3

PROGRESS IN MEDICINAL CHEMISTRY

Volume

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Part

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Progress in Medicinal Chemistry 8

PART 2

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5 Antifertility Agents

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PREFACE

The present review concerns the use of steroids in the control of fertility in the woman. Animal data is included only insofar as it appertains to the main theme or to bioassay of relevant types. This limitation of subject matter seems desirable owing to limitations of space and, in addition, by the lack of correlation that often exists between the animal and the human model. So great are species variations in the area of reproductive physiology, that the reviewer is tempted to quote the dictum enunciated by Alexander Pope in another connection, 'The proper study of mankind is man.'

INTRODUCTION

No other development in steroid chemistry has had so great an impact upon the human imagination as the introduction of the contraceptive 'pill', which was first approved, as such, by the American Food and Drug Administration. in 1960. In the succeeding years, this combination of steroids and variants thereof has been hailed by some as a major breakthrough in the control of the population explosion and by others as bad medicine that should be banned pending further evaluation [1]. Time alone will tell. The dominant role of the steroid chemist in contraception research, however, is now being slowly eroded by new developments involving entirely different types of chemical structures (cf. p. 221). It is therefore an opportune moment to review the achievements of the past and point the way to possible successes of the future.

STEROID BIOGENESIS

The role of steroid hormones in the control of fertility has its origins in foetal biochemistry. Although the sex of the embryo is determined at the

time of fertilisation, it is impossible to distinguish between the male and female foetal gonads up to the 7th week of development. At this point the 'indifferent gonad' begins the typical morphological changes that lead to its differentiation into the ovary or testis. The factors controlling this initial differentiation are unknown and there is no experimental evidence to show that steroids are involved [2].

As the indifferent gonad undergoes sexual specialisation, so it begins to function as a steroid-secreting unit. It seems likely that it is these steroids secreted by the foetal gonads that participate in some processes of sexual differentiation, particularly at the level of the genital tract (see *Figure 5.1*) [2, 3]. The role of the foetal gonads does not end at this point. As suggested by Young [4] and others, it seems likely that the gonadal hormones play a

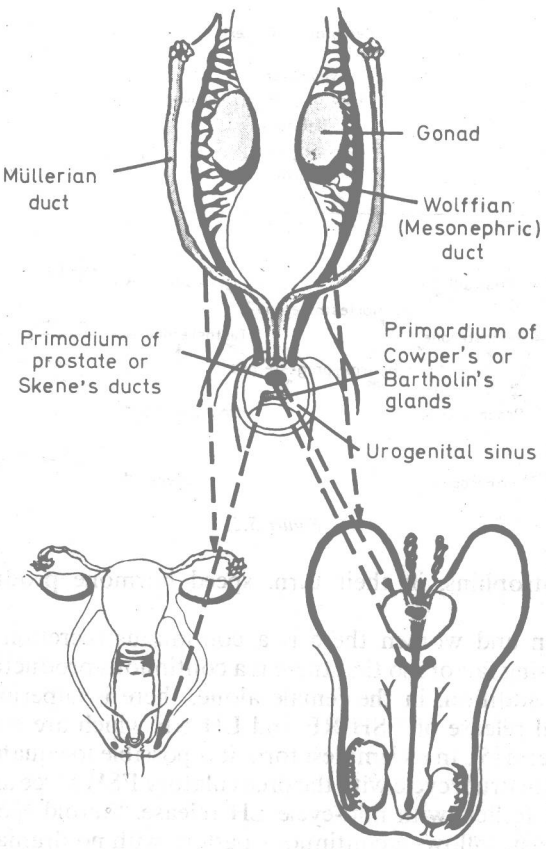


Figure 5.1.

dominant role in foetal/neonatal life in organising the sexually bipotential hypothalamus into cyclic or female, and continuous or male, patterns of gonadotrophin secretion. It is not surprising in these circumstances that the ovary and testis carry within themselves almost identical mechanisms of steroid hormone production but differ in the extent to which these diverse mechanisms are operated.

The old ideas that made the pituitary the determining factor in reproduction have given way to the concept that control of the pituitary/gonadal axis resides in the hypothalamus which, in its turn, is influenced by the cerebral cortex. This control stems from follicle stimulating hormone- and luteinising hormone-releasing factors (FSH-RF and LH-RF), respectively, acting upon the pituitary which, in its turn, releases follicle stimulating hormone (FSH) and luteinising hormone (LH), respectively (see *Figure 5.2*).

