

Georgiev Survey of Drug Research in Immunologic Disease

2 Noncondensed Aromatic Derivatives

Part I

Georgiev Survey of Drug Research in Immunologic Disease

2 Noncondensed Aromatic Derivatives

Part I



 **KARGER**



Y070484

S. Karger · Basel · München · Paris · London · New York · Tokyo · Sydney

Vassil St. Georgiev

MSc in Pharmaceutical Sciences, Faculty of Pharmacy, Higher Medical Institute, Sofia; MSc in Chemical Engineering, Higher Institute of Chemical Technology, Sofia; PhD in Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria. Head, Chemo- and Immunotherapeutics Research, Pharmaceutical Division, Pennwalt Corporation, Rochester, N.Y.; former Senior Research Associate, Department of Chemistry, The Pennsylvania State University, University Park, Pa.; Member of the American Chemical Society and of the New York Academy of Sciences; Fellow of the New York Academy of Sciences.

Survey of Drug Research in Immunologic Disease

Volume 1

Aliphatic Derivatives

X + 542 p., 1983. ISBN 3-8055-3503-1

National Library of Medicine, Cataloging in Publication

Georgiev, Vassil St.

Noncondensed aromatic derivatives (pt.1)/Georgiev. – Basel; New York; Karger, 1983

(Survey of drug research in immunologic disease; v. 2)

I. Benzene Derivatives I. Title II. Series

QV 744 S963 v. 2

ISBN 3-8055-3566-X.

Drug Dosage

The author and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

All rights reserved.

No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

© Copyright 1983 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)

Printed in Switzerland by Thür AG Offsetdruck, Pratteln

ISBN 3-8055-3566-X

General Introduction

'Survey of Drug Research in Immunologic Disease' is conceived as a series of independent volumes intended primarily as a reference library for research chemists, biologists, and other scientists.

The series brings into a single reference source the vast amount of information available for each and every chemical series or individual compound that has been found active in the last 20 years. More important drugs developed prior to that time are also included together with a comprehensive account of the patent literature. Although the number of patents covering chemical series, and sometimes seemingly identical structures, is enormous, much of the relevant information has been reported in a deliberately cursory manner in order to protect the confidentiality of the research.

The consolidation of all information related to research in this field will greatly facilitate its rapid retrieval in the continuing search for new active leads. Scientists who are directly involved in the design and synthesis of biologically active compounds, or participate in their biological screening and evaluation, will certainly need and benefit most from these books. The description of literally hundreds of organic reactions along with the brief account of reaction conditions enables chemists to quickly assess the scope and merits of different synthetic approaches and find answers and precedents helping them resolve their everyday problems in the laboratory. In a similar way, the available biological information can aid the work of biologists.

In order to give a full priority in describing the vast amount of published information and at the same time to keep the size of the books within reasonable limits, comments by the author regarding the scientific merits of the reported results are restricted to a minimum.

The description of each chemical series includes: (a) *general structure*, along with all given substituents; (b) *preparation*, with descriptions of all synthetic approaches utilized in the synthesis of a particular series, including reaction conditions whenever reported; (c) *biological activity*, with major emphasis on activity directly affecting the immune system (including pharmacology, immunology, experimental data, dosage, comparative studies, toxicology, clinical evaluation, drug metabolism, and pharmaceutical development), and coverage, wherever possible or necessary to complete the biological profile of the series, of other biological activities having indirect effects on the immune system or implicated in disease states with immunologic components; and (d) *references*.

Within each volume, the various chemical series are arranged according to their chemical nature (e.g. alcohols, amines, ketones, carboxylic acids, esters, etc.), and in order of increasing complexity of their molecules.

Listing the nature of all given substituents for a particular chemical series will undoubtedly help scientists in designing new active leads while minimizing the possibility of patent incursions. Moreover, such surveys give the reader some reasoning as to why so many patents have been issued for structurally similar

compounds, and help define the role substituents sometimes play in affecting biological activity.

