Journal of Steroid Biochemistry, 1975, Vol. 6, pp. 585–597. Pergamon Press. Printed in Great Britain

11-OXA AND 17α-HYDROXYMETHYL ANALOGUES OF STEROID HORMONES AND THEIR DERIVATIVES

CHARLES R. ENGEL, D. MUKHERJEE, M. N. ROY CHOWDHURY, G. RAMANI and V. S. SALVI

Department of Chemistry, Université Laval, Quebec, Quebec, Canada G1K 7P4

SUMMARY

In view of the markedly reduced activity in the Clauberg test of 11-oxaprogesterone and of its significantly enhanced anovulatory activity in rabbits, ovulation stimulated with copper acetate, the synthesis and biological evaluation of other 11-oxa hormone analogues was undertaken. The syntheses of 11-oxa-17-acetoxyprogesterone, 11-oxa-17α-ethynyltestosterone, 11-oxa-estradiol, 11-oxa-17α-ethynyl-estradiol, and of 11-oxatestosterone are reported and some of their biological activites are discussed. In general, the replacement of the 11-methylene group by oxygen results in a diminution of the progestational, androgenic-anabolic, and estrogenic activities, this effect being the least pronounced in the case of the progestational activity of 11-oxa-ethisterone and particularly strong in the case of the uterotropic activity of 11-oxa-estradiol.

On the other hand, the observation that the introduction of bulky 17α-substituents into progesterone and related products results in general in an increased progestational activity and that acylation of the progestationally inactive 17-hydroxyprogesterone leads to orally active progestogens and antifertility agents, prompted us to synthesize, by two pathways, 17α-acetoxymethylprogesterone and 17α-hydroxymethylprogesterone. It is shown that one of these pathways can be advantageously applied also to the synthesis of 17α-acyloxymethyl and 17α-hydroxymethyl glucocorticoids. Interestingly, 17α-acetoxymethylprogesterone proved inactive in the Clauberg test even at high dose levels.

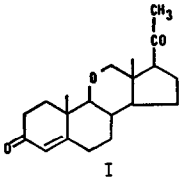
The primary objective of the investigations which we should like to present in the framework of this Symposium was, and is indeed, a contribution to the domain of structure-activity relationships of hormonal steroids. However, this lecture will be concerned to the greatest extent with results pertaining to the structural component of this tandem field—to the synthesis of new analogues of steroid hormones—and we shall touch its activity component only in a fragmentary and preliminary way; this, quite simply, because we are not yet in the possession of the full biological data. Still, we hope that the chemical aspects discussed will not be completely devoid of interest and we also hope that even some of the fragmentary biological results will not be meaningless to the intricate and problematic field of structure-activity relationships.

We should like to divide our presentation into two parts: one dealing with 11-oxa analogues of steroidal sex hormones, the other with 17α-hydroxymethyl analogues of hormones of the progesterone-corticoid group, with the emphasis on derivatives of progesterone.

PART I: 11-OXA ANALOGUES OF STEROIDAL SEX HORMONES

A. *Introduction*

Some years ago [1], we synthesized 11-oxaprogesterone (I) which was tested by Dr. E. Shipley at the



I

Endocrine Laboratories of Madison, for its subcutaneous progestational activity in the Clauberg assay, and for its activity as ovulation inhibitor in rabbits, in which ovulations were stimulated with copper acetate (cf. Fig. 1). According to expectations, the product showed little progestational activity, one quarter to one seventh of that of progesterone, but it had, in the test employed, significantly enhanced ovulation inhibitory activity, approximately twice the activity of progesterone. The substance thus showed an interesting separation of these two activities, the ratio of ovulation inhibitory activity to progestational activity being approximately eight to nine times more favourable than in the case of progesterone.

These results prompted us to synthesize and study the biological activities of 11-oxa analogues of other steroid hormones, and to investigate in particular whether further separations of activities, primarily of relevance to fertility control, would be observed.

B. *Chemistry*

1. *The synthesis of 11-oxa-17-acetoxyprogesterone* (III)

The fact that the introduction of a 17α-acyloxy substituent, for instance a 17α-acetoxy group, into the progesterone molecule results in orally active progestogens and antifertility agents, made the biological investigation of 11-oxa-17-acetoxyprogesterone (III) attractive.

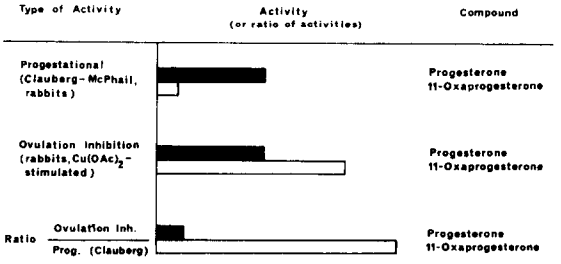
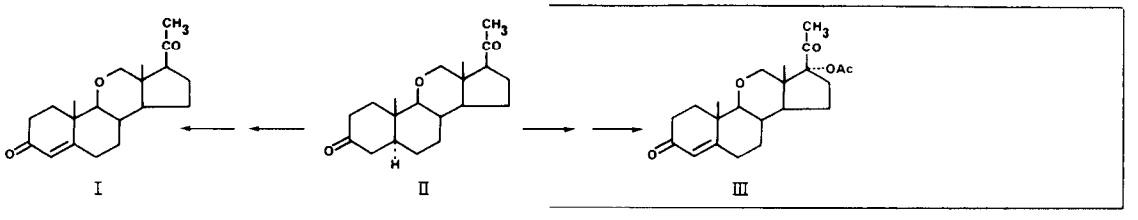


Fig. 1. Comparisons of progestational and anovulatory activities of progesterone and 11-oxaprogesterone.

For the first syntheses of 11-oxa analogues of steroid hormones we adopted the policy of using as much as possible common intermediates, in order to make these products quickly available for biological evaluation. For the preparation of larger quantities of certain products which should reveal themselves of significant biological interest, more specific routes are foreseen. Thus, 17-acetoxy-11-oxaprogesterone (III) was synthesized from an intermediate in the synthesis of 11-oxaprogesterone itself: 11-oxa-5α-pregnane-3,20-dione (II).



We recall shortly the preparation of this intermediate (II) from hecogenin acetate (IV) (cf. charts 1 and 2). Hecogenin acetate (IV) is transformed (cf. chart 1) *via* the 16-unsaturated 12,20-diketone V into 3β-acetoxy-5α-pregnane-12,20-dione (VI), the 12-keto function of which is selectively protected; the resulting 20-monoketone IX is reduced to the 20β-alcohol VIII which is acetylated and deketalized to the 12-monoketone VII, readily dehydrogenated with selenium dioxide (cf. X). Ozonolysis gives in high yield the 9,12-*seco* 11-nor 9-keto 12-acid XI, hydrolyzed to the 3β,20β-diol XII. Evidently, the 20-alchohol group has to be reoxidized at a later stage so that the question arises why the 20-keto group had to be selectively reduced: simply because saturated 12,20-diketones are dehydrogenated with selenium dioxide only in poor yields to the 9(11)-unsaturated derivatives. We may also recall that the reactions were carried out in the A/B *trans* series because the opening of ring C proceeds in unsatisfactory yields in A/B *cis* steroids [2].

The dihydroxy keto acid XII is now methylated (cf. chart 2), the dihydroxy ester XIII oxidized to the triketone XIV whose 3- and 20-keto functions are selectively protected; the resulting keto ester XVI is reduced with lithium aluminum hydride to the diol XV which is cyclized with tosyl chloride in pyridine. Liberation of the keto functions leads to 11-oxa-5α-pregnane-3,20-dione (II).

