FACULTY OF SCIENCE

THESIS

SUBMITTED

TO THE SCHOOL OF GRADUATE STUDIES

OF LAVAL UNIVERSITY

for the

DEGREE OF DOCTOR OF SCIENCE

by

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THE SYNTHESIS OF 11-HETERO STEROIDS.

May, 1968

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Acknowledgements

I wish to express my profound gratitude to Professor Charles R. Engel for the stimulating scientific discussions and constructive criticism with which he has helped me during the course of this investigation. His unfailing help and continuous encouragement played a large part in the realization of this work.

I am very much indebted to Professor R.H. Burnell for suggestions and advice and particularly for the valuable hours he has spent for me inspite of his preoccupations.

I am very thankful to Professor J.B. Stothers for his generous help in the interpretation of some of the NMR spectra described in this thesis.

I like to express my sincere appreciation to my colleagues of the Organic Chemistry Laboratories of the Chemistry Department for their cooperation and helpful attitude during the period I spent on this work. In particular, I am very much indebted to Mrs. J. Capitaine and Mr. D. Capitaine for their very generous help, kind cooperation and constant encouragement throughout this investigation. I am also very thankful to Dr. R.C. Rastogi for his help in some of the experiments, to Dr. M. Nagabhushanam and Mr. J.D. Medina for their valuable help and active cooperation on various occasions, and to Mrs. G. Pelletier for her devoted technical assistance.

I sincerely thank the National Research Council and the National Cancer Institute of Canada for awards which made this work possible.

INTRODUCTION

Steroids occupy a prominent place among the substances found in nature. This group of compounds comprises sterols, D-vitamins, bile acids, sex and adreno-cortical hormones, cardiotonics, saponins and alkaloids. Because of their important physiological properties, steroids have always been the subject of intensive investigations right from the beginning of this century. As a result, the structures of the sex and adreno-cortical hormones have been determined, and these hormones are now accessible by partial or total syntheses.

It is noteworthy that the steroid hormones, exhibiting very different biological activities, are closely related chemically, and that even relatively small changes in their chemical constitution or configuration can be responsible for striking changes in, or even total loss of, biological activity. Such intimate interdependance of biological activity and chemical structure is also found in other types of hormones; the pituitary hormones vasopressin (1) and oxytocin (2) represent excellent examples of this relationship in the field of polypeptide hormones.

From both the practical and theoretical point of view, it is of great interest to correlate chemical constitution with biological activity. The establishment of valid relationships would not only permit an insight into the mode of action of this group of biologically active compounds but also allow purposeful research for valuable synthetic substitutes of natural products.

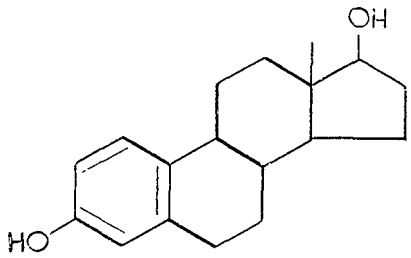
In the framework of a general study of the relationships between chemical structure and biological activity of steroids, the present project of the

synthesis of 11-hetero steroids was initiated. The investigation of such compounds appears attractive not only in view of the chemical and biological interest of natural steroid alkaloids but also in consideration of the possible biological importance of certain aza and oxa derivatives of steroid hormones. Synthetic hetero analogs of steroid hormones would closely resemble natural hormones stereochemically and differ from them only with respect to one important feature, the replacement of a hetero atom for a carbon atom in the steroid skeleton. The change in the geometry of aza hormone analogs where an -NH- function replaces a -CHOH- or $-CH_2-$ function of a natural hormone would be small, that where an -NH- function replaces a C=O function even smaller. This is also true, although to a lesser extent, for the oxa hormone analogs.

The presence of the typical structural features of natural hormones and the close geometrical resemblance with them allow us to visualize these nucleo-hetero hormone analogs not merely as a new group of potential hormones but also as potential hormone antagonists. One could indeed imagine that, because of their similarity with natural hormones, they could take their place at the receptor site, but that, in contradistinction with natural hormones, they could not exert hormonal actions because of their difference with them.

Also, there is a great volume of literature (3) on various aspects of the relationship between hormones and cancer; for example, breast and prostatic carcinomas exhibit an appreciable hormone dependance. Carcinomas of the prostate have been treated by orchidectomy, adrenalectomy and hypophysectomy with varying success (4), which indicates some hormonal dependance. Prostatic cancer has also been treated by administering female sex hormones, such as estradiol (I) and stilbesterols. Both male and female sex hormones have been used for the treatment of breast cancer. Progesterone (II), the hormone of

the corpus luteum, has been used against cancer of the cervix (5,6). Testosterone (III) is the standard androgen used in certain types of advanced breast cancer. Some androsterone (IV) derivatives have also been employed for that purpose (7).



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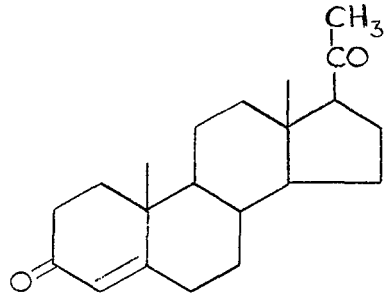
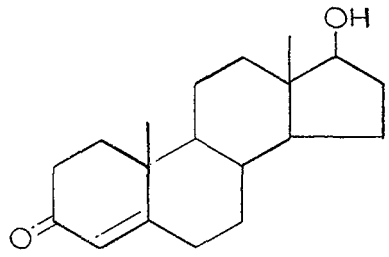
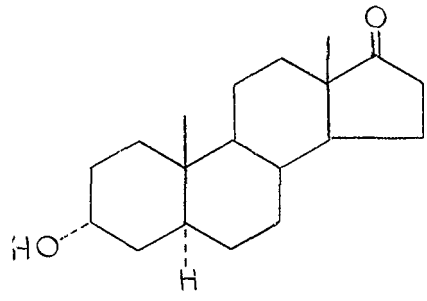


II



III

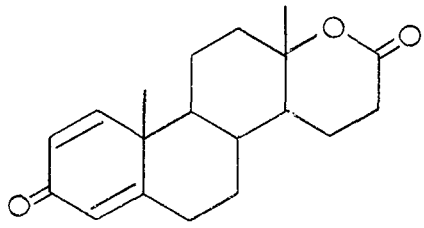


IV

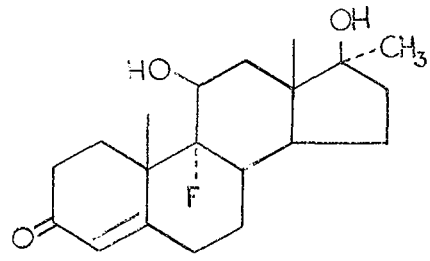
In view of the fact that suppression of hormone production or removal of hormone secreting glands influences the development of cancer, and may lead at least to its temporary control, it may be reasonable to take into consideration that hormone antagonists could play an important role in cancer chemotherapy. In this respect, the synthesis of a potential hormone antagonist could be regarded of particular interest, quite apart from the fact that the study of every new hormone analog could be of value, in view of the

known beneficial effects of certain hormones in the treatment of various kinds of cancer.

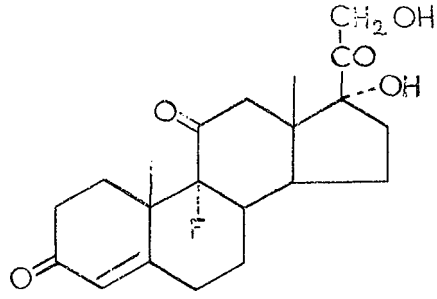
It is also worthwhile to note that Δ^1-testolactone (V) shows no trace of androgen activity, but that it was found to be extremely effective in causing objective regression of the tumor in 7 out of 23 patients with advanced breast cancer (8). Its effect was as good as that of testosterone propionate, but it had the advantage that it produced no undesirable hormonal side effects. Recently, Tagnon and co-workers (9) have reported that Δ^1-testolactone (V) is effective in patients who do not respond to testosterone propionate therapy. Among the fluorinated steroids, the most active ones against breast cancer are the 9α-fluoro steroids, namely 9α-fluoro-11β-hydroxy-17α-methyltestosterone (VI) and 9α-fluorocortisone (VII).



V

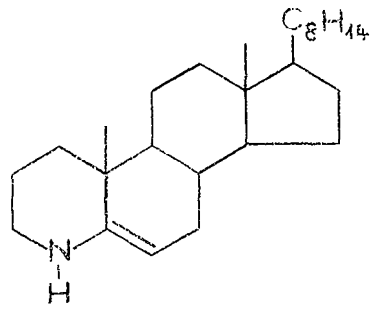


VI

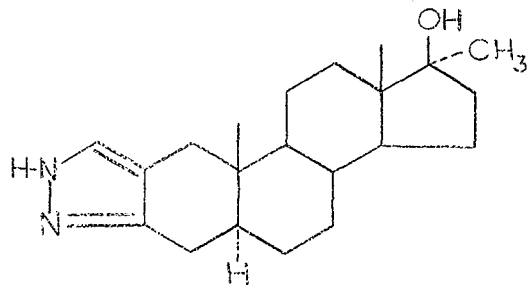


VII

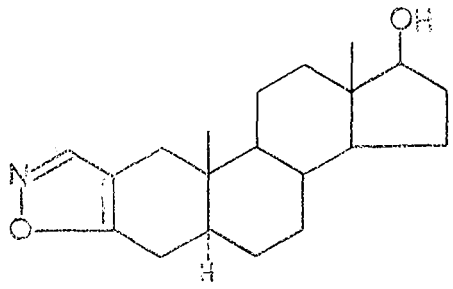
In addition to having hormonal properties, some of the heterocyclic steroids have shown other biological activities, such as to produce coronary artery dilation and to show anabolic activities. Thus, 4-aza-5-cholestene (VIII) is reported to be a potent coronary artery dilator (10). Among the heterocyclic steroids, a pyrazolo androstane (IX), an isoxazolo androstane (X),and a thiazolo androstane (XI), have been shown to be good anabolic agents (11, 12, 13, 14).



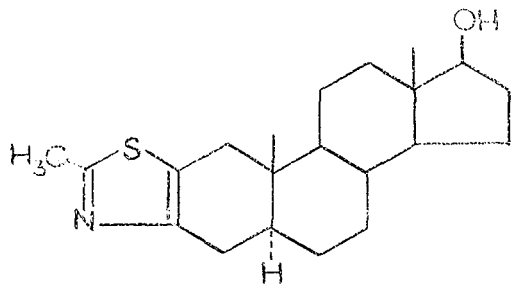
VIII



IX



X



XI

Among the great number of nucleo-hetero steroids, the synthesis of which could be contemplated, we regarded those of particular interest in which the hetero atom occupies a position of established biological significance, such as position 11 (the importance of which for glucocorticoid activity is known), since substitution at this position may have important biological effects.

Although our ultimate goal was and remains the synthesis of 11-hetero steroid hormone analogs of the progesterone-corticoid group and the study of their biological activities, we decided to concentrate our attention at first on the solution of the basic chemical problem of introducing the hetero atom into position 11 of the nucleus of steroids substituted in such a fashion as to allow their conversion, after the introduction of the hetero atom, to products with the typical structural requirements of hormones, such as the dihydroxy acetone side chain in the case of an analog of glucocorticoids. We considered the development of such structural features as a secondary problem.

It may be mentioned here that the first 11-hetero analogs of steroid hormones which we intended to synthesize were 11-hetero progesterones, not only because of the interest in progesterone and its derivatives, but also because 11-hetero progesterones may serve as precursors for the synthesis of 11-hetero corticoids. From the variety of hetero atoms which could be introduced in position 11, we were primarily interested in nitrogen and oxygen; in other words, we were primarily interested in the synthesis of 11-aza and 11-oxa progesterones.

As a matter of allied interest, we also wished to synthesize 3-amino 20-oxygenated and 3,20-diamino 11-hetero steroids. This seemed to be attractive in view of the occurrence in nature of various 3- and 20-amino

steroids with a normal carbon skeleton of the steroid nucleus and in view of their biological activities (15, 16, 17, 18)[1].

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1. 20α-Amino-3β-hydroxy-5-pregnene was isolated as its 3β-D-glucoside from the roots of Conopharyngia pachysiphon (Apocynaceae) and is a very potent hypotensive agent (15, 16). 3β-Dimethylamino-20β-methylamino-N-acetyl-5-pregnene (Saracocine) was isolated from the plant Saracocoa pruniformis (17).

   A number of alkaloids containing the typical steroid skeleton in which a nitrogen function in position 20 forms part of a five-membered ring have been isolated from plants, for example, connessine, funtuline, irehline; irehline also contains a 3β-amino group (18).

   There are also a number of other steroid alkaloids, for instance, solanum and veratrum alkaloids, possessing a nitrogen function which occupies a bridge-head position and which is part of both a five- and a six-membered ring, attached to position 16 of the steroid nucleus.

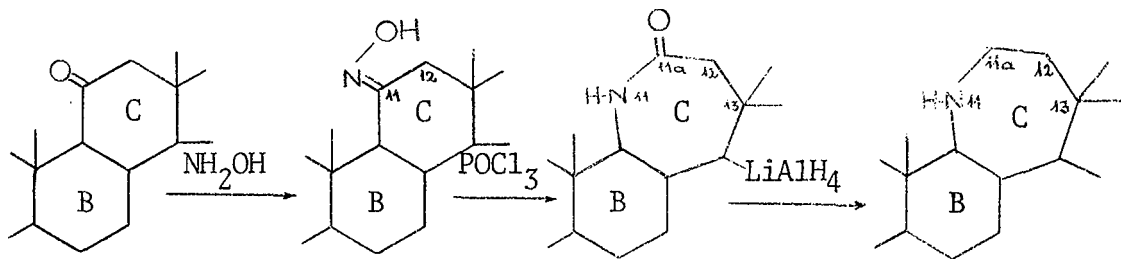
CHAPTER I

A General Outline of the Investigation

Having decided to launch on the synthesis of 11-aza and 11-oxa progesterones, there were two basic approaches which could be considered, namely that of total synthesis and that of partial synthesis.

Although several publications (20, 21, 22, 23) in which a total synthetic method was used for the synthesis of aza and oxa steroids have appeared recently, (cf. also an earlier publication on an aromatic product: 19), we have chosen the approach of partial synthesis, particularly because we wished to take advantage of starting materials with carbon-skeletons of known stereochemistry and also because we could thus deal from the onset with optically active products.

In the partial synthetic approach, an obvious choice for the synthesis of aza steroids is that of introducing the nitrogen function by a Beckmann rearrangement of a ketoxime to the corresponding lactam (24; compare also 25, 27, 28) (cf. i - iii).



i ii iii iv

However, in the case of such a procedure, an 11-ketoxime would have given a lactam[2] with the nitrogen atom in a 7-membered C ring, whereas, our aim was to synthesize 11-aza steroids with an unexpanded C-ring, products which would have a geometry almost identical to that of natural hormones.

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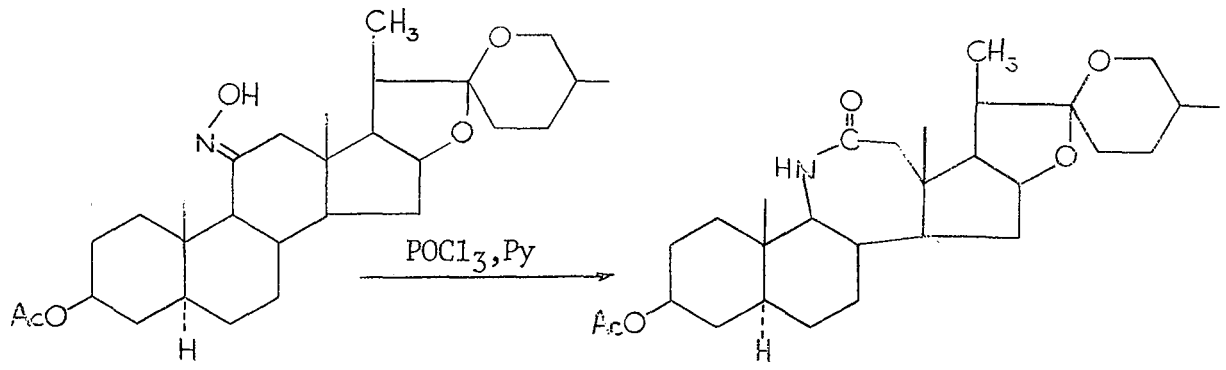
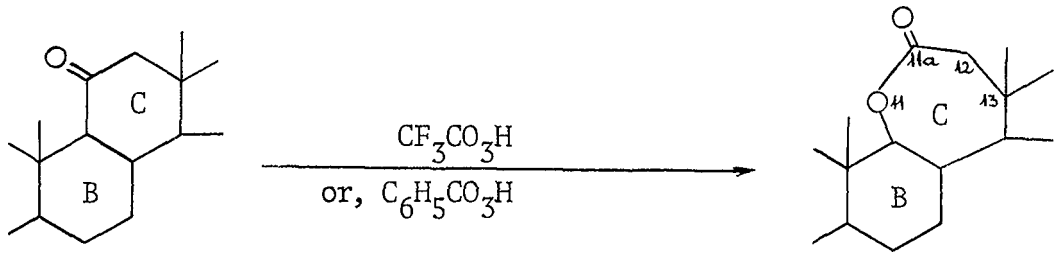
2. Of the two possible geometrical isomers of the oxime, the one with the oxime hydroxyl syn- to ring A would suffer from extreme steric compression, so that the preferentially formed oxime would be the one with the oxime hydroxyl anti- to ring A. The lactam obtained by rearrangement of an oxime of that configuration should possess the 11-aza-11a-oxo structure iii , on the basis of mechanistic considerations (119). This can also be deduced by analogy with the result of the Beckmann rearrangement of the oxime of 11-oxo tigogenin acetate (XII) which gives the lactam XIII (24).



XII XIII

In an analogous manner, one could consider the Bayer-Villiger oxidation (cf. 26, 29) of 11-keto steroids as an obvious choice for the synthesis of 11-oxa steroids.



v vi

In this case, again, one would obtain an oxa steroid[3] with the oxygen atom in a seven-membered C-ring. Furthermore, a Bayer-Villiger oxidation of 11-keto steroids may present considerable difficulties in view of the

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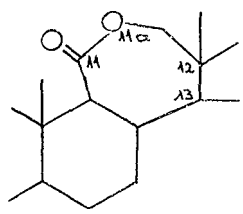
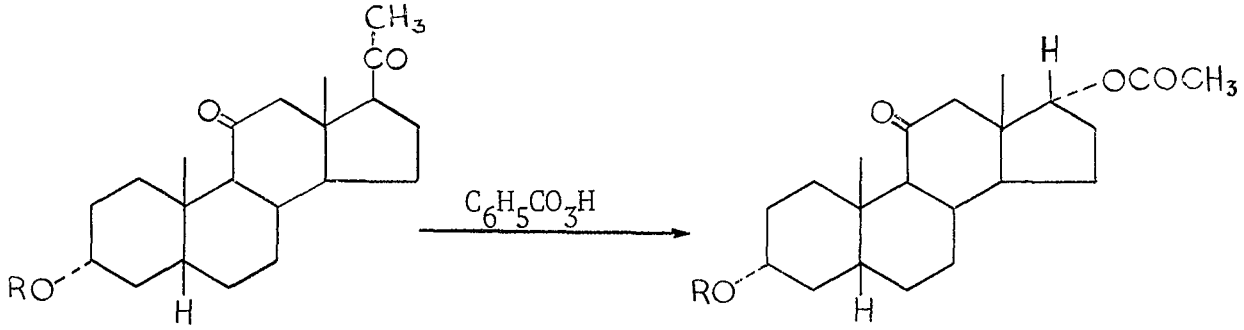
3. From mechanistic considerations (32, 33), the 11-oxa-11a-oxo structure vi of the lactone is more probable than the alternative 11-oxo-11a-oxa structure vii .



vii

fact that Sarett (31) was able to degrade 3α-acetoxy-5β-pregnane-11,20-dione (XIV) with perbenzoic acid to the 17-acetate XV, without affecting the 11-keto group.



XIV, R= $-COCH_3$, $-COC_6H_5$ XV, R= $-COCH_3$, $-COC_6H_5$

One could, of course, have considered to synthesize products with an enlarged C-ring (at least in the case of aza steroids) and to reduce the size of that ring subsequently. However, this would involve the opening of the seven-membered ring, degradation of the carbon-chain and subsequent recyclization. As has been observed in an analogous study on 17-aza steroids (30), such a procedure may present considerable difficulties.

Since we wished to embark on a combined program on the synthesis of 11-aza and 11-oxa steroids, it seemed logical to plan the two projects in such a way as to utilize the same key intermediates for both of them. Thus, our program was divided right at the onset in three different parts:

Part A: The synthesis of properly substituted ring C-seco steroids, for instance, 3,20-functionalized 9-oxo 9,12-seco 11-nor 12-acids.

Part B: The insertion of the hetero atom in position 11.

Part C: The development of the typical hormonal structures in ring A and in the side chain.

In the present thesis, we intend to discuss the realization of this program in three separate chapters as follows:

Chapter II: The synthesis of the key intermediates, namely of 3,20-functionalized ring-C-seco 11-oxo 12-acids in the 5α-pregnane series and of the corresponding 3-functionalized derivatives in the 5α-sapogenin series.

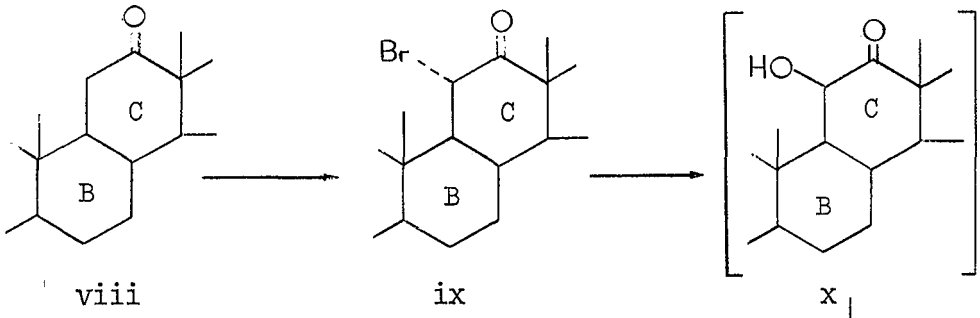
Chapter III: The synthesis of 11-oxa steroids.

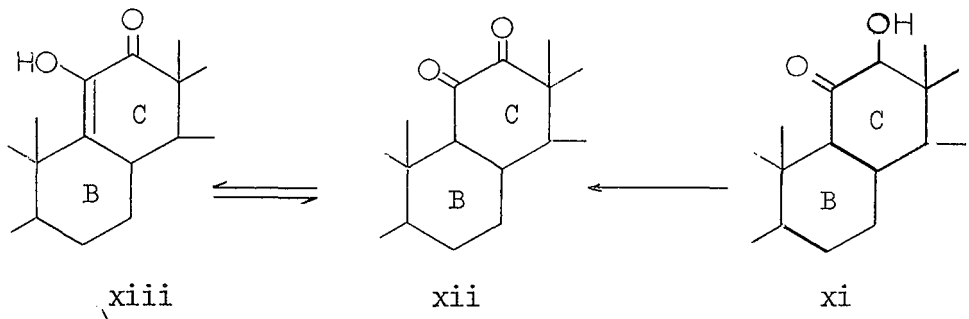
Chapter IV: The synthesis of 11-aza steroids.

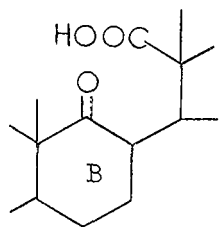
CHAPTER II

The Synthesis of 3,9,12,20-Functionalized Ring C-Seco Steroids

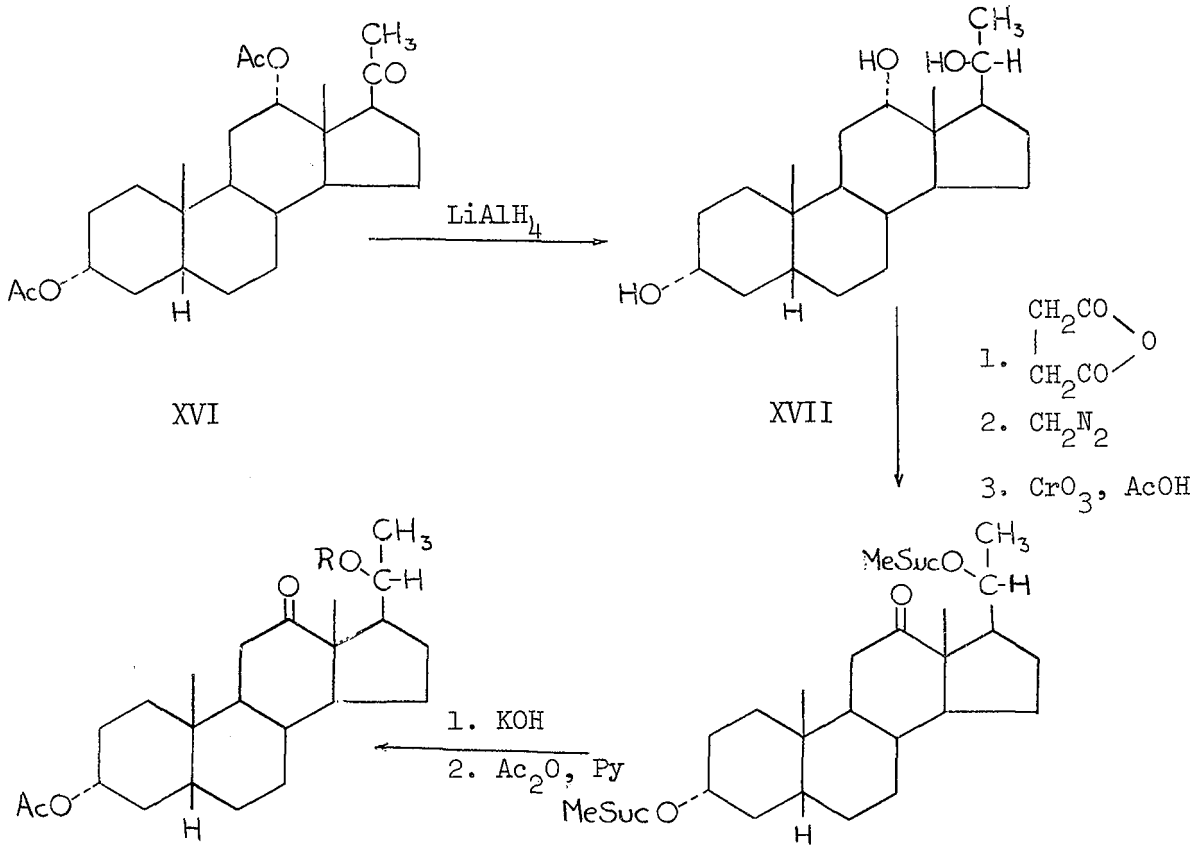
As early as in 1931, Wieland et al. (34, 35), in the course of the elucidation of the structure of bile acids, synthesized the first 9,12-seco 11-nor 9,12-oxygenated steroid derivative which had, however, no oxygen functions in positions 3 and 20. The German authors obtained their product from 12-oxocholanic acid (partial formula viii), according to the following scheme:







Later on, in 1959, Engel et al. (36) succeeded in synthesizing 9,12-seco 11-nor 9,12-dioxygenated steroid derivatives in the 5β-series, in low yield, in the presence of oxygenated functions in positions 3 and 20, using 3α,12α-diacetoxy-20-oxo-5β-pregnane (XVI) as starting material. Reduction of the 20-oxo pregnane XVI with lithium aluminum hydride to the triol XVII, protection of the 3 and 20 hydroxyl functions by partial succinylation, oxidation of the 12-hydroxyl function to the 12-oxo-derivative XVIII, and hydrolysis of the 3,20-diester to the 3,20-diol followed by acetylation gave the 3-acetoxy 20-hydroxy 12-oxo pregnane XIX and, in low yield, the diacetate XIXa (120, 121).



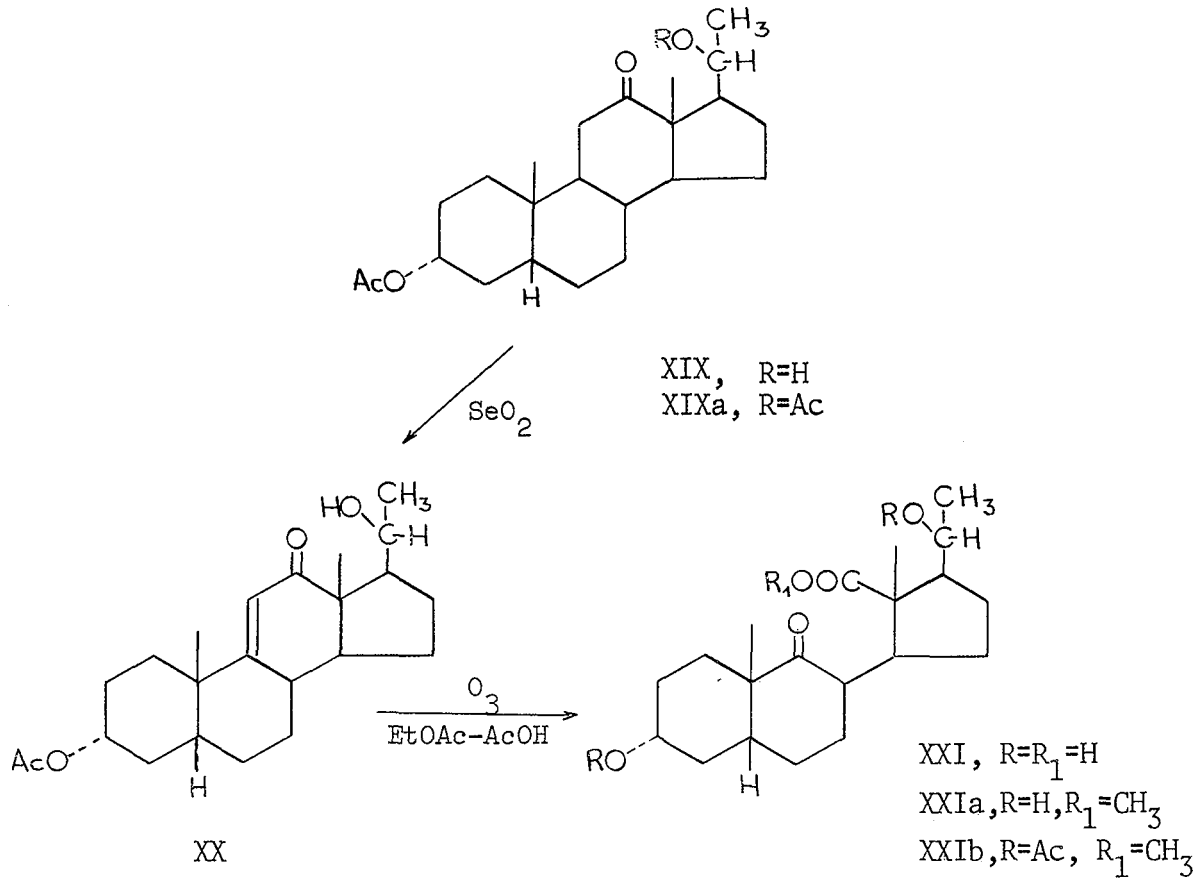
XVI

XVII

XIX, R=H
XIXa, R=Ac

XVIII

The monoacetate XIX on dehydrogenation with selenium dioxide gave the corresponding 9(11)-dehydro derivative XX, ozonolysis of which afforded the desired 3,9,12,20-tetraoxygenated 9,12-seco 11-nor steroids (cf. XXI, XXIa and XXIb).

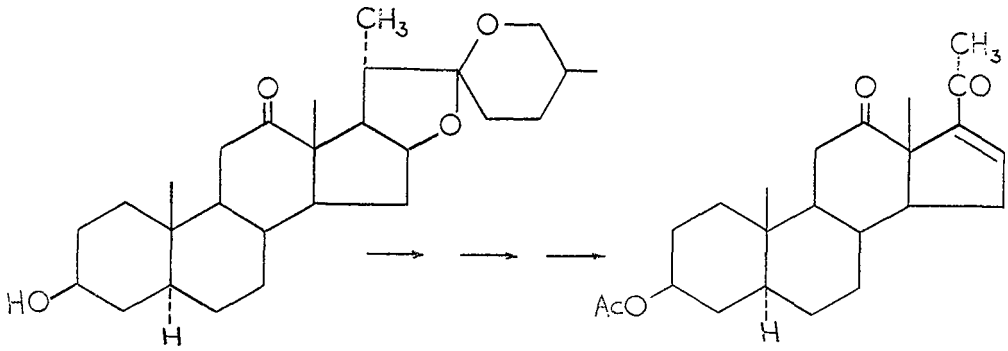


Subsequently, Engel et al. (37, 38) showed that in the unhindered 5α-series, analogous ring C-seco steroid derivatives could be obtained in good yields, since in that case the ozonolysis proceeded smoothly, with particularly high yields when carried out in pure ethyl acetate (cf. 38).

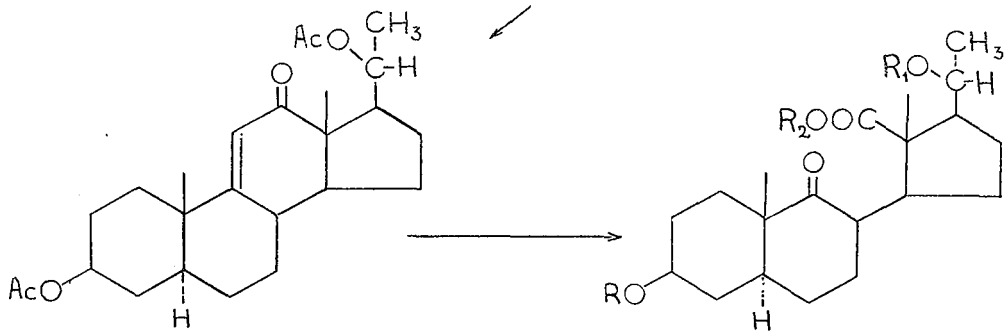
As we shall see in more detail in chapter IV, Engel et al. (38) also succeeded in introducing a nitrogen function in position 11 of the steroid nucleus, using the tetraoxygenated ring C-seco acid as starting material.

Based on these experiments, we employed as starting material for our experiments the readily available sapogenin hecogenin (XXII), which possesses the required 12-keto function and in which rings A and B are trans-fused. We could thus use the procedure which had already been elaborated in this laboratory.

Actually, there presented itself two general approaches to this problem; either degradation of the sapogenin "side chain"[4], followed by protection of the 3,20-oxygenated functions, and subsequent opening of ring C to the desired seco products (37, 38);



XXII XXIII

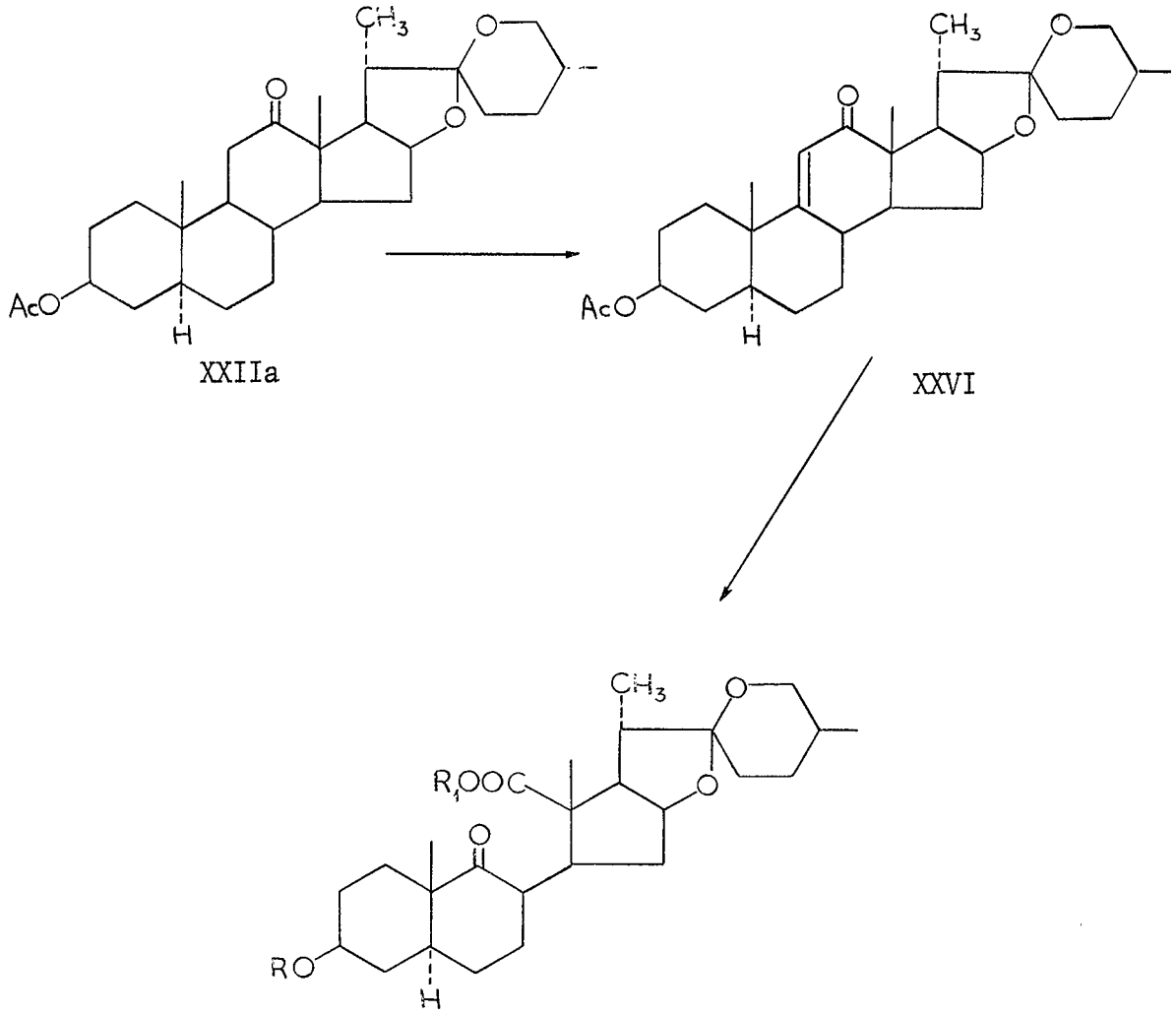


XXIV

XXV - XXVe, R = H, OAc,
R_1 = H, OAc, R_2 = H, CH_3

4. It is customary to employ the term "side chain" for the designation of the spiroketal moiety of spirostanes, although this is, actually, a hetero ring system and not a "chain".

or, opening of ring C prior to the degradation of the sapogenin side chain (cf. XXVII), and degradation of this moiety subsequent to the introduction of the hetero atom[5].



XXIIa

XXVI

XXVII - XXVIIc, R = H, OAc, R_1 = H, CH_3

5. This procedure was also first explored by Engel et al. (37), later by Kutney et al. (39).

The second approach has the obvious advantage that larger quantities of material are available for the elaboration of methods for the introduction of the hetero atom in position 11, but (as we shall see in the case of 11-oxa steroids; cf. also 39) it suffers from the disadvantage that the yields in the degradation of the side chain are much lower when the 11-carbon atom is replaced by a nitrogen or oxygen atom.

We have successfully followed both the routes for the synthesis of 11-oxa and 11-aza steroids.

Previously, this laboratory (37, 38) has used the method of Marker (40), as modified by Wall (41), for the degradation of the sapogenin side chain of hecogenin. We wished to investigate whether it would be advantageous to replace this procedure by a more recent modification (42) which differs from the classical degradation in so far as methylamine hydrochloride is used as the catalyst for pseudomerization of the sapogenin, instead of pyridine hydrochloride[6]. This modified procedure has been used in our laboratory with advantage for the degradation of smilagenin (43). However, in the case of hecogenin we found that the original method gives better results.

In the first series of experiments we followed essentially the pathway previously elaborated in this laboratory by Engel et al. (38) for the synthesis of the 3,9,12,20-functionalized ring C-seco steroids. Classical degradation of hecogenin acetate XXIIa gave the Δ^{16}-3,20-dione XXIII which, on catalytic reduction with 5% palladium-on-charcoal, gave the corresponding saturated dione XXX. Protection of the 12-ketone function by preferential ketalization with ethylene glycol and the boron trifluoride-ether complex afforded the 12-monoketal XXXI.

