HETEROCYCLIC COMPOUNDS

Volume 7

Polycyclic Compounds Containing Two Hetero Atoms in Different Rings. Five- and Six-Membered Heterocycles Containing Three Hetero Atoms and Their Benzo Derivatives

Edited by

ROBERT C. ELDERFIELD

University of Michigan

JOHN WILEY & SONS, INC.
NEW YORK · LONDON

Library of Congress Catalog Card Number: 50-7589

PRINTED IN THE UNITED STATES OF AMERICA

PREFACE

Volume 7 of *Heterocyclic Compounds* presents the chemistry of polycyclic compounds containing two oxygen or two nitrogen atoms in different rings and the chemistry of five- and six-membered monocyclic compounds carrying three hetero atoms, together with the benzo derivatives of the latter when such treatment appears to be warranted. Considerable variation in the thoroughness of the coverage of the subjects will be apparent. This was done deliberately. The material presented in Chapter 1 has never been reviewed in its entirety, and to a somewhat lesser extent this also applies to Chapter 3. It therefore seemed advisable to treat this subject matter in considerable detail. On the other hand, a number of good reviews on aspects of the chemistry of phenanthroline and *s*-triazine in particular are available, and the chemistry of these substances is covered in somewhat lesser depth.

Through unavoidable circumstances publication of this volume has been considerably delayed. Several of the manuscripts have been on hand for some years. This has been the cause of serious editorial problems as far as inclusion of the most recent work is concerned. Every effort to overcome these difficulties has been made, and parts of several chapters have been more or less completely rewritten since they were first received. In general, an attempt has been made to reflect coverage of the major English and German language periodicals through 1959 and as far into 1960 as practical considerations permit. No such claim can be made for other foreign journals in view of the inherent delays in the appearance of abstracts. If important omissions have occurred, which must surely have been the case, I ask the indulgence of the reader. Responsibility for such omissions is my own, and the individual authors should in no way be held accountable. It should be emphasized that the series is not intended to represent an encyclopedic coverage, but rather to concentrate on the principles involved through inclusion of the more important and critical references.

During the Conference on Organic Chemistry held on November 7–9, 1960, under the auspices of the Robert A. Welch Foundation of Houston, Texas, Professor Rolf Huisgen of the University of Munich delivered a lecture on the synthesis of a host of heterocycles by utilization of 1,3-dipolar additions. At present most of this work is unpub-

lished, but Professor Huisgen's lecture will appear shortly in the published lectures given at the Conference. The attention of readers of this volume is directed to the forthcoming publications of Professor Huisgen as a rich source of new and improved procedures for synthesis of a wide variety of heterocycles. It is a source of deep regret that it was impossible to include a discussion of these reactions even in general terms in the present volume.

Serious problems of nomenclature and numbering have been encountered. At the risk of criticism rather wide use of trivial names has been adopted with the more complex ring systems, in order to avoid unwieldy and cumbersome systematic names. In all instances, however, alternate nomenclature and numbering systems have been indicated so that no confusion should result. Condensed ring systems in all instances have been indexed in accordance with the practice followed by the 1960 Edition of *The Ring Index* regardless of the nomenclature used in the text.

In accordance with the precedent set in earlier volumes of this series, the general practice of omitting hydrogen atoms from cyclic formulas has been followed, unless the inclusion of such atoms is definitely indicated for reasons of clarity. In all cyclic formulas double bonds have been written.

As with previous volumes of this series, it is a pleasure to acknowledge the encouragement of many friends in the task of providing this volume. I am deeply appreciative of the efforts of the contributors and especially grateful for their forbearance and hearty cooperation in the face of delays which postponed appearance of their work. To my colleagues and to many graduate students at the University of Michigan I am indebted for many stimulating and fruitful discussions and criticisms. Finally, as in the previous volumes, I wish to acknowledge the understanding of my wife during her "book widowhood" and her help in editing, proofreading, and indexing.

