Steroid Chemistry at a Glance

Daniel Lednicer

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Contents

Preface

The term ‘steroid’ has become virtually synonymous with androgenic–anabolic compounds (mainly analogues of testosterone) to the majority of the public. The sport sections of many newspapers carry almost daily exposés of the usage of these drugs by athletes seeking to enhance their performance. The androgens in question, however, comprise only a single, relatively small, class of biologically active steroids. What may be called the athletic androgens are in reality overshadowed by a large universe of compounds that share the same tetracyclic nucleus. The term ‘androgen’ in fact represents only one-tenth (1.4×10^6 versus 13.5×10^6) of the hits when Googling the term ‘steroid’. The very sizeable number of steroids that are approved by regulatory agencies as therapeutic drugs eclipses the group of legal androgenic–anabolic drugs.

By the 1940s, about a decade after their structure had been firmly established, it became evident that steroids might well comprise a structural lead for drug design. Preliminary results from pharmacological studies, carried out at that time, suggested that selected steroids could potentially lead to drugs aimed at targets as diverse as oral contraceptives on the one hand and inflammation on the other. The potential markets for such drugs spurred major chemical efforts in industrial and to some extent in academic laboratories. Research that led to steroid-based therapeutic agents was carried out largely in the laboratories of ‘Big Pharma’ over the two decades following the end of World War 2. This resulted in the accretion of a large body of organic chemistry often denoted ‘Steroid Chemistry’, and also a sizable number of new therapeutic agents. The assignment of a USAN designation, more familiarly known as a generic name, to a potential drug indicates that the sponsor intends to take the initial steps to assess the clinical activity of the compound. Close to 130 steroids have been assigned official USAN non-proprietary names.

Reports of side-effects that accumulated as the drugs became more widely used led chemists to go back to modify the structures of the offending agent in the hope of producing better tolerated entities. It would be naïve to dismiss the aim of obtaining a place in the market by means of one’s own proprietary and patented entity as additional motivation for that task. It became evident by the mid-1970s that many of the undesired properties, that is, side-effects, were often simply another aspect of the desired hormonal activity. Research aimed at novel steroid-based drugs consequently decreased markedly. The preceding chemical research in the area had by the accumulated a significant body of specialized reactions.

All steroids, be they derived from natural sources or produced by total synthesis, share the same rigid, fixed, three-dimensional framework. Many of the chemical properties of steroids, such as the dependence of the reactivity of functional groups on their specific location, are determined by steric properties of the steroid nucleus. That nucleus incorporates over half a dozen chiral centers not counting the side chain. Cholesterol, for example, can in theory consist of no fewer than 512 stereoisomers. This compound actually occurs as a single chiral species, as do virtually all other steroid-based products. The chemistry of these compounds thus provides a rich source for the study of the effects of stereochemistry on chemical reactivity. The reactivity of a pair of ketones in the same molecule, for example, will often differ markedly due to differences in their steric milieu. Structural features of steroids generally determine biological activity. Steroids with an aromatic A ring will, for example, act as estrogens. Differing structural features found in each of those groups has a marked influence on the reactions and reaction sequences used in preparing potential drugs. A text on steroid chemistry could in theory be organized either on the basis of reactions or alternatively by structural class. Grouping compounds by reaction-based sections it is felt would lead to somewhat jumbled presentations. Many of the organic reaction schemes in used steroid chemistry are characteristic of one or another of the broad structural classes. This volume is accordingly divided into the traditional broad structural chapters. The circumstance that biological activity follows the same organization merely illustrates the concordance of structure and activity.

Rules of nomenclature appear early on in many beginning organic chemistry texts. In somewhat the same vein, the Introduction to this book starts with the conventions for naming steroids. This is followed by a concise account of the molecular mechanism of action by which many steroids exert their biological effects. More detailed descriptions of the activity of these compounds will be found in the opening paragraphs of the individual structural classes.

Chapter 1 describes the history of steroids with particular attention to the research aimed defining the chemical structure of what were at the time fairly complex molecules. The reader may find it convenient to skim over this section at first reading and to then return after acquiring more familiarity with steroid chemistry.

