CHROMENES, CHROMANONES, AND CHROMONES

Edited by

G. P. Ellis

UNIVERSITY OF WALES INSTITUTE OF SCIENCE AND TECHNOLOGY,
CARDIFF, UNITED KINGDOM

AN INTERSCIENCE ® PUBLICATION

JOHN WILEY & SONS
NEW YORK • LONDON • SYDNEY • TORONTO

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This is the Thirty-First Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

ARNOLD WEISSBERGER

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Preface

The literature on benzopyrans requires several volumes for adequate coverage. In this volume several arbitrary limitations had to be made so that a survey of the chosen field could be completed in reasonable time. Consequently this book is confined to chromenes, chromanones, chromones, and closely related compounds (the precise scope of the book is given in Chapter I). Flavones, isoflavones, and coumarins, for example, are excluded because their extensive literature justifies separate volumes. It is hoped that the writing of such books will be a slightly less daunting task now that the simpler 1-benzopyrans have been reviewed.

I am grateful to my coauthors for their cooperation. The General Editors of this series and the Publisher have been very helpful at all stages. In addition, I wish to thank the following: those researchers who sent me reprints of their own publications and exchanged views with me on points of interest; Mr. A. H. Henson, who made useful comments on the chapters that he kindly read; and my co-workers in this Department (some of whom were generously supported by Messrs. Allen and Hanburys Limited), who helped to maintain my interest in chromones. Much credit is due to Mrs. P. M. Bevan, who expertly typed many of the chapters. I wish to thank owners of copyrighted material for permission to include it in this book.

I am greatly indebted to my daughter, Rosalind, for much linguistic help with papers in several foreign languages. Finally, without the patience and assistance of my wife at all stages, writing and editing the book would have been an impossible task. Apart from giving much active help, she and my daughter tolerantly and understandingly accepted my reclusive habits while the work was in progress.

G. P. Ellis

Cardiff, Wales
November 1976

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CHROMENES, CHROMANONES AND CHROMONES

This is the Thirty-First Volume in the Series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER I

Chromenes, Chromanones, and Chromones—Introduction

G. P. ELLIS

Department of Chemistry, University of Wales Insitute of Science and Technology, Cardiff

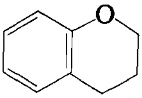
1. Introduction

Compounds in which a benzene and a pyran ring are fused together are called *benzopyrans*. The two classes of benzopyrans are shown in Figure 1 [the double bond in the pyran ring of 1-benzopyran may also be in the 2,3 position.

1-Benzopyran 2-Benzopyran

Figure 1. Types of benzopyrans.

This volume is the first of a two-part monograph intended to cover 1-benzopyrans of various levels of saturation and oxidation, namely, derivatives of chroman (**1**), 2*H*-chromene (**2**), 4*H*-chromene (**3**), 3-chromanone (**4**), 4-chromanone (**5**), 2,4-chromandione (**6**), and chromone (**7**). All of these except chroman derivatives are discussed in this book. These compounds are important because many of them occur in plants and others have considerable biological importance, especially as drugs. They also exhibit a variety of interesting chemical reactions.



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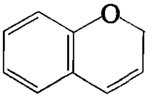

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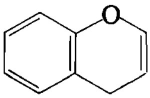

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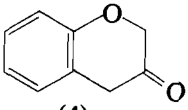

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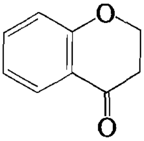

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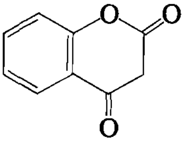

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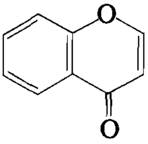
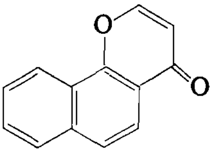


(7)

In addition to functional derivatives of these ring systems, compounds in which a benzene or other carbocyclic ring is fused to the benzene ring already present are covered, for example, benzochromones (**8**) and naphthopyrans (**9**); reduced chromones (e.g., **10**) and spiro compounds such as (**11**) and (**12**) are also included.