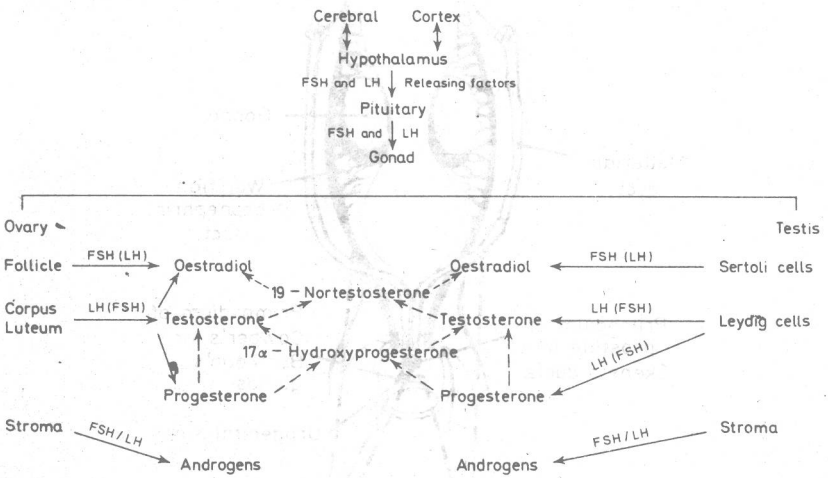


Figure 5.2.

These gonadotrophins, in their turn, speed hormone production by the gonads.

In both men and women there is a continuous secretion of the hypothalamic releasing factors so that there is a continuous production of gonadal hormones. In addition, in the female alone, there is superimposed an explosive cyclical release of FSH-RF and LH-RF which are essential for the ovulatory process [5]. In its simplest form it is possible to equate the follicular phase of the menstrual cycle with the preovulatory FSH surge and subsequent rupture of the follicle with mid-cycle LH release. Steroid biogenesis in the testis, in contrast, follows a continuous pattern with no dramatic changes in hormone output. Both ovary and testis utilise cholesterol as raw material for

steroid hormone biosynthesis. The cholesterol is first converted into 20α,22R-dihydroxycholesterol which is then degraded into pregnenolone (I) which is the basic—but probably not exclusive—progenitor of the gonadal hormones [6, 7]. This product then undergoes biogenesis, *inter alia* via its oxidation product progesterone, as outlined in simplified form in *Figure 5.2*, which demonstrates in striking manner the qualitative biosynthetic equivalence of the male and female gonadal structures. The analogy ends at this point. Testosterone production by the ovary is minute. Oestradiol [8, 9] production by the testis is hardly significant.

PROGESTERONE/TESTOSTERONE BIOSYNTHETIC PATHWAY

As shown in *Figure 5.3*, pregnenolone (I) is oxidised to progesterone (II) and thence converted via 17α-hydroxyprogesterone (III) into testosterone (V). Testosterone is the most active of the naturally occurring androgens [9, 10]. Androstenedione (VI) and dehydroepiandrosterone (DHA) (IV) form less potent but quantitatively more significant secretion products.

