

# **Steroids, Lipids and Prostaglandins**

(<http://holivo.pharmacy.uiowa.edu/46131/>)

Pharmacodynamic Agents

MNPC II (46:131), Fall 2001

Instructor: Horacio F. Olivo, Ph.D. (horacio-olivo@UIowa.Edu)

## **I. INTRODUCTION**

## **II. STRUCTURE & NOMENCLATURE**

- A. Cyclopentanoperhydrophenanthrene nucleus
- B. Cyclohexane
  - 1. Forms: chair and boat
  - 2. Substituents: axial and equatorial
- C. Decalins
  - 1. cis vs. trans
- D. Steroids
  - 1. Numbering and ring letters
  - 2. Angular methyl groups
  - 3. alpha and beta terminology
  - 4. Trans (anti) vs. cis (syn)

## **III. LIPIDS AND PROSTAGLANDINS**

- A. Simple Lipids: i) Fats and Oils, ii) Waxes
- B. Conjugated (complex) lipids
- C. Fatty Acids
  - 1. Biosynthesis via acetate-malonate pathway
  - 2. saturated vs. unsaturated fatty acids
    - a. cis-trans isomerization
    - b. polyunsaturated
    - c. prostaglandins

## **IV. CHOLESTEROL**

- A. Introduction
  - a. Functions of cholesterol in the body
  - b. Distribution
- B. Synthesis
  - i. mevalonic acid formation
  - ii. squalene formation
  - iii. cyclization and processing
- C. Cholesterol metabolism
  - 1. Bile acids and their glycine and taurine conjugates
  - 2. Therapeutic agents
- D. Cholesterol levels

## **V. ANTILIPEMIC AGENTS**

- A. Types of Hyperlipidemias
- B. Drugs that lower concentration of plasma lipoproteins
- C. Bile-Acid binding resins

## VI. STEROID HORMONE BIOSYNTHESIS

- A. Pregnelonone
- B. Progesterone
- C. Adrenocorticoids
- D. Androgens
- E. Estrogens

## VII. ADRENOCORTICOSTEROIDS

- A. General Information
- B. Natural Hormones
- C. Structure Activity Relationships
- D. Products

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- A. Natural Hormones
- B. Conjugated estrogens
- C. Structure Activity Relationships
- D. Estrogen Products
- E. Non-steroidal Estrogens
- F. Antiestrogens
- G. Estrogen Derivatives as antitumoral agents

## IX. PROGESTINS

- A. General Information
- B. Natural Hormones
- C. Structure Activity Relationships
- D. Products
- E. Oral contraceptives

## X. ANDROGENS

- A. General Information
- B. Natural Hormones
- C. Structure Activity Relationships
- D. Products

## Bibliography

Principles of Medicinal Chemistry; William O. Foye, Thomas L. Lemke, and David A. Williams; Fourth Edition; 1995; Chapter 23.

Hypercholesterolemia -- Another Silent Killer, Kathryn K. Bucci, *Am. J. Pharm. Educ.* **1992**, *56*, 186.

Cholesterol-Lowering Drugs, Manssur Yalpani, *Chem. and Ind.* **1996**, *3*, 85.

The Role of Birth Control in the Survival of the Human Race. Rudolf Wiechert. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 506-513.

Steroid Industry Honored. Raber, L. *Chem. Eng. News* **1999**, *77*(43), 78-80.

# STEROIDS, LIPIDS, PROSTAGLANDINS

- I. Introduction
- II. Structure and Nomenclature
- III. Lipids and Prostaglandins
- IV. Cholesterol
- V. Antilipemic Agents
- VI. Steroid Hormone Biosynthesis
- VII. Adrenocorticosteroids
- VIII. Estrogens
- IX. Progestins
- X. Androgens

## II. STRUCTURE & NOMENCLATURE

### A. Cyclopentanoperhydrophenanthrene nucleus

### B. Cyclohexane

1. Forms: chair and boat
2. Substituents: axial or equatorial

### C. Decalins

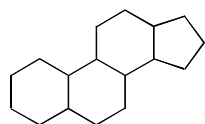
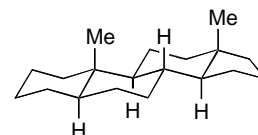
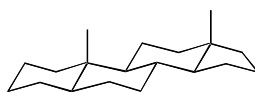
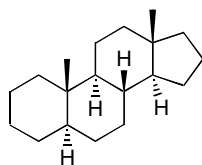
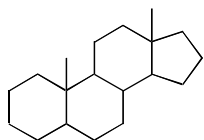
1. *cis* versus *trans*

### D. Steroids

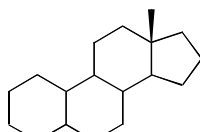
1. Numbering and ring letters
2. Angular methyl groups
3. and terminology
4. *Trans* (anti) versus *cis* (syn)

### E. Nomenclature

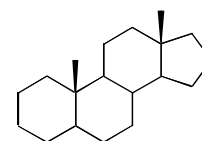
1. Common names for saturated hydrocarbon skeleton
2. Substituent nomenclature
3. Examples