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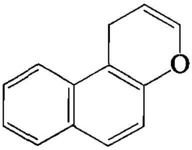

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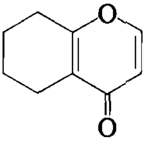

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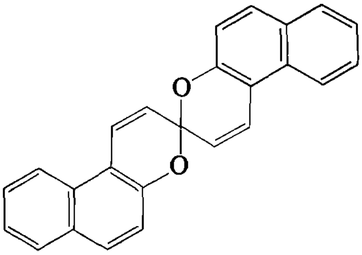

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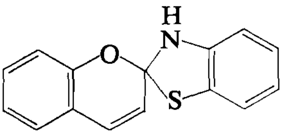
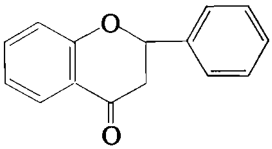
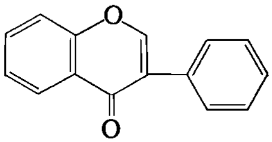


(12)

In order to write this book in a reasonable amount of time, it was necessary to omit some types of compounds that are derived from the above ring systems. For example, flavenes, flavanones (**13**), flavones, isoflavenes, isoflavanones, isoflavones (**14**), and similar compounds in which an aromatic ring is attached directly to C-2 and/or C-3 of the benzopyrans form a very large family of compounds deserving a monograph to themselves, and they are not discussed here. Moreover, compounds such as the tricyclic ketone (**15**) are beyond the scope of this survey as are compounds [for example, (**16**)] in which a ring is fused at C-2 and C-3, or C-3 and C-4, of the pyran ring. Coumarins (**17**) and compounds [such as (**18**)] formally related to it are excluded. The many benzopyrans in which a heterocyclic ring is fused to the benzene ring are also excluded; furopyrans are surveyed in another volume[1] of this series.



(**13**)



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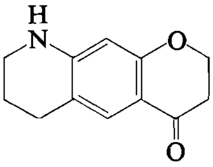

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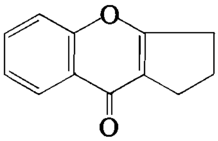

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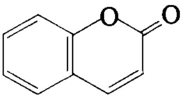

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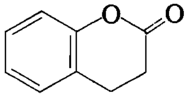
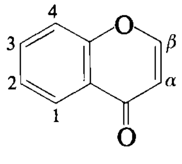


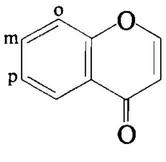
(**18**)

II. Nomenclature

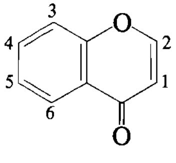
Since the discovery of 1-benzopyrans in the late nineteenth century, their nomenclature has changed several times. For example, designation of the positions in the ring system of chromone (**7**) lacked uniformity in the early literature. Some of the numbering systems used by early workers [2–10] are shown in



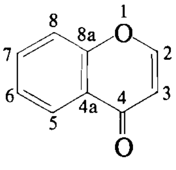
(**19**)



(**20**)



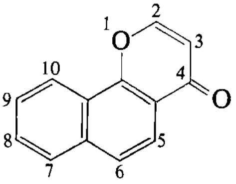
(**21**)



(**22**)

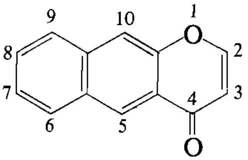
(19)–**(21)**. However, modern practice [shown in formula **(22)**, Revised Ring Index[11] No. 1728] came into use early in the twentieth century.[12]

A variety of names has been used for chromone[2] over the years, for example, benzo-γ-pyrone,[8,13] γ-benzopyrone,[14] pheno-γ-pyrone,[15] 2,3-benzopyrone-(4),[16] 4-oxo[1,4-chromen],[16] 4-oxochromen,[17] and 4*H*-1-benzopyran-4-one.[18] The last name was adopted by *Chemical Abstracts* from the beginning of 1972 for all chromones. At that time, most "trivial" names like chromone were replaced by systematic names which are more convenient for computerization of indexes. Unfortunately, the needs of the computer often lead to much longer names and while completely systematic names may be desirable for the production of subject indexes by computer, it is generally agreed[19,20] that there is little justification for abandoning such well-defined, unambiguous and convenient names as chromone in the chemical literature outside *Chemical Abstracts* indexes. It was therefore decided to retain the names chromanone and chromone except for aldehydes, nitriles, and carboxylic acids of the latter series for which the benzopyran type name was retained, as in *Chemical Abstracts* before 1972.