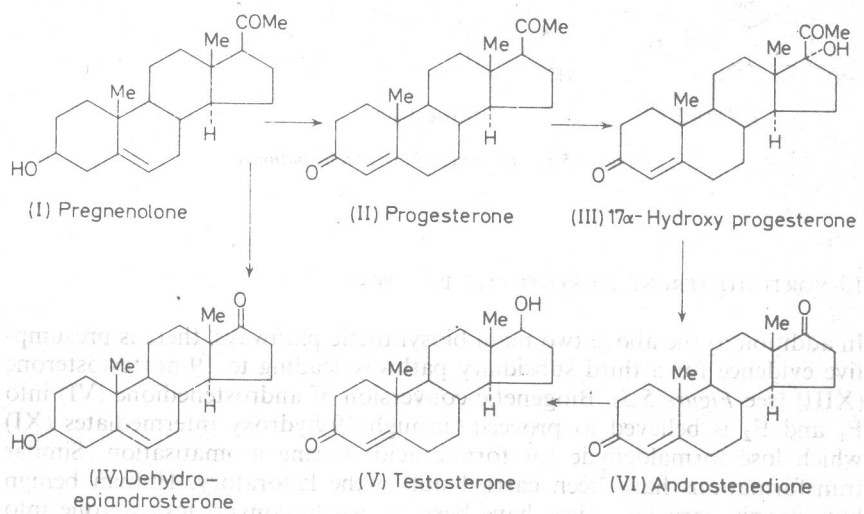


Figure 5.3. Progesterone/androgen biosynthetic pathway

OESTROGEN BIOSYNTHETIC PATHWAY

Although androstenedione (VI) represents the main precursor of oestrone (E_1)/oestradiol (E_2) (see *Figure 5.4*), it has recently been shown [11] that there

is an absolute and relative increase in oestriol (E_3) [X] production during the luteal phase of the menstrual cycle. It seems that as much as 48 per cent of luteal phase E_3 may be derived from DHA and not from E_1–E_2. Steroid pathways of biogenesis in the ovary are in a constant state of flux throughout the menstrual cycle.

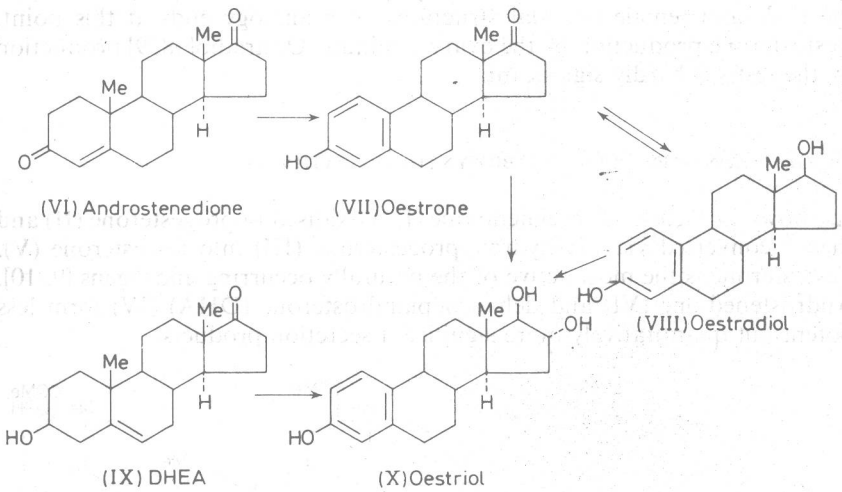


Figure 5.4. Oestrogen biosynthetic pathway

19-NORTESTOSTERONE BIOSYNTHETIC PATHWAY

In addition to the above two main biosynthetic pathways, there is presumptive evidence for a third subsidiary pathway leading to 19-nortestosterone (XIII) (see *Figure 5.5*). Biogenetic conversion of androstenedione (VI) into E_1 and E_2 is believed to proceed through 19-hydroxy intermediates (XI) which lose formaldehyde (or formic acid) during aromatisation. Similar transformations have been carried out in the laboratory. Human benign hypertrophic prostate slices have been shown to convert testosterone into 19-nortestosterone (XIII) *in vitro* [12]. In addition, 19-norandrostenedione (XIV) has been identified in the spermatic vein blood of the stallion [13] and in the follicular fluid of the mare [14]. 19-Nortestosterone (19-norandrostenedione) may consequently be regarded as the structural and biogenetic link between the androgens and the oestrogens.

As indicated in *Figure 5.2* the production of oestradiol (VIII), 19-nortestosterone (XIII), testosterone (V), 17α-hydroxyprogesterone (III) and

progesterone (II) is dependent, either directly or indirectly, upon FSH and LH release by the pituitary gland. By applying the concept of negative feedback action to the above biological systems, it can be concluded that the above hormones, in their turn, may inhibit FSH and/or LH production either directly by action upon the ovary or pituitary, or through the hypothalamus. As inhibition of FSH inhibits development of the ovarian follicle, and inhibition of LH prevents its rupture, it follows that the above five steroids represent natural starting points for the hormonal control of fertility and in particular for the inhibition of ovulation. Their application to fertility control, however, though predicted in general terms as early as 1921 [15], was not possible owing to their almost complete lack of oral activity. New products had to be discovered in the pharmaceutical laboratories of the

