Brotherton

Sex Hormone Pharmacology

SEX HORMONE PHARMACOLOGY

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ACADEMIC PRESS

LONDON NEW YORK SAN FRANCISCO

A Subsidiary of Harcourt Brace Jovanovich, Publishers

ACADEMIC PRESS INC. (LONDON) LTD.
24/28 Oval Road,
London NW1

United States Edition published by
ACADEMIC PRESS INC.
111 Fifth Avenue
New York, New York 10003

Library of Congress Catalog Card Number 76-1070
ISBN: 0 12 137250-2

Printed in Great Britain by
Willmer Brothers Limited, Birkenhead

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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STEROID CHEMISTRY, BIOCHEMISTRY AND PHARMACY

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

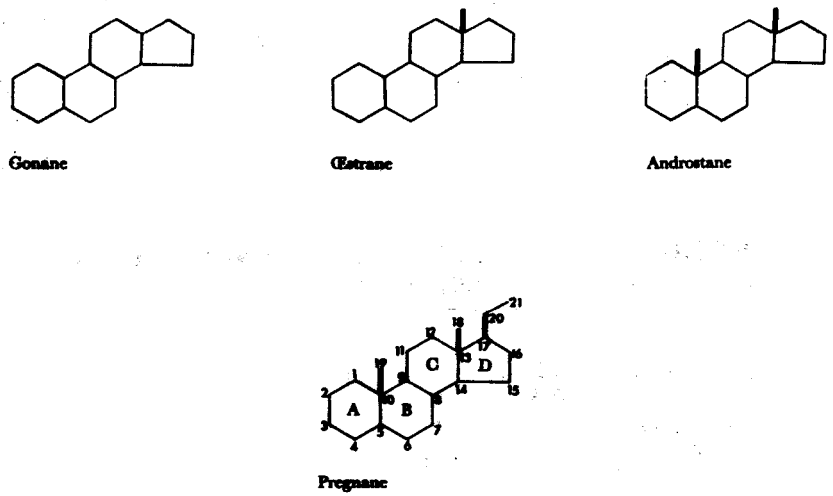
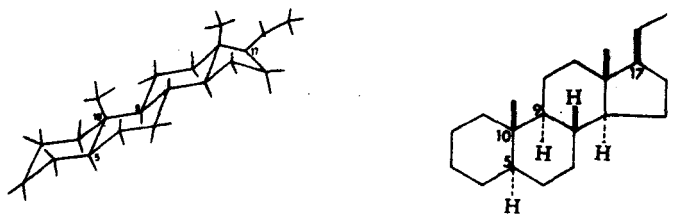


Fig. 1.1. Parent hydrocarbons showing the numbering of the steroid molecule.

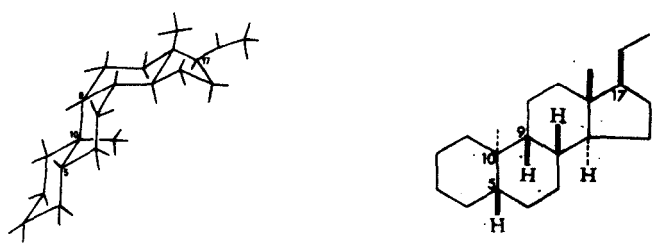
indicated by changing the suffix from -ane to -ene and indicating the position of the double bond by a number, e.g., 4-pregnene. Substituents in the rings are indicated by heavy lines if they project above the plane of the ring (β) and by dotted lines if they project below it (α). Methyl groups attached 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 9β,10α-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,



5α–Pregnane

5β–Pregnane

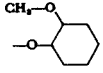
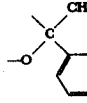
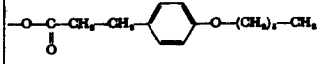
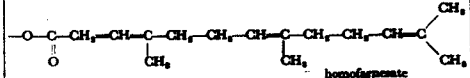


9β,10α–Pregnane

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.