Chapter 2 opens with a description of the biosynthesis of naturally occurring steroids. The conversion of two very different phytochemicals to steroids that can be elaborated to potential drugs follows. The narrative focuses on a discussion of the chemistry whereby these steroidal natural products are modified into steroid starting materials.

Specifically, this describes first the chemistry used to convert diosgenin from Mexican yam roots to dehydropregnenolone and then a discussion of the preparation of pregnenolone from stigmasterol obtained from soybeans.

Chemical manipulations of aromatic A-ring steroids, the estranes, are described in Chapter 3. The relative simplicity of the structure of estranes has led to the development of close to half a dozen syntheses that differ in approach, starting from laboratory chemicals. One of these total syntheses, in contrast to those found in subsequent chapters, is used in actual practice to prepare intermediates for the gonanes discussed in Chapter 4. There follows a description of the process long used to prepare aromatic A-ring steroids from phytochemical-derived sources. Chemical reactions of estranes close this chapter.

The chemistry of gonanes, more familiarly known as 19-nor steroids, constitutes the subject matter of Chapter 4. This chapter opens with a discussion the general methods used to prepare the gonane nucleus. Those methods include two syntheses starting from laboratory chemicals that differ markedly in their approach. The description of the chemistry of the gonanes is divided according the disparate biological activity structural variants. These comprise a section on compounds that act as androgenic–anabolic agents and another that includes progestational agents. This last section includes most of the oral contraceptives. A discussion of the newer 11-arylgonane progesterone antagonist concludes Chapter 4.

The androstanes, often called C-19 steroids in that they include methyl groups at each of the angular carbons at C_{10} and C_{13}, are described in Chapter 6. This section, like the preceding one, also starts with a description of the chemistry used to provide starting material. It also includes a discussion of a total synthesis based on an electrocyclic reaction. The bulk of the chapter comprises of a ring-by-ring description of the chemistry that has been used to prepare modified C-19 androstanes. The bulk of the compounds in this first part of the chapter exhibit androgenic-anabolic activity. Incorporation of a spirobutyrolactone at C_{17} of the C-19 androstanes leads to compounds that act as diuretics as a result of their aldosterone blocking activity. A brief section on those compounds completes Chapter 5.

Pregnanes in essence comprise androstanes that in addition feature a two-carbon side chain, almost exclusively acetyl, at C_{17}. This carbon skeleton is common to both progestins and corticosteroids. Chapter 6 is devoted to a discussion of the chemistry used to prepare derivatives of the simpler of the two, progesterone. Sources of starting materials for modified progestins from both diosgenin and stigmasterol are discussed at the beginning of the chapter. This is followed by a total synthesis that includes a cascade electrocyclization reaction that somewhat resembles the biosynthetic process by which squalane goes to lanosterol. There follows a ring-by-ring examination of the chemistry used to modify the basic pregnane nucleus.

Structurally more complex corticosteroids, commonly called corticoids, are grouped in Chapter 7, the second section on pregnanes. The biological activity of this class of pregnanes depends on the presence of an oxygen atom, either as a ketone or as an alcohol, at C_{11} in ring C. The rarity of this structural feature in Nature placed high priority on developing methods for adding that feature to more abundant steroids from Nature. Chapter 7, as in the preceding chapter, opens with a discussion of the methods that have been developed for preparing the starting 11-oxypreganes required for both clinical supplies and research on analogues. Methods for preparing analogues that include single modifications are considered first. Corticoids comprise one of the rare classes of compounds in which the potentiating effects of structural changes are additive. The closing sections of Chapter 7 discuss the chemistry for preparing compounds with multiple modification.

Groups of steroids that are too small for a full chapter are to be found in the seemingly inevitable chapter termed Miscellaneous. The first section considers steroids in which one of the ring carbon atoms is replaced by a heteroatom, more specifically oxygen or nitrogen. Two compounds in this class, both androstanes, are approved for use in humans. Cardenolides, the steroid-based compounds obtained on removal of the sugars from the so-called cardiac glycosides, are considered in the next section. The chapter closes with a brief discussion of the chemistry involved in modifying the unsaturated cholestanes related to vitamin D.