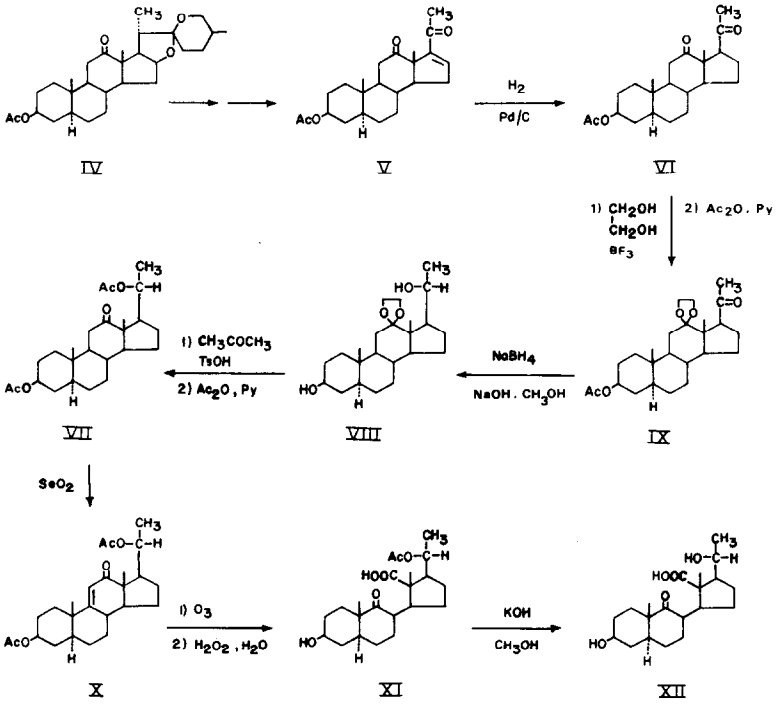


Chart 1

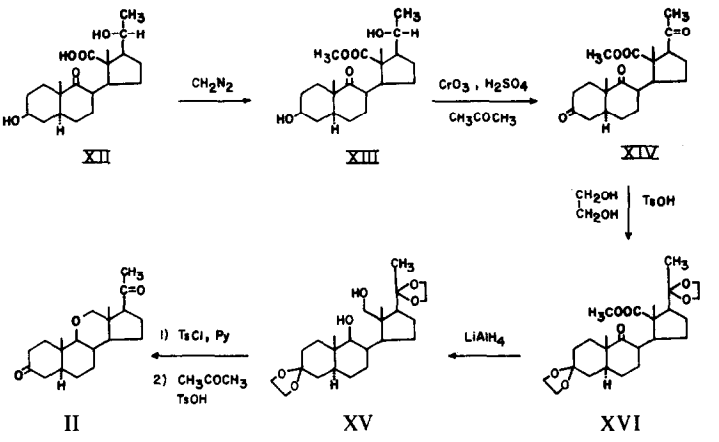


Chart 2

This product, the transformation of which into 11-oxaprogesterone we have, as mentioned, already reported [1], was now converted to 17-acetoxy-11-oxaprogesterone (III), as depicted in chart 3. The 3-keto group of dione II was selectively ketalized with ethylene glycol in methylene chloride, in the presence of selenium dioxide and *p*-toluenesulfonic acid [3], the reaction proceeding in almost 70% yield, and the resulting 20-monoketone XVII was subjected to Gardner's modification [4] of Barton's hydroxylation procedure [5]: it was treated in tetrahydrofuran with oxygen in the presence of sodium hydride, *t*-butanol, dimethylformamide and tri-ethyl phosphite at −25°C, and the so formed hydroperoxide XVIII was converted *in situ* to the hydroxy ketone XXI, by replacing the oxygen flow by a nitrogen stream and by treating the mixture with sodium hydroxide, dissolved in aqueous methanol. The over-all yield of the hydroxy ketone XXI from ketone XVII amounted to approximately 45%. The ketal protection was readily removed with acetone and *p*-toluenesulfonic acid and the structure of the resulting 11-oxa 17-hydroxy 3,20-pregnanedione XX was not only verified by the usual analytical and spectroscopic methods but also by a modified bromoform test [6] which confirmed, independently from the n.m.r. evidence, the conservation

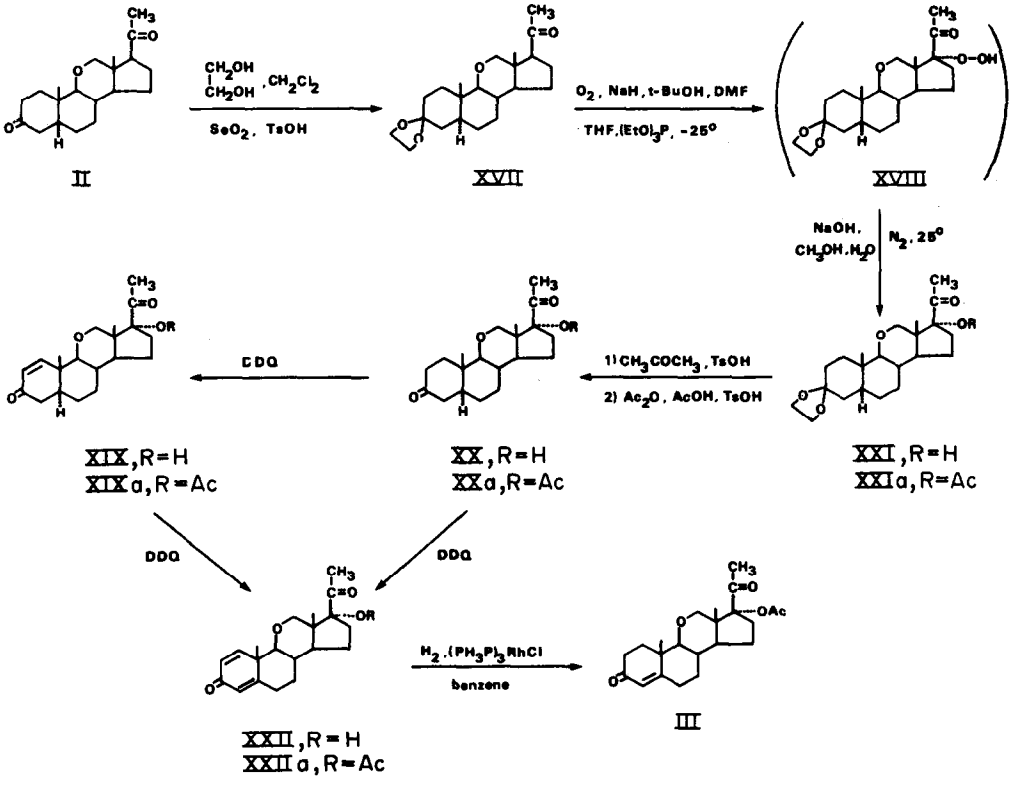


Chart 3

of the methyl ketone side chain. The hydroxy diketone XX was dehydrogenated in 40% yield with 2,3-dichloro-5,6-dicyano-*p*-quinone (DDQ) to the diene dione XXII, accompanied by small amounts of the 1-monounsaturated derivative XIX, but the solubility of the doubly unsaturated hydroxy diketone XXII was so poor that we acetylated the 17α-hydroxyl function prior to the introduction of the unsaturations in ring A, either at the stage of the monoketal XXI or at that of the diketone XX, the acetylations being carried by Turner's method [7*a*] or by that of Le Mahieu *et al.* [7*b*]. Dehydrogenation of the acetoxy diketone XXa gave in 28% yield the monounsaturated diketone XIXa, in 41% yield the diunsaturated derivative XXIIa. This product was now selectively hydrogenated, in 85% yield, with hydrogen and Tris-(triphenylphosphine)rhodium chloride [8] to the desired 11-oxa-17-acetoxyprogesterone (III).

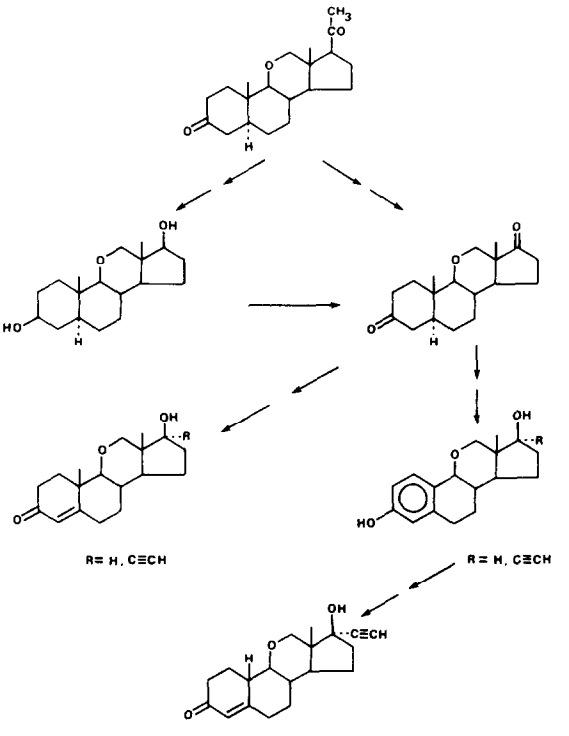
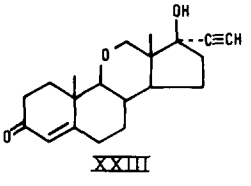


