

Recent Flavonoid Research

G. B. MARINI-BETTOLO

**L. HÖRHAMMER
G. AURNHAMMER
H. WAGNER**

H. WAGNER

**D. M. DROUMEV
D. A. PASHOV**

**R. BOGNÁR
and his collaborators**

**L. FARKAS
Á. MAJOR**

F. KÁLLAY



AKADÉMIAI KIADÓ, BUDAPEST

RECENT DEVELOPMENTS IN THE CHEMISTRY OF
NATURAL CARBON COMPOUNDS

RECENT DEVELOPMENTS IN THE CHEMISTRY OF
NATURAL CARBON COMPOUNDS

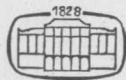
VOLUME V

Editors of the Series:

R. BOGNÁR, V. BRUCKNER, Cs. SZÁNTAY

Consultant Editors:

I. ANGYAL (Sydney), Z. CSÚRÖS (Budapest), Z. FÖLDI (Budapest),
Á. GERECS (Budapest), D. IVANOV (Sofia), N. K. KOCHETKOV (Moscow),
K. MOTHES (Halle), YU. A. OVCHINNIKOV (Moscow), F. ŠORM (Prague),
W. TREIBS (Heidelberg), B. C. L. WEEDON (London), I. WROBEL (Warsaw)



AKADÉMIAI KIADÓ
PUBLISHING HOUSE OF THE HUNGARIAN ACADEMY OF SCIENCES
BUDAPEST 1973

RECENT FLAVONOID RESEARCH

Contributions by

G. B. MARINI-BETTOLO

L. HÖRHAMMER, G. AURNHAMMER and H. WAGNER

H. WAGNER

D. M. DROUMEV and D. A. PASHOV

R. BOGNÁR and HIS COLLABORATORS

L. FARKAS and Á. MAJOR

F. KÁLLAY



Y078301



AKADÉMIAI KIADÓ

PUBLISHING HOUSE OF THE HUNGARIAN ACADEMY OF SCIENCES

BUDAPEST 1973

© Akadémiai Kiadó, Budapest 1973

PRINTED IN HUNGARY

CONTENTS

Preface	9
---------------	---

G. B. MARINI-BETTOLO

On some C₁₅ derivatives related to flavones

I. Introduction	13
II. Neoflavones	13
1. β -Phenylcoumarins	13
2. α -Phenylcoumarins	19
III. Aurones	21
IV. Condensed leucoanthocyanidins	25
References	27

L. HÖRHAMMER, G. AURNHAMMER and H. WAGNER

Synthesis of Citrus flavonoid glycosides

I. Introduction	31
II. Components of the Citrus flavonoid glycosides	32
III. Synthesis of Citrus glycosides	34
IV. Conclusion	45
References	45

H. WAGNER

The antihepatotoxic principle of Silybum marianum Gaertn.

I. Earlier investigations	51
II. Recent investigations	51
1. Substance S ₁ (silymarin, silybin, Silybum-substance E ₆)	52

2. Substance S ₂ (silydianin, <i>Silybum</i> -substance E ₅)	59
3. Substance S ₃ (silychristin)	61
4. Substance S ₄ ((+)-taxifolin)	62
5. Substance S ₅ (quercetin)	62
6. Substances S ₆ and S ₇ (dehydrosilymarin and dehydrosilychristin) ...	63
III. Toxicology and pharmacology of the active constituents of <i>Silybum</i>	63
1. Experiments for antagonizing a liver defect caused by carbon tetra- chloride	64
2. Experiments for the normalization of the renal elimination of <i>p</i> -hy- droxyphenylpyruvic acid after CCl ₄ poisoning	64
3. Experiments for counteracting liver damages caused by thioacetamide	65
4. Experiments for antagonizing liver damages caused by α -amanitine ..	65
References	68

D. M. DROUMEV and D. A. PASHOV

<i>Effect of the flavonoid mixture isolated from Agrimonia eupatoria on the cardiovascular and vegetative nervous systems</i>	69
References	76

R. BOGNÁR and his collaborators

Survey of the research on flavonoids

I. Isolation and structure elucidation of some natural flavonoid glycosides	79
II. Synthesis of flavonoid glycosides	81
III. Reductive and oxidative conversions	85
IV. Syntheses and interconversions of the parent compounds of different states of oxidation	88
1. Bromination	88
2. Reductive experiments. Reductive conversions of 2'-hydroxychalcone, flavanone and dihydroflavonol	91
V. Aminoflavonoids	95
VI. Chalcone epoxides, chalcone aziridines	101
VII. Flavonoids containing sulfur	111
VIII. Isoflavone syntheses	112
IX. Alkylation experiments	114
X. Ultraviolet spectrophotometric investigation of flavonoid compounds ..	115
XI. Investigation of the electronic structure of flavonoids by means of IR spectrometry and the quantum chemical method	118
1. Substituted acetophenones	119
2. 4- and 4'-monosubstituted chalcones	120

