Russian Chemical Reviews

Uspekhi Khimii

February 1961

STEREOCHEMISTRY OF NUCLEOPHILIC ADDITION REACTIONS TO THE CARBONYL GROUP OF CYCLIC KETONES

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INTRODUCTION

Stereochemical studies have undergone a qualitative change in the last 15–20 years, because of the development of conformational analysis. In addition to static stereochemistry, an ever increasing part is beginning to be played by studies on dynamic stereochemistry, in which a chemical reaction is investigated from the stereochemical viewpoint[1]. It is difficult to overestimate the importance of this movement in organic chemistry. In fact, the stereospecific synthesis of many compounds can be successfully achieved in practice only by using stereospecific reactions, and such syntheses are of particular importance in the chemistry of polymers and natural products, which have recently taken on an ever increasing economic significance. Conformational analysis has contributed to the successful study of the stereoselectivity of reactions and to the prediction of the possible results of a chemical process[2]. At present there exist a number of communications on the steric course of substitution and cleavage reactions at a saturated carbon atom, addition to a carbon–carbon double bond, etc.[1], but until recently, the stereochemistry of addition to the double bond of the carbonyl group, particularly in cyclic ketones, had received little attention. The original work and review articles in this field are devoted almost exclusively to the reduction of ketones to alcohols[3].

In the present review we have attempted to systematise the existing data on nucleophilic addition reactions (Ad_N) to the carbonyl group of cyclic ketones with a six-membered ring, free of additional distorting factors (*endo*- and *exo*--cyclic double bonds, oxide rings, bridge linkages, etc.).

This review embraces the literature on mono-, di-, tri-, tetra-, penta-, and hexa-substituted cyclohexanones, including polycyclic systems containing the keto-group in a six-membered ring. As reactions for comparison, we have selected chemical reduction under alkaline conditions, the acetylene and cyanohydrin syntheses, and the addition of organometallic reagents, particularly Grignard reactions.

1. MONOSUBSTITUTED CYCLOHEXANONES (see Table 1)*

Addition reactions to the carbonyl-group of monosubstituted cyclohexanones, particularly 2-methylcyclohexanone, have long been described, but the composition of the

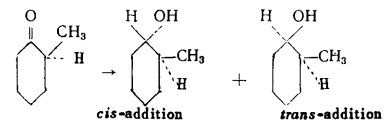
* The following symbols are used in the tables. The indices α and β, as in the steroid series, indicate the disposition of substituents above and below the plane of the diagram; 0 isomer not detected; + present in the mixture; *x* predominates in the mixture; *xx* greatly predominates in the mixture; a numeral with an asterisk * the yield (in %) based on the starting ketone; ! our suggested configuration; ? configuration (or content in the mixture) not established or doubtful; ?? configuration unknown; *a* and *e* conformation of the new substituent; substituent positions are indicated with reference to the carbonyl group.

TABLE 1. Stereosolubility of addition reactions to mono-substituted cyclohexanones.