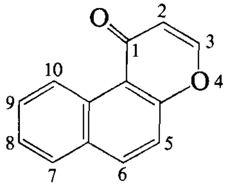
(23) RRI 3574

4*H*-Naphtho[1,2-*b*]pyran-4-one (7,8-benzochromone; 1,4-α-naphthapyrone; 1,2-naphtha-γ-pyrone; α-naphthochromone; naphtho-1′,2′:2,3-pyrone-(4))



(24) RRI 3566

4*H*-Naphtho[2,3-*b*]pyran-4-one (6,7-benzochromone; β-naphtho-β′-chromone)



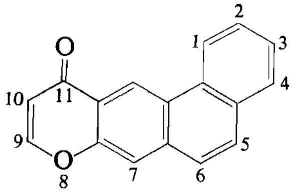
(25) RRI 3577

1*H*-Naphtho[2,1-*b*]pyran-1-one (5,6-benzochromone; 1,4-βα-naphthopyrone; 2,1-naphtha-γ-pyrone; β-naphtho-α-chromone; β-naphthochromone)

Nomenclature and numbering of the three types of benzochromones have also varied with time. The systematic names are given first under formulas (**23**)–(**25**) and are followed by alternative and obsolete names in parentheses.

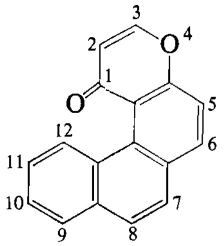
Similar developments have occurred in the nomenclature of chromenes and chromanones; these are mentioned at the beginning of Chapters II–V.

A comparatively small number of tetracyclic benzopyrans are known. These are derivatives of ring systems (**26**)–(**30**).



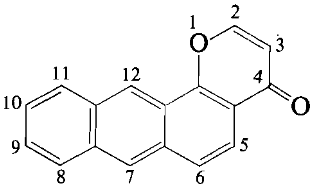
(**26**) RRI 5212

11*H*-Phenanthro[1,2-*b*]pyran-11-one



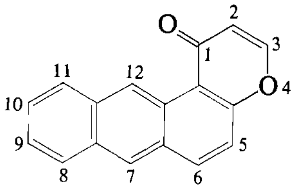
(**27**) RRI 5222

1*H*-Phenanthro[3,4-*d*]pyran-1-one



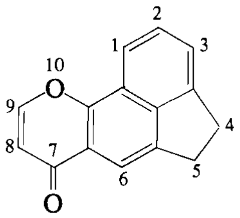
(**28**) RRI 10899

4*H*-Anthro[1,2-*b*]pyran-4-one



(**29**) RRI 10900

1*H*-Anthro[2,1-*b*]pyran-1-one

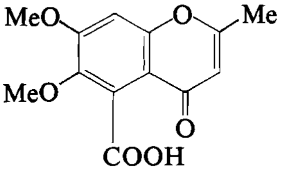


(**30**)

7*H*-Acenaphth[5,4-*b*]pyran-7-one

III. Arrangement of the Text

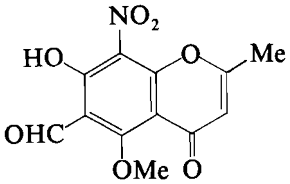
The chemistry of chromenes, 3- and 4-chromanols, and the various chromanones are dealt with in self-contained chapters, but that of chromones has had to be divided into 11 chapters according to the "principal functional group." In addition, chapters are devoted to naturally occurring chromones, analytical chemistry, general methods of preparation of chromones, and bis- and bichromones. The "principal functional group" is that which is discussed in the latest possible chapter of the book. For example, the chromone (**31**) is listed in Table 7 of Chapter XX (carboxylic acids and their derivatives). The properties which arise from the presence of the carboxyl group are discussed in that chapter, but information on the reactivity of the 2-methyl group is given in the chapter on alkylchromones (Chapter XI); methods of demethylation of the methoxyl groups are found in Chapter XIII. Degradation of chromone carboxylic acids by alkali is discussed in Chapter XX, but electrophilic substitution of the compound is subject to the effect of both types of substituents in the benzene ring, and information on this can be obtained in the relevant sections of both Chapters XIII and XX. However, if compound (**31**) has biological or other activity, this would be mentioned only in Section VI of Chapter XX.