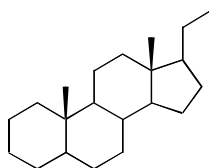
gonane 17 C's



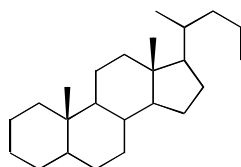
estrane 18 C's



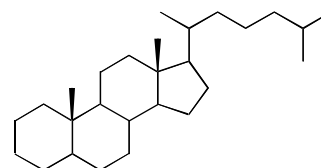
androstane 19 C's



pregnane 21 C's



cholane 24 C's

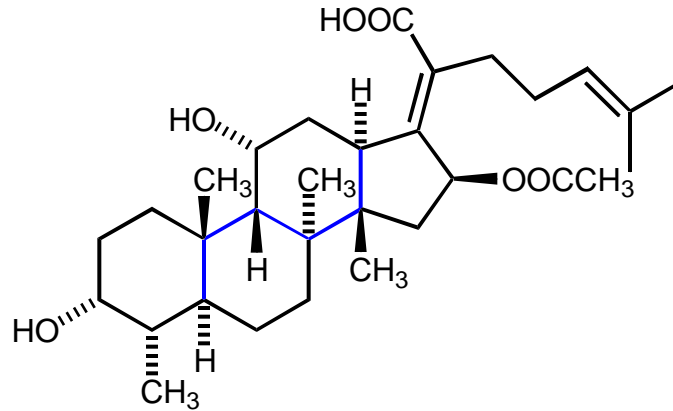


cholestane 27 C's

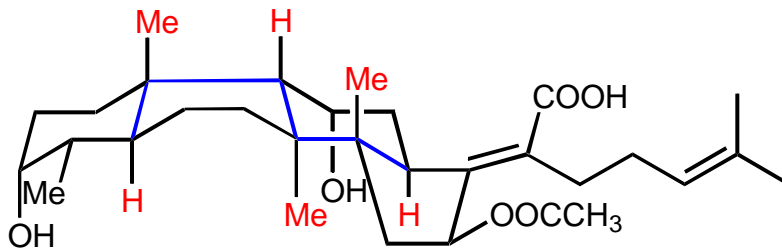
# Fusidic Acid

isolated from *Fusidium coccineum*

employed in European countries for staphylococcal infections



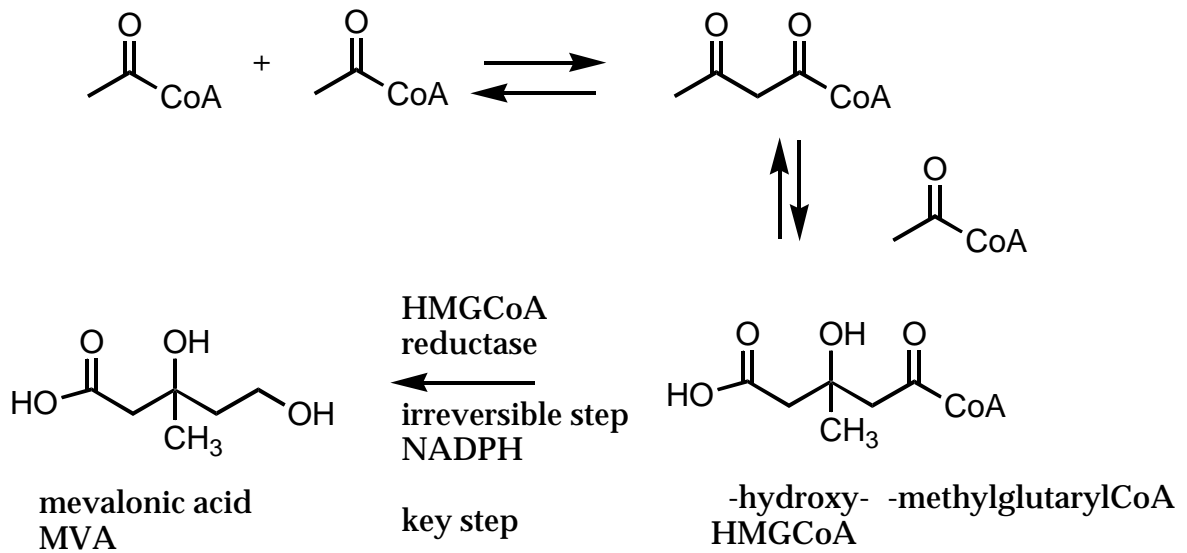
3,11,16-trihydroxy-4,8,14-trimethyl-18-nor-5,8,9,13,14-cholesta-17(20),24-dien-21-oic acid 16-acetate



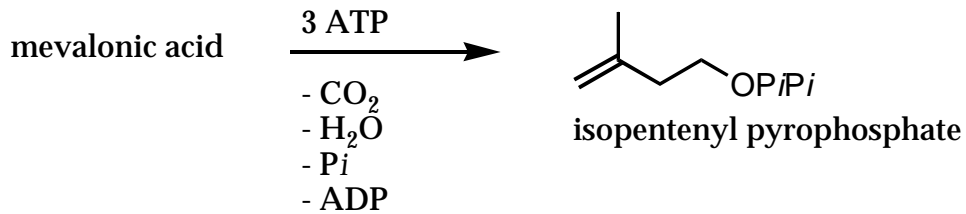
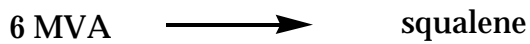
Stereochemical Relationship of the Steroid Skeleton:

<u>trans</u>	<u>syn</u>	<u>trans</u>	<u>anti</u>	<u>trans</u>
C5-C10	C10-C9	C9-C8	C8-C14	C14-C13

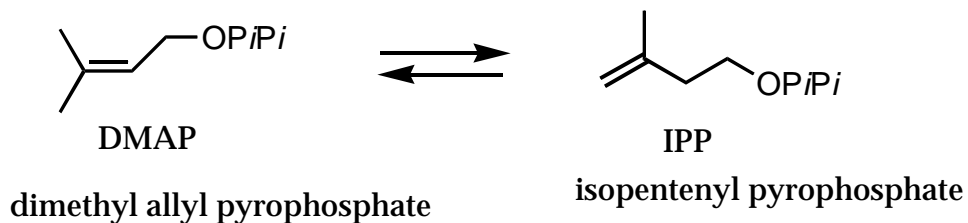
## Mevalonic Acid Formation



## Squalene Formation



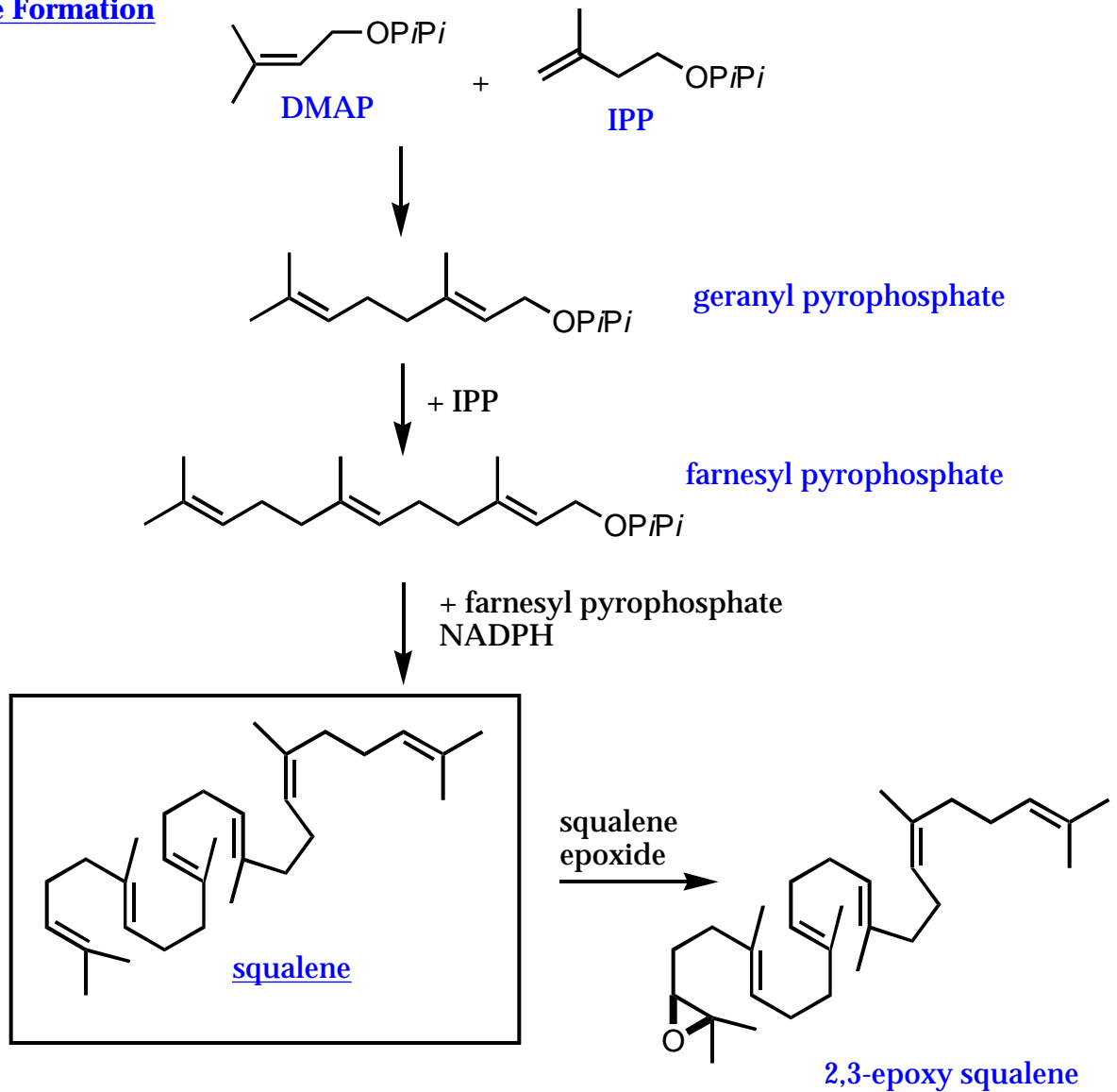
Biological isoprene compounds:



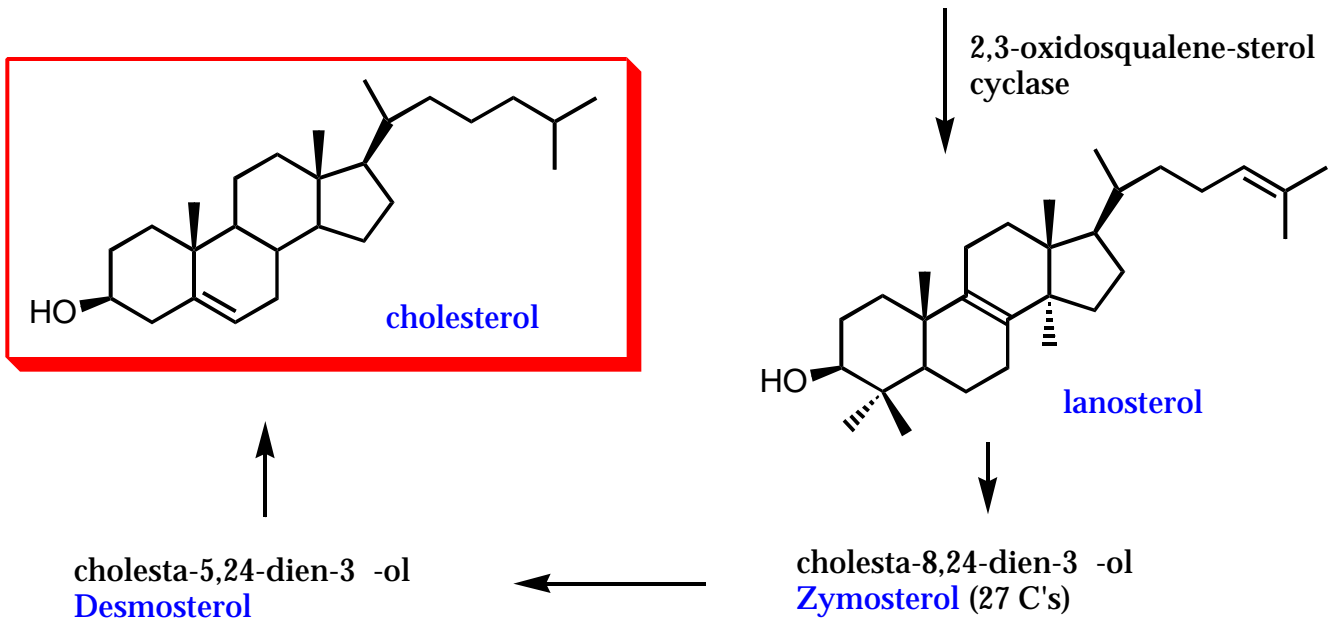
plants: carotenoids & rubber  
 Man: cholesterol

IPP + DMAP condense in a head to tail fashion to form geranyl pyrophosphate

## Squalene Formation

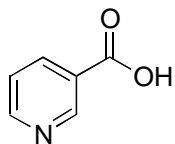


## Cyclization and processing



**Hypolipidemic Agents****A. Drugs that lower concentration of plasma lipoproteins**

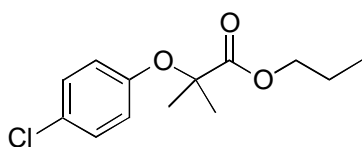
## 1. Nicotinic Acid (Niacin)



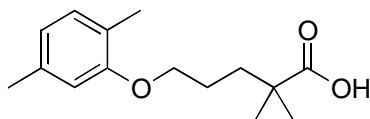
## 2. Clofibrate (Atromid-S)

Chemical Name:

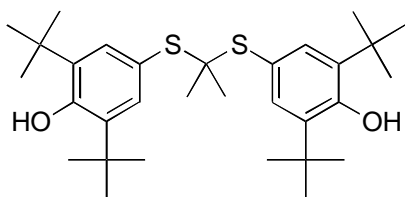
ethyl-2-(4-chlorophenoxy)-2-methylpropionate isobutyric ester



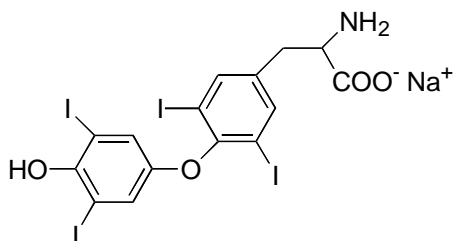
## 3. Gemfibrozil (Lopid)