3. 4- and 4'-substituted chalcone epoxides	120
4. 2'-Benzyloxy- and 4-R-substituted chalcones and their epoxides	121
References	121

L. FARKAS and Á. MAJOR

Research of flavonoid compounds (1957-1971)

I. Introduction	129
II. Syntheses proving the structures of natural isoflavones	129
III. The formylation of deoxybenzoin with zinc cyanide and hydrochloric acid; a new synthesis of isoflavones	130
IV. The preparation of 5,6,7-trisubstituted isoflavones by ring-isomeric change	131
V. Syntheses proving the structures of natural flavones	132
VI. New methods for the synthesis of 5,6,7-trisubstituted flavones	133
VII. Investigation of the keto-enol tautomerism of 2-hydroxydibenzoylmeth- anes	135
VIII. Syntheses proving the structures of natural isoflavone glycosides	135
IX. Syntheses proving the structures of chalcone- and dihydrochalcone gly- cosides	136
X. Syntheses proving the structures of aurones and aurone glycosides ..	136
XI. Syntheses proving the structures of flavone- and flavanone glycosides containing one sugar moiety	137
XII. Transacylation reactions of flavonoids	138
XIII. Syntheses of benzalchromanones and benzylchromanones	140
XIV. Synthesis of isoflavanones and isoflavanone glycosides	140
XV. Syntheses proving the structures of flavanone- and flavone glycosides containing two sugar components	143
XVI. Syntheses proving the structures of flavone glucuronides	144
XVII. Structural investigations on disaccharides; the preparation of α -aceto- bromoneohesperidose	144
References	145

F. KÁLLAY

The reactions of flavonoid compounds with hydrazines

I. Introduction	155
II. Flavanones	155
1. Flavanone and hydrazine	159

2. Flavanone and substituted hydrazines	163
3. 5-Hydroxyflavanone and 5-methoxyflavanone	164
4. Methoxyflavanones and phenylhydrazine	165
5. 3-Hydroxyflavanones	165
III. Chalcones	167
IV. Flavones	170
1. Normal carbonyl reactions of flavone	171
2. Reactions leading to pyrazoles	172
3. Substituted flavones	174
References	175
Subject index	177

PREFACE

The research of flavonoid compounds has great traditions in Hungary. As early as the end of the twenties, G. Zemlén started Hungarian chemical research activity in this field, and ever since there have always been chemists of his school who followed in his footsteps taking their share in the international efforts of solving current problems presented by this fascinating group of natural organic compounds. Those acquainted with the physiological actions of flavonoids are well aware of the early results of Hungarian scientists (A. Szent-Györgyi, E. Jeney and their collaborators) also in this field; the pharmacological line of flavonoid research has just as well its active Hungarian workers today. In fact, the flourishing and complex activity concerned with flavonoid compounds led in 1965 to the establishment of the Work-Committee for Flavonoid Research of the Hungarian Academy of Sciences.

The members of this Committee are not only chemists, but also pharmacologists and representatives of agrarian science and of industry, to permit the covering and co-ordination of all fields in the research and use of natural or synthetic flavonoids. This work is promoted by holding scientific sessions and, in every second or third year, a symposium with international participation of foreign researchers of this branch of organic chemistry. Three symposia held so far proved to be good occasions of contact to link Hungarian efforts with similar researches abroad in both the chemistry and physiological actions of flavonoids.

The material of the present volume has accumulated partly from the chemical lectures* held at the 3rd Hungarian Bioflavonoid Symposium (May, 1970, Debrecen, Hungary), which the authors have not published elsewhere in the meantime. The other part of the book is an attempt to survey and summarize Hungarian chemical research on flavonoids from 1950

* The material of a round-table conference held at the same Symposium on pharmacological topics has been published in M. Gábor's book "The Anti-inflammatory Action of Flavonoids", Akadémiai Kiadó, Budapest 1972.

until today, affording easy reference to those interested in one or the other particular detail.

We do hope that chemists engaged in the field of flavonoids and related compounds will find this volume useful and interesting, and it will be of assistance in their work. Since cultivation of the chemical science has always been, is, and will ever remain a reciprocal co-operation on international level, promoting the work of the readers of this book means the promotion of a traditional line of organic chemical research in Hungary.

