THE SYNTHESES AND REACTIONS OF 12-METHYLSTEROIDS

A Thesis

by

R. Nagarajan, M.Sc.

Submitted to the Faculty of Graduate Studies and Research of McGill University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Department of Chemistry,
McGill University,
Montreal, Canada.

July, 1961.

ACKNOWLEDGEMENTS

The author wishes to express deep gratitude and appreciation for the encouraging and inspiring interest shown by his research director, Dr. George Just, in the progress of the investigation. His constructive criticisms and stimulating discussions were of immense value. The author feels that to have worked with Dr. Just is to have experienced the most satisfactory relationships between student and research director.

Grateful acknowledgement is made to:

Dr. J.T. Edward, for the helpful suggestions in formulating the mechanism for the lithium aluminium hydride reduction of 20-ketosteroids.

Dr. C. Sandorfy, Université de Montréal, for taking and interpreting the infrared spectrum using LiF prism,

Dr. C.I. Chappel and Dr. Clara Revesz, Messrs. Ayerst, McKenna and Harrison, Montreal, for carrying out the biological tests,

Miss Pearl Woo, for technical assistance during the summer of 1960,

The Chairman, Chemistry Department, McGill University and the National Research Council for generous financial assistance,

and all my colleagues, for the helpful discussions.

TABLE OF CONTENTS

INTRODUCTION

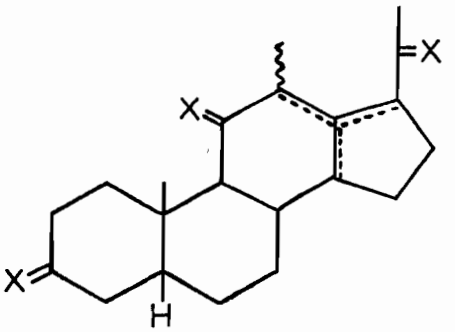
Historical review and object of the investigation.

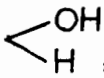
The steroids are a widely occuring group of natural products. They are colourless, crystalline solids and structurally related to the tetracyclic cyclopentanoperhydrophenanthrene. This important class of compounds has been the subject of extensive reviews and those by Fieser and Fieser[1], Shoppee[2] and Klyne[3] are some of the recent ones.

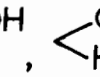
The interest in the chemistry of steroids has remained undiminished since the discovery of cholesterol by Michel Eugène Chevreul in 1815[4]. Early interest in this field was largely confined to elucidation of skeletal structure and the interrelationship of various steroids. The discovery of sex hormones and adrenal cortical hormones during the period 1929-1938 focussed attention on physiological activity and chemical structure. The next phase of research was concerned with the elucidation of the stereochemistry of steroids. The application of Hassel's concept[5] of equatorial and axial bonds[6] to carbocyclic compounds by Barton[7-9] led to the studies in conformational analysis of steroids. Since a steroid has a "rigid structure", it provides an excellent field for studies of the influences of steric and stereoelectronic

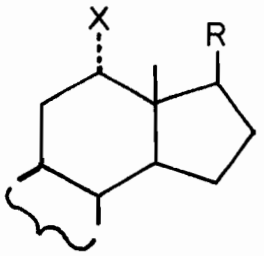
factors in reaction mechanisms[9a,10a] and rates[9b,10a], in infrared[9c,10b,1a] and ultraviolet[9c,10b,1b] spectroscopy, optical rotatory dispersion[11], molecular rotation relationships[1c] and nuclear magnetic resonance techniques[12]. A sizeable amount of research in steroids is directed on the above subjects nowadays.

In view of the current interest in steroid hormone analogues of high biological activity, an investigation to synthesise 3,11,20-trioxygenated-18-nor-12-methylsteroidal compounds with a double bond at 12,13-, 13,14-, or 13,17-positions (1), which would afford a route to 18-nor-12-methyl and 18-nor-12-methyl-13-substituted steroids hormones, was undertaken.

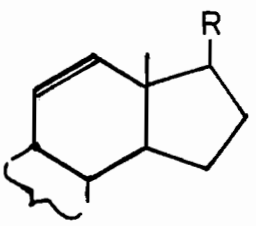


(1) X = O, 

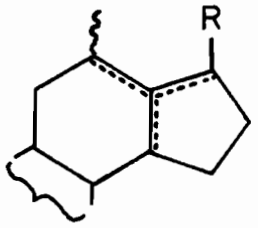
, 



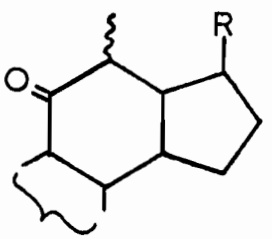
(2) X = Br, OTs, OMs.



(3)



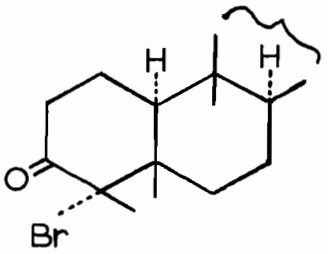
(4)



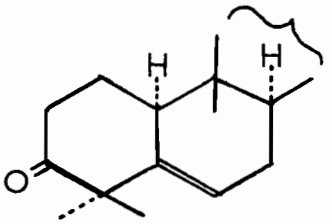
(5)

Solvolysis of 11-ketosteroids with a good 12α- leaving group (11) would be expected to yield the desired 11-keto-18-nor-12-methyl compounds (13), (14), (15) and (16) as products of Wagner-Meerwein type rearrangement. The main competing reaction would be S_N2 type substitution at C_{12} by the solvent molecule. This competing reaction could be suppressed by using a solvent of high ionising power[13a], and the conditions for the Wagner-Meerwein type rearrangement made more favourable by using an electrophilic catalyst[13b]. An alternative route to the structure of the type (1) would be solvolytic rearrangement of steroidal compounds with a good leaving group at C_{12} (2) to 18-nor-12-methyl structure (4) and subsequent introduction of an oxygen function at C_{11} (5). The latter approach did not seem to be promising, since solvolysis of steroids containing a good 12α- leaving group (2) under basic conditions gives the starting material, with minor amounts of Δ^{11}- compound (3)[14]. In the former approach the formation of Δ^{11}- compound is not possible. Furthermore, little work has been done on the behaviour of carbonium ion generated adjacent to a carbonyl group, and solvolysis of 11-keto steroids with a good leaving group at C_{12} (11) would throw light on the chemistry of such systems.

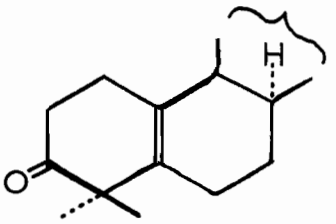
Beaton et al. have reported the conversion of 4-bromo-friedelin (6) to a mixture of alnusenone (7) and alnus-5 (10) en-3-one (8) by solvolysis in acetic acid in the presence of an electrophilic catalyst, silver acetate[15]. A few months ago, Edwards reported the results of a model study



(6)

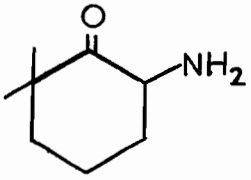


(7)

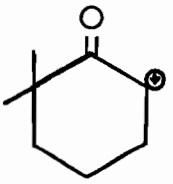


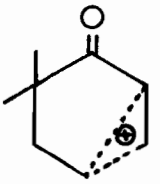
(8)

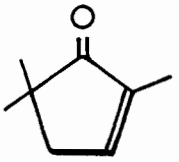
of a carbonium ion generated α to a carbonyl group. Nitrous acid deamination of 2-amino-6,6-dimethylcyclohexanone (9) gave as one of the products the cyclopentenone derivative (10)[16].



(9)





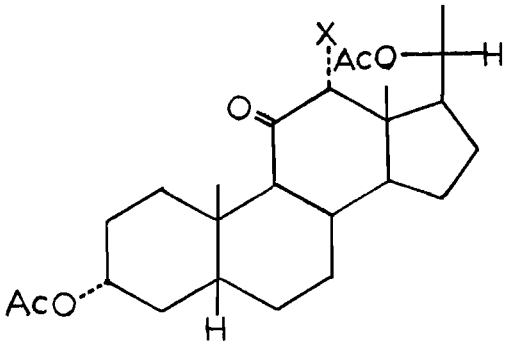


(10)

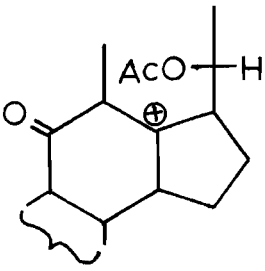
In the proposed investigation of the solvolysis of 11-ketosteroids containing a good 12α- leaving group (11), the Wagner-Meerwein type rearrangement products (13), (14), (15) and (16) would be obtained if the reaction followed a

concerted mechanism. Hirschmann et al. have shown solvolysis under basic conditions of 12α-mesylate (20) affords minor amounts of elimination product (21). Under similar reaction conditions, the 12β-mesylate (22) undergoes a C/D ring contraction-expansion rearrangement (23)·reaction[17]. It is evident from the former reaction that the geometry of the molecule is not favourably disposed for a rearrangement reaction[8a]. On the basis of this evidence, solvolysis of 11-ketosteroids possessing a good 12α- leaving group under forcing reaction conditions might yield C/D ring contraction-expansion type rearrangement products (17), (18) and (19) if the reaction follows a non-concerted mechanism, in addition to the Wagner-Meerwein type rearrangement products (13), (14), (15) and (16) obtained by a concerted mechanism.

Of the various isomeric products mentioned above, (13), (14), (17) and (18) are α,β-unsaturated ketones, and these isomers should be thermodynamically more stable than the non-conjugated ketones (15), (16) and (19). Thus, if the solvolysis reaction product contained appreciable amounts of the non-conjugated ketones (15), (16) and (19), on equilibration under acid conditions the latter would be transformed to the more stable conjugated ketones (13), (14), (17) and (18); a step which would simplify the detection and separation of the reaction products.

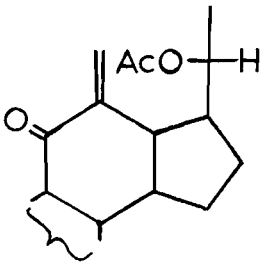


(11) X = Br, OTs

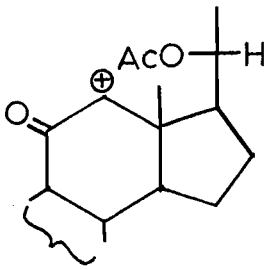


(12a)

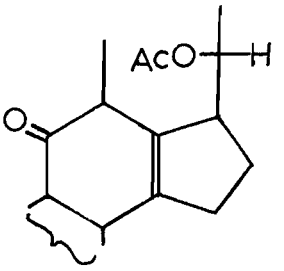
(13)



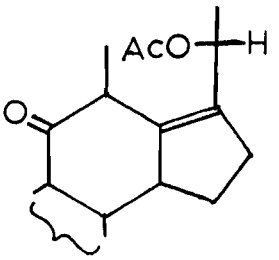
(14)



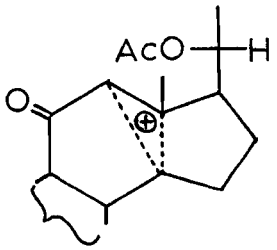
(12)



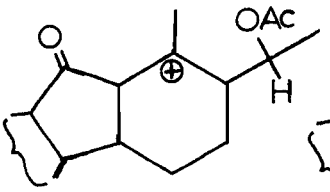
(15)



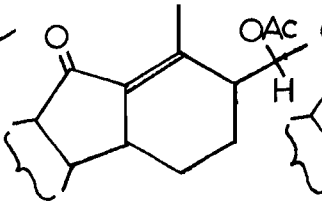
(16)



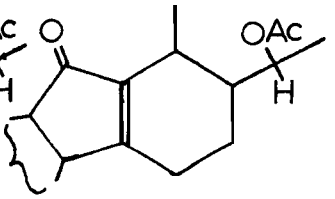
(12b)



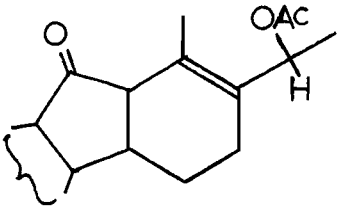
(12c)



(17)

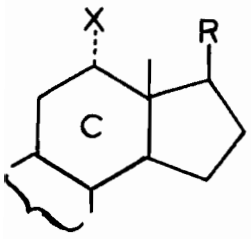


(18)

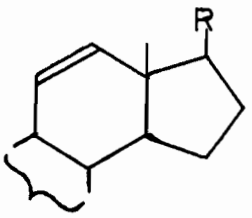


(19)

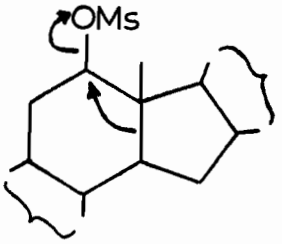
Wagner-Meerwein type methyl shifts of the angular methyl group at C_{13} to C_{17} to give 18-nor-17-methylsteroids[18,19] and C_{14} to afford 18-nor-14-methylsteroids[20] have been reported. But solvolysis of steroids with a good 12α- leaving group



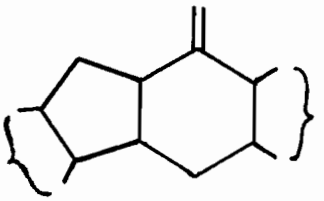
(20) X=OTs,OMs.



(21)



(22)



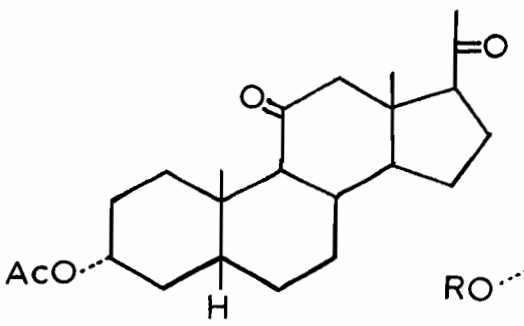
(23)

did not afford 18-nor-12-methylsteroids but only minor amounts of Δ^{11}- compound. It seemed interesting to investigate as to why such a methyl shift of the angular methyl group at C_{13} to C_{12} does not take place, and so the present work was initiated.

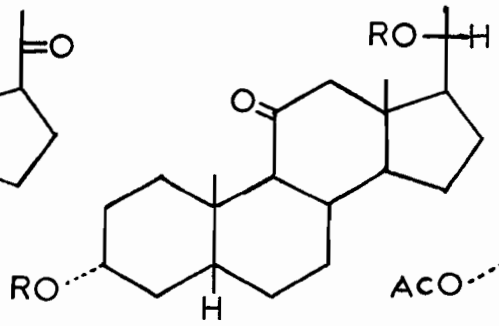
CHAPTER I

Solvolysis of 12α-bromo-3α, 20β-diacetoxypregnan-11-one.

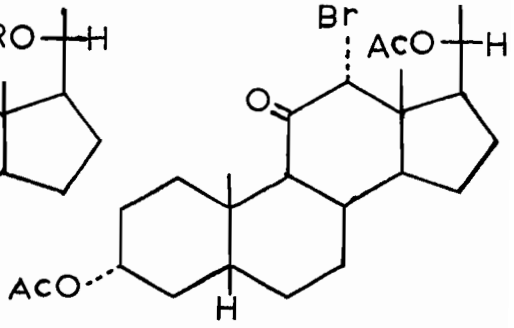
An easily accessible 11-ketosteroid with a good leaving group at C_{12} (11) for our solvolysis experiments was 12α-bromo-3α, 20β-diacetoxypregnan-11-one (26). It was prepared as follows: Partial reduction of the readily available 3α-acetoxypregnan-11, 20-dione (24)* with hydrogen and Adam's catalyst at the 20-position afforded a good yield of the 20β-hydroxy-11-ketone (25), which on acetylation gave the corresponding acetate (25a)[21]. Bromination of this ketone (25a) gave the 12α-bromo-11-ketone (26)[22].



(24)



(25) R=H
(25a) R=Ac



(26)

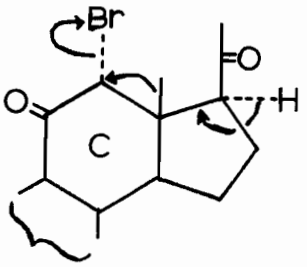
---

* We are thankful to Dr. John M. Chemerda of Merck, Sharp and Dohme Research Laboratories, Rahway, New Jersey, U.S.A. for donating this material.

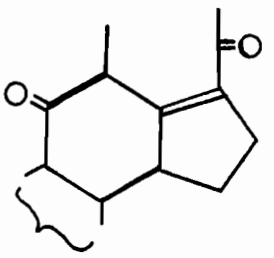
A general exploratory survey of the solvolysis of the bromo ketone (26) under various reaction conditions (see experimental p. 51) showed that the conditions for a Wagner-Meerwein type rearrangement were most favourable when the bromo ketone (26) was heated at reflux temperature with formic acid and silver acetate for 4 days. This result was expected since formic acid, possessing high ionizing power[13a], would suppress the competing S_N2 reaction. The silver acetate being an electrophilic catalyst[13b] would enhance the conditions for a Wagner-Meerwein type rearrangement. The product of solvolysis of bromo ketone (26) even after extensive chromatographic purification on alumina afforded only an oil. The product showed strong absorption bands at 1675 cm^{-1} in the infrared and at 254 mμ in the ultraviolet, indicative of the presence of an α,β-unsaturated ketone function. Of the several isomers which could be obtained from solvolysis of the bromo ketone (26), only (13), (14), (17) and (18) have an α,β-unsaturated ketone function. Since the isomers (17) and (18) are α,β-unsaturated cyclopentenones and should have absorption bands at about 1716 cm^{-1} in the infrared[23a], these structures could be ruled out. The six membered α,β-unsaturated ketones (13) and (14) would have absorption bands in the range 1684-1674 cm^{-1} in the infrared[23b]. However, by application

of Woodward rules for the calculation of λ_{max} for conjugated ketones[24], 18-nor-12-methyl-3α, 20β-dihydroxy-12-pregnene-11-one diacetate (13) should have an absorption band at about 254 mμ, and its $\Delta^{12(12a)}$ isomer (14) at 230 mμ. Thus the exo location of the double bond (14) could be excluded and the reaction product should have the 11-keto-Δ^{12} - structure (13). Other procedures commonly used to effect dehydrohalogenations[25,26] did not give any appreciable amounts of rearranged product.

As a next step, the structure of the bromo ketone (26) was modified in order to make it more amenable to a Wagner-Meerwein type reaction. The presence of a carbonyl function at the 20-position would render the 17α-hydrogen labile. Furthermore, in the bromo ketone (27a), the 12α-bromine, 13β-angular methyl group and 17α-hydrogen are trans axial to one another (17α-hydrogen is quasi-axial), and so the stereochemistry is favourably disposed for a methyl shift from C_{13} to C_{12} to give the $\alpha\beta$-unsaturated ketone (28).

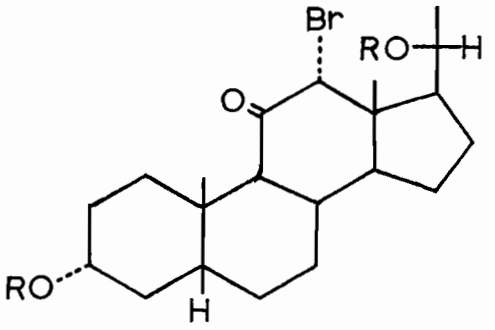


(27a)

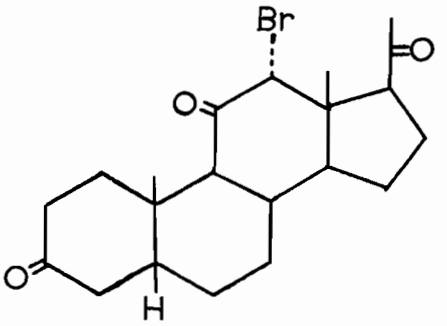


(28)

The desired bromo ketone (27) incorporating the structural features discussed above, was readily prepared by a two step procedure from the previously described bromo ketone (26) as follows: The bromo ketone (26) was hydrolysed with methanol and perchloric acid in nitrogen atmosphere[27] to give the hydroxy ketone (26a), which on oxidation with chromium trioxide gave the bromo trione (27)[28]. Solvolysis



(26) R = $COCH_3$.
(26a) R = H.