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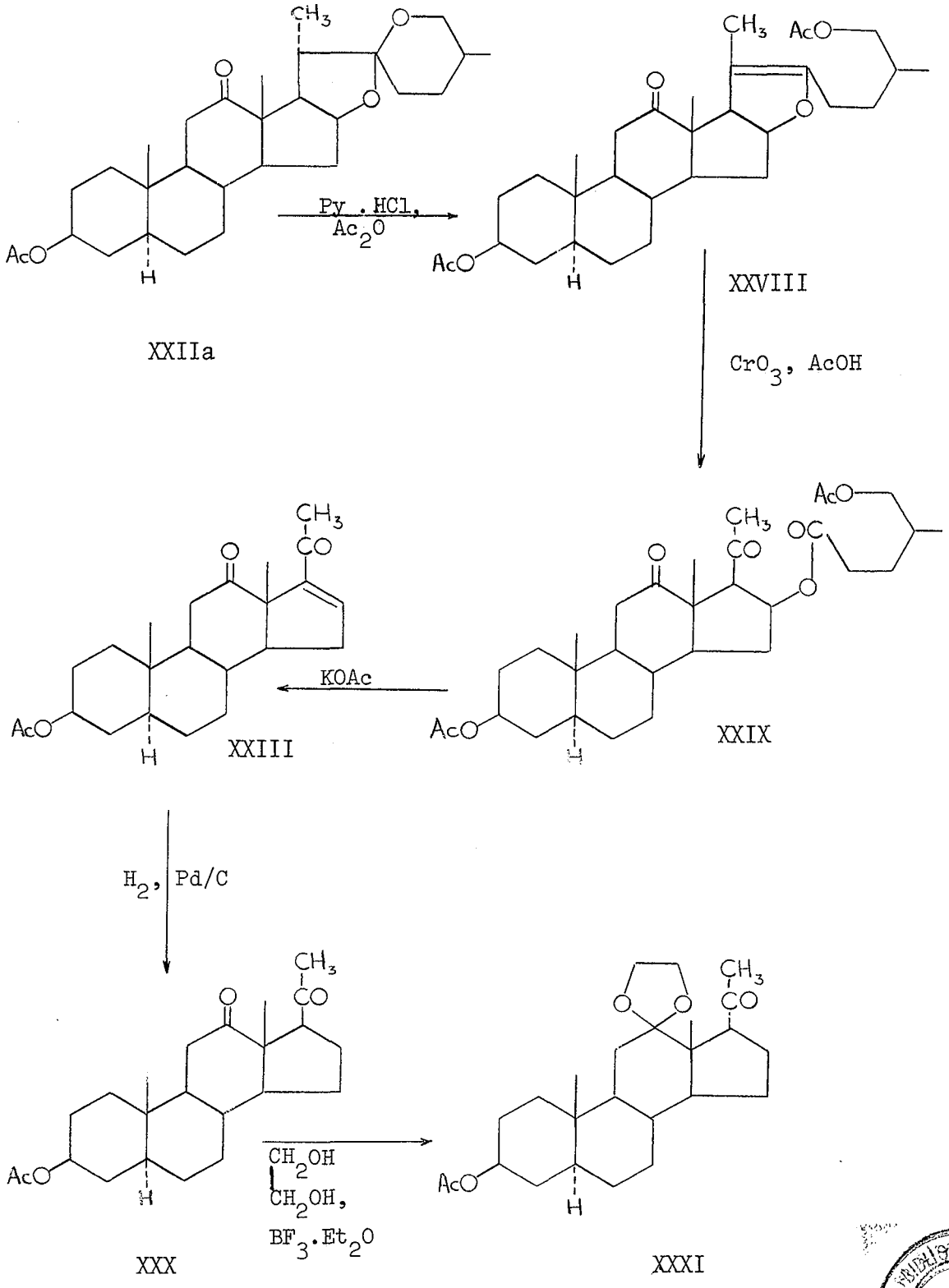
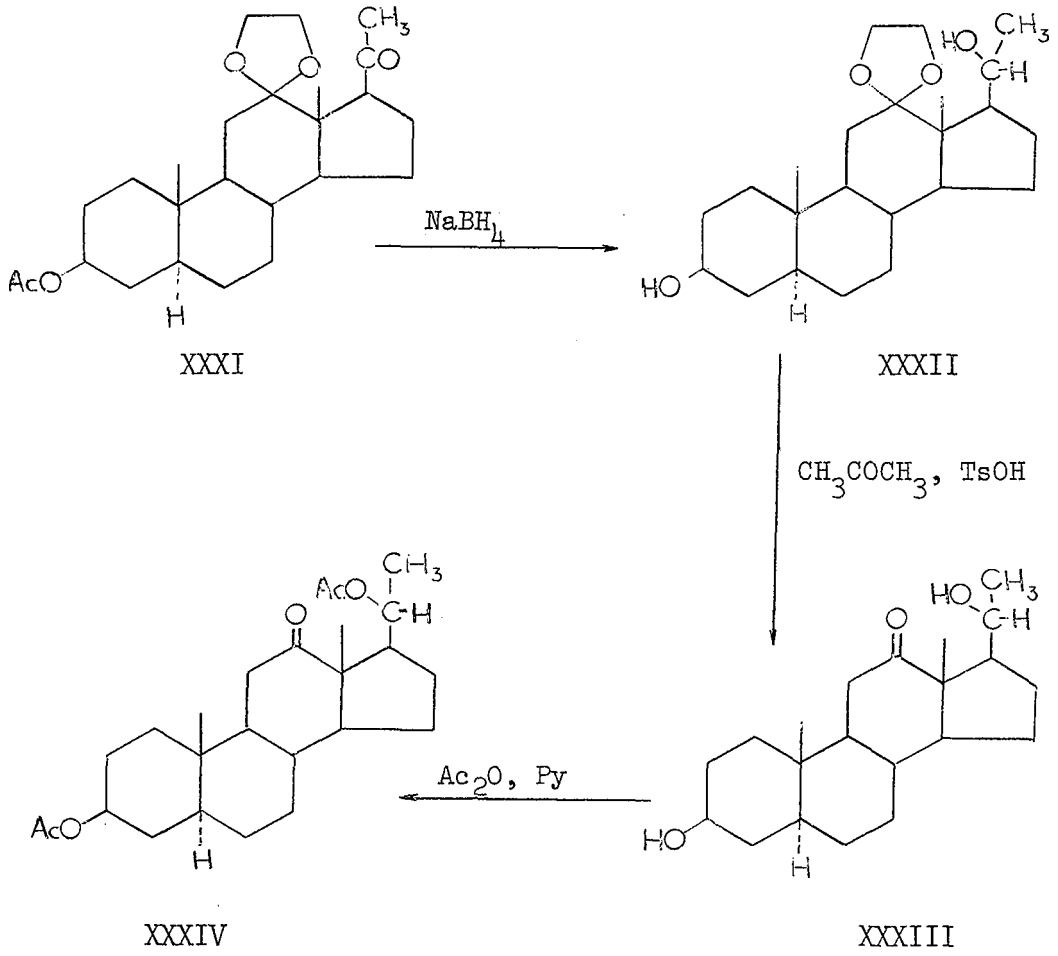
6. We express our sincerest thanks to Dr. M.E. Wall for very kindly communicating to us the details of his procedure prior to publication.



Reduction of the 12-monoketal XXXI with sodium borohydride to the dihydroxy ketal XXXII[7], removal of the 12-ketal function by an exchange reaction with acetone and p-toluenesulfonic acid (45), followed by acetylation of the dihydroxyketone XXXIII, gave the diacetoxy 12-ketone XXXIV. By using each time freshly distilled boron trifluoride-ether complex and ethylene glycol, we could raise the yield of the preferential ketalization reaction to over 80%.

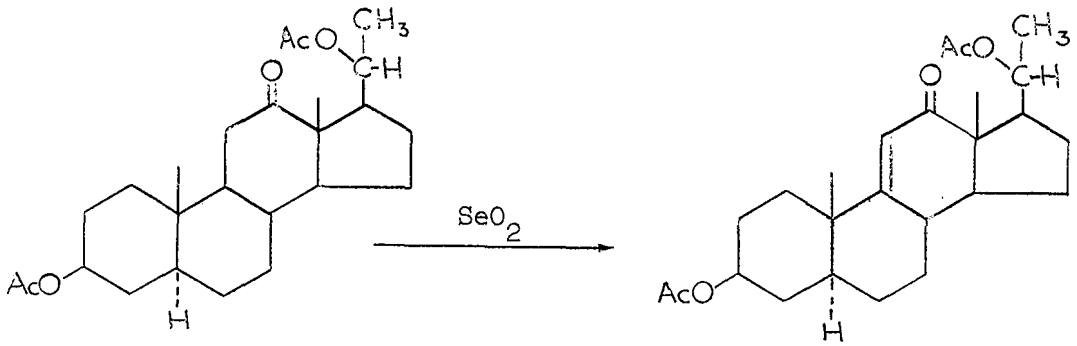


XXXI XXXII

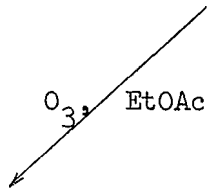
XXXIV XXXIII

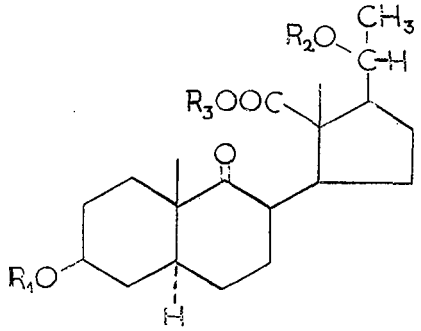
7. The β-configuration of the 20-hydroxyl function is assigned on the grounds of molecular rotational differences (38).

Dehydrogenation of the diacetoxy 12-ketone XXXIV with selenium dioxide (38), followed by ozonolysis of the resulting $\Delta^{9(11)}$-pregnen-12-one XXIV in pure ethyl acetate, gave 3β-hydroxy-20β-acetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXV). Whereas, previously (38), the acid XXV had already been prepared in this laboratory and had also been characterized as its methyl ester XXVa and the 3β-acetoxy methyl ester XXVb, we have now also prepared the 3,20-dihydroxy acid XXVc in 92% yield by hydrolysis of the acetoxy acid XXV with 2N methanolic potassium hydroxide, the diacetoxy acid XXVd by acetylation of the acid XXV with acetic anhydride in pyridine at 80°, and the dihydroxy methyl ester XXVe by methylation of the acid XXVc with diazomethane.



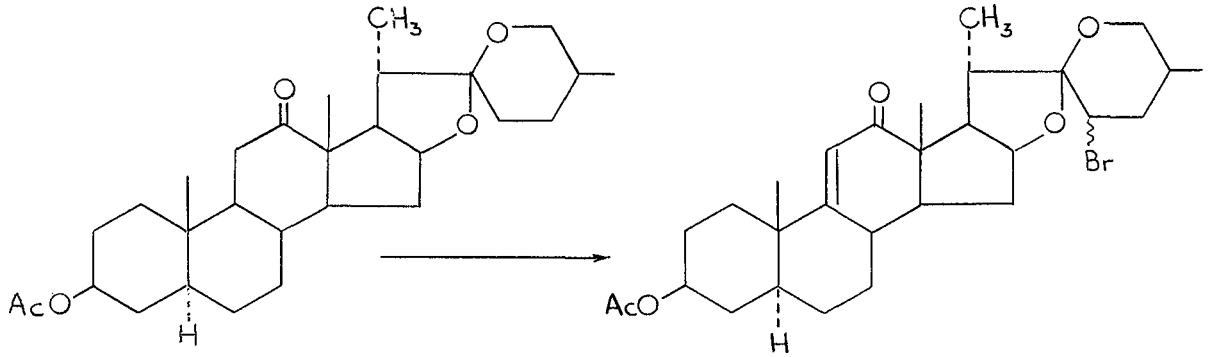
XXXIV XXIV



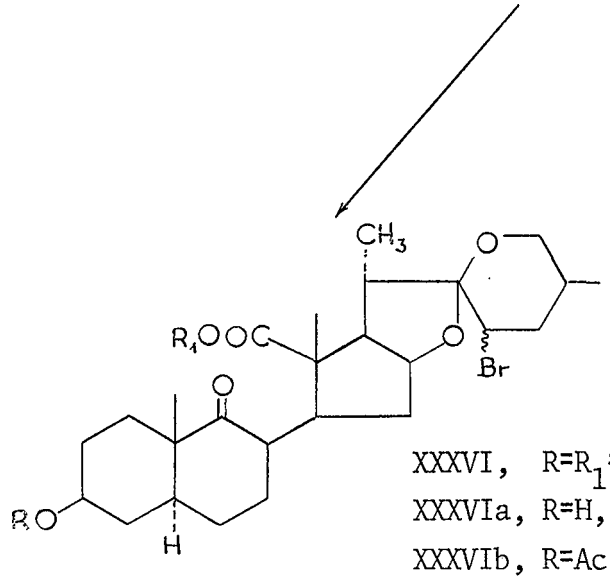


XXV, R_1=R_3=H, R_2=Ac
XXVa, R_1=H, R_2=Ac, R_3=CH_3
XXVb, R_1=R_2=Ac, R_3=CH_3
XXVc, R_1=R_2=R_3=H
XXVd, R_1=R_2=Ac, R_3=H
XXVe, R_1=R_2=H, R_3=CH_3

As already briefly mentioned, Engel et al. (37) had also opened ring C of hecogenin (in the presence of the sapogenin side chain) to prepare the 23ξ-bromo ring C-seco acid derivatives XXXVI, XXXVIa and XXXVIb.



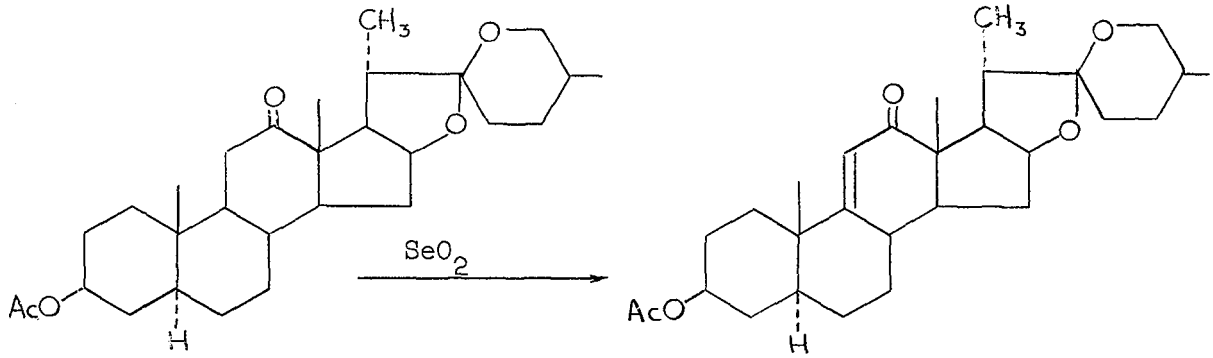
XXIIa XXXV



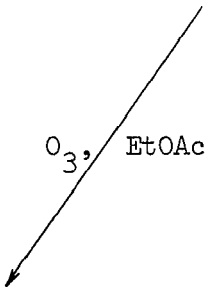
XXXVI, $R=R_1=H$
XXXVIa, $R=H$, $R_1=CH_3$
XXXVIb, $R=Ac$, $R_1=CH_3$

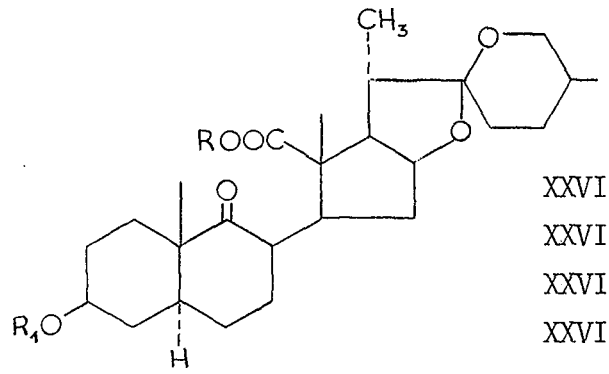
We have now prepared 9(11)-dehydrohecogenin acetate(XXVI)in 85% yield, according to the procedure of Djerassi et al. (44), by dehydrogenation with selenium dioxide in tertiary butyl alcohol; ozonolysis of the 9,11-unsaturated ketone XXVI in pure ethyl acetate gave the corresponding 3β-hydroxy 9-oxo

9,12-seco 11-nor acid XXVII in 70% yield. We have further characterized this acid as the 3β-acetate XXVIIa, as the methyl ester XXVIIb obtained from the acid XXVII with diazomethane, and as the 3β-acetoxy ester XXVIIc obtained by methylation of the 3β-acetoxy acid XXVIIa with diazomethane. Previously, Kutney et al. (39) had prepared the 3β-acetoxy acid XXVIIa, following likewise the method developed by Engel et al. (37).



XXIIa XXVI





XXVII, R_1=R=H
XXVIIa, R_1=Ac, R=H
XXVIIb, R_1=H, R=CH_3
XXVIIc, R_1=Ac, R=CH_3

We have thus synthesized the 3,9,12-trioxygenated 9,12-seco 11-nor derivatives, both in the 20-oxygenated pregnane series and in the sapogenin series. As already indicated, these compounds represent our actual starting materials for the synthesis of 11-aza and 11-oxa steroids.

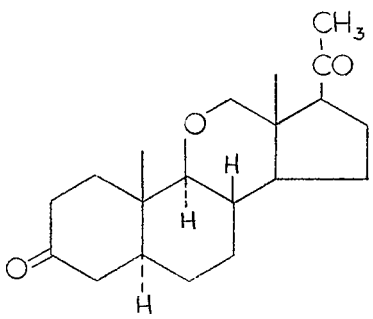
CHAPTER III

The Synthesis of 11-Oxa Steroids[8]

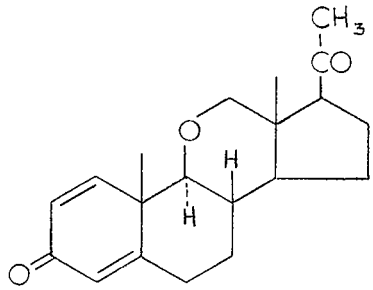
In view of their possible biological interest, a number of oxa steroids have been synthesized in the last twenty years (48-53, cf. also 20-23, 26, 29, 47). However, to date, no true 11-oxa hormone analog[9] has been synthesized.

In this chapter we describe the synthesis of the first 11-oxa analog of a steroid hormone, 11-oxaprogesterone (XXXIX).

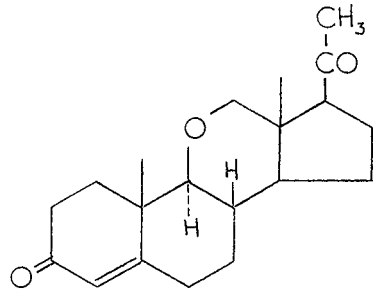
We shall first describe the synthesis of 11-oxa-5α-pregnane-3,20-dione (XXXVII) by three routes (one of which differs from the others not only superficially but also in that a different method was used for the development of the 11-oxa structure), and then the conversion of this intermediate to 11-oxa-1-dehydroprogesterone (XXXVIII) and to 11-oxaprogesterone (XXXIX).



XXXVII



XXXVIII



XXXIX

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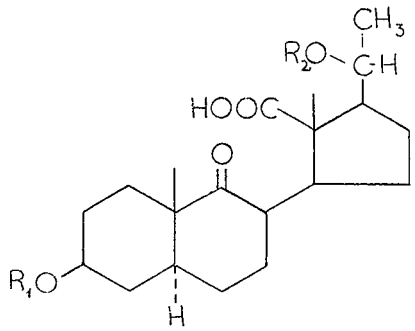
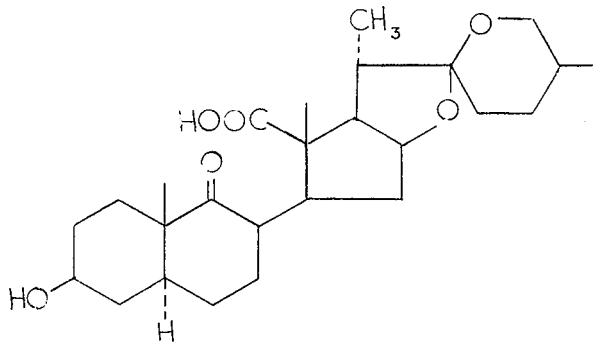
8. In conformity with the usage, we number the hetero atoms of nucleo-hetero steroids with the numbers corresponding to the carbon atoms of normal steroids which they have replaced.

9. Zderic et al. have reported the synthesis of some steroidal hormone analogs (46) which are (11→12) lactones of 12-hydroxy-11,12-seco tigogenin-11-oic acid and of 12-hydroxy-11,12-seco-5α-pregnan-11-oic acid (along with a (11→13) lactone of 13-hydroxy-11,13-seco-12-nor-tigogenin-11-oic acid). We consider such lactones as derivatives of the corresponding hydroxy acids and not as true oxa steroids.

We used the seco keto acids XXVc, XXVd and XXVII, the syntheses of which were described in Chapter II, as starting materials.



XXVc, $R_1=R_2=H$
XXVd, $R_1=R_2=Ac$



XXVII

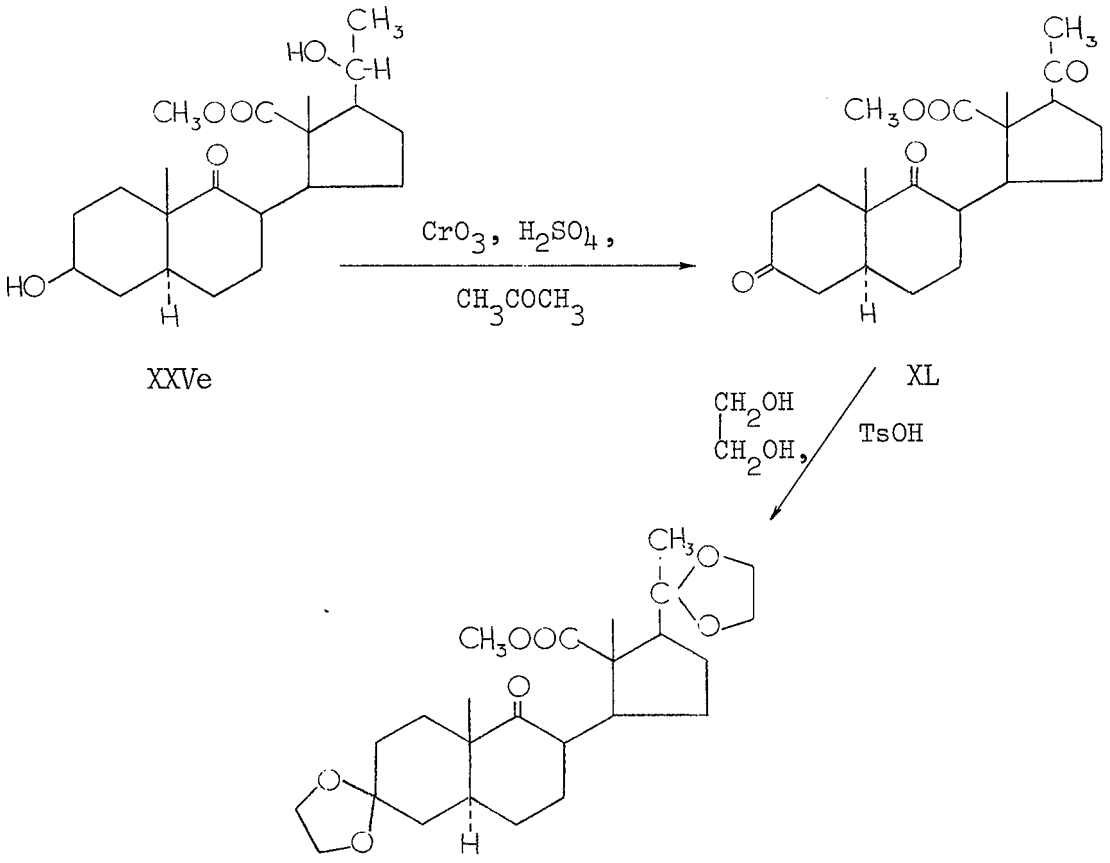
The key reaction of two pathways which we followed for the synthesis of 11-oxa steroids consists in the transformation of an 11-nor 9,12-seco 9,12-diol of type xv to an 11-oxa steroid of type xvi by acylating agents (cf. 54, 55, 56).

xv xvi

We used in particular, p-toluenesulfonyl chloride in pyridine, in excess and at elevated temperatures (cf. also 49, 50). In our third pathway, we arrived at the 11-oxa structure xvi by reducing an 11-nor 9,12-seco 9β-hydroxy 12-pregnanoic acid lactone (12→9) of type xvii, either with lithium aluminum hydride-boron trifluoride etherate (48, 52 and 57) or, catalytically, with platinum oxide in acetic acid in the presence of perchloric acid (53, 58).

xvii xvi

In the first sequence of reactions, the hydroxy methyl ester XXVe (cf. chapter II) was oxidized with Jones' reagent (59), to give methyl 3,9,20-trioxo-9,12-seco-11-nor-5α-pregnan-12-oate (XL) in 93% yield. The 3- and 20-keto functions of the triketo ester XL were preferentially ketalized with ethylene glycol and p-toluenesulfonic acid (60) to the 3,20-diketal XLI in 84% yield.

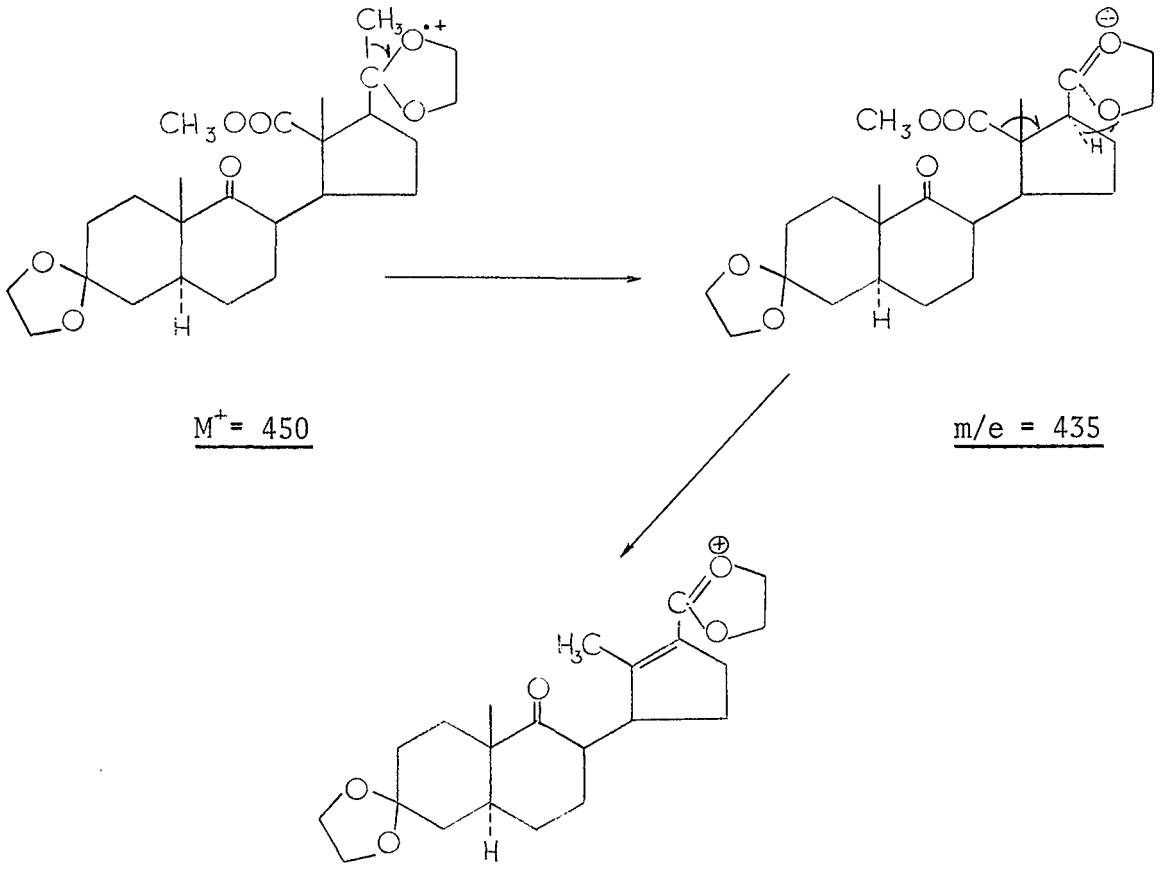


XLI

The structure of the bis-ethylenedioxy ketone XLI was confirmed by spectral and elemental analyses. The NMR spectrum[10] of this product showed (among other characteristic signals) a sharp singlet at 3.9 ppm corresponding to eight protons, which can be assigned to the two ethylene ketal functions. Since the 3-keto function in steroids forms a ketal extremely easily, even under very mild conditions (61), the diketal XLI could only be either a 3,20-diketal or a 3,9-diketal. The latter possibility is excluded because of the

10. Unless otherwise mentioned, the NMR spectra were taken in deuterochloroform on a Varian A-60 instrument with tetramethylsilane as an internal standard.

absence of the characteristic signal for the methyl ketone side chain in the NMR spectrum. The unreactivity of the 9-keto function towards ethylene glycol was easily forseen from its unreactivity towards other reagents (for instance, hydroxylamine, aluminum isopropoxide, etc; cf. also 35, 62) and follows from the severe steric hindrance in this region. The mass spectrum[11] of this product confirmed the structure; it shows the M^+ peak at 450 which confirms the presence of only two ketal groups, and its fragmentation pattern, apparent from the peaks at m/e=435, m/e=375, m/e=125, m/e=99, and m/e=87, is typical of 3- and 20-ethylene ketals (cf. for example 63-67) (Scheme I).

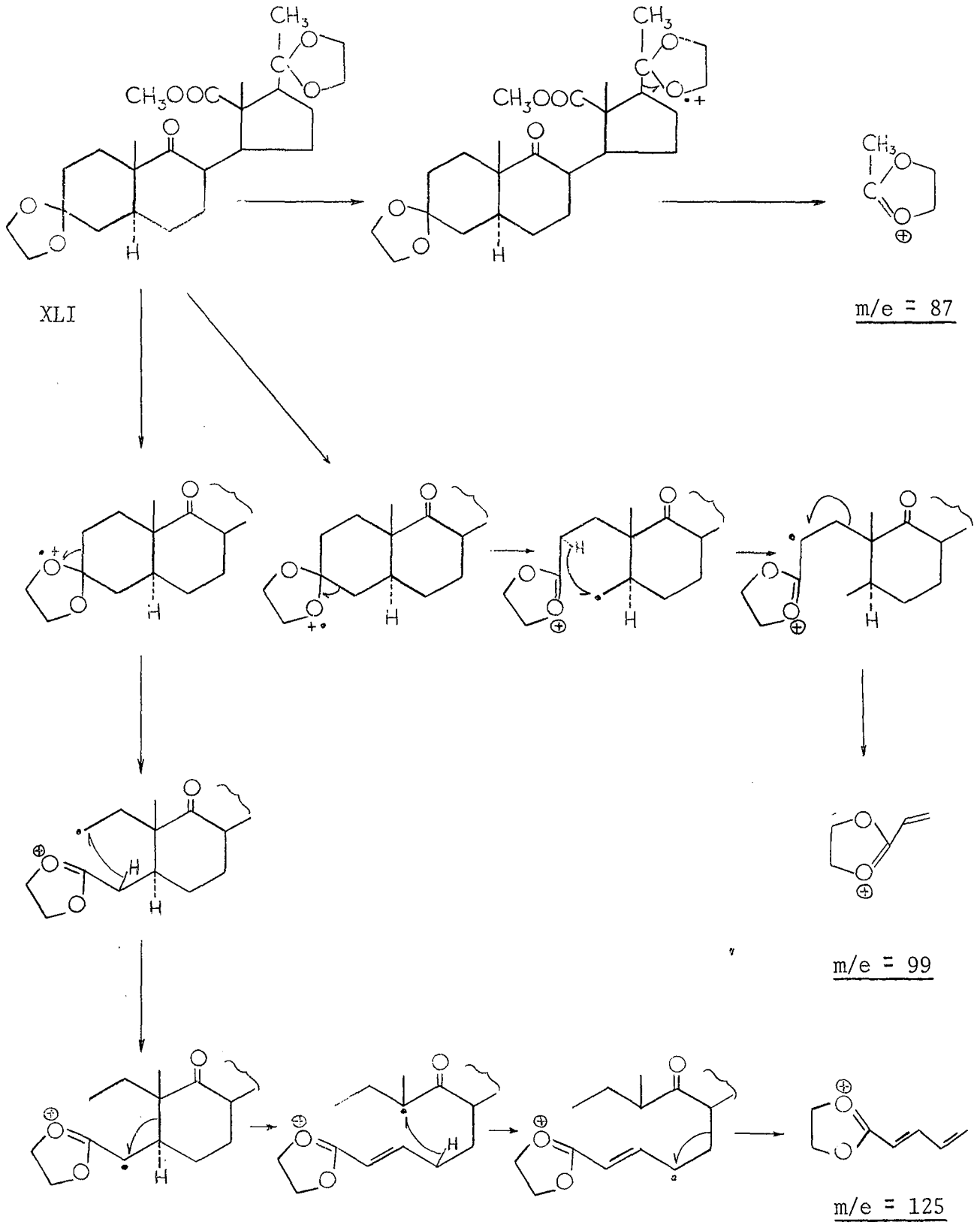


M^+= 450 m/e = 435

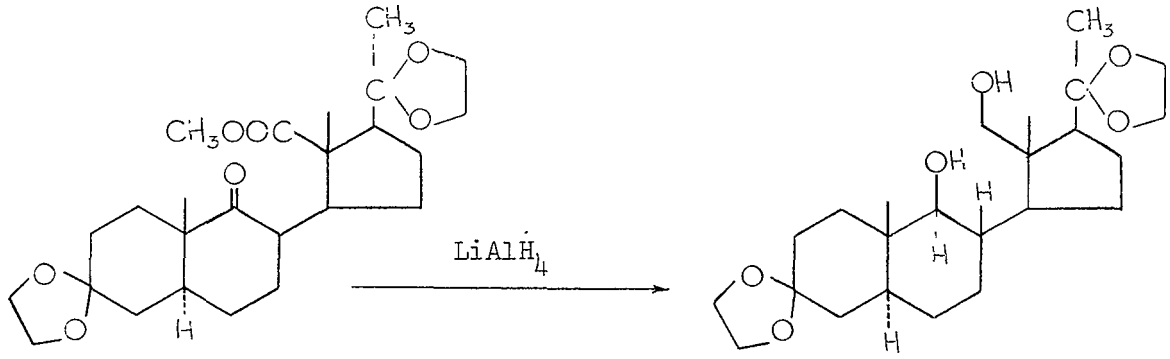
m/e = 375 (Scheme I)

11. We sincerely thank Dr. B.C. Das, Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, France, for the mass spectra of compounds XLI and XLV, and their interpretation.

(Scheme I, continued)



The bis-ethylenedioxy keto ester XLI was reduced with lithium aluminum hydride in tetrahydrofuran to the corresponding 9,12-diol XLII in 76% yield.

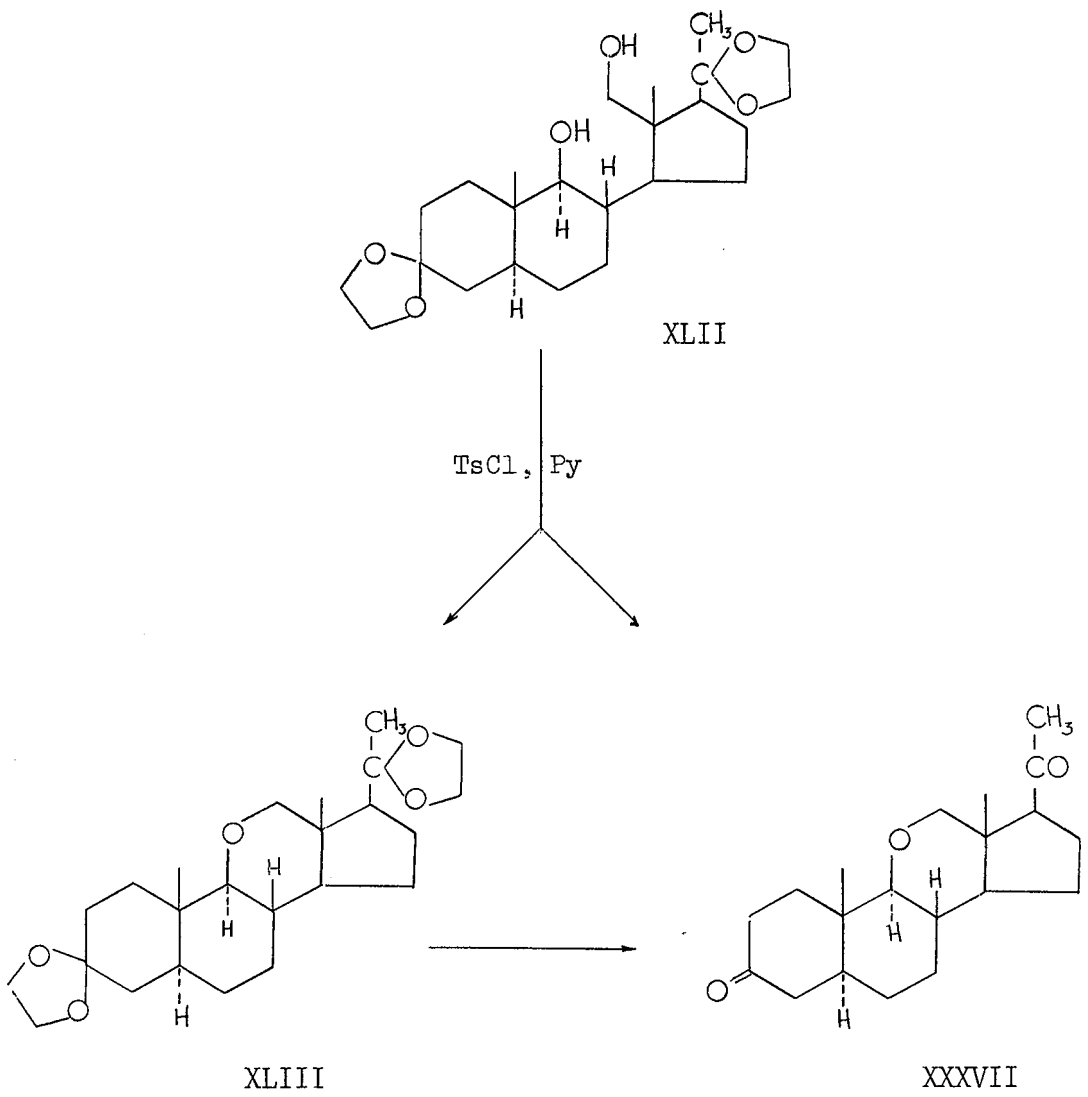


XLI XLII

The structure of the diol XLII was established by its infrared and NMR spectra and the stereochemistry of its hydroxyl group in position 9 was deduced on the basis of its NMR spectrum. This spectrum showed a singlet at 3.9 ppm, corresponding to the eight hydrogen atoms of the two ketal groups in positions 3 and 20, and a multiplet at 3.5 ppm, corresponding to the two hydroxyl protons which were exchanged with deuterium on treatment with D_2O; it also showed a pair of doublets centered at 3.67 and 3.30 ppm, each with a coupling constant of 12 cps, corresponding to the geminal coupling of the two methylene protons in position 12. In addition, there appeared in the spectrum a doublet centered at 2.93 ppm, with a coupling constant of 10 cps, corresponding to the proton in position 9 which is coupled with the C_8-proton. The magnitude of this coupling constant (10 cps) agrees very well with that expected for the coupling of two vicinal trans-diaxial protons, but not with that for two vicinal axial-equatorial protons. Since only in the case of a 9β-hydroxy compound the hydrogen atoms in positions 8 and 9 can both be axial, the axial 9α-configuration of the hydrogen, and therefore the equatorial 9β-configuration of the hydroxyl group in position 9 of the diol XLII is

established.

Treatment of the diol XLII with approximately four equivalents of p-toluenesulfonyl chloride in excess pyridine (cf. 49, 50, 56a), at 110-120°, for 4 h, gave the 11-oxa bis-ethylenedioxy pregnane XLIII, along with the partially deketalized 11-oxa pregnanedione XXXVII. It was found

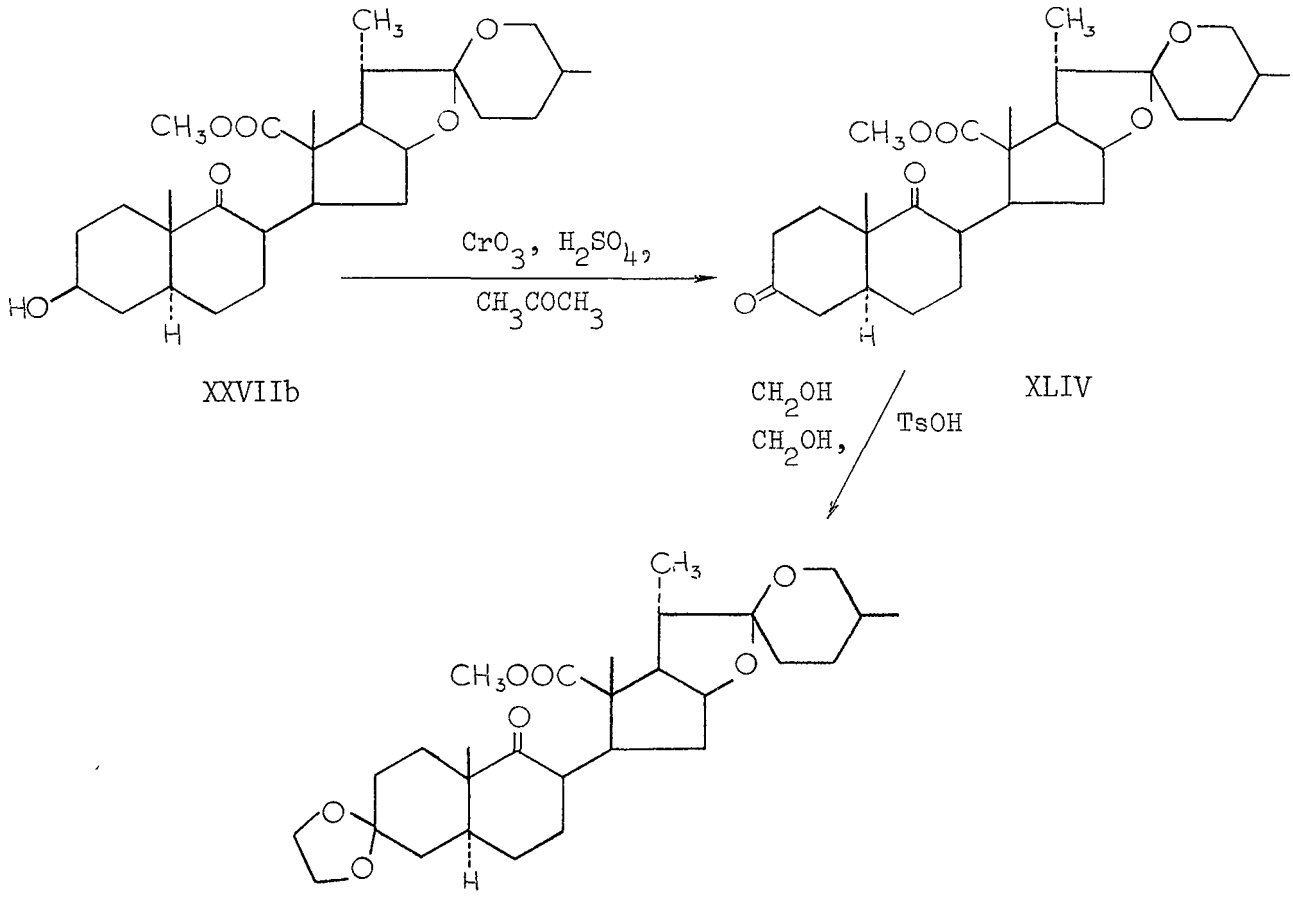


advantageous to submit the crude reaction product directly to an exchange reaction with acetone in the presence of p-toluenesulfonic acid (45) which gave the desired 11-oxa pregnanedione XXXVII in an over-all yield of 50% from the diol XLII.