Location of information is facilitated through the inclusion of three indexes, in addition to an author index, in each volume: chemical and biological subject indexes and a biological activity cross-index. In the latter, all chemical entries are divided according to their biological activity. Such an arrangement makes it convenient for the reader to locate any chemical structure by one particular activity. Of course, the full biological profile of each chemical series is described in the biological subject index where compounds are arranged alphabetically.

Volume 1 surveyed research on aliphatic derivatives. Noncondensed aromatic derivatives are covered in volumes 2-6, where compounds are arranged according to functional groups and increasing complexity of their molecules. The seventh volume will contain cumulative indexes referring to work featured in the first six volumes.

Future volumes will include alicyclic and polycyclic derivatives, heterocyclic compounds with one, two, three or more heteroatoms, and miscellaneous derivatives. Volumes containing cumulative indexes will appear at regular intervals.

Introduction

This second volume in the 'Survey of Drug Research in Immunologic Disease' series inaugurates a group of five volumes covering noncondensed aromatic derivatives. Volume 2 includes unsaturated compounds, compounds containing hydroxyl group(s) (alcohols, phenols and aminoalcohols), and ether derivatives.

As stated in the General Introduction, the scope of the series encompasses both drugs directly affecting the immune system and those working to alleviate symptoms of a disease state, such as bronchial asthma, that has immunologic components. Certainly, a variety of antihistaminic and bronchodilating agents falls into this category. Presently, a great number of aromatic derivatives containing aminoalcohol side chains confer their biological activity through the β -adrenergic receptor. Moreover, the existence of β_1 - and β_2 -type adrenergic receptors may also account for the observed myocardial or bronchodilating selectivity of different aminoalcohol derivatives. In order to illustrate the importance of some structural and steric requirements, several examples of drugs with effective myocardial selectivity over bronchodilating selectivity have also been given. The reader should nonetheless bear in mind that the observed selectivity of drugs may often be the result of an unequal tissue distribution or failure on the part of the drugs to reach a particular receptor site, rather than pharmacological difference (since no receptor selectivity has been noticed in cell-free systems).

*Dedicated to
my wife Elizabeth
and daughter Emily*

Contents

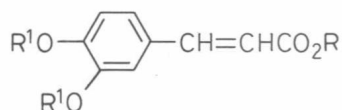
	General Introduction	VII
	Introduction	IX
Chapter I	Unsaturated Aromatic Compounds	1
	Cinnamic Acid Derivatives	2
	Cinnamanilide Compounds	17
	Cinnamoylanthranilic Acids	35
	Cinnamyl Compounds	39
	Styrene Compounds	41
	Styryl Ketones	43
	Chalcone Compounds	60
	Stilbene Compounds	66
	Arylalkylidene Compounds	73
	Acrylic Acids	73
	Acrolein Compounds	75
	Propene Compounds	76
	Butene Compounds	82
	Butenoic Acids	86
	α -Cyanoalkene Compounds	93
	Compounds Having Exocyclic Double Bond	99
	Diene Derivatives	102
	Allene Compounds	102
	Butadiene Compounds	107
	Triene Derivatives	108
	Tetraene Derivatives	110
	Arylalkyne Derivatives	113
	Alkynol and Alkynone Compounds	117
	α -Acetylenic Amine Compounds	120
	Diyne Derivatives	121
Chapter II	Aromatic Alcohols and Phenols	123
	Benzyl Alcohols	124
	Phenethyl Alcohols	131
	Propanol Compounds	135
	Propanediols	137
	Pentanol Derivatives	159
	Diaryl Carbinols	160
	Unsaturated Alcohols	167
	(Aralkyl Ether)alkanol Compounds	171
	(Phenylthio)alkanol Compounds	172
	Monophenol Compounds	176
	Diphenol Compounds	188

