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# Alkylsteroids

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Alkylsteroids constitute an important class of steroid compounds containing additional alkyl groups compared with natural hormones. The introduction of alkyl groups enhances the physiological activity and narrows the spectrum of the biological activity of steroids. Furthermore alkylsteroids are of interest for the stereochemistry of the reactions which take place with participation of condensed alicyclic systems. The methods for the direct introduction of alkyl groups based on the reactions of steroids ketones and epoxides are described.
The bibliography includes 255 references.

CONTENTS

1. Introduction 850
2. Alkylation of steroid ketones 850
3. Reactions of steroid ketones with organometallic compounds 852
4. Conjugated addition of Grignard reagents to unsaturated steroid ketones 853
5. Addition of diazomethane to steroid ketones 854
6. Opening of steroid epoxide rings by Grignard reagents 855
7. Simultaneous introduction of two alkyl substitutents 857

## 1. INTRODUCTION

One of the principal ways in which the structure of steroids is modified consists in the introduction into the latter of additional alkyl groups (mainly methyl). The alkyl steroids thus produced have in many cases an enhanced physiological activity compared with the initial compound. Even more interesting is the fact that the introduction of alkyl groups alters the relation between different types of physiological activity making it possible to prepare compounds with specific activities. Many alkylsteroids have found application in medical practice—an anabolic preparation dianabol (17α-methyl group), an anti-inflammation agent dexamethasone (16α-methyl group), antiovulatory agents dimethisterone and medroxyprogesterone (6α-methyl group), etc. The effect of methyl groups on certain types of the physiological activity of steroids is described in Table 1.

**Table 1.** Effect of methyl groups on the physiological activity of steroids (+ increase of activity, −decrease of activity, ± activity unchanged)[2].

| Type of activity | Position of methyl group | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1α | 2α | 4 | 6α | 7α | 9α | 11α | 16α | 16β | 17α | 21 |
| Androgenic | + | − | − | − | + | | − | | − | ± | |
| Anabolic | + | − | + | ± | + | | − | | | ± | |
| Gestagenic | | ± | − | + | | | | ± | − | + | − |
| Glucocorticoid | − | + | − | + | − | − | − | + | + | − | ± |
| Mineralocorticoid** | − | + | − | ± | | − | − | − | − | − | − |
| Anti-inflammation | | + | − | + | − | − | − | + | + | ± | + |

*Deposition of glycogen in the liver.
**Retention of $Na^+$ ions.

The study of alkylsteroids has made a considerable contribution both to the stereochemistry of reactions with participation of condensed alicyclic systems and to synthetic organic chemistry. Furthermore, the last available review on alkylsteroids[1] refers to work published up to 1960 and is to a considerable degree obsolete. In view of the large number of studies in which alkylsteroids were synthesised (more than 1500) and the space available, it was necessary to restrict the scope of this review, which includes only the methods for the direct introduction of alkyl groups in reactions with steroid ketones and epoxides. Numerous methods for the indirect synthesis of alkylsteroids in which oxygen- or nitrogen-containing and also unsaturated hydrocarbon substituents are initially introduced into the molecule and then transformed into alkyl groups (formylation and cyanation reactions, reactions with carbenes, Wittig, Mannich, etc. reactions) are not considered in the review. The limits of applicability of various methods for the synthesis of alkylsteroids are shown in Table 2.

**Table 2.** Different synthetic methods for the preparation of alkylsteroids (according to the data in Sections 2–7).

| Method of synthesis | Position of alkyl group introduced | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 15 | 16 | 17 | 20 | 21 |
| Alkylation of ketones | | + | | + | + | + | + | + | + | | | + | | + | + | | + |
| Reaction of ketones with organometallic compounds | + | + | + | + | | + | + | | | | + | + | + | | + | + | |
| Conjugated addition of Grignard reagents | + | | | + | + | | + | | + | | | | | + | | + | |
| Reaction of diazomethane with ketones | + | | | + | | | | | | | | | + | + | + | + | + |
| Opening of epoxy-rings by Grignard reagents | | | | + | + | + | | | + | | | + | + | + | | | |

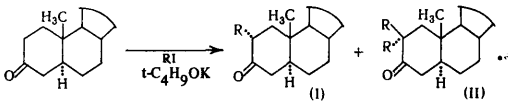
## 2. ALKYLATION OF STEROID KETONES

In this section two types of alkylation are dealt with—direct alkylation of unsaturated and saturated ketones usually by the action of alkyl iodides in an alkaline medium and reductive alkylation of unsaturated ketones. In the latter case treatment of a conjugated unsaturated ketone with lithium in liquid ammonia yields the enolate which is then treated with alkyl iodide to form the unsaturated alkyl

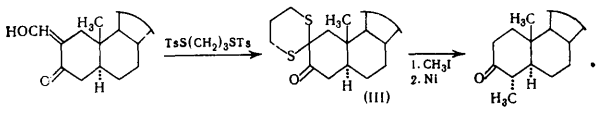
ketone. Methods for the introduction of an alkyl group into $\alpha$-bromoketones by the simultaneous action of Grignard reagents and alkyl halides and also for the introduction of alkyl groups into unsaturated ketones by treating with alkyl halides the intermediates produced in the conjugated addition of Grignard reagents (see Section 4) resemble this type of alkylation.

The enolic form of the steroid ketone takes part in direct alkylation and therefore the mode of alkylation of the ketone is determined by the mode of its enolisation. Alkaline reaction conditions favour the formation of the most stable isomers. Accordingly 3-oxo-5$\alpha$,10$\beta$- and 3-oxo-5$\beta$,10$\alpha$-steroids are alkylated predominantly at $C_2$ and 3-oxo-5$\beta$,10$\beta$- and 3-oxo-5$\alpha$,10$\alpha$-steroids[3,4] are alkylated at $C_4$. 1,3-Diketones are also alkylated at $C_2$.[5]

The alkylation of 3-oxo-5$\alpha$-steroids always yields a mixture of 2$\alpha$-monoalkylsteroids (I) and 2,2-dialkylsteroids (II) the relative amounts of which depend on the reaction conditions. Further alkylation at $C_4$ either does not occur at all or takes place with a very low yield[6-9]:



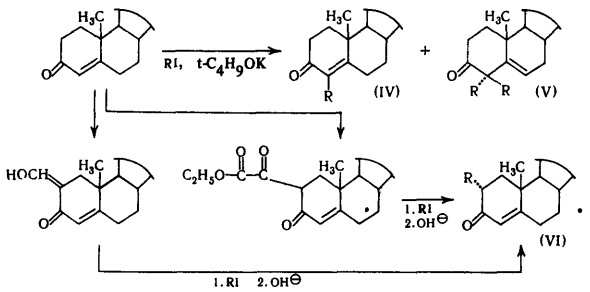

When it is necessary to prepare selectively the 2$\alpha$-alkylsteroid (I), the formyl or oxalyl derivatives of the initial ketone, which protect it from the introduction of a second group, are alkylated[6,10]. If the desired product is the 4-alkylsteroid, it is necessary to block position 2 completely. One of the possible methods for this consists in the formation of the cyclic thioketal (III) by the reaction of di-*p*-toluenesulphonate of propane-1,3-dithiol with 2-hydroxymethylene derivatives. Subsequent alkylation yields a mixture of 4-methyl derivatives from which the protecting group is readily removed by desulphuration with Raney nickel, the corresponding 4$\alpha$-methylsteroids being formed[11,13]:



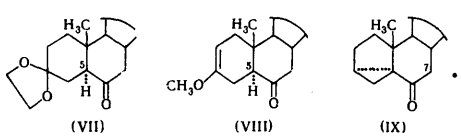

The introduction of a $\Delta^7$-bond into 3-oxo-5$\alpha$-steroids alters sharply the mode of alkylation towards the formation of 4-methyl derivatives[14-16]. A change of this kind does not take place on introduction of a $\Delta^6$-bond[17] and also in B-norsteroids[18] and $\Delta^7$-5$\beta$,10$\alpha$-steroids[19]; all these compounds are alkylated similarly to the normal series.

The alkylation of 3-oxo-$\Delta^4$-steroids, the products of which usually consist of a mixture of 4-alkyl (IV) and 4,4-dialkyl (V) derivatives, with the latter greatly predominating, has been investigated in greatest detail[6,8,20-25]. Special reaction conditions have been developed for the preferential formation of 4-monoalkylsteroids of type (IV)[26-32]; even under these conditions the presence in the molecule of the initial 3-oxo-$\Delta^4$-steroid of a 6$\alpha$-methyl group leads to the predominance of dialkyl derivatives in the reaction products[33,34]. It is noteworthy that 3-oxo-$\Delta^{4,7}$-steroids are alkylated similarly to $\Delta^4$-3-ketones, while 3-oxo-$\Delta^{4,6}$-steroids are not alkylated under the usual conditions[35]. This course of reaction was explained by the comparative stability of the conjugated anions corresponding to the successive stages in the alkylation process[36]. The alkylation of 3-oxo-$\Delta^4$-steroids with polymethylene dibromides $Br(CH_2)_nBr$ yields 4,4-spirocycloalkyl derivatives[37].

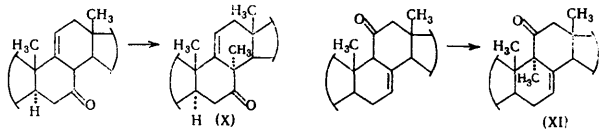
The need to prepare 2-alkyl derivatives of 3-oxo-$\Delta^4$-steroids led to the development of their synthesis via formyl[38,39] and oxalyl[40-43] derivatives. When the primary alkylation product is acted upon by alkalis, the activating groups are hydrolysed with formation of 2$\alpha$-alkylsteroids (VI).



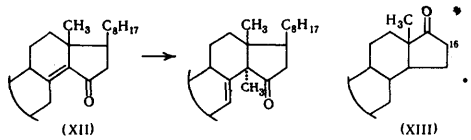

In the alkylation of 6-oxosteroids unsubstituted at $C_5$ the products are 5-alkyl derivatives the configuration of which depends on the nature of the substituents in the ring A. Thus the ketone (VII) with a dioxolane group forms the corresponding 5$\beta$-methyl derivative[44], while the enolic ether (VIII) forms the 5$\alpha$-methyl derivative[45]. The alkylation of 6-oxo-3$\alpha$,5$\alpha$-cyclosteroids (IX) yields a mixture of 7$\beta$-methyl and 7,7-dimethyl derivatives, with the latter predominating[46-49].




7-Oxo-$\Delta^5$-steroids are alkylated as a rule at $C_6$ with formation of dialkyl derivatives[50,51]. However, the introduction of a $\Delta^{9(11)}$-bond into the molecule of a 7-oxosteroid activates the 8-position as a result of which the methylation of these ketones leads to the formation of 8$\alpha$-methyl derivatives (X)[52,53]. Similarly, 9$\alpha$-methyl derivatives (XI) were obtained by the methylation of 11-oxo-$\Delta^7$-steroids[54]:

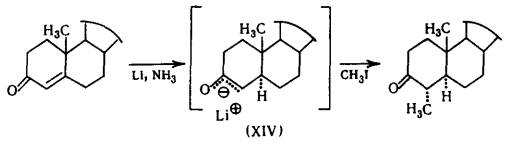



Direct methylation of the 15-oxo-$\Delta^{8(14)}$-steroid (XII) under severe conditions led to the corresponding 14$\alpha$-methylsteroid with migration of the double bond to the $\Delta^7$-position[24,55,56]. The structural analogues of compound (XII)—A-nor-3-oxosteroids—form on alkylation 5$\beta$-methyl derivatives[57]. Both 16$\alpha$-methyl and 16$\beta$-methyl derivatives were obtained from 17-oxosteroids (XIII) under different conditions[29,58,59]:



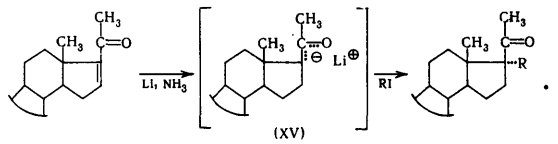
Angular methylation of 18-nor-17-oxo- and 18-nor-17a-oxo-steroids with formation of 13-methyl derivatives is one of the stages in many total syntheses of steroid compounds and has been discussed in detail in a recently published monograph[60].

