethyl-5-ethyl-2-thiobarbituric acid;[26, 27] thiamylal (Surital), 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid;[28] and Neraval, 5-(1-methylbutyl)-5-(2-methylthioethyl)-2-thiobarbituric acid.[29, 30] The last compound represents a very recent development.

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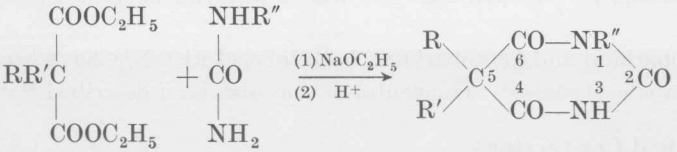
Synthesis

General Methods of Preparation. The general method most frequently used for the preparation of barbituric acids is that of Fischer and Dilthey,[13]



where R, R′, and R″ represent a hydrogen atom, aryl, saturated and unsaturated alkyl, and aralkyl groups. 2-Thiobarbiturates can be prepared similarly by substituting thiourea for urea, and 2-iminobarbiturates by substituting guanidine for urea. Most of the compounds considered in the text and tables of this review were synthesized by this general condensation method.

Substituted cyanoacetic esters can be condensed with urea in the same manner as substituted malonic esters. The condensation products are 6-iminodihydrouracils, which are hydrolyzed by strong acids to the corresponding barbituric acids. A novel group of 5-alkyl-5-alkylvinylbarbituric acids has been synthesized by the use of cyanoacetic esters.[31]

Many unique methods have been developed for the preparation of the substituted malonic and cyanoacetic esters used in the barbiturate condensation. The commonest method of alkylation involves treatment of the sodium derivative of the required ester with an alkyl halide in absolute alcohol. 5-Allyl-5-substituted barbituric acids can be prepared by direct allylation of the corresponding 5-substituted barbituric acids.[32]

While ethyl esters are generally used in the barbiturate condensation, other esters are occasionally employed. For example, a 94 per cent yield of barbital is claimed by the condensation of the dibutyl ester of diethylmalonic acid with urea, using sodium butoxide as the condensation agent.[33]

Although a sodium alcoholate is the usual condensation agent in the barbiturate synthesis, magnesium alcoholates have also been employed.[34–36]

While 1-substituted barbiturates are commonly obtained by condensation of substituted malonic esters with monosubstituted ureas, they have also been prepared by direct N-monoalkylation of the barbituric acids themselves. For example, 1-methyl-5,5-disubstituted barbituric acids have been synthesized by treatment of the sodium salts of the corresponding 5,5-disubstituted barbituric acids with dimethyl sulfate.[37]

1,3-Dimethyl-5,5-disubstituted barbituric acids (N,N′-dialkylated derivatives) have been obtained in nearly quantitative yields by the action of diazomethane on the required 5,5-disubstituted barbituric acids.[38, 39]

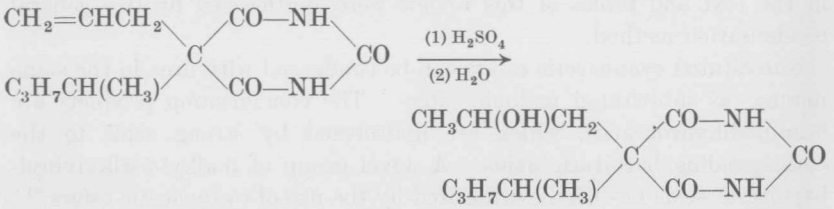
Preparation of Labeled Barbituric Acids. A number of "tagged" barbituric acids and chemically related compounds have been prepared for *in vivo* studies on metabolism, fate, and excretion.

These acids have been prepared from urea-C^{14}: barbituric acid-2-C^{14},[40, 41] barbital-2-C^{14},[42] alloxan-2-C^{14},[41] and 5-benzylidenebarbituric acid-2-C^{14}.[41]

Amobarbital and pentobarbital, both labeled with N^{15}, have been used in metabolic studies.[43] Thiopental-S^{35} has also been described.[44, 45]

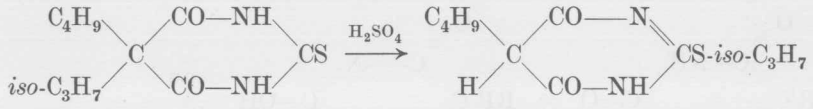
Chemical Conversions

Reaction with Sulfuric Acid. 5-Alkenylbarbituric acids apparently will add sulfuric acid across the olefinic unsaturation of the 5-alkenyl substituent. When the alkenylbarbituric acid – sulfuric acid reaction mixtures were treated with water, alcohols were obtained.[46, 47]



5,5-Disubstituted barbituric acids in which one of the 5-substituents was phenyl and one was primary alkyl, or in which both 5-substituents were primary alkyl, were stable in concentrated sulfuric acid. However, under similar treatment, 5,5-disubstituted barbituric acids which contained a secondary alkyl group lost the secondary group and gave the corresponding 5-monosubstituted acids.[48]

Certain 5,5-dialkyl-2-thiobarbituric acids were shown to rearrange in sulfuric acid to give 2-alkylated derivatives.[48]



Desulfuration of 2-Thiobarbituric Acids. The desulfuration of 2-thiobarbituric acids has given (1) barbituric acids, (2) 4,6-diketohexahydropyrimidines, and (3) their intermediate reduction products, 2-alkoxyhexahydropyrimidines.

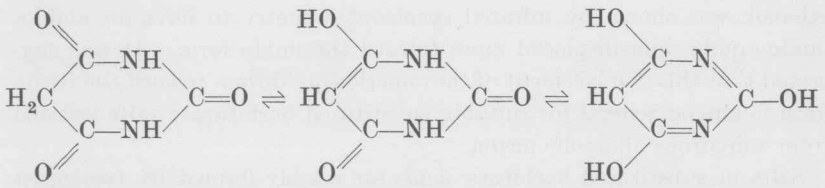
Barbital was formed upon refluxing a mixture of 5,5-diethyl-2-thiobarbituric acid, selenium dioxide, and glacial acetic acid.[49]

The reductive desulfuration of 2-thiobarbituric acids in alcohol with Raney nickel catalyst gave 4,6-diketohexahydropyrimidines.[50–52] The intermediate reduction products, 2-alkoxyhexahydropyrimidines, were obtained by use of a shorter reaction time and a less active catalyst.[53, 54]

Dehalogenation of 5-Halobarbituric Acids. 5-Halobarbituric acids may be converted readily to the corresponding halogen-free compounds. For example, 5-bromo-5-alkylbarbituric acids were reduced rapidly in the presence of platinum to the corresponding 5-alkylbarbituric acids.[55]

Chemical and Physical Properties: Their Practical Significance

Ionization and Salt Formation. The acidic character of barbituric acid is ascribed to an enolization which involves one of the hydrogen atoms of the methylene group, since the acid strength surpasses that associated with an enolic shift of an imide hydrogen atom. This postulate of a single enolization involving the methylene grouping is supported by the observed similarity of the ultraviolet absorption spectra of barbituric acid, 1-methylbarbituric acid, and 1,3-dimethylbarbituric acid.[56, 57] However, ultraviolet absorption data have also been cited which suggest that the monoenol form of barbituric acid may be in equilibrium with the trienol:[58]



Barbituric acid Monoenol Trienol

The enolization of typical 5,5-disubstituted barbituric acids in alkaline solution has been investigated via the ultraviolet absorption spectra of