## 4. Probucol (Lorelco)



## 5. Dextrothyroxine Sodium (choloxin)



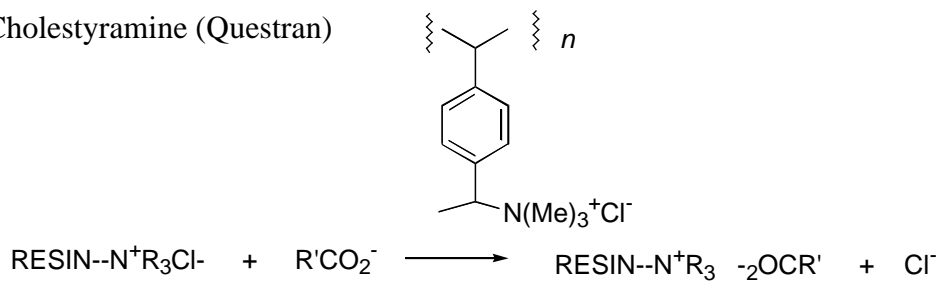
## Hypolipidemic Agents

### B. Bile-Acid Binding Resins

#### 6. Colestipol (Colestid)

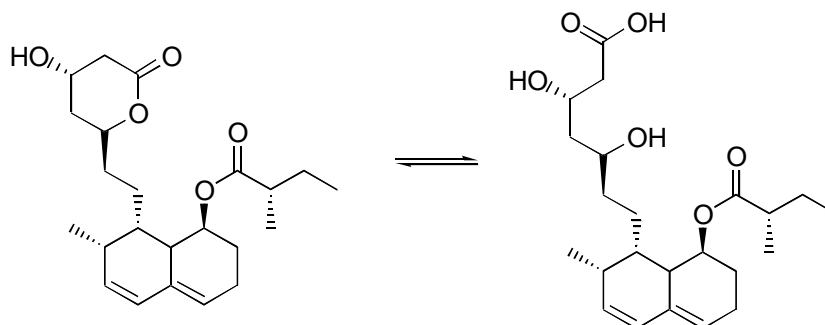


#### 7. Cholestyramine (Questran)

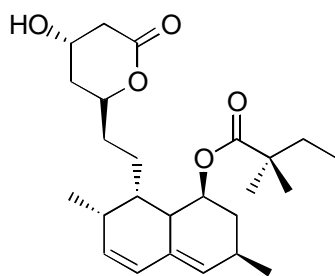


### C. HMG CoA Reductase Inhibitors

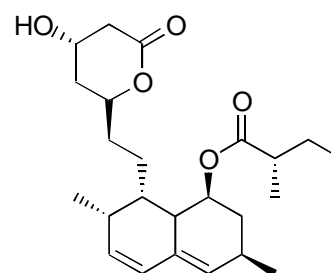
#### 8. Mevastatin



#### 9. Simvastatin

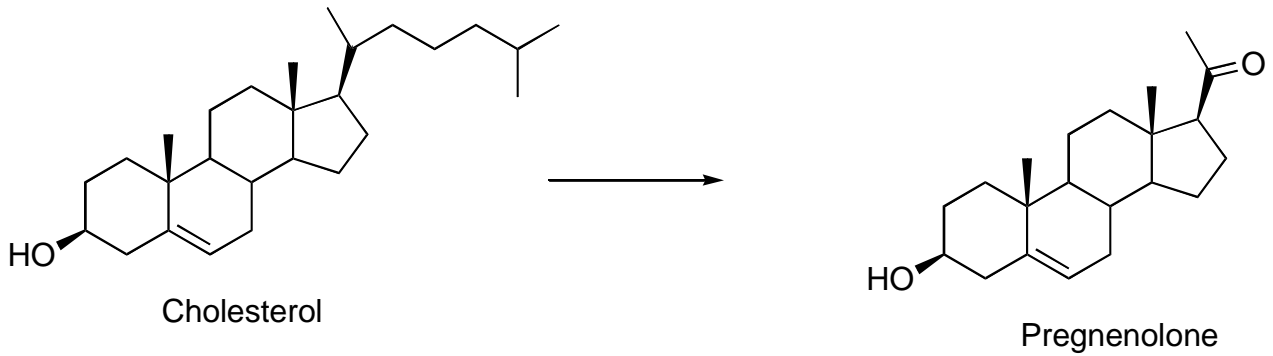


#### 10. Lovastatin

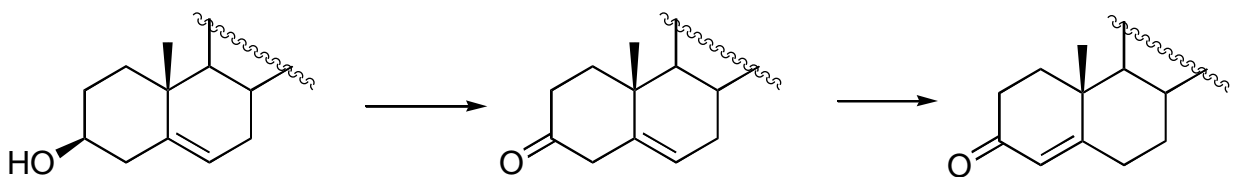
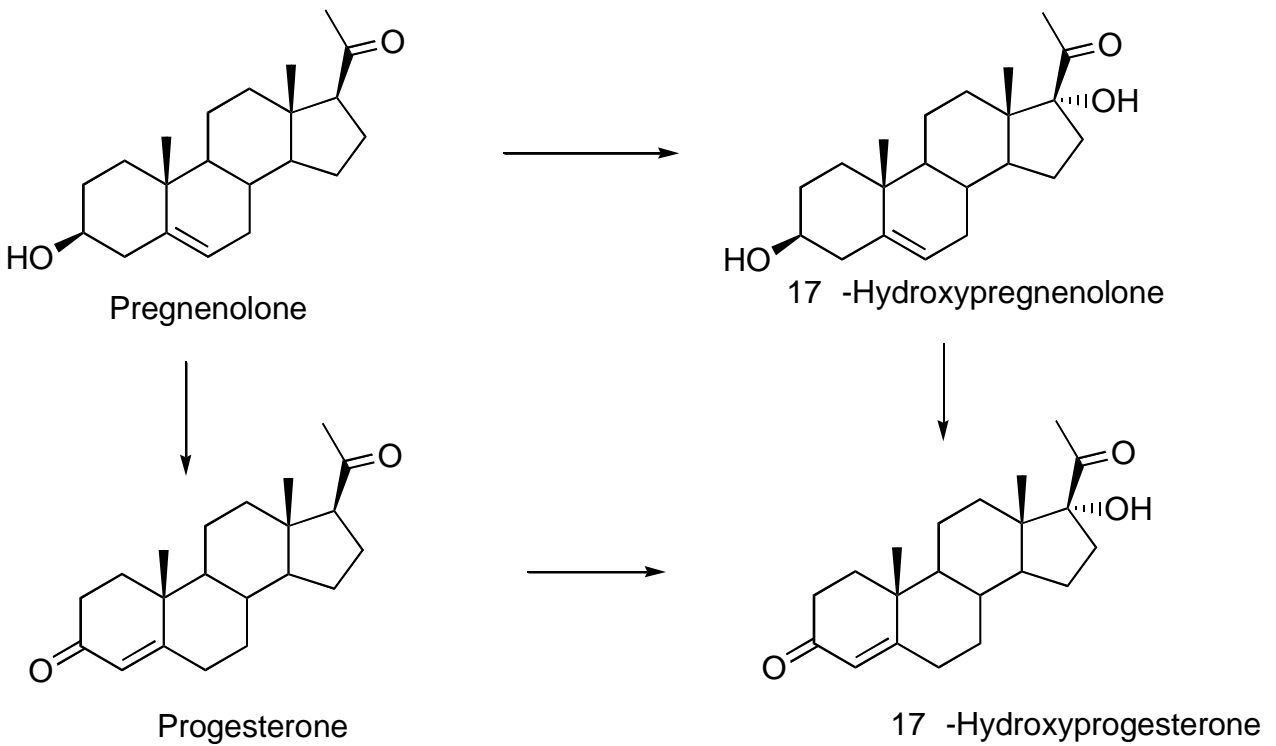