The so called "reductive alkylation" has found wide application recently in the synthesis of alkylsteroids. For example, when 3-oxo-$\Delta^4$-steroids are acted upon by alkali or alkaline earth metals (lithium, sodium, calcium, or barium) in liquid ammonia, the product is the anion (XIV), the treatment of which *in situ* with methyl iodide gives the 5$\alpha$-dihydro-4$\alpha$-methyl derivative[61,62]. When the proportions of the reactants are altered, the 4,4-dimethyl derivative is produced[63]. Similarly, 2$\alpha$-methyl derivatives were obtained from 3-oxo-$\Delta^{1,4}$-steroids[64] and 4,4-dimethyl-$\Delta^5$-derivatives from 3-oxo-$\Delta^{4,6}$-steroids[61]:



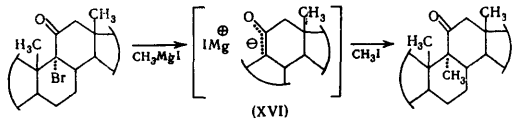

(XIV)

This method of synthesis is employed particularly frequently for the introduction of 17$\alpha$-alkyl groups into 20-oxo-$\Delta^{16}$-steroids of the pregnane series. 17$\alpha$-Bromo-, 17$\alpha$-hydroxy-, and 17$\alpha$- and 17$\beta$-acetoxy-derivatives of 20-oxosteroids, which under the action of lithium and liquid ammonia form the intermediate anion (XV), also enter into this reaction. 17$\beta$-Alkyl- and 21-alkyl-steroids are formed in a small amount as side products[56,65-68]:




(XV)

The method for the introduction of alkyl groups into $\alpha$-bromosteroids by the action of a mixture of a Grignard reagent and a large excess of an alkyl halide has a mechanism similar to that of reductive alkylation. Here the intermediate stage also involves the formation of the enolate anion of type (XV) with loss of a bromine atom; subsequent methylation of compound (XVI) leads to the corresponding 9$\alpha$-methyl derivative[12,69-71]:




(XVI)

12$\alpha$-Methylsteroids have been prepared[12] from 12$\alpha$-bromo-11-ketones by the method described above for the synthesis of 9$\alpha$-methyl derivatives from 9$\alpha$-bromo-11-oxosteroids. It proved possible to carry out the same reaction with the enolic acetates of 11-oxo- and 20-oxosteroids, 9$\alpha$,12$\beta$-dimethyl and 17$\alpha$-methyl derivatives being obtained respectively[70].

## 3. REACTIONS OF STEROID KETONES WITH ORGANOMETALLIC COMPOUNDS

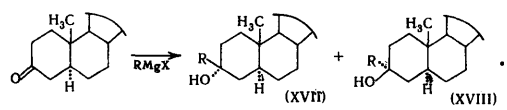
This group of reactions is most widely used for the introduction of alkyl groups into steroid compounds. In recent years it has been shown[72] that ethylene-ketals of 3-, 17-, and 20- oxosteroids also react with Grignard reagents under severe conditions.

A characteristic feature of the reactions of organometallic compounds with oxosteroids is attack from the least sterically hindered side. The stereochemistry of the reaction is influenced by polar groups in the steroid and also by the size and polarity of the attacking agent. The simultaneous effects of all these factors usually lead to the formation of a mixture of reaction products with different steric orientations of the substituted alkyl group[73,74], the isomer with the equatorial alkyl group predominating[74]. Recent studies have shown for 12-, 17-, and 17a-oxosteroids numerous deviations from the so called "rule of attack from the $\alpha$-side"[75] (opposite to the side of the angular methyl group). Therefore this rule cannot be regarded as having general applicability.

Grignard reactions have been used for the introduction of alkyl substituents into the 1-position[76,77] and the 2-position[78]; in the first case the stereochemistry was not elucidated and in the second only the 2$\alpha$-alkyl isomer, with an equatorial position of the substituted alkyl group, was obtained.

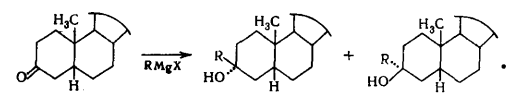
Reactions with participation of 3-oxosteroids have been investigated in incomparably greater detail. Thus in the reaction of 3-oxo-5$\alpha$-steroids with Grignard reagents a mixture of epimers (XVII) and (XVIII) is usually formed, compound (XVII) with the equatorial 3$\beta$-configuration of the substituted alkyl[79-82] or phenyl[83] group [(XVII) : (XVIII) $\simeq$ 1.5–2 : 1)] predominating; in one case the opposite ratio of reaction products was obtained. When the molecule possesses 1$\alpha$-hydroxy-[84], 1$\alpha$-methyl-[77], 2$\alpha$-bromo-[85], and 5$\alpha$-hydroxy-substituents[86], the reaction of 3-oxo-5-steroids with $CH_3MgI$ and $CH_3Li$ leads exclusively to isomer (XVII) with an equatorial 3$\beta$-methyl group. The introduction of a $\Delta^4$-bond into the steroid does not alter significantly the mode of the Grignard reaction: 3-oxo-$\Delta^4$-steroids form approximately equal amounts of 3$\alpha$- and 3$\beta$-alkyl isomers[87], while 3-oxo-$\Delta^5$-steroids yield predominately the 3$\alpha$-alkyl isomer of type (XVIII)[88].

The Norman reaction with 3-oxo-5$\alpha$-steroids[81] and ethynylation[74,81,89] involve a stereochemical orientation opposite to that in the Grignard reaction and lead to a mixture of isomers (XVII) and (XVIII), the latter (with an axial alkyl substituent) greatly predominating (1 : 6.5–7.0):



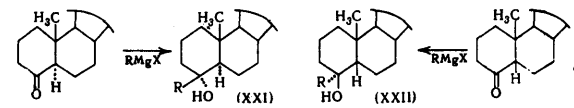

(XVII) (XVIII)

3-Oxo-5$\beta$-steroids form in a Grignard reaction mainly the isomer with the axial 3$\beta$-configuration of the alkyl group [(XIX) : (XX) = 2 : 1 when R = $C_6H_5$][90]:




(XIX) (XX)