The structure of the 11-oxa pregnanedione XXXVII was established on the grounds of its infrared and NMR spectra and of its elemental analysis. The infrared spectrum showed the 3-and 20-ketone absorption at 1719 cm^{-1} and the bands corresponding to the 11-ether function at 1080, 1050 and 1037 cm^{-1}. The NMR spectrum showed a pair of doublets at 4.13 and 3.41 ppm with a coupling constant of 10 cps, corresponding to the C_{12}-methylene protons, a singlet at 2.07 ppm, corresponding to the methyl ketone protons in position 17, and two singlets at 1.12 and 0.79 ppm, corresponding to the 19 and 18 angular methyl groups, respectively. (The signals due to the C_9-proton, was hidden in the envelope produced by other protons of the molecule).

In the second series of reactions, the 11-oxa pregnanedione XXXVII was synthesized from hecogenin by inserting the oxygen atom in position 11 in the presence of the rings E and F, typical of sapogenins, and by degrading rings E and F subsequently.

Oxidation of the methyl ester XXVIIb (cf. chapter II) with Jones' reagent gave the diketo ester XLIV in 95% yield. Preferential ketalization of the 3-keto function (as described above for the triketo ester XL) gave the corresponding 3-monoketal ester XLV in 82% yield.



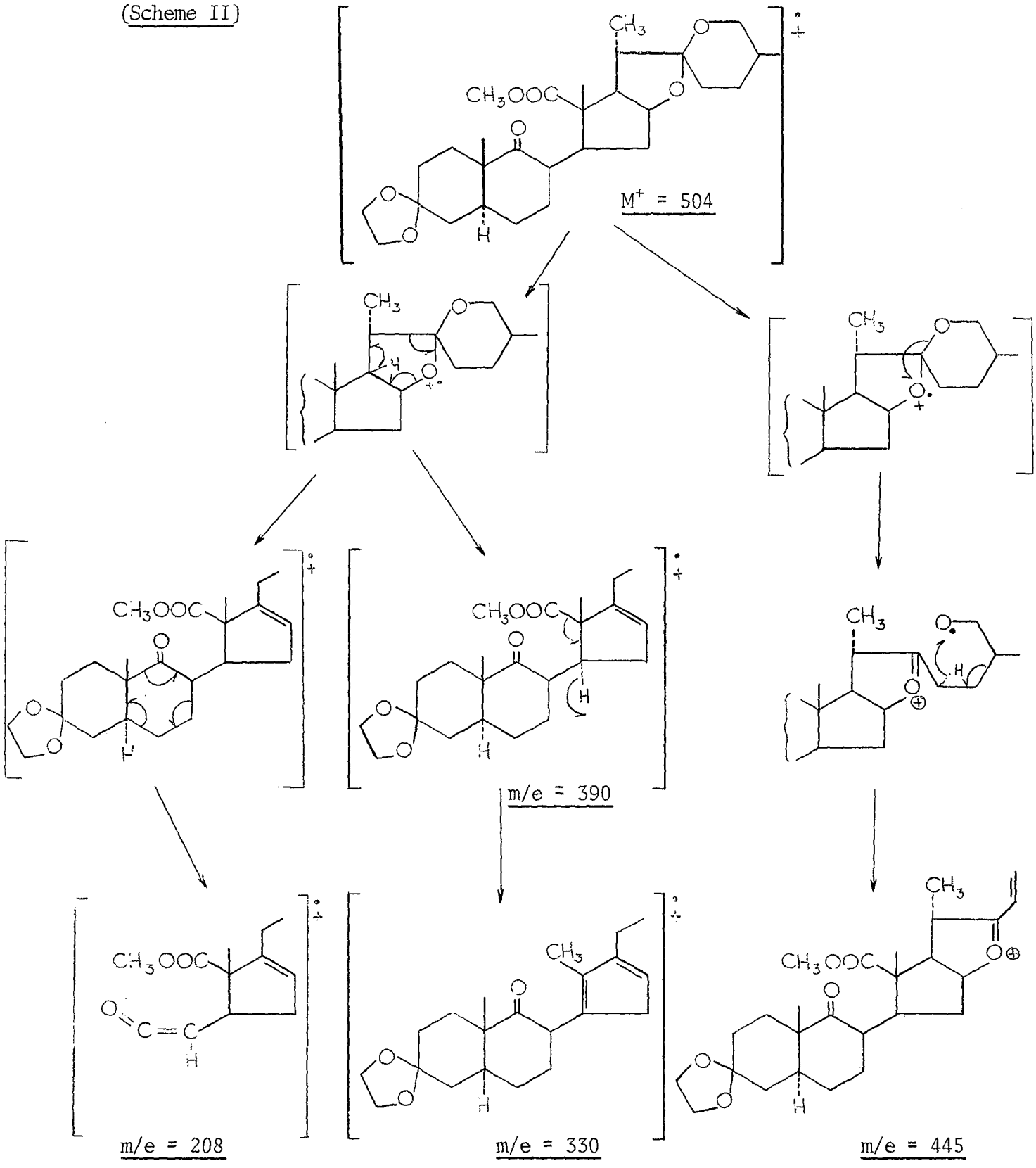
XXVIIb

XLIV

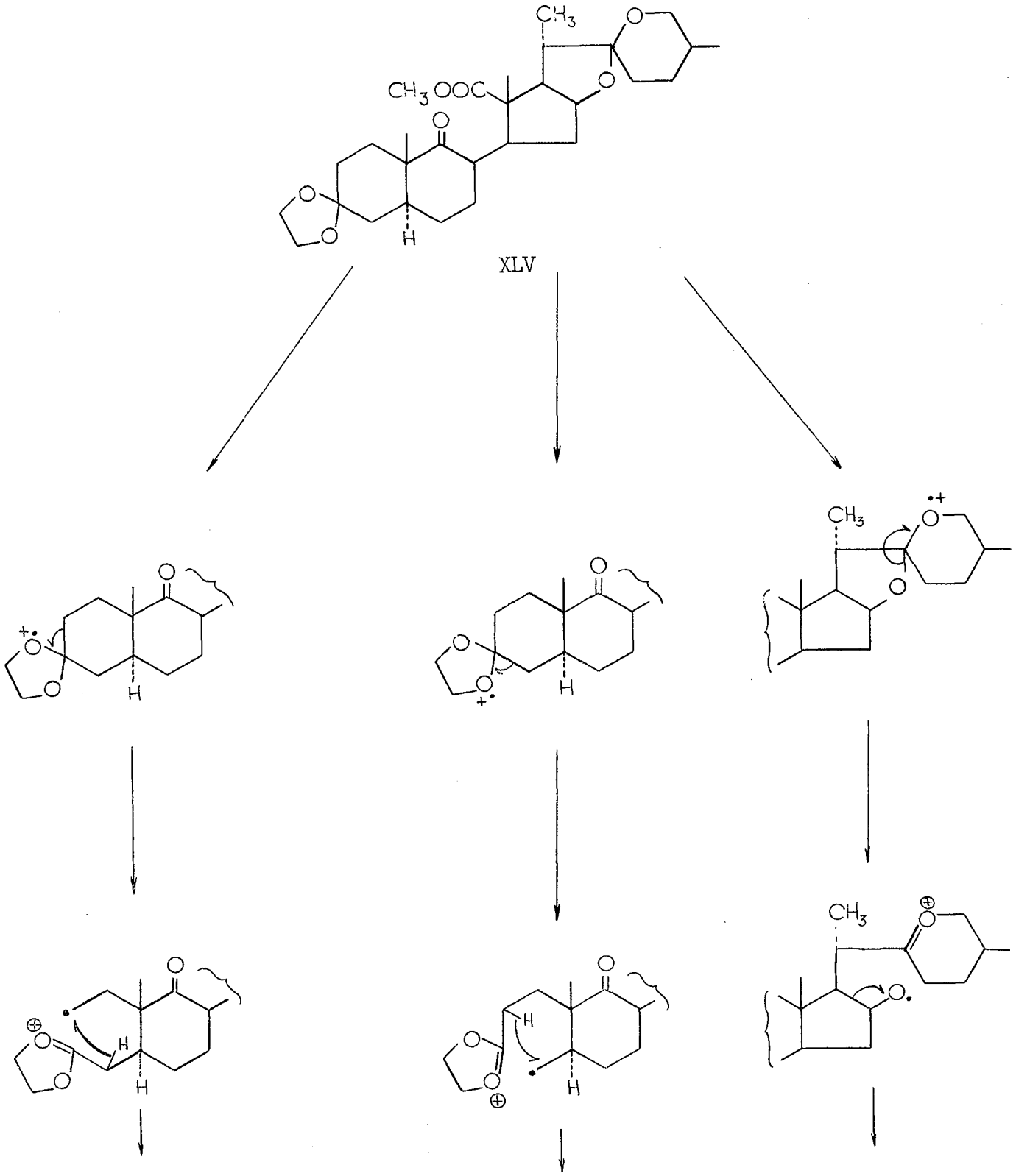
XLV

The NMR spectrum of the monoketal XLV showed a singlet at 3.9 ppm, corresponding to four protons, typical of a single ethylene ketal function. On the basis of the great ease of formation of ketals of 3-keto steroids, and the little reactivity of the 9-keto function of 9-oxo 11-nor 9,12-seco steroids (see above), the monoketal was assigned the structure XLV which was confirmed by its mass spectrum[11]. It indicated the peak for the molecular ion M^+ at 504, and the fragmentation pattern, apparent from the peaks at m/e=445, m/e=390, m/e=330, m/e=208, m/e=139, m/e=125, and m/e=99, can be rationalized (cf. 63-67) as follows (Scheme II) :

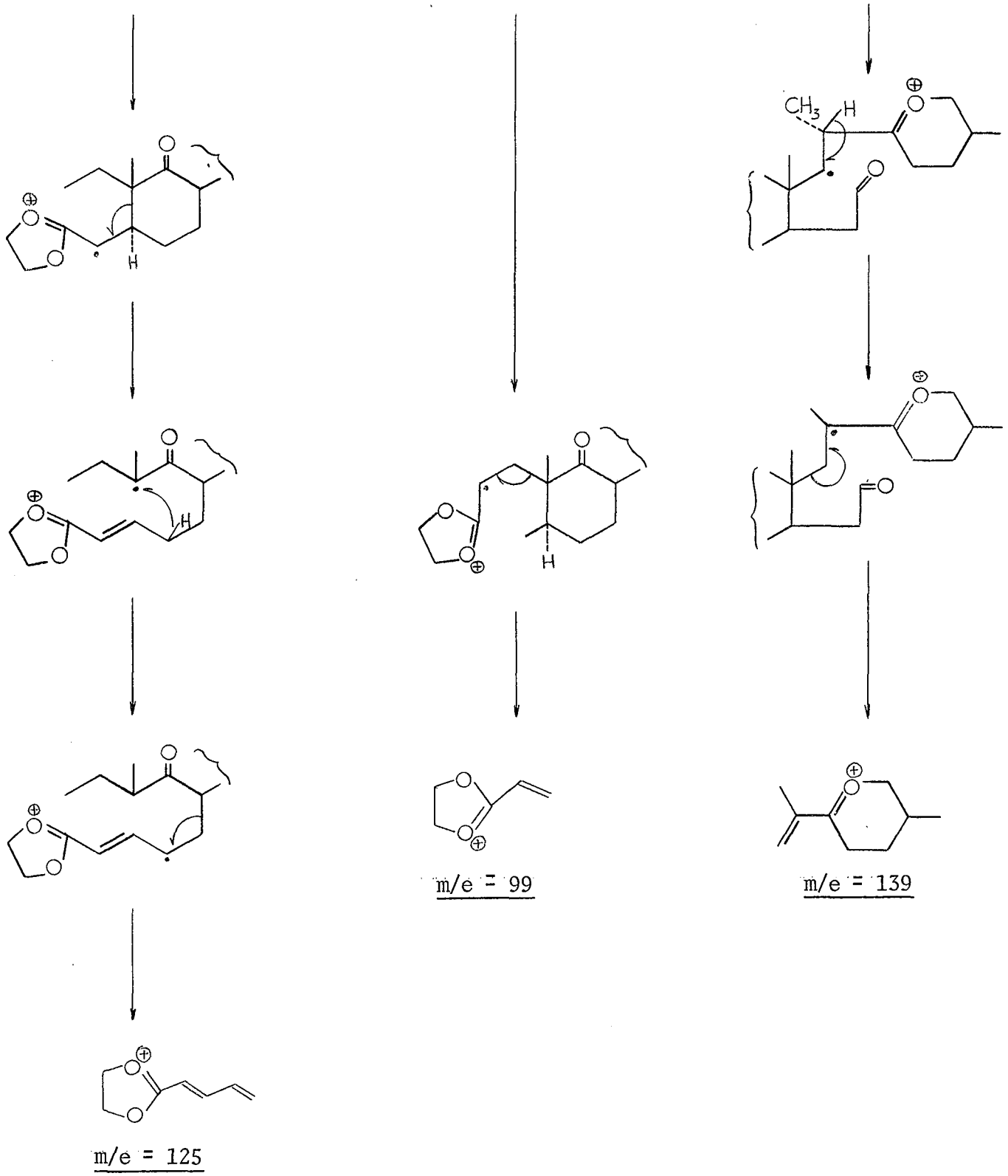
(Scheme II)



(Scheme II, continued)



(Scheme II, continued)

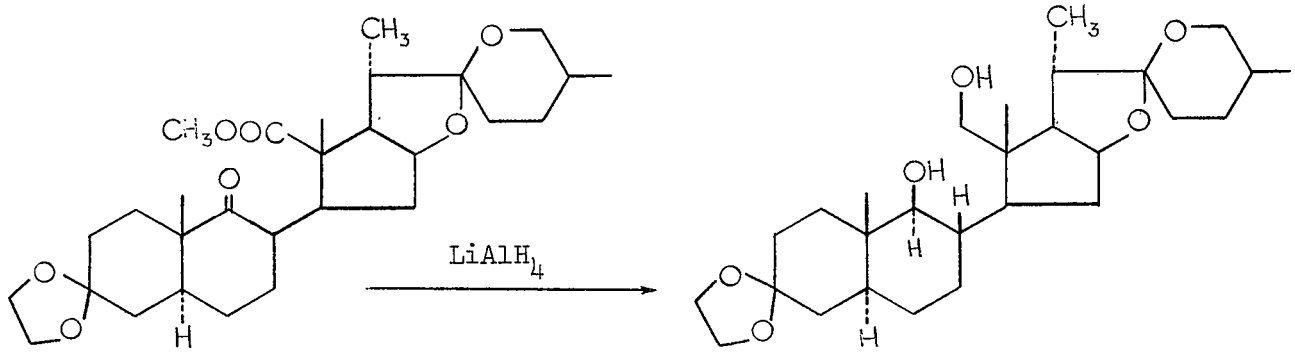


m/e = 125

m/e = 99

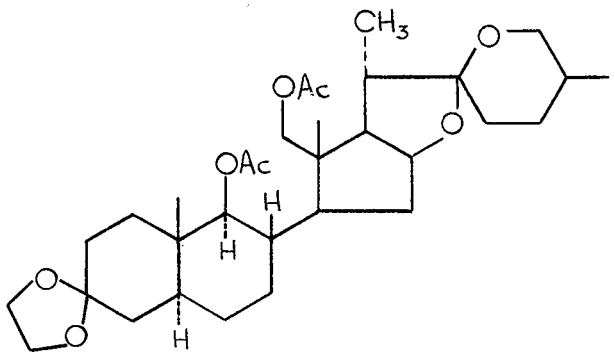
m/e = 139

The 3-ethylenedioxy keto ester XLV was reduced with lithium aluminum hydride in tetrahydrofuran to 3-ethylenedioxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane-9,12-diol (XLVI) in 74% yield. The diol XLVI was further characterized as its diacetate XLVIa.



XLV

XLVI

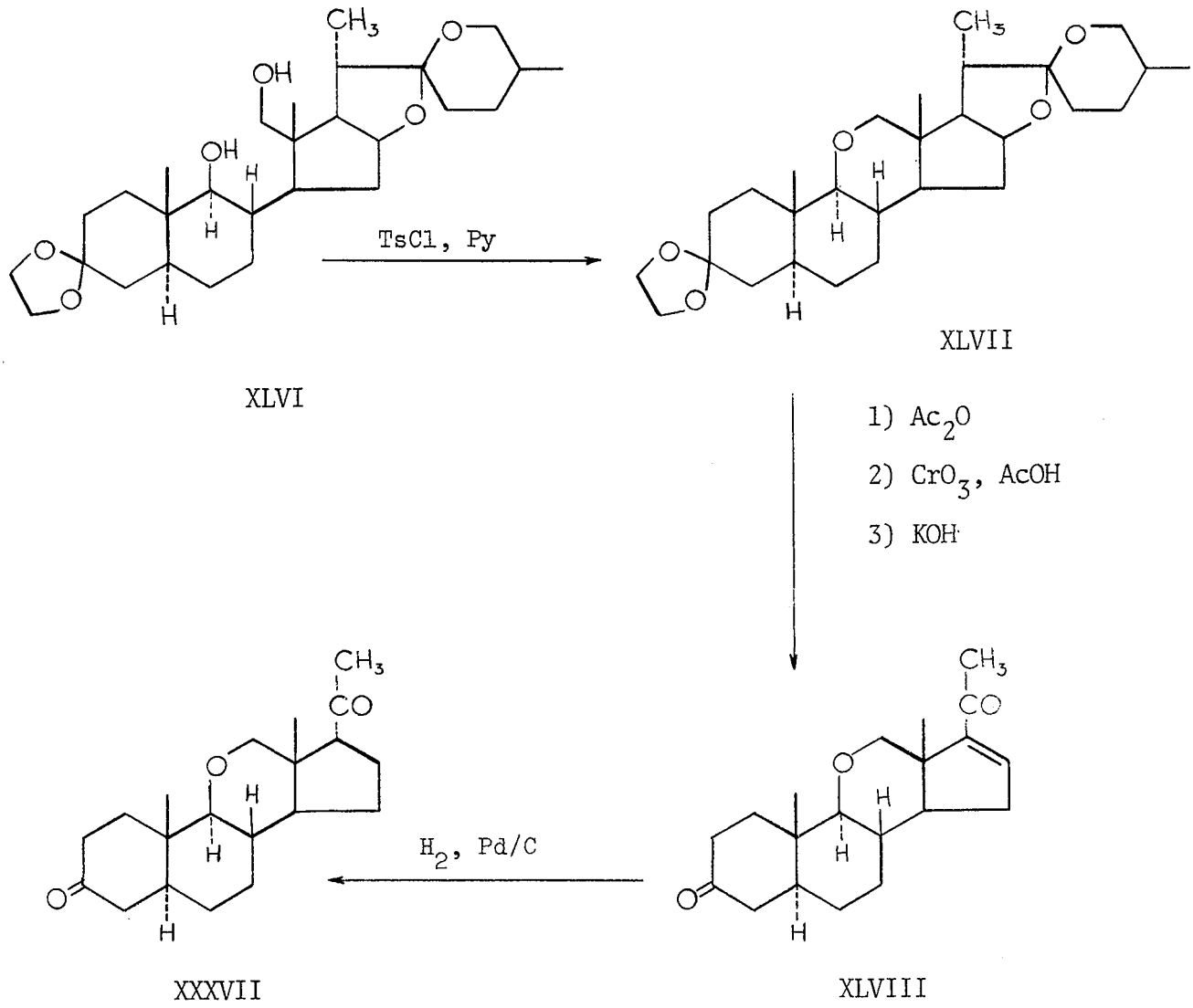


XLVIa

The stereochemistry in position 9 of the diol XLVI and its derivative XLVIa were deduced from an analysis of their NMR spectra as in the case of the diol XLII. In the spectrum of the diol XLVI (in deuteropyridine), the 12-methylene protons were seen along with the 26-methylene protons as a broad

"singlet" at 3.63 ppm, and the doublet corresponding to the C_9-proton appeared at 3.1 ppm, with a coupling constant of 10.5 cps. Here again, the magnitude of the coupling constant, arising from the coupling of the C_9- and C_8-protons established the equatorial conformation of the hydroxyl group in position 9.

The diol XLVI was smoothly converted, as described for the diol XLII, to the corresponding 11-oxa steroid XLVII (76% yield) by treatment, for 3 h, with p-toluenesulfonyl chloride in pyridine at 85°.



XLVI

XLVII

XXXVII

XLVIII

The structure of the 11-oxa steroid XLVII was established by its infrared spectrum which indicated absorption bands at 1108, 1077 and 1054 cm^{-1}, corresponding to the 11-ether function, and by its NMR spectrum. In addition to the signals corresponding to the C_{16} and C_{26} protons, the protons of the ethylene ketal function and the methyl groups 18, 19, 21 and 27, the spectrum showed two doublets centered at 3.75 and 3.10 ppm, with a coupling constant of 10.5 cps, corresponding to the 12-methylene protons, and a doublet centered at 2.44 ppm, corresponding to the axial proton in position 9.

The degradation of the rings E and F of the 11-oxa sapogenin XLVII was carried out according to the procedure of Marker et al. (40), using the experimental method described by Zderic et al. (46). However, the yield of Δ^{16}-11-oxa-5α-pregnene-3,20-dione (XLVIII) amounted only to 23% (based on the 11-oxa sapogenin XLVII)[12]. In the course of this degradation, the 3-ketal function had been removed, which is not surprising since the oxidation was carried out in an acidic medium.

Catalytic reduction of the 11-oxa pregnenedione XLVIII with 5% palladium-on-charcoal gave the saturated 11-oxa-5α-pregnane-3,20-dione (XXXVII) in 81% yield.

As already mentioned, in the third sequence of reactions, the 11-oxa pregnanedione XXXVII was synthesized via the 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (12→9) (XLIX).

This lactone (XLIX) was prepared in 62% yield by reduction of the diacetoxy keto acid XXVd with sodium borohydride in a mixture of absolute

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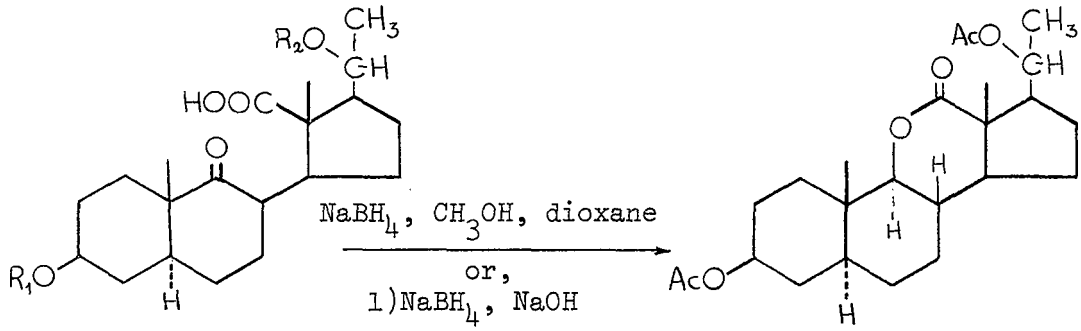
12. Similarly, Kutney et al. (68) observed that the yield in an analogous degradation of an 11-aza sapogenin was much lower than the yields obtained in the degradation of true sapogenins.

methanol and absolute dioxane. A better yield (71%) of the lactone XLIX was obtained by reducing the dihydroxy keto acid XXVc with sodium borohydride in aqueous ethanolic sodium hydroxide, and by treating the reaction product (the trihydroxy acid) with acetic anhydride and sodium acetate.

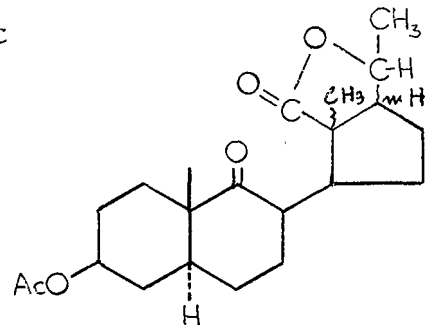


XXVc, $R_1=R_2=H$

XXVd, $R_1=R_2=Ac$

XLIX

+



L

In this case an isomeric lactone, 3β-acetoxy-20β-hydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (12→20) (L) could be isolated as a side product (in 8% yield). The structure of this product was apparent from its infrared and NMR spectra. The infrared spectrum showed the characteristic absorption maximum of a 5-membered lactone at 1784 cm^{-1}, that of an acetate at 1727 cm^{-1}, and that of a ketone at 1720 cm^{-1}. The NMR spectrum showed a multiplet at 4.51 ppm, corresponding to the C_3 and C_{20} protons, a singlet at 2.00 ppm

for the acetate methyl protons, a doublet centered at 1.35 ppm, with a coupling constant of 6 cps, corresponding to the 21-methyl group, and two singlets at 1.20 and 1.10 ppm, corresponding to the two angular methyl groups, C_{19} and C_{18}. Structure L of this 5-membered lactone was further confirmed by its elemental analysis and the mass spectrometric determination of its nominal mass.

The structure of the diacetoxy lactone XLIX was established by its infrared and NMR spectra and elemental analysis; its stereochemistry in position 9 was deduced from an analysis of its NMR spectrum. In addition to the bands for the acetoxy groups, the infrared spectrum showed the characteristic absorption of a six-membered lactone at 1750 cm^{-1}. Apart from the signals for the three methyl groups (C_{18}, C_{19} and C_{21}) and two acetoxy functions (C_3 and C_{20}), the NMR spectrum showed a multiplet at 5.05 ppm, corresponding to the two protons attached to the carbon atoms in positions 3 and 20, each carrying an acetoxy group, and a doublet centered at 3.41 ppm, with a coupling constant of 9.8 cps, corresponding to the proton at C_9 (coupled with the proton at C_8). The coupling constant of 9.8 cps establishes the axial conformation of the hydrogen atom in position 9.

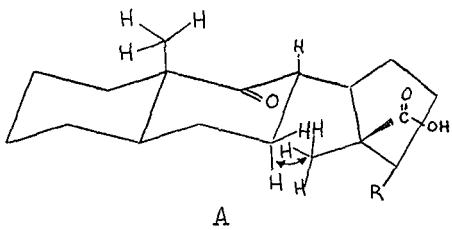
This assignment of stereochemistry in position 9 to the lactone could be anticipated also from the fact that the lactone XLIX is formed very readily, and in part spontaneously, in the course of the reduction of the 9-keto acid XXVd. An inspection of the molecular models of the two epimeric 9-hydroxy 12 acids shows that the lactone arising from the cyclization of the 9β-hydroxy 12-acid should be formed more readily than that from the 9α-hydroxy 12-acid; in fact the latter should only be formed with difficulty.

The predominant formation of the 9β-alcohol upon metal hydride reduction of the 9-ketone function of the seco keto acid XXVd can be rationalized readily

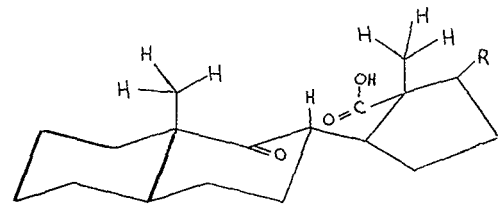
on the basis of the following considerations.

It is well known (cf., for example, 32, 76) that two factors may govern the stereochemical course of the reduction of cyclic ketones with metal hydrides; the steric hindrance to the approach of the reducing agent (steric approach control), and the thermodynamic stability of the final product (product development control) (77-79).

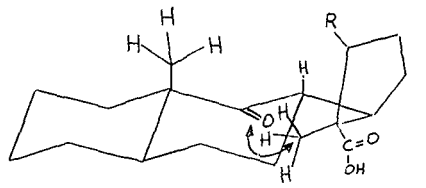
In the reduction of the keto acids XXVc and XXVd with sodium borohydride, the product development control would favor the formation of the thermodynamically more stable 9β (equatorial) alcohol. On the other hand, a study of the molecular models, particularly of the Stuart type, shows that the most stable conformation of the keto acid XXVd seems to be that having the normal "steroid-like" conformation (B); in this case the attack of the hydride reagent from the α-side is more probable than that from the β-side because of the steric hindrance on the β-side exerted by the methyl groups C_{18} and C_{19}.



A



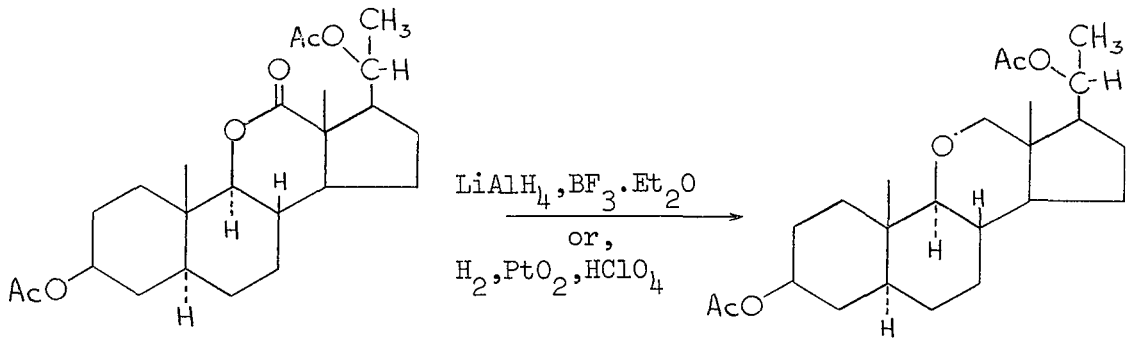
B



C

However, it should be noted that free rotation around the C_8-C_{14} bond exists within a certain (not very large) limit (cf. A and C), and consequently, in some of the possible conformations of the molecule, the β-side becomes relatively less hindered than the α-side. Therefore, in spite of the fact that conformation B represents the preferred conformation of the molecule, it would not seem justified to base the assignment of stereochemistry of the 9-alcohol solely on the consideration of the most probable direction of attack on the molecule in that particular conformation.

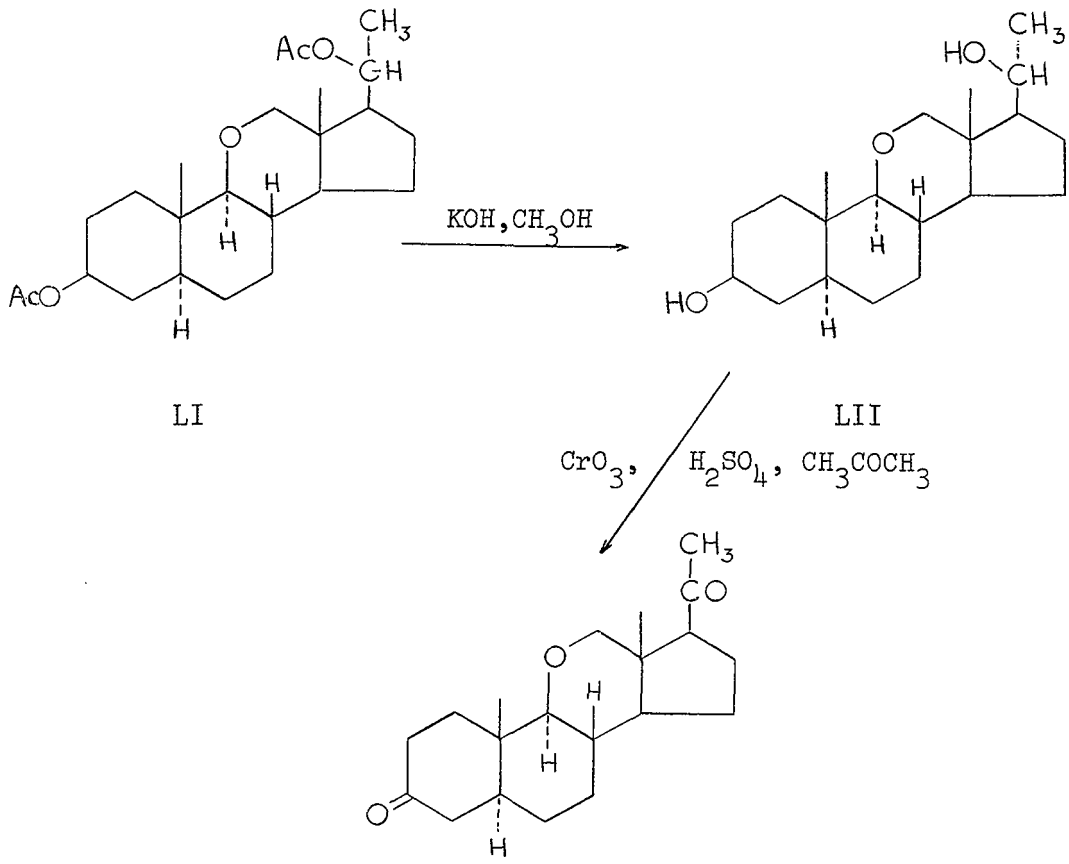
The diacetoxy lactone XLIX was reduced according to the procedure of Pettit et al. (48, 57) with lithium aluminum hydride and boron trifluoride etherate to the corresponding diacetoxy 11-oxa pregnane LI in 38% yield. The reduction of the lactone XLIX was also carried out catalytically, in 45% yield, according to the procedure of Edward et al. (53, also cf. 58), with platinum oxide in acetic acid in the presence of catalytic amounts of perchloric acid.



XLIX LI

The infrared spectrum of the 11-oxa pregnane LI shows a pair of new bands at 1052 and 1028 cm^{-1}, corresponding to the ether function in position 11. The NMR spectrum of the 11-oxa pregnane LI showed two doublets centered at 3.92 and 3.21 ppm, each with a coupling constant of 10 cps, corresponding to the newly generated 12-methylene protons. The doublet at 3.21 ppm collapsed into a singlet on spin-decoupling with a frequency difference of -40 cps, which confirmed the above assignment. The spectrum also showed a doublet centered at 2.42 ppm with a coupling constant of 9 cps, corresponding to the axial C_9-proton.

The diacetoxy 11-oxa pregnane LI was hydrolyzed with methanolic potassium hydroxide to the dihydroxy 11-oxa pregnane LII which, on oxidation with Jones' reagent, gave the 11-oxa pregnanedione XXXVII.



XXXVII

Since it is impossible to introduce a double bond directly in position 4 of 3-keto steroids of the A/B trans-series, we decided to introduce two double bonds in positions 1 and 4 and then to reduce, preferentially, the 1,2-double bond[13].

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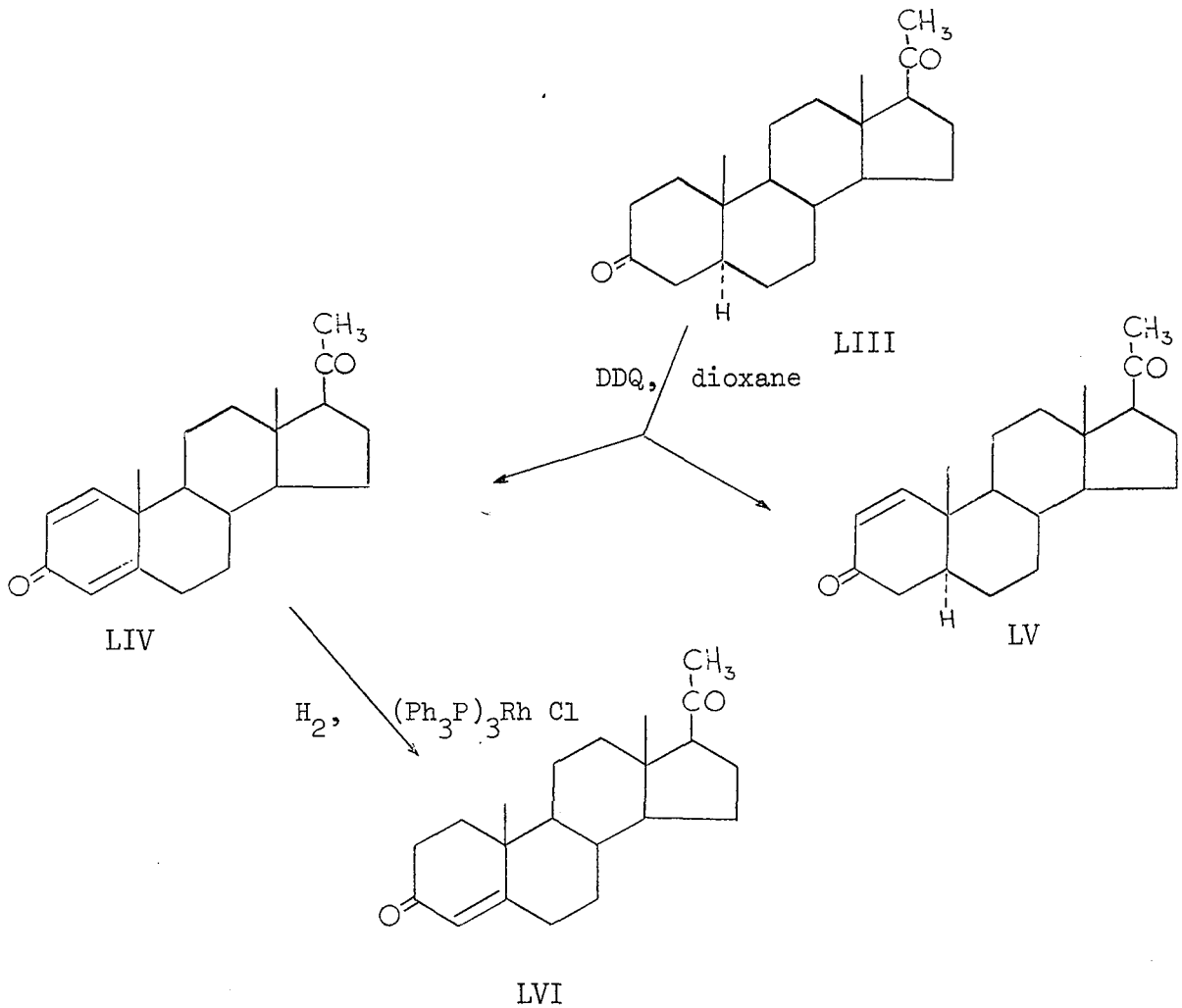
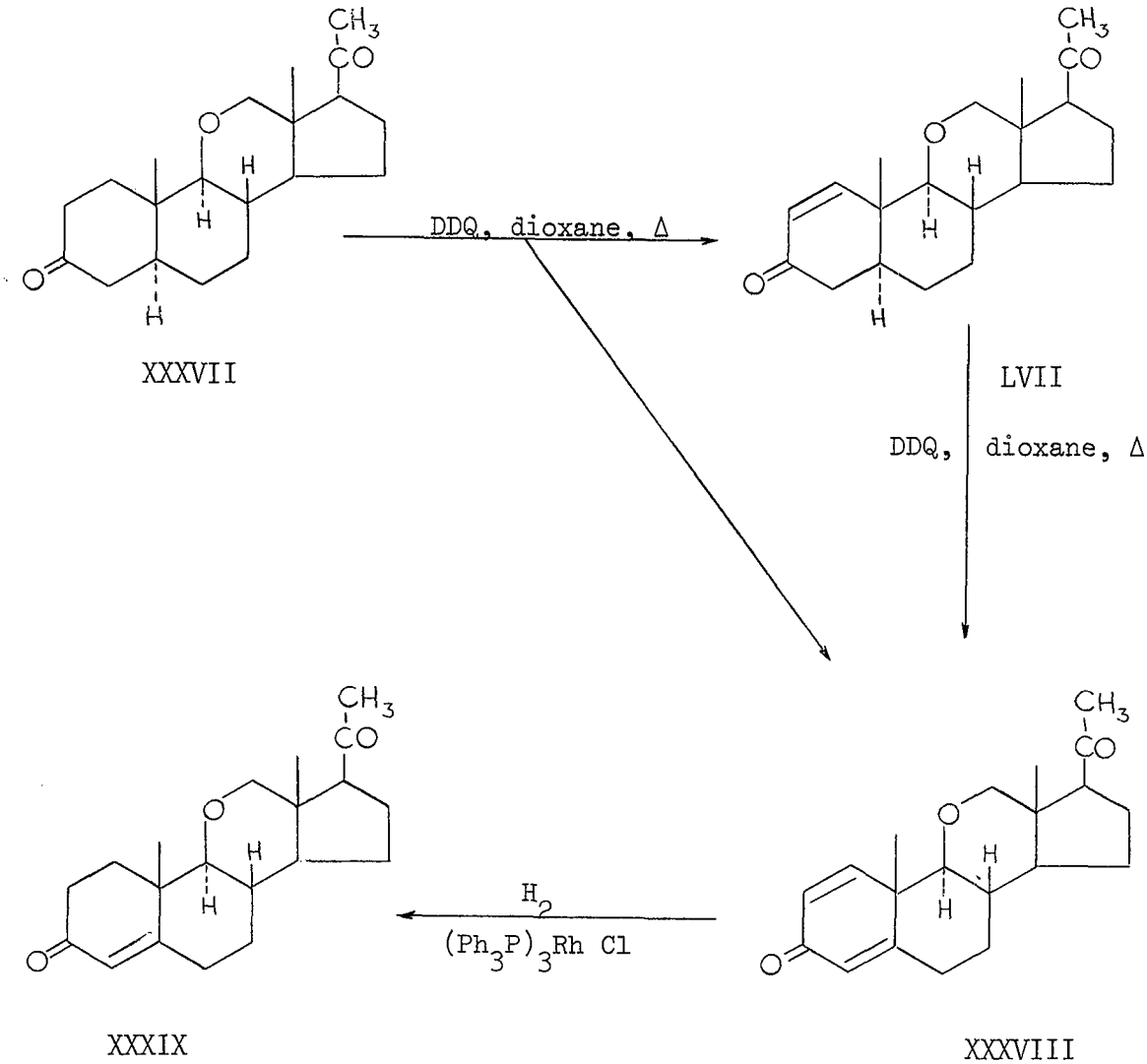
13. Before attempting the dehydrogenation of the 11-oxa pregnanedione XXXVII to the dienone XXXVIII and its preferential reduction to 11-oxa-progesterone (XXXIX), these two steps were studied on 5α-pregnane-3,20-dione (LIII) in order to elaborate the optimum conditions. The dione LIII, obtained, together with its 5-epimer, by catalytic reduction of progesterone (LVI) (43), was dehydrogenated with DDQ to give pure 1,4-pregnadiene-3,20-dione (LIV) in 33% yield; Δ^1-5α-pregnene-3,20-dione (LV) was isolated from this reaction in 7% yield. The dienone LIV was preferentially reduced, catalytically, with tris-(triphenyl-phosphine)-chloro-rhodium (72-75) to progesterone (LVI) in 85% yield.