Table I.1. *Some commonly used steroid derivatives*

Alkyl groups	Ethers	Esters	Esters
CH_3— methyl CH_2= methylene $CH.OH$= hydroxymethylene	—O—CH_3 methyl ether	—O—C(=O)—H formate	
CH_3—CH_2— ethyl CH_2=CH— vinyl CH≡C— ethinyl CCl=C— chloroethinyl	—O—CH_2—CH_3 ethyl ether	—O—C(=O)—CH_3 acetate	—S—C(=O)—CH_3 acetylmercaptate —N=N=N azido
CH_2=CH—CH_2— allyl		—O—C(=O)—CH_2—CH_3 propionate	
	—O—$Si(CH_3)_3$ trimethylsilanyl ether	—O—C(=O)—$(CH_2)_2$—CH_3 butyrate	—O—C(=O)—CH_2—CH_2—$CH(CH_3)_2$ isocaproate, 4-methyl-n-valerate
 cyclopentyl ether		—O—C(=O)—$(CH_2)_3$—CH_3 n-valerate	—O—C(=O)—CH_2—C(=O)—$(CH_2)_2$—CH_3 ketolaurate, 3-oxo-decanoate
 cyclopenten-1-yl ether		—O—C(=O)—$(CH_2)_4$—CH_3 caproate, hexanoate	—O—C(=O)—C(CH_3)$_2$—CH_3 pivalate, trimethylacetate
 1-methoxycyclohexanyl ether		—O—C(=O)—$(CH_2)_5$—CH_3 oenanthate, heptanoate	 benzoate
		—O—C(=O)—$(CH_2)_8$—CH_3 decylate, decanoate, n-caprate	 phenylacetate
 acetonide, cyclic acetal with acetone		—O—C(=O)—$(CH_2)_9$—CH_3 undecylate, undecanoate	 phenpropionate, 3-phenylpropionate
 acetophenonide		 3-(4-hexyloxyphenyl)propionate	 cypionate, cyclopentanepropionate
 cyclic acetal with propionaldehyde		 homofarnesate	—O—C(=O)—CH_2—CH_2—C(=O)—O— succinate

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
17α-Hydroxyprogesterone caproate	Methynodiol acetate
Medroxyprogesterone acetate	Oxogestone
Megestrol acetate	Amidinone
Melengestrol acetate	R-5020
Anagestone acetate	
Medrogestone	Derivatives of testosterone
Droxone	Dimethisterone
Quingestrone	Ethisterone
Proligestone	
	Derivatives of 19-nortestosterone (oestrane)
2. Halogenated progesterone	Allylestrenol
Chlormadinone acetate	Ethynerone
Chlorsuperlutin	Ethynediol diacetate
Δ'-Chlormadinone acetate	Lynestrenol
	Norethisterone
Cyproterone acetate	Norethisterone acetate
Chlometherone	Norethisterone oenanthate
Haloprogesterone	Norethynodrel
Flurogestone	Norgestrel
Clogestone	Norgestrienone
Gestaclone	Norvinodrel
	Quingestanol acetate
3. Retroprogesterone	4-Azidonorethisterone
Dydrogesterone	Cingestol
Trengestone	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.