F. Kállay

secretary

R. Bognár

chairman

of the Work-Committee for Flavonoid Research
of the Hungarian Academy of Sciences

ON SOME C₁₅ DERIVATIVES RELATED TO FLAVONES

by

G. B. MARINI-BETTOLO

Istituto Superiore di Sanità

and

Istituto Chimica, Facoltà di Medicina e Chirurgia Università Cattolica del S. Cuore
Roma, Italy

I. INTRODUCTION

In recent years a growing interest has arisen about some new substances found in plants, which are structurally and biogenetically related to the main group of flavones. These substances are considered to be of interest because they may be the biogenetical intermediates of other more complex compounds of the flavone group.

Since the beginning of this century a considerable contribution has been made in this field by Bargellini and his school in Rome.

We shall now consider three particular groups of flavone derivatives, i.e. neoflavones, aurones and peltogynols.

II. NEOFLAVONES

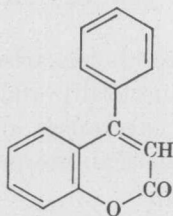
1. β -Phenylcoumarins

Prunetol, a phenolic derivative, was first obtained by Finckh [1] from the *Prunus* genus and proved to be identical with genistein isolated previously by Perkin from *Genista tinctoria* [2].

Its molecular formula $C_{15}H_{10}O_5$ may suggest a structure similar to that of flavones, but the products of alkaline degradation, phloroglucinol and *p*-hydroxyphenylacetic acid, are not in agreement with the proposed structure. It is well known that under these conditions flavones (β -phenylbenzo- γ -pyrones) yield substituted acetophenones, or phenols and hydroxybenzoic acids.

In 1911 Bargellini [3] postulated on the basis of these observations that among natural substances a number of natural C_{15} derivatives of unknown constitution could be referred to the structure of β -phenylcoumarin. In effect, while the derivatives of phenyl-1,4-benzopyrones, i.e. flavones and flavanones, were known to be widely distributed in plants, up to that time no derivatives of phenyl-1,2-benzopyrones had been found in nature, whereas several natural 1,2-benzopyrones were well known.

On the basis of these considerations Bargellini and Leonardi wrote in 1911: "Correlating the widespread occurrence of coumarins in plants (it is well known that coumarin, and other related substances like umbelliferone, aesculetin, daphnetin, limettin, fraxetin were obtained from various plants), we have had the idea that to a number of these natural products, isomeric with flavones, and of as yet unknown structure, a coumarinic structure could be attributed, that is the structure of a β -phenylcoumarin (β -phenylbenzo- α -pyrone).

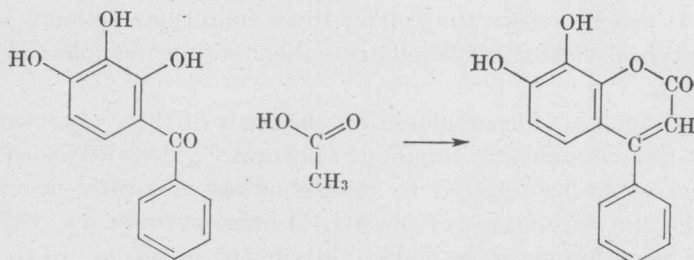


On the basis of the above structure, it would be easy to explain how a phenol and a substituted benzoic acid may be obtained on alkaline degradation. On the other hand, their isomerism with flavones is quite evident.

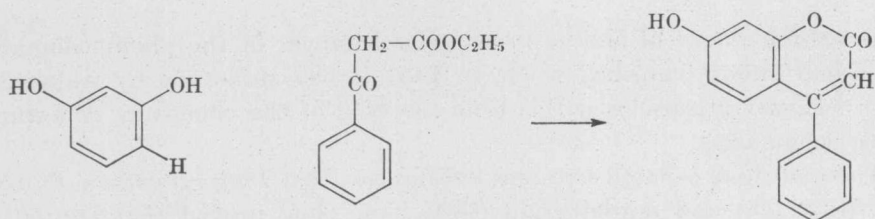
While the results of analytical investigations on these substances may support this hypothesis, we have proposed to synthesize a number of hydroxy- β -phenylcoumarins in order to learn the general properties of this group of substances, which may in the future have importance as natural products" [3].