	Triphenol Compounds	199
	Halophenols	200
	(Hydroxymethyl)phenols	203
	(Alkylamino)phenols	209
	(Aminomethyl)phenols	211
	(Acylamino)phenols	220
	(Formamido)phenols	221
	(Ureido)phenols	222
	(Sulfonamido- and Sulfamoylamino)phenols	223
	(Sulfonylmethyl)phenols	224
Chapter III	Aromatic Aminoalcohols	225
	Phenylaminoalcohols with No Other Ring Substituents	226
	Monophenol Compounds	242
	<i>p</i> -Hydroxyphenylaminoalcohols	248
	(Hydroxymethyl)phenols	264
	(<i>m</i> -Hydroxymethyl)phenols	290
	Diphenol Compounds	293
	2,3-Dihydroxyphenyl Derivatives	293
	3,4-Dihydroxyphenyl Derivatives	295
	3,5-Dihydroxyphenyl Derivatives	343
	Triphenol Compounds	386
	(Halogen-substituted)phenylaminoalcohols	390
	Arylalkyl Ether Derivatives	403
	(Alkyl- and Alkoxy)phenylaminoalcohols	425
	Diphenylmethane Derivatives	432
	(Cycloalkyl-substituted)phenylaminoalcohols	436
	3-Amino-1-propanol Derivatives	438
	(Acyloxy)phenylaminoalcohols	442
	(Aminomethyl)phenylaminoalcohols	454
	(Alkylamino)phenylaminoalcohols	456
	(Ureido)phenylaminoalcohols	458
	(Alkoxy-carbonylamino)phenylaminoalcohols	463
	(Formamido)phenylaminoalcohols	467
	(Acylamino)phenylaminoalcohols	477
	(Sulfonamido- and Sulfamoylamino)phenylaminoalcohols	481
	(Alkylsulfonylmethyl)phenylaminoalcohols	485
	Alkylenediamine Derivatives	489
	Miscellaneous Aminoalcohol Derivatives	501
Chapter IV	Ether Compounds	509
	Ether Compounds	510
	Diphenyl Ethers	530
	Thioethers	535
Indexes	Author Index	542
	Chemical Subject Index	560
	Biological Subject Index	570
	Biological Activity Cross-Index	586

Chapter I. Unsaturated Aromatic Compounds

Cinnamic Acid Derivatives

1. Caffeic Acid and Derivatives



$\text{R} = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2, \text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2, \text{CH}_2\text{CH}_2\text{N}[(\text{CH}_2)_3\text{CH}_3]_2,$

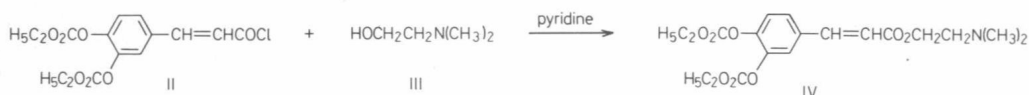
$\text{CH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2, \text{O} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{NCH}_2\text{CH}_2,$ 3-pyridylmethyl,

2-piperidinoethyl, $\text{CH}[\text{CH}_2\text{N}(\text{CH}_3)_2]_2$, 8-methyl-8-azacyclo[3.2.1]oct-3-yl, morpholino, 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 5,6-dimethylbenzimidazol-1-yl, NHNH_2 , $\text{NHNHCH}(\text{CH}_3)_2$, 2-morpholinoethylhydrazo

$\text{R}^1 = \text{H}, \text{CO}_2\text{C}_2\text{H}_5, \text{CH}_3\text{CO}$

Preparation [1]

Treatment of acid chloride II with an appropriate aminoalcohol (III) in pyridine solution led to the preparation of the corresponding caffeic acid derivative IV:



Caffeic acid ($\text{R} = \text{R}^1 = \text{H}$) itself, as well as its mono- and dicaffeate esters, were extracted from the roots of *Echinops anplexicaulis* or prepared by self-esterification [3].

Biological Activity

At oral doses of 300 mg/kg, derivatives IV and V ($\text{I}: \text{R} = 2\text{-morpholinoethyl}, \text{R}^1 = \text{H}$) showed anti-inflammatory activity against the dextran-induced edema in the plantar aponeurosis in rats [1, 2].