(27)

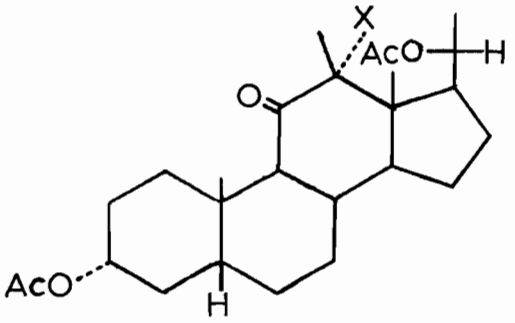
of the bromo trione (27) would be expected to yield the α,β - unsaturated ketone (28). The double bond in α,β-unsaturated ketone (28) may isomerise to the 12,13- or 12,12a- positions, depending upon which location of the double bond is most stable. In all these cases the double bond is in conjugation with the

11-carbonyl function. However, the product of solvolysis of the bromo trione (27) with formic acid and silver acetate did not show any absorption bands in the infrared or ultraviolet, characteristic of α,β-unsaturated ketones. Thus it is evident that the product of solvolysis of bromo trione (27) did not contain any appreciable amounts of rearranged products.

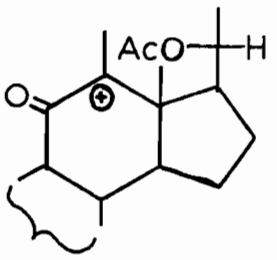
CHAPTER II

The influence of 12-substituents in lithium aluminium hydride reduction of 20-ketones.

Since solvolysis of the 12α-bromo-11-ketone (26) and the 12α-bromo-3,12,20-trione (27) failed to give any appreciable amounts of rearranged products, it seemed logical to undertake solvolysis experiments of 12β-methyl-11-ketones containing a good 12α- leaving group (29) as the next step. The intermediate carbonium ion formed (30) in the latter case would be tertiary, and so it should be more stable.



(29) X= OAc, Br.



(30)

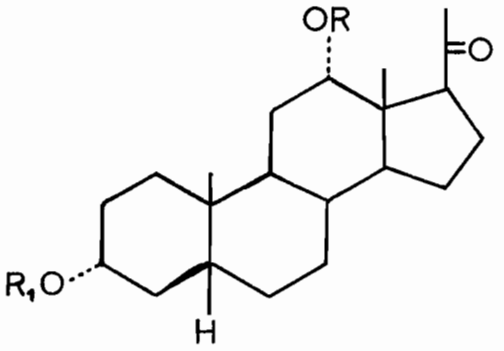
Engel and Huculak have reported the preparation of 3α, 20β-dihydroxypregnane-12-one bis-methyl succinate (36b)[29], from the readily available bile acid derivative,

3α, 12α-diacetoxypregnane-20-one* (31a)[30], through the reaction sequence (31a) → (32) → (32b) → (36b) (see p. 19). A Grignard reaction on the 12-pregnanones (36b) or (36a) would lead to the introduction of a 12-methyl substituent, and this Grignard adduct could be converted by suitable methods (see p. 36) to 12β-methyl-11-ketones containing a good 12α-leaving group (29).

Lithium aluminium hydride reduction of 3α, 12α-diacetoxypregnane-20-one (31a) gave predominantly pregnane-3α, 12α, 20β-triol (32) and a small amount of another material which Engel and Huculak[29] had tentatively formulated as pregnane-3α, 12α, 20α-triol (33). However, when the 20-keto diol (31)[30] was reduced with lithium aluminium hydride, interestingly enough, the major product was not the 20β-triol (32), but its epimer, the 20α-triol (33). Chromium trioxide oxidation of the 20α-triol (33) afforded 3,12,20-pregnanetrione (34)[31] confirming the assignment of structure. Furthermore, in accordance with the findings of Sarett;[32] the difference in the increment of molecular rotation due to the acetylation of the 20β- and the 20α-hydroxy group was of the order of 200°.

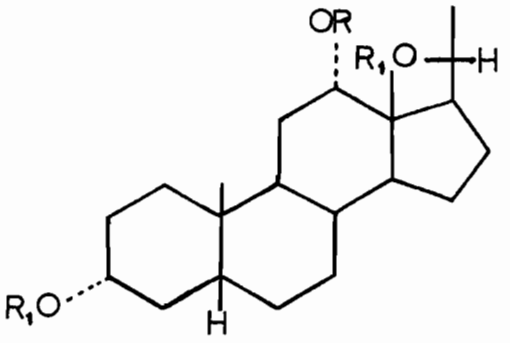
---

* Kindly supplied by Canada Packers Ltd., Toronto 9, Canada.



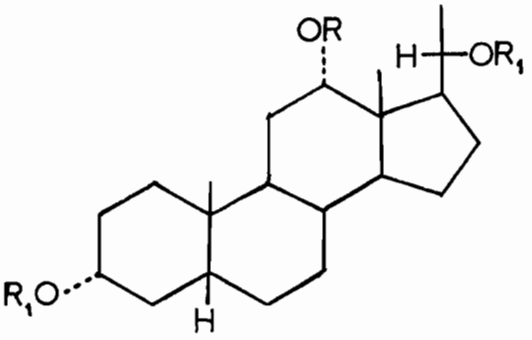
(31) $R=R_1=H$.

(31a) $R=R_1=Ac$.



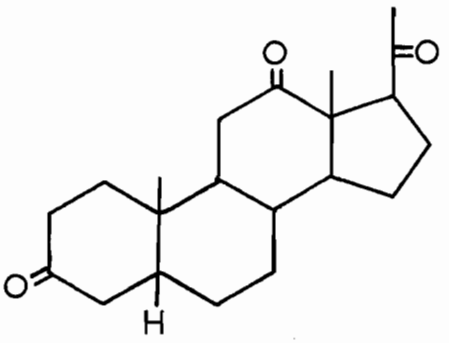
(32) $R=R_1=H$.

(32a) $R=R_1=Ac$.



(33) $R=R_1=H$.

(33a) $R=R_1=Ac$.



(34)

A detailed investigation of lithium aluminium hydride reduction of the 20-keto diacetate (31a) and 20-keto diol (31) revealed that the yields of the epimeric triols (32) and (33), depended mainly on the nature of the functional

group at 12-position, and to some extent on the solvent used in the reaction (see Table I). Thus the 20-keto diacetate (31a) with an acetate group at position 12, gave predominantly the 20β-triol, while the 20-keto diol (31), having a 12-hydroxy function, afforded 20α-triol as the major product. Furthermore, in both cases when tetrahydrofuran was used as the solvent, the yield of the 20β-isomer was greater.

TABLE I

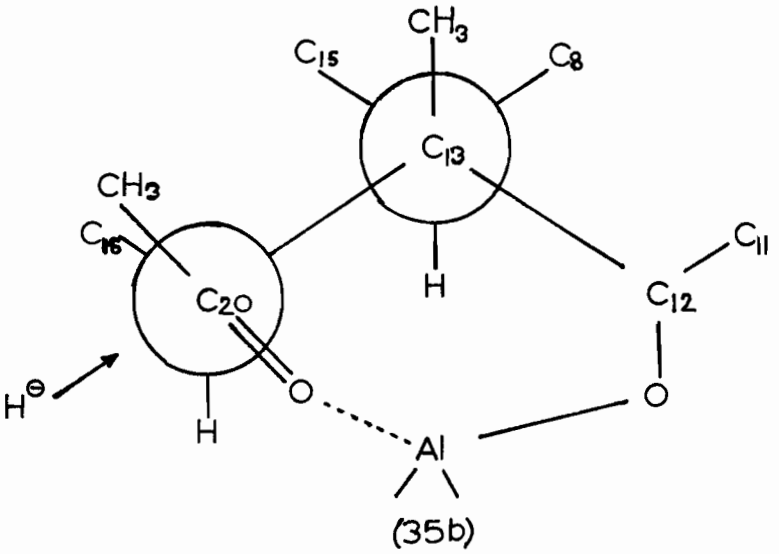
Lithium aluminium hydride reduction of 20-pregnanones

Compound reduced	Solvent used	Yield of 20α-triol(33) in %	Yield of 20β-triol(32) in %
1. Diol (31)	Tetrahydrofuran	58.5	27.0
2. Diol (31)	Diethyl ether	65.8	10.2
3. Diacetate (31a)	Tetrahydrofuran	9.2	69.7*
4. Diacetate (31a)	Tetrahydrofuran	5.8	81.0[29]
5. Diacetate (31a)	Diethyl ether	37	46.8

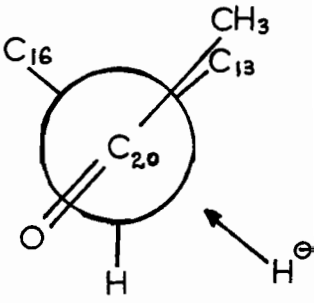
The reduction of 20-keto diacetate (31a) to the 20β-triol (32) as the major product is in accordance with the Cram's rule of steric control of asymmetric induction[33] (35a). The reduction of the 20-keto diol (31) to predominantly the 20α- triol

* This work was done by Miss Pearl Woo and her help appreciated. No attempt was made to obtain the maximum yield of 20β-triol (32).

(33), can be explained if one assumes the formation of a 7-membered ring in the transition state, and subsequently the attack of a hydride ion on the carbonyl group from the



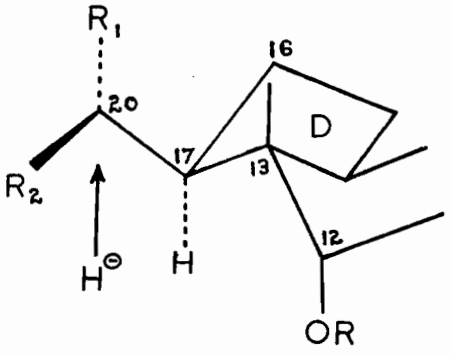
(35b)



(35a)

(35a) R_1=O, R_2=CH_3

(35b) R_2=O, R_1=CH_3



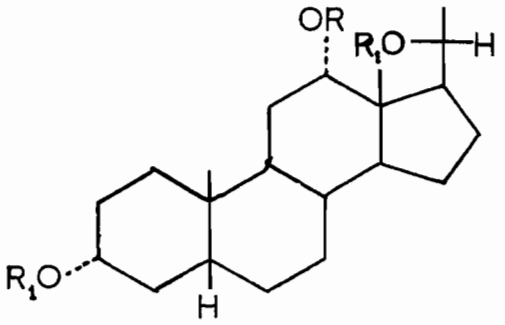
least hindered side (35b). The Meerwein-Ponndorf reduction of dehydrochloroamphenicol and its O-acetate to threo- and erythro-chloroamphenicol respectively, has been explained by Sicher et al. by a similar cyclic mechanism[34].

The coordination of aluminium hydride alcoholate by the carbonyl group competes with solvation[35], either by diethyl ether or tetrahydrofuran, according to the nature of the solvent used in the lithium aluminium hydride reduction. As tetrahydrofuran is more basic than ether[36], one would expect less coordination of the 20-carbonyl oxygen with aluminium hydride alcoholate and hence more of 20β-triol (32) would be formed when the latter is used as the solvent in the reduction reaction. This is in agreement with the results obtained (see Table I, columns 1 and 2).

The solvent effect in the reduction of 20-keto diacetate (31a) could be explained in a similar fashion, provided the 20-carbonyl function is reduced at a similar rate as the 12-acetate function. There is some justification in making such an assumption, for the hindered nature of the 20-carbonyl group[37] has been proved by preferential reductions of steroidal ketones with sodium borohydride. Thus, the selective reduction at C_3 of pregnane-3,20-diones has been reported[38].

The 12-keto disuccinate (36b) described by Engel and Huculak[29], gave on alkaline hydrolysis the hydroxy ketone

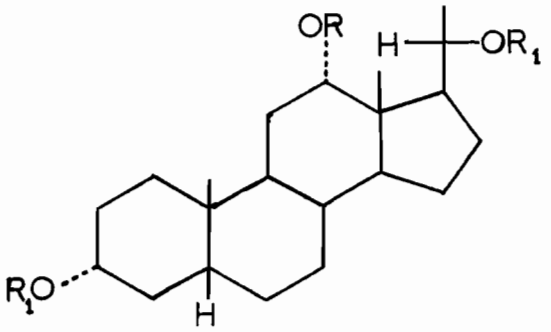
(36), which on acetylation afforded the 12-keto diacetate (36a). Since a large quantity of 20∝-triol (33) was available from



(32) $R = R_1 = H$

(32a) $R = R_1 = COCH_3$

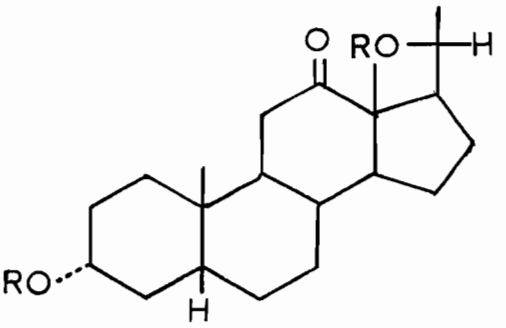
(32b) $R = H, R_1 = CO(CH_2)_2COOCH_3$



(33) $R = R_1 = H$

(33a) $R = R_1 = COCH_3$

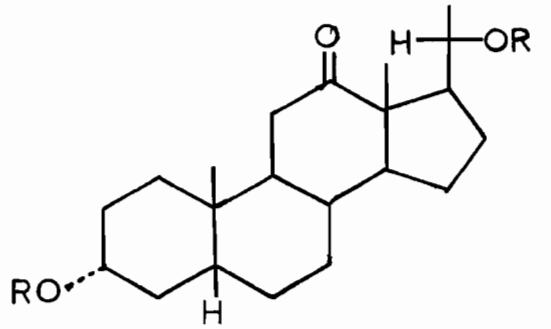
(33b) $R = H, R_1 = CO(CH_2)_2COOCH_3$



(36) R = H

(36a) $R = COCH_3$

(36b) $R = CO(CH_2)_2COOCH_3$



(37) R = H

(37a) $R = COCH_3$

(37b) $R = CO(CH_2)_2COOCH_3$

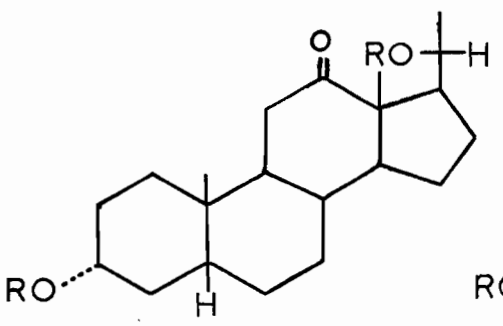
the lithium aluminium hydride reduction of 20-keto diol (31), the corresponding reaction sequence (33) ⟶ (33b) ⟶ (37b) ⟶ (37) ⟶ (37a) was carried out. The preparation of the 12-keto diols (36) and (37) and their corresponding diacetates (36a) and (37a) in the 20β- and 20α- series was undertaken, because their molecular rotation measurements enabled to confirm the assignment of configuration at C_{20} of the epimeric triols (32) and (33).

CHAPTER III

The stereochemistry of the addition of Grignard reagents to 12-ketosteroids.

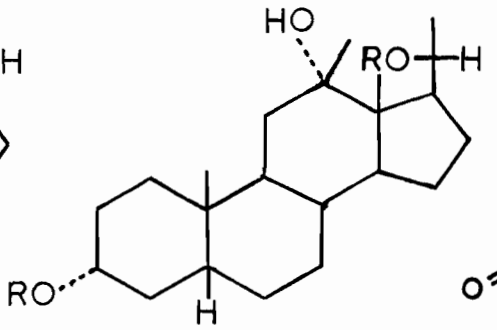
A. Syntheses of 12-methylsteroids:

As pointed out in Chapter II, the 12-keto disuccinate (36b) seemed to be a suitable compound for the introduction of a methyl group at the 12-position. But even after prolonged treatment of the 12-keto disuccinate with methyl magnesium iodide the reaction product contained sizeable amounts of starting material. However, the corresponding 12-keto diacetate (36a) was converted in 73% yield to the desired 12-methylpregnane-3α,12α,20β-triol (38), when reacted with methyl magnesium iodide. Reaction of the keto diacetate



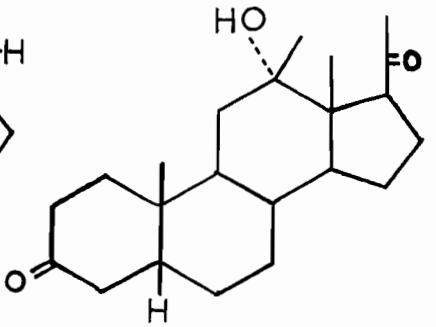
(36a) R = $COCH_3$

(36b) R = $CO(CH_2)_2COOCH_3$



(38) R = H

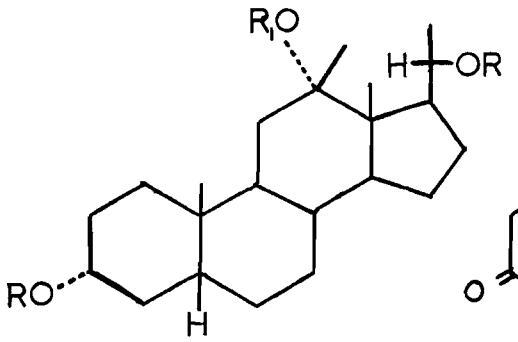
(38a) R = $COCH_3$



(39)

(36a) with methyl lithium gave only a 45% yield of the triol (38). The triol (38) formed a diacetate (38a) and on oxidation with chromium trioxide gave 12β-methyl-12α-hydroxypregnane-3,20-dione (39), thus establishing the tertiary nature of the 12-hydroxy group.

