

Brotherton



Sex
Hormone
Pharmacology

SEX HORMONE PHARMACOLOGY

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PREFACE

This is the first book to describe the modern usage of sex hormone products. The products described are those available in the United Kingdom at the time of writing, although the usage of some pending products is also described. In this rapidly expanding field, new products are constantly being added world-wide and under a variety of different trade names. Some of the more common foreign trade names are indicated for some of the products described. I would like to thank most warmly Dr. K. Fotherby, Reader in Steroid Biochemistry, The Royal Postgraduate Medical School, Hammersmith, London for reading the manuscript most attentively and making many helpful suggestions.

July 1976

J. BROTHERTON

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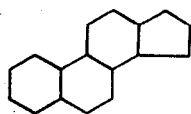
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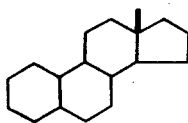
I. STRUCTURE AND NOMENCLATURE OF SEXUAL STEROIDS

A. GENERAL

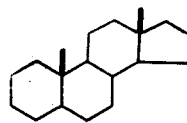
The basic steroid structure is the hydrated four-ring system of cyclopentano-perhydro-phenanthrene, in which the five-sided ring D is attached to the three six-sided rings of phenanthrene.^{1,2,3} In representing the structural form of steroids, the hydrogen and carbon symbols are omitted from the nucleus unless their precise stereochemistry must be defined. The carbon atoms of the basic ring structure are numbered 1-17, and those of the side-chain occurring in the sex-hormones are: 18 for the carbon atom attached to No. 13, 19 for the carbon atom attached to No. 10, and 20 and 21 for the side-chain attached to 17 (Fig. 1.1). All the sex hormone steroids are derivatives of gonane (for norgestrel only), oestrane (for the oestrogens), androstane (for the androgens) and pregnane (for the progestogens, although some progestogens may be derivatives of androstane and oestrane). The presence of double bonds in the rings is



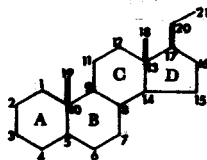
Gonane



Estrane



Androstane



Pregnane

Fig. 1.1. Parent hydrocarbons showing the numbering of the steroid molecule.

indicated by changing the suffix from -ane to -ene and indicating the position of the double bond by a number, e.g., 4-pregnene. Substituents in the rings are indicated by heavy lines if they project above the plane of the ring (β) and by dotted lines if they project below it (α). Methyl groups attached to the ring system are shown as simple lines whereas stereochemically-orientated hydrogen atoms are shown by "H". When there is no double bond at position 4, the hydrogen atom at C-5 in almost all the biologically active steroids projects below the ring system, i.e. in the α position, and the four ring system is completely planar when viewed from the side (Fig. 1.2). Most steroid metabolites have a 5β hydrogen atom at C-5 and appear bent between rings A and B. Dydrogesterone is an active progestogen that is a derivative of $9\beta,10\alpha$ -pregnane or retroprogesterone where the bend in the molecule is between rings B and C.

In the systematic nomenclature of the steroids, the position and stereochemistry of the ring substituents are indicated by a number and either α or β respectively. Ring hydroxyl groups are shown by the suffixes -ol, diol, etc. and ring keto- (also known as oxo-) groups by the suffixes -one, dione, etc. Some of the progestogens are 19-nor-steroids, the prefix "19-nor-" indicating that there is no methyl group present at position 19 as is usual for pregnane and androstane. Similarly the prefix "B-nor-" indicates that there is a carbon atom less in the B ring. All the steroids are the natural D absolute configuration with respect to D-glyceraldehyde,