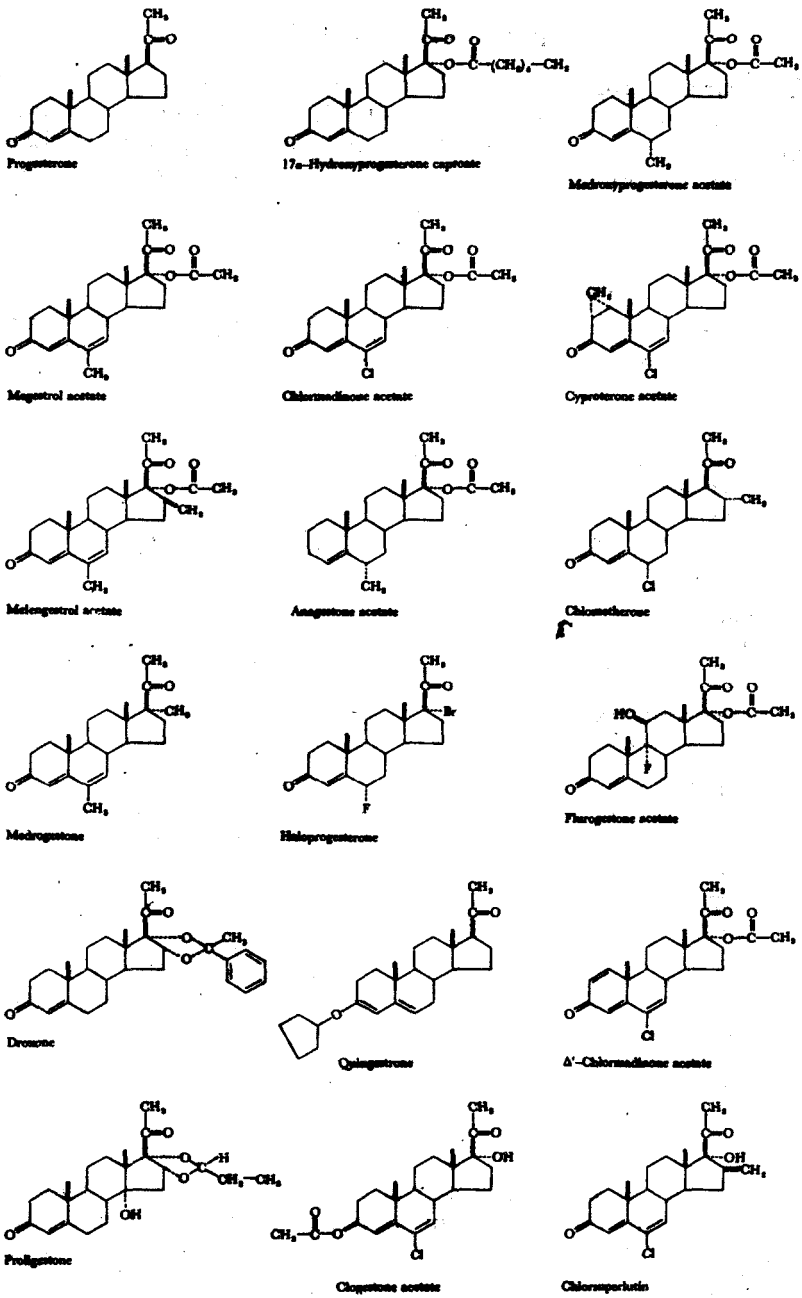


Fig. 1.3a. Structure of progestogens: a. Derivatives of progesterone.

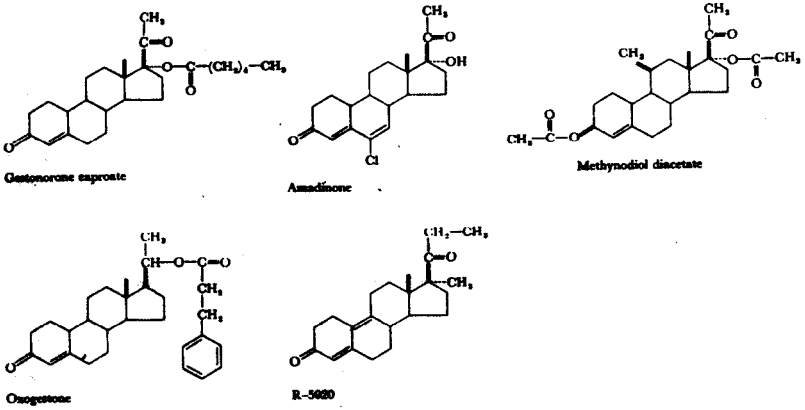


Fig. 1.3b. Derivatives of 19-norprogesterone.

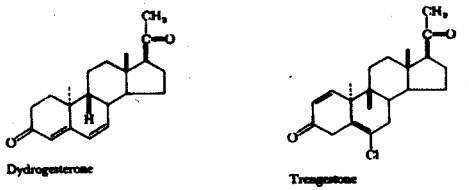


Fig. 1.3c. Derivatives of retroprogesterone.

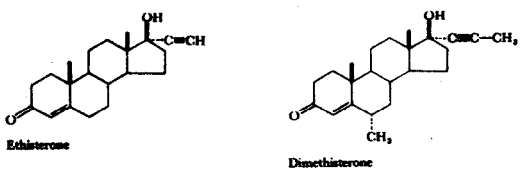


Fig. 1.3d. Derivatives of testosterone.