From the exploratory reactions carried out for the introduction of a methyl group at C_{12} in the 20β- series, it seemed that the most favourable condition for the formation of the triol (38) was when the 12-keto diacetate (36a) was reacted with methyl magnesium iodide. Hence, the corresponding 12-keto diacetate (37a) of the 20α- series was treated with excess of methyl magnesium iodide. The product was acetylated and chromatographic separation of the epimeric triols as their diacetates (40b) and (41a) proved unsuccessful. The epimeric diacetate mixture on alkaline hydrolysis and fractional crystallisation afforded the epimeric 12-methyl-12-hydroxy triols (40) and (41). The mono-, di-, and triacetates (40a-c) in the 12β-methyl-12α-hydroxy series, and the epimeric 12α-methylpregnane-3α, 12β, 20α-triol 3, 20-diacetate (41a) were prepared and interrelated (see experimental p.72-4). Since the separation of the epimeric triols (40) and (41) by crystallisation was tedious and incomplete, the mother liquors of the crystallisation of the Grignard reaction product

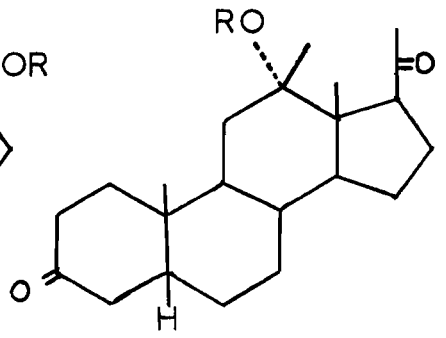


(40) R=R$_1$=H

(40a) R=R$_1$=COCH$_3$

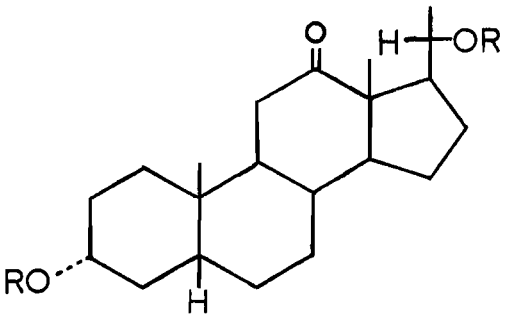
(40b) R=COCH$_3$, R$_1$=H

(40c) R=H, R$_1$=COCH$_3$

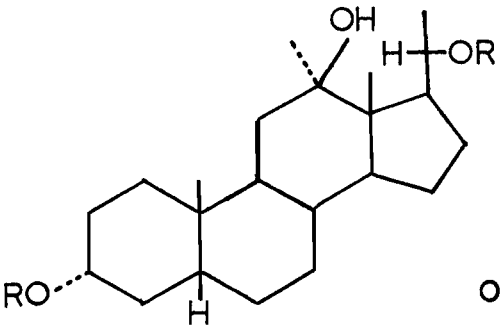


(39) R=H

(39a) R=COCH$_3$

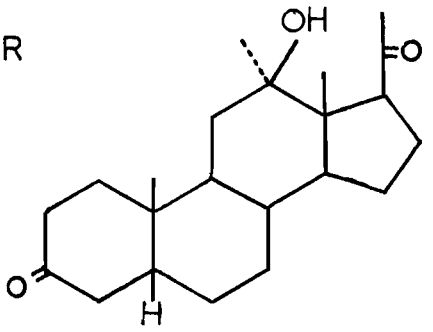


(37a) R=COCH$_3$



(41) R=H

(41a) R=COCH$_3$

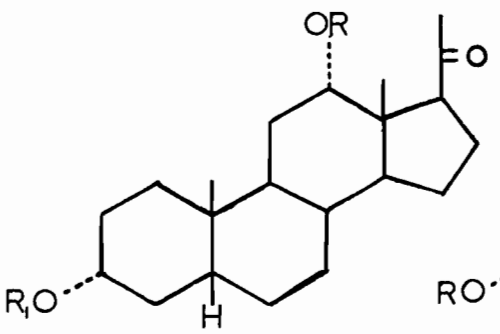


(42)

containing the epimeric triols (40) and (41) were oxidised with chromium trioxide. The oxidation product was chromatographed

on alumina, and 12β-methyl-12α-hydroxypregnane-3,20-dione (39) and its 12α-methyl-12β-hydroxy epimer (42) were obtained. The hydroxy ketone (39) was identical with 12β-methyl-12α-hydroxypregnane-3,20-dione, obtained previously by oxidation of the triol (38), which was the only product of the corresponding Grignard reaction in the 20β- series. The yields of the Grignard adducts (40) and (41) were 61% and 25% respectively.

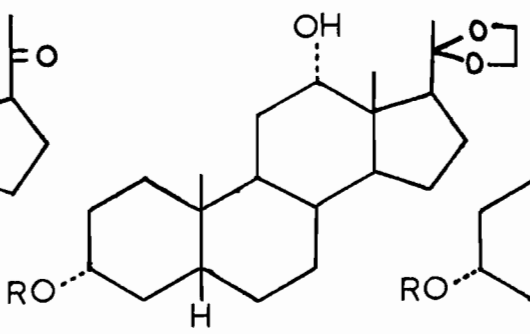
An alternative route to the synthesis of 12-methylsteroids was also investigated. Partial succinylation of 3α,12α-dihydroxypregnane-20-one (31) at the 3-position[29,39], and methylation with diazomethane afforded the methyl succinate (31b). Ketalisation of the methyl succinate (31b) at the 20-position, followed by oxidation of the ketal (43) with chromium trioxide in pyridine afforded 3α-hydroxy-12,20-pregnandione 20-ethylene ketal methyl succinate (44). This was a suitable intermediate for the introduction of a methyl group at C_{12}, and accordingly the 12-ketone (44) was reacted with methyl magnesium iodide. The Grignard reaction product was treated with p-toluene sulphonic acid and acetone, and then with methanolic potassium hydroxide to hydrolyse the ketal and methyl succinate groups respectively. The hydrolysed product was oxidised with chromium trioxide and chromatographic separation on alumina



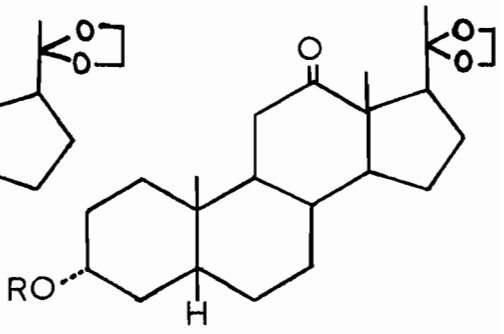
(31) R=R₁=H

(31a) R=R₁=COCH₃

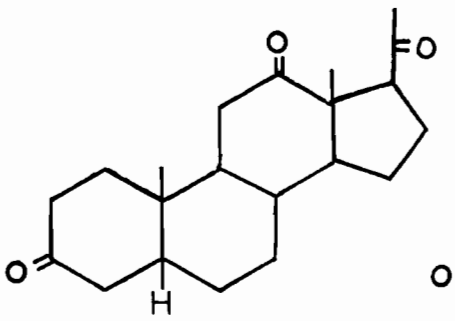
(31b) R=H, R₁=CO(CH₂)₂COOCH₃



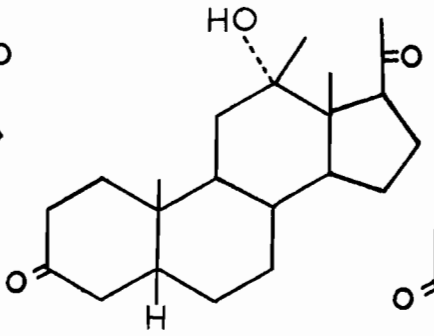
(43) R=CO(CH₂)₂COOCH₃



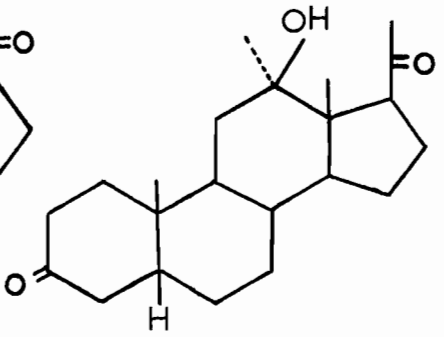
(44) R=CO(CH₂)₂COOCH₃



(34)



(39)



(42)

afforded the epimeric 12-methyl-12-hydroxypregnane-3,20-diones (39) and (42). In the above reaction sequence the yields in the ketalisation and Grignard reaction were not satisfactory.

B. Assignment of configuration at C_{12} of the epimeric tertiary alcohols:

The infrared spectrum of 12β-methyl-12α-hydroxypregnane-3,20-dione (39) showed absorption bands at 3680 cm^{-1} (free hydroxy group) and 1713 cm^{-1} (3,20-dione), while its 12α-methyl-12β-hydroxy epimer (42) showed absorption bands at 3450 cm^{-1} (LiF prism, change in concentration did not shift the frequency of absorption, intramolecular bonded hydroxyl), 1716 cm^{-1} (3-ketone) and 1695 cm^{-1} (hydrogen bonded 20-ketone)* (see infrared spectra). The presence of an intramolecular hydrogen bond between a hydroxy group and a carbonyl group in one epimer is evident. Inspection of models indicated that only a 12β-hydroxyl group could form an internal hydrogen bond with the 20-carbonyl function (minimal distance $\sim 2\text{Å}$).** This spectroscopic data made possible an unambigous assignment of configuration for the epimeric hydroxy ketones (39) and (42) and proved that the attack of methyl magnesium iodide on 12-pregnanones proceeded mainly from the β- side of the steroid molecule, contrary in this case, to the well known "rule of rear-attack" in steroids[40,41].

---

* We wish to thank Dr. C. Sandorfy, Université de Montréal for taking the infrared spectrum using LiF prism. The spectra were taken in carbon tetrachloride solution.

** Wall and Serota[42] have recently reported a similar case of intramolecular hydrogen bond between 12β-hydroxyl and 20-carbonyl functions in 3β-acetoxy-12β-hydroxy-12α-methoxy, 5α,16-pregnene-20-one and 3β-acetoxy-12β-hydroxy-12α-methoxy-5,16-pregnandiene-20-one.

Fig. 1. I.R. spectrum of the hydroxy ketone (42) using LiF prism.

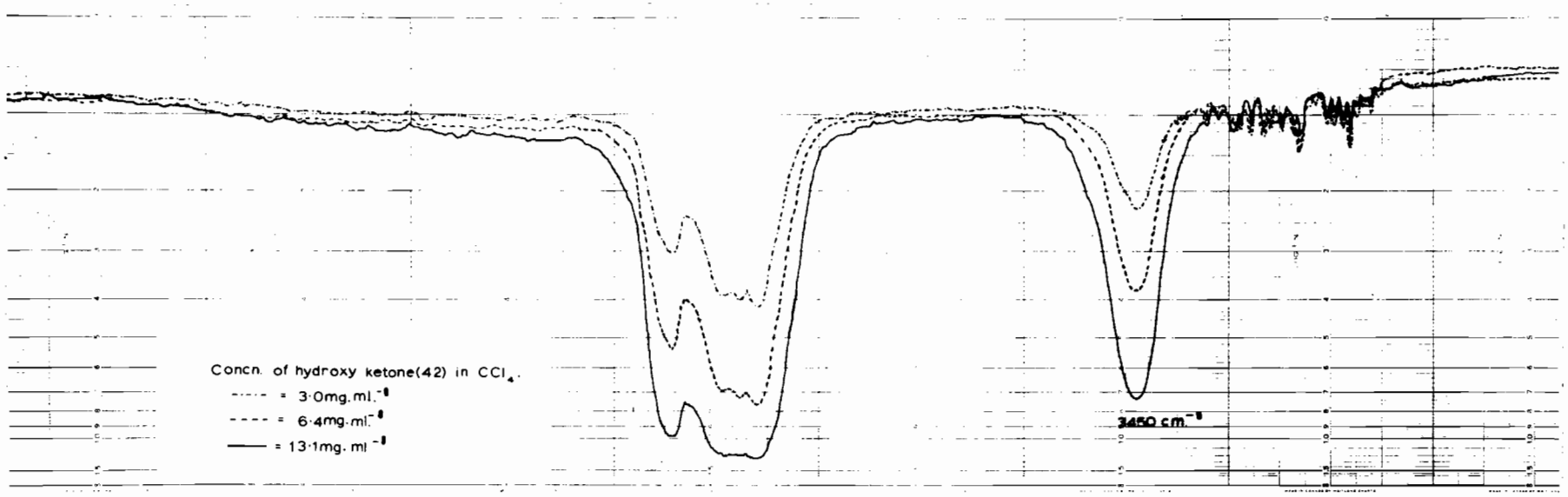
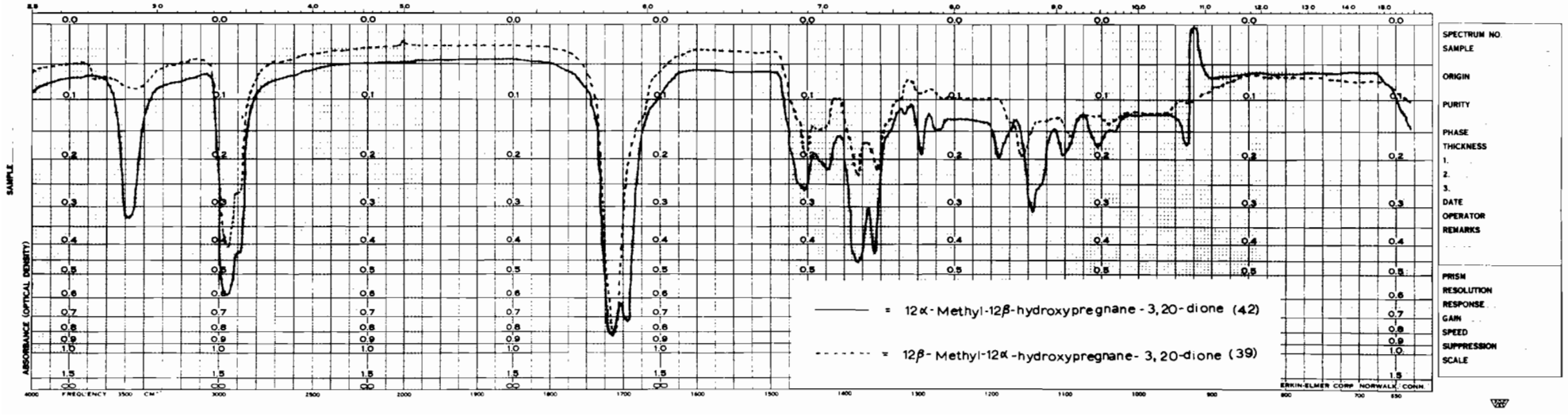
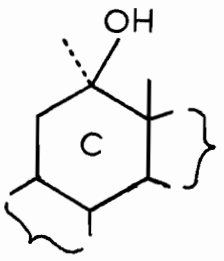


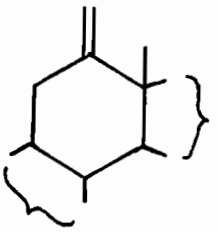
Fig. 2. I.R. spectrum of the epimeric hydroxy ketones (39) and (42).



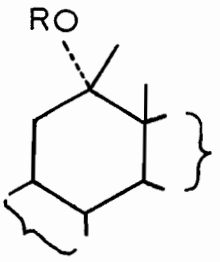
The validity of assignment of configuration at the 12-position was confirmed as follows: The tertiary alcohol (39) on treatment with acetic acid, acetic anhydride and p-toluene sulphonic acid[43] gave a 53% yield of the olefin (45)*. This olefin (45) was also obtained in 53% yield when the epimeric tertiary alcohol (42) was treated with acetic acid, acetic anhydride and p-toluene sulphonic acid. Both these dehydration reactions afforded minor amounts of the 12α-acetate (39a). The infrared spectrum of the olefin (45) showed absorption bands at



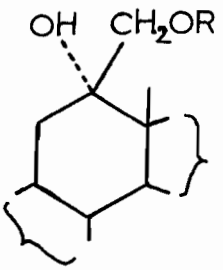
(42)



(45)



(39)R=H
(39a)R=Ac



(46)R=H
(46a)R=Ts

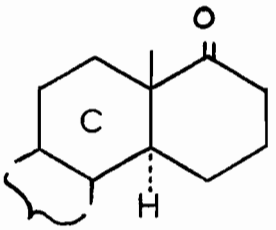
---

* The olefin (45) behaved erratically on crystallisation, probably due to polymorphism (see experimental p. 81).

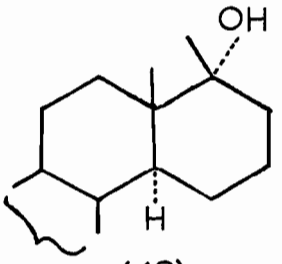
3080 cm^{-1}, 1645 cm^{-1} and 885 cm^{-1}, characteristic for a vinylidene group[23c]. The olefin on treatment with osmium tetroxide gave the diol (46), which when reacted with p-toluene sulphonyl chloride and pyridine gave the tosylate (46a). Lithium aluminium hydride reduction of the tosylate (46a), followed by chromium trioxide oxidation gave the tertiary alcohol (39), identified by its m.p., mixed m.p. and superimposability of infrared spectra. This result is compatible only on the basis of the hypothesis that the nucleophilic attack of the Grignard reagent on a 12-keto group and the electrophilic addition of osmium tetroxide to a 12-methylene group occurs from opposite sides of the steroid molecule. Since the spectroscopic data proved that the attack of methyl magnesium iodide on 12-carbonyl group proceeded mainly from the β-side, the addition of osmium tetroxide to a 12-methylene group should occur from the α- side of the molecule.

Ruzicka et al.[44] have reported the conversion of Δ^5 - 3β-acetoxy-17a-D-homoandrosterone (47) to Δ^5 - 17aβ-methyl-3β, 17aα-D-homoandrostenediol (48) by the action of methyl magnesium bromide. The Grignard adduct (48) was dehydrated to the olefin (50), which on treatment with perbenzoic acid afforded the epoxide (49). Reduction of the epoxide with lithium aluminium hydride gave the original Grignard product (48).

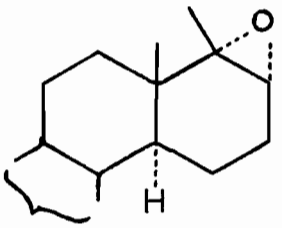
Thus the attack by the Grignard reagent and the peracid must



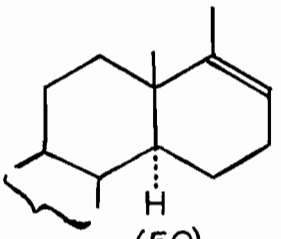
(47)



(48)



(49)



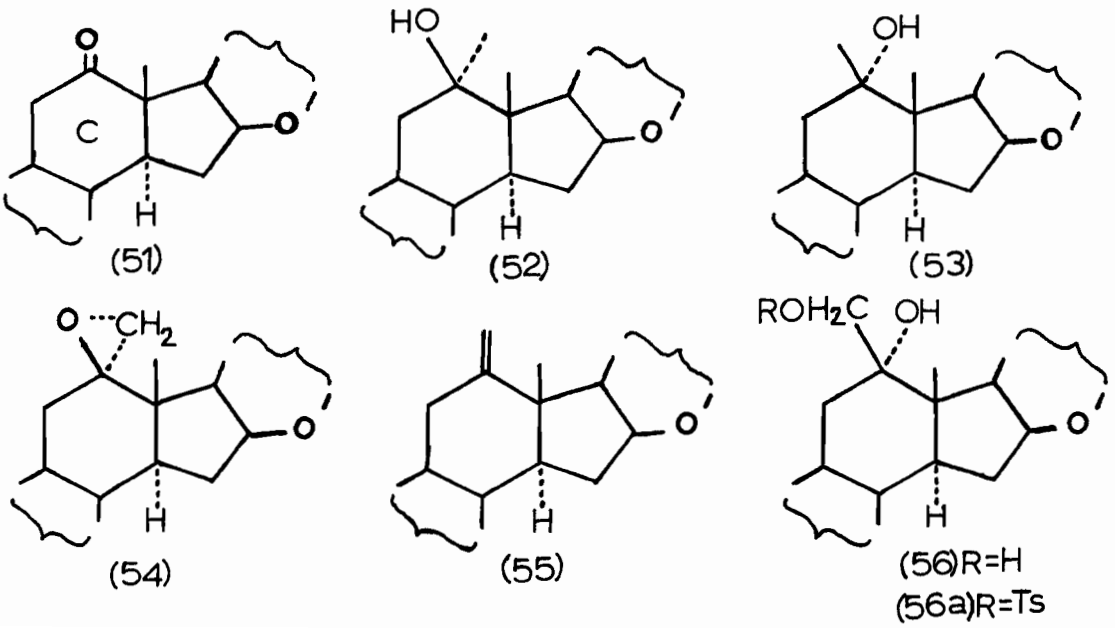
(50)

have proceeded from opposite sides of the steroid molecule. The Grignard adduct (48) was physiologically inactive and the 17aα-methyl-17aβ-hydroxy epimer was expected to show androgenic activity*. Hence Ruzicka and co-workers assumed that the methyl magnesium bromide attacked the carbonyl function from the β- side, and that the peracid attacked the double bond from the α- side of the steroid molecule, and assigned the 17aβ-methyl-17aα-hydroxy structure to the Grignard adduct (48).

---

* The 17aα-methyl-17aβ-hydroxy epimer was later prepared and it exhibited androgenic activity[45], thus confirming the assignment of structure.

Recently, Bladon and McMeekin[46] submitted the tetrahydropyranyl ether of hecogenin (51) to the action of methyl lithium. The tertiary alcohol thus obtained was assigned the 12α-methyl-12β-hydroxy configuration (52). The evidence for the assignment of configuration at the 12-position was as follows: Dehydration of the tertiary alcohol (52) to the olefin (55), followed by epoxidation and reduction of the epoxide (54) with lithium aluminium hydride afforded the original tertiary alcohol (52). Bladon and McMeekin assumed that the attack of methyl lithium on the 12-carbonyl function proceeded from the α- side, and the peracid from the β- side of the double bond in the steroid molecule. Since it is extremely unlikely that the nucleophilic and electrophilic additions in hecogenin derivatives proceed differently from the corresponding addition reactions in the pregnane series, and since Bladon and McMeekin's assignment were arbitary, we suggest that they be reversed.