ROBERT C. ELDERFIELD
Editor

Ann Arbor, Michigan
May, 1961

CONTENTS

CHAPTER 1

COMPOUNDS CONTAINING TWO HETERO OXYGEN ATOMS IN DIFFERENT RINGS

W. Basil Whalley
University of Liverpool, England

CONTENTS

INTRODUCTION

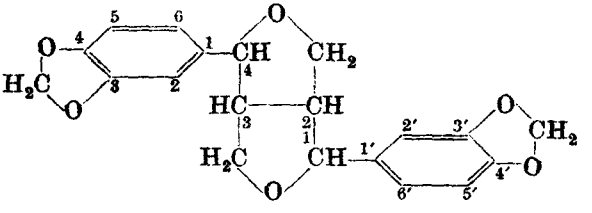
This chapter is concerned with those heterocyclic compounds which possess only oxygen as the hetero atom and contain two (or more) such hetero atoms. This class embraces a wide variety of naturally occurring substances, many of which exhibit some biological activity. The information concerning the group is widely diffused and is nowhere available in a

collective form; therefore this chapter deals in a comprehensive manner with the degradation and synthesis of both the naturally occurring members and those which are only available synthetically.

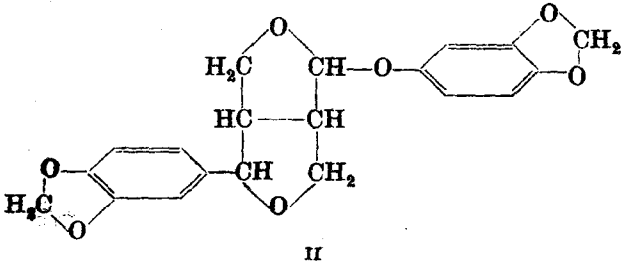
As far as possible the substances are dealt with in order of increasing molecular complexity, with compounds containing five-membered heterocyclic rings preceding those with six-membered heterocyclic systems, although some departure from this general scheme is necessitated in certain instances.

FURANOFURANS. THE BISFURANOID LIGNANS

Many furanofurans occur naturally and constitute a group of bisfuranoid lignans which consists of two subgroups, one having methylenedioxy groups at the 3, 4, 3′, and 4′ positions, and the other containing methoxyl or hydroxyl groups at these positions (I). The former class includes sesamin[1, 2] (I) and sesamolin[3] (II), which occur in sesame seeds and oil, and isosesamin,[4] *l*-sesamin,[5] and asarinin[6] (I) (epi-*l*-sesamin), originally named xanthoxylum S,[7] which occurs in many plants of oriental origin and in the bark of the prickly ash, *Xanthoxylum americanum* Mill.

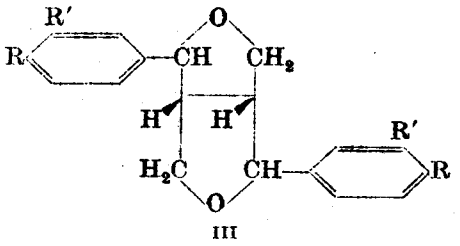


I

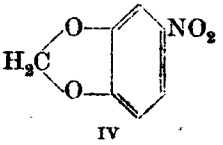


II

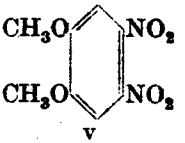
[1] Boeseken and Cohen, *Biochem. Z.*, **201**, 454 (1928).
[2] Bertram, van der Steur, and Watermann, *Biochem. Z.*, **197**, 1 (1928).
[3] Carnmalm, Erdtman, and Pelchowicz, *Acta Chem. Scand.*, **9**, 1111 (1955).
[4] Haslam and Haworth, *J. Chem. Soc.*, **1955**, 827.
[5] Beroza, *J. Am. Chem. Soc.*, **77**, 3332 (1955).
[6] Huang-Minlon, *Ber.*, **70**, 951 (1937).
[7] Dieterle and Schwengler, *Arch. Pharm.*, **277**, 33 (1939).



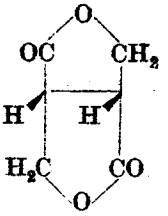
III



IV



V



VI

The latter class includes pinoresinol[8] (III, R = OH, R′ = CH_3O), from the gummy exudate of various conifers, and eudesmin[9] (III, R = R′ = CH_3O), isolated from the kino gum of eucalyptus.

Preliminary correlation of the two groups was achieved by demethylenation of the sesamin group followed by methylation; e.g., *d*-sesamin has been converted into *d*-pinoresinol O-dimethyl ether, the optical antipode of eudesmin,[10] by this process. Similarly, *l*-asarinin has been converted into *l*-eudesmin.