(**31**)

IV. The Tables of Compounds

Each chapter which deals with a particular type of compound contains one or more tables in which all known members of the group are listed together with their melting or boiling points and references. Problems arise when multifunctional compounds have to be allocated to one of several possible tables according to the functional group. In Chapter V this difficulty has been averted by insertion of notes under the titles of some tables. In the section on chromones, the "principle of the latest position" (see above) is used; for example, 7-hydroxy-5-methoxy-2-methyl-8-nitro-4-oxo-4*H*-1-benzopyran-6-carboxaldehyde (**32**) is tabulated in the chapter on aldehydes because it comes *after* chapters dealing with the other functional groups in the molecule.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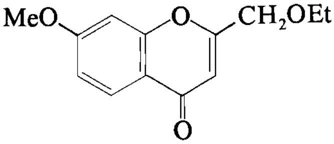
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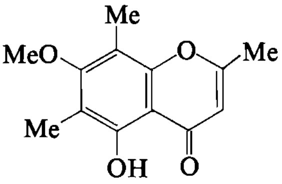

(34)

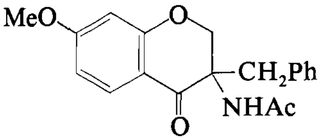
Within each table of compounds, the main entries are arranged in ascending order of molecular formula so that a compound may be located readily. Where a number of isomers exist, they are usually arranged in order of increasing *number* of substituents, for instance, among the eight chromone ethers, $C_{13}H_{14}O_4$, the disubstituted ether (**33**) is placed first and the pentasubstituted hydroxyether (**34**) last.

TABLE 1. TABLES OF COMPOUNDS: PARENTS AND DERIVATIVES

Parent compound	Derivatives
Alcohols and phenols	Acyl and sulfonyl derivatives
Aldehydes, ketones, and quinones	Acetals, ketals, oximes, semicarbazones, hydrazones, etc.
Amines	Acyl and sulfonyl derivatives, salts and quaternary compounds
Carboxylic acids	Esters, salts, acyl halides, anhydrides, amides, anilides, toluidides, and hydrazides
Sulfonic acids	Esters, salts, amides, and halides

Compounds that are commonly regarded as derivatives of the main entry compounds are listed under the parent. The list in Table 1 defines the kind of compound that is deemed to be a derivative and is therefore to be found under the formula of its parent. For example, 3-acetylamino-3-benzyl-7-methoxychromanone (**35**) is an acyl derivative of 3-amino-3-benzyl-7-methoxychromanone $C_{17}H_{17}NO_3$ which is found in Table 19 of Chapter V.

Occasionally a compound is a derivative of a derivative; for example, compound (**36**) is the 2,4-dinitrophenylhydrazone of the ethyl ester of the parent carboxylic acid $C_{13}H_{10}O_6$ (Chapter XX, Table 8).



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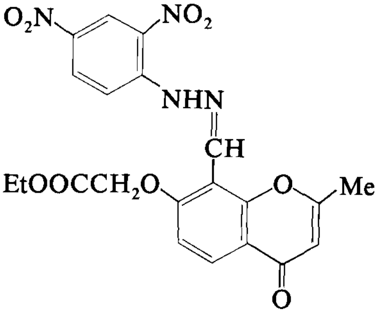

(36)

Attempts have been made to exclude compounds once described as chromones which have subsequently been shown not to be so and to insert compounds whose structure has been revised only under the correct structure. Some compounds are suspected by analogy with other work, to have different structures from those given to them originally; in such cases a footnote is added or the compounds are given in quotation marks; for example, *some* compounds have been shown to be isoxazoles and not oximes of chromones (see Chapter X, Section IV.5). The structures of all such compounds are therefore suspect, and this is indicated by quotation marks, for example, "oxime."

Chromones whose preparation has been described several times, often using different methods, are given several reference numbers in the tables. The melting or boiling point quoted is usually the highest recorded value; when these differ by more than 4° for a particular compound, a separate entry for each value is shown.

V. The Literature of Chromenes, Chromanones, and Chromones

Chromenols and chromenes were briefly reviewed[21] up to 1948, and a similar survey[22] was published on chromanones and chromanols. The earliest review of chromones was by Simonis[12] in 1917; this provided considerable detail of the state of knowledge at that time. A less comprehensive review[23] covered the literature up to about 1948. Chromenes, chromanones, and chromones, as well as flavones, isoflavones, and so forth, were discussed in a chapter of a multivolume work[24] published in 1959. A more detailed review of the syntheses and reactions of chromones was published in the same year[25]; this review has a number of useful tables but is marred by several errors in the list of references. More specialized reviews are mentioned in individual chapters.