(51) (52) (53)

(54) (55) (56)R=H (56a)R=Ts

Levine and Wall[47] have also recently reported the reaction of hecogenin acetate (51) with methyl magnesium bromide, to 12α-methyl-12β-hydroxytigogenin (52). Their proof for the assignment of configuration was based on the reaction sequence (51) ⟶ (52) ⟶ (55) ⟶ (56) ⟶ (56a) ⟶ (53). Contrary to the results obtained by Ruzicka et al.[44], Bladon and McMeekin[46] and ourselves, the two products obtained by Grignard reaction and osmium tetroxide addition were not identical, but epimeric. Though the melting points, mixed melting point and optical rotations of the "two epimers" of Levine and Wall seem to indicate that they are identical, NMR data[*] showed that the two compounds are distinctly different. The conflicting results of Levine and Wall and Bladon and McMeekin can be clarified only by further experimental work.

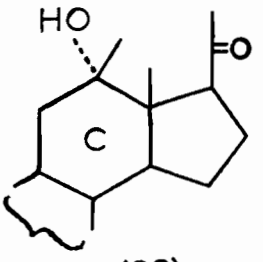
C. Dehydration of 12-methyl-12-hydroxysteroids:

Dehydration of the epimeric hydroxy ketones (39) and (42) with phosphorus oxychloride or thionyl chloride in pyridine were unsuccessful. However, treatment of the epimeric hydroxy ketones (39) and (42) with acetic acid, acetic anhydride and p-toluene sulphonic acid gave, in both cases, a 53% yield of

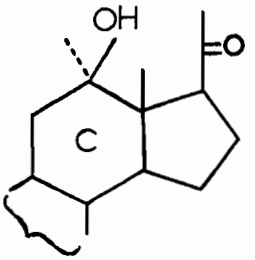
---

[*] Private communication from Dr. S. Levine.

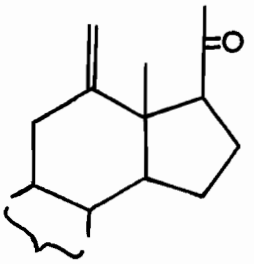
the 12-methylene compound (45) as the only product of



(39)



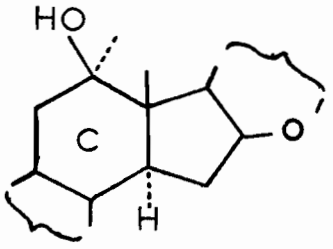
(42)



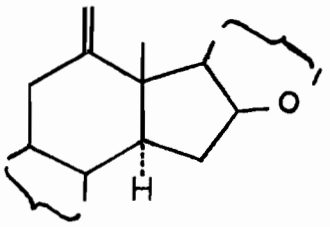
(45)

dehydration. Bladon and McMeekin[46] have reported that dehydration of 12-methyl-12-hydroxytitogenin acetate (52) with phosphorus oxychloride or thionyl chloride in pyridine were unsuccessful. However, on treatment with ethanol and hydrochloric acid they obtained minor amounts of the 12-methylene compound (55). Levine and Wall[47] have successfully dehydrated the tertiary alcohol (52) to a mixture of the isomeric exo and endo olefins (55) and (57) with thionyl chloride and pyridine. The yields of

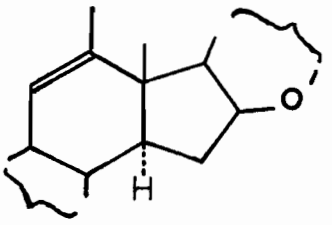
the exo (55) and endo (57) were 20% and 11% respectively. With



(52)



(55)

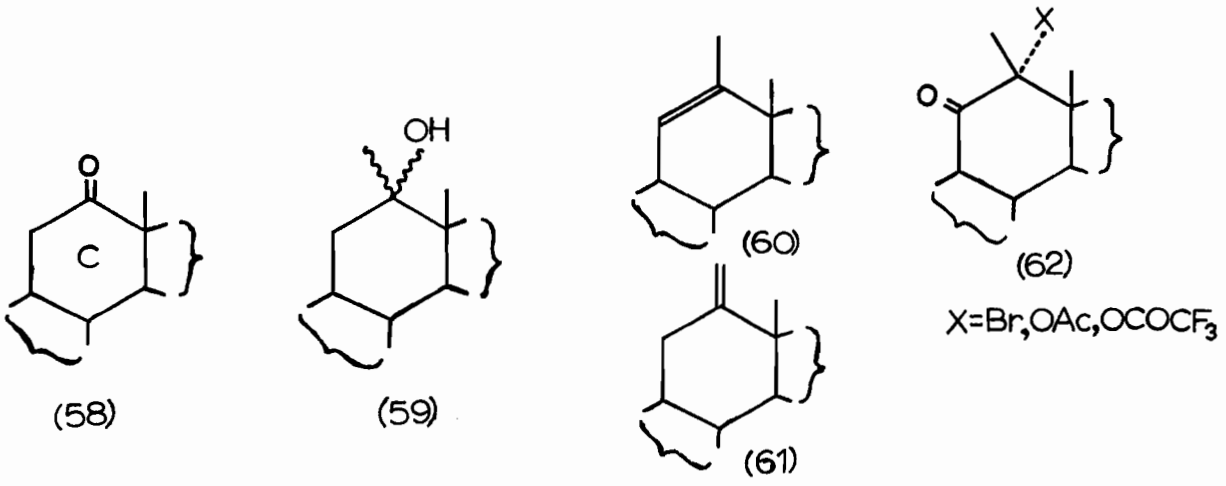


(57)

a view to determine which of these isomeric olefins would predominate under acid equilibrating conditions, the above authors treated the exo (55) and endo (57) olefins, independantly, with methanol and hydrogen chloride, but the results were inconclusive. The fact that only the exo olefins (45) and (55) were obtained by dehydration under acid conditions of the tertiary alcohols (39) and (42) of the pregnane series and (52) of the sapogenin series respectively, shows that probably the exo location of the double bond is stable. The heat of hydrogenation[48] and spectroscopic data[49] reveals the low stability of the 11,12-double bond, but the corresponding data for the isomeric 12, 12a- double bond is lacking. It is of interest to note that dehydration of 11α-methyl-11β-hydroxysteroids have been reported to give a mixture of 11-methylene- and $\Delta^{9(11)}$ - compounds, and equilibration experiments showed that

the exo location of the double bond is favoured[50], though it has been established that 1-alkylcyclohexenes (endo) are thermodynamically more stable than alkylidenecyclohexanes (exo)[51]. On the basis of the above considerations, it could be tentatively concluded that the exo location of the double bond at 12-position is more stable.

It was our intention to introduce the methyl group at the 12-position by reaction of 12-pregnanones (58) with methyl Grignard reagent. It was further proposed to dehydrate the resulting Grignard adduct (59) to the endo (60) and exo (61) olefins, and to convert the endo olefin (60) to 12β-methyl-11-ketones with a good 12α- leaving group (62) for solvolytic

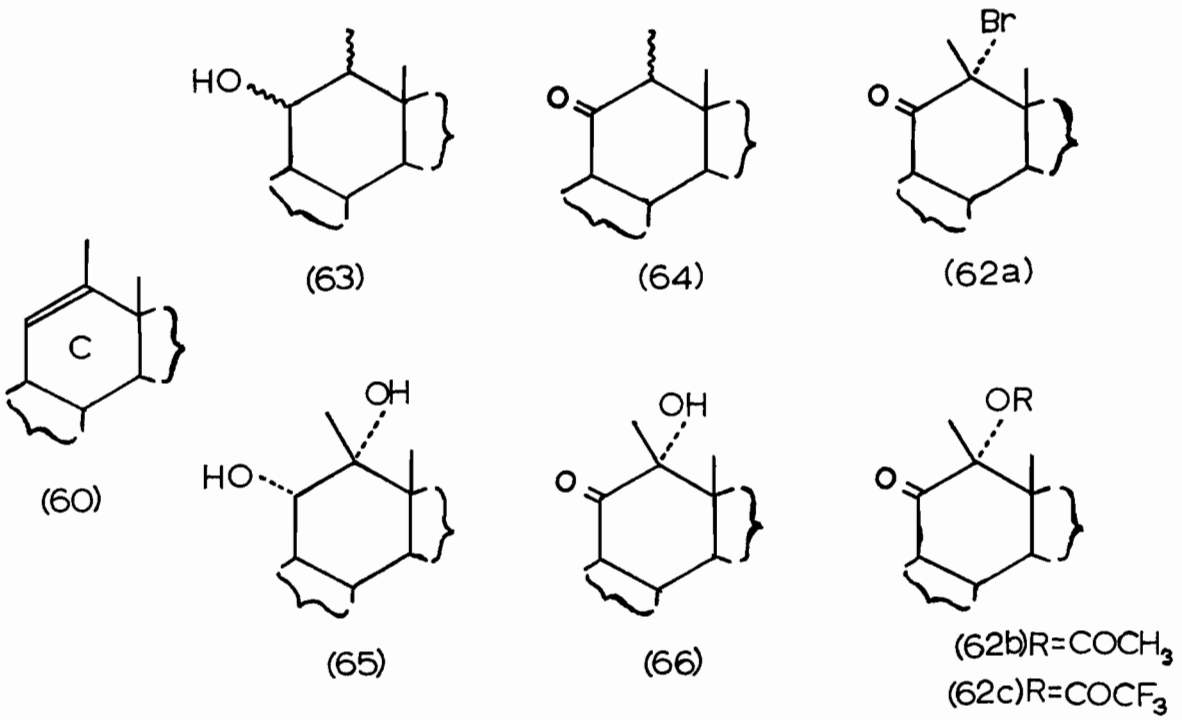


(58) (59) (60) (61) (62)

experiments (see p. 13) by one of the following methods:
(a) Hydration of the double bond of the endo olefin (60) in an anti-Markownikoff fashion[52,53] would give the 11-hydroxy-12-methyl compound (63), which on oxidation with chromium trioxide would afford the 11-keto-12-

methyl compound (64). Bromination at 12-position would yield the 11-keto-12β-methyl-12α-bromo compound (62a).

(b) Alternatively, the endo olefin (60) on treatment with



osmium tetroxide[47] would afford the diol (65). Chromium trioxide oxidation of the diol (65) would yield the hydroxy ketone (66). This hydroxy ketone (66) on treatment with acetic acid, acetic anhydride and p-toluene sulphonic acid[43] would afford the acetate (62b), and with trifluoroacetic anhydride and pyridine[54] the trifluoroacetate (62c). However, we were unable to proceed with this part of our project, since dehydration of the epimeric tertiary alcohols (39) and (42) afforded only the exo olefin (45) and not the desired endo olefin (60).

CHAPTER IV

The stereochemistry of the addition of organo-metallic complexes to steroidal ketones.

The addition of methyl magnesium iodide to 12-pregnanones contrary to the "rule of rear attack"[40,41], led to the survey of reactions of methyl magnesium halide or methyl lithium with steroidal ketones. Such a study revealed the remarkable fact, that in all cases the major product is the axial alcohol. In the case of 6-[55-58] and 11-[50,59-61] ketones the product obtained is the expected β-axial isomer, but the 3-[62,63], 12- and 17a-[44] ketones would be expected to give the β-equatorial epimer according to the "rule of rear attack". Furthermore, since the analogy between the addition reactions of Grignard reagent and lithium aluminium hydride to ketones has been well authenticated[64], a comparison of the results obtained in these two reactions for steroidal ketones seemed appropriate.

Barton summarised the results of hydride reduction of steroidal ketones known at that time with the generalisation that hydride reduction affords the equatorial epimer if the ketone is not hindered and the axial epimer if the ketone is

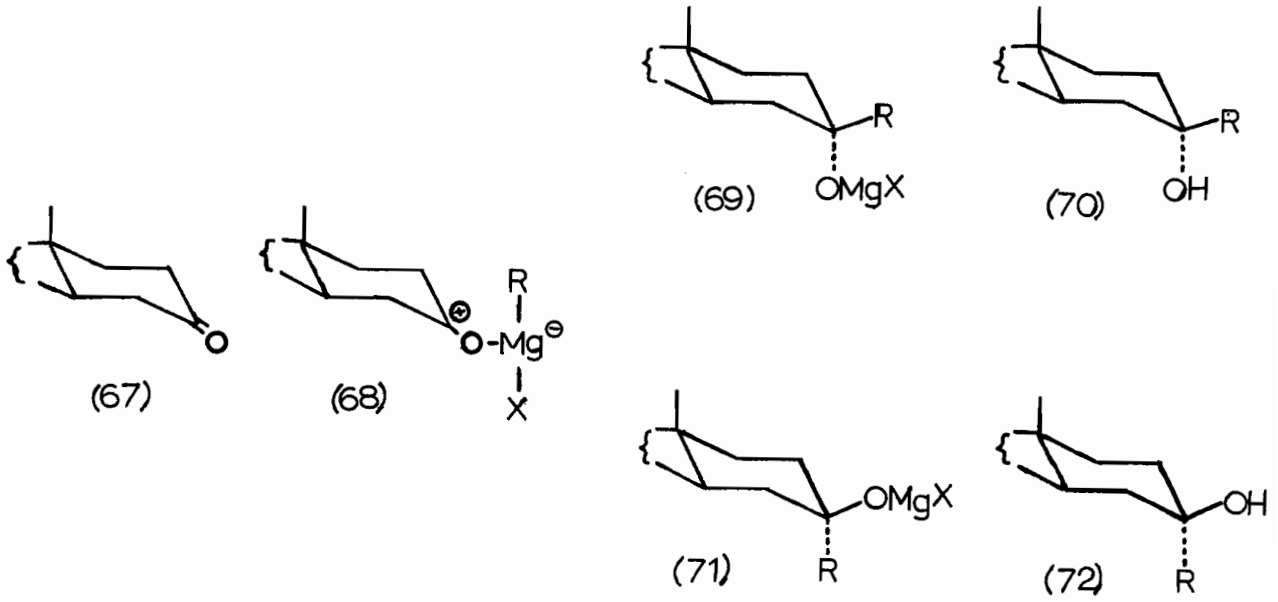
hindered or very hindered[8b]. Dauben et al. suggested that in the hydride reduction of alkylcyclohexanones two effects determine the stereochemistry of alcohol composition: (i) the ease of formation of the initial metallo-organic complex (steric approach control) and (ii) the relative energetics of the formation of the products once the complex is formed (product development control)[65,66]. The greater proportion of the unstable axial alcohol obtained by sodium borohydride reduction in comparison to lithium aluminium hydride reduction was explained by the above authors on the basis of greater size of the borohydride species due to solvation. Wheeler and Huffman have postulated that the difference in the alcohol composition is due to two different mechanism operative in lithium aluminium hydride and sodium borohydride reductions[67].

It has been suggested that the addition of Grignard reagent to ketones involves two molecules of the reagent[68,69]. The first molecule of Grignard reagent* behaves as a Lewis acid[70] and complexes with the carbonyl group to form the Grignard-carbonyl complex (68). The second molecule of RMgX adds on to this complex in a nucleophilic manner. The change in hybridisation

---

* The designation of Grignard reagent as "RMgX" is not entirely satisfactory[71]. Furthermore, $MgBr_2$ has been shown to complex better with carbonyl groups than Grignard reagent[70].

state from sp^2 of the carbonyl function in the ketone (67) to sp^3 of the Grignard adduct (69) or (71) could take place in two ways (a) by equatorial approach or (b) the axial approach



of the nucleophile RMgX. The former mode of addition would give the axial alcohol while the latter would give the equatorial alcohol. The mode of approach will in turn be determined by two factors (a) hindrance to axial approach due to 1,3-diaxial type non-bonded interaction (b) the size of the attacking nucleophile. When the 1,3-diaxial type non-bonded interaction is not considerable, and the size of the attacking nucleophilic

species small, the axial approach seems to be favoured, and consequently the equatorial alcohol is obtained in major yield. This result could be explained because when lithium aluminium hydride or RMgX coordinates with the carbonyl group the oxygen becomes the bulkiest group[33] and so orients in the equatorial position to yield the equatorial alcohol. Alternatively, the axial attack of the nucleophile could be explained on the basis of a mechanism involving stereoelectronic control, similar to that postulated by Corey[72] and Zimmerman[73]. If either the 1,3-diaxial type non-bonded atom interaction is considerable and/or the size of the attacking nucleophile is large, the axial approach should be unfavourable on steric grounds, and depending on the degree of these steric interferences the yield of the axial alcohol would increase.

The steroidal ketones of the 5α- series could be divided into three types A, B and C, according to the degree of hindrance of the nucleophile to axial approach due to 1,3-diaxial type interaction, type A being "unhindered" and type C being "highly hindered" (see Table II). The only example of type A are the 3-ketones. Two α - hydrogens at C_1 and C_5 contribute to the hindrance to axial approach, and it can be considered as "small". Thus, in lithium aluminium hydride reduction of cholestan-3-one,

where the size of the nucleophile is small, 91% of the equatorial alcohol is obtained[74,75], whereas with methyl Grignard reagent, where the size of the nucleophile is large, only 42% of the equatorial alcohol is obtained[62] (Table II). Type B comprises of 1-, 2-, 7-, and 12- steroidal ketones. In this case the hindrance due to 1,3-diaxial type interaction could be considered as "medium". These ketones on reduction with lithium aluminium hydride yield approximately equal quantities of both epimers whereas with methyl Grignard reagent they give about 75% of the axial alcohol. (In the 17a-D-homo steroidal ketone three 1,3-diaxial hydrogens contribute to the hindrance to axial approach and it can be included in type B). Type C includes 4-, 6- and 11-ketones where the hindrance due to 1,3-diaxial type interaction to axial approach could be considered as "large". In this case, both with lithium aluminium hydride and methyl Grignard reagent, irrespective of the size of the nucleophile, the product is the axial alcohol in near quantitative yield.

In the case of 11- and 12-ketones results of lithium aluminium hydride reduction and Grignard reaction of the 5β - series have also been included in this survey (Table II), since it has been shown that the configuration at C_5 has little or no influence on the composition of the product when the 11-ketone is reacted with methyl Grignard reagent[59]. Instances where

TABLE II

Lithium aluminium hydride reduction and Grignard reaction of steroidal ketones

Position of the carbonyl group	Groups contributing to 1,3-diaxial non-bonded interaction		Type	Lithium aluminium hydride reduction			MeMgX or MeLi reaction			References
	Hydrogen	Methyl		Series	Yield of alcohol in %		Series	Yield of alcohol in %		
					axial	equatorial		axial	equatorial	
3	2		A	5α	10	90	5α	56 36	42 11	62, 63 74, 75
7	3		B	5α	50	50				76, 77
12	3*			5α	50	50	5β	75	25	17, 46, 47
2	1	1		5α	52	37				66
1	3			5α	65	35				73
17a	3						Δ^5	76		44
4	2	1	C	5α	90	7				79
6	2	1		5α	94	6	5α	90		55 - 58 79, 80
11	1	2		5β and Δ^5	90	5	5α and 5β	85		59, 59 - 61 81

* 17α-hydrogen is quasi-axial.

groups or double bonds which could conceivably influence the composition of the product due to its close proximity to the carbonyl group have been carefully avoided, since in such cases the new steric or stereoelectronic effects might have to be taken into consideration. Shoppee and Summers have shown that the presence of a double bond could influence the stereochemical course of lithium aluminium hydride reduction of steroidal ketones. Thus, while cholestan-3-one on reduction gives 91% β- and 4% α- alcohols[74,75] and cholest-5-en-3-one yields 90% β- and 5% α- alcohols[74], cholest-4-ene-3-one affords approximately 75% β- and 25% α- alcohols[82]. It is of interest to note that rate of reduction with sodium borohydride differs and the following order of reactivity established[83]: Δ^5-3-keto > 3-keto (A/B trans) > Δ^4-3-keto. Furthermore, while 7-ketocholestanyl acetate gives approximately equal quantities of the epimeric cholestane-3β, 7-diols; 7-ketocholesteryl acetate affords 60% of 7β- and 5% of 7α-alcohols[76].