Chart 4

2. *The synthesis of 11-oxa-17α-ethynyltestosterone (11-oxa-ethisterone)* (XXIII)

For the same reasons which had prompted us to synthesize 11-oxa-17-acetoxyprogesterone (III), we were interested in the synthesis and biological evaluation of 11-oxa-17α-ethynyltestosterone (11-oxa-ethisterone) (XXIII), the 11-oxa analogue of the first



XXIII

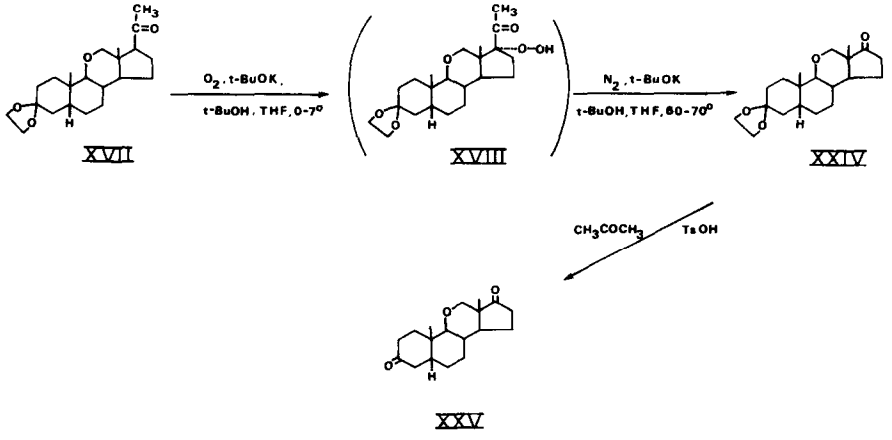
known orally active progestogen, one of the ancestors of a number of clinically used progestational and antifertility agents.

Following our strategy of using as much as possible common intermediates for our syntheses, we first investigated the possibility of arriving at 11-oxa androgens and 11-oxa estrogens by degradation of the methyl ketone side chain of 11-oxa-5α-pregnane-3,20-dione (II) (cf. chart 4).

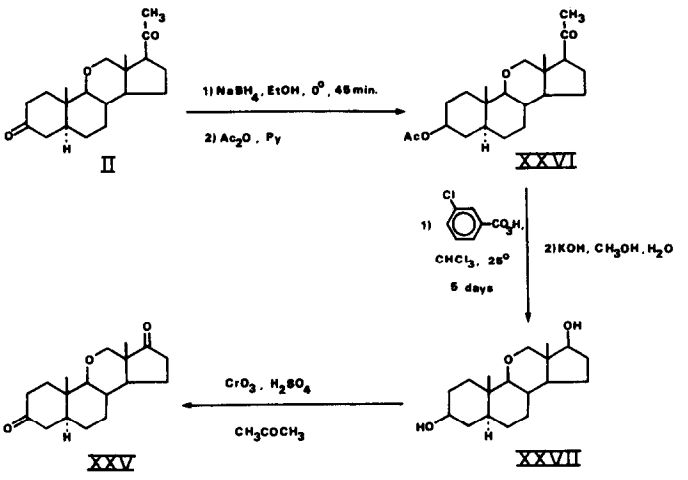
We were indeed able to degrade the 20-keto side chain of the 3-monoketal XVII of diketone II according to Siddall's procedure [9], by subjecting it to a Barton hydroperoxidation [5] and by treating the thus formed hydroperoxide XVIII *in situ* with potassium *t*-butoxide in a nitrogen atmosphere. The desired 17-ketone XXIV was obtained in only 30% yield and was transformed readily into 11-oxa-5α-androstane-3,17-dione (XXV).

We also reduced selectively, in 65% yield, the 3-keto group of diketone II with sodium borohydride in ethanol at 0°C and subjected, after acetylation, the 20-monoketone (cf. XXVI) to a Baeyer–Villiger degradation with *m*-chloroperbenzoic acid in chloroform. Saponification (cf. XXVII) and oxidation led to 11-oxa-5α-androstane-3,17-dione (XXV). However, the yields in the degradation never exceeded 25%.

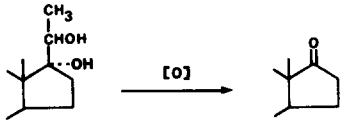
In view of the not very satisfactory results of these and other degradation experiments, we decided to arrive at the 17-keto structure by degradation of a



XVII XVIII XXIV XXV

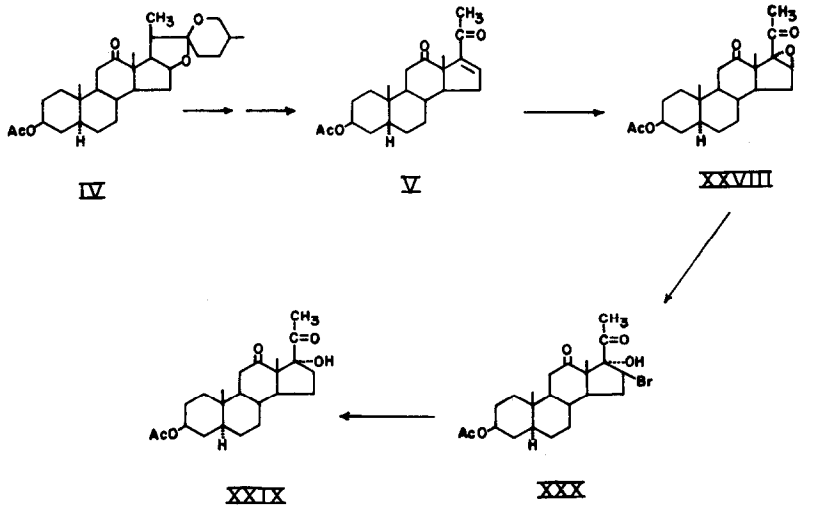


17,20-diol:



However, the not particularly attractive yields in the 17α-hydroxylation of a 20-ketone in the 11-oxa series, as well as the consideration that the degradation product of our starting material, hecogenin acetate (IV), is a 16-unsaturated 20-ketone (V), which can be readily transformed into a saturated 17α-hydroxy 20-ketone [10], prompted us to introduce the 17-hydroxy function at an early stage of the synthetic pathway, prior to the formation of the 11-oxa structure.

We therefore transformed (cf. chart 5) 3β-acetoxy-5α-pregn-16-ene-12,20-dione (V), according to Julian *et al.*[10], in 90% yield, into 3β-acetoxy-17α-hydroxy-5α-pregnane-12,20-dione (XXIX), *via* the epoxide XXVIII and the bromohydrin XXX. As before, the 12-keto function was now selectively protected (cf. chart 6) and the product was saponified completely since during the reaction the 3-acetate group had been partially hydrolyzed. The 20-keto function of the dihydroxy ketone XXXI was reduced with sodium borohydride in over 90% yield and the resulting triol XXXII was treated with acetone and *p*-toluenesulfonic acid. After acetylation, the 3-acetoxy 12-keto 17,20-acetonide XXXV was obtained in 90% yield. Dehydrogenation with selenium dioxide led in 62% yield to the enone XXXIV. Several procedures for the transformation of this product into the seco trihydroxy keto ester XXXVII were elaborated. The simplest one consists in the ozonolysis of the enone XXXIV, followed by hydrogen peroxide oxidation, which gives a neutral product, mostly composed of a mixture of the 3-acetoxy and 3-hydroxy lactols XXXIIIa and XXXIII, and an acidic product, containing predominantly the 3-acetoxy 17,20-dihydroxy keto acid XXXVIa. The combined acid and neutral fractions were treated with methanolic potassium hydroxide and the crude product (cf. XXXVI) was methylated with diazomethane. At this stage only (ester XXXVII) was the product isolated and purified. The yield of ester XXXVII, from



cf: Julian, Cochrane, Magnani and Karpel: *J. Am. chem. Soc.* **78** (1956) 3153.
Chart 5