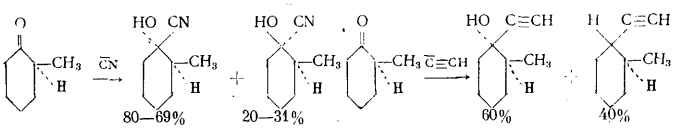
Existing substituent	Reagent	Entering substituent, R′	Content in product mixture, %		Reference
			cis-addition (R–R′)	*trans*-addition (R–R′)	
		Ortho-substitution			
CH_3	Na + ROH	H	*xx*, 98—99, 97—99, 88,72	?,2—1,3—1,12, 28	4,5,6 7,8
CH_3	$LiAlH_4$	H	82,70,69,64,60 60	18,30,31,36,40	9,10,11,12 8
CH_3	$NaBH_4$, CH_3OH	H	69	31	9
CH_3	$NaBH(CH_3O)_3$	H	70	30	9
CH_3	$NaBH_4$, pyridine	H	56	44	9
CH_3	$LiAlH_4$, $AlBr_3$	H	59—71	41—29	7,11
CH_3	KBH_4	H	41	59	8
CH_3	KCN	CN	80—75	20—25	13,14
CH_3	HCN	CN	69	31	14
CH_3	HC≡CH, KOH	C≡CH	60	40	13
CH_3	HC≡CNa, NH_3	C≡CH	51,34,23	49,66,77 (!)	15,16,17
CH_3	HC≡CK, t-C_4H_9OH	C≡CH	60	40(!)	18
CH_3	CH_3MgI	CH_3	25	75	19
C_2H_5	Na + ROH	H	*xx*	?	20,21
C_3H_7	Na + ROH	H	*xx*	?	20,22
iso-C_3H_7	$LiAlH_4$	H	69—57	31—43	11
iso-C_3H_7	$LiAlH_4$, $AlBr_3$	H	66—48	34—52	11
t-C_4H_9	Na + ROH	H	85,*xx*	15,?	11,20 23
t-C_4H_9	$LiAlH_4$	H	51	49	24,11
C_6H_{11}	Na + ROH	H	97,81	3,19	11
C_6H_{11}	$LiAlH_4$	H	71—68	29—32	11
C_6H_{11}	$LiAlH_4$, $AlBr_3$	H	57—13	43—87	25
C_6H_{11}	C_6H_5MgBr	C_6H_5	one isomer (?)		24,26
$C_6H_5CH_2$	$LiAlH_4$	H	*xx*	+	24
$C_6H_5CH_2$	KBH_4	H	*xx*	+	27
$C_6H_5CH_2$	HC≡CNa, NH_3	C≡CH	two isomers		24
C_6H_5	Na + ROH	H	100	0	28
C_6H_5	KCN	CN	44—46 (!)	+	
		Para-substitution			
CH_3	Na + ROH	H	*xx*, 83	?,17	4,29,8
CH_3	$LiAlH_4$	H	81,79—81 75,84	19,21—19,25,16	12,30 8,10
CH_3	$NaBH_4$, CH_3OH	H	75	25	9
CH_3	$NaBH_4$, pyridine	H	60	40	9
CH_3	KBH_4	H	65	35	8
CH_3	HC≡CNa, NH_3	C≡CH	one isomer (??)		31
CH_3	C_6H_5MgBr	C_6H_5	one isomer (??)		32
CH_3O	HC≡CK, t-C_4H_9OH	C≡CH	one isomer (??)	27 / 60 did not agree after hydrogenation	33
CH_3O	C_2H_5MgBr	C_2H_5	one isomer (??)	+	33
iso-C_3H_7	Na + ROH	H	*xx*	+	29,34
iso-C_3H_7	HC≡CNa, NH_3	C≡CH	12 (?)	88 (?)	35
t-C_4H_9	Na + ROH	H	*xx*	+	29
t-C_4H_9	$LiAlH_4$	H	91—93	9—7	30
t-C_4H_9	HC≡CNa, NH_3	C≡CH	86	14	35
t-C_4H_9	C_2H_5MgBr	C_2H_5	27	73	36
C_6H_{11}	Na + ROH	H	55	45	8
C_6H_{11}	$LiAlH_4$	H	43	57	8
C_6H_{11}	KBH_4	H	50	50	5
		Meta-substitution			
CH_3	Na + ROH	H	?,20,22	*xx*,80,78	4,8,37
CH_3	$LiAlH_4$	H	6—7,8,11,15,13	94—93,92,89 85,87	37,9,8 30,10
CH_3	$LiAlH_4$, $AlBr_3$	H	6—7	94—93	11
CH_3	KBH_4	H	42	58	8
CH_3	KCN	CN	25	75	38
CH_3	HC≡CNa, NH_3	C≡CH	15—25 (??)	85—75	39
CH_3	C_6H_5C≡CH, KOH	C_6H_5C≡C	one isomer (??)	95—97*	42,43
CH_3	C_6H_5C≡$CMgBr$	C_6H_5C—C			
CH_3	CH_3MgI	CH_3	60	40	38
t-C_4H_9	$LiAlH_4$	H	+	*xx*	40

resulting mixture of isomers has only rarely been determined.

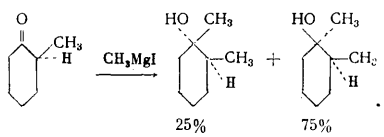
Thus in the reduction of 2-methylcyclohexanone with sodium and alcohol, Skita[4] separated only *trans*-2-methylcyclohexanol (*cis*-addition of hydrogen) from the reaction products, but he suggested that no method of reduction would give one isomer exclusively; the other would always be formed, even if in small amount. Later work has confirmed this in respect of 2-methylcyclohexanone; a number of workers[4-8] found that the reduction of 2-methylcyclohexanone with sodium and alcohol produces a mixture containing 99–72% of the *trans*- alcohol (*cis*-addition) and 1–25% of the *cis*-alcohol (*trans*-addition):