The dehydrogenation of the 11-oxa pregnanedione XXVII was effected with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in refluxing dioxane (69, 70, compare also 71); there resulted a mixture of 11-oxa-1,4-pregnadiene-3,20-dione (XXXVIII) (30%) and Δ^1-11-oxa-5α-pregnene-3,20-dione (LVII), the latter being isolated in the pure state in 4% yield. The portion of the mixture containing no 1,4-dienone XXXVIII was subjected to a renewed dehydrogenation with DDQ; thus the over-all yield of the dienone XXXVIII from the dione XXXVII was raised to 43%.



The structure of the dienone XXXVIII and of the Δ^1-11-oxa pregnenone LVII were established by elemental analyses and by ultraviolet, infrared and NMR spectroscopy. As expected, the dienone XXXVIII and the mono-unsaturated dione LVII exhibited in the ultraviolet the characteristic absorption maxima (in ethanol) at 241 mμ ($\log\varepsilon$ 4.1) and 227 mμ ($\log\varepsilon$ 3.9), respectively. In the infrared (KBr) the 1,4-dien-3-one chromophore of the dienone XXXVIII showed the typical absorption at 1673, 1638 and 1609 cm^{-1}, the 20-ketone at 1718 cm^{-1} and the ether at 1091, 1081 and 1072 cm^{-1}; the Δ^1-11-oxa pregnenedione LVII, apart from showing the corresponding characteristic bands for the 20-ketone and 11-ether, showed in the infrared a doublet typical of a Δ^1-3-keto function at 1683 and 1610 cm^{-1}. The NMR spectrum of the dienone XXXVIII showed two doublets centered at 7.25 and 6.20 ppm, with a coupling constant of 10 cps, corresponding to the C_1- and C_2- protons, respectively, and a broad "singlet" at 6.11 ppm, corresponding to the C_4-proton. It also showed a pair of doublets centered at 4.20 and 3.60 ppm with a coupling constant of 10 cps, corresponding to the 12-methylene protons, and a doublet centered at 2.66 ppm with a coupling constant of 9 cps, corresponding to the 9α-proton. The spectrum of the Δ^1-11-oxa pregnene-3,20-dione LVII showed the two olefinic protons at C_1 and C_2 as two doublets centered at 7.38 and 5.88 ppm, respectively, with a coupling constant of 10 cps, while the 12-methylene protons could be seen as a pair of doublets centered at 4.19 and 3.45 ppm, with a coupling constant of 10 cps, and the 9α-proton as a doublet centered at 2.69 ppm with a coupling constant of 9.5 cps.

The 1,2-double bond of the dienone XXXVIII was preferentially reduced with hydrogen in the presence of the tris-(triphenylphosphine)-chloro-rhodium catalyst (72, 73), following the procedure of Birch et al. (74, compare also 75), which gave the desired 11-oxaprogesterone (XXXIX) in 81% yield.

The structure of this hormone analog was established by ultraviolet, infrared and NMR spectroscopy and was confirmed by elemental analysis. Its absorption maximum in the ultraviolet at 238 mμ ($\log \varepsilon$ 4.1) agreed with the Δ^4-3-keto chromophore, while the infrared spectrum showed the characteristic absorption bands at 1715 cm^{-1} (20-ketone) 1677 and 1622 cm^{-1} (Δ^4-3-ketone), 1090, 1081 and 1052 cm^{-1} (ether).

The NMR spectrum revealed a singlet at 5.78 ppm, corresponding to the C_4-olefinic proton, and a pair of doublets centered at 4.15 and 3.44 ppm, each having a coupling constant of 10 cps, corresponding to the 12-methylene protons. The spectrum also showed a singlet at 2.05 ppm corresponding to the $-COCH_3$ protons in position 17, and two singlets at 1.25 and 0.81 ppm, corresponding to the 19-and 18-methyl protons, respectively[14].

Biological Activity:- The new hormone analog, 11-oxaprogesterone, possesses weak parenteral progestational activity in the Clauberg test (122), which can be estimated to be approximately one sixth to one seventh that of progesterone (on a molar basis). While progesterone exhibits a +2 response at approximately 0.3 mg (1 μM) total dose level, a response of +3 to +4 at a total dose level of approximately 1.0 mg (3.3 μM), and a response of +4 at total dose levels exceeding 1.5 mg (5 μM), 11-oxaprogesterone shows a response of +2 to +2.5 at a total dose level of 2.0 mg (6.7 μM).

On the other hand, 11-oxaprogesterone possesses marked ovulation-inhibiting activity. Tested on adult female Belted Dutch Rabbits, administered

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14. The doublet of the C_9-proton (which is coupled with the proton at C_8) usually seen distinctly in the NMR spectra of 11-oxa steroids (see above) could not be located with certainty in this case, although, in all probability, the doublet centered at 2.61 ppm (J=9.5 cps), appearing along with some other signals, corresponds to that proton.

in a single subcutaneous injection followed, after 24 hours, by an intravenous injection of copper acetate solution as a stimulant for ovulation, 11-oxaprogesterone showed an activity 1.5 to 2 times that of progesterone. While progesterone shows 80% ovulation-inhibition at a dose level of 1.2 mg (4 μM), 11-oxaprogesterone exhibits 100% ovulation-inhibition at 0.9 mg (3 μM) dose level, and 50% ovulation-inhibition at 0.6 mg (2 μM), dose level. The ratio of the ovulation-inhibiting activity to the progestational activity of 11-oxaprogesterone is approximately 10, if one sets the ratio of these activities for progesterone as 1 [15] *.

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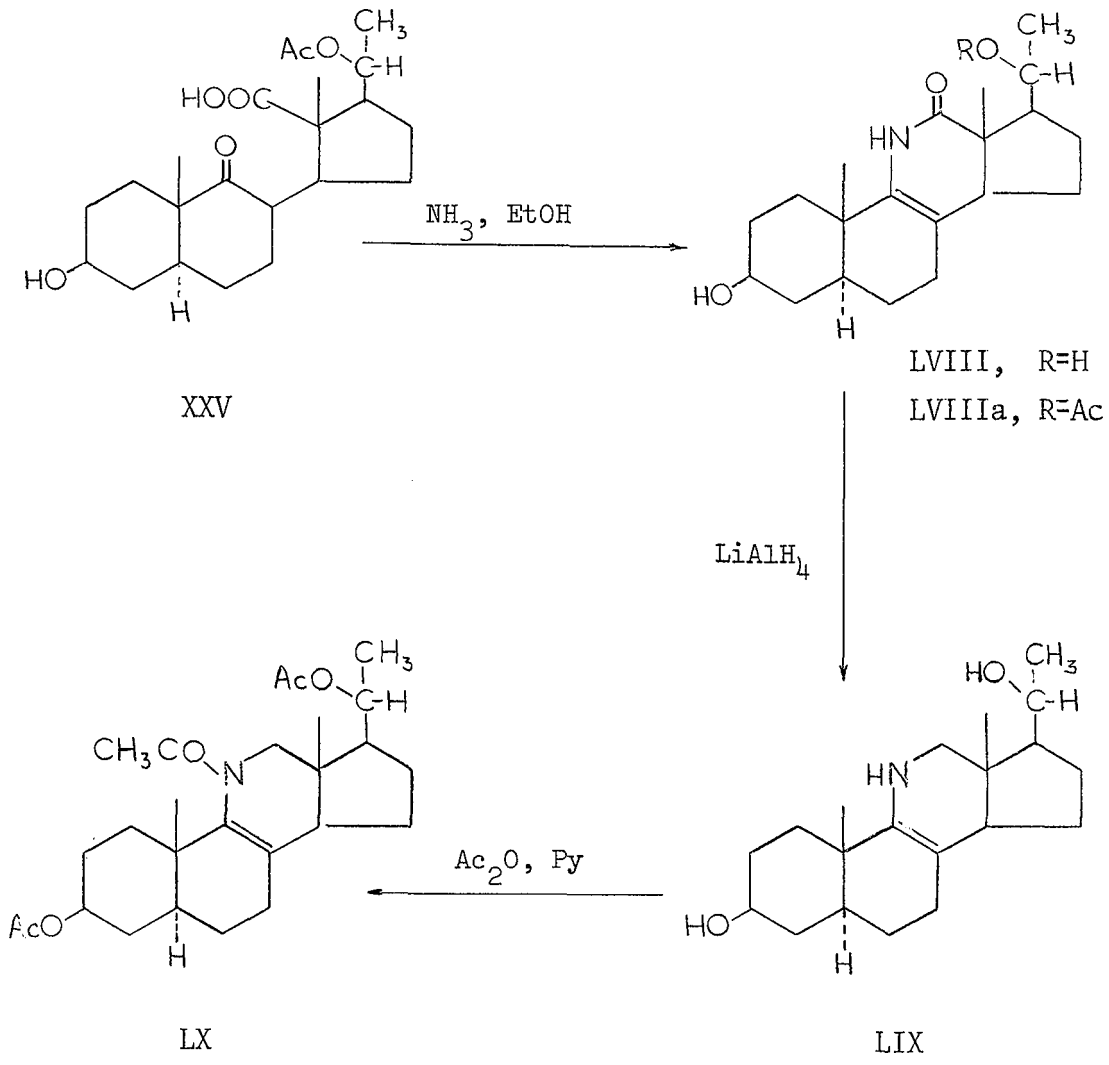
15. The Biological tests were performed by Dr. Elva G. Shipley, The Endocrine Laboratories, Madison, Wis., U.S.A., to whom we express our sincere appreciation.

* Part of the contents of this chapter was the subject of a preliminary publication (123).

CHAPTER IV

The Synthesis of 11-Aza Steroids[8]

As mentioned in Chapter II, Engel et al. (38) had succeeded in synthesizing the 8(9)-unsaturated 11-aza steroids LIX and LX from the seco keto acid XXV. Ammonolysis of this acid gave the 8(9)-unsaturated lactams LVIII and LVIIIa[16] which, on prolonged treatment with lithium aluminum hydride in tetrahydrofuran, afforded the corresponding 3,20-dihydroxy enamine LIX, characterized as its N-acetyl-3,20-diacetate LX.



XXV

LVIII, R=H
LVIIIa, R=Ac

LX

LIX

16. Whereas Engel et al. (38) had previously prepared the lactam LVIIIa, we have now also prepared and characterized the lactam LVIII.

The major problem which seemed to remain, was the elaboration of methods for the reduction of the 8,9-double bond of unsaturated 11-aza steroids of the type LIX and LX, since the transformation of saturated 3,20-dioxygenated 11-aza steroids to 11-azaprogesterone and its derivatives could be considered not to present particular difficulties.

On the other hand, one could also consider the elaboration of alternative methods for the synthesis of saturated 11-aza steroids by altogether different synthetic routes, a consideration which - as will become apparent in the sequel - became significant in view of the limited success of our experiments dealing with the reduction of 8,9-unsaturated 11-aza steroids.

We shall deal with the two approaches towards the synthesis of saturated 11-aza steroids in two separate sections of this chapter.

Section I

The Synthesis of Saturated 11-Aza Steroids by Reduction of 8(9)-Unsaturated 11-Aza Steroids

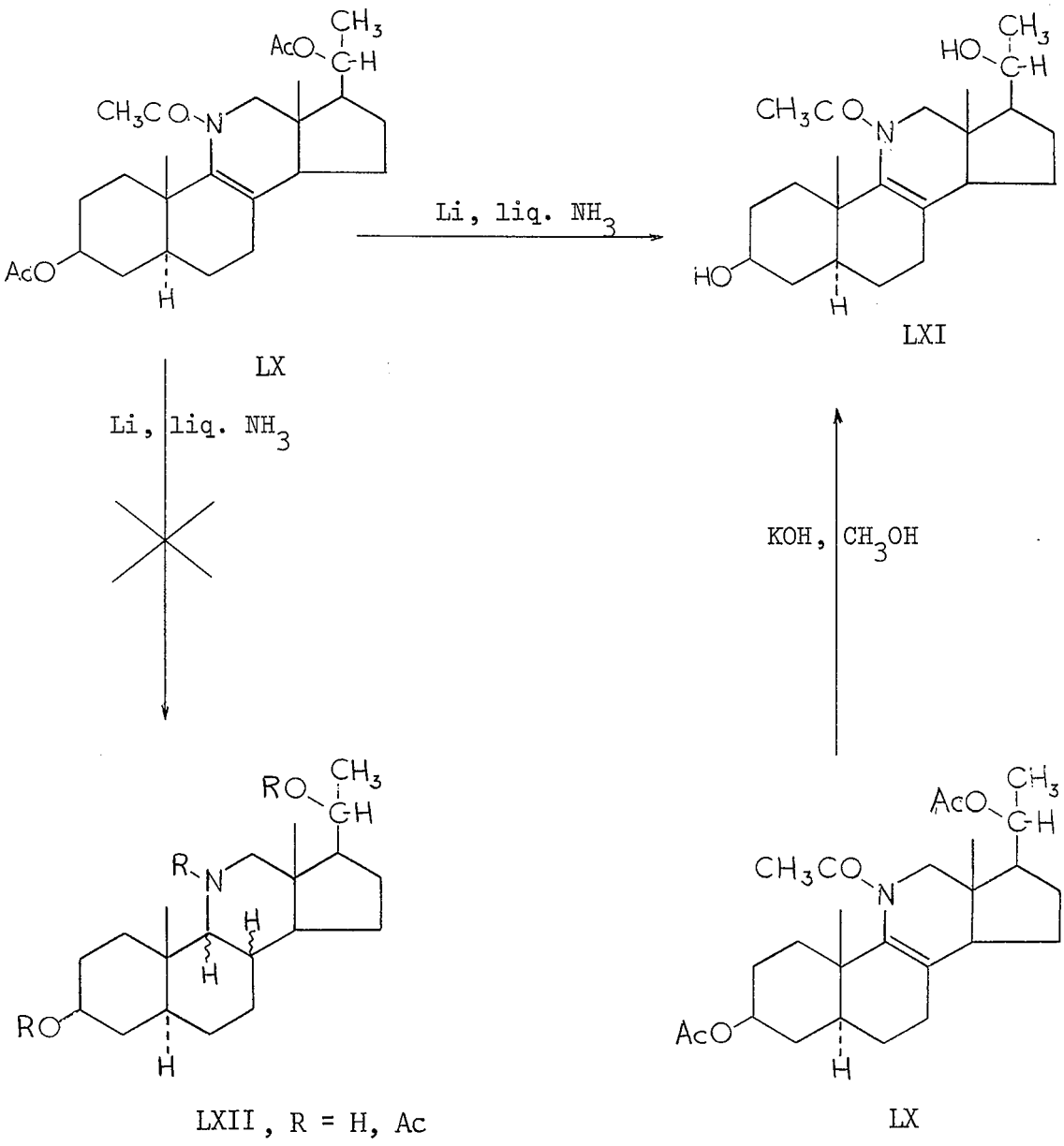
It is well known that the 8,9-double bond of normal steroids is very resistant to hydrogenation, except when it is conjugated with a keto function (80, 81, 82). However, it was demonstrated recently (58) that the 8,9-double bond of lanosterol derivatives could be reduced catalytically, with platinum oxide in the presence of perchloric acid at room temperature.

We therefore attempted to apply this method to the reduction of the enamines LIX and LX, but we could only isolate the unchanged starting materials from the reaction.

We also turned our attention to the possibility of catalytic reduction of the unsaturated lactam LVIII (cf. p 51) with platinum oxide in the presence of perchloric acid. Again, this method proved unsuccessful, either when applied under mild conditions of temperature and pressure, or at elevated temperatures and high pressures; the reaction led to untractable mixtures.

We then considered the reduction of enamines of type LIX and LX under "Birch conditions". While it is known that α,β-unsaturated ketones readily undergo Birch reduction, no prediction seemed possible with respect to the reduction of α,β-unsaturated amines. Attempts to reduce the 3,20-dihydroxy enamine LIX under these conditions proved indeed unsuccessful; the main product which could be isolated was the unchanged starting material. Similarly, attempts to reduce in an analogous manner the enamine derivative LX led only to the hydrolysis of the acetate functions in positions 3 and 20. The structure of the resulting N-acetyl 11-aza 8(9)-pregnene LXI was established

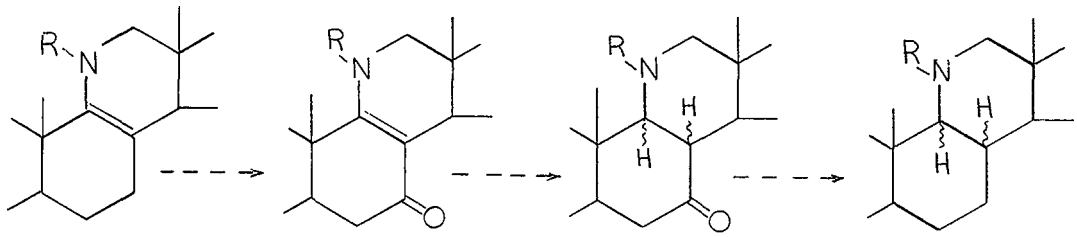
by its infrared and NMR spectra and by mass spectrometric determination[17] of its molecular weight, and was further confirmed by the preparation of the same compound by hydrolysis with 2N methanolic potassium hydroxide of the N-acetyl 3,20-diacetoxy enamine LX.



17. We are very thankful to Prof. K. Biemann of the Massachusetts Institute of Technology, Cambridge, Mass., U.S.A., for kindly taking the mass spectrum of this compound.

We also isolated another product from the reaction mixture, to which we assign tentatively the structure of an isomer of the dihydroxy enamine LXI, presumably formed by migration of the 8,9-double bond. Indeed, the product shows two hydroxyl bands at 3420 and 3370 cm^{-1}, and the amide carbonyl band at 1622 cm^{-1} in the infrared spectrum (taken in KBr) and mass spectrometric determination of its molecular weight[17] indicates that it has the same mass as the dihydroxy enamine LXI. The infrared spectra of these two compounds are not superimposable and their melting points differ from each other by 23°. The product, obtained only in low yield, was not further investigated.

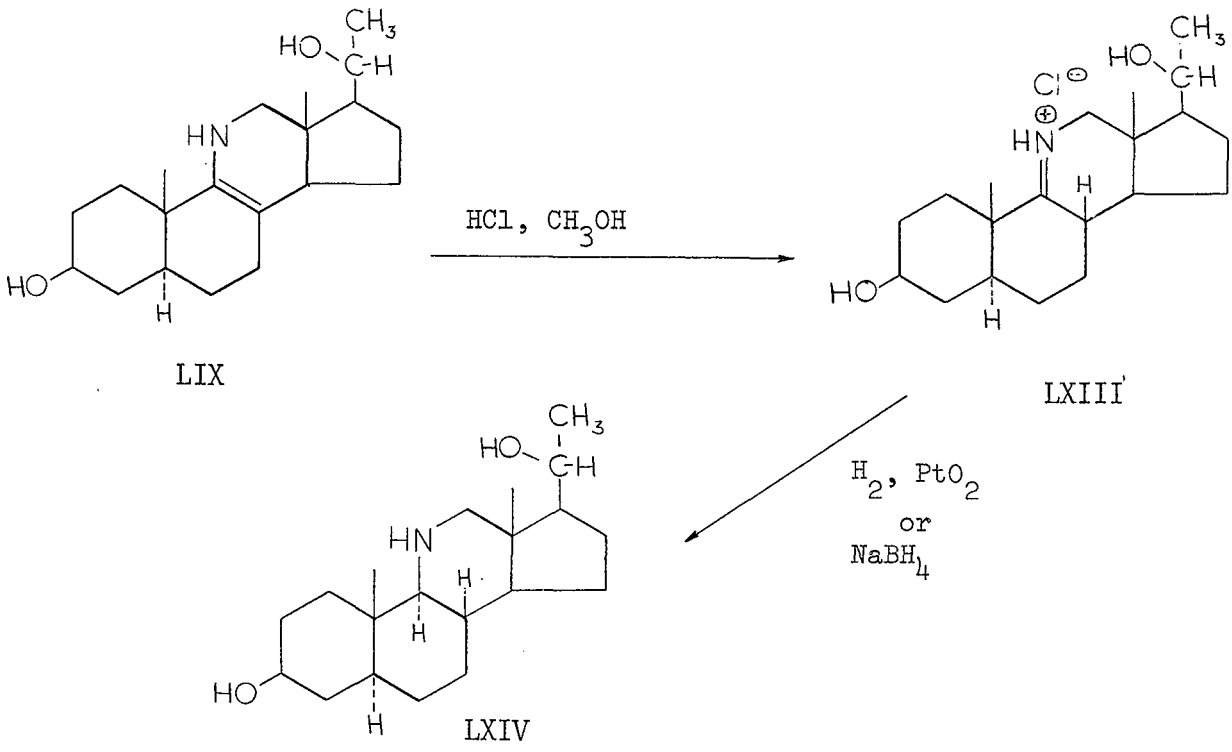
In another sequence of reactions, we attempted to circumvent the difficulties of direct reduction of the 8,9-double bond by introducing a carbonyl function in the allylic 7-position, which would afford a very readily reducible α,β-conjugated system (cf. xviii).



(LX) xviii xix xx

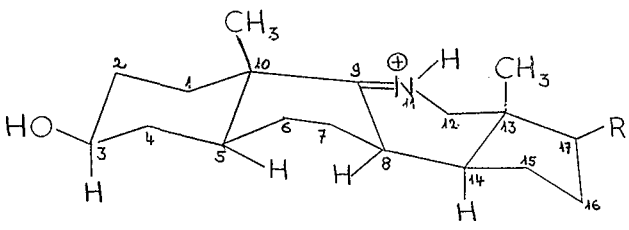
Similar reactions are known in the lanosterol series (cf. 83-86). We carried out numerous oxidation experiments with chromium trioxide under a variety of conditions (83, 84), with ozone (85), and with selenium dioxide (86), but we could not isolate an α,β-unsaturated ketone of type xviii.

Following again a different approach, we investigated the possibility of converting the enamine LIX to the iminium system LXIII (cf 87, 88 and also 89) which, we considered, should lend itself either to catalytic reduction or to reduction by means of sodium borohydride. Reduction of a double bond, albeit an unhindered one, of an enamine by its transformation to the corresponding iminium salt and its subsequent reaction with sodium borohydride has been described by Johnson et al. (89, also cf. 68). Using this principle, we were indeed able to reduce the 8,9-double bond of the crude enamine LIX. In one series of experiments we effected this reduction, catalytically, with platinum oxide in the presence of perchloric acid (cf. LXIV). The yield of the saturated 11-aza pregnane LXIV was low (15%, based on the crude enamine LIX) but exceeded that reported by Kutney et al. (68), who had used, in independent experiments, like Johnson et al., sodium borohydride in absolute methanol for the reduction of an analogous iminium salt. We also used Johnson's method, but, in our series, this procedure also proved even less satisfactory than the catalytic reduction.

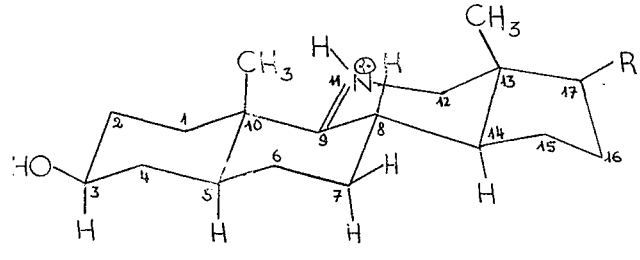


The structure of the 11-aza pregnane LXIV was established by its infrared and NMR spectra and by its elemental analysis. In its infrared spectrum the enamine absorption band at 1642 cm^{-1} disappeared,while a broad absorption band, corresponding to the hydroxyl and secondary amine functions, appeared at 3340 cm^{-1}. The NMR spectrum in deuteropyridine showed a multiplet corresponding to the C_3 and C_{20} protons at 4.0 ppm, while the three exchangeable protons (disappearing on deuterium exchange), corresponding to the two hydroxyl protons and the -NH- proton appeared as two multiplets at 3.7 and 3.47 ppm. The spectrum also showed a doublet centered at 2.7 ppm with a coupling constant of 12 cps, corresponding to the proton in position 9, coupled with the proton in position 8. The magnitude of this coupling constant established the axial conformation of both the C_9 and C_8 hydrogens (cf. chapter III). Finally, the spectrum also showed a doublet at 3.8 ppm with a coupling constant of 12 cps, corresponding to one of the two 12-methylene protons; the doublet corresponding to the other 12-methylene proton was not discernible and was probably hidden in the envelope of other protons in the higher field (the C_{12}-methylene protons were expected to appear as a pair of doublets, as in the case of 11-oxa steroids).

The trans-diaxial stereochemistry of the C_9 and C_8 hydrogen atoms was actually anticipated on the grounds of the following considerations. The initial process involving the conversion of the enamine LIX to the iminium salt LXIII generates an asymmetric center at C_8 and both the two possible isomers (8α and 8β) are represented by the structures D and E.



D (8α)



E (8β)

It can be seen that in the 8α-isomer (D), ring B adopts the boat conformation with the usual eclipsed hydrogen and "flagpole" interactions. On the other hand, in the 8β-isomer (E), ring B has a chair conformation and there are no severe interactions of the type encountered in the 8α-isomer (D). Considering that there exists an equilibrium between the enamine LIX and its iminium salt LXIII, the thermodynamically favored structure E (with an 8β-hydrogen configuration) should be formed.

On the other hand, the approach of hydrogen to the 9 position of the iminium salt LXIII occurs far more readily from the α-side since the two angular methyl groups C_{18} and C_{19} prevent effective approach from the β-side. Also, according to the studies of Bohlman et al. (90) on the stereochemistry of sodium borohydride reductions of certain iminium salts, the attack of the hydride ion occurs from the least hindered side of the molecule in its most stable conformation.

A similar argument was put forward by Kutney et al. (68) for the stereochemistry of the reduction product of their enamine derivative in the sapogenin series, but was not substantiated experimentally.

The structure of the 11-azapregnane LXIV was further confirmed by mass spectrometry[18]. In addition to the peak for the molecular ion M^+ at 321, the mass spectrum showed two other significant peaks at m/e=194 and m/e=180, which can be rationalized as follows (Scheme III):

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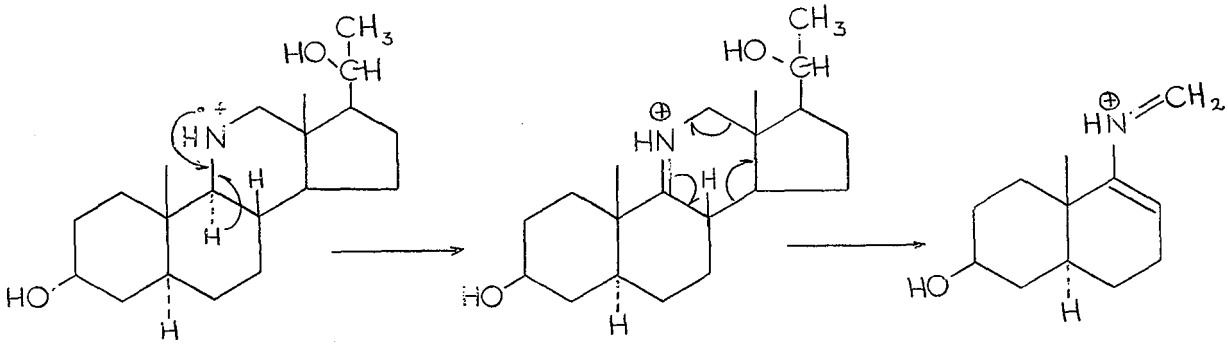
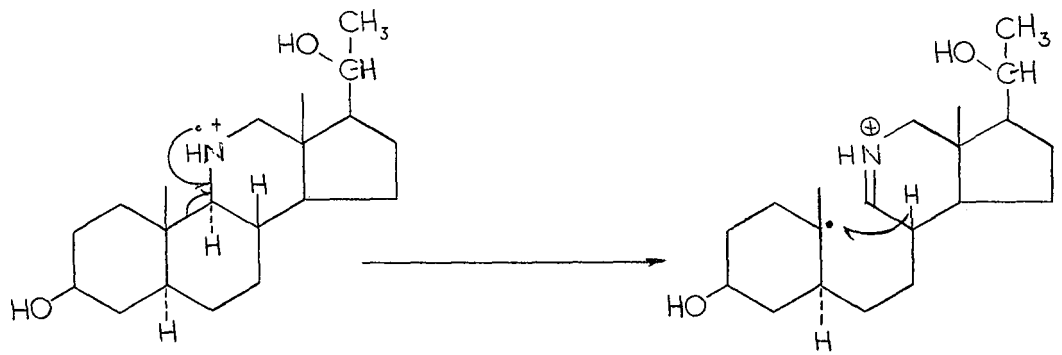
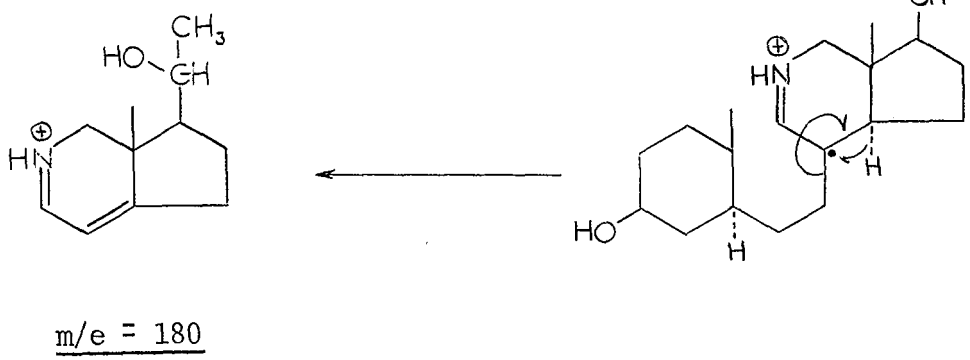
18. We are indebted to Prof. F.W. McLafferty and Mr. T. Wachs, of the Department of Chemistry, Purdue University, Lafayette, Indiana, U.S.A., for the mass spectrum of this compound, and we express to them our sincere appreciation.



$M^+ = 321$ m/e = 194



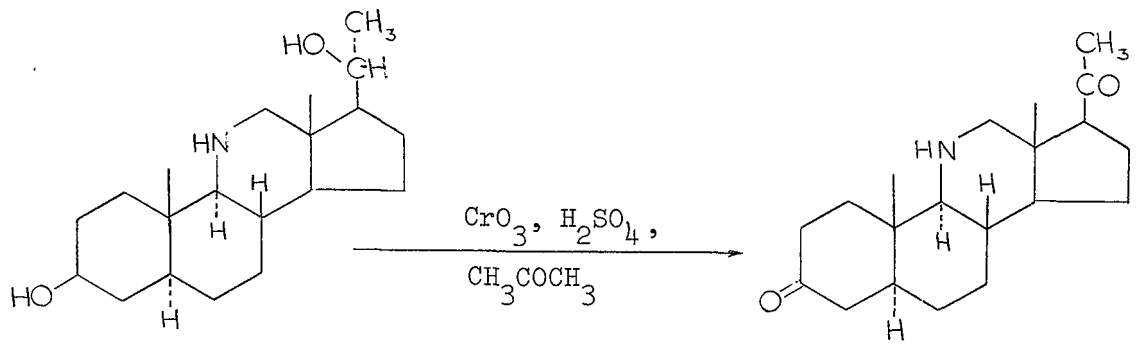
$M^+ = 321$



m/e = 180

(Scheme III)

Careful oxidation of the dihydroxy 11-aza pregnane LXIV with Jones' reagent gave the corresponding 11-aza pregnanedione LXV, the infrared



LXIV LXV

spectrum of which showed the -NH- absorption band at 3400 cm^{-1} and had an absorption at 1720 cm^{-1} corresponding to the 3,20-diketo functions. The structure of this product was confirmed by its elemental analysis and its NMR spectrum, which showed a doublet centered at 3.3 ppm with a coupling constant of 12 cps, corresponding to one of the two C_{12}-methylene protons[19], and a doublet centered at 2.7 ppm with a coupling constant of 12 cps, corresponding to the C_9-proton which is coupled with the C_8-proton. It may be noted that the doublet corresponding to the C_{12}-methylene proton in the dione LXV appeared towards higher field by about 30 cps as compared to that in the 11-aza pregnane LXIV (where it appeared at 3.8 ppm), presumably because of the "field effect" of the 17-acetyl chain on the 12-methylene protons in the dione LXV, the position of the doublet corresponding to the 9-proton remaining unchanged. As already seen earlier in the case of the 11-aza pregnane LXIV, the coupling constant of 12 cps for the C_9-proton indicates again the trans-

19. The doublet corresponding to the other C_{12}-methylene proton could not be assigned with certainty, although it probably is the one appearing at 2.2 ppm with a coupling constant of 12 cps.

diaxial stereochemistry of the hydrogens at C_8 and C_9 in these saturated 11-aza steroids. The exchangeable -NH- proton of the dione LXV appeared as a singlet at 2.55 ppm and disappeared on deuteration; the 17-acetyl protons appeared as a singlet at 2.09 ppm, while those corresponding to the 18 and 19 angular methyl groups appeared at 0.77 and 1.1 ppm, respectively.

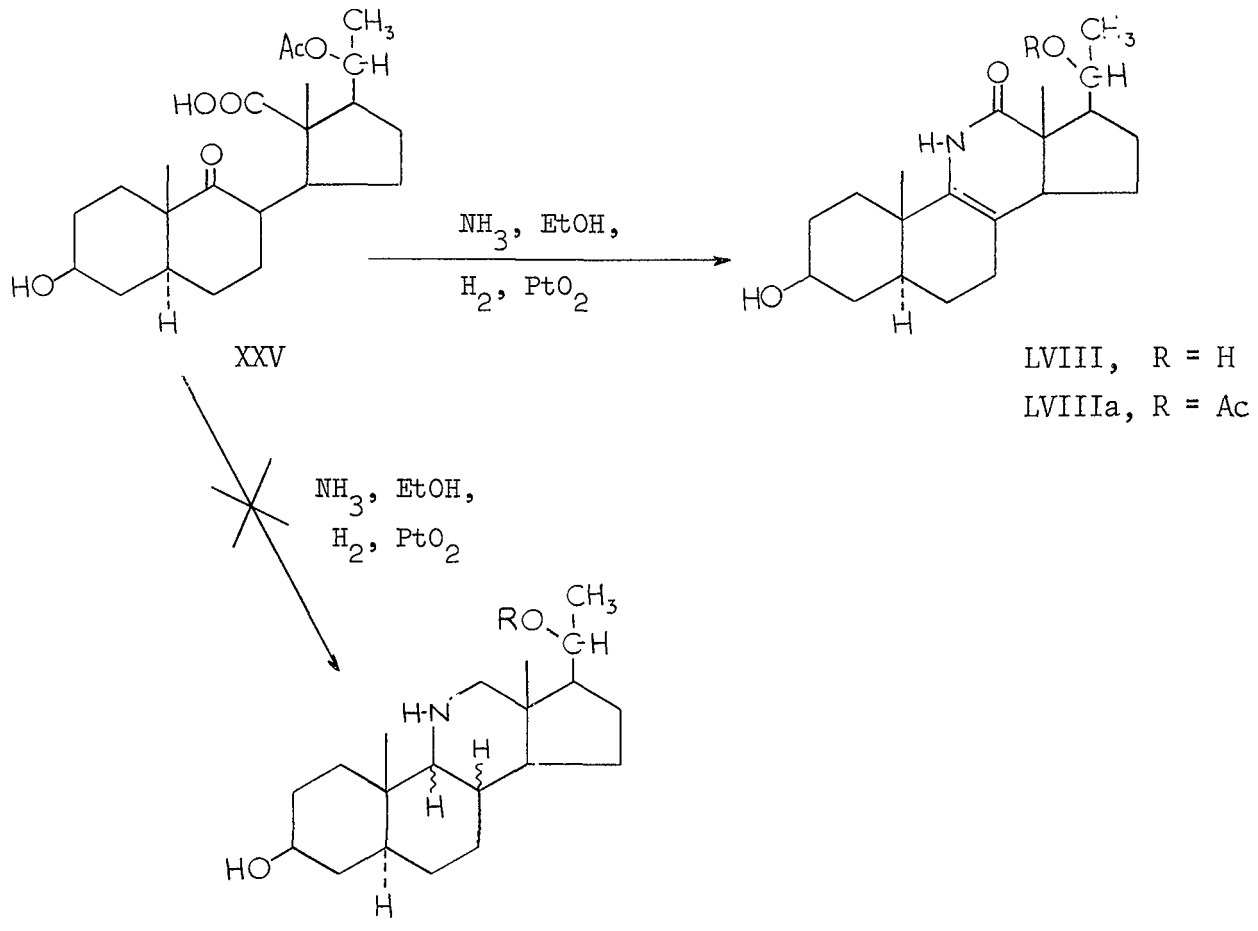
The investigation of the introduction of the double bond in position 4 of the 11-aza pregnanedione LXV is not part of this thesis, and will be discussed elsewhere.

Section 2

Contribution towards the Direct Synthesis of 8,9-Saturated 11-Aza Steroids

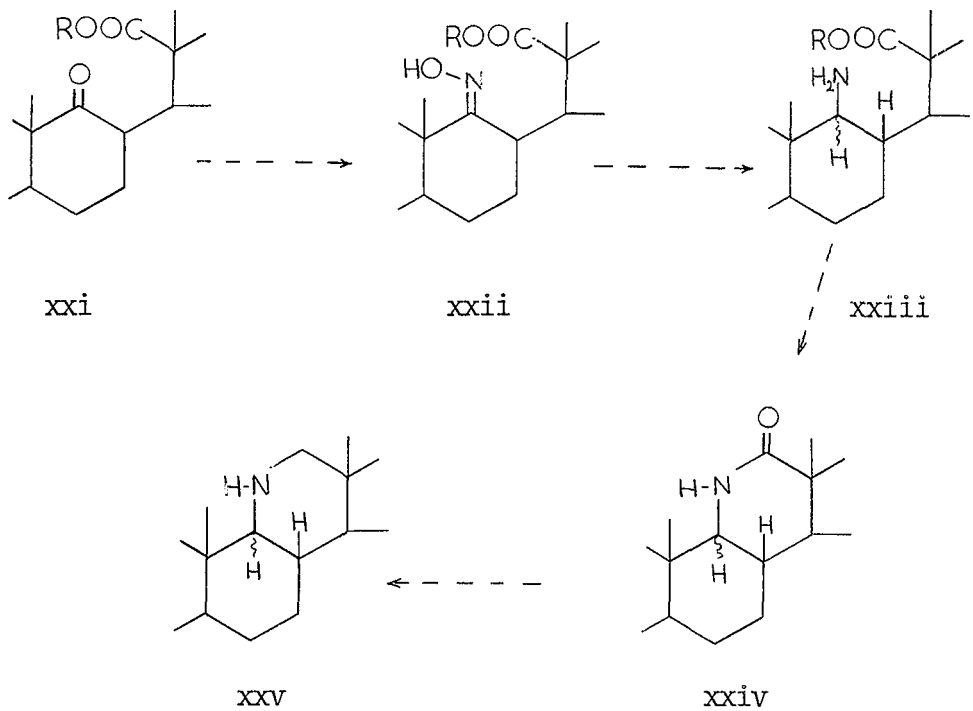
Because of the low yields of the reduction of the 8,9-double bond of 8,9-unsaturated 11-aza steroids, it seemed of interest to explore direct routes leading to 11-aza steroids.

We thus investigated the reductive amination (91, 92) of the seco keto acid XXV, a reaction which would lead in one step to an 8,9-saturated 11-aza steroid LXVI. However, this method proved unsuccessful because an ordinary ammonolysis of the seco keto acid XXV (leading to the unsaturated lactams LVIII and LVIIIa) competes with the reductive amination.



We investigated this reaction under a variety of conditions; thus, it was carried out with platinum oxide at room temperature and at slightly elevated pressure, at elevated temperature and high pressure, also, with Raney nickel under a variety of temperature and pressure conditions. The reaction gave a mixture of the unsaturated lactams LVIII and LVIIIa; no product arising from a reductive amination could be isolated.