CHAPTER V

12-substituted progesterones

The search for progesterone analogues of higher potency is particularly important because this hormone is effective only at high doses when compared with other sex hormones.

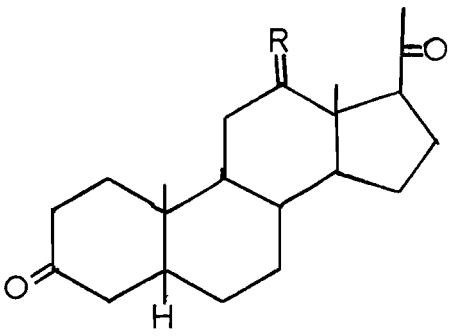
The Δ^4 -3-keto function seems to be essential for progestational activity, since the saturated ketone and the 3-hydroxy derivatives are inactive. The 20-carbonyl function does not seem to be essential for the activity[84]. The discovery that the incorporation of the following additional features: 11, 12- double bond[85], 17α-methyl[86], 17α-acetoxy[87] and 17α-halo[88], 6α-methyl[89,90] and 6α-halo[91] enhances the potency of the hormone marks the various stages of a sustained and patient effort of the search for progesterone analogues of higher activity.

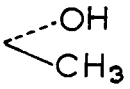
Ehrenstein degraded strophanthidin to crude 19-norprogesterone[92] and reported its high activity[93], but isolated it in the pure form much later[94] and identified as 19-nor-14β,17α-progesterone[95]. In the meantime, the introduction of metal-ammonia

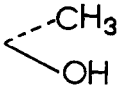
reduction by Birch and coworkers[96] opened up a simple route for the synthesis of 19-nor steroids by reduction of the aromatic ring A in estrogens[97]. Djerassi et al. synthesised 19-norprogesterone[98] and reported its high potency. These researches stirred interest in the physiological properties of 18, 19-bisnorprogesterone, which was synthesised, but it was found to be inactive[99].

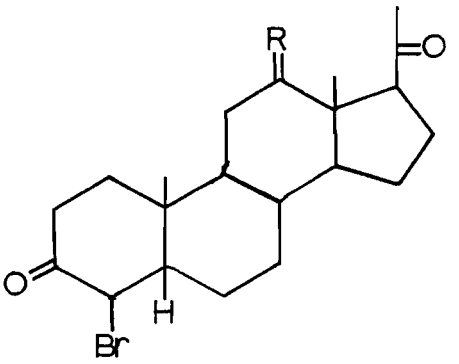
There is considerable current interest in alkyl steroid hormones. This is revealed by the fact that progesterone homologues bearing methyl groups at positions 1 [100], 6 [89,90], 7 [101], 16 [90,102] and 17[86] have been prepared and active work in this field is in progress. In view of this interest some 12-substituted progesterone derivatives were prepared. The hydroxy ketone (39) was brominated at the 4-position. The bromo ketone (73) was dehydrobrominated to the semicarbarzone (74) according to the method of McGuckin and Kendall[103]. The latter on treatment with aqueous acetic acid and pyruvic acid afforded the progesterone analogue (75). Similarly, the epimeric hydroxy ketone (42) was transformed to the progesterone derivative (75b).

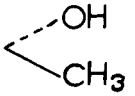
Since the Δ^{11} - dehydroprogesterone exhibits high progestational activity, the effect of the incorporation of 12,12a- double bond on the activity of the parent hormone seemed

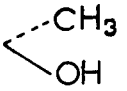


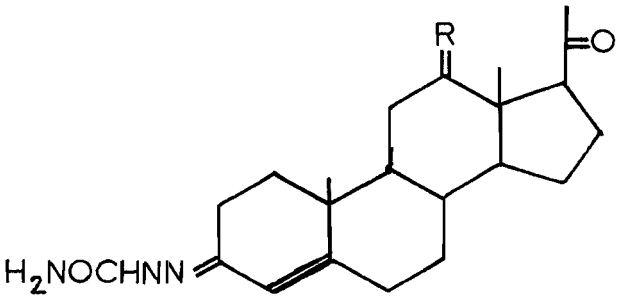
(39) R = 

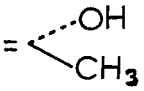
(42) R = 

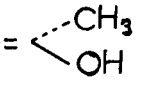


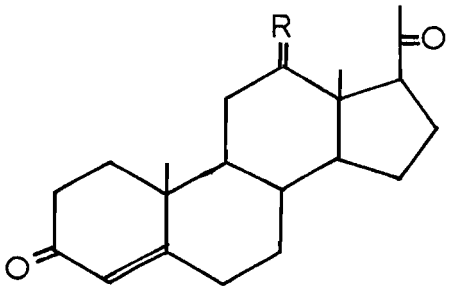
(73) R = 

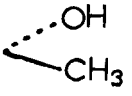
(73a) R = 

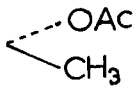


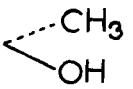
(74) R = 

(74a) R = 



(75) R = 

(75a) R = 

(75b) R = 

(75c) R = $=CH_2$

a worthwhile investigation. Consequently, the progesterone analogue (75) was dehydrated with acetic acid, acetic anhydride and p-toluene sulphonic acid to 12-methylene progesterone (75c). A minor product (75a) was obtained as an oil and it showed infrared absorption bands characteristic of acetate groups. Since the hydroxy ketone (39) on treatment with acetic acid, acetic anhydride and p-toluene sulphonic acid gave the exo olefin (45) and the 12α-acetate (39a), by analogy, the minor product (75a) was tentatively assigned the 12β-methyl-12α-acetoxyprogesterone structure. Preliminary biological tests of all the four progesterone analogues (75),(75a), (75b) and (75c) did not exhibit any notable progestational, androgenic, diuretic, hypotensive or anabolic properties[*].

[*] We wish to thank Dr. C.I. Chappel and Dr. Clara Revesz of Messers. Ayerst, McKenna and Harrison, Montreal for carrying out the biological tests.

EXPERIMENTAL

(a) All melting points were corrected.

(b) Only the best yields obtained were reported.

(c) The commercially available aluminium oxide (Woelm) was used for chromatography.

(d) The infrared spectra were taken using a Perkin-Elmer Model 21 double beam spectrophotometer, equipped with sodium chloride prism.

(e) The ultraviolet spectra were taken using a Beckman Model DK-1 spectrophotometer.

(f) The micro analyses were carried out by Dr. A. Bernhardt, Mülheim, Germany and Dr. C. Daesslé, 5757 Decelles St., Montreal.

(g) Biological tests were carried out by Dr. C.I. Chappel and Dr. Clara Revesz, Messrs. Ayerst, McKenna and Harrison, Ltd., Montreal.

CHAPTER I

12α-Bromo-3α, 20β-Diacetoxypregnan-11-one (26).

A solution of 35 g. of the ketone (24) in acetic acid was selectively reduced with hydrogen using platinum oxide monohydrate (Adam's catalyst) as catalyst. Ether extraction afforded 35.606 g. of crude product, which on crystallisation from ether-hexane afforded 28.3 g. of the 20β-alcohol (25)[21], m.p. 204-5° (yield 80%).

Acetylation of 27.1 g. of the 20β-alcohol with pyridine and acetic anhydride afforded on crystallisation from ether-hexane 29.3 g. of the diacetate (25a)[21], m.p. 159-60° (yield 98%).

A solution of 27.27 g. of the 11-ketone (25a) in 270 ml. of acetic acid, containing 15 drops of 50% (w/v) hydrobromic acid in acetic acid, was brominated in dark, at 50°, in nitrogen atmosphere with 11.45 g. of bromine in 15 ml. of acetic acid for 15 minutes. Crystallisation from methanol afforded 20.47 g. of the bromo ketone (26)[22], m.p. 176-7°. The mother liquors were acetylated with pyridine and acetic anhydride and on crystallisation afforded 5.47 g. of the bromo ketone (26), m.p. 176-7° (yield 80%).

Solvolysis of 12α-Bromo-3α, 20β-Diacetoxypregnan-11-one (26).

A solution of 300 mg. of bromo ketone (26) in 50 ml. of formic acid containing 600 mg. of silver acetate was heated at reflux temperature for 4 days. Ether extraction afforded 235 mg. of a brown semi-crystalline material. Its infrared spectrum showed strong absorption bands at 1722 cm^{-1} and 1167 cm^{-1} due to the formylation[23d] of acetate groups and weak absorption band at 1675 cm^{-1} showing presence of small quantities of α,β - unsaturated ketone.

The formate groups were hydrolysed by heating a solution of the crude product (235 mg.) in 10 ml. of methanol containing 0.5 ml. of 70% perchloric acid, in nitrogen atmosphere, at reflux temperature for 3 hours[27]. The usual extraction procedure afforded 216 mg. of an oil, which showed no absorption bands in the infrared characteristic of formate groups.

Acetylation of the product (216 mg.) afforded 237 mg. of brown oil, which was chromatographed on 9 g. of alumina (4.5% water). The hexane-benzene (4:1, 1:1) eluates (67 mg.) showed absorption bands in the infrared at 1727 cm^{-1}, 1230 cm^{-1} (acetate), 1712 cm^{-1} (11-carbonyl of unreacted material) and 1675 cm^{-1} (α,β -unsaturated ketone). The impure α,β -unsaturated

ketone (67 mg.) was rechromatographed on 3 g. of alumina (4.5% water). The hexane-benzene (4:1, 1:1) eluates (12 mg.) contained about 50% of the α,β-unsaturated ketone (13), which showed infrared absorption bands at 1712 cm^{-1} and 1675 cm^{-1}. The presence of the α,β-unsaturated ketone (13) was confirmed by U.V. spectrum, λ_{max}^{EtOH} 254 mμ (ϵ 6,300).

The bromo ketone (26) was heated at reflux temperature with (a) formic acid and sodium formate for 5 days, (b) acetic acid and silver acetate,[15] for 3 days, (c) acetic acid and silver acetate at 170-180° under pressure for 2 days (d) trichloroacetic acid and sodium acetate for 20 hours (e) dimethylformamide and silver acetate for 6 days. In all these cases, infrared analyses of the reaction products showed absence of α,β-unsaturated ketone.

Dehydrohalogenation reactions.

The familiar dehydrohalogenation reactions did not give α,β-unsaturated ketone. The bromo ketone (26) was subjected to the following reaction conditions (a) dimethylformamide and lithium bromide[25] at reflux temperature for one day (b) dimethylformamide and lithium perchlorate at reflux temperature for 4 days (c) semicarbazide hydrochloride, sodium acetate and acetic acid[26] at reflux temperature for 4 days (d) quinoline and silver acetate at reflux temperature for 4 days.

12α-Bromo-3α, 20β-Dihydroxypregnan-11-one (26a).

A solution of 2 g. of the bromo ketone (26) in 75 ml. of methanol containing 1.3 ml. of 70% perchloric acid was heated in a nitrogen atmosphere at reflux temperature for 3 hours[27]. The usual extraction procedure afforded the bromo ketone (26a), which crystallised from methanol as needles, 1.16 g., m.p. 228-30° (decompn.). Crystallisation of mother liquors afforded 0.10 g., m.p. 226-7° (yield 76%).

A portion of the bromo ketone was recrystallised twice from methanol for analysis, m.p. 229-30° (decompn.), $[\alpha]_D^{27}$ - 17° (c 0.71 in $CHCl_3$. A few drops of ethanol was added to bring the bromo ketone (26a) into solution[1d]).

Calcd. for $C_{21}H_{33}O_3Br$	:	C	60.99	H	8.04	Br 19.33
Found	:	C	60.80	H	8.13	Br 19.34

12α-Bromopregnane-3,11,20-trione (27)[28]

To a solution of 1.17 g. of the bromo ketone (26a) in 60 ml. of acetic acid was added with stirring a solution of 0.625 g. of chromium trioxide in 7 ml. of 90% acetic acid, and left at room temperature for 20 hours. The reaction mixture was worked up in the usual manner, and when the ethereal extract

was evaporated to about 20 ml., 695 mg. of the bromo trione (27)[28] crystallised as plates, m.p. 186-7°. The mother liquors were crystallised from acetone-hexane, 222 mg., m.p. 182-4°, (yield 79%).

The bromo trione (27) was recrystallised from acetone-hexane for analysis, m.p. 186-7°.

Calcd. for $C_{21}H_{29}O_3Br$	:	C	61.60	H	7.14	Br	19.52
Found	:	C	61.49	H	7.12	Br	19.67

Solvolysis of 12α-Bromopregnane-3,11,20-trione (27).

The bromo trione (27) was heated at reflux temperature with formic acid and silver acetate for 3 days. An infrared spectrum analysis showed absence of any α,β-unsaturated ketone.

CHAPTER II

Reduction of 3α, 12α-Diacetoxypregnan-20-one (31a) in ether.

A solution of the diacetate (31a)[30] (30.0 g., 0.0717 mole, m.p. 122-3°) in absolute ether (500 ml.) was added with stirring to a solution of lithium aluminium hydride (33.0 g.) in absolute ether (1500 ml.). The reaction mixture was heated at reflux temperature for one hour and left at room temperature for 18 hours. The excess lithium aluminium hydride was destroyed by adding ethyl acetate (175 ml.) and then 2N sulfuric acid (450 ml.). The solvents were removed by distillation and the reaction mixture extracted with chloroform. The chloroform layer was washed with 5% sodium bicarbonate solution, water, saturated sodium chloride solution, and dried over magnesium sulphate.

Repeated crystallisations from chloroform gave fluffy needles of the 20α-alcohol (33), (8.902 g., 37.0%), m.p. 225-6°, $[\alpha]_D^{29}$ 46° (c 0.59 in $CHCl_3$). The substance was slightly hygroscopic. Crystallisation from acetone gave cubic crystals of 20α-alcohol (33), but there was no change in the melting point.

Calcd. for $C_{21}H_{36}O_3$	:	C 74.98	H 10.78
Found	:	C 74.94	H 10.66

Crystallisation of the mother liquors from acetone gave needles of the 20β-alcohol (32)[29], (11.260 g., 46.8%), m.p. 236-8°, $[\alpha]_D^{29}$ 35° (c 0.78 in $CHCl_3$).

Calcd. for $C_{21}H_{36}O_3$	:	C 74.98	H 10.78
Found	:	C 74.84	H 10.61

Reduction of 3α, 12α-Diacetoxypregnan-20-one(31a) in tetrahydrofuran[29].

A solution of the diacetate (31a) (30.9 g., 0.0739 mole, m.p. 122-3°) in absolute tetrahydrofuran (200 ml.) was reduced with lithium aluminium hydride (36.0 g.) in 1500 ml. of absolute tetrahydrofuran[29]. Chloroform extraction afforded 21.1 g. (85% yield) of the crude product. Separation of the triols, as described above, afforded 2.40 g. of the 20α-triol (33), m.p. 221-4° (9.5% yield), and 17.3 g. of the 20β-triol (32), m.p. 231-3° (69.7% yield).

Reduction of 3α, 12α-Dihydroxypregnan-20-one (31) in ether.

A solution of the diol (31)[30] [1.414 g., 0.00423 mole, m.p. 168-72°; crude product obtained by alkaline hydrolysis of the diacetate (31a)], in absolute ether (200 ml.) was added with stirring to a solution of lithium aluminium hydride (1.5 g.)

in absolute ether (100 ml.). The reaction mixture was worked up as described previously. The yield of 20α-alcohol (33), m.p. 225-6° and of 20β-alcohol (32), m.p. 236-8°, was 65.5% and 10.5% respectively. The alcohols were identified by mixed m.p. and comparison of I.R. spectra.

Reduction of 3α, 12α-Dihydroxypregnan-20-one (31) in tetrahydrofuran.

A solution of the diol (31) [2.635 g., 0.00789 mole, m.p. 168-72°, crude product obtained by alkaline hydrolysis of the diacetate (31a)] in absolute tetrahydrofuran (200 ml.) was added dropwise with stirring to a solution of lithium aluminium hydride (3.0 g.) in absolute tetrahydrofuran (250 ml.). The reaction mixture was worked up as described previously. The yield of the 20α-alcohol (33), m.p. 225-6°, and of 20β-alcohol (32), m.p. 236-8°, was 58.5% and 27.2% respectively. The identity of the alcohols were confirmed by mixed m.p. and superimposability of I.R. spectra.

Pregnane-3,12,20-trione (34)[31]

In parallel runs, a solution of triol (32) and of triol (33) (300 mg.) in acetic acid (15 ml.) was treated with a solution of chromium trioxide (300 mg.) in 3 ml. of 90% acetic acid at room temperature for 20 hours. Extraction and

crystallisation gave in each case an 80-90% yield of the trione (34)[31], m.p. 203-5. The identity of the samples in both cases was confirmed by mixed m.p. and superimposability of I.R. spectra.

3 α, 12 α, 20 α-Triacetoxypregnane (33a).

Triol (33) (130 mg., m.p. 225-6°) was heated at reflux temperature for one hour in pyridine (3 ml.) and acetic anhydride (1 ml.). The reaction mixture was worked up as usual. The triacetate (33a) crystallised from ether-hexane as cubic crystals, m.p. 147-8°, $[\alpha]_D^{28}$ 95° (c 0.73 in $CHCl_3$).

Calcd. for $C_{27}H_{42}O_6$	:	C	70.09	H	9.15
Found	:	C	70.27	H	9.20.

3 α, 12 α, 20 β-Triacetoxypregnane (32a)[29].

Triol (32) (130 mg., m.p. 236-8°) was treated as described above. The triacetate (32a)[29] crystallised from ether-hexane as colourless needles, m.p. 201-2°, $[\alpha]_D^{28}$ 127° (c 0.81 in $CHCl_3$). The m.p. was not depressed upon admixture with an authentic sample* and the I.R. spectra were identical.

---

* Kindly supplied by Prof. Ch. R. Engel, Department of Chemistry, Laval University, Quebec.

3α, 12α, 20β-Trihydroxypregnane 3, 20-bis-methyl succinate (32b)[29].

To a solution of 4.38 g. of the triol (32) in pyridine (40 ml.), succinic anhydride (10.2 g.) was added. The reaction mixture was heated at 90° on a water-bath for 4 hours, and left at room temperature for 16 hours. It was diluted with ice-cold water (1500 ml.) and left for one hour. The solution was extracted with ether, washed with 2N sulphuric acid, and twice with water. The ethereal extract was dried over magnesium sulphate. Upon evaporation of the solvent to 250 ml., 4.054 g. of the needles of bis-hemisuccinate, m.p. 188-9°, crystallised. Crystallisation of mother liquors from acetone-hexane afforded 2.192 g. of the bis-hemisuccinate, m.p. 188-9°.

Recrystallisation for analysis raised the m.p. to 190-1° (m.p. 182-4° has been previously reported[29]).

Calcd. for $C_{29}H_{44}O_9$	:	C 64.91	H 8.26
Found	:	C 64.79	H 8.35.

A solution of the bis-hemisuccinate (6.152 g.) in ether (1500 ml.) was methylated with an excess of diazomethane in ether. The bis-methyl succinate (32b)[29] (5.855 g.) crystallised from ether-hexane as broad needles, m.p. 96-7°, $[\alpha]_D^{29}$ 67° (c 0.97 in $CHCl_3$). Crystallisation of the mother liquors gave 0.257 g. of (32b), m.p. 94-5° (yield 84%).

3α, 20β-Dihydroxypregnan-12-one bis-methyl succinate (36b)[29].

Oxidation with chromium trioxide in acetic acid of 6.025 g. of the bis-methyl succinate (32b) afforded 5.971 g. of needles of the keto bis-methyl succinate (36b)[29], m.p. 112-3°, $[\alpha]_D^{29}$ 110° (c 0.91 in $CHCl_3$).

3α, 20β-Dihydroxypregnan-12-one (36).