The literature concerning these substances is very extensive (for references, see Carnmalm et al.[3]), and only those references concerning the final phases of the elucidation of the structures are cited.

The gross structures of these substances have been established (1) by oxidation which furnishes piperonylic or veratric acids together with the di-γ-lactone of α,β-bis(hydroxymethyl)succinic acid (VI), and (2) by degradation with nitric acid (sometimes with prior bromination) to nitro (or nitrobromo) phenols; e.g., *l*-asarinin[6] and sesamin[1] are degraded by concentrated nitric acid to 4-nitrocatecholmethylene ether (IV), and

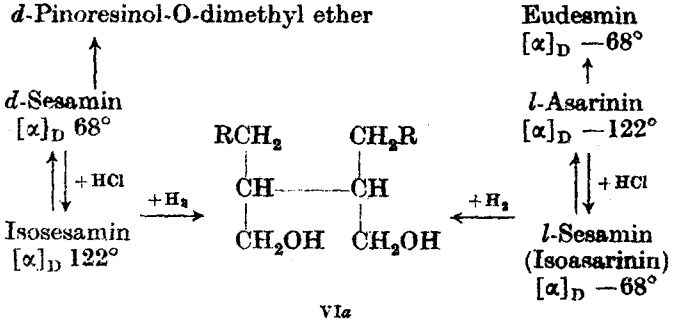
[8] Erdtman, *Svensk Kem. Tidskr.*, **48**, 230, 236, 250 (1936).
[9] Robertson and Smith, *J. Proc. Roy. Soc. N.S. Wales*, **84**, 449 (1914).
[10] Kaku and Ri, *J. Pharm. Soc. Japan*, **57**, 1015 (1937).

permanganate oxidation furnishes piperonylic acid. Similarly, pinoresinol-O-dimethyl ether (from pinoresinol and alkaline dimethyl sulfate) and eudesmin furnish 4,5-dinitroveratrole (V) with fuming nitric acid, and permanganate oxidation yields veratric acid.

These conclusions are further substantiated by the hydrogenation of asarinin and sesamin, which splits the tetrahydrofuran ring[11] (compare homopterocarpin and pterocarpin, p. 56, and rotenone, p. 153), with the formation of the 1,4-diglycol (VI*a*), which is the antipode of the reduction product of the naturally occurring aldehyde cubebin.

The principal obstacle to the complete elucidation of the structures of these substances is the presence of four asymmetric centers (carbons, 1, 2, 3, and 4 in formulas I and II), which present a stereochemical problem similar to that of biotin (Vol. 1, p. 269).

Natural sesamin is partially converted into isosesamin by boiling alcoholic hydrogen chloride, a reaction which is ascribed to the epimerization of center 1 or 4, and, being reversible, results in an equilibrium mixture of sesamin and isosesamin when applied to either substance. Asarinin is the optical antipode of isosesamin and when treated with boiling alcoholic hydrogen chloride produces in a like manner an equilibrium mixture of isosesamin and *l*-sesamin.[6] These transformations may be summarized as follows:



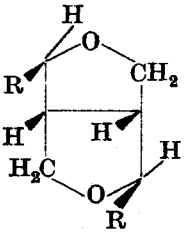
VI*a*

The lactone (VI) obtained by oxidation of sesamolin, sesamin, and pinoresinol is optically active and must therefore be the *cis*-lactone,[12] a conclusion in agreement with general considerations indicating that the *trans*-lactone would be too strained to exist.[5, 12]

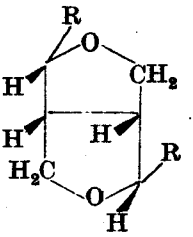
Consequently the structures of these bisfuranoids can be rationalized in terms of VI*b*, VIc, or VI*d*.

[11] Bruckhausen and Gerhard, *Ber.*, **72**, 830 (1939).

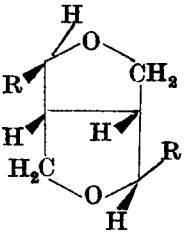
[12] Erdtman and Gripenberg, *Acta Chem. Scand.*, **1**, 71 (1947).