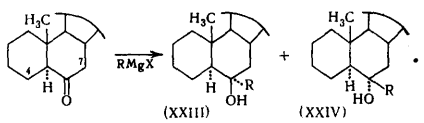
In the Grignard and Iotsich reactions, 4-oxosteroids of the 5$\alpha$-series yield the axial 4$\beta$-alkyl isomer (XXI), while the Iotsich reaction with 4-oxosteroids of the 5$\beta$-series results in the formation of the axial 4$\alpha$-alkyl isomer (XXII)[91-93]:




(XXI) (XXII)

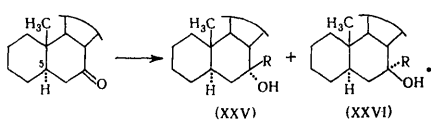
6-Oxosteroids form with $CH_3MgI$ only isomer (XXIII) with an equatorial alkyl group[94-98] and introduction of 5$\alpha$-hydroxy-[99-103] or 7-alkyl[46] substituents does not alter

the stereochemistry of the reaction. At the same time in the presence of a 4α-methyl group in the steroid, a 6β-methyl derivative of type (XXIV) was found to predominate [104]. According to some data [105], arylmagnesium bromides form the isomer (XXIII), while according to others [106] the product is the isomer (XXIV). In the Grignard reaction 6-oxo-3α,5α-cyclosteroids form the isomer (XXIV) [107]:



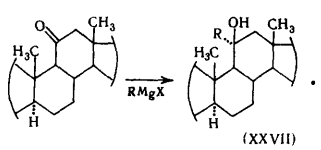
(XXIII) (XXIV)

The Grignard reaction with participation of 7-oxo-5α-steroids yields predominately equatorial 7β-alkyl isomers of type (XXV) [108,109]. As with 3-oxosteroids, the introduction of a $\Delta^5$-bond alters sharply the stereochemistry of the process and isomers of type (XXVI) with an axial methyl group [109,110] at $C_7$ greatly predominate in the mixture of products of the reaction of 7-oxo-$\Delta^5$-steroids with $CH_3MgI$ and $CH_3Li$:



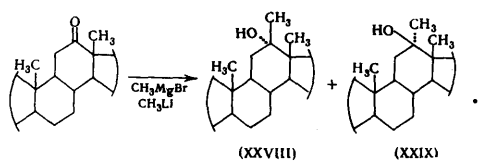
(XXV) (XXVI)

The sterically hindered 11-oxo-group is nevertheless susceptible to attack by organometallic compounds. Only the equatorial 11-alkyl derivatives of type (XXVII) were observed in all cases; methyl-lithium and the Iotsich agent form this product in higher yields than methylmagnesium bromide [111-117]. The reaction is more difficult with 11-ketones of the 5β-series and also in the presence in the steroid molecule of a free 17α-hydroxy-group; in both cases the approach of the reactant from the α-side of the steroid molecule is sterically hindered [112,118,119]:



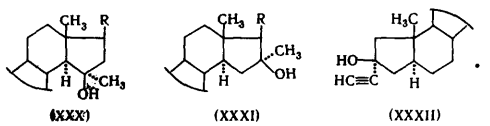
(XXVII)

Despite earlier data [120,121], 12-oxosteroids form with organometallic compounds a mixture of isomers (XXVIII) and (XXIX) in which the equatorial 12β-methyl derivative (XXVIII), formed as a result of attack from the β-side of the steroid molecule [122-125], predominates:



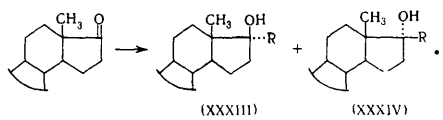
(XXVIII) (XXIX)

The reaction of 15-oxosteroids of the pregnane series with methylmagnesium bromide yields the 15α-methyl derivative (XXX) [126]. Both in the presence and absence of a 17β-hydroxy-group, 16-oxosteroids form with methylmagnesium bromide [127,128] and ethynyl-lithium [129,130] only 16α-alkyl derivatives of type (XXXI). The $C_{16}$ position is stereochemically equivalent to the $C_2$ position in A-norsteroids. Therefore 2-oxo-A-norandrostanes react with ethynyl-lithium, forming a mixture of isomers in which the 2α-ethynyl derivative (XXXII) greatly predominates [131,132]:



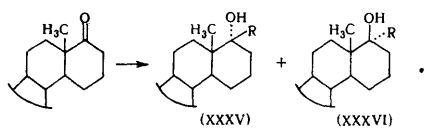
(XXX) (XXXI) (XXXII)

In the reaction of organometallic compounds with 17-oxosteroids, the products are mainly 17α-alkyl derivatives of type (XXXIII) [133]. The stereochemistry of the reaction does not alter when the molecule contains 16α-methyl and 16-spirocyclopropyl groups [29,134,135]. The reaction with methyl-lithium gives higher yields and is more stereospecific than the reactions with Grignard reagents [136,137]. In a number of studies small amounts of the 17β-alkyl isomer (XXXIV) were detected in the mixture of products of reactions of 17-oxosteroids with methyl [138], phenyl [139], and allyl [139,140] Grignard reagents. The isomer (XXXIV) predominates when the 17-oxosteroid molecule contains 12β-hydroxy- [141], 16α-acetoxy- [127], and 16α-fluoro-substituents [142] and also in the reaction of the methyl ether of oestrone with $KC{\equiv}CCH(OC_2H_5)_2$ (the potassium derivative of the diethylacetal of propiolic aldehyde) [143]:



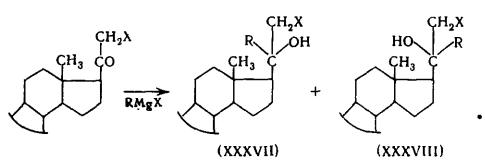
(XXXIII) (XXXIV)

The reaction of 17α-oxo-derivatives of D-homosteroids with organometallic compounds yields a mixture of isomers, the composition of which depends on the reagent employed. Grignard reagents form mainly the isomer (XXXV), corresponding to the equatorial substitution of an alkyl group, while methyl- and ethynyl-lithium give rise to a mixture of products in which the isomer (XXXVI) with an axial methyl (ethynyl) group predominates [144-149]:



(XXXV) (XXXVI)