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Introduction

The isoprene unit (Figure 1) is one of the ubiquitous naturally occurring hydrocarbons. This five carbon latent diene serves as starting material for a host of natural products in both plants and animals. The reactive diphosphate of this five carbon unit, often called isoprene pyrophosphate (IPP), readily couples with itself to form dimers that comprise a bewildering variety of open chain, cyclic, polycyclic and bridged polycyclic compounds known collectively as terpenes. The first coupling product, the straight chain C_{10} dimer may react further by either adding another isoprene or by condensing with other activated terpenes. Products from IPP range all the way at one extreme of a single isoprene to the polyisoprenoid, rubber, at the other extreme.

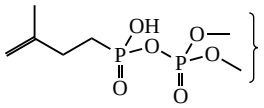


Figure 1 Isoprene unit (isopentenyl diphosphate)

Steroids comprise the singular set of effector molecules, crucial for life processes, derived from one of the multitude of other C_{30} triterpenes (see Chapter 2). These compounds, which arise from further transformations of the triterpene lanosterol, share a common rigid four-ring carbon skeleton. The association of steroids with vertebrates is believed to date back at least 540 million years, as shown by the detection of steroid-derived compounds, called steranes, in ancient fossils. The majority of the endogenous animal steroids are considered hormones since they control various bodily functions at very low concentrations. Estrogens, one of the first groups to be identified, are secreted mainly by the ovary. These compounds control reproductive function in females and also maintenance of female genitalia. Progesterone, secreted by the corpus luteum on that same organ, is involved in many of the same functions as the estrogens and in addition supports pregnancy. The male counterpart to those compounds, testosterone, secreted mainly by the testes, controls the production of sperm and maintains male genitalia; the anabolic, nitrogen-conserving activity of androgens enhances muscle mass. The structurally more complex glucocorticoids, such as cortisone, which are secreted by the adrenal cortex, act on glucose metabolism and to some extent mineral levels in blood. Aldosterone, structurally yet more complex, acts directly on the kidney to maintain electrolytes and blood volume. Ergosterol, which is converted to vitamin D by exposure to sunlight, controls calcium levels and consequently bone health.

Cholesterol, whether ingested or formed endogenously, provides the starting material for the biosynthesis of all the other steroids found in mammals. Excess cholesterol is oxidized in the liver to polar compounds called cholic acids. This process converts the terminal side chain in cholesterol to a carboxylic acid and introduces hydroxyl groups. These polyhydroxylated, steroidal acids play a central role in absorption of fats from the intestine and also excretion of superfluous cholesterol.

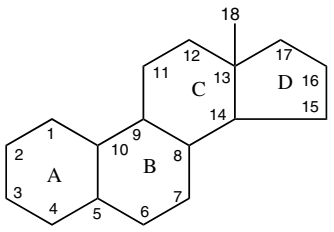
Nomenclature

Structural Bases for Naming Steroids

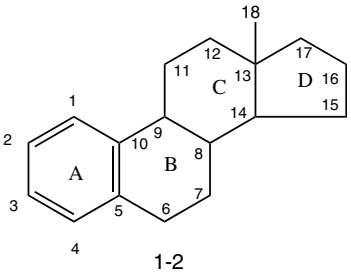
Steroids are designated by names that range from those based on IUPAC rules to the trivial (the term 'trivial' as used in the following paragraphs is not a value judgment but instead notes that the relevant name does not conform to formal naming conventions). The rigorous IUPAC name sidesteps the steroid nucleus entirely, naming these compounds as derivatives of cyclopenta[*a*]phenanthrene; the IUPAC name for estrone, for example, is (8*R*,9*S*,13*S*,14*S*)-3-hydroxy-13-methyl-7,8,9,11,12,14,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17-one. A somewhat less rigorous system names steroids as derivatives of a set of hypothetical steroid hydrocarbons. Steroid chemists, it should be noted, often use watered-down versions of the hydrocarbon system and in addition use colloquial names that are accepted by other scientists working in the same field. As an example, steroids lacking the 19-methyl group are more often designated 19-nor compounds than derivatives of the theoretical gonane hydrocarbon, The names that are used in this volume generally follow the earlier IUPAC convention based on the hypothetical hydrocarbons.