To a solution of 10.0 g. of the keto bis-methyl succinate (36b) in methanol (700 ml.) and water (100 ml.), was added potassium carbonate (12.5 g.) and the reaction mixture was heated at reflux temperature for 17 hours. The major part of the methanol was distilled off in vacuo. The reaction mixture was poured into one litre of water, extracted with ether, the ethereal layer washed twice with saturated sodium chloride solution and dried over magnesium sulphate. The solvent was evaporated and 2.868 g. of hydroxy ketone (36) crystallised from acetone-hexane, m.p. 221-2°. The I.R. spectrum of the mother liquors showed that the hydrolysis was not complete. The mother liquors were further hydrolysed with 5% methanolic potassium hydroxide for 8 hours at reflux temperature and worked up as usual. The hydroxy ketone (36) (3.044 g.) crystallised from acetone-hexane as needles, m.p. 220-2° (yield 96%).

Two crystallisations of the hydroxy ketone (36) from acetone-hexane for analysis raised the m.p. to 222-3°, $[\alpha]_D^{29}$ 132° (c 0.95 in $CHCl_3$).

Calcd. for $C_{21}H_{34}O_3$	:	C	75.41	H	10.24
Found	:	C	75.20	H	10.06.

3α, 20β-Diacetoxypregnan-12-one (36a).

A solution of 400 mg. of the hydroxy ketone (36) in pyridine (10 ml.) and acetic anhydride (10 ml.) was heated at 90° for 16 hours. Ether extraction gave 511 mg. of crude product. The ketone (36a) (416 mg.) crystallised from ether-hexane as needles, m.p. 136-7°. Crystallisation of the mother liquors afforded 53 mg. of (36a), m.p. 135-6° (yield 93%).

Two crystallisation of the ketone (36a) from ether-hexane did not raise the m.p., $[\alpha]_D^{29}$ 179° (c 1.09 in $CHCl_3$).

Calcd. for $C_{25}H_{38}O_5$	:	C	71.73	H	9.15
Found	:	C	71.91	H	9.25

3α, 12α, 20α-Trihydroxypregnane 3,20-bis-methyl succinate (33b).

A solution of 7.0 g. of the triol (33) and succinic anhydride (12.0 g.) in absolute pyridine (40 ml.) was heated at

90° for 4 hours, and left at room temperature for 15 hours. The reaction mixture was poured into one litre of ice water, and after one hour it was extracted with ether. The ethereal layer was washed with water, cold 2N hydrochloric acid and water. The organic solution was dried over magnesium sulphate, filtered and treated with excess ethereal diazomethane solution. The bis-methyl succinate (33b) (10.10 g.) crystallised from acetone-hexane as leaflets, m.p. 109-10°. Repeated crystallisations of the mother liquors from acetone-hexane gave 0.571 g. of (33b), m.p. 109-10° (yield 91%). Recrystallisation did not raise the m.p., $[\alpha]_D^{29}$ 43° (c 1.02 in $CHCl_3$).

Calcd. for $C_{31}H_{48}O_9$:	C	65.92	H	8.57
Found	:	C	66.09	H	8.41.

3 α, 20 α-Dihydroxypregnan-12-one bis-methyl succinate (37b).

A solution of chromium trioxide (1.19 g.) in 90% acetic acid (12 ml.) was added to a solution of 6.088 g. of the bis-methyl succinate (33b) in acetic acid (210 ml.) and left at room temperature for 16 hours. Methanol (5 ml.) was added to the reaction mixture, which was then poured into two litres of water and extracted with ether. The ethereal layer was washed with 5% sodium bicarbonate solution and then with water until the washings were neutral. The organic layer was

dried over magnesium sulphate. Evaporation of the solvent afforded 6.071 g. of the crude keto bis-methyl succinate (37b), m.p. 65-6°.

Two crystallisations from ether-hexane raised the m.p. of the keto bis-methyl succinate (37b) to 65.5-6.5°, clusters of leaflets, $[\alpha]_D^{29}$ 87° (c 0.84 in $CHCl_3$).

Calcd. for $C_{31}H_{46}O_9$	:	C	66.16	H	8.24
Found	:	C	65.94	H	8.04.

3α, 20α-Dihydroxypregnan-12-one (37).

A solution of the keto bis-methyl succinate (37b) (6.004 g., crude product obtained from the above reaction) in 5% methanolic potassium hydroxide (500 ml.) was heated at reflux temperature for four hours. The methanol was removed by distillation until the volume of the reaction mixture was about 150 ml. After cooling, it was poured into one litre of water with stirring. The hydroxy ketone (37), which separated out, was filtered, washed with water and dried in vacuo (3.49 g., m.p. 260-1°). The filtrate was extracted with ether and the ethereal solution was washed with saturated sodium chloride solution. Evaporation of the solvent afforded 0.077 g. of (37),

m.p. 250-60°.

Two crystallisations of the hydroxy ketone (37) from methanol gave broad needles, m.p. 260-1°, $[\alpha]_D^{29}$ 120° (c C.56 in $CHCl_3$. A few drops of ethanol was added to bring the hydroxy ketone (37) into solution[1d]).

Calcd. for $C_{21}H_{34}O_3$	:	C 75.41	H	10.24
Found	:	C 75.70	H	10.14.

3α, 20α-Diacetoxypregnan-12-one (37a).

Absolute pyridine (30 ml.) and acetic anhydride (25 ml.) were added to 3.4 g. of the hydroxy ketone (37), and the mixture was heated at reflux temperature for 10 minutes until the crystals dissolved. The reaction mixture was left at 90° for 12 hours, then it was cooled, and poured into 500 ml. of water. The usual extraction procedure gave 4.243 g. of the crude ketone (37a), m.p. 210-2°. The ketone (37a) crystallised from acetone-hexane as plates, 4.082 g., m.p. 211-2°. Crystallisation of mother liquors gave 0.127 g., m.p. 211-2°. The overall yield for the reaction sequence (33b) ⟶ (37b) ⟶ (37) ⟶ (37a) was 99%.

Two crystallisations of the ketone (37a) from acetone-hexane raised the m.p. to 212-2.5°, $[\alpha]_D^{29}$ 103° (c 1.25 in $CHCl_3$).

Calcd. for $C_{25}H_{38}O_5$	:	C 71.73	H	9.15
Found	:	C 71.54	H	8.97.

CHAPTER III

12β-Methylpregnane-3α, 12α, 20β-triol (38).

To 200 ml. of an ethereal solution of methyl magnesium iodide (from 270 mg. of magnesium and 0.7 ml. of methyl iodide) was added with stirring a solution of 575 mg. of the ketone (36a) dissolved in 200 ml. of absolute ether. The reaction mixture was refluxed for 20 hours. A solution of ammonium chloride (10 g.) in water (200 ml.) was added to the reaction mixture and extracted with ether. The ethereal extract was washed with water until the washings were neutral and dried over magnesium sulphate. On evaporating the ether to about 15 ml., the triol (38) crystallised as cubes, 110 mg., m.p. 213-4°. Crystallisation of the mother liquors from ether-hexane afforded 98 mg., m.p. 210-3°.

Recrystallisations of the triol (38) from aqueous methanol and methanol raised the m.p. to 213-5°, leaflets $[\alpha]_D^{29}$ 39° (c 0.88 in $CHCl_3$).

Calcd. for $C_{22}H_{38}O_3$	:	C 75.37	H	10.92
Found	:	C 75.21	H	10.92.

The mother liquors were acetylated and the resulting oil (435 mg.) chromatographed on 14 g. of alumina (4.5% water).

The hexane-benzene (4:1) eluates consisted mainly of the unreacted ketone (36a). Hexane-benzene (1:1) fractions were collected and on crystallisation from hexane gave 73 mg. of the diacetate (38a), m.p. 119-21°. The mother liquors on crystallisation from hexane afforded 15 mg., m.p. 119-21°.

Two recrystallisations of the diacetate (38a) from hexane for analysis raised the m.p. to 122-4°, needles, $[\alpha]_D^{29}$ 79° (c 1.01 in $CHCl_3$).

Calcd. for $C_{26}H_{42}O_5$	:	C	71.86	H 9.74
Found	:	C	71.66	H 9.99.

The mother liquors of the hexane-benzene (1:1) eluates and the remainder of the fractions of the chromatogram afforded upon alkaline hydrolysis and crystallisation from ether-hexane 71 mg. of the triol (38), m.p. 208-10° (overall yield 73%).

Reaction of the ketone (36a) with eight-fold excess of methyl lithium in ethereal solution at reflux temperature for twenty hours, afforded a 45% yield of the triol (38). An infrared spectrum analysis of the mother liquors showed that it contained mainly the unreacted ketone (36a).

12β-Methyl-12α-hydroxypregnan-3,20-dione (39)

Chromium trioxide (490 mg.) in 90% acetic acid (5 ml.) was added with stirring to a solution of 750 mg. of the triol (38) in acetic acid (50 ml.) and left at room temperature for 15 hours. Ether extraction afforded 723 mg. of crude hydroxy ketone (39), m.p. 184-6°. The hydroxy ketone (39) crystallised from acetone-hexane as needles, 663 mg., m.p. 187-8°. Crystallisation of mother liquors afforded 15 mg., m.p. 186-7° (yield 92%).

A portion of the hydroxy ketone (39) was crystallised twice from acetone-hexane for analysis, m.p. 187-8°, $[\alpha]_D^{29}$ 102° (c 1.05 in $CHCl_3$), $\nu_{max}^{CCl_4}$ 1713 cm^{-1} (3,20-dione), 3680 cm^{-1} (C_{12} - hydroxyl).

Calcd. for $C_{22}H_{34}O_3$	:	C	76.25	H	9.89
Found	:	C	76.10	H	9.87.

12β-Methylpregnan-3α, 12α, 20α-triol (40) and 12α-Methylpregnan-3α, 12β, 20α-triol (41).

To 300 ml. of an ethereal solution of methyl magnesium iodide (from 4.984 g. of magnesium and 13.0 ml. of methyl iodide) was added with stirring a solution of 10.68 g. of the ketone (37a) in two litres of absolute ether. The

reaction mixture was heated at reflux temperature for 16 hours, cooled, and a solution of ammonium chloride (50 g.) in water (1 litre) was added. Ether extraction afforded 10.28 g. of the Grignard adduct melting between 194° and 202°, which was acetylated with 65 ml. of pyridine and 55 ml. of acetic anhydride at 90° for 14 hours. The usual extraction procedure afforded 12.25 g. of a foam, which was chromatographed on 350 g. of alumina (4.5% water). The hexane-benzene (3:1) eluates crystallised from ether-hexane and there was obtained 520 mg. of fine needles of the triacetate (40a), m.p. 171-2°. Recrystallisation from ether-hexane raised the m.p. to 172-3°, $[\alpha]_D^{28}$ 90° (c 1.11 in $CHCl_3$).

Calcd. for $C_{28}H_{44}O_6$	:	C	70.57	H 9.32
Found	:	C	70.57	H 9.21.

The hexane-benzene (1:1) and benzene eluates (4.485 g.) on hydrolysis with 5% methanolic potassium hydroxide gave 3.587 g. of crystals, m.p. 208-16°. Repeated crystallisation from methanol afforded 3.216 g. of triol (40), m.p. 240-1°, $[\alpha]_D^{28}$ 70° (c 0.97 in $CHCl_3$).

Calcd. for $C_{22}H_{38}O_3$	:	C	75.37	H 10.92
Found	:	C	75.33	H 10.83.

The benzene-ether and ether-methanol eluates (4.273 g.) were hydrolysed with 5% methanolic potassium hydroxide and there was obtained 3.604 g. of a mixture of epimeric triols (40) and (41), m.p. 204-16°. Fractional crystallisation from methanol afforded 1.22 g. of the triol (40), m.p. 240-1°, and 1.376 g. of the triol (41), m.p. 201-3°. Recrystallisation of triol (41) from acetone afforded needles and did not raise the m.p., $[\alpha]_D^{22}$ 38° (c 1.07 in $CHCl_3$).

Calcd. for $C_{23}H_{38}O_3$	:	C	75.37	H	10.92
Found	:	C	75.50	H	10.96.

An ether solution of the mother liquors of the hexane-benzene (3:1) fractions and the hexane-benzene (9:1 and 4:1) eluates were deacetylated with lithium aluminium hydride, and the triol mixture thus obtained was combined with the mother liquors of crystallisation of triols (40) and (41). To a solution of this combined triol mixture (3.181 g.) in acetic acid (150 ml.) was added a solution of chromium trioxide (2.13 g.) in 90% acetic acid (25 ml.) and the mixture was left at room temperature for 16 hours. The usual extraction procedure afforded 2.85 g. of a pale-brown semi-crystalline product, which was chromatographed on 80 g. of alumina (4.5% water).

The hexane-benzene (4:1) eluates (170 mg.), on crystallisation from acetone-hexane, gave 80 mg. of pregnane-3,12,20-trione[31], m.p. 198-200°, identified by mixed m.p. and comparison of I.R. spectra with an authentic sample.

Hexane-benzene (3:1, 2:1, 1:1) and benzene eluates (950 mg.) crystallised as needles from ether-hexane and there was obtained 741 mg. of the hydroxy ketone (42), m.p. 125-6°. The mother liquors were combined with the benzene-ether (95:5) fractions and crystallisation from ether-hexane gave 113 mg. of (42), m.p. 122-3°.

A portion of the hydroxy ketone (42) was crystallised from ether-hexane for analysis, m.p. 125-6°, $[\alpha]_D^{28}$ 30° (c 0.90 in $CHCl_3$), $\nu_{max}^{CCl_4}$ 1716 cm^{-1} (3-ketone), 1695 cm^{-1} and 3480 cm^{-1} ($C_{20}=O \cdots H - O - C_{12}$ -).

Calcd. for $C_{22}H_{34}O_3$	:	C	76.25	H	9.89
Found	:	C	76.16	H	9.90.

The rest of the benzene-ether and ether-methanol eluates on crystallisation from acetone-hexane afforded 465 mg. of the hydroxy ketone (39), m.p. 187-8° (also obtained via the Grignard reaction in 20β-series). Crystallisation of mother liquors gave 121 mg. of (39), m.p. 184-6°.

Taking into consideration the isolation at different stages in the above experiment of the triacetate (40a) by chromatography, the triols (40) and (41) by crystallisations and the hydroxy ketones (39) and (42) by chromatography, the overall yields of 12β-methylpregnane-3α, 12α, 20α-triol and 12α-methylpregnane-3α, 12β, 20α-triol were 61% and 25% respectively.

The following reactions were also undertaken as part of the exploratory survey to determine the best reaction conditions for the formation of 12-methyl-12-hydroxy pregane derivatives from 12-keto pregnane compounds:

a) the ketone (37a) with an eight-fold excess of methyl lithium in tetrahydrofuran at reflux temperature for 16 hours.

b) the ketone (37a) with an eight-fold excess of methyl lithium in ether at reflux temperature for 14 hours.

c) the ketone (37b) with an eight-fold excess of methyl magnesium iodide in ether at reflux temperature for 15 hours.

Infrared spectra analyses of the reaction products showed that in all the above cases there were appreciable amounts of starting material.

12β-Methyl-12α-hydroxypregnan-3,20-dione (39) from 12β-Methyl-pregnane-3α,12α,20α-triol (40).

To a solution of 200 mg. of the triol (40) in 5 ml. of acetic acid was added with stirring 130 mg. of chromium trioxide dissolved in 2.5 ml. of 90% acetic acid and the reaction mixture left at room temperature for 18 hours. Ether extraction and crystallisation from acetone-hexane afforded 156 mg. of the hydroxy ketone (39), m.p. 188-9°. Crystallisation of mother liquors afforded 5 mg., m.p. 187-8° (yield 87%). The identity of this compound with the hydroxy ketone (39) was proved by a comparison of I.R. spectra and mixed m.p.

12α-Methyl-12β-hydroxypregnan-3,20-dione (42) from 12α-Methyl-pregnane-3α,12β, 20α-triol (41).

Chromium trioxide oxidation of 200 mg. of the triol (41) as described above, gave 199 mg. of an oil, which on chromatography on 6 g. of alumina and crystallisation from ether-hexane afforded 83 mg. of the hydroxy ketone (42) as needles, m.p. 124-5°. Crystallisation of mother liquors gave 51 mg., m.p. 123-4° (yield 68%). Mixed m.p. of the hydroxy ketone (42) obtained by this experiment, with the hydroxy ketone (42) obtained by chromatography of the epimeric hydroxy ketone mixture (see p. 69), showed no depression.

12β-Methylpregnane-3α, 12α, 20α-triol 12-acetate (40c).

A solution of 200 mg. of the triacetate (40a) in 25 ml. of 5% methanolic potassium hydroxide was heated at reflux temperature for 10 hours. Ether extraction gave 194 mg. of oil. Fractional crystallisation from ether-hexane afforded 56 mg. of the monoacetate (40c), m.p. 183-4° (yield 34%), and 10 mg. of the triol (40), m.p. 240-1°. The latter was identified by comparison of I.R. spectra and mixed m.p. with an authentic sample of the triol (40).

Recrystallisation of the monoacetate (40c) from ether-hexane raised the m.p. to 184-5°, leaflets, $[\alpha]_D^{28}$ 90° (c 1.07 in $CHCl_3$).

Calcd. for $C_{24}H_{40}O_4$	:	C	73.40	H	10.27
Found	:	C	73.23	H	10.20.

12β-Methyl-12α-acetoxypregnane-3,20-dione (39a).

To a solution of the monoacetate (40c) [165 mg., crude product obtained by alkaline hydrolysis of 170 mg. of the triacetate (40a)] in 5 ml. of acetic acid, was added with stirring a solution of 112 mg. of chromium trioxide in 2.5 ml. of 90% acetic acid, and the reaction mixture left at room temperature for 14 hours. Ether extraction afforded 140 mg.

of oil, which was chromatographed on 5 g. of alumina (4.5% water). The hexane-benzene (1:1) and benzene eluates crystallised from ether-hexane, and there was obtained 52 mg. of leaflets of the ketone (39a), m.p. 175-6°. Crystallisation of mother liquors gave 16 mg., m.p. 174-5° (yield 49%). Two crystallisations of the ketone (39a) from ether-hexane raised the m.p. to 175.5-6°, $[\alpha]_D^{22}$ 102° (c 1.04 in $CHCl_3$).

Calcd. for $C_{24}H_{36}O_4$	:	C	74.18	H	9.34
Found	:	C	74.31	H	9.37.

12β-Methylpregnane-3α, 12α, 20α-triol 3,20-diacetate (40b).

A solution of 150 mg. of the triol (40) in 5 ml. of pyridine and 5 ml. of acetic anhydride was left at room temperature for 16 hours. The usual extraction procedure afforded 190 mg. of the diacetate (40b), which crystallised from ether-hexane as needles, 175 mg., m.p. 188-9°. Crystallisation of mother liquors gave 7 mg. of (40b), m.p. 186-8° (yield 98%).

Recrystallisation of the diacetate (40b) from ether-hexane for analysis did not raise the m.p., $[\alpha]_D^{28}$ 80° (c 0.98 in $CHCl_3$).

Calcd. for $C_{28}H_{42}O_5$	:	C	71.86	H	9.74
Found	:	C	71.69	H	9.67.

12α-Methylpregnane-3α, 12β, 20α-triol 3,20-diacetate (41a).

Acetylation of 100 mg. of the triol (41) at room temperature as described above, gave 124 mg. of crude diacetate (41a), which crystallised from ether-hexane as clusters of needles, 117 mg., m.p. 189-90° (yield 94%). Mixed m.p. of the diacetate (41a) with the diacetate (40b) showed a depression in m.p. . Recrystallisation of the diacetate (41a) from ether-hexane for analysis did not raise the m.p., $[\alpha]_D^{28}$ 56° (c 0.99 in $CHCl_3$).

Calcd. for $C_{28}H_{42}O_5$	:	C	71.86	H	9.74
Found	:	C	71.91	H	9.67.