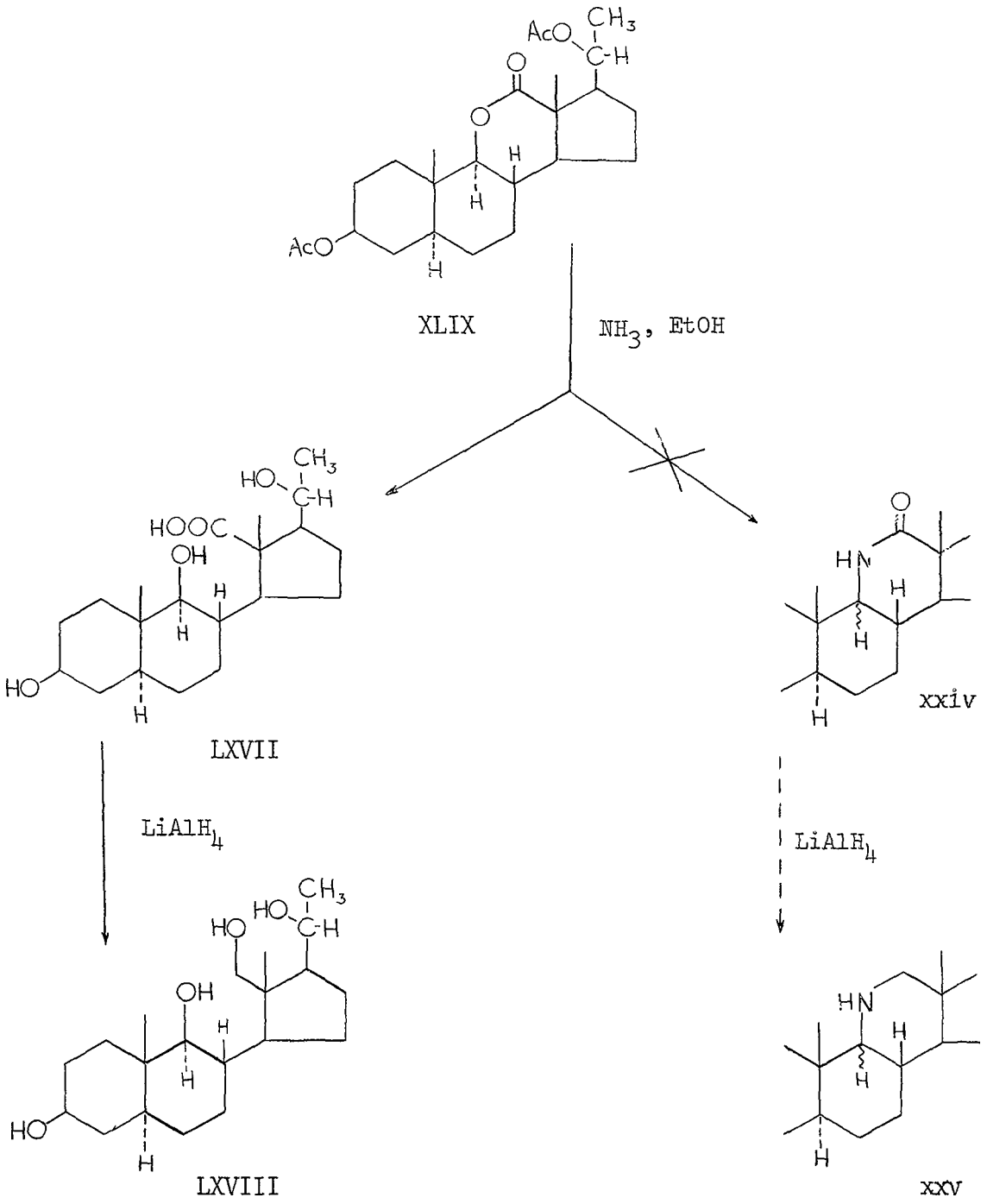
In a second series of experiments, we reinvestigated the possibility of synthesizing the saturated 11-aza steroids from 9-oxo 9,12-seco 11-nor 12-pregnanoic acids or esters of type xxi through the formation of an oxime which one could hope to reduce to an amine (cf. xxiii) suitable for cyclization to the corresponding lactam.



This procedure had led to the synthesis of the first nucleo-aza steroid, 4-azacholestane (93). A preliminary and unsuccessful experiment for the oximation of a keto acid of type xxi had already been carried out by Engel and Huculak (62). However, because of the availability of a number of excellent new methods for preparing oximes of highly hindered ketones (94-96), we considered it worthwhile to reinvestigate this possibility. Unfortunately, none of the methods, used under a variety of conditions, gave a positive result. We subjected, for instance, the keto acid XXV to the action of hydroxylamine hydrochloride in refluxing pyridine (94), hydroxylamine hydrochloride and sodium methoxide in boiling methanol (95), and to the "lethargic reaction conditions" recently described by Pearson and Keaton (96), consisting in exposing the ketone to the action of hydroxylamine hydrochloride and potassium tertiary amylate for six months at room temperature.

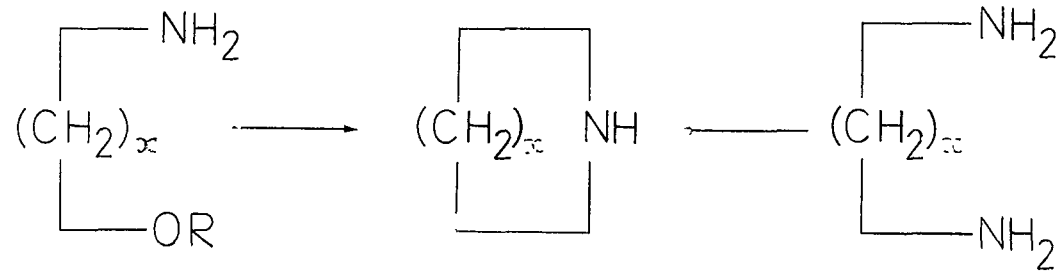
Following another approach, the seco keto acid XXVd was converted to the lactone XLIX (as described in Chapter III) and this product was subjected to ammonolysis, which one might have expected to lead to a saturated lactam (cf. xxiv). Such a reaction has, to our knowledge, not been described in the case of saturated δ-lactones, although similar transformations of γ-lactones to γ-lactams have been reported (97-99), and are also known in the case of enol-lactones (100).

Again, this approach failed, the only product which could be isolated being the trihydroxy acid LXVII, the structure of which was substantiated by its reduction with lithium aluminum hydride to the tetrahydroxy derivative LXVIII.



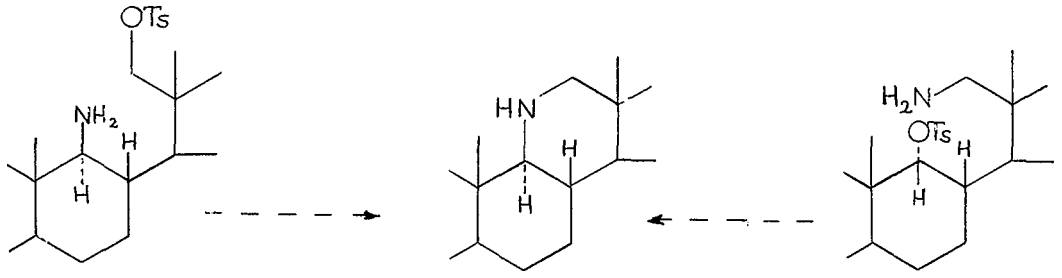
The lack of success of the procedures outlined induced us to turn our attention to the investigation of two methods which have never been employed for the synthesis of nucleo-hetero steroids (one, as a matter of fact, has not even been used for the synthesis of six-membered hetero cycles).

One of the procedures involves the cyclization of ω-amino ω′-sulfonyloxy derivatives of type xxvi to cyclic amines of type xxviii, a method which has been used with success in the sugar series for the synthesis of 2,6- and 3,6-benzimino desoxy sugars (101, 102) and aziridine derivatives (117). The other method consists of the classical pyrolysis of ω,ω′-diamines of type xxvii to cyclic amines (cf. xxviii), employed for the synthesis of a number of indoles and carbazoles (103, 104).

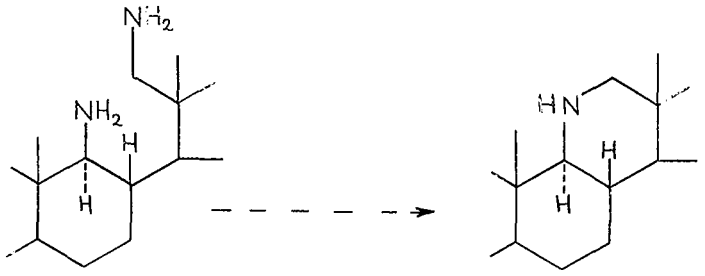


xxvi, R = Ms, Ts xxviii xxvii

In order to be in a position to utilize these methods for the synthesis of 11-aza steroids with the stereochemistry of natural steroids, it seemed necessary to synthesize 9,12-substituted 9,12-seco 11-nor steroids of the types xxix, xxx, and xxxi, which have in position 9 a stereochemistry allowing cyclization to 11-aza products with a 9α-hydrogen substituent. In the work to be described presently, we concentrated on the development of methods for the synthesis of such intermediates, while the further elaboration of the methods and the actual cyclization experiments form part of another investigation.

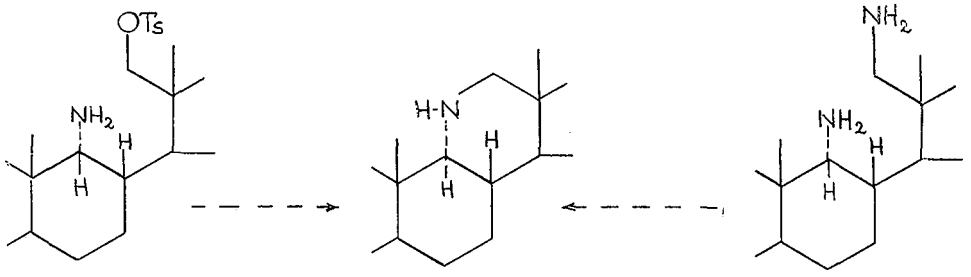


xxix xxxii xxx



xxxi xxxii

On the other hand, we wished to take advantage of this study to investigate pathways leading to 9-iso 11-aza steroids (cf. xxxv), in which we were interested in connection with structure-activity correlations. For this project, the synthesis of 9α-amino 12-tosylates of type xxxiii and 9α,12-diamines of type xxxiv seemed desirable.



xxxiii xxxv xxxiv

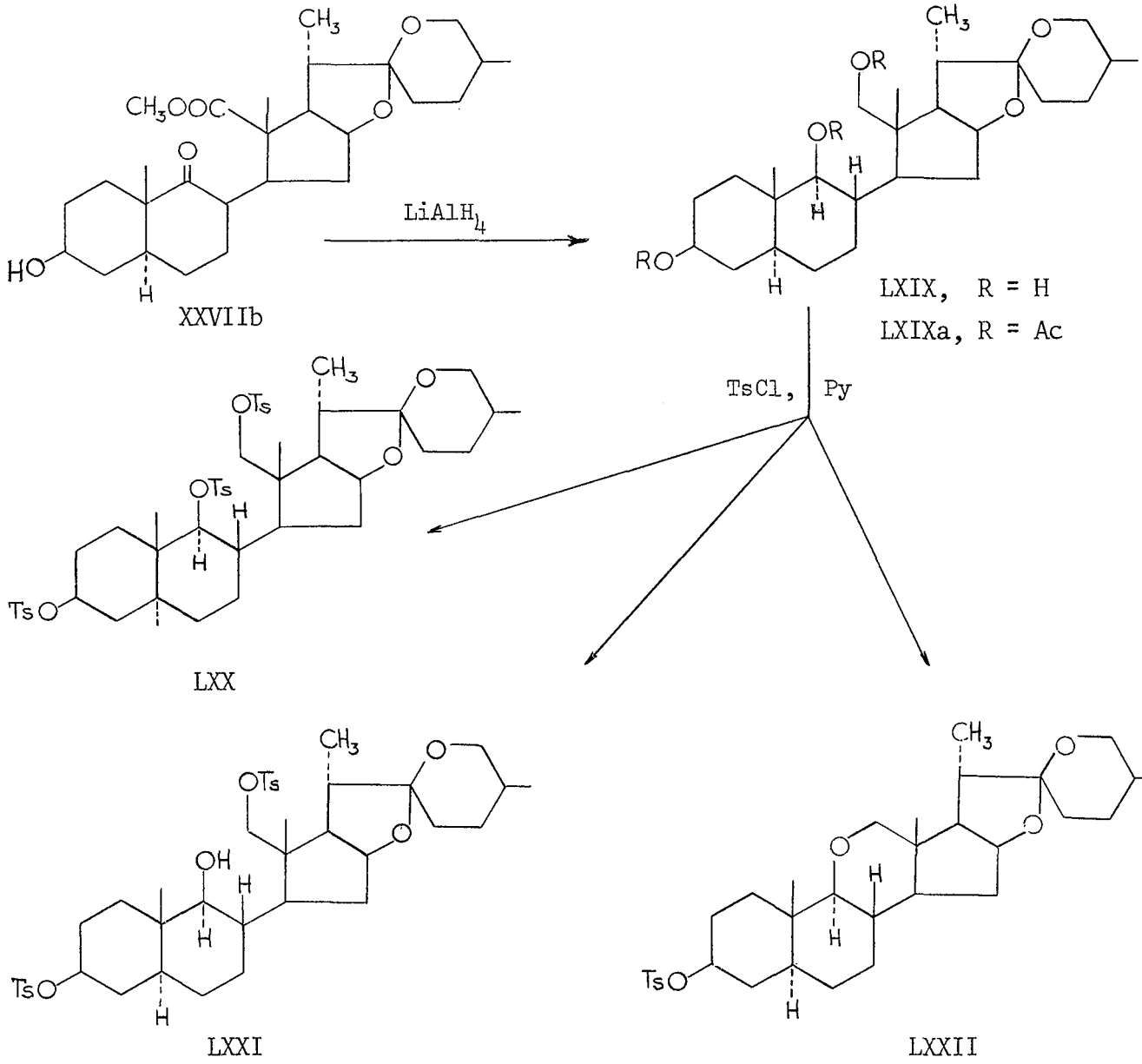
As a matter of fact, the interest in the synthesis of 9-iso 11-aza steroids was increased because of the relative ease with which 9α-amino derivatives of types xxxiii and xxxiv should be obtainable from the corresponding 9β-tosyloxy derivatives.

Since 9β-amino derivatives, the intermediates which were to be used for the preparation of 11-aza steroids with the natural (9α-hydrogen) configuration, should be conveniently prepared from 9α-tosylates through the formation of the corresponding 9β-azides, it would have been desirable to synthesize 9α-hydroxy derivatives for this purpose.

However, we were not able to reduce the 9-keto ester XXVIIb to the corresponding 9α-hydroxy derivative, either by catalytic reduction with platinum oxide in acid medium (105), or by reduction with Raney nickel (106), or by a Meerwein-Pondorf reduction with a limited reaction time (107); in all these cases the only product isolated was the unchanged starting material. On the other hand, attempts to invert the configuration of the 9β-tosylate function of 9β-tosyloxy 9,12-seco steroids with sodium benzoate (108,109) have not been successful because of the facility of cyclization of 9β-hydroxy 12-oxygenated compounds and their acyl derivatives.

In the following paragraphs, we shall describe our exploratory experiments for the synthesis of the key intermediates (9,12-diamines, and 9,12-tosyloxy amines of the types mentioned above), suitable for conversion to 11-aza steroids having both the "normal" and "iso" configuration in position 9.

The 3β-hydroxy 9-oxo ester XXVIIb, obtained as described in Chapter II, was converted by reduction with lithium aluminum hydride in tetrahydrofuran to the 3,9,12-triol LXIX in 91% yield. This triol, which was also characterized as its triacetate LXIXa, was converted to a mixture of the tritosylate LXX, the ditosylate LXXI, and the monotosyloxy 11-oxa spirostane LXXII, in 40%, 11.5%, and 19.5% yields, respectively, by treatment with p-toluenesulfonyl chloride in pyridine at 25° for seven days. The ditosylate LXXI could



be obtained in 62% yield from the triol LXIX by tosylation at 25° for only 20 h.

The structure of the triol LXIX was established by its infrared and NMR spectra and by elemental analysis. The equatorial (β) stereochemistry of the hydroxyl group in position 9 follows from that of the 9,12-diols XLII and XLVI (described in Chapter III), obtained by analogous reductions of the corresponding keto esters XLI and XLV with lithium aluminum hydride. It is confirmed by an analysis of the NMR spectra of the ditosylate LXXI and of the tosyloxy 11-oxa spirostane LXXII in which the stereochemistry in posision 9 must be the same as that in the parent triol LXIX. The NMR spectrum of the ditosylate LXXI shows a doublet centered at 2.7 ppm with a coupling constant of 9 cps, corresponding to the C_9-proton. The spectrum of the monotosylate LXXII in benzene solution shows a doublet centered at 2.33 ppm with a coupling constant of 10 cps, corresponding to the C_9-proton. In both these cases the coupling constants established that the C_9-proton has the axial conformation. The structures of the tritosylate LXX, ditosylate LXXI, and 11-oxa monotosyloxy spirostane LXXII were established by their spectroscopic data and elemental analyses.

We were able to replace selectively one of the tosyl groups of the tritosylate LXX by an azide function by means of sodium azide in dimethyl formamide at 70°, and thus to obtain,in 87% yield, the monoazide LXXIII[20].

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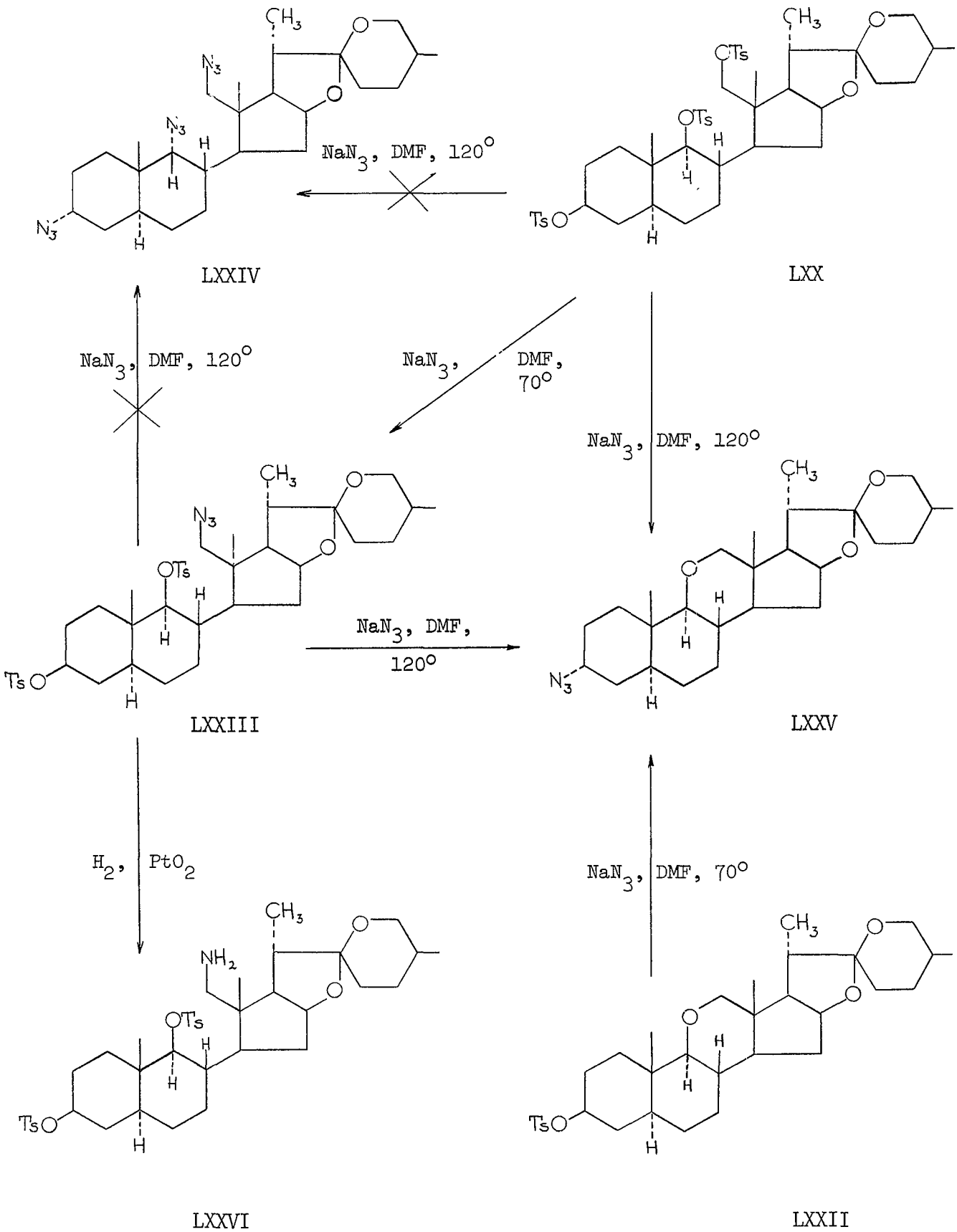
20. The ditosyloxy monoazide is represented by structure LXXIII since one can assume that the primary tosyloxy substituent is the one to be replaced preferentially.



LXXIV LXX

LXXIII LXXV

LXXVI LXXII

Prolonged treatment of the tritosylate LXX, and also of the tosyloxy monoazide LXXIII, with sodium azide at elevated temperatures, afforded the 3-azido 11-oxa spirostane LXXV[21], and not the desired triazide LXXIV. The same 3-azido 11-oxa spirostane LXXV was obtained in 86% yield from the 3β-toxyloxy 11-oxa spirostane LXXII by direct replacement of the 3-tosyloxy group by an azido substituent, by treatment with sodium azide. The monoazide LXXIII was catalytically reduced with platinum oxide to the ditosyloxy amine LXXVI in 75% yield.

The structure of the ditosyloxy monoazide LXXIII was established by its ultraviolet, infrared and NMR spectra and its elemental analysis. The ultraviolet spectrum showed a maximum at 225 mμ (log ε 4.4), typical of the tosylate chromophore (110). The infrared spectrum showed a sharp absorption band at 2110 cm^{-1} corresponding to the azide function. The NMR spectrum showed a multiplet centered at 7.55 ppm for the aromatic protons and a doublet centered at 4.2 ppm with a coupling constant of 10.5 cps corresponding to the axial C_9-proton. The spectrum also showed the C_3 and C_{16} protons as a multiplet centered at 3.87 ppm, the C_{26}-methylene protons as a multiplet centered at 3.4 ppm, the C_{12}-methylene protons as a pair of doublets centered at 3.5 and 3.12 ppm with a coupling constant of 10 cps, the two methyl groups of the tosyl functions at 2.5 and 2.43 ppm, and the 18, 19, 21 and 27 methyl groups as an unresolved multiplet between 1.0 and 0.5 ppm.

The structure of the 3-azido 11-oxa spirostane LXXV was likewise supported by its infrared and NMR spectra. The NMR spectrum showed a broad "singlet"

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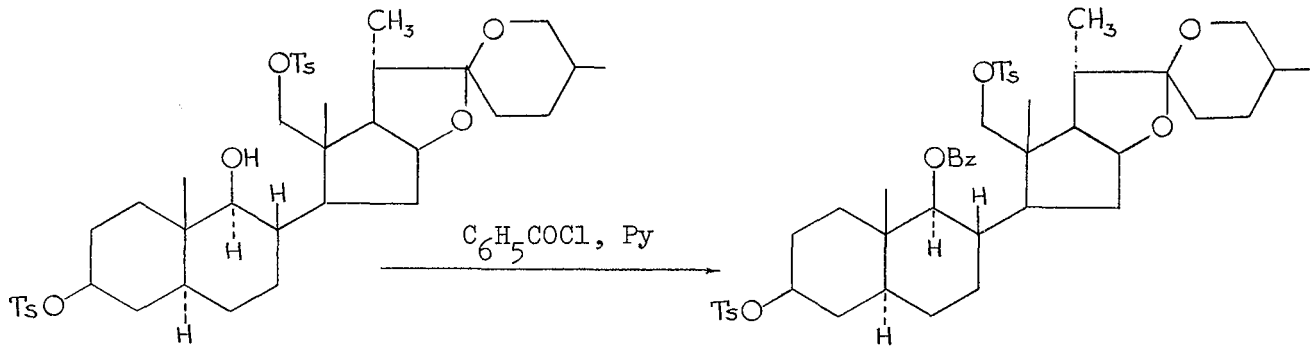
21. The 3-monoazido 11-oxa spirostane LXXV and the diazide LXXVIII (see p74) are represented as 3α-azides, since one may assume inversion of configuration upon azidolysis of the 3β-tosylate. This is also supported by an NMR analysis (described later in this section).

at 3.9 ppm which we assign to the C_3 equatorial proton. This broad "singlet" is equivalent to an unresolved multiplet with a small coupling constant, such as would be expected for the coupling between e-e and e-a protons and thus agrees well with an equatorial conformation of the C_3-proton. Consequently, the 3-azide function of the azido oxa spirostane LXXV has an axial conformation and an α-configuration.

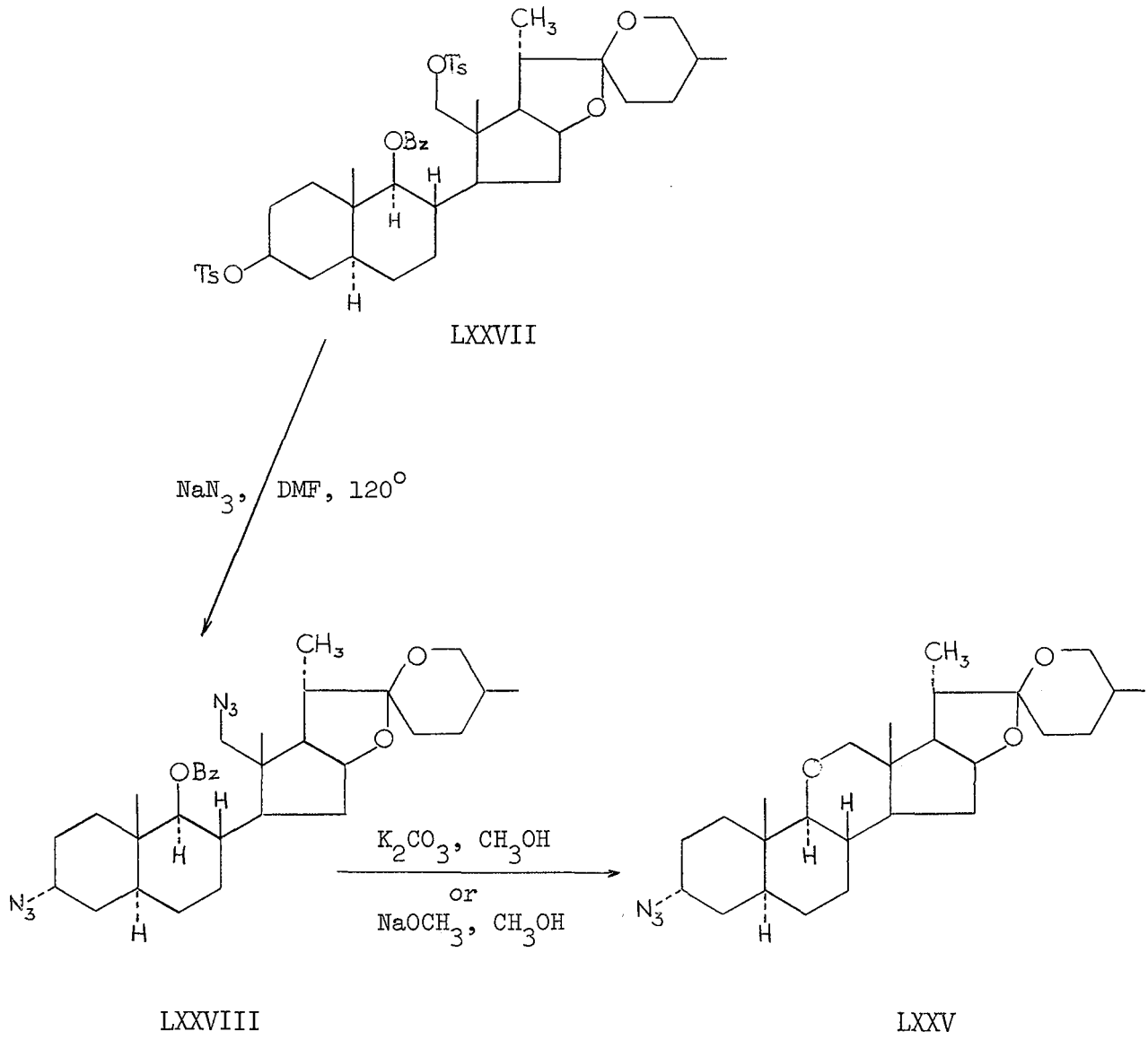
The structure of the ditosyloxy amine LXXVI follows from its method of preparation and is confirmed by its infrared spectrum and elemental analysis.

In another attempt to prepare the 3,9,12-triazide LXXIV, we tried to avoid the cyclization to an 11-oxa steroid during the replacement of a 12-tosyloxy substituent by an azide group (cf. above), by protecting first the 9β-hydroxy group of the hydroxy ditosylate LXXI through benzoylation. Treatment



LXXI LXXVII

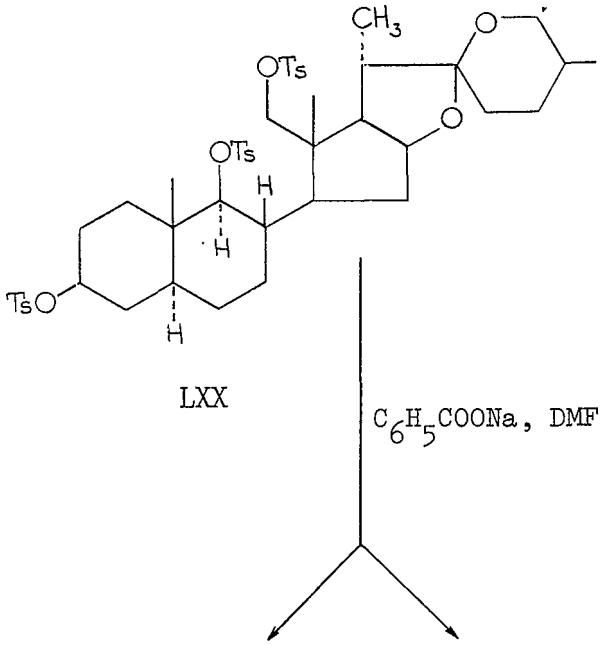
of the resulting 9β-benzoyloxy ditosylate LXXVII with sodium azide in dimethylformamide at 120° gave indeed the desired 9β-benzoyloxy 3,12-diazide LXXVIII in 72% yield,but in the course of the saponification of the benzoate function (carried out in order to liberate the protected hydroxyl group for subsequent tosylation) cyclization to the 3-azido 11-oxa spirostane LXXV occurred.



The structures of the 9β-benzoyloxy ditosylate LXXVII and the 9β-benzoyloxy diazide LXXVIII were deduced from their method of preparation and further confirmed by their ultraviolet, infrared, and NMR spectra. The NMR spectrum of the diazide LXXVIII showed, in addition to other signals, a broad "singlet" (which was actually an unresolved multiplet with a small coupling constant) at 3.87 ppm, corresponding to the equatorial C_3-proton.

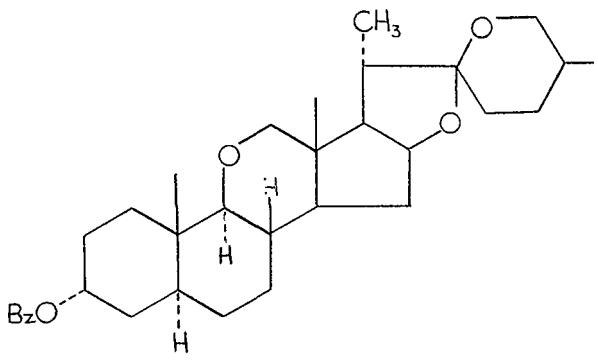
As indicated earlier, we did not succeed in preparing a 9α-hydroxy compound by reduction of the 9-keto ester XXVIIb under various conditions (cf.105-107).

Similarly, as also mentioned, our attempts to invert the configuration of the 9β-tosyloxy function of the tritosylate LXX with sodium benzoate in dimethylformamide were unsuccessful ; we isolated instead the 11-oxa steroids LXXIX and LXXX in 7% and 9% yields, respectively. No other reaction product (except the starting material) could be isolated from this reaction.

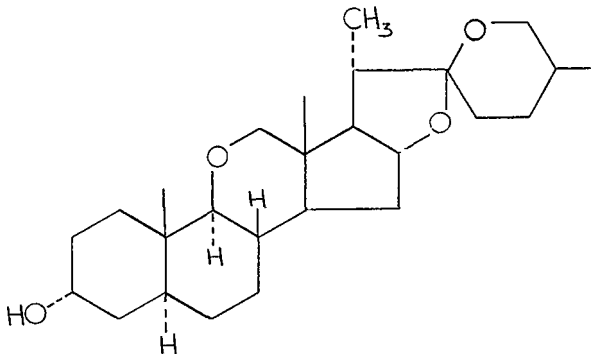


LXX

C_6H_5COONa, DMF



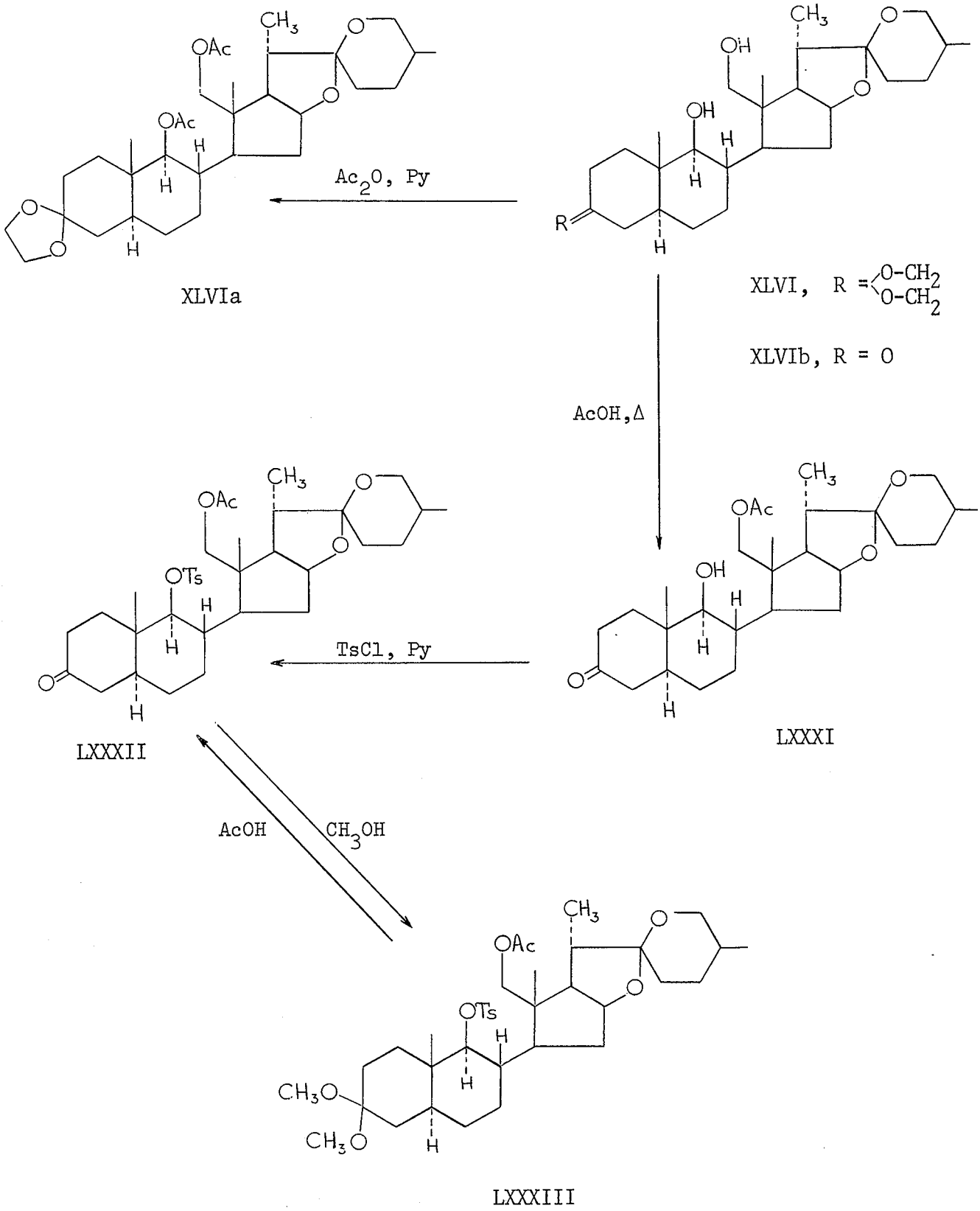
LXXIX



LXXX

The structures of the oxa steroids LXXIX and LXXX were established on the basis of their spectroscopic data. The α-configuration of the 3-benzoyloxy substituent of compound LXXIX, which seemed probable in view of its mode of formation, was supported by its NMR spectrum which showed a broad "singlet" at 5.30 ppm corresponding to the equatorial C_3-proton, the small "coupling constant" indicating an equatorial conformation of the hydrogen atom in position 3. The α-configuration of the 3-hydroxyl group of the oxa steroid LXXX, formed by hydrolysis of the 3-benzoate LXXIX during the working up, was likewise supported by its NMR spectrum.

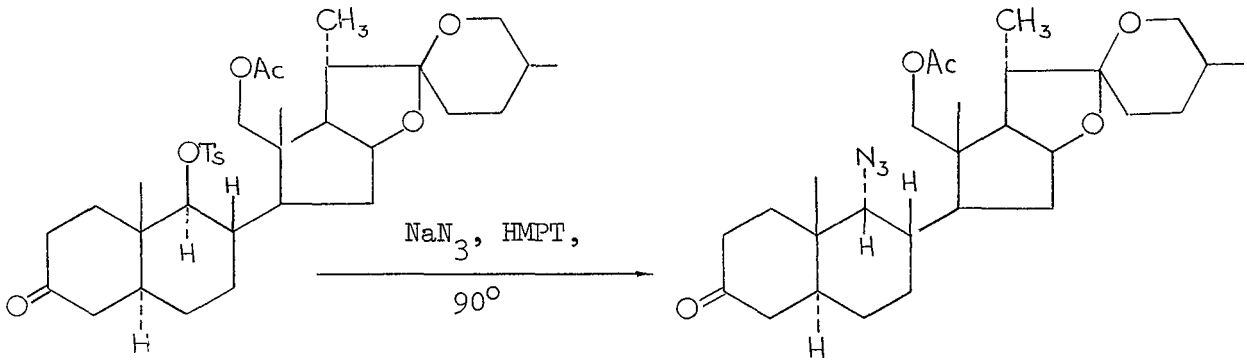
Other routes, which are expected to lead to 9α,12-dihydroxy 9,12-seco 11-nor steroids, are being investigated in this laboratory but are not part of the work described in this thesis . In the present program we rather studied further the differential functionalization in positions 9 and 12. Thus, in the series of 3-keto steroids described in Chapter III, the 9,12-dihydroxy ketal XLVI, which gave the diacetate XLVIa on treatment with acetic anhydride in pyridine, was mono-acetylated with acetic acid, in 73% yield, to the 9β-hydroxy 12-acetoxy derivative LXXXI, in which the 3-ketone had been simultaneously liberated in the acidic medium. The 9β-hydroxy 12-acetate LXXXI was tosylated with an excess of p-toluenesulfonyl chloride in pyridine to the 9β-tosylate LXXXII in 60% yield. This product gave the corresponding 3,3-dimethoxy derivative LXXXIII in 81% yield when treated with methanol for 5 days; the free 3-ketone was regenerated upon treatment with acetic acid.


OAc
CH3
OAc
H
H
H
Ac2O, Py
OH
CH3
OH
H
H
R
H
XLVIa
XLVI, R = O-CH2 / O-CH2
XLVIb, R = O
AcOH,Δ
OAc
CH3
OTs
H
H
H
TsCl, Py
OAc
CH3
OH
H
H
H
LXXXII
LXXXI
AcOH
CH3OH
OAc
CH3
OTs
H
H
CH3O
CH3O
H
LXXXIII

The structure of the mono-acetate LXXXI was confirmed by its infrared and NMR spectra. The formulation of this product as a 12-mono-acetoxy 9-hydroxy derivative was based on the assumption that preferential mono-acetylation of the diol XLVI would surely lead to acetylation of the primary hydroxyl group in position 12. This was further supported by a comparison of the NMR spectra of the mono-acetate LXXXI and of the 3-oxo 9,12-diol XLVIb which indicated that the singlet due to the 12-methylene protons appearing at 3.35 ppm in the 3-oxo 9,12-diol XLVIb was shifted by 0.55 ppm (33 cps) towards lower field (the 12-methylene protons of the mono-acetate LXXXI appeared as a singlet at 3.9 ppm) on mono-acetylation, as could be expected (118).

The infrared spectrum indicated characteristic absorptions for the hydroxyl group at 3480 cm^{-1}, for the acetate function at 1745 and 1242 cm^{-1}, and for the ketone at 1719 cm^{-1}. The NMR spectrum showed a multiplet centered at 4.35 ppm corresponding to the C_9 and C_{16} hydrogen atoms, a singlet at 3.9 ppm corresponding to the C_{12}-methylene protons, a multiplet centered at 3.43 ppm corresponding to the C_9-hydroxyl proton and the C_{26}-methylene protons, a singlet at 2.07 ppm corresponding to the methyl protons of the acetate, while the 18, 19, 21, and 27 methyl protons could be seen as an unresolved multiplet between 1.15 and 0.8 ppm. The structures of the 3-keto monotosylate LXXXII and the 3,3-dimethoxy tosylate LXXXIII were deduced on the basis of their method of preparation and of their elemental analyses and confirmed by their ultraviolet, infrared, and NMR spectra.