VI*b*



VI*c*



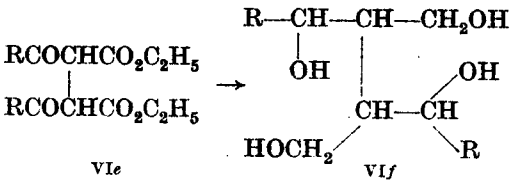
VI*d*

Erdtman[8] and Gripenberg[13] have ingeniously shown that pinoresinol and eudesmin are "symmetrical" and thus must be represented as VI*b* or VI*c*, whereas epipinoresinol VI*d* is not "symmetrical."[13]

The correlations shown in the table thus follow. Sesamolin has been shown to possess the acetal structure (II),[3–5] and faragol is identical with *dl*-sesamin.[3]

"Symmetrical"		"Unsymmetrical"
l-Sesamin	⇄	*l*-Asarinin
l-Eudesmin	⇄	*l*-Epieudesmin
d-Sesamin	⇄	*d*-Isosesamin
d-Pinoresinol dimethyl ether	⇄	*d*-Epipinoresinol dimethyl ether

The synthesis of *dl*-sesamin, and thus of *dl*-asarinin into which it may readily be epimerized, has been achieved[14] from the diethyl ester of α,α′-dipiperonylsuccinic acid (VI*e*). This substance exists in crystalline and oily modifications. Reduction with lithium aluminum hydride of the oily form to the tetrahydroxy compound (VI*f*) followed by ring closure with dilute hydrochloric acid furnishes *dl*-sesamin.

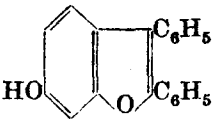


VI*e* VI*f*

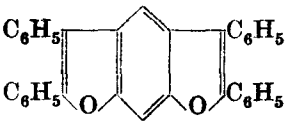
[13] Gripenberg, *Acta Chem. Scand.*, **2**, 82 (1948).

[14] Beroza and Schechter, *J. Am. Chem. Soc.*, **78**, 1242 (1956).

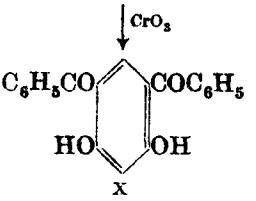
Furanobenzofurans. Comparatively few members of this class of compound containing two furan rings as the only heterocyclic system fused to a benzene ring are known, and most of them have been prepared by the condensation of benzoins with dihydric phenols.[15–18] The interaction of benzoin and resorcinol in the presence of concentrated sulfuric acid yields a mixture of the compounds VII, VIII, and IX.



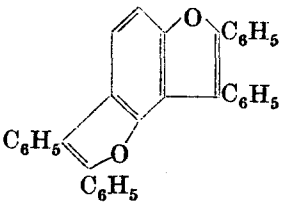
VII



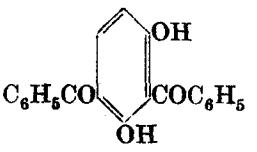
VIII



X

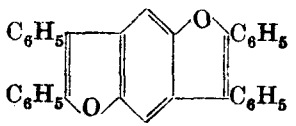


IX

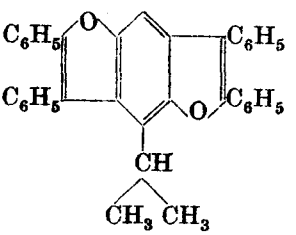


XI

The angular and linear structures (IX and VIII) are readily differentiated by chromic acid oxidation, which forms 2,4-dibenzoyl- and 4,6-dibenzoyl-resorcinol (XI and X), respectively. Similarly the condensation of benzoin and hydroquinone by the action of 73% sulfuric acid for 15 min. at 150° gives a small yield of the furanobenzofuran (XII). Under com-



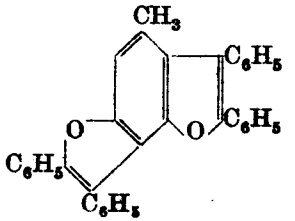
XII



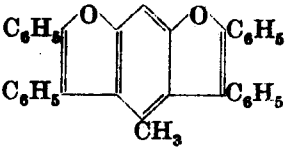
XIII

[15] Dischendorfer, *Monatsh.*, **62**, 263 (1933).
[16] Dischendorfer, *Monatsh.*, **66**, 201 (1935).
[17] Dischendorfer, *Monatsh.*, **68**, 41 (1936).
[18] Dischendorfer, *Monatsh.*, **74**, 25 (1941).

parable conditions benzoin and thymohydroquinone produce the analog (XIII), and benzoin and orcinol furnish a mixture of the angular and linear compounds (XIV and XV), respectively.

