

ANALYSIS OF STEROID HORMONE DRUGS

By

S. GÖRÖG
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ELSEVIER

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PREFACE

The importance of steroid hormones in therapy has grown extremely rapidly in the past 20 years, since the discovery of semi-synthetic routes for the industrial-scale preparation of the most important natural hormones and numerous highly active derivatives. About 200 steroid hormone compounds and related materials are now known, representing roughly 5–10 per cent* of the world's total production of pharmaceuticals. These facts are coupled with continuously increasing demands on the quality of the products and the economy of their production; analysts dealing with the analysis of hormone preparations, bulk hormones and the raw materials and intermediates in their production are thus brought face to face with ever more difficult tasks. It does not seem an overstatement that the analysis of steroid hormone formulations is one of the most delicate tasks in pharmaceutical analysis.

Nevertheless, the pharmaceutical and industrial analytical applications comprise only a small proportion of the tremendous amount of material published on the analysis of steroid hormones: most of the publications deal with various aspects of biological–clinical steroid analysis and these methods can hardly be adopted in pharmaceutical and industrial analysis as a consequence of the entirely different natures of the problems. The situation is similar as regards monographs. The several books published on the analysis of steroid hormones deal with problems of biological–clinical analysis and the elucidation of steroid structures, but as yet no book has been devoted to the analysis of steroid hormone drugs. The most comprehensive work in this latter field is the long chapter by A. A. Forist and L. J. Johnson in *Pharmaceutical Analysis*, edited by T. Higuchi and E. Brochmann-Hanssen (Interscience Publishers, New York–London), which is a unique source of the classical methods and literature. Having been published in 1961, however, it naturally cannot reflect the present situation in pharmaceutical and industrial steroid analysis.

Our monograph aims at making good the above deficiency. Its primary object is to satisfy the demands of analysts working in official and industrial quality-control laboratories and of those dealing with steroid hormones and their intermediates in the pharmaceutical industry and research laborato-

* Private communication of N. Appelzweig.

ries, but we hope that some of the chapters may also be of use to organic chemists and biochemists working in the steroid field.

The scope of the book is restricted on the one hand to hormonal steroids: of the other groups of steroids, only those which are of importance as the starting materials of the above-mentioned semi-syntheses are dealt with briefly. On the other hand, we wish to deal with pharmaceutical and industrial steroid analysis only as described above. The methods of biological-clinical steroid analysis will not be treated here, not even the determination of steroid drugs in biological fluids. In some instances, however, concessions have to be made in this respect, as some of these methods have been applied to pharmaceutical analysis as well. The methods for the determination of steroid structures are discussed only briefly so as to meet the requirements of pharmaceutical analysis.

Our book consists of 7 chapters. Chapters 1-3 contain the basic knowledge on steroids (chemical, pharmacological and historical) which is essential for analysts dealing with steroids. In Chapters 4 and 5 the chromatography and gas chromatography of steroids are described separately as fundamental methods for the qualitative and quantitative analysis of these compounds. Chapter 6 deals with all methods used in the qualitative and quantitative analysis of steroids. A detailed presentation of the quantitative analysis is given in Chapter 7, where the material is classified on the basis of the functional groups in steroid hormones. The discussion of the quantitative analysis of formulations in Chapter 8 is presented in the traditional manner based on their pharmacological classification. Finally, Chapter 9 provides a brief survey of the analysis of the most important raw materials of steroid semi-syntheses.

We express our thanks to the referees of this book, Prof. K. Burger and Dr. T. Fehér, for their careful work and useful advice. We are also indebted to Dr. L. Chafetz, Dr. C. A. Johnson and Dr. T. Urbányi for sending samples for our tests, as well as to Dr. Zs. Budvári-Bárány, Dr. É. Csizér, Miss M. Fütő, Mrs. M. Gál, Dr. G. Garzó, Mrs. A. Laukó, Mrs. M. Rényi, Dr. Sz. Szeberényi, Dr. G. Szepesi and Mr. Á. Szöllősy for their kind assistance in the experimental work and the preparation of the text.

The Authors

1. FUNDAMENTAL STEROID HORMONE CHEMISTRY

1.1 Introduction

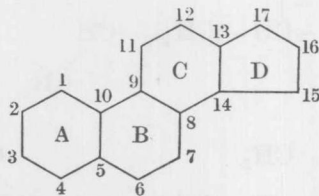
This chapter contains a summary of the fundamental principles of the chemistry of steroid hormones, a knowledge of which is indispensable for those who wish to deal with the analysis of this significant group of pharmaceuticals.

In addition to the presentation of the most essential topics (nomenclature and stereochemical problems), a number of subdivisions deal with the raw materials for steroid hormone synthesis and the formation of the most important functional groups, with the aim of demonstrating to the analyst the antecedents of the materials investigated and the origins of their impurities. In order to show the organic chemical basis of the reactions used in steroid analysis and presented in Chapters 4–7, a brief summary of the analytically important reactions of steroid hormones will also be given.

For those readers who desire to obtain more detailed information on the chemistry of the steroids, a number of excellent monographs devoted to this subject are recommended [4, 15, 25, 29, 44, 50, 51, 53, 85].

1.2 Steroid skeleton types

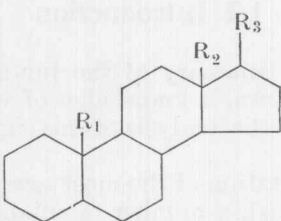
Those naturally occurring or synthetic materials which have a cyclopentanoperhydrophenanthrene skeleton are called steroid compounds. In addition to the steroid hormones, the analysis of which is the subject of this book, the following materials of plant or animal origin belong to this group of compounds: sterols, bile acids, sapogenins, some alkaloids, cardiac glycosides and toad poisons.



The cyclopentanoperhydrophenanthrene skeleton

Angular methyl groups are occasionally present on C-10 and C-13, their carbon atoms being assigned the numbers 19 and 18, respectively: together with the various side-chains attached to C-17, these are of great importance from the point of view of the classification of the steroids. A number of types of skeleton can be derived on the above basis, but most of the steroid hormones belong to the four types given in Table I.

Table I. Main types of skeleton in steroid hormones



	R ₁	R ₂	R ₃
Oestrane	H	CH ₃	H
Androstane	CH ₃	CH ₃	H
Pregnane	CH ₃	CH ₃	C ₂ H ₅
19-Norpregnane	H	CH ₃	C ₂ H ₅

With $R_1 = R_2 = \text{CH}_3$, R_3 can be various other hydrocarbon groups in addition to the ethyl group of pregnanes. Among those skeletons which do not belong to the group of hormones but which are of great importance as starting materials for their production, mention can be made of the cholestane and stigmastane skeletons which occur in the sterols, the cholane skeleton characteristic of bile acids, and the most important skeleton of the saponinins, the spirostane skeleton.