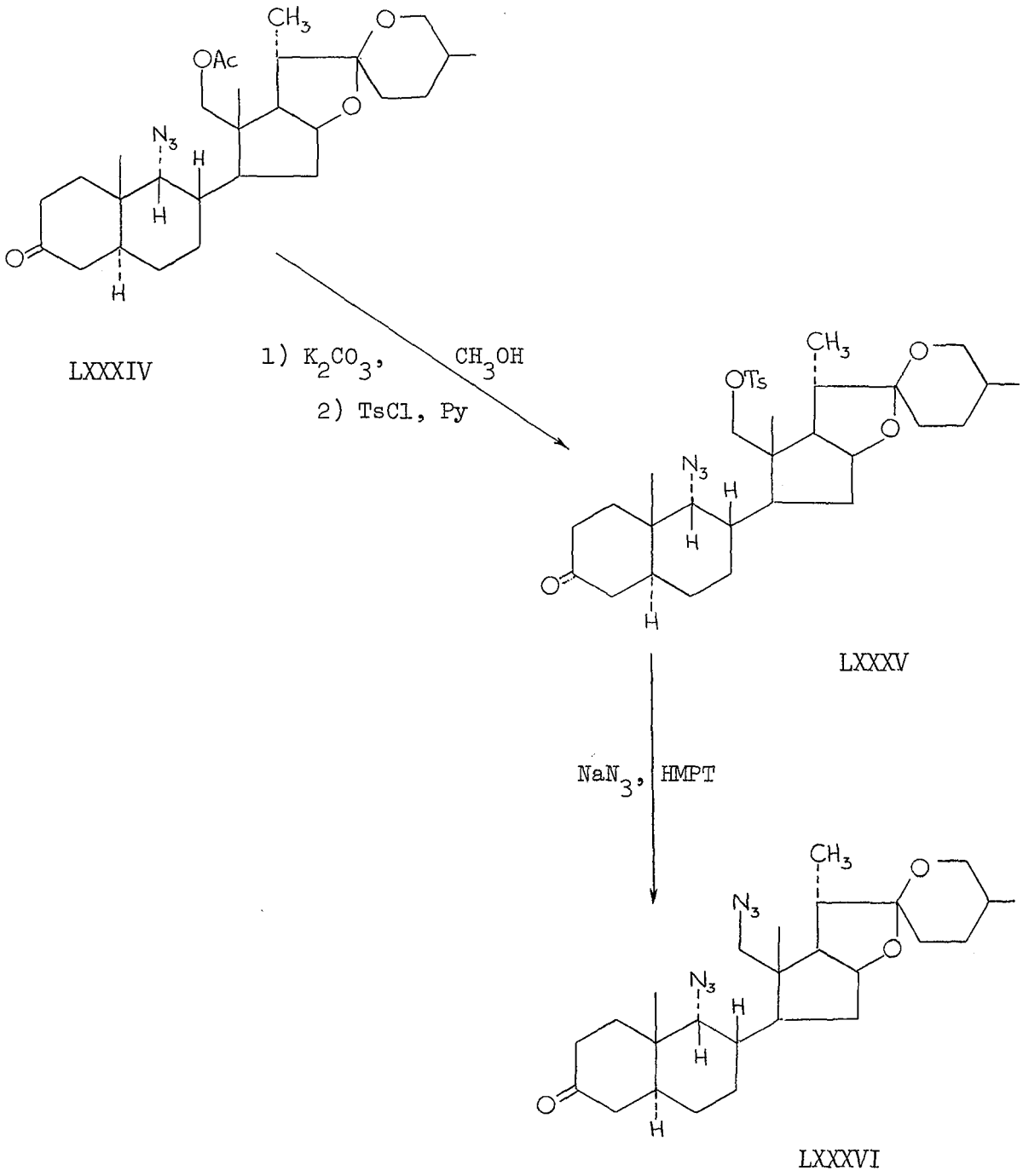
The 9β-tosyloxy 12-acetate LXXXII was converted to the 9α-azido 12-acetate LXXXIV in approximately 90% yield by treatment with sodium azide in hexamethyl phosphoric triamide (HMPT) at 90° for 3 h (111).



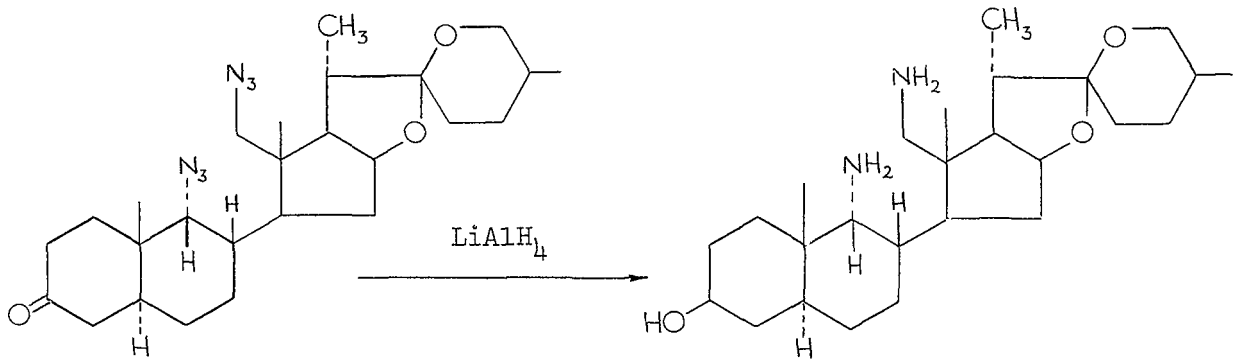
LXXXII LXXXIV

The structure of the 9α-azido 12-acetate LXXXIV was established by its infrared and NMR spectra. The 9α-stereochemistry of the azide function, anticipated from its method of preparation, was supported by the NMR spectrum. The axial (α) stereochemistry of the 9-azide function of the 9-azido steroids LXXXIV, LXXXV, and LXXXVI, and that of the 9-amino function of the diamine LXXXVII (see below), was confirmed by the appearance in the NMR spectrum of the 9α-azido 12-tosylate LXXXV, of a clear doublet centered at 3.2 ppm with a coupling constant of 4 cps, corresponding to the C_9-proton. The coupling constant of 4 cps for this doublet agrees very well with that between two vicinal axial-equatorial protons.

The 9α-azido 12-acetate LXXXIV was converted to the 9α-azido 12-tosylate LXXXV by hydrolysis of the 12-acetate function with methanolic potassium carbonate followed by tosylation of the liberated hydroxyl group with p-toluenesulfonyl chloride in pyridine (74% yield from the 12-acetate LXXXIV). The monoazido tosylate LXXXV was then converted to the 9α,12-diazide LXXXVI with sodium azide in hexamethyl phosphoric triamide (HMPT) in 91% yield.



The structures of the 9α-azido 12-tosylate LXXXV and of the 9α,12-diazide LXXXVI were confirmed by their spectra. Reduction of the diazide LXXXVI with lithium aluminum hydride in ether afforded the diamine LXXXVII in 91% yield, in the amorphous state; the crystalline product could be isolated only in 25% yield.



LXXXVI LXXXVII

The structure of the diamine LXXXVII[22], which followed from its method of preparation, was confirmed by its infrared and NMR spectra and its elemental analysis.

The diamine LXXXVII and the 9α-azido 12-tosylate LXXXV have the stereochemical features of the types of compounds represented by xxxiv and xxxiii, respectively. Studies on the cyclization of the diamine LXXXVII and on the reductive cyclization of the 9α-azido 12-tosylate LXXXV, which should afford 9-iso 11-aza steroids (cf.xxxv, p67) are in progress but are not part of this study.

In our preliminary experiments for the synthesis of key intermediates having the stereochemistry suitable for conversion to 11-aza steroids of natural configuration in position 9, the 9β-tosyloxy 12-acetate LXXXII was

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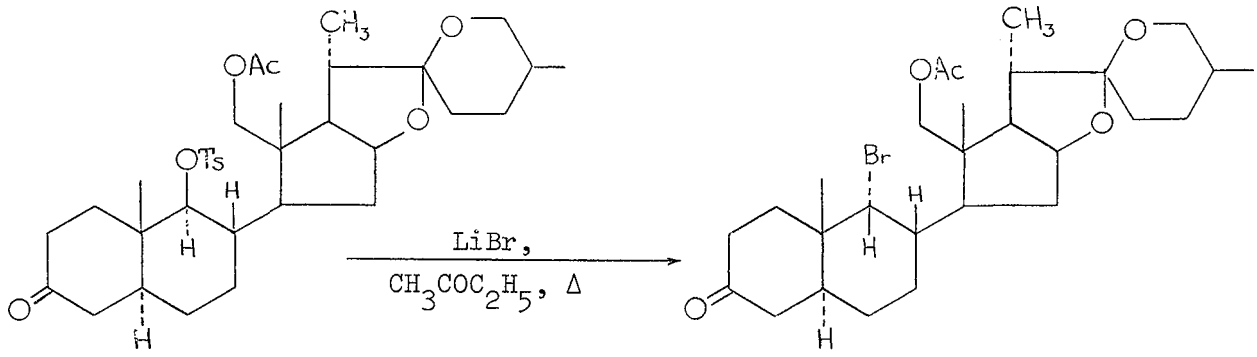
22. The β-configuration of the hydroxyl group of the 3-hydroxy diamine LXXXVII is assigned tentatively on the basis of the consideration that metal hydride reductions of 3-keto 5α-steroids give predominantly equatorial (β) alcohols (112-114).

converted to the 9α-bromo 12-acetate LXXXVIII, obtained only in an amorphous form, by refluxing with lithium bromide in methyl ethyl ketone.



LXXXII LXXXVIII

The infrared spectrum of this crude product showed the characteristic absorption for the acetate function at 1748 and 1241 cm^{-1}, and that for the 3-ketone at 1720 cm^{-1}. The NMR spectrum showed a multiplet centered at 4.25 ppm corresponding to the C_{16}-proton, a broad "singlet" at 4.2 ppm corresponding to the equatorial C_9-proton, a singlet at 3.98 ppm corresponding to the C_{12}-methylene protons, a multiplet centered at 3.48 ppm corresponding to the C_{26}-methylene protons, and a singlet at 2.07 ppm corresponding to the methyl protons of the acetate, while the 18, 19, 21, and 27 methyl protons were visible as an unresolved multiplet between 1.16 and 0.65 ppm. Investigations on the purification of this product and the elaboration of optimum reaction conditions for its preparation are in progress but will be discussed elsewhere.

The availability of the 9α-bromo 12-acetate LXXXVIII encourages us to foresee a successful completion of the project of the synthesis of 11-aza steroids with the normal steroid stereochemistry in position 9 (Compare Scheme IV, p. 83)[23].

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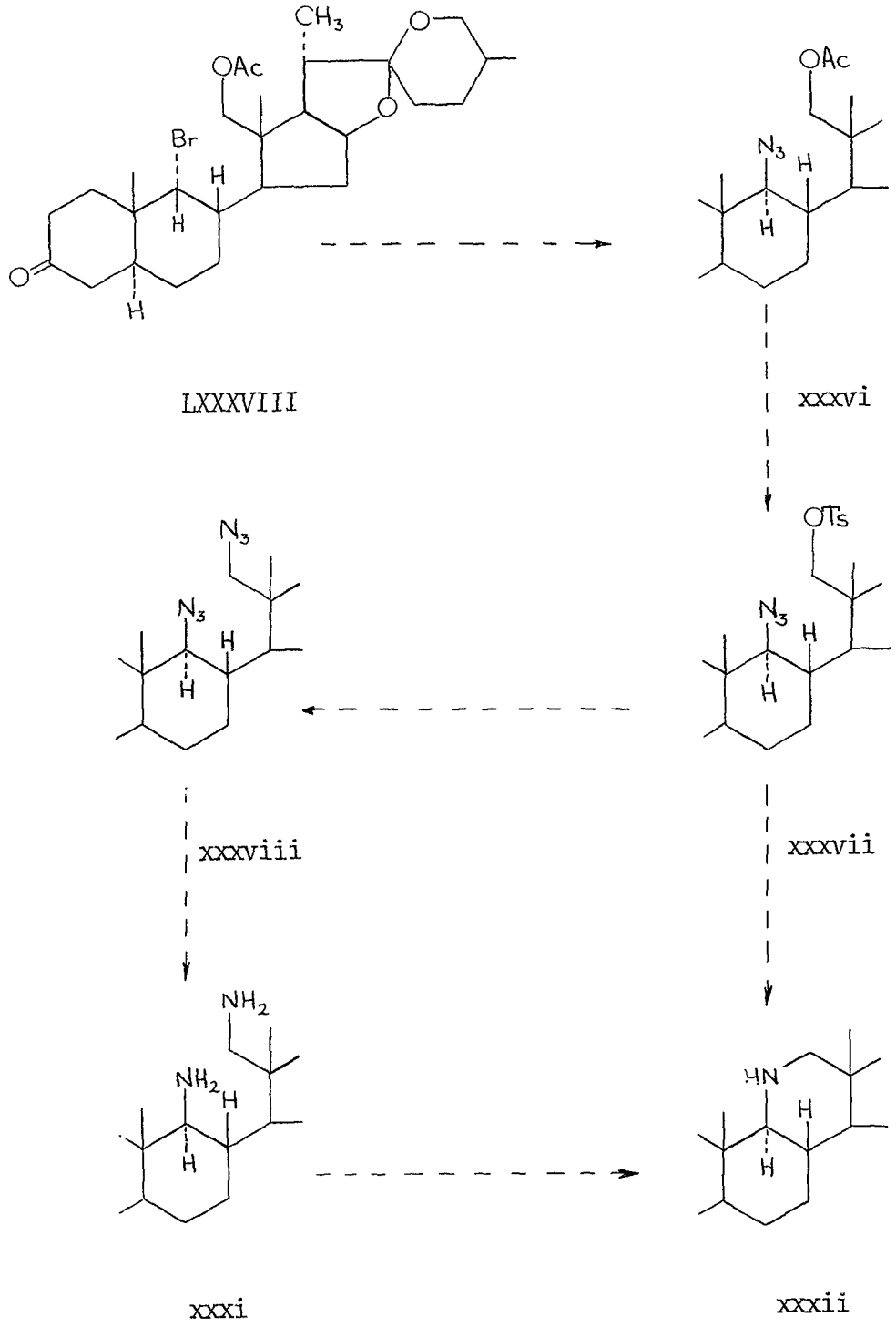
23. The 3-keto function of 9β-azido 12-tosylates (xxxvii) and that of diazides (xxxviii) could be easily protected through the formation of an ethylene ketal, before the reduction steps.

(Scheme IV)


CH3
OAc
Br
H
H
O
O
H
LXXXVIII
OAc
N3
H
H
xxxvi
OTs
N3
H
H
xxxvii
N3
N3
H
H
xxxviii
NH2
NH2
H
H
xxxi
HN
H
H
xxxii

In concluding this chapter, we wish to emphasize again the exploratory nature of the experiments described in the section dealing with the approaches towards the synthesis of 8,9-saturated 11-aza steroids involving cyclization of ω-sulfonyloxy ω′-azido derivatives and of the pyrolysis of ω,ω′-diamino steroids. We believe, however, to have shown that this approach is promising since we have been able to prepare the important intermediates in these routes and, in part, the actual starting materials for these types of cyclization reactions.

CONCLUSION

In our program on the synthesis of 11-hetero steroids of potential biological interest, we synthesized the first known 11-oxa pregnanes and steroidal 11-oxa spirostanes which we were able to transform into the first 11-oxa analog of a hormone, 11-oxaprogesterone. The new hormone analog possesses weak progestational and interesting ovulation-inhibiting activities.

We also succeeded in synthesizing saturated 3,20-dioxygenated 11-aza steroids by reducing the 8,9-double bond of the corresponding 8,9-unsaturated 11-aza pregnene derivative.

In our exploratory investigations on the development of pathways for the synthesis of 9-iso 11-aza steroids, we have succeeded to prepare two key intermediates, 9α-azido 12-tosyloxy and 9α,12-diamino spirostane derivatives, suitable for cyclization to 9-iso 11-aza steroids. On the other hand, in pursuance of the synthesis of 11-aza steroids with the natural steroid configuration in position 9, we have succeeded to prepare, as an important intermediate, a 9α-bromo 12-acetoxy 11-nor 9,12-seco spirostane derivative, albeit in the crude form, which we consider suitable for transformation into an 11-aza steroid.

EXPERIMENTAL

GENERAL REMARKS

All melting points were taken in evacuated capillaries and the temperatures were corrected. If not otherwise stated, non-alkaline aluminum oxide, Woelm activity III, and Davison's silica gel NO. 923, were used for chromatography. The infrared spectra were recorded on a Beckman model IR-4 spectrophotometer and the ultraviolet spectra on a Beckman model DK-1A Spectrophotometer. The NMR spectra were taken on a Varian A-60 spectrometer and tetramethylsilane was used as an internal standard with its signal set at 0 cps; the values of the chemical shifts reported are accurate upto ± 0.5 cps. The following abbreviations have been used throughout this thesis;-

cps = cycles per second

ppm = parts per million

s = singlet

d = doublet

t = triplet

m = multiplet

b.s. = broad singlet.

The microanalyses were performed by Mr. A. Bernhardt, Mülheim, Germany, and by Dr. F. Pascher, Bonn, Germany, to whom we express our sincere appreciation.

CHAPTER I

The Synthesis of 3,9,12,20-Functionalized Ring C-seco Steroids.

3β,20β-Dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXVC)

A solution of 9.4 g of 3β-hydroxy-20β-acetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXV) (cf.38), m.p. 210-212°, in 40 ml of methanol was refluxed for 4 h with 80 ml of 2N methanolic potassium hydroxide. The mixture was cooled and acidified with cold 2N sulfuric acid to the Congo blue reaction. The organic product was extracted with dichloromethane, the organic layer was washed repeatedly with water and was dried over sodium sulfate. Removal of the solvent afforded 8.2 g of a crystalline solid which upon recrystallization from acetone-ether gave 7.4 g (88%) of 3β,20β-dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXVC), m.p. 207-209°. A sample was recrystallized three times from dichloromethane for analysis. Colourless plates; m.p. 211-212°; $|\alpha|_D^{22}$ - 44.2° (c, 1.000 in CH_3OH); ν_{max}^{KBr} 3380 - 2600 cm^{-1} (3,20-hydroxyls and acid hydroxyl), 1718 cm^{-1} (acid), 1695 cm^{-1} (9-ketone); $\delta_{ppm}^{CD_3OD}$ 4.9 (m) (3,20-hydroxyls and 12-carboxyl-3H, exchanged with CD_3OD), 3.55 (m) (3,20-2H), 1.2 (s) (19-CH_3), 1.1 (d) (J = 6.5 cps) (21-CH_3), 0.98 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15.

Found : C, 68.11; H, 9.24.

3β,20β-Diacetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic Acid (XXVd)

80 mg of 3β-hydroxy-20β-acetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXV), m.p. 207-208°, was treated with 1 ml of acitic anhydride and 2 ml of pyridine at room temperature for 16 h, 1.5 ml of water was added and the mixture was refluxed for 1.5 h, poured into ice and extracted with ether. The ethereal solution was washed with iced 2N hydrochloric acid, a cold saturated solution of sodium bicarbonate and finally with water and was dried over

sodium sulfate. Removal of the solvent gave 105 mg of crude product which upon crystallization from ether gave 75 mg (85%) of crystalline 3β,20β-diacetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXVd), m.p. 196-197°. A sample was recrystallized twice from ether for analysis. Colourless plates; m.p. 199.5-200.5°; $|\alpha|_D^{22}$ - 31° (c 1.000 in $CHCl_3$); ν_{max}^{KBr} 3390 - 2640 cm^{-1} (associated hydroxyl of -COOH), 1740 cm^{-1} (acetate), 1712 cm^{-1} (acid), 1698 cm^{-1} (9-ketone), 1246 cm^{-1} (acetate); δ_{ppm} 9.58 (b.s.) (-COOH), 4.7 (m) (3,20-2H), 2.0 (s) (acetate-$2CH_3$), 1.14 (d) (J=6 cps) (21-CH_3), 1.12 (s) (19-CH_3), 0.78 (s) (18-CH_3).

Anal. Calc. for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31.
Found : C, 66.02; H, 8.32.

Methyl 3β,20β-Dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (XXVe)

At 0°, 30 ml of a 2% ethereal diazomethane solution was added slowly to a solution of 1.45 g of the dihydroxy seco acid XXVc, m.p. 207-209°, in 50 ml of absolute ether and 50 ml of absolute methanol, and the yellow mixture was allowed to warm to room temperature. After 16 h, the excess reagent was destroyed with a few drops of acetic acid and the solution was taken to dryness in vacuo to give 1.55 g (quantitative yield) of crystalline methyl ester XXVe, m.p. 153-155°, which upon recrystallization from dichloromethane-ether afforded 1.26 g of pure dihydroxy ester XXVe. A portion was recrystallized twice from dichloromethane-ether for analysis. Colourless needles, m.p. 154-155°; $|\alpha|_D^{25}$ - 73.5° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 3400 cm^{-1} (hydroxyl), 1718 cm^{-1} (9-ketone and ester), 1263 cm^{-1} (ester); δ_{ppm} 3.63 (s) (methyl ester-CH_3), 2.25 (m), 1.88 (m) (3,20-hydroxyl-2H, exchanged with D_2O), 2.70 (m)(3,20-2H), 1.12 (m) and (J=6 cps) (21-CH_3), 1.15 (s) (19-CH_3), 0.93 (s) (18-CH_3).

Anal. Calc. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35.
Found : C, 68.96; H, 9.22.

$\Delta^{9(11)}$-3β-Acetoxy-25-iso-5α,22β-spirosten-12-one (XXVI)

Following the procedure of Djerassi et al. (44), 63.0 g of hecogenin acetate was dehydrogenated with 31.5 g of selenium dioxide in 2.8 ml of refluxing dry butanol in the presence of 9.5 ml of pyridine for 4 days. The dark brown reaction mixture was filtered through sodium sulfate and celite and the solution was evaporated to dryness. The residue was extracted with ethyl acetate, the solution was washed with 2N hydrochloric acid, with a saturated solution of sodium bicarbonate, and with water, and was dried over sodium sulfate. Removal of the solvent gave the 9-dehydrohecogenin acetate coloured by the presence of small amounts of selenium, which was removed by filtering the ethereal solution of the product repeatedly through short columns of aluminum oxide (activity III). Crystallization from methanol gave 53.8 g (85%) of pure 9-dehydrohecogenin acetate (XXVI), m.p. 217-218°. A portion was recrystallized twice from methanol for analysis. Needles; m.p. 218-219°; $|\alpha|_D^{22}$ - 8.6° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 238 mμ (log ε 4.05) [Lit. (44), m.p. 215-217°; $|\alpha|_D$ - 9°; λ_{max}^{EtOH} 238 mμ (log ε 4.07)]; ν_{max}^{KBr} 1747 cm^{-1} (acetate); 1679 cm^{-1}, 1600 cm^{-1} ($\Delta^{9(11)}$-12-ketone); 1254 cm^{-1} (acetate); δ_{ppm} 5.69 (s) (11-H), 4.53 (m) (3,16-2H), 2.0 (s) (acetate-CH_3), 1.1 (d) (J=7 cps) (21-CH_3), 1.1 (s) (19-CH_3), 0.9 (s) (18-CH_3), 0.76 (d) (J=7 cps) (27-CH_3).

Anal. Calc. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00.

Found : C, 73.97; H, 9.11.

3β-hydroxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oic Acid (XXVII)

At -30° to -60°, a stream of oxygen containing 4.5% of ozone was passed at a rate of 170 ml per minute, for a period of 1.5 h, through a solution of 6.5 g of 9-dehydrohecogenin acetate (XXVI), m.p. 217-218°, in 150 ml of pure ethyl acetate. To the product there were added 5 ml of a 30% hydrogen peroxide solution and 8 ml of water and the mixture was kept stirred at room temperature

for 16 h. Water and ethyl acetate were added and the organic product was extracted with ethyl acetate. The organic layer was washed with water, with a cold 3N sodium hydroxide solution, and again with water, was dried over sodium sulfate and the solvent was removed. Thus 1.4 g of neutral material was obtained. The sodium hydroxide washings were combined with the water washings and the solution was acidified with cold 3N sulfuric acid to the Congo blue reaction. The organic product was extracted with ethyl acetate, the solution was washed repeatedly with water and dried over sodium sulfate. Removal of the solvent afforded 4.9 g of the acidic material which upon crystallization from methanol-dichloromethane gave 4.2 g (70%) of crystalline 3β-hydroxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oic acid (XXVII), m.p. 254-256°. A portion was recrystallized twice from methanol-ether for analysis. Colourless plates; m.p. 256.5-257.5°; $|\alpha|_D^{22}$ -82.6° (c, 0.461 in methyl cellosolve); ν_{max}^{KBr} 3425 cm^{-1} (associated hydroxyls), 1740 cm^{-1} (acid), 1705 cm^{-1} (9-ketone); $\delta_{ppm}^{pyridine}$ 4.67 (m) (16-H), 3.4 (m) (-OH and -COOH - 2H, exchanged with D_2O), 3.52 (m) (26-2H), 3.3 (m) (3-H), 1.21 (d) (J=6.5 cps) (21-CH_3), 1.2 (s) (19 - CH_3), 1.14 (s) (18 - CH_3), 0.69 (d) (J=6 cps) (27 - CH_3).

Anal. Calc. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99.
Found: C, 69.62, H, 9.10.

3β-Acetoxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oic acid (XXVIIa)

A quantity of 900 mg of the 3β-hydroxy seco keto acid XXVII, m.p. 254-256°, was acetylated in the usual way with 3 ml of acetic anhydride and 5 ml of pyridine at room temperature for 16 h. The usual working up and crystallization from dichloromethane-ether gave 850 mg (87%) of crystalline 3β-acetoxy seco keto acid XXVIIa, m.p. 259-261°. A sample was recrystallized twice from

dichloromethane-ether for analysis. Colourless prisms, m.p. 261-262°; $|\alpha|_D^{22}$ - 86.2° (c, 1.000 in $CHCl_3$); [Lit. (39) m.p. 264-265°, $|\alpha|_D$ - 87°] ν_{max}^{KBr} 3100 cm^{-1} (associated hydroxyl), 1733 and 1241 (acetate), 1716 cm^{-1} (ketone and acid); δ_{ppm} 10.41 (b.s.) (-COOH), 4.55 (m) (3,16-2H), 2.0 (s) (acetate - CH_3), 1.13 (s) (19-CH_3) 0.98 (s) (18-CH_3), 0.91 (d) (J=7cps) (21-CH_3), 0.76 (d) (J=5 cps) (27-CH_3).

Anal. Calc. for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63.

Found : C, 68.49; H, 8.73.

Methyl 3β-Hydroxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate-(XXVIIb)

At 0°, 60 ml of a 2.2% ethereal diazomethane solution was added slowly to a suspension of 3.2 g of 3β-hydroxy seco acid XXVII, m.p. 254-256°, in 200 ml of absolute methanol (vigorous reaction started and the acid dissolved completely within an hour to give a deep yellow solution). The solution was stored at room temperature for 14 h, the excess reagent was destroyed with a few drops of acetic acid and the solution was taken to dryness in vacuo to give 3.3 g (quantitative yield) of crystalline methyl 3β-hydroxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate, (XXVIIb), m.p. 161-163°. A portion was recrystallized twice from ether for analysis. Colourless needles; m.p. 163.5-164.5°; $|\alpha|_D^{22}$ - 88.5° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 3520 cm^{-1} (hydroxyl); 1720 cm^{-1} (ketone and ester), 1258 cm^{-1} (ester); δ_{ppm} 4.48 (m) (16-H), 3.7 (s) (methyl ester-CH_3), 2.83 (m) (3-H), 2.75 (s) (3-OH, exchanged with D_2O); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.16 and 0.85 ppm.

Anal. Calc. for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15.

Found : C, 70.13; H, 9.09.

Methyl 3β-Acetoxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XXVIIc)

At 0°, 80 ml of a 2% ethereal solution of diazomethene was added slowly to a solution of 2.7 g of the 3β-acetoxy seco keto acid XXVIIa, m.p. 255-256°, in 100 ml of absolute ether and 100 ml of absolute methanol. The mixture was allowed to warm to room temperature; after 20 h the excess reagent was destroyed with a few drops of acetic acid and the solution was taken to dryness in vacuo to give 2.63 g (93% yield) of crystalline methyl ester XXVIIc, m.p. 139-141°. A portion was recrystallized twice from dichloromethane-ether for analysis. Colourless needles, m.p. 140-141°; $|\alpha|_D^{25}$ - 80.4° (c, 1.250 in $CHCl_3$); ν_{max}^{KBr} 1736 cm^{-1} (acetate and methyl ester), 1715 cm^{-1} (9-ketone), 1252 cm^{-1} (acetate and ester); δ_{ppm} 4.57 (m) (3,16-2H); 3.71 (s)(methyl ester-CH_3), 2.47 (m) (26-2H), 2.00 (s) (acetate-CH_3); the 18, 19, 21 and 27 methyl groups appear as an unresolved multiplet between 1.19 and 0.69 ppm.

Anal. Calc. for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79.

Found : C, 69.03; H, 8.79.

CHAPTER II

The Synthesis of 11-Oxa Steroids

Methyl 3,9,20-Trioxo-9,12-seco-11-nor-5α-pregnan-12-oate (XL)

To an ice-cold solution of 408 mg of methyl 3β,20β-dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (XXVe), m.p. 153-155°, in 45 ml of absolute acetone, was added dropwise and with stirring, a solution of Jones' reagent (59) until a faint brownish colour of the reagent persisted (total volume added: 0.8 ml). The solution was kept at 0° for 10 min and then poured into ice water. The organic product was extracted with ether, the ethereal solution was washed once with a cold saturated solution of sodium bicarbonate and then with water and dried over sodium sulfate. Removal of the solvent gave 398 mg of a crystalline product which, on recrystallization from ether, gave 372 mg (93%) of pure methyl 3,9,20-trioxo-9,12-seco-11-nor-5α-pregnan-12-oate (XL), m.p. 124-125°. A sample was recrystallized once from ether for analysis. Colourless needles, m.p. 124-125°; $|\alpha|_D^{22}$ - 50.2° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1718 cm^{-1} (ketone and ester), 1264 cm^{-1} (ester); δ_{ppm} 3.76 (s) (methyl ester-CH_3), 2.02 (s) (17-acetyl-CH_3), 1.33 (s) (19-CH_3), 0.83 (s) (18-CH_3).

Anal. Calc. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34.

Found : C, 69.81; H, 8.40.

Methyl 3,20-Bis-ethylenedioxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (XLI)

Following the procedure of Allen et al. (60), 4.04 g of methyl 3,9,20-trioxo-9,12-seco-11-nor-5α-pregnan-12-oate (XL), m.p. 124-125°, was preferentially ketalized in positions 3 and 20 with 700 ml of freshly distilled ethylene glycol in the presence of 185 mg of p-toluenesulfonic acid, by slow distillation of ethylene glycol, at 72-75° and 0.4 mm of Hg. The residue was cooled and poured into an ice cold saturated solution of sodium bicarbonate. The

organic product was extracted with dichloromethane, the solution was washed several times with water and dried over sodium sulfate. Removal of the solvent gave 5.0 g of a crude solid which upon crystallization from ether gave 4.2 g (84%) of crystalline methyl 3,20-bis-ethylenedioxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (XLI), m.p. 122-123°. A sample was recrystallized twice from ether for analysis. Colourless plates; m.p. 123.5-124.5°; $|\alpha|_D^{22}$ - 35° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1725 cm^{-1} (ketone and ester), 1252 cm^{-1} (ester), 1092 and 1079 cm^{-1} (ketal); δ_{ppm} 3.9 (s) (3,20-ethylene ketals-8H), 3.7 (s) (methyl ester-CH_3), 1.2 (s) (21-CH_3), 1.15 (s) (19-CH_3), 0.93 (s) (18-CH_3).

Mass spectrum[24]: Peaks at m/e 450 (M^+), 435, 375, 125, 99 and 87.

Anal. Calc. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50.

Found : C, 66.58; H, 8.28.

3,20-Bis-ethylenedioxy-9,12-seco-11-nor-5α-pregnane-9β,12-diol (XLII)

A solution of 4.2 g of methyl 3,20-bis-ethylenedioxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oate (XLI), m.p. 122-123°, in 250 ml of absolute tetrahydrofuran, was added dropwise over a period of 25 min and with vigorous stirring to a slurry of 4.5 g of lithium aluminum hydride in 300 ml of absolute tetrahydrofuran. While the stirring was continued the mixture was refluxed for 40 h. The excess reagent was decomposed in the cold by addition of moist ethyl acetate and, subsequently, of ice water. A cold solution of ammonium chloride was added and the organic product was extracted with dichloromethane. The organic layer was washed with cold water, and dried over sodium sulfate. Removal of the solvent gave 4.0 g of a crude product which upon crystallization

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24. We sincerely thank Dr. B.C. Das, Institut de Chimie des Substances Naturelles, C.N.R.S., Gif-sur-Yvette, France, for taking the mass spectra of compounds XLI and XLV.

from dichloromethane-ether gave 3.0 g (76%) of crystalline 3,20-bis-ethylene-dioxy 9,12-diol XLII, m.p. 149-150°. A portion was recrystallized twice from dichloromethane-ether for analysis. Colourless plates; m.p. 154-155°; $|\alpha|_D^{22}$ 8.5° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 3440 and 3380 cm^{-1} (hydroxyls), 1095 and 1070 cm^{-1} (ketal); δ_{ppm} 3.9 (s) (3,20-ethylene ketals-8H), 3.5 (m) (9,12-hydroxyl-2H, exchanged with D_2O), 3.67 (d) and 3.3 (d) (J=12 cps) (12-2H), 2.93 (d) (J=10 cps) (9α-H), 1.31 (s) (21-CH_3), 0.85 (s) and 0.70 (s) (19,18-2CH_3).

Anal. Calc. for $C_{24}H_{40}O_6$: C, 67.89; H, 9.50; O, 22.61.

Found : C, 67.65; H, 9.67; O, 22.54.

3,20-Bis-ethylenedioxy-11-oxa-5α-pregnane (XLIII)

A solution of 340 mg of 3,20-bis-ethylenedioxy-9,12-seco-11-nor-5α-pregnane-9β,12-diol(XLII), m.p. 149-150°, and 605 mg of p-toluenesulfonyl chloride, in 10 ml of pyridine was heated for 4 h at 90°. The reaction mixture was poured into ice water, the organic product was extracted with ether and the ethereal solution was washed with cold sodium bicarbonate solution, with water and dried over sodium sulfate. Removal of the solvent by distillation followed by removal of the last traces of pyridine in vacuo gave 380 mg of a yellow residue, which was absorbed on 12 g of aluminum oxide (activity III). Elutions with petroleum ether-benzene (9:1) gave 76 mg (23.4%) of crystalline 3,20-bis-ethylenedioxy-11-oxa-5α-pregnane (XLIII), m.p. 142-144°. A portion was recrystallized twice from ether for analysis. Colourless plates; m.p. 145-146°; $|\alpha|_D^{22}$ 9.1° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1099, 1068 and 1052 cm^{-1} (ether and ketal); δ_{ppm} 3.94 (s) (3,20-ethylene ketal-8H), 4.15 (d) and 3.2 (d) (J=10 cps) (12-2H), 2.49 (d) (J=9.5 cps) (9α-H), 1.23 (s) (19-CH_3) 0.91 (s) (21,18-2CH_3).

Anal. Calc. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68.

Found : C, 71.01; H, 9.54; O, 19.58.

11-Oxa-5α-pregnane-3,20-dione (XXXVII)

(a) From 3,20-bis-ethylenedioxy-9,12-seco-11-nor-5α-pregnane-9β,12-diol (XLII). A solution of 1.5 g of the 3,20-bis-ethylenedioxy 9,12-diol XLII, m.p. 149-150°, and 2.6 g of p-toluenesulfonyl chloride in 41 ml of pyridine was heated for 4 h to 120°. The reaction mixture was poured into ice water and the organic product was extracted with ether. The ethereal solution was washed with cold sodium bicarbonate solution and with water, and was dried over sodium sulfate. The solvent was removed by distillation and last traces of pyridine were removed in vacuo to give 1.4 g of an amorphous product. This was dissolved in 90 ml of absolute acetone, the solution was refluxed with 270 mg of p-toluenesulfonic acid for 35 min, after which the cold mixture was poured into ice cold saturated solution of sodium bicarbonate. The organic product was extracted with ether, the solution was washed with water till neutral and was dried over sodium sulfate. Removal of the solvent gave 1.1 g of a solid residue which on crystallization from ether gave 625 mg of crystalline 11-oxa-5α-pregnane-3,20-dione (XXXVII), m.p. 214-216°. The mother liquor, on chromatography on non-alkaline aluminum oxide (activity III) and elution with Petroleum ether-benzene mixtures (4:1, 1:1 and 1:4) yielded another 120 mg of the dione XXXVII, m.p. 213-215° (total yield 50%). A sample was recrystallized twice from ether for analysis. Colourless needles, m.p. 217-218.5°; $|\alpha|_D^{22}$ 82.2° (c, 0.900 in $CHCl_3$); ν_{max}^{KBr} 1718 cm^{-1} (ketone), 1080, 1050 and 1037 cm^{-1} (ether); δ_{ppm} 4.13 (d) and 3.41 (d) (J=10 cps) (12-2H), 2.07 (s) (17-acetyl-CH_3), 1.12 (s) (19-CH_3), 0.79 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; O, 15.07.

Found : C, 75.22; H, 9.59; O, 15.14.

(b) From 11-oxa-5α-pregn-16-ene-3,20-dione (XLVIII). A solution of 185 mg of the 11-oxa-pregnene dione XLVIII , m.p. 267-270°, in 25 ml of 95% ethanol was

hydrogenated with~1 moleculer equivalent of hydrogen (17 ml) in the presence of 40 mg of a 5% palladium-on-charcoal catalyst at 25° and at 760 mm of Hg. The solution was filtered over sodium sulfate and taken to dryness. Crystallization of the crude product (180 mg) from ether gave 150 mg (81%) of pure crystalline 11-oxa-5α-pregnane-3,20-dione (XXXVII), m.p. 217-218°. The identity of this product with that prepared as described under (a) was established by the determination of a mixed melting point and by comparison of the infrared and NMR spectra.

(c) From 3β,20β-dihydroxy-11-oxa-5α-pregnane (LII). To an ice-cold solution of 28 mg of the crude dihydroxy 11-oxa pregnane LII (obtained from the mother liquor of the crystallization of the pure product) in 10 ml of absolute acetone was added 0.2 ml of Jones' reagent (59) and the solution was kept stirred for 15 min. The product was poured into ice water and the precipitate was extracted with ether. The ethereal solution was washed with cold sodium bicarbonate solution, with water, and was dried over sodium sulfate and the solvent was removed. The crude product thus obtained (23 mg) was crystallized from ether to give 16 mg (59% from the crude dihydroxy 11-oxa pregnane LII) of 11-oxa-5α-pregnane-3,20-dione (XXXVII), m.p. 217-218.5°. The identity of this product with that prepared as described under (a) and (b) was established by the determination of a mixed melting point and by comparison of the infrared and NMR spectra.

Methyl 3,9-Dioxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XLIV)

To an ice-cold solution of 2.0 g of methyl 3β-hydroxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XXVIIb), m.p. 161-163°, in 200 ml of absolute acetone, was added dropwise and with stirring a solution of Jones' reagent (59) until a faint brown colour of the (excess) reagent persisted (total volume added: 2.1 ml). The solution was kept at room temperature for 15 min, and was

then poured into ice water. The organic product was extracted with ether, the ethereal solution was washed with cold saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of solvent gave 1.9 g (95%) of crystalline methyl-3,9-dioxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XLIV), m.p. 133-134°. A portion was recrystallized twice from ether for analysis. Colourless needles; m.p. 134-135°; $|\alpha|_D^{22}$ - 64° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1735 cm^{-1} (ester), 1708 cm^{-1} (ketone), 1248 cm^{-1} (ester); δ_{ppm} 4.5 (m) (16-H), 3.7 (methyl ester-CH_3), 3.52 (m) (26-2H), 1.33 (s) (19-CH_3), 1.0 (s) (18-CH_3), 0.9 (d) (J=8 cps) (21-CH_3), 0.8 (d) (J=7 cps) (27-CH_3).

Anal. Calc. for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75.

Found : C, 70.35; H, 8.67.

Methyl 3-Ethylenedioxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XLV)

According to the procedure of Allen et al. (60), 0.6 g of methyl-3,9-dioxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XLIV), m.p. 133-134°, was preferentially ketalized in position 3 with 55 ml of freshly distilled ethylene glycol in the presence of 23 mg of p-toluenesulfonic acid, by slow distillation of ethylene glycol at 72-75° at 0.4 mm of Hg. The residue was cooled and poured into an ice-cold saturated sodium bicarbonate solution. The organic product was extracted with dichloromethane, the solution was washed with water and was dried over sodium sulfate. Removal of the solvent gave 670 mg of a solid material which upon crystallization from ether, yielded 540 mg (82%) of pure methyl 3-ethylenedioxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XLV); m.p. 215-216°. A sample was recrystallized twice from ether for analysis. Colourless needles; m.p. 215-216°; $|\alpha|_D^{22}$ - 76.7° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1733 cm^{-1} (12-ester), 1715 cm^{-1}

(9-ketone), 1250 cm^{-1} (ester), 1075 and 1055 cm^{-1} (ketal); δ_{ppm} 4.47 (m) (16-H), 3.9 (s) (ethylene ketal-4H), 3.69 (s) (methyl ester-CH_3), 3.42 (m) (26-2H), 1.13 (s) (19-CH_3), 0.97 (s) (18-CH_3), 0.90 (d) (J=7 cps) (21-CH_3), 0.79 (d) (J=7 cps) (27-CH_3).

Mass spectrum[24]: Peaks at m/e 504 (M^+), 445, 390, 330, 208, 139, 125 and 99.

Anal. Calc. for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79.

Found : C, 69.07; H, 8.60.

3-Ethylenedioxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane-9β,12-diol (XLVI)

A solution of 410 mg of methyl 3-ethylenedioxy-9-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostan-12-oate (XLV), m.p. 215-216°, in 40 ml of absolute tetrahydrofuran, was added dropwise over a period of 15 min to a well stirred slurry of 400 mg of lithium aluminum hydride in 30 ml of absolute tetrahydrofuran. While the stirring was continued, the mixture was refluxed for 28 h. The excess reagent was decomposed, after cooling, by addition of moist ethyl acetate and, subsequently, of ice water. A cold solution of ammonium chloride was then added and the organic product was extracted with dichloromethane. The organic layer was washed with cold water and was dried over sodium sulfate. Removal of the solvent gave 355 mg of an amorphous solid which upon crystallization from dichloromethane-ether, gave 285 mg (74%) of crystalline 3-ethylenedioxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane-9β,12-diol (XLVI), m.p. 217-219°. A portion was recrystallized twice from dichloromethane-ether for analysis. Colourless plates; m.p. 222-223.5°; $|\alpha|_D^{22}$ - 56°; (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 3240 cm^{-1} (hydroxyls), 1095, 1062 and 1041 cm^{-1} (ketal); $\delta_{ppm}^{C_5D_5N}$ 6.42 (m) and 5.37 (m) (9,12-hydroxyls, disappearing on exchange with D_2O), 4.45 (m) (16-H), 3.89 (s) (ethylene ketal-4H), 3.63 (b.s.) (12,26-4H), 3.1 (d) (J=10.5 cps) (9α-H), 1.15 (s) (19-CH_3), 1.02 (d) (J=5 cps) (21-CH_3), 0.90 (s) (18-CH_3), 0.70 (d) (J=6 cps) (27-CH_3).