3α, 12α-Dihydroxypregnan-20-one 3-methyl succinate (31b)[29]

To a solution of the diol (31) [12.2 g., m.p. 164-7°; crude product obtained by alkaline hydrolysis of 15.0 g. of the diacetate (31a)] in pyridine (125 ml.), succinic anhydride (32.5 g.) was added and the resulting solution was heated at 90° for 2 hours and left at room temperature for 12 hours. The reaction mixture was extracted with ether. The organic layer was washed with 2N hydrochloric acid, water and then dried over magnesium sulphate. The ethereal solution was methylated with diazomethane. Crystallisation from acetone-hexane afforded 13.427 g. of the methyl succinate (31b)[29], m.p. 125-7° (yield 84%).

3α, 12α-Dihydroxy-20-pregnanone ethylene ketal 3-methyl succinate (43).

To a solution of 8.99 g. of the methyl succinate (31b) in absolute benzene (200 ml.) was added ethylene glycol (20 ml.) and p-toluene sulphonic acid (100 mg.), and heated at reflux temperature for 12 hours. The water formed during the reaction was continously removed. The reaction mixture was extracted with ether, the ethereal layer washed with sodium bicarbonate solution and with water, until the washings were neutral, and dried over magnesium sulphate. Repeated crystallisations from ether-hexane afforded 3.92 g. of broad needles of the ketal (43), m.p. 181-4° (yield 40%).

Two crystallisations from ether-hexane raised the m.p. of (43) to 182-4°, $[\alpha]_D^{27}$ 57° (c 1.01 in $CHCl_3$).

Calcd. for $C_{28}H_{44}O_7$	:	C	68.26	H	9.00
Found	:	C	68.40	H	9.07.

3α-Hydroxy-12,20-pregnandione 20-ethylene ketal 3-methyl succinate (44).

A solution of 3.2 g. of the ketal (43) in pyridine (36 ml.) was added to a slurry of chromium trioxide (3.2 g.) in pyridine (32 ml.)[104] with stirring and left at room temperature

for 16 hours. The reaction mixture was poured into 500 ml. of water and extracted with chloroform. The organic layer was washed with iced 2N hydrochloric acid, 5% sodium bicarbonate solution and water, until the washings were neutral. The chloroform solution was dried over magnesium sulphate and evaporated to about 40 ml. On addition of 20 ml. of hexane to it, the ketone (44) crystallised as needles, 2.404 g., m.p. 239-40°. The mother liquors on crystallisation from methylene chloride-hexane afforded 0.364 g., m.p. 237-9° (yield 98%).

Recrystallisation of the ketone (44) for analysis did not raise the m.p., $[\alpha]_D^{27}$ 96° (c 0.78 in $CHCl_3$).

Calcd. for $C_{28}H_{42}O_7$	:	C	68.55	H	8.63
Found	:	C	68.64	H	8.65.

Reaction of methyl magnesium iodide with 3α-Hydroxy-12,20-pregnandione 20-ethylene ketal 3-methyl succinate (44).

To 300 ml. of an ethereal solution of methyl magnesium iodide (from 700 mg. of magnesium and 2.0 ml. of methyl iodide) was added with stirring a solution of 1.0 g. of the ketone (44) in benzene, and the resulting mixture was heated at reflux

temperature for 18 hours. A solution of ammonium chloride (20 g.) in water (500 ml.) was added to the reaction mixture. The usual extraction procedure afforded 930 mg. of oil.

To a solution of the Grignard adduct (930 mg. of oil) in 50 ml. of acetone was added with stirring, 75 mg. of p-toluene sulphonic acid and left at room temperature for 22 hours[61]. Ether extraction afforded 884 mg. of oil. An infrared spectrum analysis of the oil showed strong absorption band at 1707 cm^{-1} (C_{20}-ketone), and weak absorption band at 1725 cm^{-1} (C_3 - methyl succinate).

A solution of this oil in 25 ml. of 5% methanolic potassium hydroxide was heated at reflux temperature for 45 minutes. The usual extraction procedure afforded 735 mg. of foam, which was dissolved in 10 ml. of acetic acid, and to it was added with stirring a solution of 250 mg. of chromium trioxide in 3 ml. of 90% acetic acid. The reaction mixture was left at room temperature for 12 hours. Ether extraction afforded 740 mg. of oil, and it was chromatographed on 23 g. of alumina (4.5% water).

The hexane-benzene (1:1) eluates on crystallisation from acetone-hexane afforded 106 mg. of the trione (34),

m.p. 197-9°, identified by mixed m.p. and comparison of I.R. spectra with an authentic sample. Crystallisation of mother liquors from acetone-hexane gave 21 mg., m.p. 192-7°.

The first half of the benzene fractions on crystallisation from ether-hexane afforded 67 mg. of the hydroxy ketone (42), m.p. 123-4°.

The rest of the benzene eluates and the benzene-ether (9:1, 4:1) fractions on crystallisation from acetone-hexane afforded 80 mg. of the hydroxy ketone (39), m.p. 187-8°. Crystallisation of mother liquors gave 29 mg., m.p. 184-7°.

The ether-methanol (9:1) eluates on crystallisation from acetone-hexane afforded 34 mg. of needles of 3α, 12α-dihydroxy-12β-methylpregnan-20-one, m.p. 225-9°. Recrystallisation from acetone-hexane raised the m.p. to 228-30°, $[\alpha]_D^{27}$ 106°(c 0.74 in $CHCl_3$).

Calcd. for $C_{22}H_{36}O_3$	:	C 75.80	H	10.41
Found	:	C 75.96	H	10.07.

Chromium trioxide oxidation of 3α, 12α-dihydroxy-12β-methylpregnan-20-one (10 mg.) afforded 3 mg. of the hydroxy ketone (39), m.p. 186-8°, identified by mixed m.p. and comparison of

I.R. spectra with an authentic sample.

Taking into consideration the unreacted ketone (44) [isolated as the trione (34)] , the yields of 12α- alcohol and 12β- alcohol were 25% and 12% respectively.

12-Methylene pregnane-3,20-dione (45) from 12α-Methyl-12β-hydroxypregnan-3,20-dione (42).

To a solution of 330 mg. of the hydroxy ketone (42) in 25 ml. of acetic acid were added 5 ml. of acetic anhydride and 330 mg. of p-toluene sulphonic acid monohydrate[43] and the suspension was stirred until the solid dissolved. The reaction mixture was left at room temperature for 4 hours, then poured into 500 ml. of iced water. After 30 minutes, the usual extraction procedure afforded 390 mg. of an oil, which showed absorption bands in the infrared at 3080 cm^{-1}, 1645 cm^{-1}, 890 cm^{-1} ($>C=CH_2$)[23c]; 1755 cm^{-1}, 1218 cm^{-1} ($\Delta^{17(20)}$-enol acetate)[105]; 1713 cm^{-1} (3-ketone). Under the above reaction conditions the $\Delta^{17(20)}$-enol acetate is known to be formed[106]. The enol acetate (390 mg. of oil) was converted to the C_{20}-ketone by heating a solution of it in 30 ml. of methanol and 700 mg. of potassium carbonate in 10 ml. of water at reflux temperature

for two hours. Ether extraction afforded 360 mg. of product showing no bands at 1750 cm^{-1} and 1218 cm^{-1} characteristic of enol acetates and it was chromatographed on 10 g. of alumina (4.5% water). The hexane-benzene (4:1, 1:1) eluates containing the olefin (45) crystallised from ether-hexane as needles, 134 mg., m.p. 89-90°. Crystallisation of mother liquors afforded 33 mg., m.p. 89-90° (yield 53.4%).

A portion of the olefin (45) was recrystallised from ether-hexane for analysis, m.p. 89-90°, $[\alpha]_D^{27}$ 133° (c 1.02 in $CHCl_3$), $\nu_{max}^{CS_2}$ 3075 cm^{-1}, 1645 cm^{-1}, 888 cm^{-1} ($>C=CH_2$); 1713 cm^{-1} (3,20- dione).

Calcd. for $C_{22}H_{32}O_2$	:	C	80.41	H	9.82
Found	:	C	80.18	H	9.84.

The benzene and benzene-ether eluates on crystallisation from acetone-hexane afforded 56 mg. of leaflets of (39a), m.p. 175-6° (yield 15.1%). (Also obtained by partial hydrolysis of the triacetate (40a) to the monoacetate (40c), and subsequent oxidation).

<u>12-Methylene pregnane-3,20-dione (45) from 12β-Methyl-12α-hydroxypregnan-3,20-dione (39)</u>.

The hydroxy ketone (39) (500 mg.) was transformed to

the olefin (45) as described as before. The crude olefin (45) (555 mg. of oil) was chromatographed on 15 g. of alumina (4.5% water) and the hexane and hexane-benzene eluates on crystallisation from hexane afforded 145 mg. of feathery needles of the olefin (45), m.p. 72-3°.* A portion of it was recrystallised from hexane for analysis, m.p. 73-4°; $[\alpha]_D^{22}$ 139° (c 1.0 in $CHCl_3$); $\nu_{max}^{CS_2}$ 3080 cm^{-1}, 1645 cm^{-1}, 885 cm^{-1} ($>C=CH_2$); 1713 cm^{-1} (3,20-dione).

Calcd. for $C_{22}H_{32}O_2$	:	C	80.41	H	9.82
Found	:	C	80.02	H	9.66.

Recrystallisation of mother liquors gave 45 mg. of needles, m.p. 71-3° (yield 40%).

The mother liquors were dissolved in 5 ml. of hexane and left in a refrigerator. After one week, 80 mg. of crystalline olefin (45) was obtained. Repeated crystallisation afforded 63 mg. of fine needles of the olefin (45), m.p. 100-1°* (yield 13%). One crystallisation from hexane for analysis

---

* A mixed m.p. of the two forms of olefin (45) melting at 73-4° and 89-90° on a Kofler block, showed the form melting at 72-3°, melted at that latter temperature, but crystallised on further raising the temperature and the whole mass melted at 89-90°. The two forms of olefin melting at 89-90° and 101-2° were melted side by side, and the molten mass was seeded with a crystal of the form melting at 89-90°, and cooled. The whole mass melted at 89-90°. Furthermore, the I.R. spectra and the rotations of the three forms were identical within experimental error. In view of the above evidence, it is presumed that this is a case of polymorphism.

raised the m.p. to 101-2°; $[\alpha]_D^{22}$ 130° (c 0.95 in $CHCl_3$); $\nu_{max}^{CS_2}$ 3080 cm^{-1}, 1645 cm^{-1}, 885 cm^{-1} (>C=CH_2); 1713 cm^{-1} (3,20-dione).

Calcd. for $C_{22}H_{32}O_2$	:	C	80.41	H	9.82
Found	:	C	80.19	H	9.86.

The benzene eluates of the chromatogram on crystallisation from acetone-hexane afforded 76 mg. of (39a), m.p. 175-6° (yield 12%). (Also obtained by partial hydrolysis of the triacetate (40a) to the monoacetate (40c), and subsequent oxidation).

The later fractions consisted mainly of the starting material (39), as identified by infrared spectra. No attempt was made to recover it.

Attempts of dehydration of epimeric hydroxy ketones (39) and (42) with phosphorus oxychloride and thionyl chloride did not yield any olefinic material.

Conversion of 12-methylene pregnane-3,20-dione (45) to 12β-methyl-12α-hydroxypregnane-3,20-dione (39).

To a solution of 175 mg. of the olefin (45) (m.p. 71-3°) in 20 ml. of absolute ether containing 0.2 ml. of pyridine was

added 150 mg. of osmium tetroxide (1.1 mole equivalent) and the reaction mixture was left at room temperature for two days[47]. It was then heated at reflux temperature for 30 minutes with 100 ml. of an 80% solution of ethanolic sodium sulphite. After cooling, the reaction mixture was filtered through celite, and the usual extraction procedure afforded 208 mg. of an oil. Its infrared spectrum showed no characteristic bands due to a vinylidene group. Crystallisation from acetone-hexane afforded 36 mg. of crystalline diol (46). Two recrystallisations from acetone gave 13 mg. of fine needles of the diol (46), m.p. 196-9°, $[\alpha]_D^{22}$ 22° (c 0.88 in $CHCl_3$).

Calcd. for $C_{22}H_{34}O_4$	:	C 72.88	H	9.45
Found	:	C 72.81	H	9.42.

The crude diol (46) (the mother liquors containing 170 mg. as oil) was tosylated with 170 mg. of p-toluenesulphonyl chloride and 5 ml. of pyridine at room temperature for 18 hours. Ether extraction afforded 195 mg. of the tosylate (46a) as oil, which showed absorption bands at 1375 cm^{-1}, 1193 cm^{-1} and 1190 cm^{-1} in the infrared region, characteristic of tosyl groups[23e].

A solution of the tosylate (195 mg. of oil) in 20 ml. of absolute tetrahydrofuran was heated at reflux temperature for 16 hours with 200 mg. of lithium aluminium hydride. The reduction

product was worked up in the usual fashion, and there was obtained 155 mg. of semi-crystalline compound. Its infrared spectrum indicated the absence of tosyl groups.

To a solution of the above product (155 mg.) in 5 ml. of acetic acid was added with stirring a solution of 105 mg. of chromium trioxide in 2 ml. of 90% acetic acid and the reaction mixture was left at room temperature for 16 hours. The reaction mixture was worked up in the usual manner, and when the ethereal extract was evaporated to about 5 ml., there was obtained 58 mg. of needles, m.p. 188-9°. Admixture with an authentic sample of the hydroxy ketone (39) did not depress the m.p. and the infrared spectra were also identical. Chromatographic purification and crystallisation from acetone-hexane of the mother liquors afforded an additional 27 mg. of (39), m.p. 181-6° (yield 57%).

CHAPTER V

12β-Methyl-12α-hydroxyprogesterone (75).

A solution of bromine (141 mg.) in acetic acid (9.4 ml.) was added with stirring to a solution of 300 mg. of the hydroxy ketone (39) in acetic acid (10 ml.) containing a drop of 50% (w/v) solution of hydrobromic acid. After five minutes when the colour of bromine had disappeared, the reaction mixture was poured into ice-water (500 ml.), and extracted with ether. The organic layer was washed with 5% sodium bicarbonate solution, water until the washings were neutral and dried over magnesium sulphate. There was obtained 395 mg. of an oil, which resisted crystallisation.

The crude bromo ketone (73) was dissolved in 10 ml. of absolute chloroform and 20 ml. of dry t-butanol. To this solution was added 150 mg. of semicarbazide (m.p. 95-6°) in carbon dioxide atmosphere, stirred until the base dissolved[103]. The colour of the solution turned progressively bright yellow and then faded away. The reaction mixture was left at room temperature for 2 hours, and then the solvents removed in vacuo. The crude semicarbazone (74) was dissolved in 15 ml. of ethanol, and poured into 500 ml. of ice-water with stirring when the semicarbazone separated as a solid. It was dissolved in 20 ml.

of acetic acid, 5 ml. of pyruric acid and 20 ml. of water. The reaction mixture was left at room temperature for 15 hours. Ether extraction afforded 240 mg. of oil which crystallised from ether-hexane and there was obtained 125 mg. of the progesterone analogue (75) as leaflets, m.p. 140-150°. Repeated crystallisations gave 97 mg. of analytically pure (75), m.p. 152-3°, (yield 33%), $[\alpha]_D^{29}$ 182° (c 1.01 in $CHCl_3$), λ_{max}^{EtOH} 239 mμ(ϵ 17,500), $\nu_{max}^{CCl_4}$ 1710 cm^{-1} (20-ketone), 1680 cm^{-1}, 1620 cm^{-1} (Δ^4-3-ketone).

Calcd. for $C_{22}H_{32}O_3$	:	C	76.68	H	9.37
Found	:	C	76.40	H	9.40.

12α-Methyl-12β-hydroxyprogesterone (75b).

A solution of bromine (306 mg.) in acetic acid (15.2 ml.) was added with stirring to a solution of 600 mg. of the hydroxy ketone (42) in acetic acid (5 ml.), containing a drop of 50% (w/v) solution of hydrobromic acid. The reaction mixture was stirred for five minutes and poured in 250 ml. of ice-water. The bromo ketone (73a), which separated out as a solid was filtered, dried and it crystallised from ether-hexane as needles, 332 mg., m.p. 172-3° (decompn.), $\nu_{max}^{CCl_4}$ 1695 cm^{-1}, 3480 cm^{-1}

(C_{20}=O ··· H-O-C_{12}-), 1735 cm^{-1} (4β-bromo-3-ketone).

The filtrate was extracted with ether and combined with the mother liquors of the crystallisation of the bromo ketone (73a). Since recrystallisation was tedious and afforded only 114 mg. of the bromo ketone (73a), m.p. 168-9° (decompn.), the second crop and the mother liquors (533 mg. of oil) were reduced by heating with 550 mg. of zinc dust, 5.5 ml. of acetic acid and 0.5 ml. of water at 90° for one hour. Ether extraction, chromatographic purification and crystallisation from ether-hexane gave 276 mg. of the hydroxy ketone (42), m.p. 124-5°. Taking into consideration the recovery of the hydroxy ketone (42) the yield of pure bromo ketone (73a) was 83%.

The bromo ketone (73a) (330 mg., m.p. 172-3° decompn.) was dehydrobrominated according to the method of McGuckin and Kendall[103]. The resulting oil was chromatographed on 9 g. of alumina (4.5% water). The benzene, benzene-ether and ether eluates crystallised from ether-hexane as needles, and there was obtained 120 mg. of the progesterone derivative (75 b), m.p. 142-3°. The mother liquors on crystallisation afforded 19 mg. of (75b), m.p. 139-42° (yield 48%). The second crop was recrystallised and added to the first batch. Recrystallisation gave 126 mg. of analytically pure (75b), m.p. 142-3°, $[\alpha]_D^{22}$ 113°

(c 1.07 in $CHCl_3$), λ_{max}^{EtOH} 238 mμ (ε 18,600), $\nu_{max}^{CCl_4}$ 1695 cm^{-1} and 3480 cm^{-1} ($>C_{20}=O \cdots H-O-C_{12}-$), 1680 cm^{-1} and 1622 cm^{-1} (Δ^4 -3-ketone).

Calcd. for $C_{22}H_{32}O_3$	:	C 76.68	H	9.37
Found	:	C 76.68	H	9.41.

12-Methylene progesterone (75c) and 12β-Methyl-12α-acetoxyprogesterone (75a).

According to the procedure previously described, 900 mg. of the hydroxy ketone (39) was transformed to the progesterone analogue (75). Crystallisation from ether-hexane afforded 330 mg. of (75), m.p. 152-3°. The mother liquors (590 mg.) were chromatographed on 17 g. of alumina (4.5% water). The benzene and benzene-ether eluates on crystallisation from ether-hexane afforded 160 mg. of the progesterone analogue (75), m.p. 152-3°. Crystallisation of mother liquors afforded 51 mg., m.p. 135-42° (yield 61%).

To a solution of the progesterone analogue (75) (475 mg., m.p. 152-3°) in 25 ml. of acetic acid and 5 ml. of acetic anhydride was added 475 mg. of p-toluene sulphonic acid and stirred until it dissolved. The reaction mixture was left

room temperature for 2 hours. Ether extraction afforded 540 mg. of an oil, and it was dissolved in 25 ml. of methanol. To the methanol solution was added 750 mg. of potassium carbonate dissolved in 10 ml. of water and the reaction mixture was heated at reflux temperature for 2 hours. The usual extraction procedure afforded 520 mg. of an oil, which was chromatographed on 15 g. of the alumina (4.5% water). The hexane-benzene (4:1, 1:1) and benzene eluates on crystallisation from ether-hexane afforded 121 mg. of cubic crystals of 12-methylene progesterone (75c) m.p. 104-5°, (yield 27%). Two recrystallisations with ether-hexane raised the m.p. to 105-6°[*], $[\alpha]_D^{27}$ 189° (c 0.92 in $CHCl_3$), λ_{max}^{EtOH} 240 mμ (ε 18,500), $\nu_{max}^{CCl_4}$ 3070 cm^{-1}, 1643 cm^{-1}, 890 cm^{-1} (>C=CH_2), 1707 cm^{-1} (20-ketone), 1675 cm^{-1}, 1617 cm^{-1} (Δ^4-3-ketone).

Calcd. for $C_{22}H_{30}O_2$	:	C	80.91	H	9.25
Found	:	C	80.70	H	9.05.