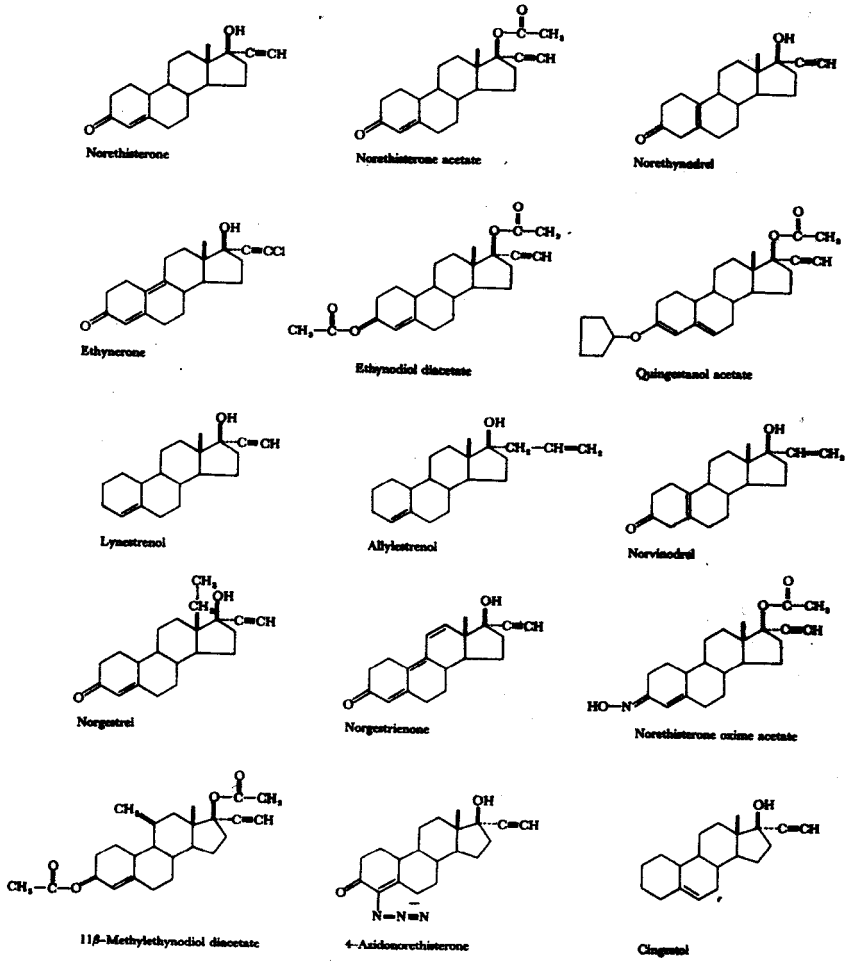


Fig. 1.3e. Derivatives of oestrane (19-nortestosterone).

Table 1.3. *Trade names of progestogens*

Progestogen	Dosage	Trade names	
		U.K.	Other
Oral			
Allylestrenol	5 mg	Gestanin	
Chlormadinone acetate	0·5 mg	Normenon; Verton	
	2 mg		Gestafortin
Cyproterone acetate	100 mg	Androcur	Sinovir
Dimethisterone	5 mg	Secrosteron	
Dydrogesterone	10 mg	Duphaston; B.P.	Gynorest
Ethisterone	5, 10, 25 mg	B.P.	Pranone; Progestoral
			Anhydrohydroxyprogesterone U.S.P.
Ethynodiol diacetate	0·5 mg	Femulen	
	2 mg		Luto-metrodiol
Flurogestone acetate			Cronolone
Haloprogesterone			Prohalone
Lynestrenol	0·5 mg		Exluton
	5 mg		Orgametril
Medrogestone			Colprone, Colpro
Medroxyprogesterone acetate	5 mg	Provera	Farlutal, Clinovir, Provestrol
Megestrol acetate	5 mg		Niagestin
	20 mg		Megace
DL-Norgestrel	0·075 mg	Neogest	
D-Norgestrel	0·030 mg	Microlut	
Norethisterone	0·35 mg	Micronor	
	5 mg	Primolut N; B.P.	Norlutin
Norethisterone acetate	2·5 mg	Norlutin A	Norlutate
	10 mg	SH 420	
Quingestanol acetate			Demovis
2,3-Isoxazole-ethisterone	200 mg	Danol	Danazol
Intramuscular			
Gestonorone caproate	200 mg	Depostat	Primostat
17α-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	injection B.P.	
	100 mg	Micryston Progesterone	