Anal. Calc. for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69.

Found : C, 70.07; H, 9.64.

3-Ethylenedioxy-9β,12-diacetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (XLVIa)

To 100 mg of the 3-ethylenedioxy-9β,12-diol XLVI, m.p. 217-219°, in 3 ml of pyridine was added 2 ml of acetic anhydride and the mixture was left at room temperature for 16 h; the usual working up and crystallization from ether-hexane afforded 85 mg of pure 9β,12-diacetoxy 3-ketal XLVIa, m.p. 192-193°. A sample was recrystallized twice for analysis. Colourless needles, m.p. 193-194°, $|\alpha|_D^{25}$ - 20.4° (c, 1.100 in $CHCl_3$); ν_{max}^{KBr} 1748 cm^{-1} (acetate), 1240 cm^{-1} (acetate), 1102, 1077 and 1060 cm^{-1} (ketal); δ ppm (C_5D_5N) 4.7 (d) (J=11 cps) (9α-H), 4.4 (m) (16-H), 4.18 (d) and 3.74 (d) (J=11 cps) (12-2H), 3.85 (s) (ethylene ketal-4H), 3.5 (m) (26-2H), 2.13 (s) and 2.03 (s) (acetates-$2CH_3$), 1.07 (s) (19-CH_3), 0.95 (d) (J=6 cps) (21-CH_3), 0.90 (s) (18-CH_3), 0.70 (d) (J=5 cps) (27-CH_3).

Anal. Calc. for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96.

Found : C, 68.55; H, 8.78.

3-Ethylenedioxy-11-oxa-25-iso-5α,22β-spirostane (XLVII)

A solution of 5.0 g of 3-ethylenedioxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane-9β,12-diol (XLVI), m.p. 217-219°, and 8.5 g of p-toluenesulfonyl chloride, in 90 ml of pyridine was heated for 3 h at 85°. The reaction mixture was poured into ice, the organic product was extracted with ether and the ethereal solution was washed with cold sodium bicarbonate solution, with water and was dried over sodium sulfate. Removal of the solvents gave 5.0 g of a solid material which upon crystallization from methanol-ether, afforded 3.5 g (76%) of 3-ethylene-dioxy-11-oxa-25-iso-5α,22β-spirostane (XLVII), m.p. 191-192°. A sample was recrystallized twice from methanol-ether for analysis. Colourless needles; m.p. 191.5-193°; $|\alpha|_D^{22}$ - 87.5° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1108 cm^{-1} , 1077 cm^{-1},

1055 cm^{-1} (ketal and ether); δ_{ppm} 4.37 (m) (16-H), 3.9 (s) (ethylene ketal-4H), 3.75 (d) and 3.10 (d) (J=10 cps) (12-2H), 3.51 (m) (26-2H), 2.44 (d)(J=9.5 cps) (9α-H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 0.90 and 0.74 ppm.

Anal. Calc. for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63; O, 17.37.

Found : C, 72.84; H, 9.68; O, 17.58.

11-Oxa-5α-pregn-16-ene-3,20-dione (XLVIII)

A mixture of 2.0 g of 3-ethylenedioxy-11-oxa-25-iso-5α,22β-spirostane (XLVII), m.p. 191-192°, and 16 ml of acetic anhydride was heated in a sealed tube for 55 min at 202°. After cooling, methanol was added and the solution was taken to dryness in vacuo to give a dark oil. A solution of this oil in 20 ml of dichloroethane and 20 ml of glacial acetic acid was oxidized at 0° with a solution of 800 mg of chromic oxide in 16 ml of 90% acetic acid and the mixture was kept stirred for 1 h at 0°, and was then poured on ice. The organic product was extracted with ethyl acetate, the solution was washed with a saturated solution of sodium bicarbonate, and finally with water. It was then dried over sodium sulfate and the solvent was removed to give a viscous oil. To a solution of this crude product in 25 ml of acetone was added a solution of 800 mg of potassium hydroxide in 8 ml of water and the mixture was refluxed for 1 h. The solution was poured on ice and the precipitate was extracted with ethyl acetate. The solution was washed with water till neutral, dried over anhydrous sodium sulfate and the solvent was removed to yield 1.7 g of a semisolid mass which was chromatographed on 50 g of aluminum oxide (activity III), and eluted with petroleum ether-benzene mixtures (1:1 and 1:4), to give 380 mg of a solid product, which upon crystallization from ether, afforded 315 mg (23%)of crystalline 11-oxa-5α-pregn-16-ene-3,20-dione XLVIII), m.p. 267-270°. A portion was recrystallized twice from ether for analysis.

Colourless plates; m.p. 281-282°; $|\alpha|_D^{22}$ 50.0° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 237 mμ (log ε 3.9); ν_{max}^{KBr} 1722 cm^{-1} (3-ketone), 1663 cm^{-1} and 1585 cm^{-1} (Δ^{16}-20-ketone), 1075, 1060 and 1044 cm^{-1} (ether); δ_{ppm} 6.76 (m) (16-H), 4.41 (d) and 3.38 (d) (J=10.5 cps) (12-2H), 2.55 (d) (J=9 cps), 2.25 (s) (17-acetyl-CH_3), 1.15 (19-CH_3), 1.02 (18-CH_3).

Anal. Calc. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17.

Found : C, 75.92; H, 9.03; O, 15.29.

3β,20β-Diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic Acid Lactone (12→9) (XLIX)

(a) From the 3,20-diacetoxy seco keto acid (XXVd). To a solution of 200 mg of 3β,20β-diacetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXVd), m.p. 196-197°, in a mixture of 6.7 ml of absolute dioxane and 4.2 ml of absolute methanol, 280 mg of sodium borohydride was added and the mixture was kept stirred for 3 h under anhydrous conditions. The product was poured into ice water and acidified with a few drops of 2N hydrochloric acid. The organic material was extracted with ether, the ethereal solution was washed with cold saturated sodium bicarbonate solution and with water, and was dried over sodium sulfate. Removal of the solvent afforded 185 mg of a crude product which was chromatographed on 20 g of silica gel. Elutions with benzene-ethyl acetate mixtures (9:1 and 4:1) afforded 121 mg (62%) of crystalline 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (9→12) (XLIX), m.p. 170-171°. A sample was recrystallized twice for analysis. Colourless needles; m.p. 171.5-172.5°; $|\alpha|_D^{22}$ 89° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1750 cm^{-1} (six-membered lactone), 1730 cm^{-1} (acetate), 1245 cm^{-1} (acetate); δ_{ppm} 5.05 (m) (3,20-2H), 3.41 (d) (J=9.8 cps) (9α-H) (the doublet collapsed into a singlet on spin decoupling with a frequency difference of +90 cps), 2.05 (s) and 2.0 (s) (3,20-acetates-2CH_3), 1.21 (d) (J=6.5 cps) (21-CH_3), 1.06 (s) (19-CH_3), 0.98 (s) (18-CH_3).

Anal. Calc. for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63.
Found : C, 68.32; H, 8.77.

(b) From the 3β,20β-dihydroxy seco keto acid XXVc. To a solution of 230 mg of 3β,20β-dihydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXVc), m.p. 207-209°, in 5 ml of ethanol, a solution of 250 mg of sodium hydroxide in 1 ml of water and 3 ml of ethanol was added. To this mixture, 100 mg of sodium borohydride was then added with stirring and stirring was continued for 5 h at room temperature. The mixture was poured into ice water and acidified with 2N hydrochloric acid. The organic product was extracted with ethyl acetate, the solution was washed with water, dried over sodium sulfate and the solvent was removed to give 229 mg of a crude product. This material was refluxed in 5 ml of acetic anhydride with 75 mg of anhydrous sodium acetate for 4 h. The reaction mixture was cooled, 10 ml of methanol was added and solvents were evaporated. The organic product was extracted with ether, the ethereal solution was washed repeatedly with water and dried over sodium sulfate. Removal of the solvent afforded 270 mg of a semisolid mass which, on crystallization from ether-hexane gave 195 mg (71%) of pure 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (9→12) (XLIX), m.p. 170-171°. The identity of this product with the lactone prepared as described under (a) was established by the determination of a mixed melting point and by comparison of the infrared and NMR spectra.

3β-Acetoxy-20β-hydroxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic Acid Lactone (12→20) (L)

The residue of mother liquor from the crystallization of the lactone XLIX [prepared according to (b)] on further crystallization with ether-hexane afforded 24 mg (8%) of crystalline 3β-acetoxy-20β-hydroxy-9-oxo-9,12-seco-11-nor-5α-pregn-12-oic acid lactone (12→20) (L), m.p. 172-173°. A sample was

recrystallized once from ether-hexane for analysis. Colourless plates; m.p. 173-174°; $|\alpha|_D^{22}$ - 67.5° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1784 cm^{-1} (five-membered lactone), 1727 and 1246 cm^{-1} (acetate); δ_{ppm} 4.51 (m) (3,20-2H), 2.00 (s) (3-acetate-CH_3), 1.35 (d) (J=6 cps) (21-CH_3), 1.20 (s) (19-CH_3), 1.11 (s) (18-CH_3).

Anal. Calc. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57.

Found: C, 69.98; H, 8.53.

Nominal mass by mass spectrometry (376.3)corresponds to the required value (376).

3β,20β-Diacetoxy-11-oxa-5α-pregnane (LI)

(a) By Lithium Aluminum Hydride-Boron Trifluoride Reduction of the Lactone XLIX. A solution of 400 mg of 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (9→12) (XLIX), m.p. 170-171°, in 12 ml of absolute ether and 8 ml of freshly distilled boron trifluoride etherate was added slowly, with stirring, to an ice cold suspension of 80 mg of lithium aluminum hydride in 15 ml of absolute ether. The reaction mixture was kept stirred for 1 h at 0° and was then refluxed for 1.5 h. The excess reagent was destroyed cautiously with iced 2N hydrochloric acid, and the organic product was extracted with ether. The ethereal solution was washed with a cold saturated solution of sodium bicarbonate and with water, dried over sodium sulfate and the solvent was removed to give 385 mg of a product which was chromatographed over 12 g of aluminum oxide (activity III). Elutions with petroleum ether-benzene (9:1 and 4:1) mixtures afforded 150 mg (38%) of crystalline 3β,20β-diacetoxy-11-oxa-5α-pregnane (LI), m.p. 121-123°. A portion was recrystallized twice from hexane for analysis. Colourless needles; m.p. 123-124°; $|\alpha|_D^{22}$ 7.9° (c, 1.000 in $CHCl_3$); ν_{max}^{KBr} 1740 and 1245 cm^{-1} (acetate), 1052 and 1028 cm^{-1} (ether); δ_{ppm} 4.75 (m) (3,20-2H), 3.93 (d) and 3.21 (d) (J=10 cps) (12-2H)

(the doublet appearing at 3.21 ppm collapsed into a singlet on spin decoupling with a frequency difference of -40 cps, indicating that these two doublets correspond to the geminal coupling of 12-methylene protons), 2.42 (d) (J=9 cps) (9α-H), 2.0 (s) (3,20-acetates-2CH_3), 1.15 (d) (J=6 cps) (21-CH_3), 0.93 (s) (19-CH_3), 0.76 (s) (18-CH_3).

Anal. Calc. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42; O, 19.68.

Found : C, 71.11; H, 9.52; O, 19.49.

(b) By Catalytic Reduction (with Platinum Oxide-Perchloric acid) of the Lactone XLIX. A solution of 70 mg of 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (9→12) (XLIX), m.p. 170-171°, in 5 ml of acetic acid was hydrogenated over 70 mg of platinum oxide catalyst in presence of 0.2 ml of 70% perchloric acid for 6.5 h at room temperature and atmospheric pressure. The reaction mixture was filtered through a bed of sodium sulfate and celite and the organic material was extracted with ether, the solution was washed with a cold saturated solution of sodium bicarbonate and with water, and was dried over anhydrous sodium sulfate and the solvent was removed to yield 65 mg of a crude product which, upon crystallization from hexane, gave 33 mg (45%) of pure 3β,20β-diacetoxy-11-oxa-5α-pregnane (LI), m.p. 120-122°. The identity of this product with that prepared as described under (a) was established by the determination of a mixed melting point and by comparison of the infrared and NMR spectra.

3β,20β-Dihydroxy-11-oxa-5α-pregnane (LII)

A quantity of 52 mg of 3β,20β-diacetoxy-11-oxa-5α-pregnane (LI), m.p. 120-122°, was refluxed with 8 ml of a 2N methanolic potassium hydroxide solution for 4 h. The mixture was poured into ice water and the organic product was extracted with ether. The solution was washed with water, dried over sodium sulfate and the solvent was removed to give 40 mg of a crude product which upon

crystallization from dichloromethane-ether gave 25 mg (61%) of pure 3β,20β-dihydroxy-11-oxa-5α-pregnane (LII), m.p. 192-193°. A sample was recrystallized twice from dichloromethane-ether for analysis. Colourless needles; m.p. 193-194°; $|\alpha|_D^{22}$ - 11.1° (c, 0.720 in $CHCl_3$); ν_{max}^{KBr} 3460 and 3440 cm^{-1} (hydroxyls), 1082, 1045 and 1028 cm^{-1} (ether); δ_{ppm} 4.18 (d) and 3.17 (d) (J=10.5 cps) (12-2H), 3.58 (b.s.) (hydroxyls, exchanged with D_2O), 3.52 (m) (3,20-2H), 2.37 (d) (J=9.5 cps) (9α-H), 1.23 (d) (J=6.5 cps) (21-CH_3), 0.93 (s) (19-CH_3), 0.87 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63; O, 14.82.

Found : C, 74.66; H, 10.68; O, 14.78.

5α-Pregnane-3,20-dione (LIII)

A solution of 600 mg of progesterone (LVI), m.p. 120-121°, in 30 ml of 95% ethanol was hydrogenated with one moleculer equivalent of hydrogen (52 ml) in the presence of 65 mg of a 5% palladium-on-charcoal catalyst at 25° and at 760 mm of Hg. The solution was filtered over sodium sulfate and taken to dryness to give 595 mg of a white solid, which upon crystallization from ether-ethanol afforded 5α-pregnane-3,20-dione (LIII), m.p. 197-198°, $|\alpha|_D^{25}$ 120° (c, 1.000 in $CHCl_3$), along with its 5β-isomer. The identity of the dione LIII with an authentic sample previously prepared in this laboratory (43) was established by the determination of a mixed melting point and by a comparison of the infrared and NMR spectra.

Pregna-1,4-diene-3,20-dione (LIV) and 5α-Pregn-1-ene-3,20-dione (LV) from the Dione (LIII)

To 400 mg of 5α-pregnane-3,20-dione (LIII), m.p. 196-198°, was added 800 mg of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and 30 ml of absolute dioxane and the mixture was refluxed for 8 h. The product was cooled and the solvent was removed in vacuo to give a brown amorphous residue which was dissolved in

acetone and filtered through 40 g of non-alkaline aluminum oxide (activity III). Repeated elutions with acetone gave 290 mg of a yellow product which was absorbed on 10 g of aluminum oxide (activity III). Elutions with pure petroleum ether gave 39 mg of a crystalline material which, upon recrystallization from ether, gave 28 mg (7%) of pure 5α-pregn-1-ene-3,20-dione (LV), m.p. 203-204°; two recrystallizations from ether gave an analytical sample. Colourless plates; m.p. 206-207°; $|\alpha|_D^{22}$ 129° (c, 1.000 in $CHCl_3$); [Lit (115) m.p. 209°, $|\alpha|_D$ 132° ($CHCl_3$)] λ_{max}^{EtOH} 230 mμ (log ε 4.1); ν_{max}^{KBr} 1705 cm^{-1} (20-ketone), 1685 and 1618 cm^{-1} (Δ^1-3-ketone); δ_{ppm} 7.11 (d) (J=10 cps) (1-H), 5.83 (d) (J=10 cps) (2-H), 2.07 (s) (17-acetyl-CH_3), 1.01 (s) (19-CH_3), 0.66 (s) (18-CH_3).

Anal. Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62.
Found : C, 80.08; H, 9.69.

Elutions with petroleum ether-benzene mixtures (1:1 and 1:4) gave 159 mg of a crystalline material which upon recrystallization from ether yielded 132 mg (33%) of pure pregna-1,4-diene-3,20-dione (LIV), m.p. 149-150°. A sample was recrystallized twice from ether for analysis. Colourless plates; m.p. 152-153°; $|\alpha|_D^{22}$ 128° (c, 1.000 in $CHCl_3$); [Lit (116) m.p. 155-157°, $|\alpha|_D^{20}$ 131.7°] λ_{max}^{EtOH} 244 mμ (log ε 4.1); ν_{max}^{KBr} 1703 cm^{-1} (20-ketone), 1655, 1628 and 1603 cm^{-1} ($\Delta^{1,4}$-3-ketone); δ_{ppm} 7.08 (d) (J=10 cps)(1-H), 6.2 (d) (J=10 cps) (2-H), 6.07 (s) (4-H), 2.11 (s) (17-acetyl-CH_3), 1.24 (s) (19-CH_3), 0.70 (s) (18-CH_3).

Anal. Calc. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03.
Found : C, 80.71; H, 8.98.

The middle fractions of the chromatogram, eluted with petroleum ether-benzene mixtures (9:1 and 4:1), contained a mixture of the 1-mono-unsaturated ketone

LV and the 1,4-diunsaturated ketone LIV, as evidenced by the ultraviolet and infrared spectra.

Pregna-1,4-diene-3,20-dione (LIV) from Progesterone (LVI)

To 1.14 g of progesterone (LVI), m.p. 120-121°, was added 1.2 g of "DDQ" and 60 ml of dioxane and the mixture was refluxed for 6 h. The product was worked up as described under (a). Chromatography on non-alkaline aluminum oxide (activity III) and elutions with petroleum ether-benzene mixtures (4:1, 1:1 and 1:4) gave 545 mg of crystalline material which, on recrystallization from ether, afforded 455 mg (40%) of pure pregna-1,4-diene-3,20-dione (LIV), m.p. 148-149°. The identity of this product with that obtained as described under (a) was established by the determination of a mixed melting point and by comparison of the infrared and NMR spectra.

11-Oxa-5α-pregn-1-ene-3,20-dione (LVII) and 11-Oxa-1,4-pregnadiene-3,20-dione (XXXVIII)

To 470 mg of 11-oxa-5α-pregnane-3,20-dione(XXXVII), m.p. 214-216°, was added 1.0 g of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) and 40 ml of absolute dioxane and the mixture was refluxed for 8 h. The product was cooled and the solvent was removed in vacuo to give a brown amorphous residue which was dissolved in acetone and filtered through 50g of non-alkaline aluminum oxide (activity III). Repeated elutions with acetone gave 390 mg of a yellow product which was absorbed on 15 g of aluminum oxide (activity III). Elutions with pure petroleum ether gave 25 mg of a crystalline product which upon recrystallization from ether gave 18 mg (4%)of pure 11-oxa-5α-pregn-1-ene-3,20-dione (LVII), m.p. 217-218°; two recrystallizations from ether gave an analytical sample. Colourless plates; m.p. 218-219°; $|\alpha|_D^{22}$ 99.3° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 227 mμ (log ε 3.9); ν_{max}^{KBr} 1710 cm^{-1} (20-ketone), 1683 and 1610 cm^{-1}

(Δ^1-3-ketone), 1068, 1052 and 1036 cm^{-1} (ether); δ_{ppm} 7.38 (d) (J=10 cps) (1-H), 5.88 (d) (J=10 cps) (2-H), 4.19 (d) and 3.45 (d) (J=10 cps) (12-2H), 2.69 (d) (J=9.5 cps) (9α-H), 2.07 (s) (17-acetyl-CH_3), 1.12 (s) (19-CH_3), 0.79 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17.

Found : C, 76.09; H, 8.75; O, 15.06.

Elutions with petroleum ether-benzene mixtures (1:1 and 1:4) gave 167 mg of a crystalline material which upon recrystallization gave 140 mg (30%) of pure 11-oxa-1,4-pregnadiene-3,20-dione (XXXVIII), m.p. 194-195°. A sample was recrystallized twice from dichloromethane-ether for analysis. Colourless plates; m.p. 195-196°; $|\alpha|_D^{22}$ 104.3° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 241 mμ (log ε 4.12); ν_{max}^{KBr} 1718 cm^{-1} (20-ketone), 1673, 1638 and 1609 cm^{-1} ($\Delta^{1,4}$-3-ketone); 1081 and 1072 cm^{-1} (ether); δ_{ppm} 7.25 (d) (J=10 cps) (1-H), 6.20 (d) (J=10 cps) (2-H), 6.11 (s) (4-H), 4.2 (d) and 3.4 (d) (J=10 cps) (12-2H), 2.66 (d) (J=10 cps) (9α-H), 2.06 (s) (17-acetyl-CH_3), 1.32 (s) (19-CH_3), 0.84 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.27.

Found : C, 76.43; H, 8.31; O, 15.43.

The middle fractions of the chromatogram, eluted with petroleum ether-benzene mixtures (9:1 and 4:1), contained a mixture of the 1-mono-unsaturated ketone LVII and the 1,4-diunsaturated ketone XXXVIII, as evidenced by the ultraviolet and infrared spectra. Renewed dehydrogenation of this mixture with "DDQ" gave another 61 mg of the dienone XXXVIII ; (total yield of 11-oxa-1,4-pregnadiene-3,20-dione (XXXVIII) from the 11-oxa pregnanedione XXXVII was 43%).

11-Oxaprogesterone (XXXIX)

To a solution of 100 mg of 11-oxa-1,4-pregnadiene-3,20-dione (XXXVIII), m.p. 194-195°, in 40 ml of absolute benzene was added 90 mg of the tris-(triphenyl

phosphine)-chloro-rhodium catalyst (72,73) prepared according the method of Birch et al (74) and the solution was hydrogenated with 1 moleculer equivalent of hydrogen over a period of 5 h at room temperature and atmospheric pressure. The clear red solution was concentrated in vacuo to one-fourth of its volume and filtered through 30 g of aluminum oxide (activity III). Elutions with absolute benzene yielded 85 mg (85%) of crystalline 11-oxaprogesterone (XXXIX), m.p. 181-182°. A sample was recrystallized twice from ether for analysis. Colourless prisms; m.p. 182.5-184°; $|\alpha|_D^{22}$ 149° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 238 mμ (log ε 4.13); ν_{max}^{KBr} 1715 cm^{-1} (20-ketone), 1677 and 1622 cm^{-1} (Δ^4-3-keto-doublet), 1090, 1081 and 1052 cm^{-1} (ether); δ_{ppm} 5.78 (s) (4-H), 4.15 (d) and 3.44 (d) (J=10 cps) (12-2H), 2.05 (s) (17-acetyl-CH_3), 1.25 (s) (19-CH_3), 0.81 (s) (18-CH_3). [The doublet corresponding to the 9α-proton (which is coupled with C_8-proton) could not be located with certainty in this case].

Anal. Calc. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17.

Found : C, 75.74; H, 8.87; O, 15.25.

CHAPTER III

The Synthesis of 11-Aza Steroids

3β,20β-Dihydroxy-9-amino-9,12-seco-11-nor-5α-pregn-8(9)-en-12-oic Acid Lactam (12→9) (LVIII)

Through a solution of 6.5 g of 3β-hydroxy-20β-acetoxy-9-oxo-9,12-seco-11-nor-5α-pregnan-12-oic acid (XXV) (cf. 38), m.p. 212-214°, in 120 ml of absolute ethanol, ammonia gas was passed for a period of 3 h at 0°. Subsequently, the solution was heated in a sealed tube at 170° for 22 h. The product was taken to dryness in vacuo and the brown residue (6.01 g) was dissolved in a (4:1) mixture of benzene-ethyl acetate and was absorbed on 600 g of silica gel, deactivated by addition of 10% water. Elutions with benzene-ethyl acetate (40:60) and pure ethyl acetate afforded 4.6 g (75%) of the crystalline 3,20-dihydroxy lactam LVIII, m.p. 238-240°. A sample was recrystallized three times from acetone-hexane for analysis. Colourless plates, m.p. 246-247°. $|\alpha|_D^{25}$ 233° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 257 mμ (log ε 3.56); ν_{max}^{KBr} 3340 cm^{-1} (hydroxyls), 3240 cm^{-1} (N-H stretching), 1665 and 1650 cm^{-1} (lactam); δ_{ppm} 6.3 (s) (N-H), 3.6 (m) (3,20-hydroxyl-2H), 3.4 (m) (3,20-2H), 1.13 (d) (J = 6.5 cps) (21-CH_3), 1.1 (s) (19-CH_3), 0.90 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{31}NO_3$: C, 72.03; H, 9.37; N, 4.20.

Found : C, 72.12; H, 9.23; N, 4.42.

3β,20β-Dihydroxy-11-aza-N-acetyl-5α-pregn-8(9)-ene (LXI) from the Diacetoxy N-acetyl pregnene LX

(a) By reaction with Lithium in Liquid Ammonia. A solution of 100 mg of $\Delta^{8(9)}$-3β,20β-diacetoxy-11-aza-N-acetyl-5α-pregnene (LX) (cf. 38), m.p. 226-228°, in 15 ml of absolute ether was added to 100 ml of liquid ammonia at -70° and

5 ml of absolute ethanol was then added with continuous stirring followed by 100 mg of lithium metal (in small pieces). After the blue colour had disappeared, the reaction mixture was gradually warmed to drive off excess of ammonia. The organic product was extracted with ether, was washed carefully with water until neutral, and the ethereal solution was dried over sodium sulfate. Removal of the solvent yielded 75 mg of an amorphous product which, on crystallization from ether, gave 50 mg (62%) of crystalline 3β,20β-dihydroxy 11-aza pregnene LXI, m.p. 241-242°. A sample was recrystallized twice from ether for analysis. Colourless plates, m.p. 248-249°, $|\alpha|_D^{25}$ - 30° (c, 0.751 in $CHCl_3$); ν_{max}^{KBr} 3350, 3200 cm^{-1} (hydroxyls), 1618 cm^{-1} (amide carbonyl); δ_{ppm} 4.67 (m) (3-H), 4.17 (m) (3,20-hydroxyl-2H, exchanged with CD_3OD), 3.6 (m) (12,20-2H), 2.91 (d) (J=14.5 cps) (12-H), 2.2 (s) (N-acetate-CH_3), 1.03 (d) (J=6.5 cps) (21-CH_3), 0.97 (s) (19-CH_3), 0.77 (18-CH_3).

Mass spectrum:[25] Peaks at m/e 361 (M^+), 249, 236 and 207.

Anal. Calc. for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87.

Found : C, 72.98; H, 9.76; N, 4.07.

(b) By Hydrolysis with Methanolic Potassium Hydroxide. A quantity of 65 mg of the 3β,20β-diacetoxy-11-aza-N-acetyl-5α-pregn-8(9)-ene (LX) was dissolved in 5 ml of 2N methanolic potassium hydroxide and the solution was refluxed for 2 h. The organic product was extracted with ether, the ethereal solution was washed with water and dried over sodium sulfate. Removal of the solvent afforded 50 mg of a foam which, on crystallization from ether, gave 35 mg (66% yield) of crystalline 3β,20β-dihydroxy-11-aza-N-acetyl-5α-pregn-8(9)-ene (LXI), m.p. 240-242°. The identity of this product with that prepared as described under (a) was established by a mixed melting point and by the comparison of the infrared and NMR spectra.

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25. We are very thankful to Prof. K. Biemann of the Massachusetts Institute of Technology, Cambridge, Mass, U.S.A., for kindly taking the mass spectrum of this compound.

3β,20β-Dihydroxy-11-aza-5α-pregnane (LXIV) from 3β,20β-Dihydroxy-11-aza-5α-pregn-8(9)-ene (LIX) via the Iminium Hydrochloride LXIII

(a) By Catalytic hydrogenation with Platinum Oxide. Through a solution of 1.0 g of crude dihydroxy enamine LIX in 100 ml of absolute methanol was passed dry hydrogen chloride at 0^{o} for 1.5 h till the solution was strongly acidic. The solvent was removed at 25^{o} in vacuo and 1.02 g of the crude 3β,20β-dihydroxy-11-aza-5α-pregn-9(11)-ene hydrochloride (LXIII), ν_{max}^{KBr} 3350 cm^{-1} (hydroxyls and -NH-), 1666 cm^{-1} (imine), was obtained. A solution of 1.02 g of the crude iminium salt LXIII in 35 ml of absolute methanol and 2 ml of acetic acid was hydrogenated at room temperature and at 37,968 Kg/sq. meter (54 lbs./sq. in.) pressure with 500 mg of platinum oxide catalyst for 36 h. The solution was filtered through a bed of sodium sulfate, made alkaline with ammonia and the product was extracted with dichloromethane. The organic layer was washed with water and dried over sodium sulfate. Removal of the solvent afforded 800 mg of a crude product which was absorbed on 80 g of silica gel deactivated by addition of 10% water. Elutions with methanol afforded 228 mg of a semi-crystalline solid which on recrystallization from acetone-hexane gave 144 mg (15% based on the crude enamine LIX) of crystalline dihydroxy-11-aza-pregnane LXIV, m.p. 175-177°. Two recrystallizations from acetone-hexane gave an analytical sample. Colourless plates, m.p. 195-197°; $|\alpha|_{D}^{25}$ 18.5° (c, 1.000 in CH_3OH); ν_{max}^{KBr} 3340 cm^{-1} (hydroxyls and N-H stretching); δ_{ppm} 4.0 (m) (3.20-2H), 3.47 (m) (3,20-hydroxyls, and N-H—3H, disappearing on deuteration), 2.7 (d) (J=12 cps) (9α-H), 3.8 (d) (J=12 cps) (12-H), 1.2 (s) (19-CH_3), 1.14 (d) (J=6.5 cps) (21-CH_3), 0.94 (s) (18-CH_3).

Mass spectrum:[26] Peaks at m/e 321 (M^{+}), 194 and 180.

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26. We express our sincerest thanks to Prof. F.W. McLafferty and Mr. T. Wachs of the Department of Chemistry, Purdue University, Lafayette, Indiana, U.S.A., for the mass spectrum of this compound.

Anal. Calc. for $C_{20}H_{35}NO_2$: C, 74.71; H, 10.97; O, 9.95; N, 4.36.
Found : C, 74.75; H, 10.85; O, 10.07; N, 4.57.

(b) By Reduction with Sodium Borohydride. To a solution of 1.01 g of the crude iminium hydrochloride LXIII in 600 ml of absolute methanol was added 4.3 g of sodium borohydride and the mixture was refluxed for 20 h. The solvent was removed at 25° in vacuo and the residue was extracted with a (1:1) chloroform-ether mixture, washed with water, and dried over sodium sulfate. Removal of the solvent gave 700 mg of an oily product which on chromatography on silica gel and crystallization, as described under (a), yielded 98 mg (10% based on the crude enamine LXI) of crystalline dihydroxy-11-aza-pregnane LXIV, m.p. 174-176°. The identity of this product with that prepared as described under (a) was established by the determination of a mixed melting point and by comparison of the infrared and NMR spectra.

11-Aza-5α-pregnane-3,20-dione (LXV)

A stirred solution of 195 mg of dihydroxy-11-aza pregnane LXIV, m.p. 174-176°, in 90 ml of absolute acetone was cooled in an ice bath and 0.2 ml of Jones' reagent (59) was added dropwise. The mixture was stirred for 10 min. at 0° and then poured into 200 ml of ice water and extracted with ether. The ethereal solution was washed with cold saturated sodium bicarbonate solution and with water and was dried over sodium sulfate. Removal of the solvent afforded 120 mg of a yellow solid which, on crystallization from ether, gave 102 mg (55%) of crystalline 11-aza pregnanedione LXV, m.p. 197-199°. A sample was recrystallized twice from ether for analysis. Colourless plates, m.p. 201.5-202.5°; $|\alpha|_D^{22}$ 103° (c, 1.000 in CH_3OH); ν_{max}^{KBr} 3400 cm^{-1} (N-H), 1720 cm^{-1} (3,20-ketone); δ_{ppm} 3.3 (d) (J=12 cps) (12-H), 2.55 (s) (N-H, exchanged on deuteration), 2.7 (d) (J=12 cps) (9α-H), 2.09 (s) (17-acetyl-CH_3), 1.1 (s) (19-CH_3), 0.77 (s) (18-CH_3).

Anal. Calc. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41; O, 10.08.

Found : C, 75.56; H, 9.73; N, 4.34; O, 10.36.

3β,9β,12,20β-Tetrahydroxy-9,12-seco-11-nor-5α-pregnane (LXVIII), from the 3β,20β-diacetoxy lactone XLIX via the 3β,9β,20β-trihydroxy-9,12-seco-11-nor-5α-pregnan-12-oic Acid (LXVII)

Through a solution of 400 mg of 3β,20β-diacetoxy-9β-hydroxy-9,12-seco-11-nor-5α-pregnan-12-oic acid lactone (9→12) (XLIX), m.p. 170-171°, in 10 ml of ethanol, ammonia gas was passed for 1 h at 0°. Subsequently, the solution was heated in a sealed tube at 145° for 18 h. The product was taken to dryness in vacuo to give 395 mg of a brown product which on crystallization from dichloromethane yielded 200 mg of the crystalline trihydroxy acid LXVII, m.p. 272-273°, ν_{max}^{KBr} 3420 and 3305 cm^{-1} (hydroxyls and associated hydroxyl) .

A solution of 200 gm of the trihydroxy acid LXVII in 60 ml of tetrahydrofuran was added, with continuous stirring over a period of 25 min, to a slurry of 500 mg of lithium aluminum hydride in 90 ml of tetrahydrofuran and the mixture was refluxed, while the stirring was continued, for 1 h and then stored at room temperature for 18 h. The excess reagent was decomposed by addition of moist ethyl acetate and powdered ice, the inorganic material was filtered off and the solution was dried over sodium sulfate. Removal of the solvent and crystallization from methanol-ether afforded 81 mg of crystalline tetrahydroxy pregnane LXVIII, m.p. 292-293°. A sample was crystallized from methanol for analysis. Colourless plates; m.p. 292-293°; $|\alpha|_D^{22}$ 17.4° (c, 1.060 in pyridine); ν_{max}^{KBr} 3380 cm^{-1} (hydroxyls).

Anal. Calc. for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66.

Found : C, 70.42; H, 10.95.

9,12-Seco-11-nor-25-iso-5α,22β-spirostane-3,9,12-triol (LXIX)

A solution of 4.0 g of the 3β-hydroxy methyl ester XXVIIb, m.p. 161-163°, in 500 ml of absolute tetrahydrofuran was added, dropwise with vigorous stirring over a period of 25 min, to a slurry of 4.5 g of lithium aluminum hydride in 350 ml of absolute tetrahydrofuran. While the stirring was continued, the mixture was refluxed for 40 h. The excess reagent was decomposed in the cold by addition of moist ethyl acetate and, subsequently, of powdered ice. A cold solution of ammonium chloride was then added and the organic product was extracted with dichloromethane. The organic layer was washed with cold water and dried over sodium sulfate. Removal of the solvent gave 3.8 g of a crude product which on crystallization from dichloromethane-ether gave 3.4 g (90%) of the crystalline triol LXIX, m.p. 215-216°. Two recrystallizations from dichloromethane-ether gave an analytical sample. Colourless plates; m.p. 217-218°; $|\alpha|_D^{22}$ - 63.6° (c, 1.100 in $CHCl_3$); ν_{max}^{KBr} 3250 cm^{-1} (hydroxyls). δ_{ppm} 5.73 (m) and 5.05 (m) (3,9,12-hydroxyl-3H, exchanged on treatment with D_2O), 4.2 (m) (3,9,16-3H), 3.5 (m) (12,26-4H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.03 and 0.83 ppm.

Anal. Calc. for $C_{26}H_{44}O_5$: C, 71.52; H, 10.16.

Found : C, 71.82; H, 9.89.

3β,9β,12-Triacetoxy-9,12-Seco-11-nor-25-iso-5α,22β-spirostane (LXIXa)

A solution of 300 mg of the 3,9,12-triol LXIX, m.p. 215-216°, in 3 ml of pyridine was acetylated at room temperature with 3 ml of acetic anhydride for 16 h. The usual working up and crystallization from ether afforded 247 mg (64%) of pure crystalline 3β,9β,12-triacetoxy-spirostane LXIXa, m.p. 176-177°. A sample was recrystallized twice from dichloromethane-ether for analysis. Colourless prisms, m.p. 177-178°, $|\alpha|_D^{22}$ - 89.2° (c, 1.300 in $CHCl_3$); ν_{max}^{KBr} 1750 cm^{-1}, 1242 cm^{-1} (acetate); δ_{ppm} 4.4 (m) (3,9-2H), 3.95 (m) (16-H), 3.46 (m)

(12,26-4H), 2.03 (s) (3,9-acetate-$2CH_3$),1.97 (s) (12-acetate-CH_3); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.12 and 0.7 ppm.

Anal. Calc. for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96.
Found : C, 68.44; H, 9.08.

3β,9β,12-Tritosyloxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXX), 9β-Hydroxy-3β,12-ditosyloxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXI), and 3β-Tosyloxy-11-oxa-25-iso-5α,22β-spirostane (LXXII)

A quantity of 3.5 g of the 3β,9β,12-triol LXIX, m.p. 215-216°, was treated with 10 g of p-toluenesulfonyl chloride in 25 ml of pyridine and the mixture was left at room temperature for seven days. The usual working up gave 6.6 g of a product which was chromatographed on 180 g of neutral alumina. Elutions with petroleum ether-benzene (4:1) afforded 900 mg (20% yield) of crystalline 11-oxa 3β-tosylate LXXII, m.p. 168-170°. A sample was recrystallized twice from ether for analysis. Colourless needles, m.p. 169-170°; $|\alpha|_D^{22}$ - 71.1° (c, 1.040 in $CHCl_3$); λ_{max}^{EtOH} 225 mμ (log ε 4.15); ν_{max}^{KBr} 1600, 1351, 1186 and 1170 cm^{-1} (tosylate), 1098, 1084 and 1050 cm^{-1} (ether); δ_{ppm} 7.81 (d) (J=8 cps) and 7.31 (d) (J=8 cps) (aromatic-4H), 4.45 (m) (3,16-2H), 3.76 (d) (J=10 cps) and 3.07 (d) (J=10 cps) (12-2H), 3.43 (m) (26-2H), 2.41 (s) (aromatic-CH_3); $\delta_{ppm}^{C_6H_6}$ 2.33 (d) (J=10 cps) (9α-H), 1.0 (d) (J=6 cps) (21-CH_3), 0.93 (s) (19-CH_3), 0.82 (s) (18-CH_3), 0.71 (d) (J=6 cps) (27-CH_3). [These signals were not resolved in $CDCl_3$] .

Anal. Calc. for $C_{33}H_{48}O_6S$: C, 69.20, H, 8.45; S, 5.59.
Found : C, 69.16; H, 8.25; S, 5.68.

Further elutions with petroleum ether-benzene (1:1) gave 3.2 g (40% yield) of crystalline 3β,9β,12-tritosylate LXX, m.p. 100-101°. Three recrystallizations from dichloromethane-hexane gave an analytical sample. Colourless

needles, m.p. 101-102°; $|\alpha|_D^{22}$ - 54° (c, 1.300 in $CHCL_3$); λ_{max}^{EtOH} 226 mμ (log ε 4.75); ν_{max}^{KBr} 1600, 1361, 1188 and 1175 cm^{-1} (tosylate); δ_{ppm} 7.58 (m) (aromatic-12H), 4.2 (m) (3,9,16-3H), 3.38 (m) (12,26-4H), 2.4 (s) (aromatic-$3CH_3$). The 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.03 and 0.67 ppm.

Anal. Calc. for $C_{47}H_{62}O_{11}S_3$: C, 62.77; H, 6.95; S, 10.70.
Found : C, 62.75; H, 7.05; S, 10.98.

Elution with benzene-ether (1:1) gave 689 mg (12% yield) of the 3β,12-ditosylate LXXI, m.p. 143-145°. A sample was recrystallized twice from ether-hexane for analysis. Colourless prisms, m.p. 144-145°; $|\alpha|_D^{22}$ - 58.7° (c, 2.200 in $CHCL_3$); λ_{max}^{EtOH} 225 mμ (log ε 4.43); ν_{max}^{KBr} 3470 cm^{-1} (hydroxyl), 1605, 1365, 1188 and 1176 cm^{-1} (tosylate); δ_{ppm} 7.63 (m) (aromatic-8H), 4.43 (m) (3,16-2H), 3.8 (s) (12-2H), 3.42 (m) (26-2H), 3.11 (s) (-OH, exchanged with D_2O), 2.7 (d) (J=9 cps) (9α-H), 2.45 (s) (aromatic-2 CH_3). The 18, 19, 21 and 27 methyls appeared as an unresolved multiplet between 1.0 and 0.67 ppm.

Anal. Calc. for $C_{40}H_{56}O_9S_2$: C, 64.48; H, 7.57; S, 8.60.
Found : C, 64.72; H, 7.66; S, 8.70.

Selective Tosylation of the Triol LXIX. To a solution of 300 mg of the triol LXIX, m.p. 215-216°, in 10 ml of pyridine was added 1.5 g of p-toluenesulfonyl chloride and the mixture was left at 25° for 20 h. The usual working up gave 550 mg of a crude product which, on crystallization from ether-hexane, gave 320 mg (63% yield) of the 3β,12-ditosylate LXXI, m.p. 143-145°. The identity of this product with that obtained as described above was established by a mixed melting point and by comparison of their infrared and NMR spectra.

