Georgiev

Survey of Drug Research in Immunologic Disease

2 Noncondensed Aromatic Derivatives

Part I

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Survey of Drug Research in Immunologic Disease

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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.

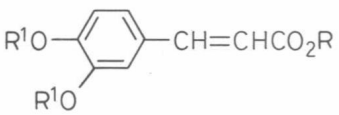
As stated in the General Introduction, the scope of the series encompasses both drugs directly affecting the immune system and those working to alleviate symptoms of a disease state, such as bronchial asthma, that has immunologic components. Certainly, a variety of antihistaminic and bronchodilating agents falls into this category. Presently, a great number of aromatic derivatives containing aminoalcohol side chains confer their biological activity through the ß-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

Chapter I. Unsaturated Aromatic Compounds

1. Caffeic Acid and Derivatives



R = $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(C_2H_5)_2$, $CH_2CH_2N[(CH_2)_3CH_3]_2$,

3-pyridylmethyl,

2-piperidinoethyl, $CH[CH_2N(CH_3)_2]_2$, 8-methyl-8-azacyclo[3.2.1]oct-3-yl, morpholino, 10,11-dihydro-5H-dibenz[b,f]azepin-5-yl, 5,6-dimethylbenzimidazol-1-yl, $NHNH_2$, $NHNHCH(CH_3)_2$, 2-morpholinoethylhydrazo

R^1 = H, $CO_2C_2H_5$, CH_3CO

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:

II III IV

Caffeic acid (R = R^1 = 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

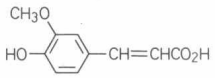
At oral doses of 300 mg/kg, derivatives IV and V (I: R = 2-morpholinoethyl, R^1 = H) showed anti-inflammatory activity against the dextran-induced edema in the plantar aponeurosis in rats [1, 2].

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).

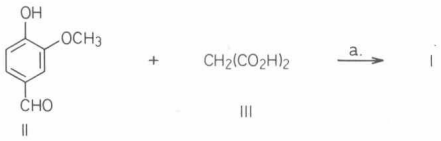
1.1 Ferulic Acid



I

Preparation

Method A [1, 2]
Treatment of vanillin (II) with malonic acid (III) in the presence of base furnished ferulic acid in 73% yield:



II III

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

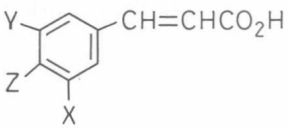
Method B
Comte et al. [3] have reported the preparation of *cis*- and *trans*-ferulic acids via the irradiation (UV light for 12 h) of the corresponding cinnamic acid. The final products were purified by chromatography (in 2% acetic acid solution) on powdered wood ('Solka Floc').

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. hebd. 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



I

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:

trans- *cis-*

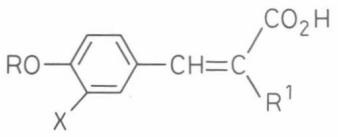
Biological Activity [1]

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*-Alkoxycinnamic Acid Derivatives



I

R = *iso*-Pr, *iso*-Bu, cyclo-C_6H_{11}, $PhCH_2$, Me, CH_2=$CHCH_2$
R^1 = 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.

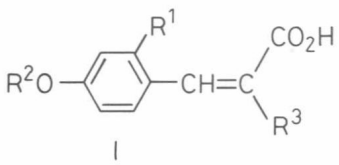
Biological Activity [1]

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).

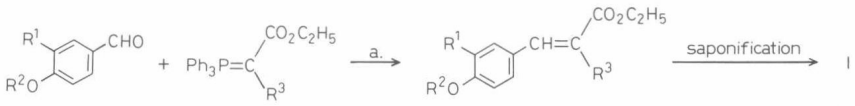
4. Substituted Cinnamic Acids



I

R^1 = H, Cl, OMe
R^2 = C_{1-6} alkyl, cyclohexyl, benzyl, allyl, propargyl
R^3 = H, Me

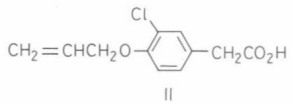
Preparation [1]



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).

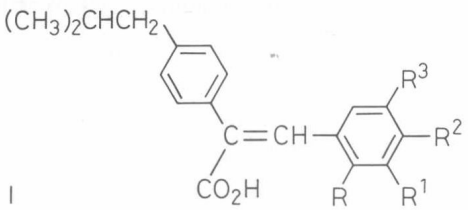


II

Reference

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

5. *p*-Isobutylphenylacetic Acid Derivatives



I

R = H, Cl
R^1 = H, OMe, NO_2
R^2 = H, Me, OMe, OAc, NO_2
R^3 = H, OMe
R^1R^2 = e.g. CH_2O_2

Preparation [1]

The reaction of appropriate benzaldehydes with *p*-$(Me_2CHCH_2)C_6H_4CH_2CO_2H$ produced the *p*-isobutylphenylacetic derivatives I.