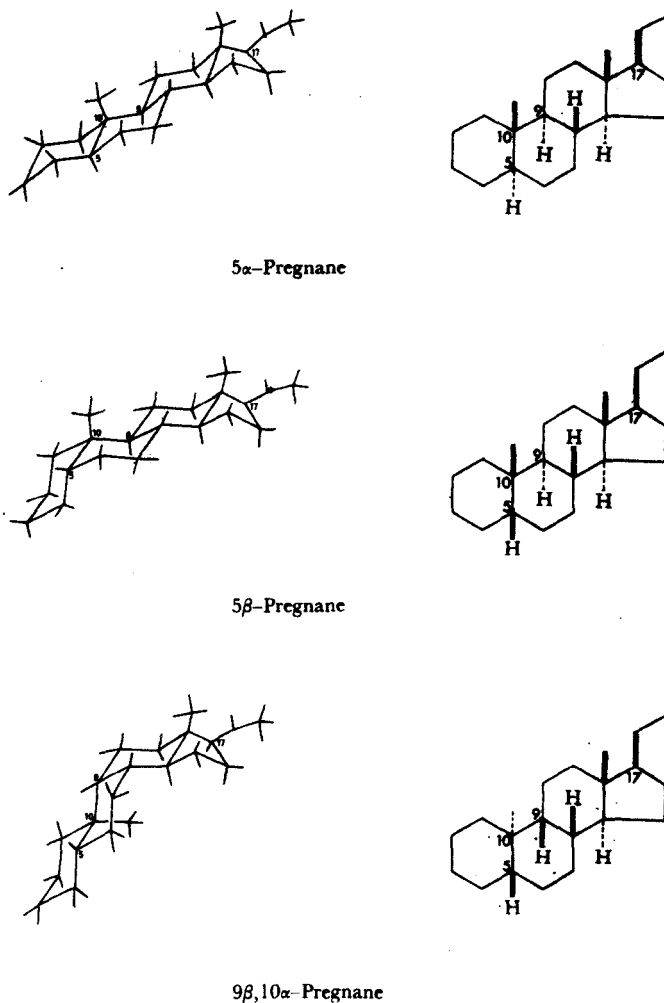


Fig. 1.2. Steroid structure viewed from the side and from above.

with the exception of norgestrel, which is totally synthetic. It is available as the racemic DL mixture or as the D isomer. In all the biological tests D-norgestrel is twice as potent as DL-norgestrel and L-norgestrel is completely inactive. Table I.1 shows the structure of some commonly used steroid derivatives.

B. PROGESTOGENS

The earliest progestogens to be used clinically were derivatives of testosterone and 19-nortestosterone (Table I.2). These have varying degrees of concomitant oestrogenic and androgenic properties. Later derivatives of progesterone itself were used. The degree of anti-gonadotrophic potency of these compounds varies greatly and is nil for

Table I.2. *Structural classification of the progestogens*

Derivatives of progesterone	Derivatives of 19-norprogesterone
1. Plain progesterone	Gestonorone caproate
17 α -Hydroxyprogesterone caproate	Methynodiol acetate
Medroxyprogesterone acetate	Oxogestone
Megestrol acetate	Amidinone
Melengestrol acetate	R-5020
Anagestone acetate	
Medrogestone	Derivatives of testosterone
Droxone	Dimethisterone
Quingestron	Ethisterone
Proligestone	
2. Halogenated progesterone	Derivatives of 19-nortestosterone (oestrane)
Chlormadinone acetate	Allylestrenol
Chlorsuperlutin	Ethynorone
Δ' -Chlormadinone acetate	Ethynodiol diacetate
Cyproterone acetate	Lynestrenol
Chlomethorone	Norethisterone
Haloprogestone	Norethisterone acetate
Flurogestone	Norethisterone oenanthate
Clogestone	Norethynodrel
Gestaclone	Norgestrel
	Norgestrienone
3. Retroprogesterone	Norvinodrel
Dydrogesterone	Quingestanol acetate
Trengestone	4-Azidonorethisterone
	Cingestol
	R-2323

the derivatives of retroprogesterone. The halogenated derivatives of progesterone are the most potent progestogens known and are not yet in general use. The structures of the different types of progestogens are shown in Fig. 1.3, their trade names where available in Table I.3 and their full scientific nomenclature in Table I.4.