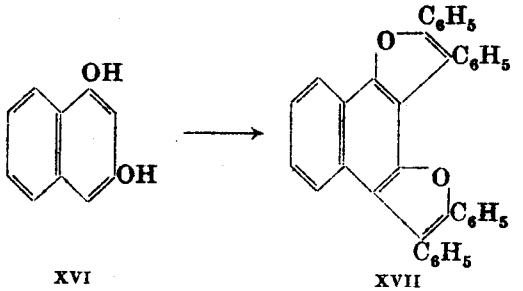


XIV



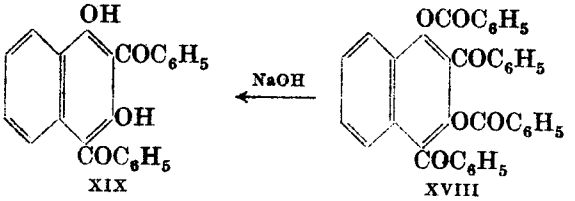
XV

In a like manner the condensation of 1,3-dihydroxynaphthalene (XVI) with benzoin gives the tetraphenylnaphthodifuran (XVII), which on



XVI

XVII



XIX

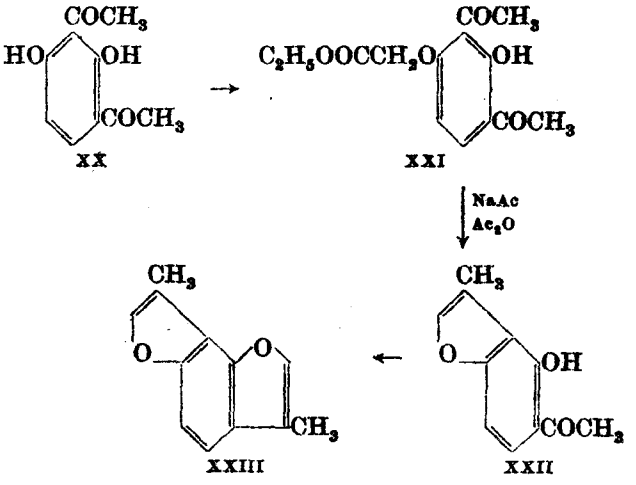
XVIII

oxidation with chromic oxide undergoes fission of the furan rings, with the production of 1,3-dibenzoyloxy-2,4-dibenzoylnaphthalene (XVIII), which is hydrolyzed by alkali to 1,3-dihydroxy-2,4-dibenzoylnaphthalene (XIX), thus establishing the orientation of the progenitor (XVII).

Furanobenzofurans can also be synthesized by the double application of the general methods available for the production of benzofurans.[19, 20]

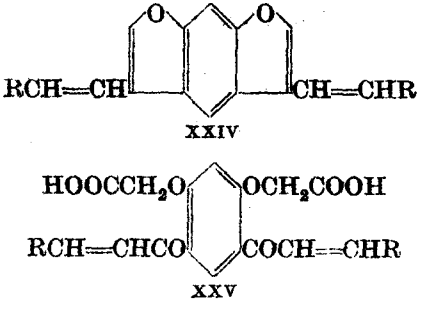
[19] Limaye and Nagarkar, *Rasayanam*, **1**, 255 (1943).
[20] Limaye and Panse, *Rasayanam*, **1**, 231 (1941).