A certain number of β -phenylcoumarins were synthesized by Bargellini and co-workers from 1911 to 1925 by different routes [4]:

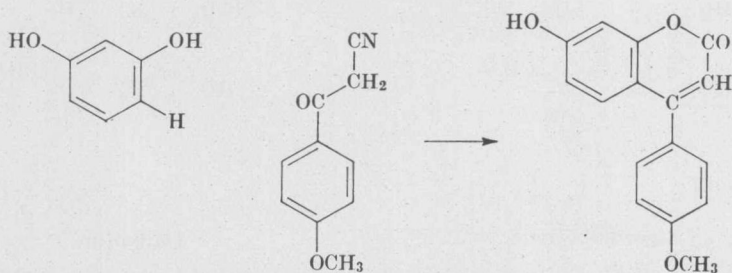
(1) Reaction of substituted hydroxybenzophenones with acetic anhydride and sodium acetate:



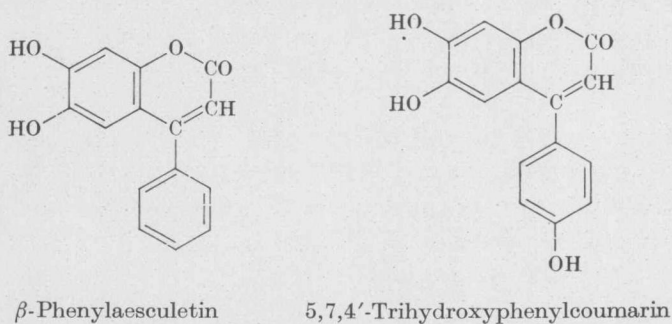
(2) Reaction of phenols with benzoylacetic acid:



(3) Reaction of nitriles of hydroxybenzoylacetic acids (cyanoacetyl derivatives) with phenols in the presence of ZnCl₂:



By method (2), Bargellini and Martegiani [5] condensed hydroxyhydroquinone and methyl benzoylacetate to 6,7-dihydroxy-4-phenylcoumarin or β -phenylaesculetin (m.p. of acetyl derivative: 156°C).



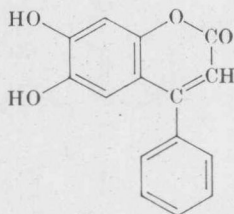
Later 5,7,4'-trihydroxyphenylcoumarin was also synthesized by Bargellini [6] according to the method of Sonn [7], which is a modification of method (3).

None of the trihydroxyphenylcoumarins prepared by Bargellini could be identified with prunetol (genistein). On the other hand, Robinson and Baker [8] synthesized 4',5,7-trihydroxyisoflavone which proved to be identical with prunetol (genistein).

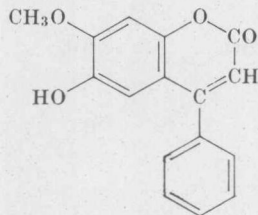
This work has opened — as known — a new field of chemistry of natural products: the isoflavones.

Bargellini's hope of finding in nature substances of the phenylcoumarin type had almost vanished when, in 1957, a new discovery by Ahluwalia and Seshadri [9] disclosed this time the field of the chemistry of natural phenylcoumarins.

These authors isolated two new substances from *Dalbergia sissoi*, dalbergin ($C_{16}H_{22}O_4$) and nordalbergin ($C_{15}H_{20}O_4$). They proved that the latter was identical with 6,7-dihydroxy- β -phenylcoumarin, synthesized by Bargellini and Martegiani in 1911, as reported above [5].

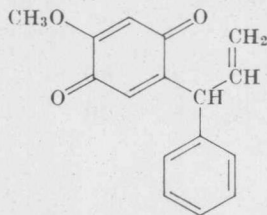


Nordalbergin

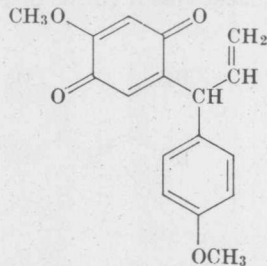


Dalbergin

The further finding in *Dalbergia* wood of the quinones related to dalbergin, the dalbergiones $C_{15}H_{14}O_3$ (I) and $C_{17}H_{16}O_4$ (II) [10, 11],



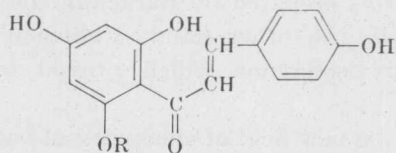
I



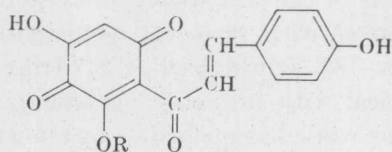
II

is another confirmation of Bargellini's hypothesis [12].

Dalbergiones represent a further example of quinones structurally related to benzopyrones, like carthamone and carthamin in the flavanone-chalcone series [13].



Carthamin



Carthamone