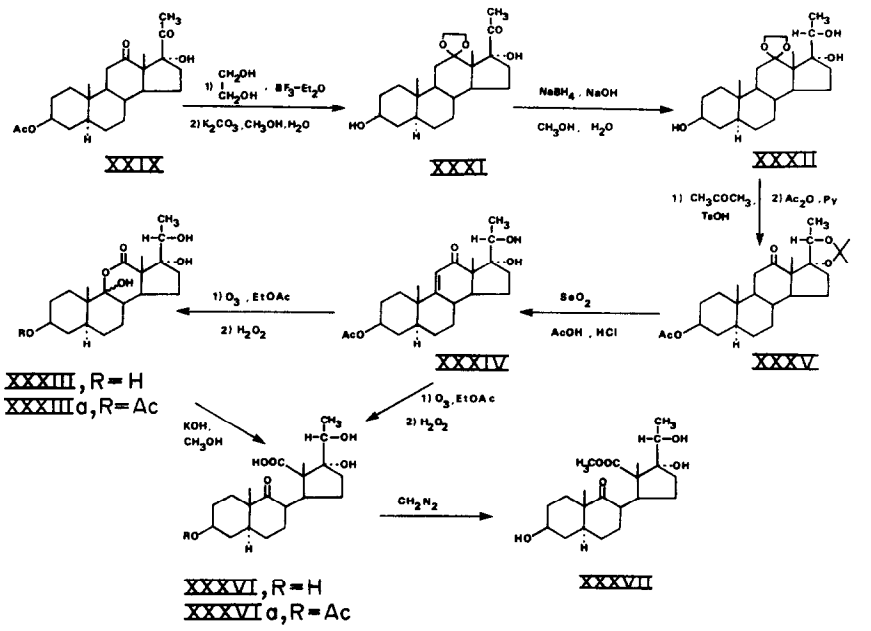


Chart 6

the dihydroxy enone XXXIV, amounted to approximately 50%.

The trihydroxy seco keto ester XXXVII was now degraded in high yield (cf. chart 7), according to the method of Robinson *et al.*[11], with sodium bismuthate in aqueous acetic acid, to the 17-ketone XXXVIII which was oxidized with Jones' reagent to the seco triketo ester XXXIX. This product underwent readily selective ketalization in positions 3 and 17 and the resulting 9-monoketo ester XLI was reduced with lithium aluminum hydride in almost 90% yield to the 9β,12-diol XL. Treatment with tosyl chloride in pyridine and subsequent deketalization led in 75% yield to 11-oxa-5α-androstane-3,17-dione (XXV). This

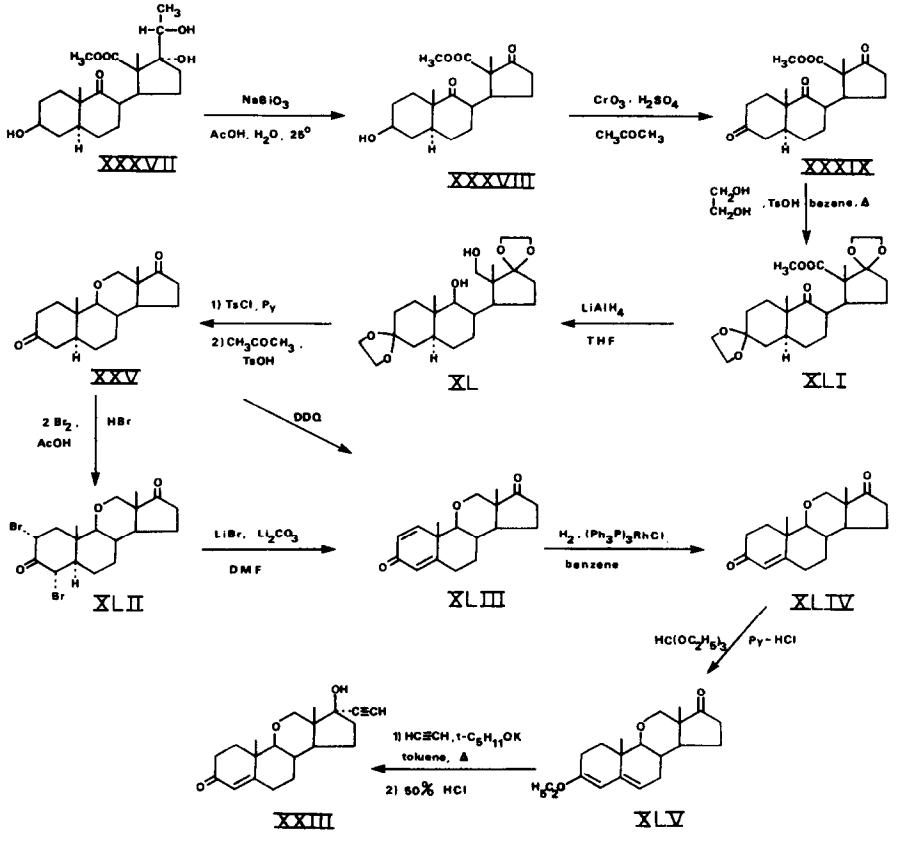
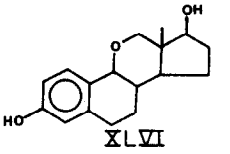


Chart 7

diketone was brominated with molecular bromine in acetic acid to the 2,4-dibromide XLII which was dehydrobrominated with lithium bromide and lithium carbonate in dimethylformamide to the diene dione XLIII, obtained in 60% yield from the saturated precursor XXV. The yields in the direct DDQ-dehydrogenation of diketone XXV were significantly lower. Selective hydrogenation led to 11-oxa-4-androstene-3,17-dione (XLIV), which was converted, according to Djerassi's procedure [12], *via* the 3-mono-enol ether XLV, to the desired 11-oxa-ethisterone (XXIII). We found other selective protections of the 3-keto group unsatisfactory.

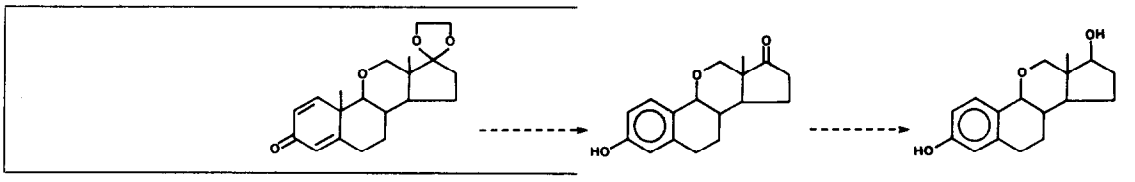
to effects of the same changes on other types of hormonal activity.

As the first 11-oxa analogue of a non-progestational hormone, we synthesized 11-oxa-estradiol (XLVI). A reasonable route to this hormone analogue



XLVI

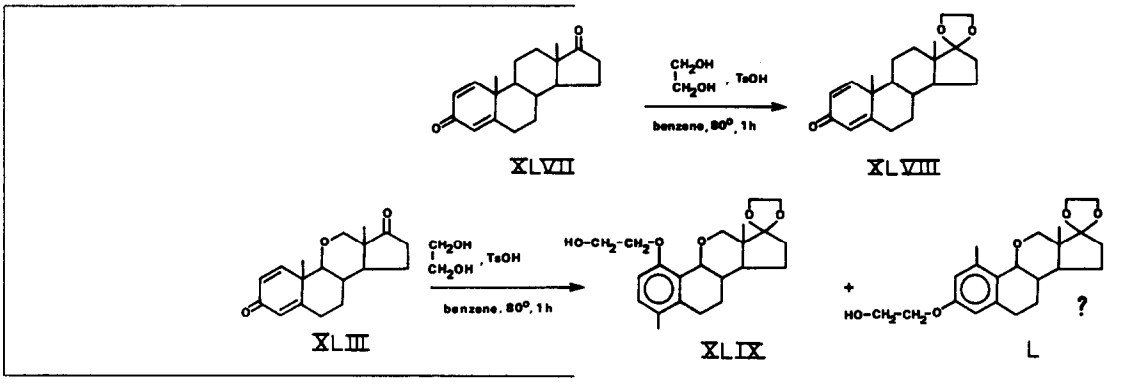
seemed the aromatization of the 17-monoketal of 11-oxa-1,4-androstadiene-3,17-dione (XLIII), described above in connection with the synthesis of 11-oxa-ethisterone (XXIII).