Steroid Chemistry at a Glance Daniel Lednicer

The nuclei that serve as templates for naming steroids are depicted in Scheme 1. The four rings are commonly denoted by the capital letters A, B, C and D reading from left to right. The ring letter designation, it should be noted, is used only in discussion sections of publications as they are have no role in formal nomenclature. The apparently eccentric numbering system used to denote steroid carbon atoms traces back to the days of the major structure determination work and reflects the then uncertainty about the overall structure (see Chapter 1). As noted previously, systematic names for steroids are based on a set of hypothetical hydrocarbons. Omitting the methyl group 19 at position 10, for example, affords gonanes (**1**-**1**) as noted above, more commonly known to practitioners as 19-nor steroids. This nucleus, as noted, serves as the base for several oral contraceptives. Estranes comprise compounds in which ring A is aromatic (**1-2**); these comprise an important part of oral contraceptives. Androstanes, the compounds that support male reproductive function, include a methyl group at position 10 (**1-3**). The other so-called sex hormones, the pregnanes (**1-4**), retain the intact 19 carbon atom nucleus and in addition sport a two-carbon side chain at position 17. The glucocorticoids, best know for their anti-inflammatory activity, are also named as derivatives of pregnane. Nucleus **1-5** (cholestane) depicts the most generalized structure that serves as the base for molecules with larger side chains at position 17, such as cholesterol and ergosterol and their derivatives.



1-1



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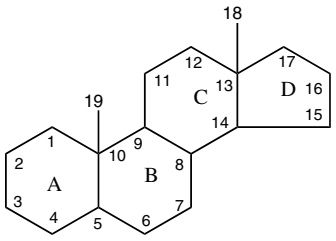

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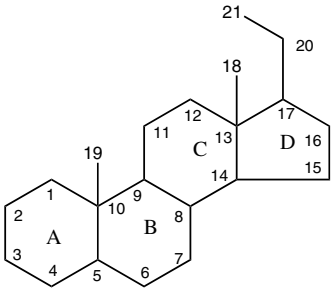
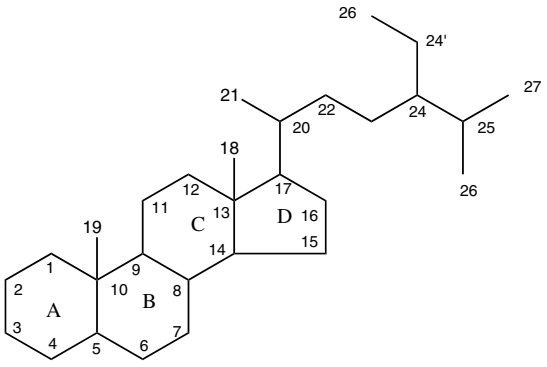


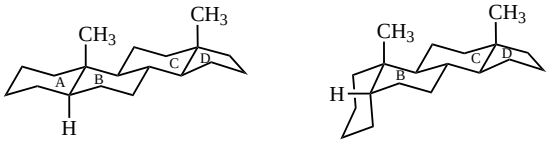
1-4



1-5

Scheme 1

Standard depictions for steroids, such as those in Scheme 1, overlook the three-dimensional nature of the molecule. The structures in Scheme 2 represent the stereochemical arrangement implicit in the more customary formulas. The junction between rings B and C and also that between rings C and D involve transoid stereochemistry. It is of note in passing that the latter in fact comprises a disfavored *trans* hydrindane fusion. The ring junction between rings A and B is also transoid but can in selected cases assume a cisoid configuration (**2-2**). Note further that the stereochemical