A product with the 19-*S*-configuration is formed in the reaction of steroid 19-aldehydes with methyl-lithium [150]. 20-Oxosteroids unsubstituted at $C_{21}$ react with methylmagnesium iodide, forming almost exclusively the 20β-methyl derivative (XXXVII) [151]. The 21-acetoxy-derivative (X = OAc) forms a mixture of isomers containing up to one-third of the 20α-alkyl derivative (XXXVIII) [152]:



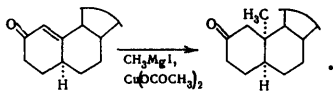
(XXXVII) (XXXVIII)

## 4. CONJUGATED ADDITION OF GRIGNARD REAGENTS TO UNSATURATED STEROID KETONES

In 1941 it was shown [153] that in the presence of copper(I) salts Grignard reagents add to αβ-unsaturated ketones in the 1,4-position forming β-alkyl ketones. The mechanism of this addition is probably similar to that of the Michael reaction but, in contrast to the latter, conjugated addition

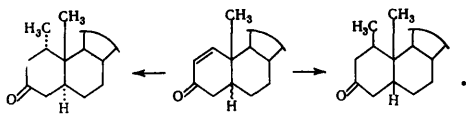
is an irreversible reaction[154]. A special review has been devoted[155] to the stereochemistry of conjugated addition involving cyclic $\alpha\beta$-unsaturated ketones.

Several types of steroid structures allowing the conjugated addition of Grignard reagents have been described. Thus 2-oxo-$\Delta^{1(10)}$-steroids combine with methylmagnesium iodide to form 10$\alpha$-methylsteroids (XXXIV)[156,157]:



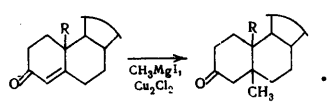

(XXXIX)

The reaction of a Grignard reagent with 3-oxo-$\Delta^1$-steroids of the 5$\alpha$-series yields the 1$\alpha$-methyl derivatives (XL)[158-161], while the 1$\beta$-methyl derivatives (XLI) are formed from the 5$\beta$-analogues[162-164]:



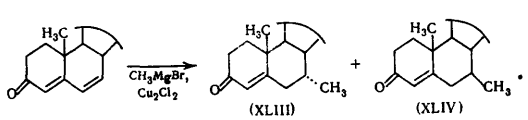
(XL) (XLI)

3-Oxo-$\Delta^4$-steroids usually react with Grignard reagents by a mechanism involving 1,2-addition even in the presence of copper salts[165]. Only with testosterone was it possible to obtain a low yield of the 5$\beta$-methyl derivative (XLII; R = $CH_3$)[166]. Much higher yields (60–80%) were obtained with 19-norsteroids (R = H) where the absence of a methyl group at $C_{10}$ considerably reduces the steric hindrance to the approach of the bulky Grignard reagent[165,166]:



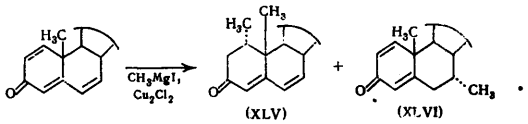

(XLII)

Conjugated 3-oxo-$\Delta^{4,6}$-steroids combine with methylmagnesium bromide in the 1,6-position with formation of 7$\alpha$-methyl derivatives (XLIII)[29,167]; however, when the steroid contains an 11$\beta$-hydroxy-group, a mixture of 7$\alpha$- and 7$\beta$-methyl derivatives is formed, with the 7$\beta$-isomer (XLIV) predominating[168]:



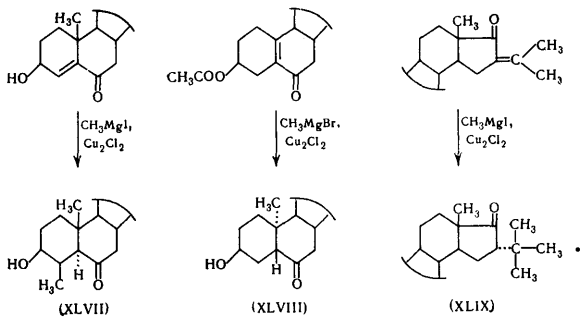

(XLIII) (XLIV)

The addition of Grignard reagents to 3-oxo-$\Delta^{1,4,6}$-steroids takes place in one or other conjugated system depending on the structure of the steroid and either the 1$\alpha$-methyl derivative (XLV) or the 7$\alpha$-methyl derivative (XLVI) predominates in the reaction products, with a small admixture of 1$\alpha$,7$\alpha$-dimethyl derivatives[169,170]:



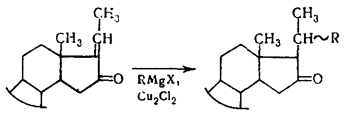

(XLV) (XLVI)

6-Oxo-$\Delta^4$-steroids[171] and 6-oxo-$\Delta^{5(10)}$-steroids[172] form with Grignard reagents 4$\beta$-methyl (XLVII) and 10$\alpha$-methyl (XLVIII) derivatives respectively. The reaction of 16-isopropylidene-17-oxosteroids yields the 16$\alpha$-t-butyl derivative (XLIX)[78]:



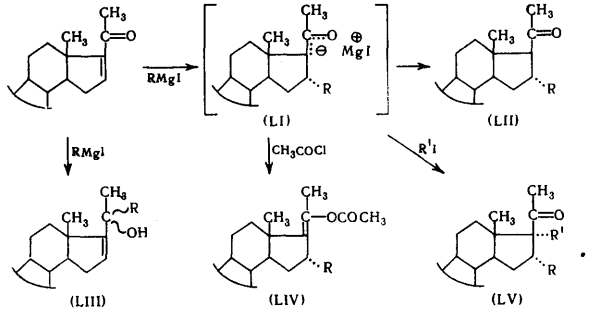

(XLVII) (XLVIII) (XLIX)

16-Oxo-$\Delta^{17(20)}$-steroids react with Grignard reagents to form a mixture of approximately equal amounts of 20$\alpha$-alkyl- and 20$\beta$-alkyl-steroids (L)[173]:




(L)

The conjugated addition of Grignard reagents to 20-oxo-$\Delta^{16}$-steroids has been investigated in greatest detail. Without added copper salts, products of both 1,2-addition [compound (LIII)] and 1,4-addition [compound (LIV)] are formed, the fraction of the latter increasing with the size of the alkyl radical R.[174] The addition of copper salts displaces the reaction almost entirely towards 1,4-addition with formation of 16$\alpha$-alkylsteroids (LII)[175-182]. Structural changes in rings A and B have hardly any effect on the yield of compound (LII) but the presence of a 21-hydroxy-group lowers it significantly[183]. The presence of a 16-methyl group in the initial 20-oxo-$\Delta^{16}$-steroids does not preclude high yields of 16,16-dimethyl derivatives[184,185]. Treatment of the intermediate enolate (LI) with acetyl chloride yields the enol acetate (LIV) which constitutes the starting material for the synthesis of 17$\alpha$-hydroxysteroids[183,186] and treatment of compound (LI) with alkyl halides gives 16$\alpha$,17$\alpha$-dialkylsteroids (LV)[187]. All these findings greatly extend the scope of the synthetic applications of the conjugated addition reactions of Grignard reagents.