## VI. STEROID HORMONES. BIOSYNTHESIS

### A. PREGNENOLONE

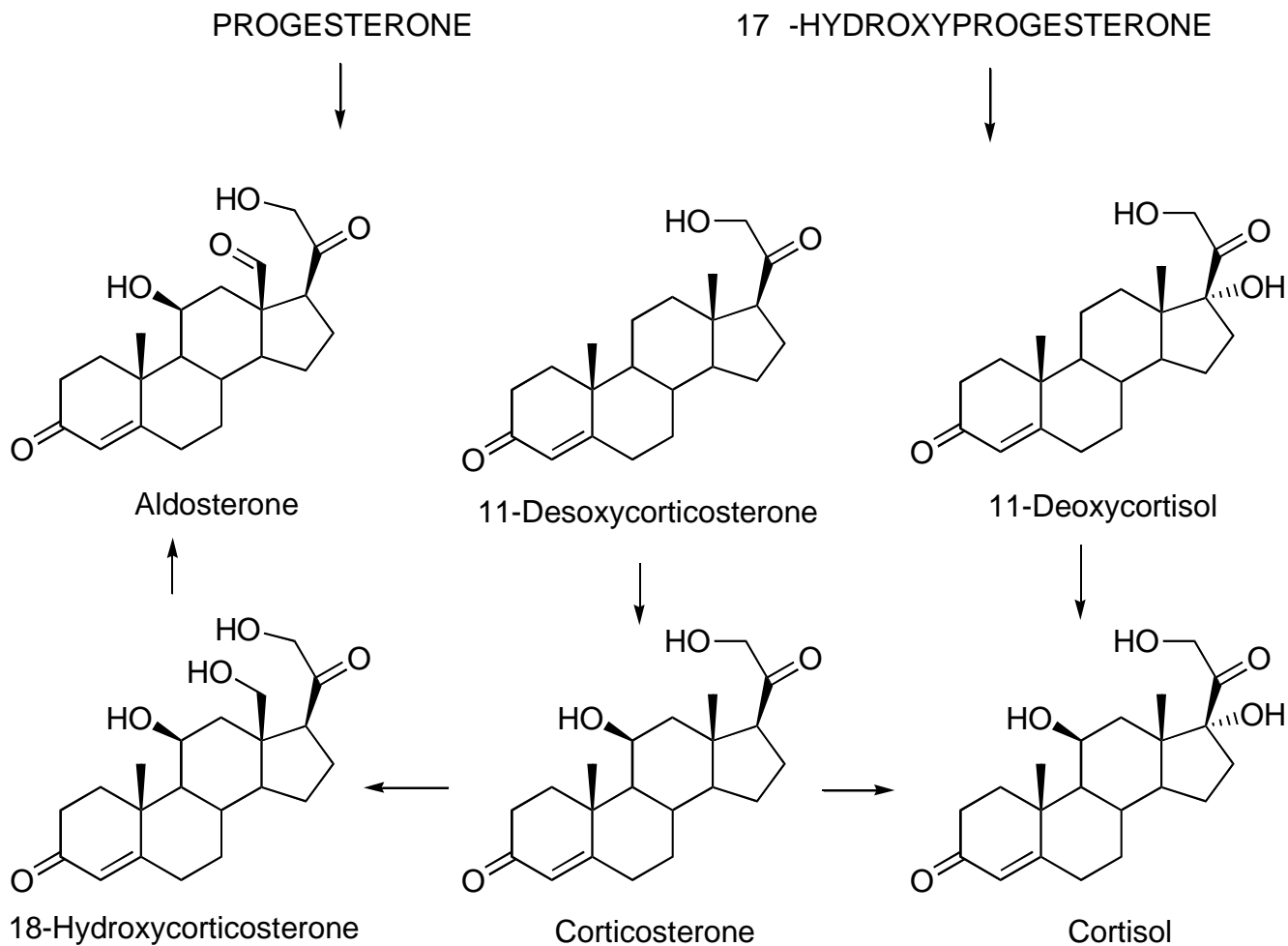


### B. PROGESTERONE

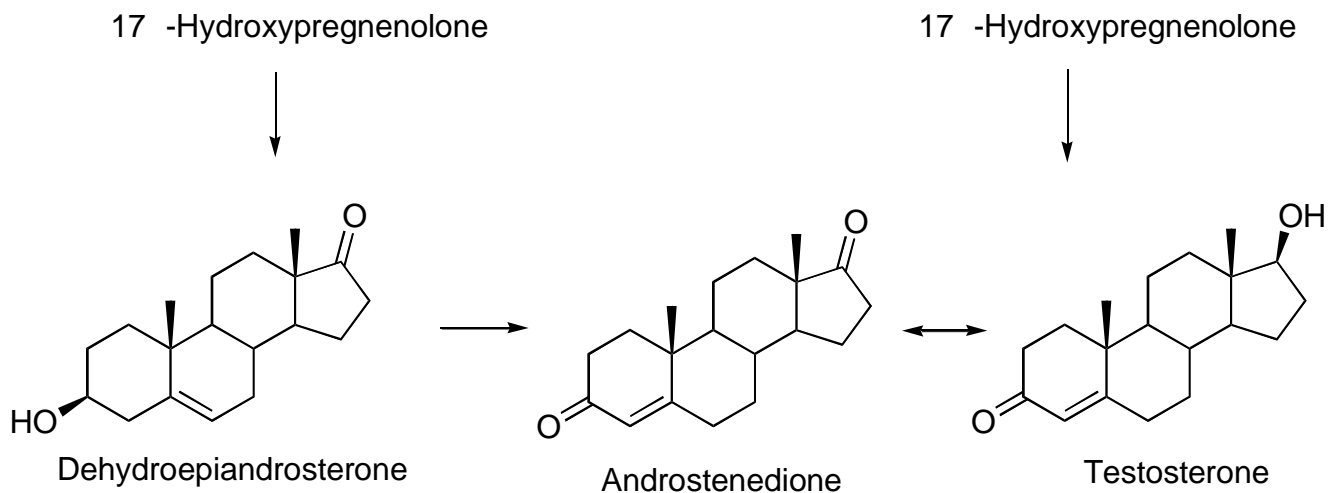


## C. ADRENOCORTICOCIDS

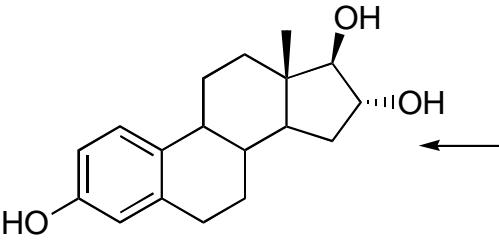
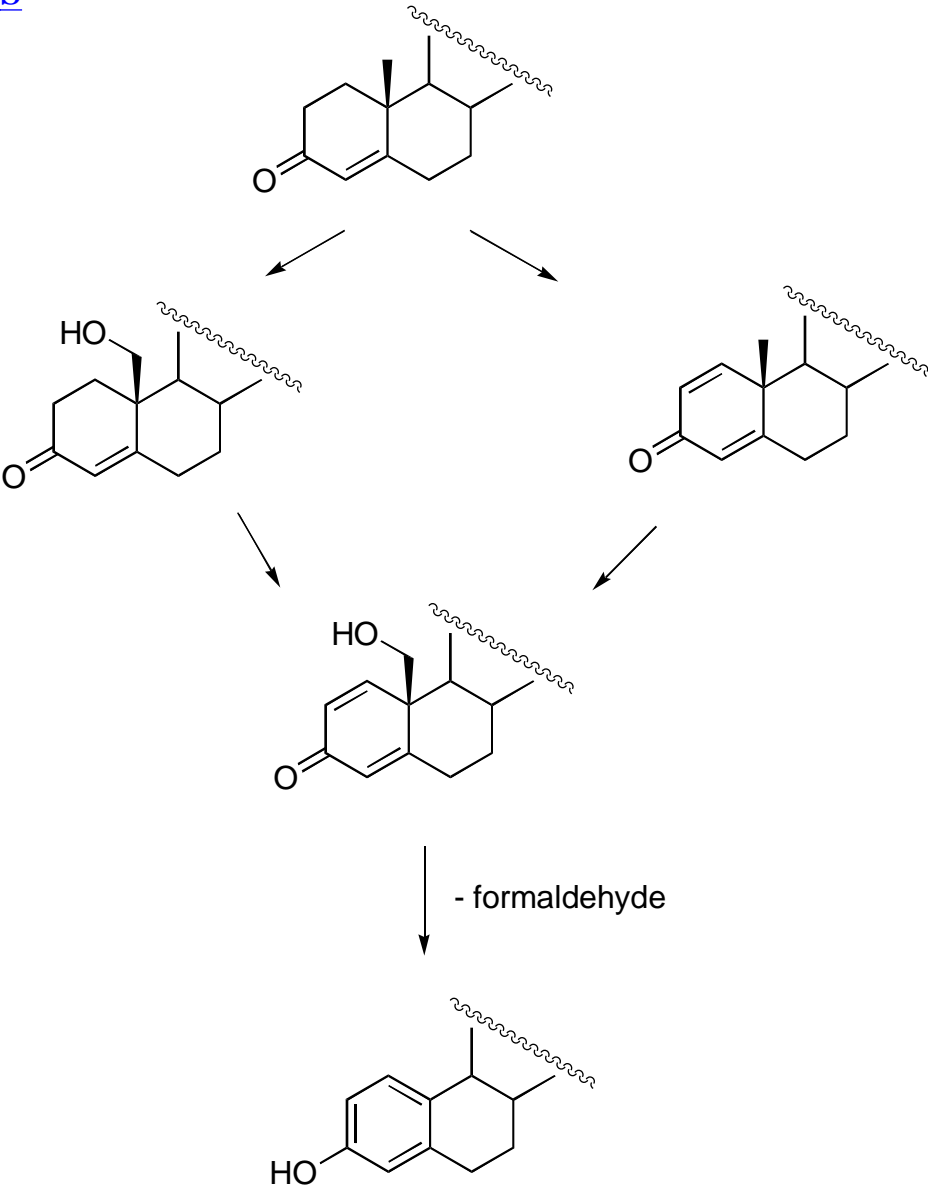
1. Oxidation of 3-OH and Isomerization to  $\Delta^4$ -unsaturated ketone
2. Hydroxylation at C-21, C-11, C-17a, and/or C-18
3. Oxidation of 18-OH to aldehyde