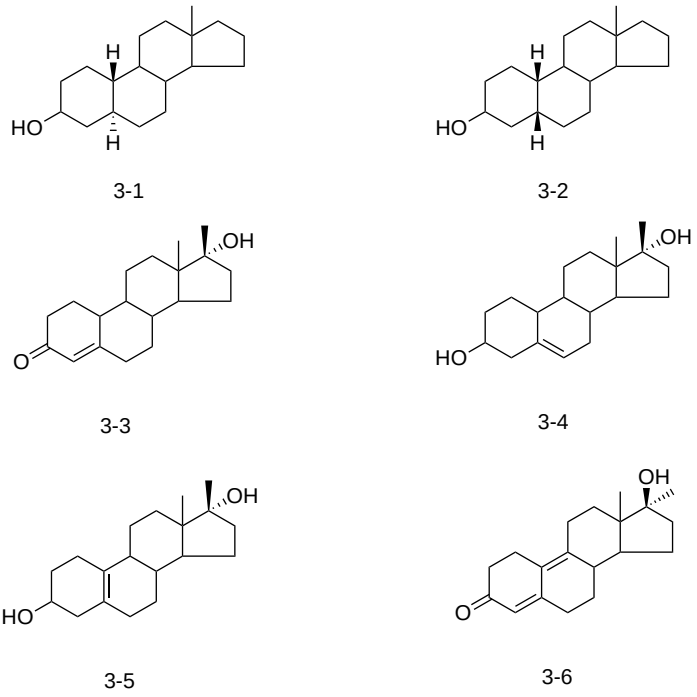


Scheme 2

depictions **2-1** and **2-2** in fact also present the absolute configuration of steroids from natural sources. This assignment is supported by detailed X-ray crystallographic studies. The founders of steroid chemistry can be said to have picked the correct depiction from a 50:50 choice. Substituents below the plane of the molecule are designated α, and those above are named β. The plane of the paper serves as the plane of the molecule for customary depictions.

Gonanes

Many if not most organic compounds are named as derivatives of some appropriate hypothetical hydrocarbon. This convention also holds true for steroids. Trivial names, other than those for 19-nor compounds, are uncommon in the gonane series, since these compounds have virtually no counterparts in Nature. The stereochemistry of the product to be named is assumed to be the same as that of the hydrocarbon. The arrangement is, however, made explicit for positions that can vary, for example, substituents at positions 3 and 5 in gonane **3-1** (Scheme 3). Proceeding systematically, compound **3-1** is a gonane with a hydroxyl at the 3-position oriented above the plane of the molecule, thus provisionally gonan-3β-ol. The hydrogen at carbon 5 can occur in either one of two orientations; the two resulting compounds are considered to be different systems for nomenclature. The hydrogen in this particular compound is oriented below the plane, assigning it to the 5Hα-gonane class. Compound **3-1** is thus named 5*H*α-gonan-3β-ol. Compound **3-2** differs from the foregoing in the *cis* rather than *trans* fusion of rings A and B, with the result that hydrogen a position 5 is now β. This steroid is thus named 5*H*β-gonan-3β-ol.