For example, the condensation of 2,4-diacetoresorcinol (XX) with ethyl bromoacetate yields the phenoxyacetate (XXI), which after hydrolysis to the phenoxy acid is readily cyclized and simultaneously decarboxylated to 5-acetyl-4-hydroxy-3-methylcoumarone (XXII) by heating with sodium acetate and acetic anhydride. Repetition of this process forms



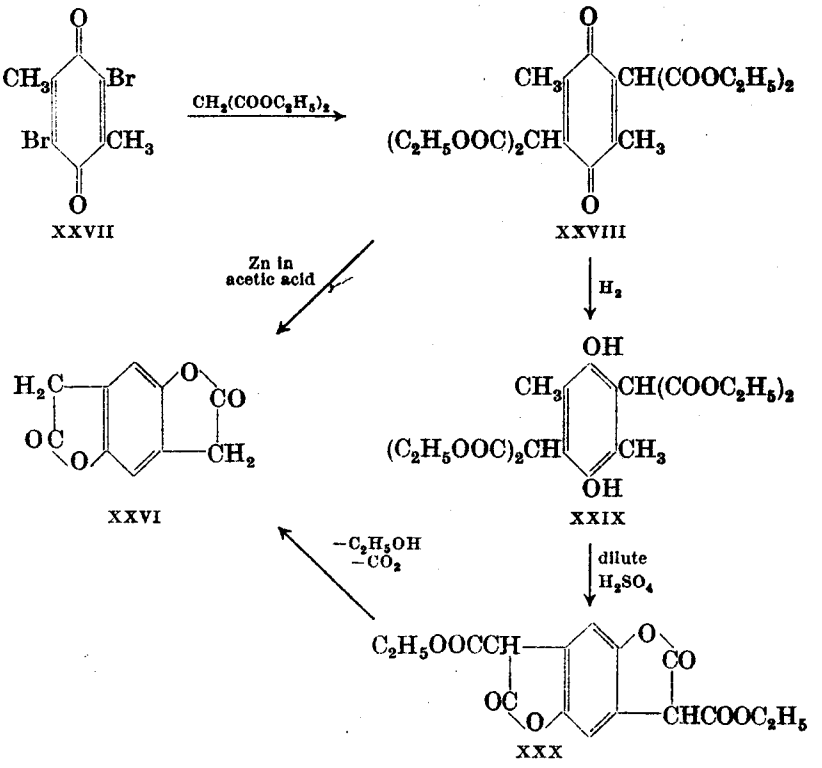
the furanobenzofuran (XXIII) identical with the "benzodimethyldifuran" of Hantzch,[21] to which no structure was assigned.

Linear furanobenzofurans of type XXIV are formed[22] by the cycliza-



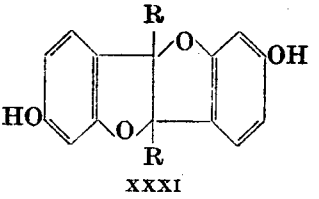
tion with sodium acetate and acetic anhydride of the corresponding distyryl ketones (XXV). A compound of type XXVI has been synthesized[23] by the condensation of dibromo-*p*-xyloquinone (XXVII) with sodiomalonic ester, to give the xyloquinone (XXVIII), which may be converted

[21] Hantzch, *Ber.*, **19**, 2928 (1896).
[22] Algar, Barry, and Twomey, *Proc. Roy. Irish Acad.*, **B41**, 8 (1932).
[23] Smith and Nichols, *J. Am. Chem. Soc.*, **65**, 1739 (1943).



directly to XXVI by treatment with zinc dust in acetic acid. Alternatively, the quinone (XXVIII) may be reduced to the hydroquinone (XXIX) followed by cyclization to the furanobenzofuran (XXX) and decarboxylation to XXVI.

Benzofuranobenzofurans. When resorcinol is treated under appropriate conditions with acetic anhydride and acetic acid, the benzofuranobenzofuran (XXXI, R = CH_3) is formed.[24] Similarly, benzoin yields the



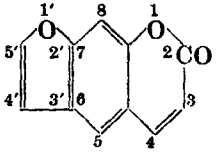
XXXI

diphenyl analog (XXXI, R = C_6H_5).

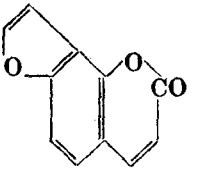
[24] Niederl and Nagel, *J. Am. Chem. Soc.*, **63**, 580 (1941).