3. *The synthesis of 11-oxa-estradiol* (XLVI)

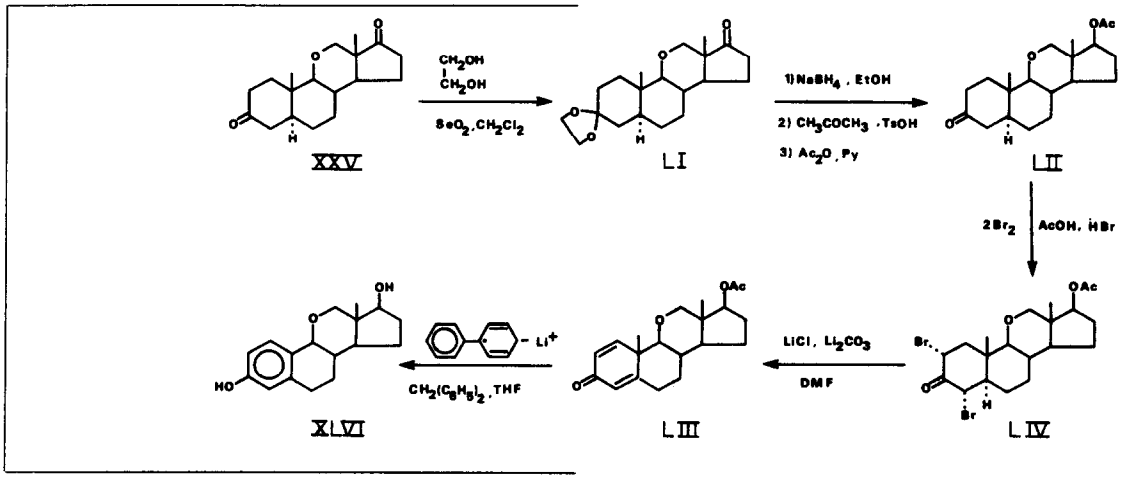
The preliminary biological results obtained with 11-oxaprogesterone, enticed us to investigate the biological effects of the replacement by oxygen of the 11-methylene group (in the case of glucocorticoids, of the 11-carbinol, respectively carbonyl group), also

However, in contradistinction to 1,4-androstadiene-3,17-dione (XLVII) which is readily monoketalized in position 17, under preservation of the dienone structure in ring A (cf. XLVIII), the 11-oxa analogue XLIII underwent, under identical conditions, a dienone-phenol rearrangement.



on other steroid hormones. In engaging in this programme, we were, of course, perfectly aware of the fact that one cannot extrapolate from the effects of structural changes on one type of hormonal activity

We therefore ketalized, in excellent yield, the saturated 11-oxa 3,17-diketo androstane XXV selectively, with ethylene glycol and selenium dioxide in dichloromethane, and reduced the resulting 3-ethylenedioxy

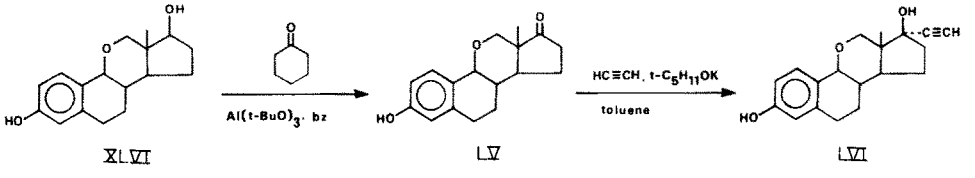


17-monoketone LI with sodium borohydride in ethanol; liberation of the 3-keto group and acetylation led to 17β-acetoxy-11-oxa-5α-androstan-3-one (LII). Dibromination and dehydrobromination gave the acetoxy dienone LIII which was reductively aromatized, according to Dryden's method [13], to 11-oxa-estradiol (XLVI). The yield in the reductive aromatization of the oxa dienone LIII was significantly lower than in the ordinary steroid series.

4. *11-Oxa-17α-ethynylestradiol* (LVI)

We next turned our attention to the synthesis of the 11-oxa analogue of 17α-ethynylestradiol, a product which has gained considerable interest in the field of fertility control.

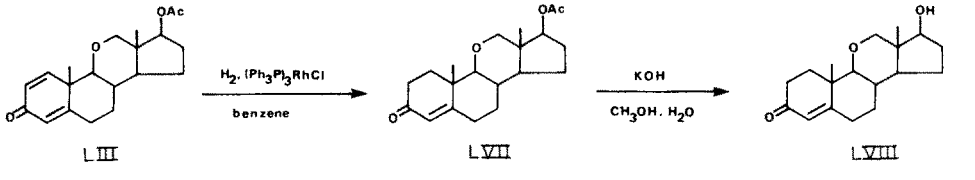
Oppenauer oxidation of 11-oxa-estradiol (XLVI) gave in 70% yield 11-oxaestrone (LV) which was transformed, in the classical fashion, with acetylene and tertiary potassium amylate, into 17α-ethynyl-11-oxa-estradiol (LVI).



XLVI LV LVI

5. *11-Oxatestosterone* (LVIII)

A suitable intermediate for the synthesis of the 11-oxa analogue LVIII of the male sex hormone, testosterone, was available from the synthesis of 11-oxa-estradiol (XLVI). Indeed, the 17β-acetoxy dienone LIII, the aromatization of which had led to the analogue of estradiol, could be reduced selectively, in 87% yield, with hydrogen and tris(triphenylphosphine)-rhodium chloride, to 11-oxatestosterone acetate (LVII) which was hydrolyzed with aqueous methanolic potassium hydroxide to 11-oxatestosterone (LVIII).



LIII LVII LVIII

C. *Biological activities*

We can now say a few words about the results of preliminary and, as already mentioned, fragmentary biological investigations of some of the 11-oxa hormone analogues synthesized.

The first point concerns new results on the *anovulatory activity* of *11-oxaprogesterone* (I) itself. The Contraceptive Development Branch of the Center for Population Research of the NICHD has tested the product in rats, the material being administered subcutaneously two days prior to the expected estrus, the animals being sacrificed on the expected day of estrus, and their oviducts examined for ova. While, as can be seen in Table 1, progesterone is in that assay

TABLE 1

Ovulation Inhibition Assays on Progesterone and 11-Oxaprogesterone

Assay	Dose (mg)	% Inhibition Progesterone	% Inhibition 11-Oxaprogesterone
Rats, subcut. administr. 2 days prior to estrus	0.5	30	
	1.0	90	0
	2.0	100	
	5.0		0
Rabbits, mating-stim., subcut. administration	1.0	66	
	2.0	66	
	3.0		0
	4.0	75	
Rabbits, Cu(OAc)$_2$-stim., subcut. administration	0.6		50
	0.9	80	100
	1.2		100
	2.3		100

100% active at a dose level of 2 mg, and 30% active at a dose level of 0·5 mg, 11-oxaprogesterone is inactive even at a dose of 5 mg. The Center for Population Research has also tested 11-oxaprogesterone (I) in a preliminary fashion for its ovulation inhibitory activity in the rabbit, ovulation-stimulated by mating, and has found the product to be inactive at a dose level of 3 mg, whereas progesterone shows a 66% activity at 1 mg, and a 75% activity at 4 mg.

We thus see an important difference between the results obtained on one hand when the material is tested in rabbits in which ovulation is induced by injection of copper acetate and, on the other hand, when it is tested in rats, or in rabbits in which ovulation is induced by mating. Further investigations seem necessary and are to be carried out as soon as larger quantities of the product are available.

In Table 2 are summarized preliminary *progestational tests* on *11-oxa-17-acetoxyprogesterone* (III) and *11-oxa-ethisterone* (XXIII), compared respectively to 17-acetoxyprogesterone and ethisterone.

TABLE 2

Progestational Activities of 17-Acetoxyprogesterone, 11-Oxa-17-acetoxyprogesterone, Ethisterone, and 11-Oxa-ethisterone

Assay	Dose (mg)	Activity (mean values) 17-Acetoxy-progesterone	11-Oxa-17-acetoxy-progesterone
Clauberg-McPhail	0.025	< +0.5	
	0.050	+1.9	
Oral	0.100	+2.9	
	0.5		< +0.5
	1.0		< +0.5
	4.0		+1.9

Assay	Dose (mg)	Activity (mean values) Ethisterone	11-Oxa-ethisterone
Clauberg-McPhail	0.5		< +0.5
	1.0		< +0.5
Subcutaneous	2.0	+2.6	
	4.0	+3.4	+3.0
	8.0	+3.8	

TABLE 3

Effects of 11-Oxatestosterone and Testosterone on the Seminal Vesicles, Ventral Prostate and Levator Ani of the Castrated Rat

Compound	Total Dose (mg)	Mean Tissue Weight (mg) Seminal Vesicle	Ventral Prostate	Levator Ani
0 (Control)	0	9	12.8	42
11-Oxa-testosterone	3	26.8	44	53
Testosterone	0.6	33.8	59.8	52.5
		p-value: < 0.02		

In the *oral* Clauberg assay, 11-oxa-17-acetoxyprogesterone behaves qualitatively as expected, and shows only weak progestational activity, approximately one eightieth of the activity of 17-acetoxyprogesterone (cf. Fig. 2). As a matter of fact, the diminution of activity in this case is much greater than the diminution of the subcutaneous progestational activity of progesterone upon replacement of the 11-methylene group by oxygen.