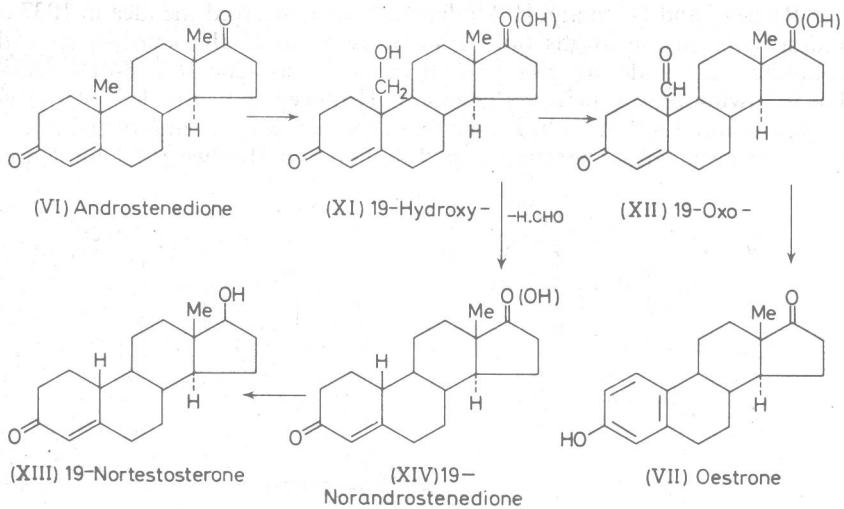


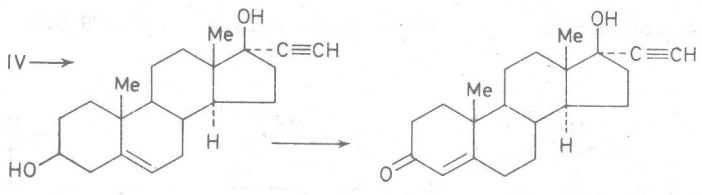
Figure 5.5. 19-Nortestosterone biosynthetic pathway

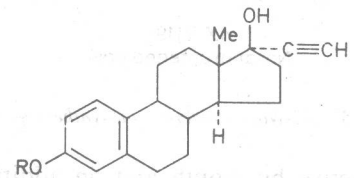
world that would be active by mouth and, in addition, would meet the strictest requirements of safety ever levelled against any type of therapeutic product by the health regulatory agencies of the world. When, at long last, such contraceptive steroids had become available, they were found to be derivatives of oestradiol, (17α-hydroxy)progesterone, 19-nortestosterone and testosterone. Their discovery, it is true, had been governed by chance, by an element of serendipity, and by a courageous projection of animal data to the human model, yet it seems difficult to avoid the conclusion that their success as contraceptive steroids stems from their chemical derivation from those very hormones that control the reproductive process in man.

THE DISCOVERY OF THE OESTROGENS AND PROGESTAGENS USED IN CONTRACEPTION

The discovery of oestrone (VII) in 1929 by Doisy and independently by Butenandt was followed in 1934 by the isolation of progesterone (II) from corpus luteum tissue and of dehydroepiandrosterone (IV) from urine (see review by Petrow [16]). Although their chemical structures were not fully elucidated, a relationship between them and cholesterol was assumed.

Progesterone, in contrast to oestrone, was only slightly active by mouth so that the need for a more active product was readily apparent. Dehydroepiandrosterone (IV) had become readily available in 1935 from oxidative degradation of cholesterol (acetate dibromide). As it was a C_{19} keto-alcohol and as progesterone was a C_{21} diketone, Kathol, Logemann and Serini [17] and Ruzicka and Hofmann [18] independently conceived the idea in 1937 of adding two carbon atoms onto (IV) by reaction of the keto group with potassium acetylide to give 17α-ethynylandrost-5-ene-3β,17β-diol (XV). The following year, Inhoffen, Logemann, Hohlweg and Serini [19] converted the last compound into ethisterone (XVI), which was the first of the orally-active progestagens. The same year, Inhoffen and Hohlweg [20] condensed