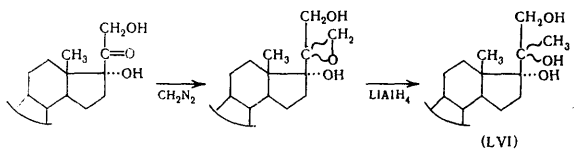

(LI) (LII) (LIII) (LIV) (LV)

## 5. ADDITION OF DIAZOMETHANE TO STEROID KETONES

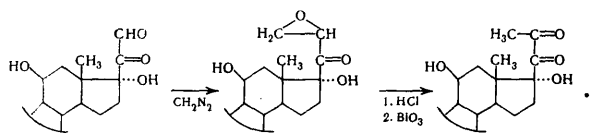
Diazomethane can react with carbonyl-containing steroids in two ways. Either by addition to the carbonyl group with formation of an epoxide or by addition to the

C=C double bond adjacent to the oxo-group with formation of pyrazoline †. The cleavage of the primary addition products leads to the formation of alkylated homologues of steroids.

The first addition mechanism obtains in reactions of diazomethane with 20-ketones [188] and 21-aldehydes [189,190] of the steroid series. The epoxides formed, containing one carbon atom more than the initial compounds, serve as the starting material for the synthesis of 20-methylsteroids (LVI) and 21-methylsteroids (LVII):

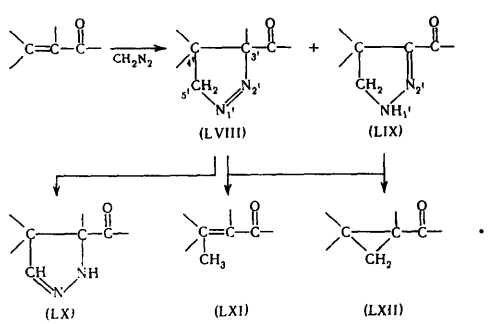


(LVI)



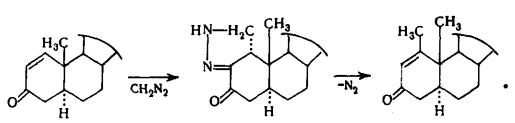
(LVII)

Diazomethane adds to the double bond of $\alpha\beta$-unsaturated ketones with formation of $\Delta^{1'}$-pyrazolines (LVIII) or the isomeric $\Delta^{2'}$-pyrazolines (LIX). Pyrolysis, photolysis, or acidolysis of these pyrazolines can lead to two main products—the methyl ketone (LXI) or the cyclopropyl ketone (LXII)—depending on the reaction conditions and the position of the pyrazoline group in relation to the steroid skeleton. For $\Delta^{1'}$-pyrazoline (LVIII), the possibility of isomerisation to the more stable $\Delta^{5'}$-pyrazoline (LX) has also been noted [39,191,192].



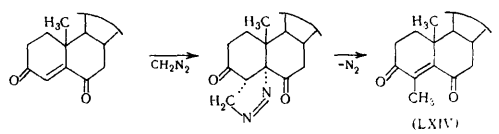
(LVIII) (LIX) (LX) (LXI) (LXII)

In the reaction of 3-oxo-$\Delta^1$-steroids with diazomethane the product is a pyrazoline derivative which on heating or on contact with an acid adsorbent splits off nitrogen forming the 1-methylsteroid (LXIII) as the main reaction product [77,160,193,194]. 3-Oxo-$\Delta^{1,4,6}$-steroids react with diazomethane similarly, forming products of the addition to the $\Delta^1$-bond adjacent to the oxo-group [160,194]:

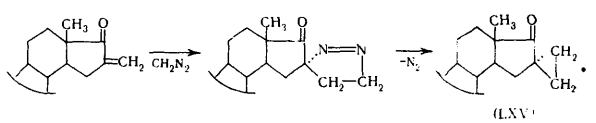


(LXIII)

The products of the addition of diazomethane to 3,6-dioxo-$\Delta^4$-steroids form the 4-methyl derivative (LXIV) on pyrolysis and a mixture of equal amounts of compound (LXIV) and the corresponding $4\alpha,5\alpha$-cyclopropyl derivatives on photolysis [195,196]. At the same time the pyrazoline derivatives obtained from the 16-methylene-17-oxosteroids form 16-spirocyclopropylsteroids (LXV) as the sole product both in pyrolysis and in the reaction with $BF_3$ in acetone [135]:

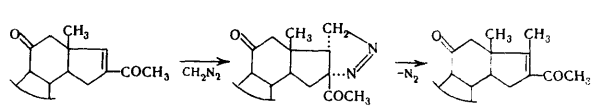


(LXIV)

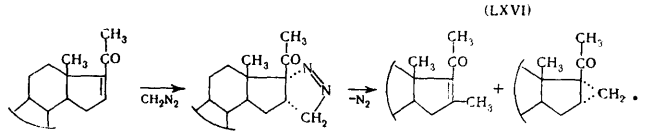


(LXV)

The reaction of 16-acetyl-$\Delta^{16}$-steroids with diazomethane and subsequent pyrolysis yield the 17-methyl derivative (LXVI) [197], while the isomeric 20-oxo-$\Delta^{16}$-steroid can serve as the starting material for the synthesis of 16-methyl derivatives of type (LXVII). Pyrolysis of the intermediate pyrazoline derivative gives predominantly compound (LXVII) and photolysis and acidolysis yield the $16\alpha,17\alpha$-methylenesteroid (LXVIII) [194,196,198-203]. Compounds of type (LXVIII) were also obtained in the reaction of 20-oxo-$\Delta^{16}$-steroids with diazoethane [39] and the diazoacetic ester [204]; at the same time $\Delta^{16}$-etianic acids form 16-methyl derivatives of type (LXVII) [205]:



(LXVI)



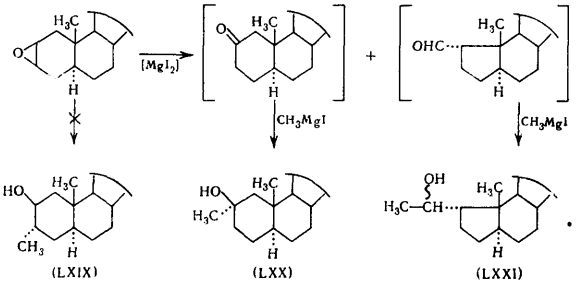
(LXVII) (LXVIII)

## 6. OPENING OF STEROID EPOXIDE RINGS BY GRIGNARD REAGENTS

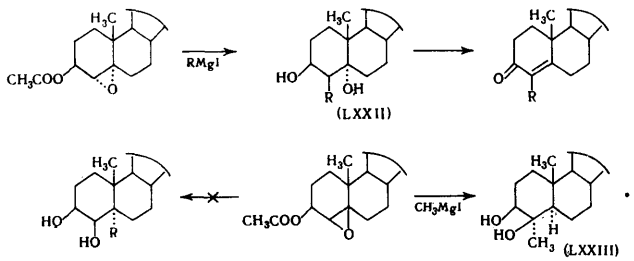
The opening of steroid epoxide rings by Grignard reagents was achieved for the first time in 1939 by Ushakov and Madaeva [206,207]. This reaction is carried out under severe conditions—refluxing in tetrahydrofuran (THF) or a mixture of ether and benzene using a large excess of the Grignard reagent. Therefore, apart from the main ring-opening reaction, various types of rearrangement also take place, due to the effect of magnesium halide in the Grignard reagent [208,209]. Thus in the reaction of the $2\beta,3\beta$-epoxide of the cholestane series with methylmagnesium iodide, a mixture of compounds (LXX) and (LXXI) was obtained instead of the expected ring-opening product (LXIX) [210]. These compounds are formed as a result of the attack of the Grignard reagent on the corresponding ketone and A-noraldehyde, which are the isomerisation products of the initial $2\beta,3\beta$-epoxide. Similar rearrangements also occur in Grignard reactions with participation of steroid $3\alpha$-acetoxy-$4\alpha,5\alpha$-epoxides [86,211], $3\beta$-acetoxy-$4\beta,5\beta$-epoxides [212], $3\beta$-acetoxy-$5\beta,6\beta$-epoxides [213], and $11\beta,12\beta$-epoxides. [214]; in the last case rearrangement can be avoided by using

† The ring expansion in reactions of diazomethane with steroid ketones is not discussed in this review.

dimethylmagnesium instead of methylmagnesium 10-dide[214,215].

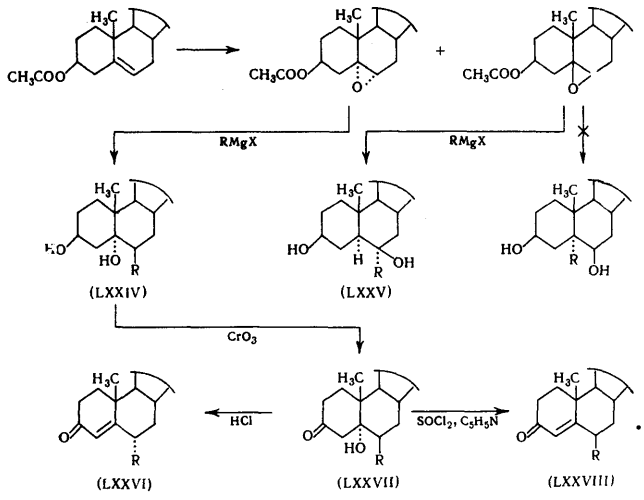



Normal ring opening of the epoxides of the steroid series by Grignard reagents results in the formation of *trans*-diaxial products. For example, the reaction of 3β-acetoxy-4α,5α-epoxide with Grignard, Norman, and Iotsich reagents yields 4β-alkyl(vinyl, ethynyl)-5α-hydroxy-derivatives (LXXII)[216-221]. The presence of a methyl group in the 6α-position does not alter the stereochemistry of the ring-opening reaction[33,222]. By oxidising compounds of type (LXXII) and subsequent dehydration, the corresponding 4-alkyl-3-oxo-Δ⁴-steroids were obtained. Despite earlier data[223], 3β-acetoxy-4β,5β-epoxides do not give rise to normal ring-opening products under the action of Grignard reagents; under these conditions, compound (LXXIII), formed as a result of the rearrangement of the epoxide ring to the 4-ketone and the attack of methylmagnesium iodide on this compound, was isolated[212]:

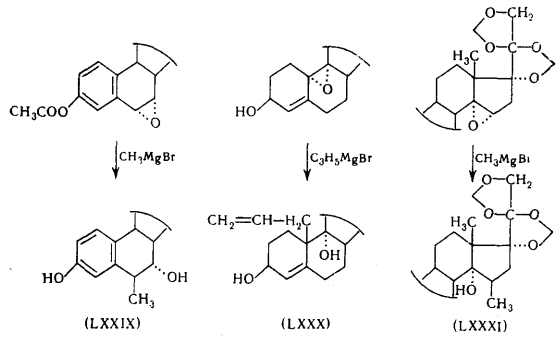



The introduction of epoxy-groups into Δ⁵-steroids leads as a rule to a mixture of both epimeric 5,6-epoxides, in which the 5α,6α-isomer greatly predominates. The opening of the epoxy-ring in the latter under the influence of Grignard reagents yields the 6β-alkyl-5α-hydroxy-derivative (LXXIV)[180,224-232]. Despite earlier data[233], the Grignard reaction involving 5β,6β-epoxides is anomalous. In the first stage the epoxy-ring isomerises with formation of a 6-oxosteroid, which, on being attacked by Grignard reagents, gives rise ultimately to the 6β-hydroxy-6α-methyl derivative (LXXV)[234].