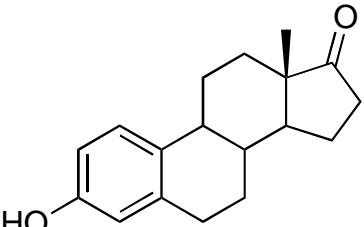
## D. ANDROGENS



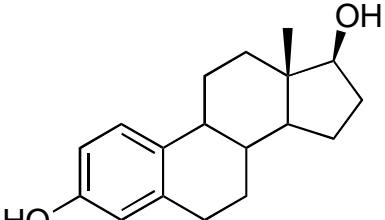
**E. ESTROGENS**



Estriol

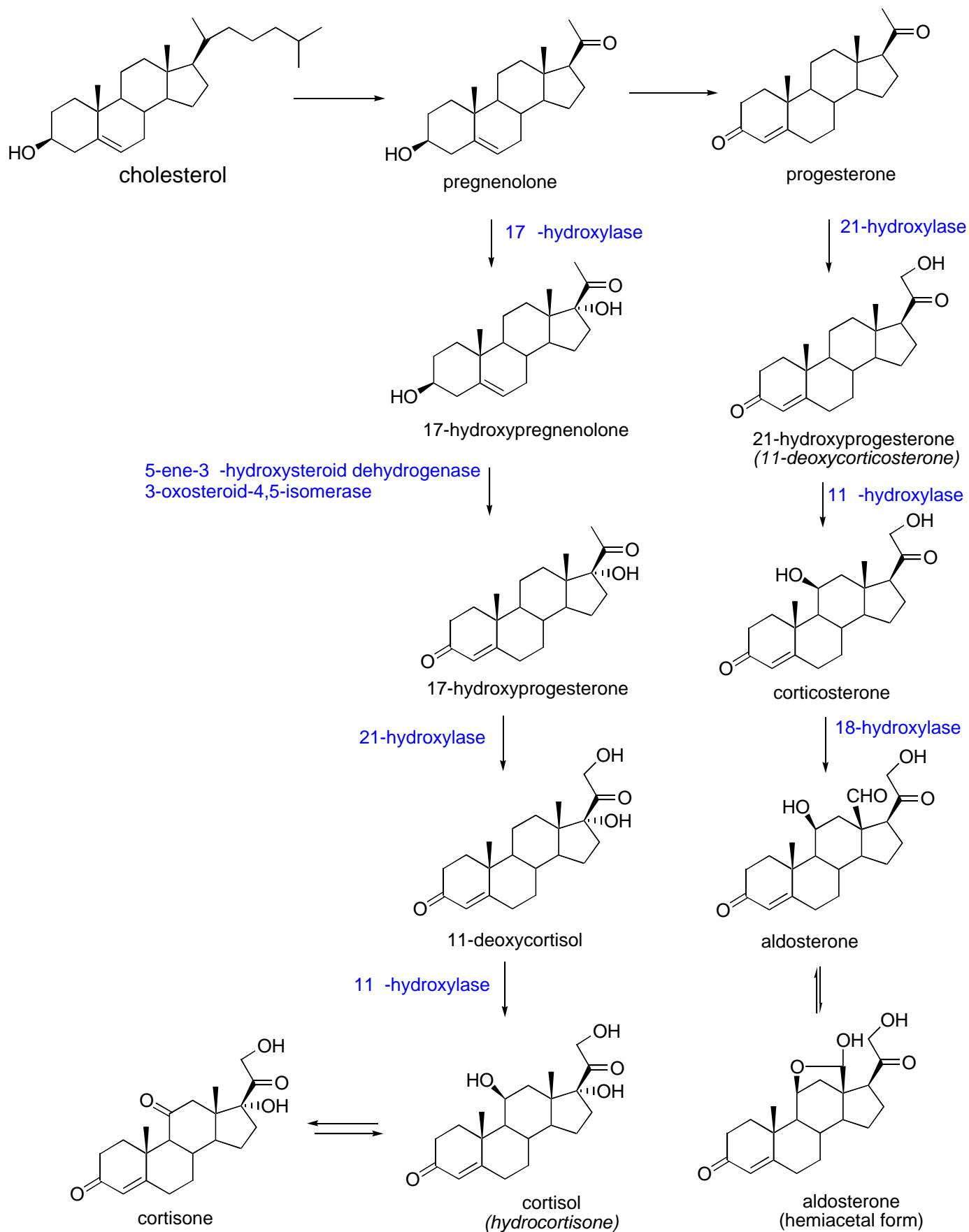


Estrone

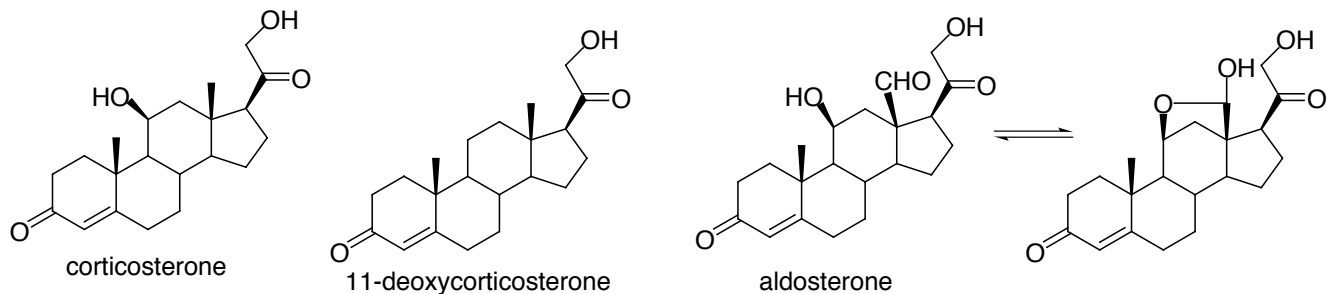


Estradiol

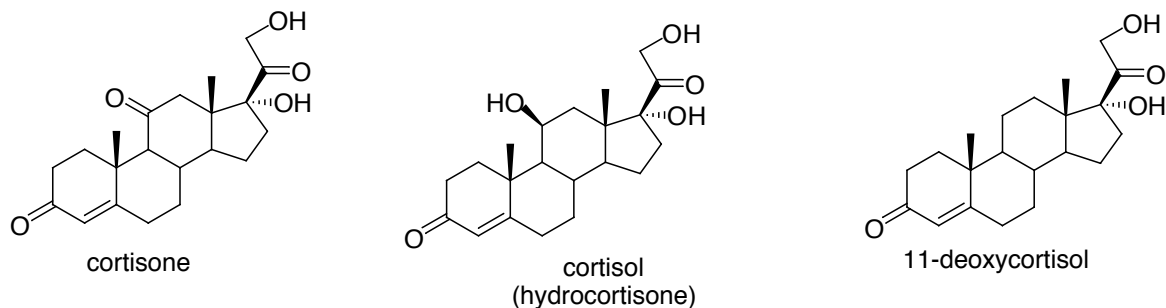
## VII. Adrenocorticosteroids



## Mineralcorticoids



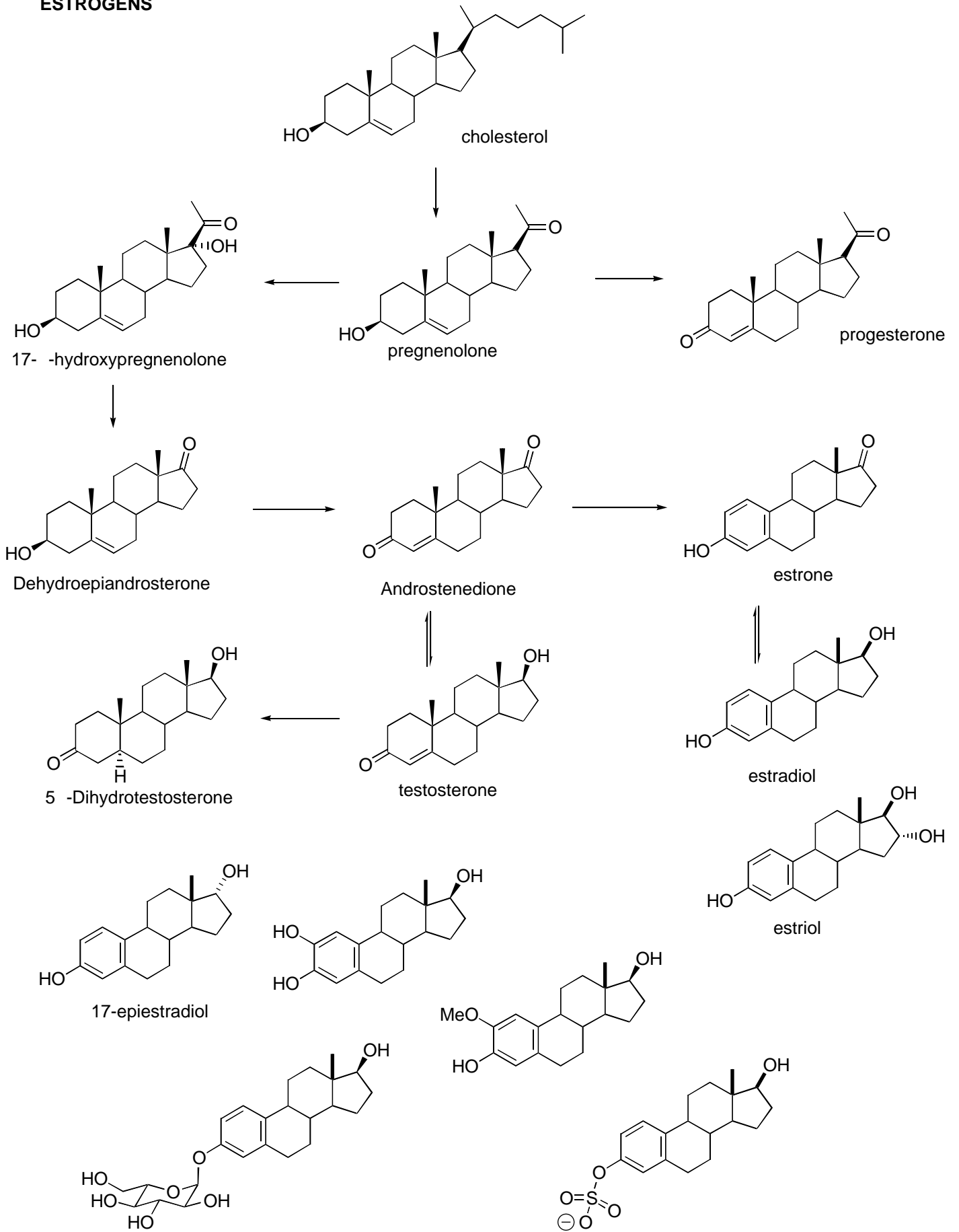
## Glucocorticoids



Aldosterone	11 $\beta$ ,21-dihydroxy-3,20-dioxopregn-4-en-18-al
11-Deoxycorticosterone	21-hydroxypregn-4-en-3,20-dione
Corticosterone	11 $\beta$ ,21-dihydroxypregn-4-en-3,20-dione
Cortisol	11 $\beta$ ,17 $\alpha$ ,21-trihydroxy-pregn-4-en-3,20-dione
Cortisone	17 $\alpha$ ,21-trihydroxy-pregn-4-en-3,11,20-trione

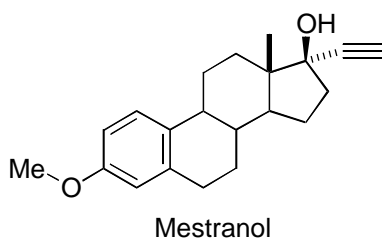
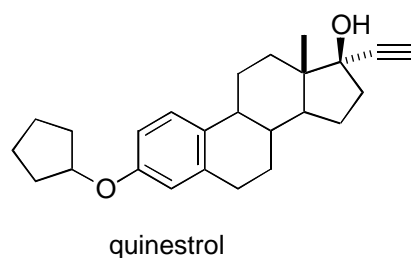
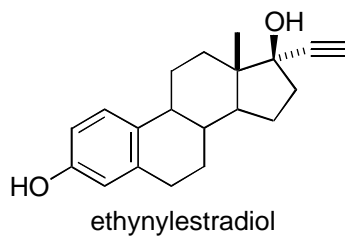
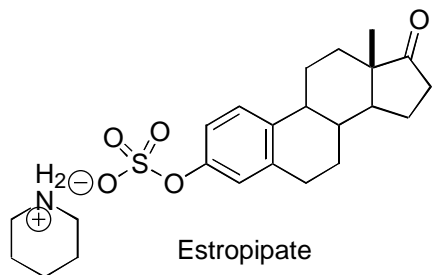
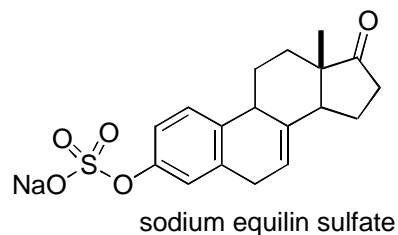