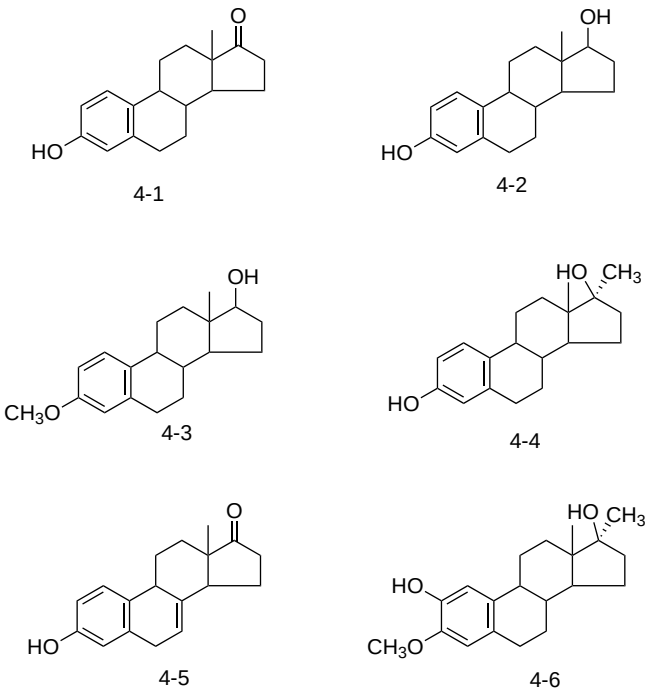
Scheme 3

Carbonyl groups are denoted by 'one' as in simpler non-steroidal compounds. The name for **3-3** thus starts as gonan-3-one. A double bond is indicated as an 'ene' and numbered for the lowest carbon that encompasses the unsaturation. This changes the name to gon-3-en-4-one. Taking into account the substitution on carbon 17, we get 17β-methyl-17α-hydroxygon-4-en-3-one. Proceeding in the same manner, the name for **3-4** becomes 3β,17α-dihydroxy-17β-methyl-gon-5-ene. Both termini of a double bond; with the higher in parentheses, are indicated in the name when they cannot be numbered sequentially. The isomer of the foregoing in which the double bond includes both bridgehead carbon atoms will be named 3β,17α-dihydroxy-17β-methylgon-5(10)-ene.

The methyl group at position 13 is replaced by ethyl in a series of gonanes prepared by total synthesis. One approach for naming for **3-6** posits deleting the methyl group at 17 by the notation '13-nor' and then putting in place an ethyl fragment: 17β-methyl-18-nor-13-ethylgon-4-en-3-one. The preferred name in a 1989 IUPAC publication simply elongates the methyl group by one carbon and designates the new group by the term 'homo'; **3-6** thus becomes 18-homo-17β-methylgon-4-en-3-one.

Estranes

Estrogenic activity in mammals is mediated by several estranes. A good number of these compounds are better known by their trivial as opposed to systematic names. The estrane nucleus is fairly similar to a gonane in that the double bonds in ring A are actually enumerated. Structure **4-1** (Scheme 4) thus becomes estra-1,3,5-trien-17-one. This steroid is far better known as estrone. Its reduced counterpart **4-2** is named estra-1,3,5-triene-3,17β-diol. The more prevalent name for this compound is estradiol or, somewhat less commonly, β-estradiol, The isomer with the hydroxyl group below the plane of the paper is named estra-1,3,5-trien-17α-ol or α-estradiol. The systematic name for the methyl ether of estradiol becomes 3-methoxyestra-1,3,5-trien-17β-ol. The product **4-4** from alkylation at position 17 can be named 17β-methylestra-1,3,5-trien-17α-ol. That compound is also known as equilin, a name derived from the fact that it was first isolated from horse urine. An additional double bond as in **4-5** is simply added to three already present, thus estra-1,3,5,7-tetraen-17-one. Additional substituents on the aromatic ring as in **4-6** are simply enumerated. The systematic name for this compound thus becomes 3-methoxy-17α-methylestra-1,3,5-triene-2,17β-diol.



Scheme 4

Androstanes

Continuing the perusal of the steroid sex hormones leads to the series that has had extensive coverage in the popular press. The hypothetical hydrocarbon that forms the nucleus for this series features the full four-ring nucleus with methyl groups at both bridgehead carbon atoms. Applying rules similar to those used above, the formal name for compound **5-1** (Scheme 5) becomes 17β-hydroxyandrost-4-en-3-one. This steroid is again far better known by its trivial name testosterone. The double bond in testosterone is reduced *in vivo* to afford 5*H*α,17β-hydroxyandrost-3-one (**5-2**), a compound that is significantly more potent than its precursor (**5-1**); this compound may well be the proximate hormone. The steroid from adding a methyl group at position 17 will be named 17α-methyl-17β-hydroxyandrost-4-en-3-one. Compound **5-4**, 3β-hydroxyandrost-5-en-17-one, is the widely used 'health supplement' dihydroepiandrosterone, abbreviated as DHEA. Substitution at position 6, as will be noted later, often increases potency. One such androgen, **5-5**, will be named 7α-methyl-17β-hydroxyandrost-4-en-3-one. Multiple