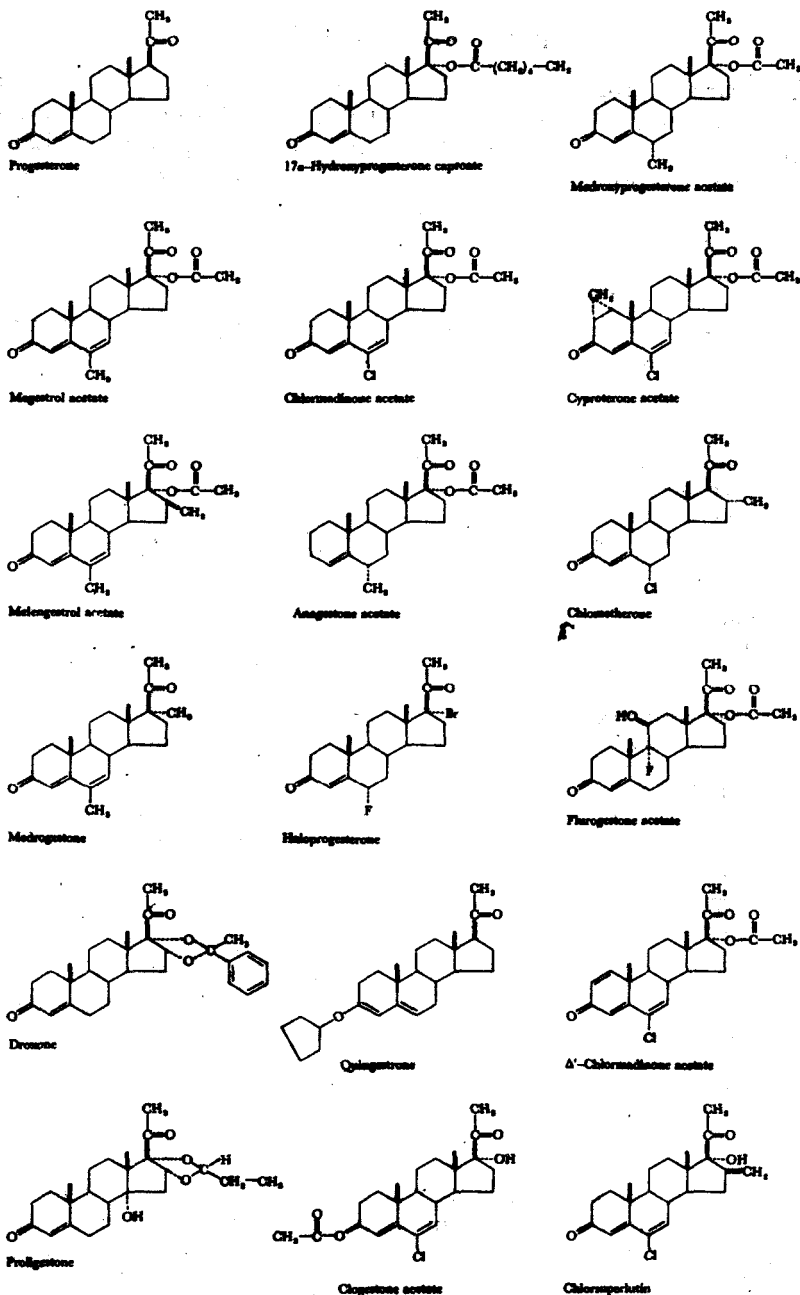


Fig. 1.3a. Structure of progestogens: a. Derivatives of progesterone.

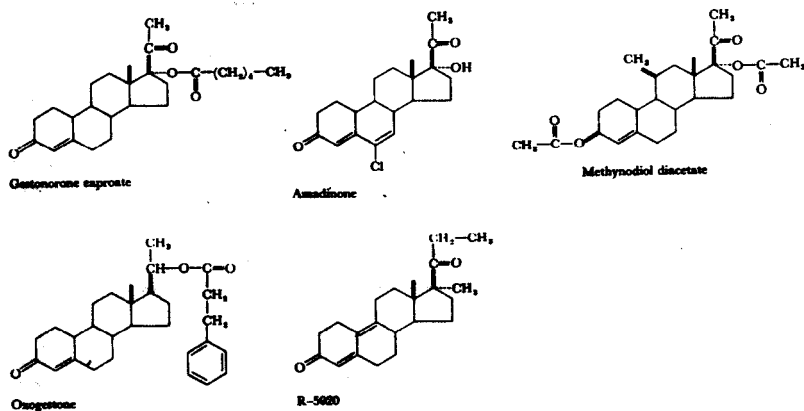


Fig. 1.3b. Derivatives of 19-norprogesterone.

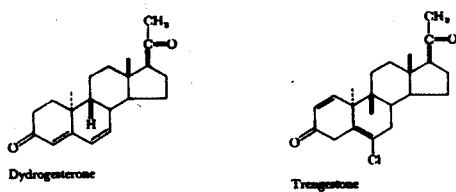


Fig. 1.3c. Derivatives of retroprogesterone.

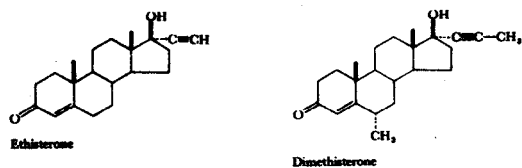


Fig. 1.3d. Derivatives of testosterone.