(XVII) R=H; Ethynyloestradiol (EE)
(XVIIa) R=Me; Mestranol
(XVIIb) R=Cyclopentyl; quinestrol

oestrone (VII) with potassium acetylide and obtained ethynyloestradiol (EE) (XVII), which was the first—and still remains the most important—of the orally active contraceptive oestrogens. A decade later its 3-methyl ether, mestranol (XVIIa), which represents the second most important contraceptive oestrogen, was found as a minor impurity in early commercial samples

of norethynodrol (XIX) and norethindrone (XVIII) [21], being formed from the oestrone 3-methyl ether used as starting material for their production (*vide infra*). Following its identification and the recognition of its contribution to the contraceptive efficacy of these two 19-nor steroids, it was added to them to provide variants of the combination pill.

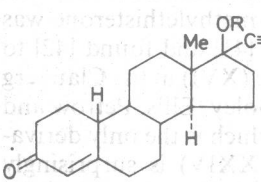
One more contraceptive oestrogen needs mention. Quinestrol (XVIIb), the 3-cyclopentyl ether of ethynyloestradiol, was prepared by Ercoli, Pellegrini and Falconi [22, 23] as part of a broad programme dealing with the cyclopentyl ethers and enol ethers of steroidal hormones. 3-Etherification of (XVII) with cyclopentyl alcohol enhanced and prolonged the oral and decreased the subcutaneous activity of the oestrogen. Meli, Wolff and Hourath [24] subsequently showed that in the rat storage in, and release from, body fat is the mechanism responsible for the increased oral activity of the product. Similar findings were reported in man [25]. The depot action of this oestrogen was exploited by Greenblatt [26] in his pill-a-month regimen.

The development of the progestagens used in contraception likewise had its origins in 1938 when ethisterone (XVI) was prepared (*vide supra*) and, for the next decade, no further progress was apparent.

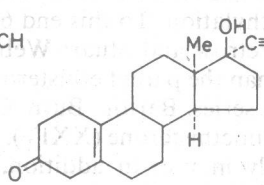
In 1949, Birch and Mukherji [27] reduced oestrone glyceryl ether with sodium in liquid ammonia and obtained 17β-hydroxyoestra-5(10)-en-3-one, which may be regarded as the parent structure corresponding to norethynodrel (XIX). In the following year, Birch [28] completed the sequence by converting the 5(10)-en-3-one into 19-nortestosterone (XIII). The resulting compound was initially a chemical curiosity—a steroid hormone lacking the C_{19}-angular methyl group. Its relevance to ovarian steroidogenesis was entirely unsuspected at the time, nor was it possible to predict that its derivatives would usher in the contraceptive revolution.

In 1951, Djerassi, Miramontes and Rosenkranz [29] converted 19-nortestosterone into 19-norandrostenedione (XIV) and thence into norethindrone (19-norethisterone) (XVIII). Two years later, Colton [30] prepared norethynodrel (XIX). These two 19-nor steroids achieved immediate success as orally active progestagens. In retrospect, the enhanced biological potency of (XVIII) over ethisterone (XVI) is not surprising as 19-nor steroids form the biogenetic link between the androgens and the quantitatively more potent oestrogens. At the time, however, the results were baffling.

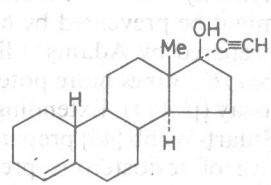
Progestagens derived from 19–Nortestosterone



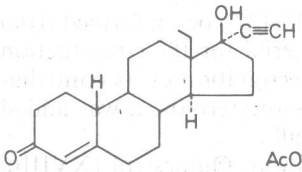
(XVIII) R=H, Norethindrone
(XVIIIA) R=Ac,
19-Noresthisterone acetate