Additionally, a number of derivatives I were found to be active in rats as antipyretic agents (at oral doses of 300 mg/kg), as well as to affect the psychomotor behavior (at oral doses of 750 mg/kg) [1, 2].

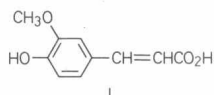
At doses of 2 μg , both caffeic acid and its esters completely abolished the activity of 20 μg rattlesnake venom phosphodiesterase [3].

References

- 1 Flammang, M.; Wermuth, C.G.; Schreiber, J.; Barth, J.; Cahn, J.; Herold, M.: *Chim. ther.* **4**: 112 (1969).
- 2 Flammang, M.; Wermuth, C.G.; Schreiber, J.; Barth, J.; Herold, M.; Cahn, J.: *Chim. ther.* **4**: 120 (1969).
- 3 Agoro, J.W.: U.S. Patent 4,124,724; *Chem. Abstr.* **90**: 103649f (1979).

1.1

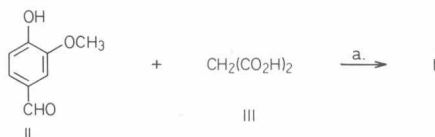
Ferulic Acid



Preparation

Method A [1, 2]

Treatment of vanillin (II) with malonic acid (III) in the presence of base furnished ferulic acid in 73% yield:



a. pyridine, piperidine, room temperature, 3 weeks.

Method B

Comte et al. [3] have reported the preparation of *cis*- and *trans*-ferulic acids via the irradiation (UV light for 12 h) of the corresponding cinnamic acid. The final products were purified by chromatography (in 2% acetic acid solution) on powdered wood ('Solka Floc').

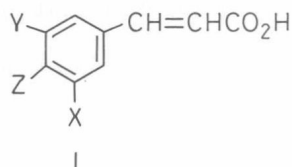
Biological Activity [4]

Ferulic acid (I), when administered to mice, potentiated the phagocytic activity of the macrophages.

References

- 1 Vorsatz, F.: J. prakt. Chem. 145: 265 (1936).
- 2 Pearl, I.A.; Beyer, D.L.: J. org. Chem. 16: 216 (1951).
- 3 Comte, P.; Zwingelstein, G.; Ville, A.; Mentzer, C.: C. r. hebdom. Séanc. Acad. Sci., Paris 245: 1144 (1957).
- 4 Xu, L.; Ouyang, R.; Yin, Z.; Zhang, L.; Ji, L.: Yaoxue Xuebao 16: 411 (1981).

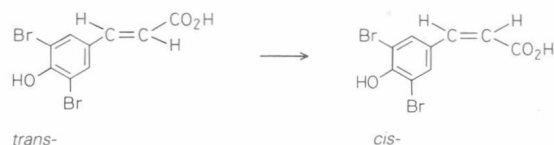
2. Halogenated *cis*-Cinnamic Acids



X = Br, Cl, I
 Y = H, Br, Cl, I
 Z = e.g. OH

Preparation
 [1]

The *cis*-I derivatives were obtained from the corresponding *trans*-analogs via irradiation with UV light:



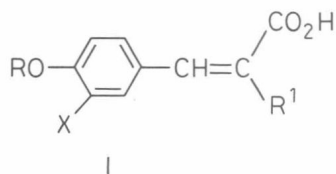
Biological
 Activity [1]

The *cis*-I derivatives were found to exhibit anti-inflammatory activity and to reduce the capillary fragility.

Reference

- 1 Freedman, L.; Merritt, A.J.: U.S. Patent 3,396,193; Chem. Abstr. 69: 96270m (1968).

3. *p*-Alkoxybenzoic Acid Derivatives



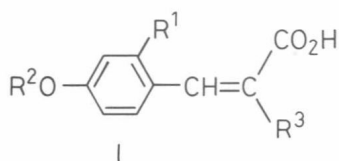
R = *iso*-Pr, *iso*-Bu, cyclo-C₆H₁₁, PhCH₂, Me, CH₂=CHCH₂
 R¹ = H, Me
 X = H, Cl

Preparation
 [1]

Derivatives I were prepared by Wittig reaction of benzaldehyde precursors with an ethoxycarbonylmethylenephosphorane, or with an α -ethoxycarbonylethylidenephosphorane.