3β,9β-Ditosyloxy-12-azido-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXIII)

To a solution of 2.0 g of the 3β,9β,12-tritosylate LXX, m.p. 100-101°, in 15 ml of

dimethyl formamide was added 1.5 g of sodium azide and the mixture was heated to 70° for 2 h. The cold mixture was poured into water, the organic material was extracted with ether and was washed with water. Drying over sodium sulfate and removal of the solvent afforded 1.65 g of a crude product which, on crystallization from methanol-ether, yielded 1.5 g (87%) of crystalline 3β,9β-ditosyloxy 12-azide LXXIII, m.p. 164-166°. Two recrystallizations from methanol-ether gave an analytical sample. Colourless needles, m.p. 165-166°; $|\alpha|_D^{22}$ - 40° (c, 1.230 in $CHCl_3$); λ_{max}^{EtOH} 225 mμ (log ε 4.4); ν_{max}^{KBr} 2110 cm^{-1} (azide), 1610, 1360, 1180 and 1170 cm^{-1} (tosylate); δ_{ppm} 7.55 (m) (aromatic - 8H), 4.2 (d) (J=10.5 cps) (9α-H), 3.9 (b.s.) (3β-H), 3.85 (m) (16-H); 3.5 (d) and 3.12 (d) (J=10 cps) (12-2H), 3.4 (m) (26-2H), 2.43 (s), 2.5 (s) (aromatic-$2CH_3$); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.0 and 0.5 ppm.

Anal. Calc. for $C_{40}H_{55}N_3O_8S_2$: C, 62.39; H, 7.20; N, 5.46; S, 8.33.
Found : C, 62.31; H, 7.29; N, 5.59; S, 8.43.

3α-Azido-11-oxa-25-iso-5α,22β-spirostane (LXXV)

(a) From the 11-Oxa 3β-Tosylate LXXII. To a solution of 700 mg of the 11-oxa-3β-tosylate LXXII, m.p. 168-170°, in 10 ml of dimethyl formamide was added 700 mg of sodium azide and the mixture was heated at 70° for 4 h. The usual working up afforded 615 mg of amorphous material which on crystallization from methanol gave 468 mg (86%) of crystalline 11-oxa 3α-azide LXXV, m.p. 188-189°. A sample was recrystallized twice from methanol for analysis. Colourless prisms, m.p. 189-190°; $|\alpha|_D^{22}$ - 50° (c, 1.300 in $CHCl_3$); ν_{max}^{KBr} 2080 cm^{-1} (azide), 1100, 1080 and 1058 cm^{-1} (ether); δ_{ppm} 4.37 (m) (16-H), 3.9 (b.s.) (3β-H), 3.76 (d) and 3.1 (d) (J=10.5 cps) (12-2H), 3.4 (m) (26-2H), 2.5 (d) (J=9.5 cps) (9α-H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.1 and 0.7 ppm.

Anal. Calc. for $C_{26}H_{41}N_3O_3$: C, 70.39; H, 9.32; N, 9.47.
Found : C, 70.19; H, 9.29; N, 9.29.

(b) From the 3β,9β-Ditosyloxy 12-Azide LXXIII. A solution of 750 mg of the ditosylate 12-azide LXXIII, m.p. 164-166°, in 15 ml of dimethyl formamide was heated with 1.0 g of sodium azide at 120° for 4 h. The usual working up and crystallization from methanol yielded 358 mg (83%) of crystalline 11-oxa 3α-azide LXXV, m.p. 188-189°. The identity of this product with that obtained as described in (a) was established by a mixed melting point and by comparison of their infrared and NMR spectra.

(c) From the 3β,9β,12-Tritosylate LXX. A solution of 1.1 g of the tritosylate LXX, m.p. 100-101°, in 15 ml of dimethyl formamide was heated with 1.0 g of sodium azide at 120° for 4 h. The usual working up afforded 600 mg of a crude product which was absorbed on 30 g of neutral alumina. Elutions with petroleum ether-benzene (4:1, and 1:1) mixture afforded 426 mg of a semi-crystalline product which, on crystallization from methanol, yielded 363 mg (66%) of crystalline 11-oxa 3α-azide LXXV, m.p. 188-189°. The product was found identical in all respects with that obtained as described under (a) and (b).

3β,9β-Ditosyloxy-12-amino-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXVI)

A quantity of 500 mg of the ditosyloxy 12-azide LXXIII, m.p. 164-166°, in 40 ml of ethanol, was hydrogenated in the presence of 400 mg of a platinum oxide catalyst at room temperature and at atmospheric pressure for 3 h. (The reduction was complete after 3 h as was evident by the disappearance of the azide band in the infrared spectrum). The mixture was filtered through celite and the filtrate was taken to dryness to give 437 mg of a residue which on crystallization from methanol gave 361 mg of crystalline 3β,9β-ditosyloxy 12-amine LXXVI, m.p. 99-101°. A sample was recrystallized twice from methanol for

analysis. Colourless plates, m.p. 100-101°; $|\alpha|_D^{22}$ - 36.1° (c, 1.700 in $CHCl_3$); λ_{max}^{EtOH} 226 mμ (log ε 4.5); ν_{max}^{KBr} 3360 cm^{-1} (-NH), 1610, 1360, 1184 and 1173 cm^{-1} (tosylate).

Anal. Calc. for $C_{40}H_{57}NO_8S_2$: C, 64.57; H, 7.72; N, 1.88; S, 8.62.
Found : C, 64.42; H, 7.74; N, 2.01; S, 8.75.

9β-Benzoyloxy-3β,12-ditosyloxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXVII)

To a solution of 2.3 g of 9β-hydroxy 3β,12-ditosylate LXXI, m.p. 143-145°, in 25 ml of pyridine, 1.5 ml of benzoyl chloride was added and the mixture was allowed to stand at room temperature for 16 h. The usual working up afforded 2.5 g of a crude product which, on crystallization from methanol-ether, yielded 1.98 g (76%) of 9β-benzoyloxy 3β,12-ditosylate LXXVII, m.p. 167-169°. A sample was recrystallized twice from methanol-ether for analysis. Colourless needles, m.p. 168-169°; $|\alpha|_D^{22}$ - 36.7° (c, 1.200 in $CHCl_3$); λ_{max}^{EtOH} 226 mμ (log ε 4.4); ν_{max}^{KBr} 1720 cm^{-1} (benzoate), 1600, 1362, 1188 and 1178 cm^{-1} (tosylate).

Anal. Calc. for $C_{47}H_{60}O_{10}S_2$: C, 66.48; H, 7.12; S, 7.55.
Found : C, 66.63; H, 7.19; S, 7.46.

9β-Benzoyloxy-3α,12-diazido-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXVIII)

To a solution of 1.5 g of 9β-benzoyloxy 3β,12-ditosylate LXXVII, m.p. 167-169°, in 30 ml of dimethyl formamide 3.5 g of sodium azide was added; the mixture was heated at 120° for 16 h, and was worked up in the usual fashion to give 960 mg of a crude product which on crystallization from methanol afforded 802 mg (77%) of crystalline 9β-benzoyloxy 3α,12-diazide LXXVIII, m.p. 146-147°. A sample was recrystallized twice from methanol for analysis. Colourless needles, m.p. 146-147°; $|\alpha|_D^{22}$ - 48.1° (c, 1.600 in $CHCl_3$); ν_{max}^{KBr} 2080 cm^{-1} (azide), 1718 cm^{-1} (benzoate); δ_{ppm} 8.1 (m) and 7.5 (m) (aromatic-5H), 4.77 (d)

(J=10.5 cps) (9α-H), 4.27 (m) (16-H), 3.87 (b.s.) (3β-H), 3.4 (m) (26-2H), 3.2 (d) and 2.9 (d) (J=11 cps) (12-2H); the 18, 19, 21 and 27 methyl protons appeared between 1.1 to 0.63 ppm as an unresolved multiplet.

Anal. Calc. for $C_{33}H_{46}N_6O_4$: C, 67.09; H, 7.85; N, 14.23.

Found : C, 67.28; H, 8.00; N, 14.09.

3α-Benzoyloxy-11-oxa-25-iso-5α,22β-spirostane (LXXIX) and 3α-hydroxy-11-oxa-25-iso-5α,22β-spirostane (LXXX)

To a solution of 6.8 g of the 3β,9β,12-tritosylate LXX, m.p. 100-101°, in 125 ml of dimethyl formamide was added 17.0 g of sodium benzoate and the mixture was refluxed for 6 h. The cold product was poured into an iced sodium bicarbonate solution and the organic material was extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate and was taken to dryness. The residue (3.2 g) was absorbed on 120 g of neutral alumina. Elutions with petroleum ether-benzene (4:1) afforded 250 mg (6%) of crystalline 3α-benzoyloxy-11-oxa-25-iso-5α,22β-spirostane (LXXIX), m.p. 196-198°. A sample was recrystallized twice from ether for analysis. Colourless needles, m.p. 197-198°; $|\alpha|_D^{22}$ - 55.9° (c, 1.400 in $CHCl_3$); ν_{max}^{KBr} 1726 cm^{-1} (benzoate), 1100, 1078 and 1053 cm^{-1} (ether); δ_{ppm} 8.07 (m) and 7.47 (m) (aromatic-5H), 5.3 (b.s.) (3β-H), 4.4 (m) (16-H), 3.8 (d) and 3.13 (d) (J=11 cps) (12-2H), 3.4 (m) (26-2H), 2.57 (d) (J=9 cps) (9α-H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.1 and 0.65 ppm.

Anal. Calc. for $C_{33}H_{46}O_5$: C, 75.82; H, 8.87.

Found : C, 75.46; H, 8.95.

Further elutions with benzene and with ether yielded 300 mg (9%) of crystalline 3α-hydroxy-11-oxa-25-iso-5α,22β-spirostane (LXXX), m.p. 222-224°. A sample was recrystallized twice from methanol-ether for analysis. Colourless

plates, m.p. 223-224°; $|\alpha|_D^{22}$ - 88.7° (c, 1.400 in $CHCl_3$); ν_{max}^{KBr} 3500 cm^{-1} (hydroxyl), 1100, 1078 and 1054 cm^{-1} (ether); δ_{ppm} 4.43 (m) (16-H); 4.05 (b.s.) (3β-H), 3.8 (d) and 3.1 (d) (J=10.5 cps) (12-2H), 3.45 (m) (26-2H), 2.5 (d) (J=9 cps) (9α-H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.05 and 0.70 ppm.

Anal. Calc. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11.

Found : C, 74.63; H, 10.30.

3-Oxo-9β-hydroxy-12-acetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXI) and 3-Oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostane 9β,12-diol (XLVIb), from the 3-ethylenedioxy 9β,12-diol(XLVI)

A solution of 7.5 g of the 3-ethylenedioxy-9,12-diol XLVI, m.p. 217-219°, in 80 ml of glacial acetic acid was heated at 100° for 7 h. The mixture was cooled, neutralized with 2N sodium hydroxide and the organic product was extracted with ether. The ethereal solution was washed with water and dried over sodium sulfate. Removal of the solvent afforded 7.5 g of an amorphous product which was chromatographed on 150 g of non-alkaline alumina. Elutions with petroleum ether-benzene (1:1, 1:4) and benzene yielded 5.46 g (73%) of amorphous 9β-hydroxy 12-acetate LXXXI which resisted all attempts of crystallization. The product gave a single spot on thin layer chromatography [silica gel, (1:1)ether-petroleum ether]; ν_{max}^{KBr} 3480 cm^{-1} (hydroxyl), 1745 and 1242 cm^{-1} (acetate), 1719 cm^{-1} (ketone); δ_{ppm} 4.3 (m) (9,16-2H), 3.9 (s) (12-2H), 3.43 (m) (26-2H and 9-OH), 2.07 (s) (acetate-CH_3); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.1 and 0.8 ppm.

Anal. Calc. for $C_{28}H_{44}O_6$: C, 70.55; H, 9.31; CH_3CO, 9.12.

Found : C, 70.05; H, 9.30; CH_3CO, 9.81.

Further elutions with benzene – ether (1:1) gave 1.0 g (13%) of crystalline 3-oxo-9,12-seco-11-nor-25-iso-5α,22β-spirostane-9β,12-diol (XLVIb), m.p.

253-255°; ν_{max}^{KBr} 3360 cm^{-1} (hydroxyls), 1700 cm^{-1} (3-ketone); δ_{ppm} 4.33 (m) (16-H), 3.7 (m) (hydroxyls -2H, exchanged with CD_3OD), 3.45 (m) (26-2H), 3.35 (s) (12-2H), 2.93 (d) (J=10 cps) (9α-H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.15 and 0.65 ppm.

3-Oxo-9β-tosyloxy-12-acetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXII)

To a solution of 9.5 g of the 9β-hydroxy 12-acetate LXXXI in 45 ml of pyridine was added 12.3 g of p-toluenesulfonyl chloride and the mixture was heated at 40° for 8 days. The usual working up gave 11.5 g of a crude product which was dissolved in petroleum ether-benzene (3:1) and absorbed on 250 g of non-alkaline alumina. Elutions with petroleum ether-benzene (4:1, 1:1 and 1:4) and pure benzene afforded 7.53 g (60%) of crystalline 3-oxo 9β-tosyloxy 12-acetate LXXXII, m.p. 141-142°. A sample was recrystallized twice for analysis. Colourless needles, m.p. 141-142°; $|\alpha|_D^{25}$ - 29.1° (c, 0.800 in $CHCl_3$); λ_{max}^{EtOH} 226 mμ (log ε 4.2); ν_{max}^{KBr} 1746 cm^{-1} (acetate), 1718 cm^{-1} (ketone), 1598, 1361 and 1176 cm^{-1} (tosylate); δ_{ppm} 7.57 (m) (aromatic-4H), 4.27 (d) (J=10.5 cps) (9α-H), 3.7 (m) (16-H), 3.58 (d) and 3.2 (d) (J=11 cps) (12-2H), 3.5 (m) (26-2H), 2.45 (s) (aromatic-CH_3), 2.01 (s) (acetate-CH_3); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.15 and 0.75 ppm.

Anal. Calc. for $C_{35}H_{50}O_8S$: C, 66.64; H, 7.99; S, 5.07.

Found : C, 66.79; H, 7.91; S, 5.23.

3,3-Dimethoxy-9β-tosyloxy-12 acetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXIII)

A solution of 1.13 g of 3-oxo 9β-tosyloxy 12-acetate LXXXII, m.p. 141-142°, in 10 ml of methanol was allowed to stand at room temperature for 5 days, after which period the solvent was evaporated to give 1.21 g of a residue which on crystallization from ether-hexane afforded 987 mg of 3,3-dimethoxy 9β-tosyloxy

12-acetate LXXXIII, m.p. 130-131°. Two recrystallizations from ether-hexane gave an analytical sample. Colourless needles, m.p. 130-131°; $|\alpha|_D^{22}$ - 38° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 225 mμ (log ε 4.4); ν_{max}^{KBr} 1741 cm^{-1} (acetate), 1598, 1361, 1186 and 1175 cm^{-1} (tosylate), 1103 and 1060 cm^{-1} (acetal); δ_{ppm} 7.60 (m) (aromatic-4H); 4.27 (d) (J=10.5 cps) (9α-H), 3.9 (m) (16-H), 3.57 (d) and 3.2 (d) (J=10 cps) (12-2H), 3.45 (m) (26-2H), 3.19 (s) and 3.13 (s) (acetal-$2CH_3$), 2.43 (s) (aromatic-CH_3), 2.0 (s) (acetate-CH_3); the 18, 19, 21 and 27 methyl protons appeared between 1.05 and 0.65 ppm as an unresolved multiplet.

Anal. Calc. for $C_{37}H_{56}O_9S$: C, 65.66; H, 8.34; S, 4.73.

Found : C, 65.78; H, 8.25; S, 4.86.

3-Oxo-9α-azido-12-acetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXIV)

To a solution of 2.5g of 3-oxo 9β-tosyloxy 12-acetate LXXXII, m.p. 141-142°, in 25 ml of hexamethyl phosphoric triamide (HMPT) was added 4.0 g of sodium azide and the mixture was heated at 90° for 3 h. The cold product was poured into water and the organic material was extracted with ether. The ethereal layer was washed with water, dried over sodium sulfate and taken to dryness to give 2.01 g of a residue which was dissolved in petroleum ether-benzene (4:1) and was absorbed on 60 g of neutral alumina. Elutions with petroleum ether-benzene (4:1, 1:1 and 1:4) afforded 1.79 g (90%) of an amorphous solid which resisted crystallization and which represented 3-oxo-9α-azido-12-acetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXIV). The product gave a single spot on thin layer chromatography [silica gel, (1:1) petroleum ether-ether]; ν_{max}^{KBr} 2080 cm^{-1} (azide), 1748 and 1240 cm^{-1} (acetate), 1722 cm^{-1} (ketone); δ_{ppm} 4.45 (m) (16-H), 3.93 (s) (12-2H), 3.45 (m) (26-2H), 3.2 (b.s.) (9β-H), 2.08 (s) (acetate-CH_3); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.2 and 0.7 ppm.

Anal. Calc. for $C_{28}H_{43}N_3O_5$: C, 67.03; H, 8.64; N, 8.38.

Found : C, 66.89; H, 8.51; N, 8.16.

3-Oxo-9α-azido-12-tosyloxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXV)

To a solution of 1.75 g of 3-oxo 9α-azido 12-acetate LXXXIV in 90 ml of methanol was added a solution of 2.4 g of potassium bicarbonate in 12 ml of water and the mixture was heated at 60° for 48 h. The product was cooled and poured into water and the organic material was extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate and the solvent was removed. The white amorphous residue (1.6 g) resisted crystallization and represented 3-oxo-9α-azido-12-hydroxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane; ν_{max}^{KBr} 3460 cm^{-1} (hydroxyl), 2080 cm^{-1} (azide), 1718 cm^{-1} (ketone). To a solution of this product in 40 ml of pyridine was added 1.6 g of p-toluenesulfonyl chloride and the mixture was kept at room temperature for 16 h. The usual working up afforded 2.0 g of a yellow residue which on crystallization from ether-hexane gave 1.63 g (73%) of crystalline 3-oxo-9α-azido-12-tosyloxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXV), m.p. 188-189°. A sample was recrystallized twice from ether-hexane for analysis. Colourless prisms, m.p. 192-193°; $|\alpha|_D^{22}$ - 50.1° (c, 1.000 in $CHCl_3$); λ_{max}^{EtOH} 225 mμ (log ε 4.2); ν_{max}^{KBr} 2075 cm^{-1} (azide), 1715 cm^{-1} (ketone), 1598, 1364 and 1179 cm^{-1} (tosylate); δ_{ppm} 7.55 (m) (aromatic-4H), 4.38 (m) (16-H), 3.8 (s) (12-2H), 3.45 (m) (26-2H), 3.2 (d) (J=4 cps) (9β-H), 2.48 (s) (aromatic-CH_3); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.2 and 0.6 ppm.

Anal. Calc. for $C_{33}H_{47}N_3O_6S$: C, 64.58; H, 7.72; N, 6.85; S, 5.22.

Found : C, 64.60; H, 7.72; N, 6.91; S, 5.21.

3-Oxo-9α,12-diazido-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXVI)

To a solution of 1.63 g of 3-oxo 9α-azido 12-tosylate LXXXV, m.p. 188-189°,

in 50 ml of hexamethyl phosphoric triamide (HMPT) was added 3.2 g of sodium azide and the mixture was heated at 90° for 3 h. The cold product was poured into water and extracted with ether. The ethereal layer was washed with water, with cold 2N hydrochloric acid, with a cold saturated sodium bicarbonate solution and with water. The solution was dried over sodium sulfate, the solvent was removed and the residue (1.34 g) was chromatographed on 80 g of silica gel. Elutions with ether-petroleum ether (1:3) afforded 1.17 g (90%) of an amorphous material which resisted crystallization and which represented 3-oxo-9α,12-diazido-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXVI). This product gave a single spot on thin layer plate [silica gel, (1:1) petroleum ether-ether]; ν_{max}^{KBr} 2098 cm^{-1} (azide), 1720 cm^{-1} (ketone); δ_{ppm} 4.4 (m) (16-H), 3.45 (m) (26-H), 3.27 (s) (12-2H), 3.2 (b.s.) (9β-H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.2 and 0.8 ppm.

Anal. Calc. for $C_{26}H_{40}N_6O_3$: C, 64.43; H, 8.32; N, 17.34.

Found : C, 64.58; H, 8.45; N, 17.23.

3β-Hydroxy-9β,12-diamino-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXVII)

A quantity of 1.0 g of the 3-oxo 9β,12-diazide LXXXVI was reduced with 2.5 g of lithium aluminum hydride in 150 ml of absolute ether at room temperature for 5 h. The usual working up afforded 810 mg of a white amorphous material which on crystallization from methanol-ethyl acetate yielded 200 mg (22%) of crystalline 3β-hydroxy 9β,12-diamine LXXXVII, m.p. 155-160°. Two recrystallizations from methanol afforded an analytical sample. Colourless plates; m.p. 161-163°; $[\alpha]_D^{22}$ - 49.7° (c, 0.800 in $CHCl_3$); ν_{max}^{KBr} 3340 cm^{-1} (hydroxyl and N-H); δ_{ppm} 4.33 (m) (3,16-2H), 3.48 (m) (9,26-3H), 3.37 (s) (12-2H), 2.47 (s) (hydroxyl-H), 2.25 (s) (amine-4H); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.15 and 0.62 ppm.

Anal. Calc. for $C_{26}H_{46}N_2O_3$: C, 71.84; H, 10.67; N, 6.45.

Found : C, 71.89; H, 10.59; N, 6.45.

3-Oxo-9α-bromo-12-acetoxy-9,12-seco-11-nor-25-iso-5α,22β-spirostane (LXXXVIII)

To a solution of 1.02 g of 3-oxo 9β-tosyloxy 12-acetate LXXXII, m.p. 141-142°, in 100 ml of methyl ethyl ketone was added 3.0 g of lithium bromide and the mixture was refluxed for 44 h. The solvent was partly removed in vacuo, the mixture was poured into ice water and the organic product was extracted with ether. The ethereal layer was washed with water and dried over sodium sulfate. Removal of the solvent afforded 1.24 g of a yellowish residue which was dissolved in benzene and chromatographed on 100 g of silica gel deactivated by addition of 10% water. Elutions with benzene-ethyl acetate (95:5 and 90:10) gave 568 mg of a white amorphous solid which resisted crystallization and which represented crude 3-oxo 9α-bromo 12-acetate LXXXVIII. This product gave a positive Beilstein test; ν_{max}^{KBr} 1748 cm^{-1} and 1248 cm^{-1} (acetate), 1720 cm^{-1} (ketone); δ_{ppm} 4.25 (m) (16-H), 4.2 (b.s.) (9β-H), 3.98 (s) (12-2H), 3.48 (m) (26-2H), 2.07 (s) (acetate-CH_3); the 18, 19, 21 and 27 methyl protons appeared as an unresolved multiplet between 1.16 and 0.65 ppm.

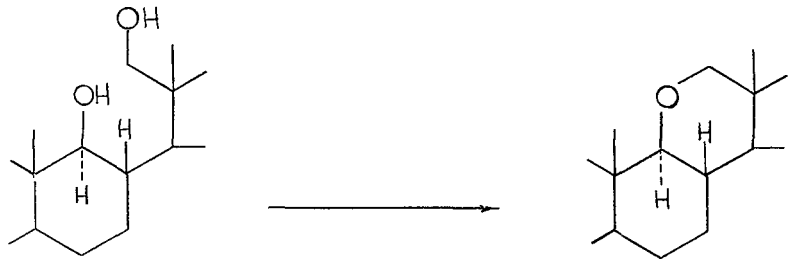
Anal. Calc. for $C_{28}H_{43}O_5Br$: Br, 14.85.

Found : Br, 12.86.

SUMMARY

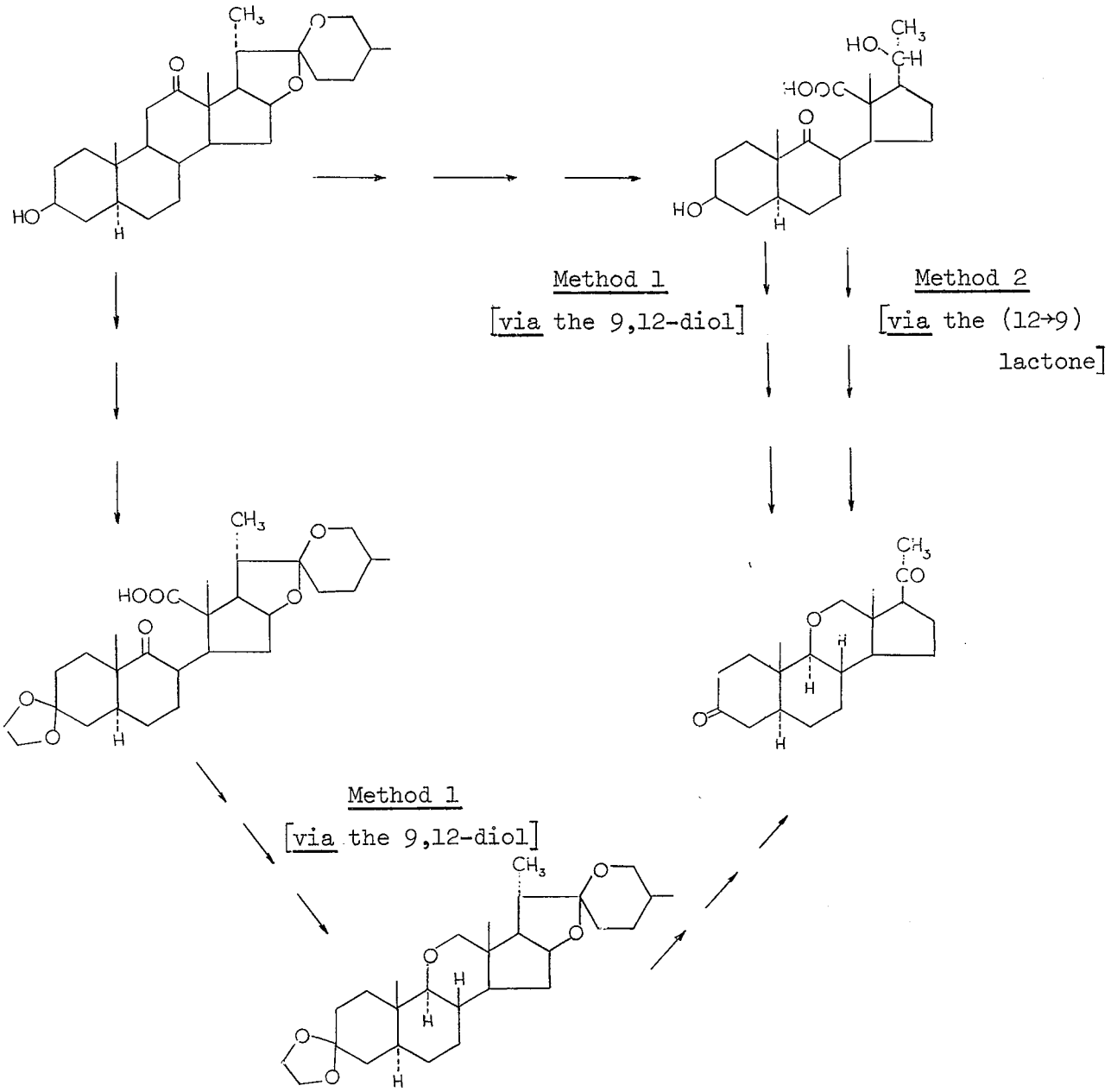
With the object of synthesizing nucleo-hetero steroids of potential biological interest and of correlating chemical structure and biological activity in this field, we undertook a program on the synthesis of 11-oxa and 11-aza steroids.

We have accomplished the first synthesis of an 11-oxa hormone analog, 11-oxaprogesterone. The key intermediate in this synthesis, 11-oxa-5α-pregnane-3,20-dione, was synthesized by three pathways, in two of which the same method for the formation of the hetero cycle was used. This method consists in the treatment of an 11-nor 9,12-seco 9,12-diol with an excess of p-toluenesulfonyl chloride in pyridine, at elevated temperatures, and gives in good yields the desired 11-oxa steroids.

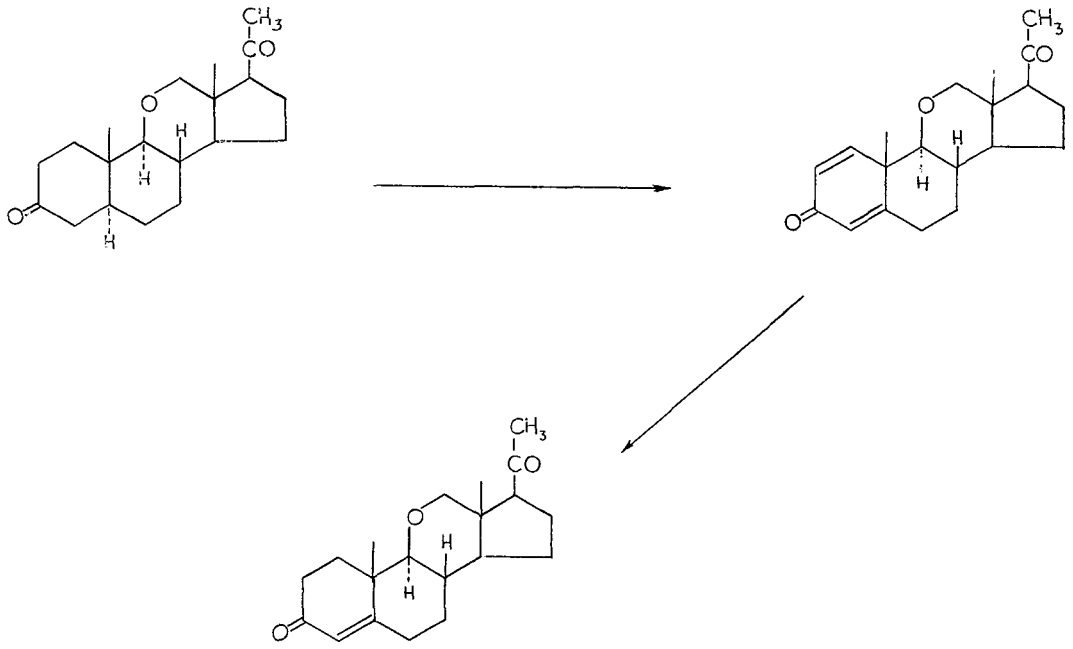


In the third pathway, the 11-oxa structure was developed by reducing an 11-nor 9,12-seco 9β-hydroxy 12-pregnanoic acid lactone (12→9), either with lithium aluminum hydride-boron trifluoride etherate or, catalytically, with platinum oxide in acetic acid in the presence of perchloric acid.

Hecogenin served as the starting material for the three synthetic routes. In two series, hecogenin was first degraded and the resulting 16-pregnene derivative was transformed into a 3,20-dioxygenated 9-oxo 9,12-seco 11-nor 12-acid which was then converted by the two methods outlined to 11-oxa-5α-pregnane-3,20-dione, whereas in the third series the hetero atom was introduced prior to the degradation of rings E and F of hecogenin.



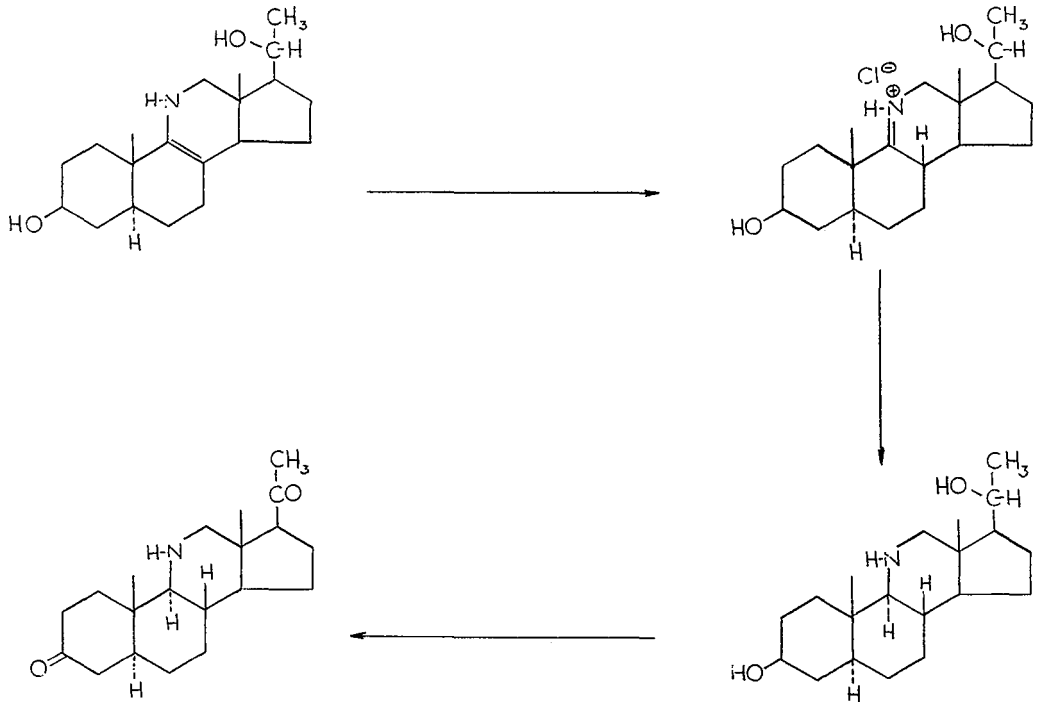
The 11-oxa-5α-pregnane-3,20-dione thus synthesized was then converted via 11-oxa-pregna-1,4-diene-3,20-dione to 11-oxaprogesterone.



The new hormone analog shows only weak progestational activity but possesses a marked ovulation-inhibiting action and is of interest because of the separation of these two types of activities.

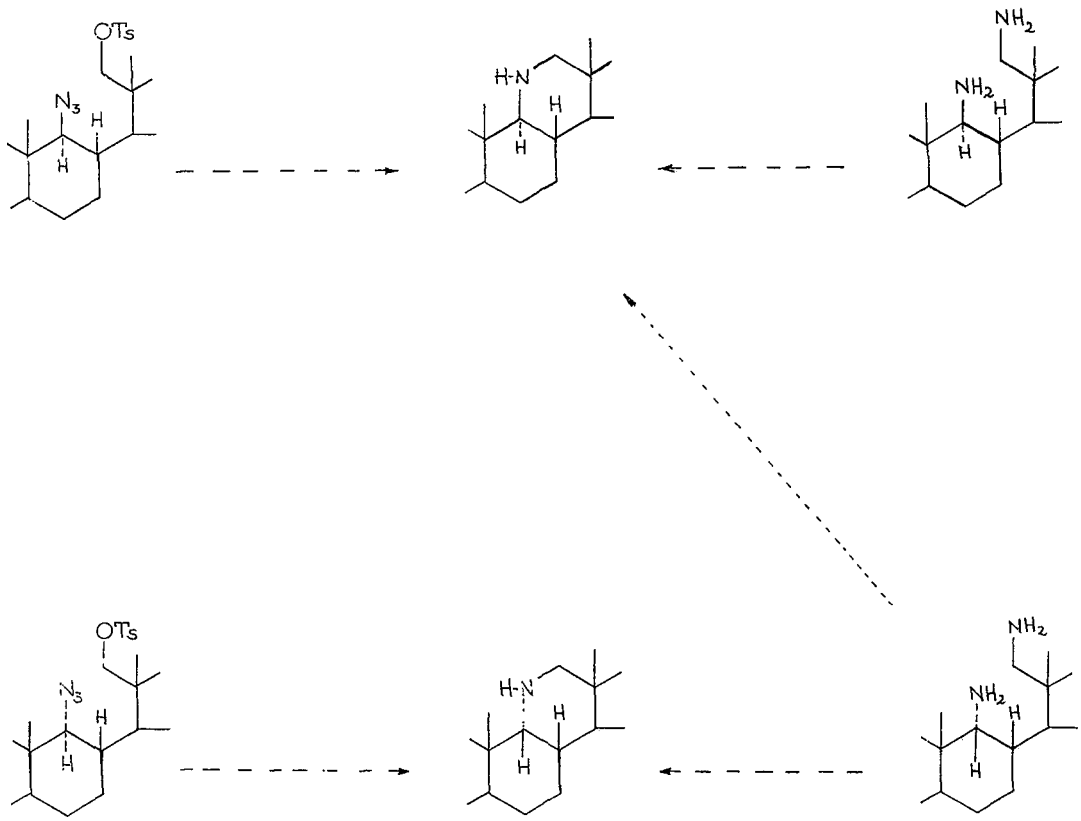
As a contribution to our program on the synthesis of 11-aza hormone analogs, we investigated pathways towards 11-aza steroids saturated in positions 8 and 9.

We succeeded in reducing the 8,9-double bond of 3,20-dihydroxy-11-aza-5α-pregn-8(9)-ene, by reducing its iminium salt either with platinum oxide in acetic acid or with sodium borohydride, and thus obtained 3,20-dihydroxy-11-aza-5α-pregnane which was readily converted to 11-aza-5α-pregnane-3,20-dione.

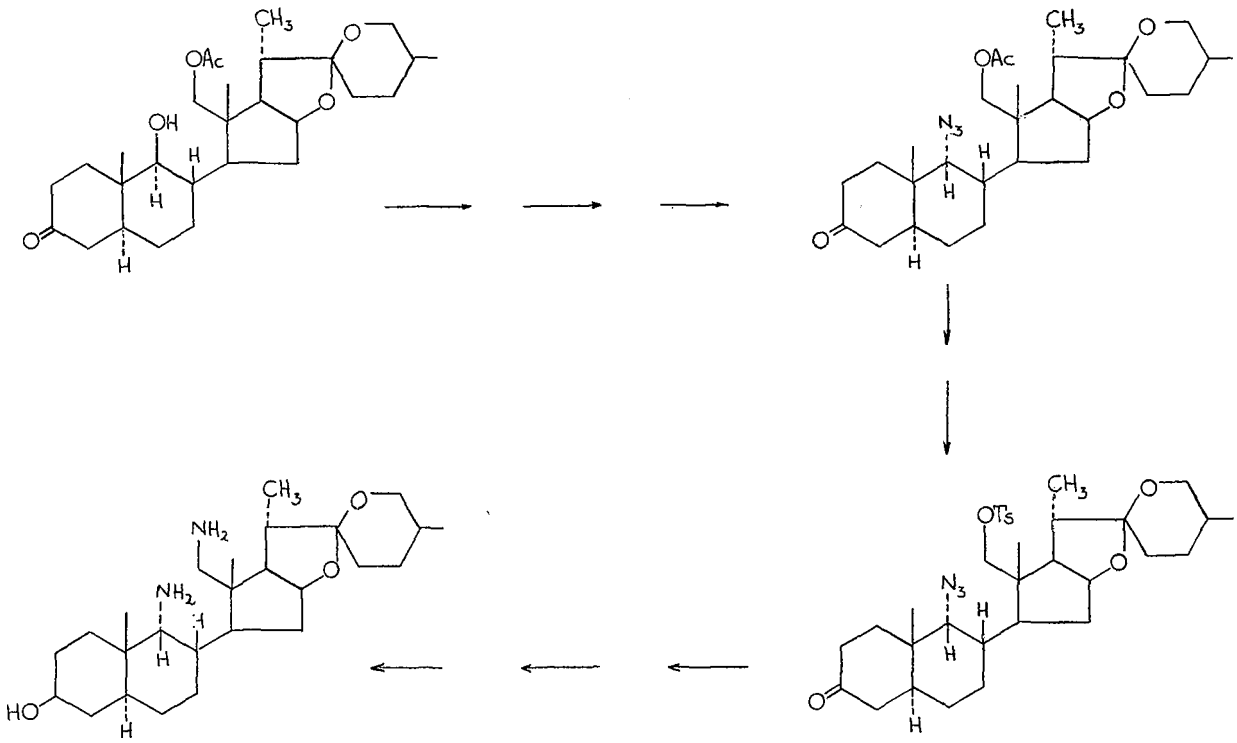


A number of other routes towards saturated 11-aza steroids were investigated without any positive result. Thus, we studied the reductive amination of 9-oxo 9,12-seco 11-nor 12-acids to 8,9-saturated 11-aza steroids; the oximation of such keto acids, employing methods which normally allow the oximation of highly hindered ketones (the expected oxime was to be reduced to an amine, for cyclization to a saturated lactam); the replacement of the oxygen atom of a (12→9)-lactone of a 9β-hydroxy 11-nor 9,12-seco 12-acid by nitrogen; and a number of other approaches — all of no avail.

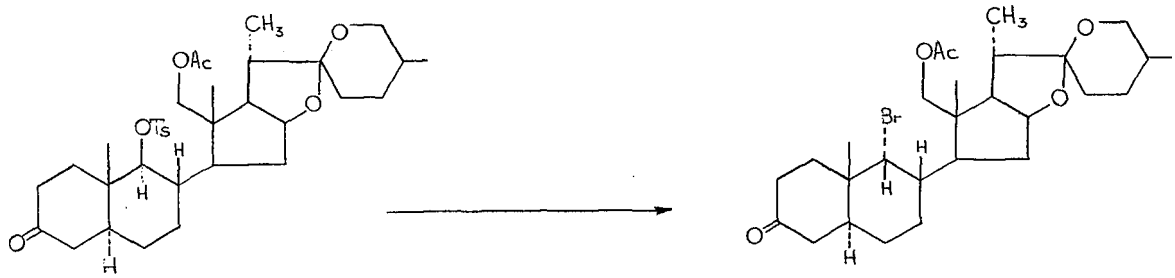
Finally, we undertook leading experiments towards the synthesis of 11-aza steroids saturated in positions 8 and 9 and towards the synthesis of their 9-epimers by a method, never used for the synthesis of similar systems, in which the desired products were to be obtained by reductive cyclizations of 9-azido 12-tosylates or by pyrolysis of 9,12-diamines of the 11-nor 9,12-seco series:



We have thus succeeded in synthesizing 9α-azido-12-tosyloxy-3-oxo-9,12-seco 11-nor-5α,22β-spirostane and 9α,12-diamino-3β-hydroxy-9,12-seco-11-nor-5α,22β-spirostane, suitable for cyclization to 9-iso 11-aza steroids.



On the other hand, we were able to prepare, in a preliminary experiment, in the amorphous form, 9α-bromo-12-acetoxy-3-oxo-9,12-seco-11-nor-5α,22β-spirostane, which may be regarded suitable for the transformation into 11-aza



steroids with a normal configuration in position 9.

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