FURANOCOUMARINS

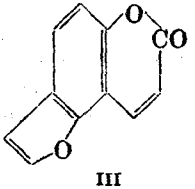
Introduction. The furanocoumarins[1, 2] are fish poisons and insecticides (compare rotenone and its derivatives). Plants of the Rutaceae and Umbelliferae families are the principal source of the many naturally occurring members of this group. Others, so far not obtained from natural sources, have been prepared by the application of the methods developed for the synthesis of the naturally occurring members. Several linear and angular structurally isomeric furanocoumarins are theoretically possible, but, with the exception of halfordin and isohalfordin (p. 32), derivatives of only two of these isomers have been obtained from natural sources. The two categories are: (1) derivatives of psoralene (I), 2′,3′,7,6-furanocoumarin—the linear type; and (2) derivatives of angelicin (II), 2′,3′,7,8-furanocoumarin—the angular type. Furanocoumarins of



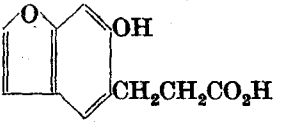
I



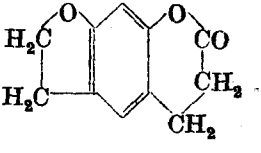
II



III



IV



V

type III have been synthesized, but representatives of the other possible isomers are unknown.

Degradation. The principal degradative weapons used in the elucidation of the structure of furanocoumarins are (1) hydrogenation, usually followed by oxidation, (2) oxidation, (3) alkaline methylation, and (4) fusion with alkali.

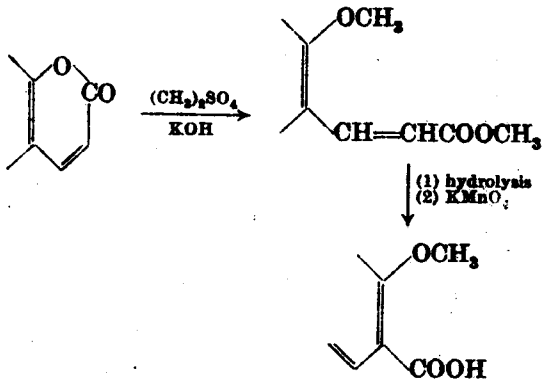
1. Reduction of furanocoumarins with sodium amalgam forms dihydrocinnamic acids of the type of IV, whereas catalytic hydrogenation with platinum or palladium rapidly saturates the 4′,5′ bond of the furan system after which slow reduction of the α-pyrone system occurs to furnish the 3,4,4′,5′-tetrahydrofuranocoumarins (type V). When the

[1] Späth, *Ber.*, **A70**, 83 (1937)—a review.
[2] Sethna and Shah, *Chem. Revs.*, **36**, 1 (1945)—a review.

lactone ring is opened by solution in 5% caustic potash, the resultant *o*-hydroxycinnamic acid readily hydrogenates over a palladium catalyst, and the free *o*-hydroxydihydrocinnamic acids (type IV) obtained by either method may then be converted to the corresponding 3,4-dihydrocoumarins by vacuum sublimation or by heating above the melting point. The dihydro- and tetrahydro-furanocoumarins are readily dehydrogenated to the furanocoumarins by heating with palladium black.[3]

2. Potassium permanganate oxidation destroys the terminal heterocyclic rings, with the production of substituted benzoic acids from the central benzenoid nucleus, together with the formation of fatty acids from unsaturated side chains. Ozonolysis likewise disrupts the heterocyclic rings, and the benzenoid system appears bearing *o*-hydroxycarbonyl residues, with the simultaneous production of ketones and aldehydes from unsaturated side chains. In contrast to the action of potassium permanganate, hydrogen peroxide cleaves the α-pyrone and benzene rings, leaving intact the furan moiety, which is isolated as a derivative of furan-2,3-dicarboxylic acid. Oxidation of 3,4-dihydrofuranocoumarins with nitric acid at room temperature, during several days, forms succinic acid by disruption of the α-pyrone system. It may be noted that the carbon atoms of both carboxyl groups in the furan-2,3-dicarboxylic acid and the carbon atom of one of the carboxyl groups of the succinic acid are derived from the central benzene ring.

3. When the furanocoumarins are subjected to methylation with alkaline dimethyl sulfate,[4] the coumarin ring is opened, with the production of the methyl ester of an *o*-methoxycinnamic acid, which on hydrolysis to the cinnamic acid followed by potassium permanganate oxidation



gives an *o*-methoxybenzoic acid, with the simultaneous destruction of the

[3] Späth and Galinovsky, *Ber.*, **70**, 235 (1937).
[4] Canter and Robertson, *J. Chem. Soc.*, **1931**, 1875.