- Biological Activity [1] The title derivatives have shown anti-inflammatory activity in the kaolin-induced edema assay, as well as ability to stabilize the membrane of rat erythrocytes against hypotonic hemolysis. Some structure-activity correlations using the Hansch method have also been discussed.
- Reference 1 Kuchar, M.; Brunova, B.; Rejholec, V.; Roubal, Z.; Grimova, J.; Nemecek, O.: Colln Czech. chem. Commun. 40: 3545 (1975).

4. Substituted Cinnamic Acids

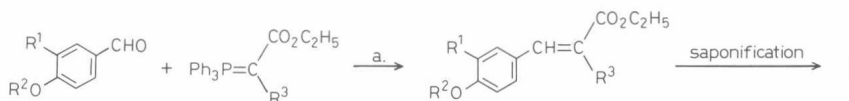


$R^1 = \text{H, Cl, OMe}$

$R^2 = \text{C}_{1-6} \text{ alkyl, cyclohexyl, benzyl, allyl, propargyl}$

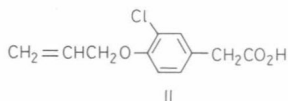
$R^3 = \text{H, Me}$

Preparation [1]



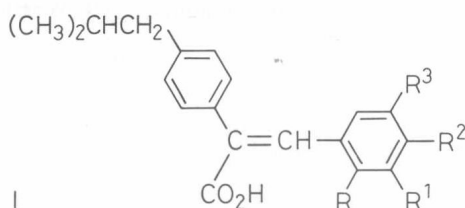
a. benzene, reflux (under N_2); compounds I were also converted to their corresponding cyclohexylamine and N-methylpiperazine salts.

- Biological Activity [1] Derivatives I were reported to be effective in inhibiting the kaolin-induced edema in rats with some of the analogs having activity comparable to that of mervan (alclofenac) (II).



- Reference 1 Kuchar, M.; Brunova, B.; Grimova, J.; Nemecek, O.: Czech. Patent 172,738; Chem. Abstr. 90: 22612m (1979).

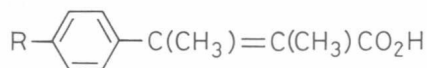
5. *p*-Isobutylphenylacetic Acid Derivatives



$R = H, Cl$
 $R^1 = H, OMe, NO_2$
 $R^2 = H, Me, OMe, OAc, NO_2$
 $R^3 = H, OMe$
 $R^1R^2 = \text{e.g. } CH_2O_2$

Preparation [1]	The reaction of appropriate benzaldehydes with <i>p</i> -(Me ₂ CHCH ₂)C ₆ H ₄ CH ₂ CO ₂ H produced the <i>p</i> -isobutylphenylacetic derivatives I.
Biological Activity [1]	Anti-inflammatory, antipyretic, and analgesic activities. The MeCHO, PhCH=CHCHO, and 3,4-(MeO) ₂ C ₆ H ₃ CH=CHCHO analogs of I (similarly prepared as compounds I) were also shown to have the above activities.
Reference	1 De Witt, P.; Ramacci, M.T.: Farmaco, Ed. Sci. 27: 897 (1972).

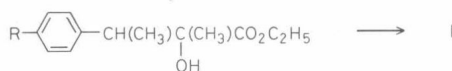
6. *p*-Substituted (E)- and (Z)- α,β -dimethylcinnamic Acids



(E)- and (Z)-I

$R = Br, Cl, F, Me, MeO$

Preparation [1]	Dehydration of the <i>erythro</i> - and <i>threo</i> - <i>p</i> -substituted hydroxy esters II, followed by alkaline hydrolysis, led to the preparation of the corresponding cinnamic acids I:
--------------------	--



erythro-/threo-II

The stereochemistry of I was determined on the basis of their nmr spectra.