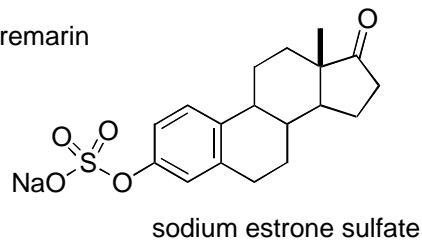
Adrenocorticoid	Mineralocorticoid Activity	Glucocorticoid Activity
Hydrocortisone	1.0	1.0
Cortisone	0.8	0.8
Prednisone	0.6	3.5
Prednisolone	0.6	4.0
Methylprednisolone	0	5.0
Triamcinolone	0	5.0
Paramethasone	0	10.0
Dexamethasone	0	30.0
Betamethasone	0	35.0
Fludrocortisone	800	10.0
Fluprednisolone	0	10.0
Aldosterone	800	0.2
11-Desoxycorticosterone	40	0
Corticosterone	5	0.5

# ESTROGENS

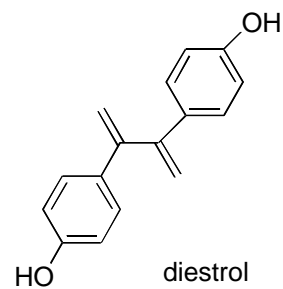
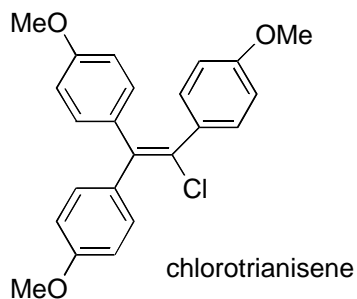
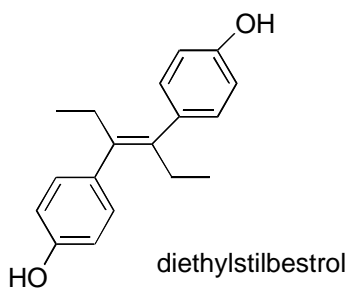


## ESTROGENS

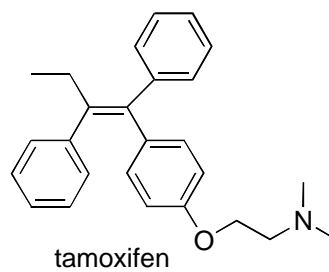
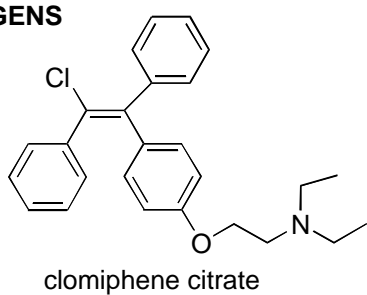
Premarin



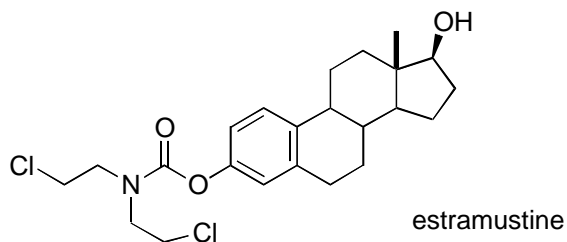
## NON-STEROIDAL ESTROGENS



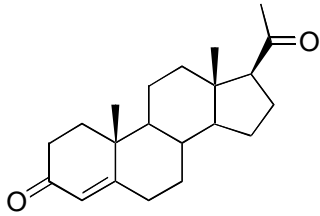
## ANTIESTROGENS



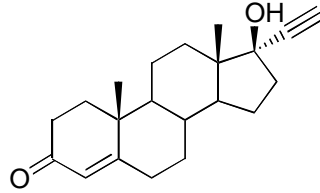
## ESTROGEN DERIVATIVES AS ANTITUMOR AGENTS