On the other hand, qualitatively analogous to the situation with respect to progesterone (cf. Fig. 2), the introduction of the 11-oxa structure into ethisterone results also in a diminution of *subcutaneous* progestational activity, however to a much smaller degree. Almost surprisingly, the activity of 11-oxa-ethisterone reaches approximately two thirds to three quarters of that of ethisterone. Normally, the correlation of the effect of a particular chemical change on one and the same type of biological activity in various hormonal steroids is closer. However, a combination of so many factors is responsible for the magnitude of a biological manifestation, that it would seem unwise to speculate on the exact causes of such "deviations" in structure-activity relationships, particularly when only preliminary biological data are available.

We have as yet no information on eventual ovulation inhibitory activities of the 11-oxa analogues of 17-acetoxyprogesterone and of ethisterone.

The first results on the *androgenic activity* of *11-oxatestosterone* (LVIII) are summarized in Table 3.

In the seminal vesicle, ventral prostate, and levator ani assays on the castrated rat, 11-oxatestosterone is definitely active, although less active than testosterone. At a dose of 3 mg, 11-oxatestosterone has approximately the same effect on the levator ani as 0·6 mg of testosterone, whereas a relatively weaker effect on the seminal vesicle and the prostate is observed. In other words: the replacement of the 11-methylene group by oxygen has, on the androgenic and anabolic activities (if one can consider the levator ani test as authentically reflecting anabolic potency), an effect comparable to that on progestational activity: the 11-oxa product is active but to a significantly lesser extent than the natural hormone.

We have also received the preliminary results on the *uterotropic effect of 11-oxa-estradiol* (XLVI). According to the Center for Population Research, the product has only extremely low uterotropic activity, the potency estimate being less than 0·1%, which means that it has less than one thousandth the activity of estradiol. The diminution of estrogenic activity upon replacement of the 11-methylene group by oxygen, seems to exceed very considerably that observed for other hormonal activities upon the analogous chemical modification.

No results are available on the ovulation inhibitory activity of 11-oxa-estradiol. If this product were to possess ovulation inhibitory activity of any consequence, it should merit—because of its very low estrogenic activity—considerable interest. This should also hold for other 11-oxa estrogens.

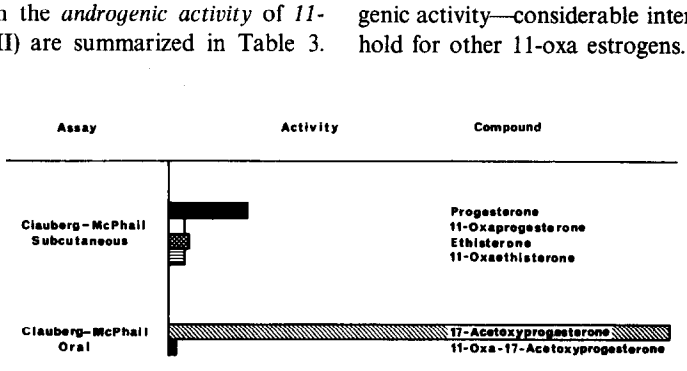
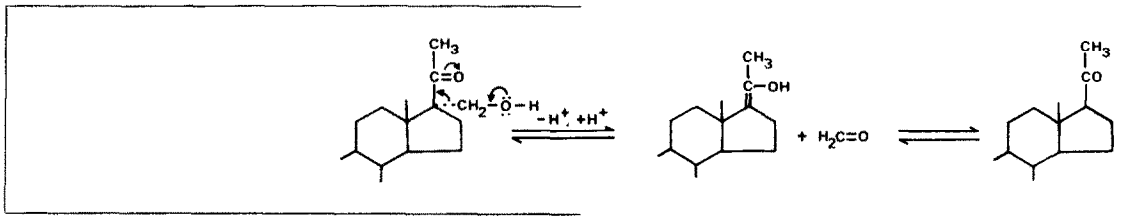


Fig. 2. Comparisons of progestational activities of progesterone and 11-oxaprogesterone, ethisterone and 11-oxaethisterone, 17-acetoxyprogesterone and 11-oxa-17-acetoxyprogesterone.

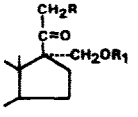
In summary, replacement of the 11-methylene group by oxygen diminishes the progestational, androgenic, anabolic, and estrogenic activities of the sex hormones, this effect being apparently particularly strong in the case of estrogenic activity. With the exception of 11-oxa-progesterone, the 11-oxa hormone analogues synthesized have not yet been tested for their ovulation inhibitory or for other antifertility activities. In one of the anovulatory assays, 11-oxaprogesterone showed significantly enhanced ovulation inhibitory activity, whereas it was inactive, at the dose levels studied, in the other anovulatory tests performed.



PART II: 17α-HYDROXYMETHYL AND 17α-ACYLOXYMETHYL ANALOGUES OF STEROID HORMONES

A. *Introduction*

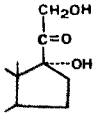
As already implied, we shall not discuss here 11-oxa analogues of corticoid hormones. We should rather like to report shortly on hormone analogues of a very different kind, in which the ring system of natural hormones has not been changed: 17α-hydroxymethyl and 17α-acyloxymethyl hormone analogues of the progesterone-corticoid group.

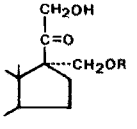


R=H, OH, O-acyl

R_1=H, acyl

The biological investigation of 11-oxygenated 21-hydroxylated analogues of this family seemed of interest, not only because of their chemical analogy or, if we may say so, homology, with potent 17α-hydroxylated glucocorticoids and anti-inflammatory agents, but also because the comparison of the activities of 17α-hydroxymethylated and 17α-hydroxylated glucocorticoids might possibly shed some light on the biochemical rôle of the 17α-hydroxy function of this latter group of therapeutically important substances cf. [14].





On the other hand, as we have suggested already several years ago [14, 15], there seems to exist a strong, we believe convincing, evidence to the effect that bulky substituents in position 17α, such as alkyl, bromine, and acyloxy groups, increase in general the progestational activity of progesterone and its derivatives. In this perspective, the synthesis of 17α-acyloxymethylprogesterones appeared attractive. It became even more tempting when considering that 17α-acyloxyprogesterones are potent orally active progestogens and antifertility agents.

The interest in the biological activities of free 17α-hydroxymethylprogesterones seemed more debatable, not only because of the inactivity of 17-hydroxyprogesterone, but also because such systems could be chemically labile. However, one kind of chemical lability could be of interest. Indeed, if under physiological conditions a retro-aldol reaction were to occur, 17α-hydroxymethylprogesterone could actually act as a progesterone releaser.

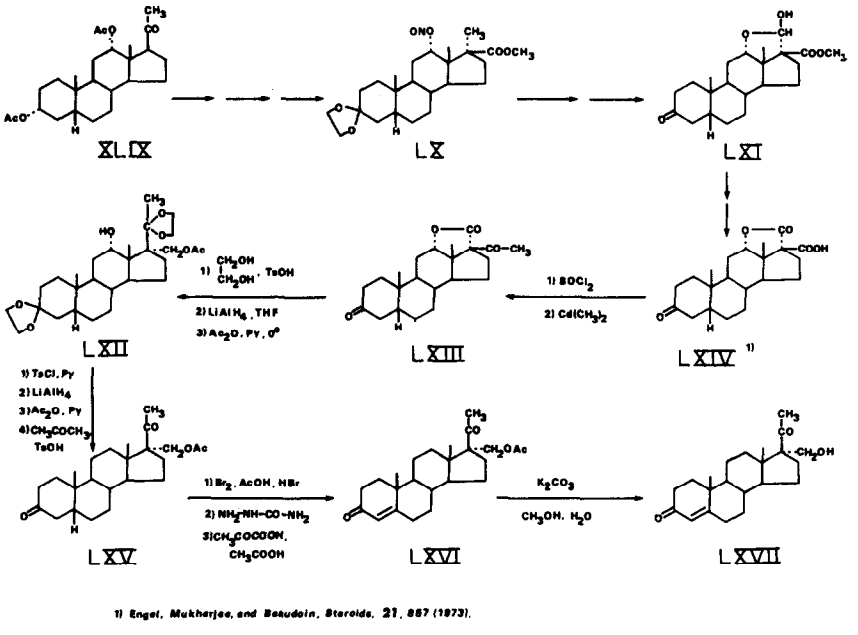
In the present communication we shall be mostly concerned with 17α-acetoxymethyl and 17α-hydroxymethylprogesterone.