Biological
Activity [1]

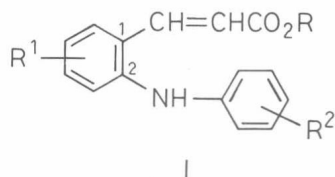
Anti-inflammatory and antiallergic activities.

Reference

1 Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F.; Martinelli, A.; Santini, S.; Sorriso, S.: *Gazz. chim. ital.* 110: 327 (1980).

7.

Cinnamic Acid Derivatives



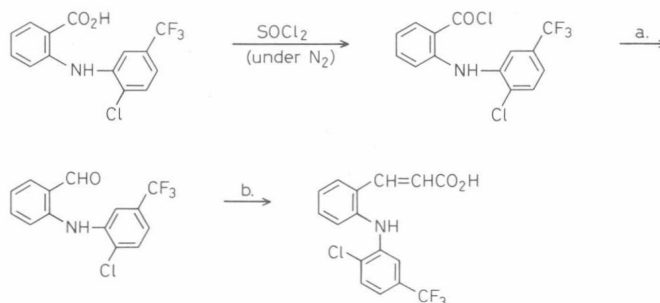
R = H, Me, Et

R¹ = 5-MeO, 4-Cl

R² = 2,6-Cl₂, 3,6-CF₃(Cl), 2,6,3-Cl₂(Me), 2,3-Me₂, 2,5-Me₂, 2,6-Me₂, 3-CF₃

Preparation
[1]

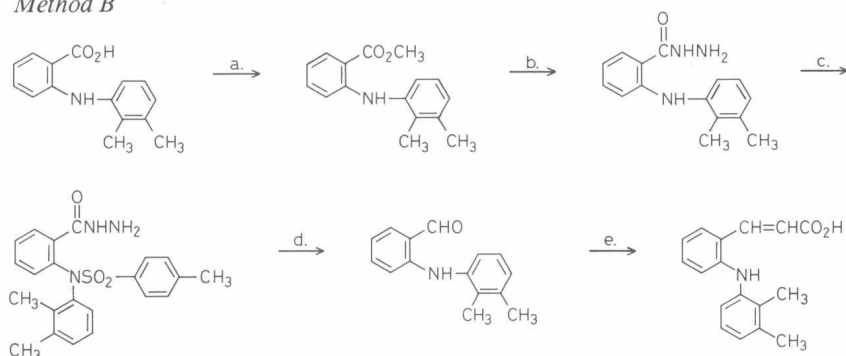
Method A



a. Li(*tert*-BuO)₃AlH, -75 °C, anhydrous diglyme, 2 h;

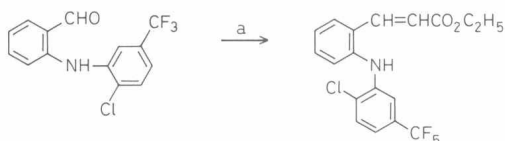
b. CH₂(CO₂H)₂, piperidine, pyridine, 100 °C, 3 h.

Method B



- a. dimethyl sulfate, aqueous NaOH, 20–30 °C, 14 h;
- b. 85% hydrazine hydrate, reflux (under N₂);
- c. *p*-MeC₆H₄SO₂Cl, pyridine, room temperature, 12 h;
- d. sodium carbonate, HOCH₂CH₂OH, 160 °C;
- e. CH₂(CO₂H)₂, pyridine, piperidine, 130 °C, 30 min.

In another example,



- a. ethyl (triphenylphosphoranylidene)acetate, benzene, reflux, 16 h.

Biological
Activity [1]

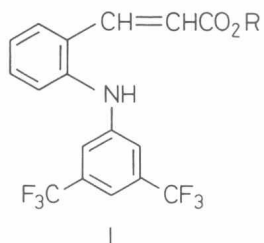
Anti-inflammatory, analgesic, and antipyretic activities.

Reference

- 1 Sallmann, A.; Fitzi, K.; Pfister, R.: South African Patent 67 05,990; Chem. Abstr. 70: 67938a (1969).

8.

Substituted Cinnamic Acids



R = e.g. H, Et