Georgiev

Survey of Drug Research in Immunologic Disease

3 Noncondensed Aromatic Derivatives

Part II

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Part II

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 volume 2 and following volumes, where compounds are arranged according to functional groups and increasing complexity of their molecules.

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

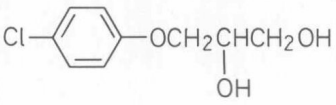
The present volume represents the second of a series of volumes providing information on the chemistry and biological activities of noncondensed aromatic derivatives. It covers compounds containing halogen atoms as well as a variety of nitrogen derivatives. For the sake of unity (the presence of a unique common pharmacophor, the oxamic acid residue), a number of heterocyclic oxamic acids were also included and discussed along with their aromatic counterparts.
As usual, within the volume all chemical series and individual compounds have been arranged according to functional groups and in order of increasing molecular complexity.

Contents

Indexes

Chapter I. Halide Compounds

1. 3-(4-Chlorophenoxy)-1,2-propanediol (Chlorphenesin)



I

Preparation [1]

Treatment of *p*-chlorophenol (II) with glycidol (III) in the presence of base gave chlorphenesin:

II III I

a. pyridine methiodide, 90–95 °C, 7 h.

Biological Activity

Chlorphenesin, a topical antifungal agent, was found to inhibit effectively the release of histamine [2].

The drug suppressed the release of histamine induced by human serum activated with zymosan (such activation by zymosan is usually associated with the generation of a factor, C5a from the complement system, that releases histamine from autologous basophils) [3].

Stites et al. [4] have described an in vitro immunosuppressive activity of chlorphenesin on the lymphocyte functions in both humans and mice. At doses of 20–50 μg/ml the drug suppressed the mitogenic responses of mouse and human B and T cells, and the mixed lymphocyte reactions (in inbred strains of mice and in unrelated humans) as well.

Berger et al. [5] have found that when chlorphenesin was administered simultaneously with sheep or chicken erythrocytes, or with penicillin conjugates, it suppressed in a dose-dependent manner the antibody-producing capacity of the isolated spleen cells. The production of humoral antibodies was also depressed. The drug has been shown to inhibit the tuberculin reaction in guinea pigs when administered at the time of the challenge [5].

Experiments conducted by *Pick* [6] have demonstrated that chlorphenesin inhibited the production of the macrophage migration inhibitory factor (MIF) by antigen-stimulated sensitized guinea pig lymph node cells. Chlorphenesin is also known to elevate the levels of the endogenous cyclic AMP which may act as a regulator of the MIF production [6].

Burka and Eyre [7] have reported that chlorphenesin, when given at high concentration, inhibited the release of the slow-reacting substance of anaphylaxis from bovine lung in vitro.

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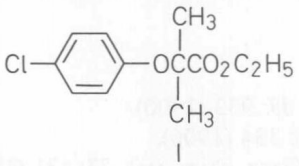
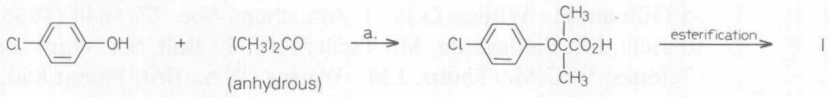
2. Ethyl 2-(*p*-Chlorophenoxy)-2-methylpropionate (Clofibrate)



Preparation [1–8]



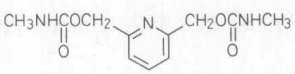
a. sodium hydroxide (pellets), chloroform, reflux, 4 h; then, H_3O^+.

Biological Activity

Clofibrate is known for its hypocholesterolemic and hypolipidemic activities [9–21]. In vivo and in vitro experiments have shown that the drug underwent a rapid hydrolysis to the corresponding free acid, which is presumed to confer the activity [9, 26, 27] by displacing the thyroxine from its binding proteins in the plasma, followed by redistribution of the hormone between the plasma and the liver [11, 13, 28, 29]. In another hypothesis, the inhibition of the cholesterol synthesis was advanced as the predominant mechanism of action of clofibrate [30–34].

At doses of 140, 280, or 420 mg/kg, clofibrate inhibited in a dose-dependent manner the acute-phase globulin response in rats, following intramuscular administration 6 h before initiation of inflammation induced by turpentine [35]. The drug did not affect the localized inflammation and did not prevent such inflammation-associated manifestations as hypozincemia, hypoalbuminemia, and enhanced hepatic amino acid uptake.

Szondy et al. [36] have found that a combination of clofibrate and pyridinol carbamate (II) induced a decrease in the quantity of the circulating immune complexes and a diminution of the migration inhibition in rabbits with experimental atherosclerosis. Both drugs did not affect the concentration of the immune complexes and the migration inhibition when administered alone [36].



II

Nemirovskii et al. [37] have shown that clofibrate produced higher indexes of blast transformation induced by phytohemagglutinin, an increased phagocytic index of the monocytes, and an increase in the peroxidase levels and lysosomal activity of the monocytes.

Clofibrate decreased the levels of cyclic AMP in the plasma, liver, and the adipose tissue of rats [38]. A decrease in the activities of protein kinase and adipose tissue triglyceride lipase was also observed [38].