Compounds of type (LXXIV) are converted into the corresponding physiologically active 6-alkyl-3-oxo-Δ⁴-steroids by various methods, depending on the structure of the initial compounds. Oppenauer oxidation or oxidation with $CrO_3$ of the 3-hydroxy-group yields the 3-oxosteroid (LXXVII), the dehydration of which under acid conditions is accompanied by the inversion of the 6β-alkyl group and the formation of the 6α-alkyl steroid (LXXVI). When the 6β-alkylsteroid (LXXVIII) is required, the dehydration is carried out under neutral or weakly alkaline conditions[29,177,178,235-242].

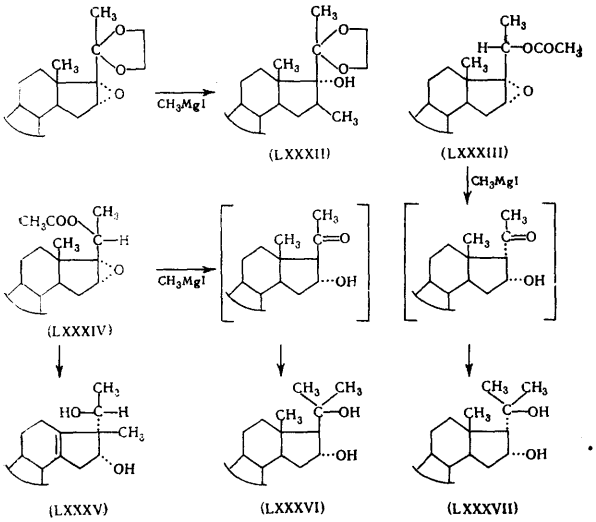



By opening the epoxy-ring of the 6α,7α-epoxide of the oestrane series, the 7α-hydroxy-6β-methyl derivative (LXXIX) was obtained[243]. The 9α,10α-epoxide produced by total synthesis forms the normal epoxy-ring opening product (LXXX) with allylmagnesium bromide; it is interesting to note that this reaction does not take place with Grignard reagents containing saturated alkyl radicals[244]. The reaction of the 14α,15α-epoxide with methylmagnesium bromide yielded the 14-hydroxy-15β-methylsteroid (LXXXI)[245]:



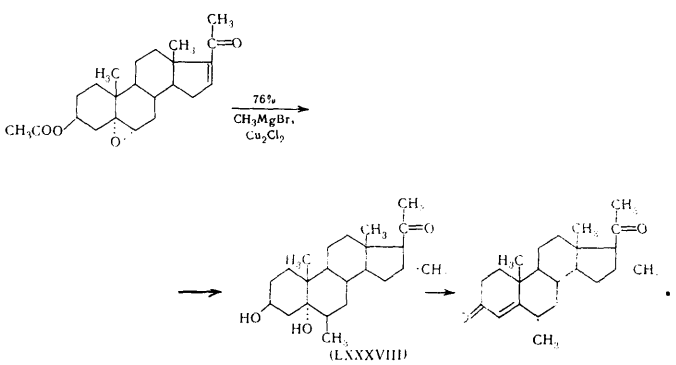

The Grignard reaction of the 20-ethyleneketal of the 16α,17α-epoxy-20-oxosteroid involves the opening of the epoxy-ring and the formation of the 17α-hydroxy-16β-methyl derivative (LXXXII)[246-248]. The Grignard reactions of epimeric 20-acetoxy-16α,17α-epoxysteroids are unusual. Apart from undergoing the Wagner–Meerwein rearrangement to compound (LXXXV), the acetoxy-derivative (LXXXIV) also isomerises to the corresponding 16α-hydroxy-20-ketone which reacts further with the Grignard reagent to form the 20-methylsteroid (LXXXVI). Under the action of the Grignard reagent, the epimeric 20α-acetate (LXXXIII) forms the 20-methyl steroid (LXXXVII) with the 17α-configuration of the side chain, which suggests the

intermediate formation of the 16α-hydroxy-17α,20-oxo-compound[249-254].



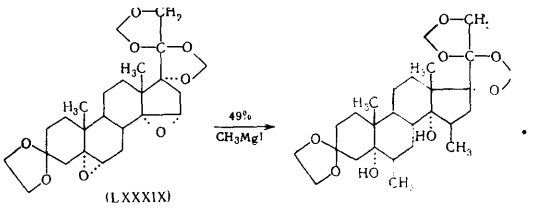

## 7. SIMULTANEOUS INTRODUCTION OF TWO ALKYL SUBSTITUENTS

The application of the methods discussed in Sections 2–6 to bifunctional steroid derivatives permits the introduction of two alkyl groups in a single stage. An example of this is provided by the reaction of methylmagnesium bromide with the epoxide of hydroxydehydropregnenone in which the epoxy-ring is opened with the introduction of a 6-methyl group and there is conjugated addition to the αβ-unsaturated ketone with the introduction of a 16-methyl group. The product (LXXXVIII) serves as the starting material for the synthesis of 6α, 16α- and 6β, 16α-dimethylsteroids[177,178,182,186]:




The synthesis of compound (LXXXVIII) is an example of reactions with two different functional groups. Other examples of this kind are provided by Grignard reactions with 3,17-dioxo-Δ[1]-steroids[160] and 6,20-dioxo-Δ[16]-steroids[177,182] where dialkyl steroids are formed as a result of 1,2-addition to one of the oxo-groups and conjugated 1,4-addition to the unsaturated group incorporating the second oxo-group.

Dialkylsteroids can also be obtained by the action of organometallic compounds on steroids with two similar reactive groups. Thus, following ring opening under the action of methylmagnesium bromide, the 5α,6α; 14α,15α-diepoxide (LXXXIX) forms the 6,15-dialkyl derivatives[245]:




Two alkyl groups are introduced in the corresponding positions of the steroid skeleton under the action of Grignard reagents on 3,17-dioxo-[82] and 11,17-dioxo-steroids[111]; dialkyl derivatives are also formed as side products form 7,11-dioxosteroids[255]. When an attempt was made to introduce simultaneously two methyl groups by a Grignard reaction with 6,17-diketones, individual products could not be isolated[94].

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