B. *Chemistry*

1. *The synthesis of 17α-acetoxymethylprogesterone* (LXVI) *and of 17α-hydroxymethylprogesterone* (XLVII)

Since a short report on the syntheses of these products has already been presented last June at the International IUPAC Symposium on Natural Products in Ottawa [16], we shall only summarize the salient facts.

The products were obtained by two pathways. In the first one (cf. Chart 8), the 12-nitrite LX of methyl 3-ethylenedioxy-12α-hydroxy-17α-methyl-5β-etianate, prepared from 3α,12α-diacetoxy-5β-pregnan-20-one (LIX) by the use of a Favorsky rearrangement of its 17α-bromide, was subjected to a Barton photolytic transfer reaction and the hemiacetal LXI of the hydroxy aldehyde, obtained in the usual manner, was oxidized to the lactone ester, the methyl ester group of which was selectively saponified (cf. LXIV). This part of the synthesis has already been published [17]. The classical development of the methyl ketone side chain was followed by protection of the two keto functions, reduction of the lactone to the 12α-hydroxy 17α-hydroxymethyl derivative and by selective acetylation of the primary alcohol group (cf. LXII). Removal of the 12-hydroxy function by lithium aluminum hydride reduction of its tosylate and liberation of the keto groups led to the 3,20-diketone LXV, into which the 4-double bond was introduced in a classical fashion. The resulting 17α-acetoxymethylprogesterone (LXVI) was readily hydrolyzed with potassium carbonate to the hydroxymethyl derivative LXVII.



1) Engel, Mukherjee, and Beaudoin, Steroids, 21, 867 (1973).

Chart 8

The second pathway (cf. chart 9) is much shorter and more versatile and is based on our alkyloxycarbonylation procedure of saturated ketones (cf. [16]). The enol diacetates LXIX of pregnenolone LXVIII were transformed with methyllithium in dimethoxyethane into the mixture of lithium enolates (LXX) which was treated with dimethyl carbonate. Hydrolysis with aqueous methanolic bicarbonate gave methyl Δ^5-17β-acetyl-17α-etienate (LXXIII), also obtained by a Stork carboxylation [18] of the lithium enolates LXX, followed by methylation. Oppenauer oxidation gave the 4-unsaturated 3,20-diketo ester LXXII. After protection of the keto groups, the ester function was reduced with lithium aluminum hydride and the protecting ketal functions of the resulting product (LXXI) were liberated in the classical fashion. Thus, 17α-hydroxymethylprogesterone (LXVII) was obtained in excellent yield. It was readily acetylated to 17α-acetoxymethylprogesterone (LXVI). Alternatively, the hydroxy diketal LXXI may be acetylated and the ketal functions removed subsequently.

2. *17α-Hydroxymethyl derivatives of corticoids*

We can not enter into a detailed discussion of our work on 17α-hydroxymethyl and 17α-acyloxymethyl analogues of corticoids, but we may illustrate by one

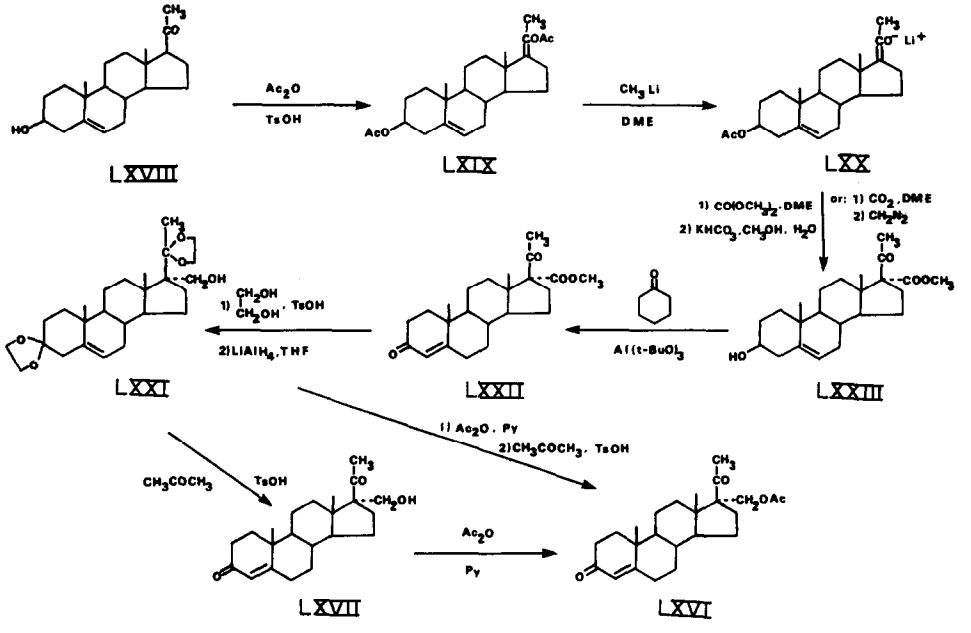


Chart 9

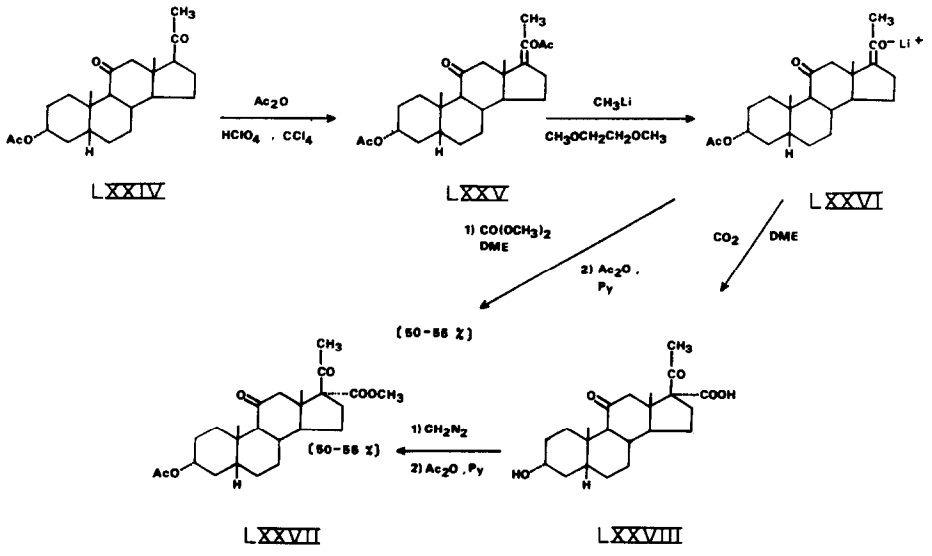


Chart 10

example the fact that the 17-alkoxycarbonylation or 17-carboxylation of a 20-ketone may be carried out in the presence of an 11-ketone. As is well known, the 20-keto function of 3α-acetoxy-5β-pregnane-11,20-dione (LXXIV) can be selectively enol-acetylated [19] (cf. chart 10). The resulting mixture of enol acetates (LXXV) can now be transformed into the mixture of the lithium enolates LXXVI which undergoes in very satisfactory yield alkoxycarbonylation with methyl carbonate [16] or carboxylation according to Stork[18].

It is at this point that we should like to conclude the discussion of the syntheses of 17α-hydroxymethyl hormones of the progesterone-corticoid group and consider the biological results obtained on 17α-acetoxymethylprogesterone (LXVI).

C. *Biological data*

The homologue of "Provera", 17α-acetoxymethylprogesterone (LXVI), was tested both under the auspices of the Contraceptive Development Branch of the Center for Population Research of NICHD, and by Dr. E. Shipley of the Endocrine Laboratories of Madison, for its subcutaneous progestational activity in the Clauberg–McPhail assay. At 2, 2·7, 5·3, and 11 times the dose level at which progesterone is fully active (+4 response in the McPhail scale), the product proved completely inactive, which means that it cannot have more than one eightieth to one hundredth of the activity of progesterone; that it is, like 17-hydroxyprogesterone, for all practical purposes, progestationally inactive.

To our knowledge, this is the first example, of course with the exception of 17-hydroxyprogesterone, of a 17α-substituted progesterone or progesterone analogue, not having other structural features which diminish progestational activity, which does not show significant activity in the Clauberg test.