The benzene-ether eluates afforded 210 mg. of an oil which resisted crystallisation. Its infrared spectrum showed absorption bands at 1727 cm^{-1} (12-acetate); 1705 cm^{-1} (20-ketone); 1675 cm^{-1} and 1617 cm^{-1} (Δ^4-3-ketone). It was tentitatively assigned the 12β-methyl-12α-acetoxyprogesterone configuration on the basis of its infrared spectrum, and from the analogous

---

[*] The progesterone derivative (75c) was obtained in another polymorphic modification as needles m.p. 135-6°.

reaction that 12β-methyl-12α-hydroxypregnan-3,20-dione with acetic acid, acetic anhydride and p-toluene sulphonic acid gives 12β-methyl-12α-acetoxypregnan-3,20-dione as the minor product of the reaction (see p.82).

Results of Biological Tests

12β-Hydroxy-12α-methylprogesterone (75b):

Clauberg Test

Daily dose/rabbit	route	Proliferation
0.1 mg.	s.c.	Ø +1 +1 +1
5.0 mg.	oral	+1 +1 +1

The compound was inactive at the dose levels tested.

12β-Methyl-12α-hydroxyprogesterone (75):

Clauberg Test

Daily dose/rabbit	route	Proliferation
0.1 mg.	s.c.	Ø Ø Ø ØØ

Androgenic-Anabolic Activity in Rats

no. of rats	Compound	Daily dose mg. s.c.	Ventral Prost.mg.	Semin. Ves.mg.	Lev. ani mg.	body weight Initial	body weight Final
47	Ses. oil	0.2 ml.	8.9±0.6	10.1±0.5	14.6±0.5	41±0.9	66±1.2
12	(75)	0.1 mg.	10.2±0.5	9.3±0.3	14.3±0.6	41±1.1	62±2.7

Diuretic activity in Adrenalectomized Rats

	Dose	Urine Vol. ml.	Sodium mg/vol.	Potassium mg/vol.	Na/K ratio
Operated controls		2.9 ± 0.2	3.1 ± 0.5	8.9 ± 1.0	0.35
(75)	500 γ	2.3 ± 0.3	2.8 ± 0.7	7.8 ± 1.4	0.36

The compound did not show any activity in the above tests.

12 α-acetoxy-12 β methylprogesterone (75a) and 12-methylene progesterone (75c).

Clauberg Test

Compound	Dose mg/kg	Route	Proliferation
Sesame oil	0.2 ml.	s.c.	Ø Ø Ø Ø
Progesterone	0.1	s.c.	+4 +4 +4 +4
(75a)	0.1	s.c.	Ø Ø Ø +1
(75c)	0.1	s.c.	Ø Ø +1 +1

Results

(75a) and (75c) were inactive in the Clauberg test when administered subcutaneously at daily doses of 0.1 mg.; at the same dose level progesterone gave a +4 proliferation.

REFERENCES

1. Fieser, L.F., and Fieser, M., "Steroids", Reinhold Publishing Co., New York, 1959; (a) 169-174; (b) 15-24, 174-177; (c) 177-180; (d) p. 25.

2. Shoppee, C.W., "Chemistry of Steroids", Butterworths Scientific Publications, London, 1958.

3. Klyne, W., "The Chemistry of Steroids", Methuen and Co. Ltd., London, 1957.

4. Elsevier's "Encyclopedia of Organic Chemistry", Vol. 14, Series III, p. 38, 1940.

5. Hassel, O., Tidsskr. Kjemi, Bergvesen Met., 3, 32 (1943).

6. Barton, D.H.R., Hassel, O., Pitzer, K.S., and Prelog, V., Nature, 172, 1096 (1953).

7. Barton, D.H.R., Experientia, 6, 316 (1950).

8. Barton, D.H.R., "The Stereochemistry of Cyclohexane Derivatives" (Tilden Lecture), J. Chem. Soc., 1027 (1953); (a) p. 1032-3; (b) p. 1029.

9. Barton, D.H.R., and Cookson, R.C., "The principles of Conformational Analysis", Quart. Revs., 10, 44 (1956); (a) p. 65-72; (b) p. 58-62; (c) p. 64.

10. Klyne, W., "Progress in Stereochemistry", Vol. 1, Butterworths Scientific Publications, London, 1954; (a) 109, 118; (b) 167-170.

11. Djerassi, C., "Optical rotatory dispersion - Application to organic chemistry", McGraw-Hill Book Co., New York, 1960.

12. Roberts, J.D., "Nuclear Magnetic Resonance - Application to organic chemistry", McGraw-Hill Book Co., New York, 1959, p. 36-38; Shoolery, J.N., and Rogers, M.T., J. Am. Chem. Soc. 80, 5121 (1958).

13. Ingold, C.K., "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1953, (a) p. 321-24; (b) p. 357-58.

14. Meystre, Ch., and Wettstein, A., Helv. Chim. Acta, 31, 1890 (1948); Meystre, Ch., Tschopp, E., and Wettstein, A., ibid., p. 1463; von Euw, J., and Reichstein, T., ibid., p. 2076.

15. Beaton, J.M., Spring, F.S., Stevenson, R., Stewart, J.L., Tetrahedron 2, 250 (1958).

16. Edwards, O.E., Chemistry in Canada, Vol. 13, No. 1, p. 42, 1961.

17. Hirschmann, R., Snoddy, C.S., Hiskey, C.F., and Wendler, N.L., J. Am. Chem. Soc. 76, 4013 (1954).

18. Cohen, A., Cook, J.W., and Hewett, C.L., J. Chem. Soc. 445 (1935).

19. Heusler, K., and Wettstein, A., Ber. 87, 1301 (1954).

20. Lardón, A., Sitg, M.P., and Reichstein, T., Helv. Chim. Acta, 42, 1457 (1959).

21. Sarett, L.H., J. Am. Chem. Soc. 70, 1692 (1948).

22. Evans, E.R.H., and Wenka, D.J., J. Chem. Soc. 907 (1959).

23. Bellamy, L.J., "The infrared spectra of complex molecules", Methuen and Co. Ltd., London, 1958; (a) p. 148-149; (b) p. 147-148; (c) p. 34; (d) p. 189; (d) p. 364.

24. Woodward, R.B., J. Am. Chem. Soc. 63, 1123 (1941); ibid, 64, 76 (1942).

25. Holysz, R.P., J. Am. Chem. Soc., 75, 4432 (1953).

26. Kritchevsky, T.H., Garmaise, D.L., and Gallagher, T.F., J. Am. Chem. Soc. 74, 483 (1952).

27. Bowers, A., Sanchez, M.B., and Ringold, H.J., J. Am. Chem. Soc. 81, 3702 (1959).

28. Hegner, P., and Reichstein, T., Helv. Chim. Acta, 26, 726 (1943).

29. Engel, Ch. R., and Huculak, W.W., Can. J. Chem., 37, 2031 (1959).

30. Hoehn, W.F., and Mason, H.L., J. Am. Chem. Soc. 60, 1493 (1938).

31. Reichstein, T., and von Arx, E., Helv. Chim. Acta, 23, 747 (1940).

32. Sarett, L.H., J. Am. Chem. Soc. 71, 1175 (1949); see also Fukushima, D.K., and Meyer, E.D., J. Org. Chem. 23, 174 (1958).

33. Cram, D.J., and Abd Elhafez, F.A., J. Am. Chem. Soc. 74, 5828 (1952).

34. Sicher, J., Svoboda, M., Hrdá, M., Rudinger, J., and Šorm, F., Coll. Czech. Comm., 4, 487 (1953).

35. Paddock, N.L., Chem. and Ind., 63 (1953).

36. Brown, H.C., and Adams, R.M., J. Am. Chem. Soc., 64, 2557 (1942).

37. Elisberg, E., Vanderhaeghe, H., and Gallagher, T.F., J. Am. Chem. Soc. 74, 2814 (1952).

38. Mancera, O., Ringold, H.J., Djerassi, C., Rosenkranz, G., and Sondheimer, F., J. Am. Chem. Soc. 75, 1286 (1953); Soloway, A.H., Deutsch, A.S., and Gallagher, T.F., ibid., 75, 2356 (1953).

39. Schwenk, E., Riegel, B., Moffett, R.B. and Stahl, E., J. Am. Chem. Soc. 65, 549 (1943); Sorkin, M., and Reichstein, T., Helv. Chim. Acta, 31, 1890 (1948).

40. Fieser, L.F., Experientia, 6, 312 (1950).

41. Gallagher, T.F., and Kritchevsky, T.H., J. Am. Chem. Soc., 72, 882 (1950).

42. Wall, M.E., and Serota, S., Tetrahedron, 10, 238 (1960).

43. Turner, R.B., J. Am. Chem. Soc., 75, 3489 (1953).

44. Ruzicka, L., Wahba, N., Herzig, P. Th., and Heusser, H., Ber., 85, 491 (1952).

45. Heusser, H., Wahba, N., and Winternitz, F., Helv. Chim. Acta, 37, 1052 (1954).

46. Bladon, P., and McMeekin, W., J. Chem. Soc., 2191 (1960).

47. Levine, S.G., and Wall, M.E., J. Am. Chem. Soc., 82, 3391 (1960).

48. Turner, R.B., Meador, W.R., and Winkler, R.E., J. Am. Chem. Soc. 79, 4122 (1957).

49. Henbest, H.B., Meakins, G.D., and Wood, G.W., J. Chem. Soc. 800 (1954).

50. Elks, J., J. Chem. Soc., 3333 (1960).

51. Cope, A.C., Ambros, D., Ciganek, E., Howell, C.F., and Jacura Z., J. Am. Chem. Soc., 81, 3153 (1959), and references cited therein.

52. Brown, H.C., and Subba Rao, B.C., J. Am. Chem. Soc. 81, 6423 (1959).

53. Wolfe, S., Nussim, M., Mazur, Y., and Sondheimer, F., J. Org. Chem., 24, 1034 (1959).

54. Peterson, P.E., J. Am. Chem. Soc., 82, 5834 (1960).

55. Fieser, L.F., and Rigaudy, J., J. Am. Chem. Soc. 73, 4660 (1951).

56. Shiota, M., Nippon Kagaku Zassi, 75, 1217 (1954); 76, 1272 (1955); 77, 778 (1956); Chem. Abstr., 51, 17969 (1957); 52, 416, 417 (1958).

57. Sneen, R.A., J. Am. Chem. Soc., 80, 3982 (1958).

58. Davis, M., and Summers, G.H.R., J. Chem. Soc., 4707 (1960).

59. Fonken, G.S., J. Org. Chem. 23, 1075 (1958).

60. Fonken, G.S., Hogg, J.A., and McIntosh, A.V., J. Org. Chem., 24, 1600 (1959).

61. Zderic, J.A., Batres, E., Limón, D.C., Carpio, H., Lisci, J., Monroy, G., Necoechea, E., and Ringold, H.J., J. Am. Chem. Soc. 82, 3404 (1960).

62. Barton, D.H.R., Campos-Neves, A.D.S., and Cookson, R.C., J. Chem. Soc., 3500 (1956).

63. Pelc, B., Coll. Czech. Comm., 25, 1624 (1960).

64. Gaylord, N.G., "Reductions with complex metal hydrides", Intersceince Publishers, Inc., New York, 1956, p. 91-2 and references cited therein.

65. Dauben, W.G., Fonken, G.J., and Noyce, D.S., J. Am. Chem. Soc. 78, 2579 (1956).

66. Dauben, W.G., Blanz, E.J., Jiu, J., and Micheli, R.A., ibid., 78, 3752 (1956).

67. Wheeler, D.M.S., and Huffman, J.W., Experientia, 16, 516 (1960).

68. Swain, C.G., J. Am. Chem. Soc., 69, 2396 (1947).

69. Kharash, M.S., and Reinmuth, O., "Grignard reaction of nonmetallic substances", Prentice-Hall, Inc., New York, 1954, p. 142.

70. Swain, C.G., and Boyles, H.B., J. Am. Chem. Soc., 73, 870 (1951).

71. Dessy, R.E., J. Org. Chem., 25, 2260 (1961); Wright, G.F., in M.S. Newman, "Steric Effects in Organic Chemistry", John Wiley and Sons, Inc., New York, 1956, p. 397-402, and references cited therein.

72. Corey, E.J., J. Am. Chem. Soc., 76, 175 (1954); Corey, E.J., and Sneen, R.A., ibid., 78, 6269 (1956).

73. Zimmerman, H.E., J. Org. Chem., 20, 549 (1955).

74. Shoppee, C.W., and Summers, G.R.H., J. Chem. Soc. 687, (1950).

75. Nace, H.R., and O'Connor, G.L., J. Am. Chem. Soc. 73, 5824 (1951).

76. Fieser, L.F., Fieser, M., and Chakravarti, R.N., J. Am. Chem. Soc. 71, 2229 (1949).

77. Cremlyn, R.J.W., and Shoppee, C.W., J. Chem. Soc. 3515 (1954).

78. Henbest, H.B., and Wilson, R.A.L., J. Chem. Soc. 3289 (1956).

79. Jones, D.N., Lewis, J.R., Shoppee, C.W., and Summers, G.R.H., J. Chem. Soc. 2876 (1955).

80. Shoppee, C.W., and Summers, G.R.H., J. Chem. Soc. 3361 (1952).

81. Sarett, L.H., Feurer, M., and Folkers, K., J. Am. Chem. Soc. 73, 1777 (1951); Rosenkranz, G., Pataki, J., and Djerassi, C., J. Org. Chem., 17, 290 (1952); Bernstein, S., Lenhard, R.H., and Williams, J.W., J. Org. Chem. 18, 1166 (1953).

82. Dauben, W.G., Micheli, R.A., and Eastham, J.F., J. Am. Chem. Soc., 74, 3852 (1952).

83. Mateos, J.L., J. Org. Chem. 24, 2034 (1959); Wheeler, O.W., and Mateos, J.L., Can. J. Chem., 36, 1049 (1958).

84. Zander, J., Forbes, T.R., von Münstermann, A.M., and Neher, R., J. Clin. Endocrinol. Metab., 18, 337 (1958).

85. Hegner, P., and Reichstein, T., Helv. Chim. Acta, 26, 715 (1943); von Euw, J., and Reichstein, T., ibid., 29, 654 (1946).

86. Plattner, Pl. A., Heusser, H., and Herzig, P. Th., Helv. Chim. Acta, 32, 270 (1949); Heusser, H., Engel, Ch. R., Herzig, P. Th., and Plattner, ibid., 33, 2229 (1950); Günthard, Hs. H., Beriger, E., Engel, Ch. R., and Heusser, H., ibid., 35, 2437 (1952).

87. Junkmann, K., Arch. Exp. Pathol. Pharmakol., 223, 244 (1954); Davies, M.E., and Wied, G.L., J. Clin. Endocrinol. Metab., 15, 923 (1955).

88. Marshall, D.J., and Gaudry, R., Can. J. Chem., 38, 1495 (1960).

89. Ringold, H.J., Batres, E., and Rosenkranz, G., J. Org. Chem., 22, 99 (1957); Miramontes, L., Aguinaco, P., and Romero, M.A., J. Am. Chem. Soc., 82, 6153 (1960).

90. Bernstein, S., Centrall, E.W., and Dusza, J.P., J. Org. Chem., 26, 269 (1961), and references cited therein.

91. Ringold, H.J., Batres, E., Bowers, A., Edwards, J., and Zderic, J., J. Am. Chem. Soc. 81, 3485 (1959).

92. Ehrenstein, M., J. Org. Chem., 9, 435 (1944).

93. Allen, W.M., and Ehrenstein, M., Science, 100, 251 (1944).

94. Barber, G.W., and Ehrenstein, M., Ann., 603, 89 (1957).

95. Djerassi, C., and Ehrenstein, M., Ann., 612, 93 (1958).

96. Birch, A.J., Quart. Rev., 4, 69, (1950), and references cited therein.

97. Birch, A.J., and Mukherji, S.M., J. Chem. Soc. 2531 (1949); Birch, A.J., ibid., 367 (1950); Wilds, A.L., and Nelson, N.A., J. Am. Chem. Soc., 75, 5360, 5366 (1953).

98. Djerassi, C., Miramontes, L., and Rosenkranz, G., J. Am. Chem. Soc. 73, 3540 (1951); 75, 4440 (1953).

99. Nelson, N.A., and Garland, R.B., J. Am. Chem. Soc. 79, 6313 (1957); Stork, G., Khastgir, H.N., and Solo, A.J., ibid. 80, 6457 (1958).

100. Djerassi, C., Lippman, A.E., and Grosman, J., J. Am. Chem. Soc. 78, 2479 (1956).

101. Robinson, C.H., Gnoj, O., Charney, W., Gilmore, M.L., and Oliveto, E.P., J. Am. Chem. Soc. 81, 408 (1959); Kishida, Y., Ann. Report Takamine Lab., 11, 27 (1959).

102. Marker, R.E., and Crooks, H.M., J. Am. Chem. Soc., 64, 1280 (1942); Wettstein, A., Helv. Chim. Acta, 27, 1803 (1944); Graber, R.P., and Meyers, M.B., Chem. and Ind., 1478 (1960).

103. McGuckin, W.F., and Kendall, E.C., J. Am. Chem. Soc. 74, 5811 (1952).

104. Poos, G.I., Arth, G.E., Beyler, R.E., and Sarett, L.H., J. Am. Chem. Soc., 75, 422 (1953).

105. Vanderhaeghe, H., Katzenellenbogen, E.R., Dobriner, K., and Gallagher, T.F., J. Am. Chem. Soc. 74, 2810 (1952).

106. Marshall, C.W., Kritchevsky, T.H., Lieberman, S., and Gallagher, T.F., J. Am. Chem. Soc. 70, 1837 (1948); Bedoukian, P.Z., ibid., 67, 1430 (1945).

SUMMARY AND CONTRIBUTION TO KNOWLEDGE

1. Solvolysis of 12α-bromo-3α, 20β-diacetoxypregnane-11-one in formic acid and silver acetate afforded the 1:2-methyl shifted compound 18-nor-12-methyl-3α, 20β-diacetoxy-12-pregnene-11-one in poor yield. The latter compound was identified by spectroscopic data. However, extensive chromatographic purification and attempted crystallisation failed to yield a pure sample of the 1:2-methyl shifted compound.

2. An investigation of lithium aluminium hydride reduction of 3α, 12α-dihydroxypregnane-20-one and 3α, 12α-diacetoxypregnane-20-one in diethyl ether and tetrahydrofuran led to the following conclusion: 3α, 12α-dihydroxypregnane-20-one with a 12-hydroxy function gave predominantly the 20α-alcohol, while 3α, 12α-diacetoxypregnane-20-one having an acetate function at the 12-position afforded the 20β-alcohol as the major product. When tetrahydrofuran was used as the solvent in the reduction reaction the yield of 20β-alcohol increased. A mechanism has been advanced to interpret the effect of 12-substituent, and the solvent effect has been explained in terms of its basicity.

3. The reaction of 12-ketopregnane derivatives with methyl Grignard reagent gave predominantly the 12β-methyl-12α-hydroxy epimer, contrary in this case, to the "rule of rear-attack". This conclusion was based on spectroscopic and chemical evidence.

4. A tentative conclusion that in the 12-methyl steroids the exo location of the double bond at the 12-position is thermodynamically more stable than the endo has been drawn. Evidence, though not unambigous, has been presented to support this conclusion.

5. A literature survey of lithium aluminium hydride reduction and methyl Grignard or methyl lithium reaction of steroidal ketones revealed that the composition of the epimeric alcohols obtained, are in some cases contrary to the "rule of rear-attack". A theory based on the steric influences of (a) the 1:3-diaxial non-bonded interactions and (b) the relative size of the organo-metallic complex to axial approach of the attacking nucleophile (either lithium aluminium hydride, methyl Grignard or methyl lithium as the case may be) has been advanced. The relevant experimental facts could be explained on the basis of this hypothesis.

6. Four new 12-substituted progesterone analogues have been prepared, but the preliminary biological tests did not exhibit any notable progestational, androgenic, diuretic, hypotensive or anabolic properties.