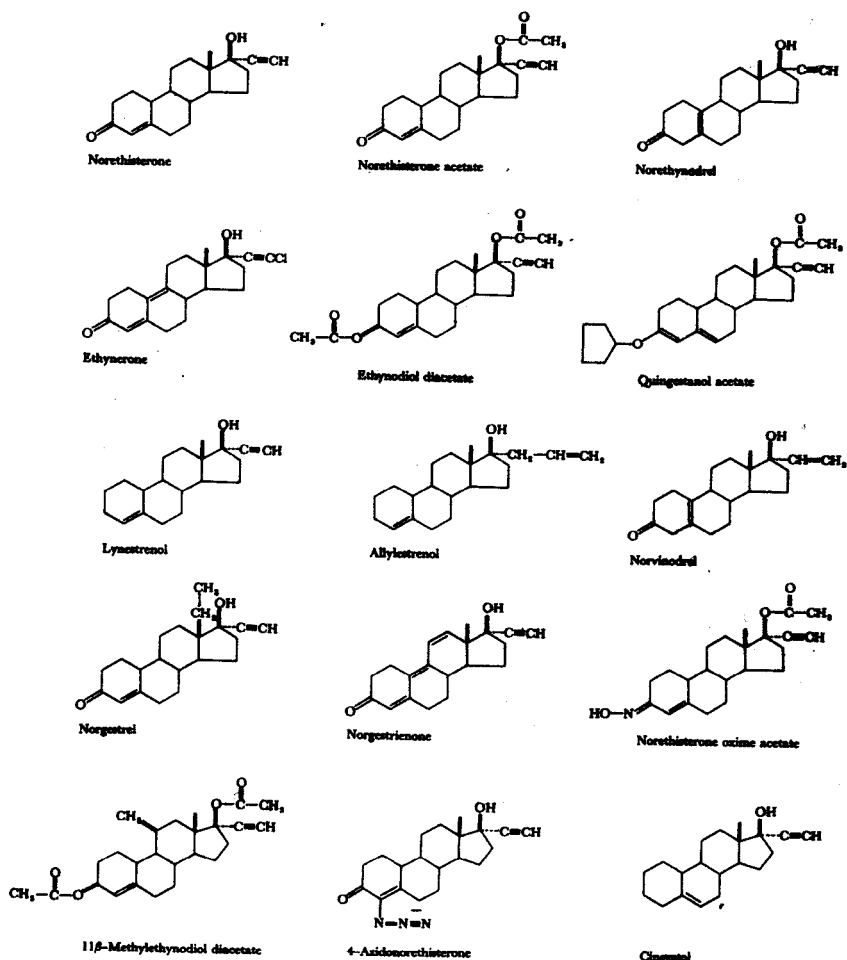


Fig. 1.3e. Derivatives of oestrane (19-nortestosterone).

Table 1.3. Trade names of progestogens

Progestogen	Dosage	U.K.	Trade names	Other
Oral				
Allylestrenol	5 mg	Gestanon		
Chlormadinone acetate	0.5 mg 2 mg	Normenon; Verton	Gestafortin Sinovir	
Cyproterone acetate	100 mg	Androcur		
Dimethisterone	5 mg	Secrosteron		
Dydrogesterone	10 mg	Duphaston; B.P.	Gynorest Pranone; Progesterol	
Ethisterone	5, 10, 25 mg	B.P.	Anhydrohydroxyprogesterone U.S.P.	
Ethinodiol diacetate	0.5 mg 2 mg	Femulen	Luto-metrolol Cronolone Prohalone Exluton	
Fluogestone acetate			Orgametril	
Haloprogesterone	0.5 mg 5 mg		Colprone, Colpro Farlutal, Clinovir, Provestrol	
Lynestrenol			Niagestin Megace	
Medrogestone				
Medroxyprogesterone acetate		Provera		
Megestrol acetate	5 mg 5 mg 20 mg			
DL-Norgestrel	0.075 mg	Neogest		
D-Norgestrel	0.030 mg	Microlut		
Norethisterone	0.35 mg	Micronor		
	5 mg	Primolut N; B.P.		
Norethisterone acetate	2.5 mg 10 mg	Norlutin A SH 420	Norlutin Norlutate	
Quingestanol acetate	200 mg	Danol	Demovis Danazol	
2,3-Isoxazole-ethisterone				
Intramuscular				
Gestonorone caproate	200 mg	Depostat	Primostat	
17 α -Hydroxyprogesterone caproate	125, 250, 500 mg	Primolut Depot	Luteocrin Depot; Proluton Depot; Corlutin L.A. 125 & 250	
Medroxyprogesterone acetate	50, 250 mg	Depo-Provera	Depo-Climovir 150	
Norethisterone oenanthate.	200 mg		Noristerat	
Progesterone	5, 10, 25, 50 mg 100 mg	injection B.P. Micryson Progesterone		