In this book, the literature of 2*H*- and 4*H*-benzopyrans has been covered through Volume **78** (June 1973) of *Chemical Abstracts* and of chromanones and chromones through Volume **79** (December 1973) of *Chemical Abstracts,* but many more recently published papers are also mentioned.

VI. Abbreviations and Conventions

Chemical shifts in nuclear magnetic resonance spectra are expressed in terms of δ parts per million (δ ppm) from tetramethylsilane.[26,27] The following abbreviations are used:

Ac, acetyl
Bu, butyl
Bu^t, *t*-butyl
Bz, (substituent is) attached to the benzene ring
d, with decomposition (after m.p.)
DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone
DMF, *N,N*-dimethylformamide
DNP, dinitrophenylhydrazone
Et, ethyl
HMT, hexamethylenetetramine
Me, methyl
m/e, mass to charge ratio
mw, molecular weight
NBS, *N*-bromosuccinimide
Ph, phenyl
Pr, propyl
Pr^i, isopropyl
Ts, toluene-4-sulfonyl

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CHAPTER II

2*H*- and 4*H*-1-Benzopyrans

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I. Introduction

This chapter encompasses the spirobenzopyrans, 2*H*- and 4*H*-1-benzopyrans with aryl groups fused to or substituted on the benzene moiety as well as alkyl groups in any position. The preparations, reactions, and physical properties of these species are reviewed. An examination of the sources and structural elucidation of naturally occurring benzopyrans is also undertaken.

Ubichromenols and cannabichromene are not included because of their natural placement in chapters covering the tocopherols and cannabinols respectively. Also excluded are pyrans substituted with ethers or thioethers on the pyran ring at C-2 and C-4, except for the spirobenzopyrans, and large fused ring systems containing two or more heterocycles such as chromenochromones.

II. Nomenclature

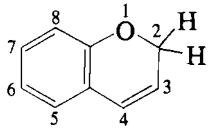
While researching the literature for information on benzopyrans the area which caused most problems was nomenclature. Both 2*H*- and 4*H*-1-benzopyrans have had many names. For example, 2*H*-1-benzopyran (**1**) has been called β-chromenone[1] and Δ^3-chromene[2] in the literature and α-chromene and benzo-α-pyran in the early *Chemical Abstracts*. The same holds for 4*H*-1-benzopyran (**2**) which was called 1,4-coumaran and γ-chromene in the early *Chemical Abstracts*, 4*H*-chromene and benzo-γ-pyran in the Ring Index and α-chromene[1] and γ-pyran[3] in the primary sources.

The common name *chromene* for 2*H*- and 4*H*-1-benzopyrans was probably coined in 1904 by Houben.[4] Today, using *Chemical Abstracts* as the authority, the names 2*H*-1-benzopyran and 4*H*-1-benzopyran are employed.

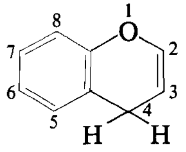
Until recently naphthopyrans were named as benzo derivatives of 2*H*-1-benzopyran. Now 5,6-benzo- and 7,8-benzo-2*H*-1-benzopyran are called 3*H*-naphtho[2,1-*b*]pyran (**3**) and 2*H*-naphtho[1,2-*b*]pyran (**4**) respectively.

In the section on natural products the authors used the common or trivial names because the systematic nomenclature, based on the *Chemical Abstracts*, is too cumbersome.

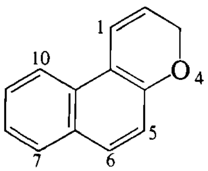
To aid the reader, the parent compounds are listed (**1–14**) together with the structures, Revised Ring Index code numbers, numbering system, and name employed in this chapter using the new *Chemical Abstracts* and Ring Index nomenclature.



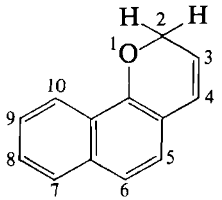
(**1**)
RRI 1727
2*H*-1-benzopyran



(**2**)
RRI 1728
4*H*-1-benzopyran



(**3**)
RRI 3578
3*H*-naphtho[2,1-b]pyran



(**4**)
RRI 3573
2*H*-naphtho[1,2-b]pyran