At a daily oral dose of 300 mg/kg, administered for a period of 30 days, clofibrate diminished the activities of superoxide dismutase and glutathione peroxidase in the liver [39]. *Ciriolo* et al. [39] have found that the effect of the drug was associated with an increased susceptibility of the tissue to enhanced peroxidative risk.

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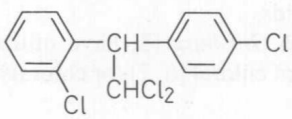
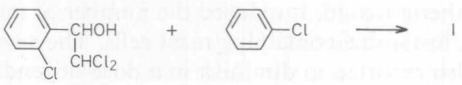
3. 1,1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (*o,p'*-DDD, Mitotane)



I

Preparation

The 1,1-dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (mitotane) (I), a known antineoplastic agent, is a constituent of the commercial DDT which contains about 10% of this *o,p'*-isomer. It has been synthesized by *Haller* et al. [1] from 2,2-dichloro-1-(*o*-chlorophenyl)ethanol and chlorobenzene in the presence of sulfuric acid:



Biological Activity

The effects of mitotane on the immune response in malnourished rats have been investigated by *Hamid* et al. [2]. In comparison to control animals, thymocytes and spleen cells of the *o,p'*-DDD-treated rats responded better to phytohemagglutinin than to pokeweed mitogen.

References

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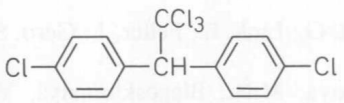
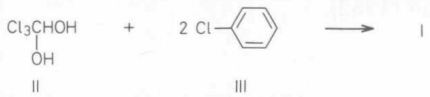
4. 1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT, *p,p'*-DDT)



I

Preparation

Back in 1874, *Zeidler* [1] has reported the first synthesis of DDT (I) via condensation of chloral hydrate (II) (or chloral) with chlorobenzene (III):



II III I

Over the years, several improvements have been described in the search for more effective condensation agents. *Rueggeberg* and co-workers [2–5] have reported that the use of stoichiometric amounts of chlorosulfonic acid, $ClSO_3H$ (initially at −10 to +20 °C for a period of 5 h, followed by room temperature for 15–18 h), supplied DDT in 67–69% overall yields.

Mosher et al. [6], *Neil* et al. [7], and *Ginsburg* [8] have utilized concentrated sulfuric acid during the condensation of chloral [6, 7] (or chloral hydrate [8]) with chlorobenzene.

Haller et al. [9] have made an extensive investigation on the chemical composition of technical DDT (usually representing mixtures that may contain as much as 14 compounds).

Bailes and Payne [10] have developed a colorimetric procedure for the quantitative determination of DDT.

Biological Activity

Pediculicidic and insecticide activities [11–15]. Experiments conducted by *Gabliks* et al. [16] have demonstrated that when DDT was added to the diet of rats immunized with diphtheria toxoid, it reduced the number of mesenterial, metachromatically stained, histamine-containing mast cells. The severity of the anaphylactic shock was also reported to diminish in a dose-dependent manner.

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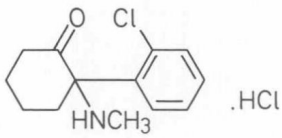
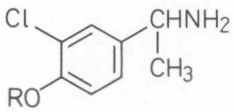
5. 2-(*o*-Chlorophenyl)-2-(methylamino)cyclohexanone (Ketamine)



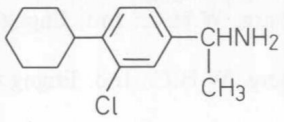
See 259.

6. (4-Alkoxybenzyl)amine Derivatives



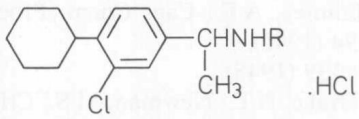
See 199.

7. **α-(3-Chloro-4-cyclohexylphenyl)ethylamine**



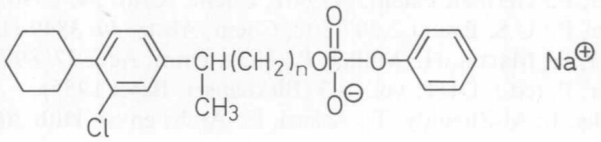
See 204.

8. **(3-Chloro-4-cyclohexyl-α-methylbenzyl)amine Hydrochlorides**



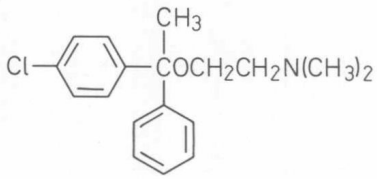
See 205.

9. **O-(Phenylalkyl)-O-phenylphosphoric Acid Derivatives**



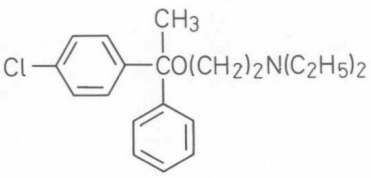
See vol. 4, 228.

10. **2-[1-(4-Chlorophenyl)-1-phenylethoxy]-N,N-dimethylethanamine (Chlorphenoxamine)**



See 322.

11. **(α,α-Diarylalkoxyalkyl)dialkylamine Derivatives**



See 323.