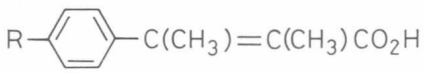
Biological Activity [1]

Anti-inflammatory, antipyretic, and analgesic activities.
The MeCHO, PhCH=CHCHO, and 3,4-$(MeO)_2C_6H_3CH$=CHCHO analogs of I (similarly prepared as compunds 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

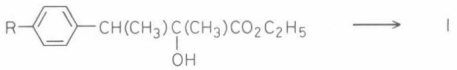


(E)- and (Z)-I

R = Br, Cl, F, Me, MeO

Preparation [1]

Dehydration of the *erythro-* and *threo-p*-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.

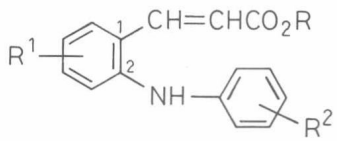
Biological Activity [1]

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

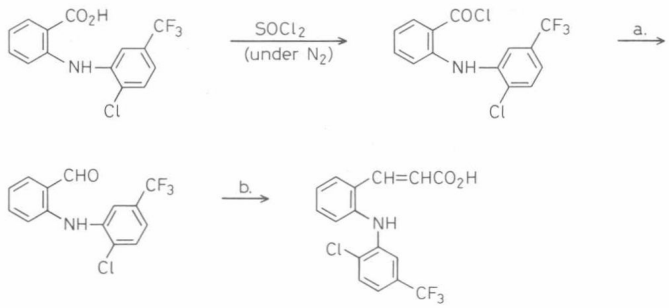


I

R = H, Me, Et
R^1 = 5-MeO, 4-Cl
R^2 = 2,6-Cl_2, 3,6-CF_3(Cl), 2,6,3-Cl_2(Me), 2,3-Me_2, 2,5-Me_2, 2,6-Me_2, 3-CF_3

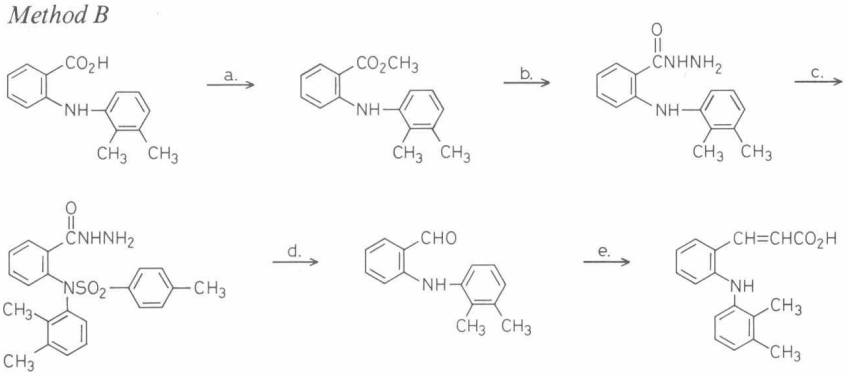
Preparation [1]

Method A



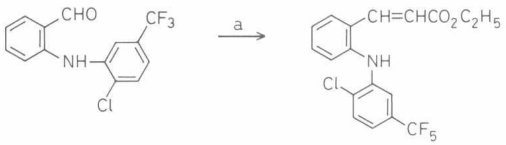
a. Li(*tert*-BuO)$_3$AlH, −75 °C, anhydrous diglyme, 2 h;
b. $CH_2(CO_2H)_2$, piperidine, pyridine, 100 °C, 3 h.

Method B



a. dimethyl sulfate, aqueous NaOH, 20–30 °C, 14 h;
b. 85% hydrazine hydrate, reflux (under N_2);
c. *p*-$MeC_6H_4SO_2Cl$, pyridine, room temperature, 12 h;
d. sodium carbonate, $HOCH_2CH_2OH$, 160 °C;
e. $CH_2(CO_2H)_2$, pyridine, piperidine, 130°C, 30 min.

In another example,



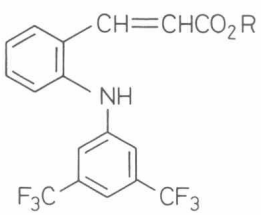
a. ethyl (triphenylphosphoranylidene)acetate, benzene, reflux, 16 h.

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



I

R = e.g. H, Et