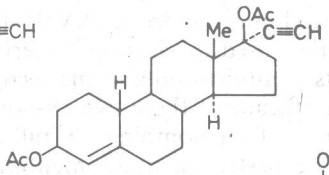
(XIX) Norethynodrel



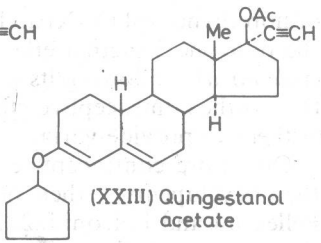
(XX) Lynestrenol



(XXI) Norgestrel



(XXII) Ethynodiol diacetate



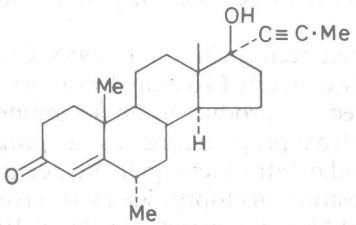
(XXIII) Quingestanol acetate

Other 19-nor steroidal progestagens were prepared in rapid succession. In 1954, Colton prepared ethynodiol (17α-ethynyloestr-4-ene-3β,17β-diol) by reduction of norethindrone with sodium borohydride [31]. Eleven years later its diacetate 'ethynodiol diacetate' (XXII) was introduced as a contraceptive in combination with mestranol. Engelfried, Kaspar, Popper and Schenck [32], following up earlier work on the acetylation of ethisterone, prepared 19-norethisterone acetate (XVIIIA). The 3-deoxy analogue (XX) of norethindrone was prepared by Szpilfogel [33] and given the generic name of lynestrenol. Ercoli extended his studies on the 3-cyclopentyl derivatives of steroid hormones (*vide supra*) to 19-norethisterone acetate, obtaining the highly potent quingestanol acetate (XXIII) [34]. Finally, Herchel Smith—a pupil of Birch—in collaboration with Hughes prepared the totally synthetical 'norgestrel' (XXI) [35], which represents the last member of the first generation 19-nor progestagens.

Parallel with these discoveries, another group of progestagens based upon the naturally occurring 17α-hydroxyprogesterone (III) was being developed. The last compound had been isolated from adrenal glands by Pfiffner and North [36] and had been found to be inactive in the Clauberg assay for progestational activity by the intramuscular route (see p. 183). Its 17-esters were examined by Junkmann [37] in his search for a depot progestagen, for which purpose he had finally selected the 17-caproate. Surprisingly, he failed to examine them for oral activity. It fell to the Upjohn group [38, 39] to make this important advance and establish the progestational activity of 17α-acetoxyprogesterone when administered by the oral route.

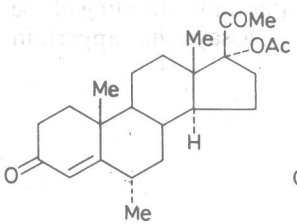
A year previously, Burstein, Dorfman and Nadel [40] had found that metabolic deactivation of hydrocortisone in man occurred through 6β-hydroxylation. It occurred to the reviewer that such metabolic deactivation might be prevented by 6-methylation. To this end 6α-methylethisterone was prepared by Adams, Ellis, Petrow and Stuart-Webb [41] and found [42] to be *c.* 6·5 times more potent than the parent ethisterone (XVI) in the Clauberg assay (p. 183). Extending the series, Barton, Burn, Cooley, Ellis, Petrow and Stuart-Webb [43] prepared dimethisterone (XXIV), which is the only derivative of testosterone presently in use. In addition, (XXIV) is surprisingly effective in endometrial carcinoma [44].

Progestagens derived from testosterone

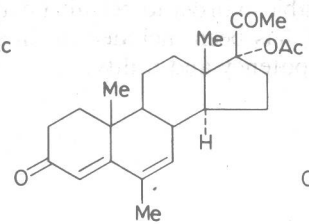


(XXIV) Dimethisterone

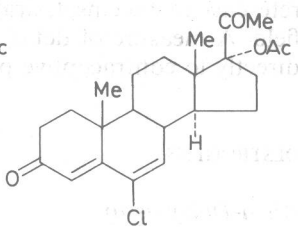
Progestagens derived from 17α-Hydroxyprogesterone



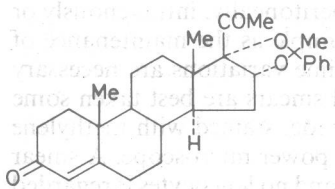
(XXV)
Medroxyprogesterone acetate



(XXVI)
Megesterol acetate



(XXVII)
Chlormadinon acetate



(XXVIII)
Algestone acetophenide

Other 6-methylated progestagens followed in rapid succession. Spero [45, 46] prepared medroxyprogesterone acetate (XXV), which was the first 17α-hydroxyprogesterone derivative to find use in oral contraception. The related megesterol acetate (XXVI) [47] was prepared at about the same time