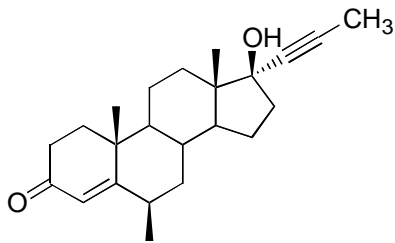
# Oral Contraceptives Hand-Out



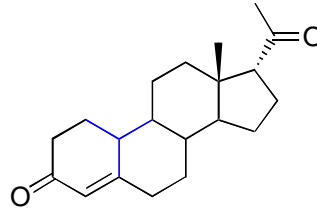
progesterone  
natural contraceptive



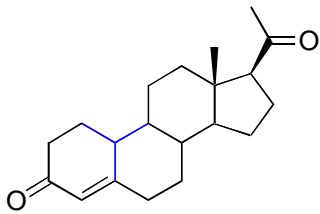
ethisterone



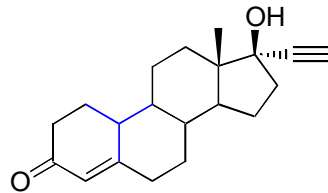
dimethisterone



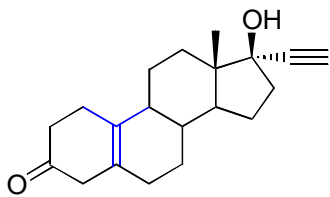
19-nor-14,17 -pregn-4-ene-3,20-dione



19-norprogesterone

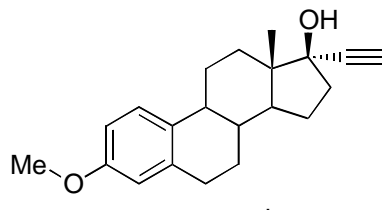


norethindrone

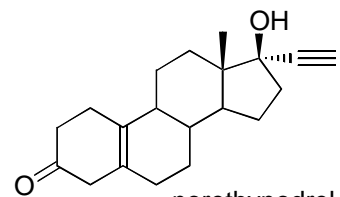


norethynodrel

First oral contraceptive

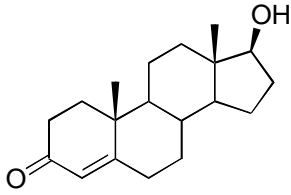


mestranol

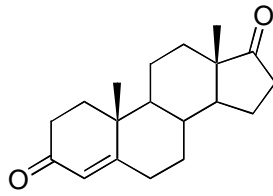


norethynodrel

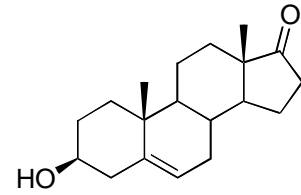
# Androgens Hand-out



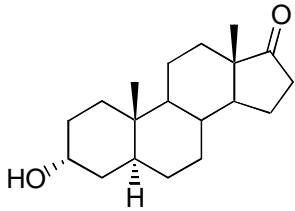
testosterone



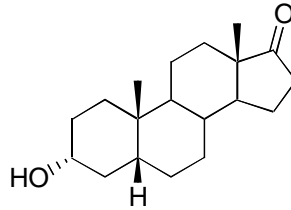
androstenedione



dehydroepiandrosterone

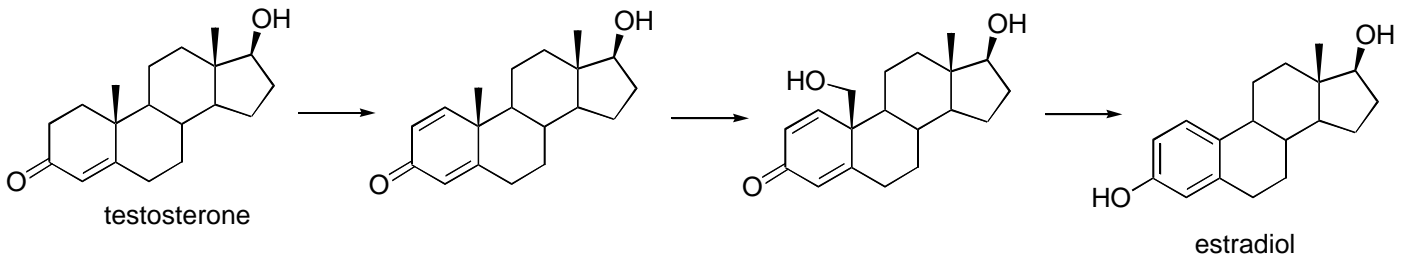


androsterone



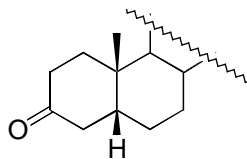
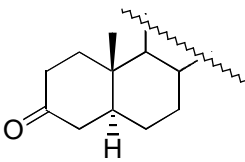
ethiocholanolone

## Metabolism of testosterone:

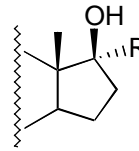


## Structure-Activity-Relationships:

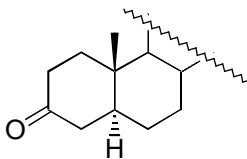
A.



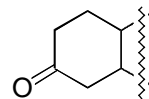
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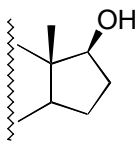
B.



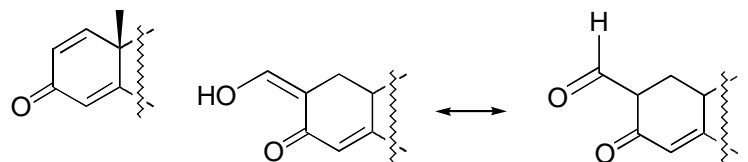
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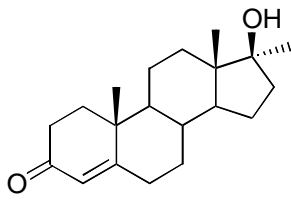
C.



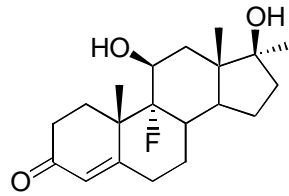
F.



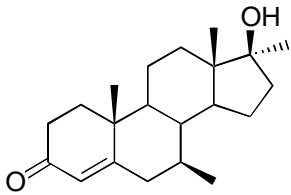
# Androgens



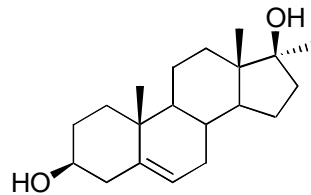
**Methyltestosterone**  
**Metandren**



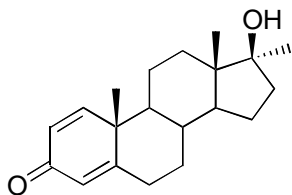
**Fluoxymesterone**  
**Halotestin**



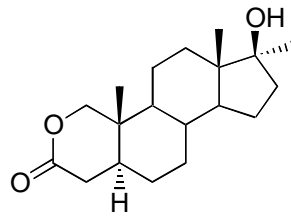
**Calusterone**  
**Methosarb**



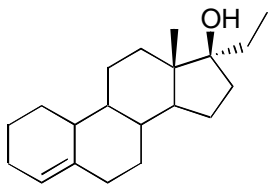
**Methandriol**  
**Anabol**



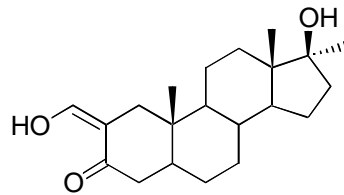
**Methandrostenolone**  
**Dianabol**



**Oxandrolone**  
**Anavar**



**Ethylestrenol**  
**Maxibolin**



**Oxymetholone**  
**Anadrol, Adroyd**