The evidence for the positive effect of bulky substituents in position 17α on the progestational activity of progesterone and chemically related products is such that we are not yet inclined to dismiss, even in the light of the just reported result, the concept that such groups generally increase progestational activity. We believe that we should rather look for an explanation of the inactivity of 17α-acetoxymethylprogesterone.

One of the possible explanations would be based on the assumption that the acetate ester of 17α-acetoxymethylprogesterone be hydrolyzed under physiological conditions which would lead to 17α-hydroxymethylprogesterone (LXVII). Like the biologically inactive 17-hydroxyprogesterone, this product shows hydrogen bonding (between the 17^1-hydroxy group and the 20-ketone). It is conceivable that such hydrogen bonding would, in itself, not be beneficial to the interaction of the product with the receptor but, furthermore, the examination of models reveals readily that, if such hydrogen bonding occurs, the conformation of the side chain is, similarly to that of the intramolecularly hydrogen-bonded* (and biologically inactive) 17-hydroxyprogesterone, such that the C=O linkage of the 20-carbonyl group points "down", towards the α-face of the molecule (cf. Fig. 3). As we have suggested already several years ago [20], it would be quite plausible that this conformation be unfavorable for progestational activity or, to put it

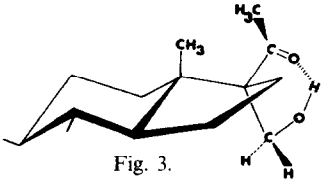


Fig. 3.

* Dr. W. L. Duax, the Medical Foundation, Buffalo, N.Y., kindly informs us that in one *crystalline* form of 17-hydroxyprogesterone no intramolecular hydrogen bonding can be detected by X-ray analysis.

differently, it could be that only those progesterones whose 20-carbonyl groups are directed towards the "upper" (β) face of the molecule, would show significant progestational activity.

Evidently, other explanations of the inactivity of 17α-acetoxymethylprogesterone are conceivable, such as the occurrence, under physiological conditions, of rearrangements. Our very tentative hypothesis may become less tentative—or may have to be abandoned—in the light of experiments presently in progress. At first, within a very short time, we should have the results on the progestational activity of 17α-hydroxymethylprogesterone (LXVII)—which, according to our hypothesis, should be inactive—and we shall also test other, less readily hydrolyzed esters of 17α-hydroxymethylprogesterone which, according to our hypothesis, should be active. We hope to be able to report soon on these investigations.*

Acknowledgements—The biological assays were carried out under the auspices of the Contraceptive Development Branch of the Center for Population Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, and by Dr. E. Shipley, Endocrine Laboratories of Madison, Inc., Madison, Wisconsin; we express to our colleagues and to the administrations of these institutions our gratitude for their splendid cooperation. Sincere thanks are due to Dr. T. Iwadare for his cooperation in some of the experiments, to Mrs. J. Capitaine for her constant help and collaboration, and to Mrs. G. Pelletier and Miss D. Thibeault for devoted technical assistance. The research upon which a considerable part of this communication is based was performed pursuant to Contracts No. NIH-NICHD-72-2714 and NO1-HD-2-2714 with the National Institutes of Health, U.S. Department of Health, Education, and Welfare; this support is greatefully acknowledged. We further express our appreciation to the National Research Council of Canada, to the Ministère de l'Education du Québec, and to Ayerst Laboratories, Montreal, who have also supported parts of the reported investigations. Sincere thanks are due to Ayerst Laboratories and to its Director of Research, Dr. R. Deghenghi, for having most generously degraded substantial amounts of hecogenin acetate for us, and to Canada Packers Ltd., Toronto, Ontario, Canada, and to Ciba-Geigy Ltd., Basle, Switzerland, for having kindly supplied other starting materials used in our syntheses. We sincerely thank the Organizing Committee of the 4th International Congress on Hormonal Steroids for the kind invitation to present this paper.

* *Note added in proof.* 17α-Hydroxymethylprogesterone (LXVII) seems to be indeed inactive in the subcutaneous Clauberg assay; however, so are also—according to very recent preliminary results—its benzoate and pivalate esters. Since it does not appear probable that these esters are hydrolyzed rapidly and completely *in vivo*, another explanation than the one tentatively advanced above, for the remarkable progestational inactivity of 17α-acyloxymethylprogesterones, and possibly also for the inactivity of 17α-hydroxymethylprogesterone itself, will have to be sought.

REFERENCES

1. (*a*) Engel Ch. R. and Roy Chowdhury M. N.: *Tetrahedron Lett.* (1968) 2107–2111; (*b*) Engel Ch. R., Rastogi R. C. and Roy Chowdhury M. N.: *Steroids* **19** (1972) 1–24.
2. (*a*) Engel Ch. R., Rakhit S. and Huculak W. W.: *Can. J. Chem.* **40** (1962) 921–929; (*b*) Engel Ch. R. and Rakhit S.: *Can. J. Chem.* **40** (1962) 2153–2162.
3. (*a*) Oliveto E. P., Smith H. Q., Gerold C., Rausser R. and Hershberg E. B.: *J. Am. chem. Soc.* **78** (1956) 1414–1416; (*b*) Nussbaum A. L., Popper T. L., Oliveto E. P., Friedman S. and Wender I.: *J. Am. chem. Soc.* **81** (1959) 1228–1231; (*c*) cf. also: Capitaine J., Deghenghi R. and Engel Ch. R.: *J. Med. Chem.* **6** (1963) 79–82.
4. Gardner J. N., Carlon F. E. and Gnoj O.: *J. org. Chem.* **33** (1968) 3294–3297.
5. Bailey E. J., Barton D. H. R., Elks J. and Templeton J. F.: *J. chem. Soc.* (1962) 1578–1591.
6. Adachi J.: *J. chem. Soc. Japan* **71** (1950) 566.
7. (*a*) Turner R. B.: *J. Am. chem. Soc.* **75** (1953) 3489–3492; (*b*) LeMahieu A., Boris A., Carson M., Guthrie R. W. and Kierstead R. W.: *J. med. Chem.* **16** (1973) 647–649.
8. (*a*) Jardine F. H., Osborn J. A., Wilkinson G. and Young J. T.: *Chem. and Ind.* (*London*) (1965) 560; (*b*) Bennett M. A. and Longstaff P. A.: *Chem. and Ind.* (*London*) (1965) 846.
9. Siddall J. B., Baddeley G. V. and Edwards J. A.: *Chem. and Ind.* (*London*) (1966) 25–26.
10. Julian P. L., Cochrane C. C., Magnani A. and Karpel W. J.: *J. Am. chem. Soc.* **78** (1956) 3153–3158.
11. Robinson C. H., Finckenor L., Oliveto E. P. and Gould D.: *J. Am. chem. Soc.* **81** (1959) 2191–2195.
12. Djerassi C., Miramontes L., Rosenkranz G. and Sondheimer F.: *J. Am. chem. Soc.* **76** (1954) 4092–4094.
13. (*a*) Dryden H. L. Jr., Webber G. M. and Wieczorek J. J.: *J. Am. chem. Soc.* **86** (1964) 742–743; (*b*) Dryden H. L. Jr. and Webber G. M.: *Belg. Patent 64404* (Aug. 20, 1964).
14. Engel Ch. R.: *Acta endocr., Copenh. Suppl.* **51** (1960) 931.
15. Rakhit S., Deghenghi R. and Engel Ch. R.: *Can. J. Chem.* **41** (1963) 703–710.
16. Engel Ch. R., Dionne G. and Mukherjee D.: Abstracts, 9th International Symposium on the Chemistry of Natural Products, Ottawa (1974) p. 43A.
17. Engel Ch. R., Mukherjee D. and Beaudoin G. J.: *Steroids* **21** (1973) 857–875.
18. Stork G., Rosen P., Goldman N., Coombs R. V. and Tsuji J.: *J. Am. chem. Soc.* **87** (1965) 275–286.
19. Cf., for instance, (*a*) Anderson H. V., Garrett E. R., Lincoln F. H. Jr., Nathan A. H. and Hogg J. A.: *J. Am. chem. Soc.* **76** (1954) 743–746; (*b*) Barton D. H. R., Evans R. M., Hamlet J. C., Jones P. G. and Walker T.: *J. chem. Soc.* (1954) 747–751; (*c*) Engel Ch. R., Hoegerle R.-M. and Deghenghi R.: *Can. J. Chem.* **38** (1960) 1199–1208.
20. Rakhit S. and Engel Ch. R.: *Can. J. Chem.* **40** (1962) 2163–2170.