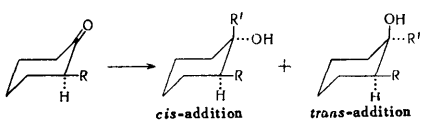
Reduction of this ketone with lithium aluminium hydride gives[8-12] from 60 to 82% of the *trans*-alcohol (*cis*-addition) and from 8 to 40% of the *cis*-alcohol (*trans*-addition). The predominant formation of the *trans*-alcohol is also found in the reduction of 2-methylcyclohexanone with sodium borohydride[9]. The addition of carbon-containing nucleophilic reagents to 2-methylcyclohexanone has also been much described, but apart from a few data on the acetylene synthesis, the stereochemistry of these reactions has not been studied at all until recently. The data on the acetylene synthesis[15-18] are so contradictory that no conclusions can be drawn. The recent study of the stereochemistry of the cyanohydrin, acetylene, and Grignard reactions of 2-methylcyclohexanone showed that a mixture of isomers is formed here also, *cis*-addition predominating in the cyanohydrin and acetylene syntheses. Thus the cyanohydrin synthesis produces a mixture containing, depending on the reaction conditions, from 80 to 69% of *cis*-1-cyano-2-methylcyclohexanol and from 20 to 31% of the *trans*-compound, while under the Nazarov–Favorskii conditions reaction with acetylene under pressure gives 60% of *cis*-1-ethynyl-2-methylcyclohexanol and 40% of the *trans*-compound[13]:



On the other hand, it has been shown[19] that the stereochemistry of the Grignard reaction is quite different, *trans*--1,2-dimethylcyclohexanol (*trans*-addition) predominating (75%) in the resulting mixture:

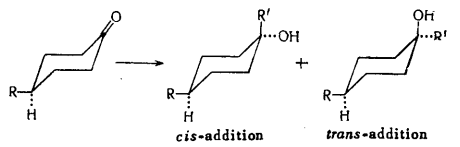


Comparison of data on the reduction of other 2-substituted cyclohexanones shows that reduction with sodium[11,20-22,24] or complex metal hydrides[11,23,24,26] also produces mainly the *trans*-alcohols with *cis*-configuration between the 2-substituent and the entering substituent (H):



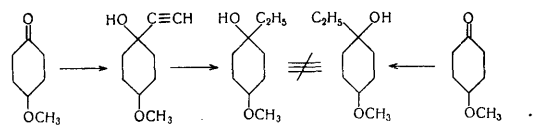
The position in respect of 4-substituted cyclohexanones is analogous, reduction of the ketones with sodium in alcohol[4,8,29,34] or with alkali metal hydrides[5,8-10,12,30] also

producing predominantly the *trans*-alcohol with the *cis*-arrangement between the existing and the new (H) substituent:

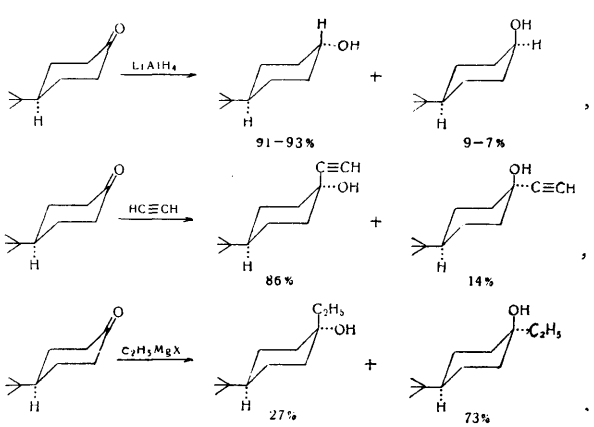


Information on the stereochemistry of the addition of carbon-containing substituents is very sparse in this series also.

Marvel's results[33] are interesting. By condensing 4-methoxycyclohexanone with acetylene in the presence of potassium t-butoxide he obtained, in low yield (27%), one isomer of 1-ethynyl-4-methoxycyclohexanol, which on hydrogenation gave 1-ethyl-4-methoxycyclohexanol. The reaction between the same ketone and ethylmagnesium bromide gave a different stereoisomer of 1-ethyl-4-methoxycyclohexanol in 63% yield. However, he did not establish the configurations of these compounds:

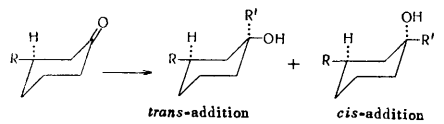


More is known about addition to 4-t-butylcyclohexanone. It has been shown[40] that this ketone exists only in one conformation, in which the t-butyl-group is in the equatorial position. Stork and White[29] show that when it is reduced with sodium in alcohol, it forms almost exclusively a product with an axial hydrogen atom at C_1, *i.e. trans*-4-t-butylcyclohexanol. The reduction of 4-t-butylcyclohexanone with lithium aluminium hydride produces, according to Elie and Ro[30], a mixture containing 91–93% of the same *trans*-alcohol. Moreover, Hennion[36] showed that condensation of this ketone with sodium acetylide in liquid ammonia gives a mixture of acetylenic alcohols in which 86% have the axial disposition of the ethynyl group. On the other hand, the Grignard reaction with ethylmagnesium bromide produces a mixture in which the tertiary alcohol with an equatorial ethyl group, *i.e. trans*-1-ethyl-4-t-butylcyclohexanol, predominates (73%)[36]:

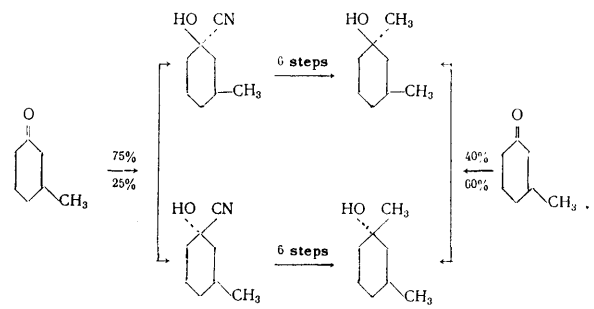


In this case, therefore, the reduction with sodium in alcohol or with lithium aluminium hydride, and the acetylene synthesis, take place predominantly in the same sense with respect to the double bond of the carbonyl group, while the Grignard reaction takes place predominantly in the opposite sense.

Goering and Serres[41] showed in 1952 that the configurations which had been given to the stereoisomeric 3-substituted cyclohexanols should in fact be reversed, and the stereochemical results obtained by the earlier workers on the reduction of *meta*-substituted cyclohexanones must also therefore be reversed. Taking this into account, it may be concluded that reduction both with sodium in alcohol and with complex metal hydrides produces in this case mainly the *cis*-alcohols (*trans*-addition):

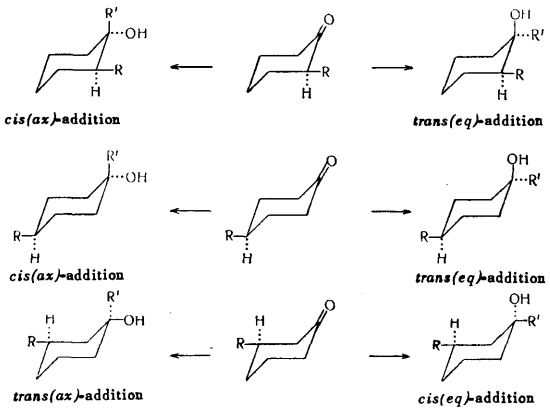


Iotsich[42] condensed 3-methylcyclohexanone with phenylethynylmagnesium bromide and obtained one of the two possible phenylacetylenic alcohols in 97% yield, while Bertond[43] condensed 3-methylcyclohexanone with phenylacetylene by the Favorskii method in the presence of potassium hydroxide and apparently obtained the same isomer, in 95% yield. It is interesting that 3-methylcyclohexanone also reacts with acetylenedimagnesium bromide to form only one glycol, in 93% yield[44]. Study of the stereochemistry of the cyanohydrin synthesis and the Grignard reaction of 3-methylcyclohexanone has shown that as with 2-methylcyclohexanone, both reactions have opposed spatial directivity[38]. In the cyanohydrin synthesis the resulting mixture consists of 75% of the *trans*-1-cyano-3-methylcyclohexanol (*trans*-addition) and 25% of the *cis*-compound. The Grignard reaction produces a mixture containing 60% of *cis*-1,3-dimethylcyclohexanol (*cis*-addition) and 40% of *trans*-1,3-dimethylcyclohexanol:

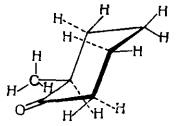


All addition reactions to the carbonyl group of monosubstituted cyclohexanones can be provisionally divided into two groups, of which the first comprises reactions (reduction with sodium and complex metal hydrides, the cyanohydrin and acetylene syntheses) which normally take place with a spatial directivity in one sense (predominantly *cis*-addition in the case of 2- and 4-substituents and *trans*-addition in the case of 3-substituents), and the second comprises the Grignard reaction, which normally shows the opposite spatial specificity (predominantly *trans*-addition with 2- and 4-substituted ketones and *cis*-addition with 3-substituted ketones). In deciding the spatial directivity of the reactions under review, it is of great importance to establish the conformation of the substituents in the

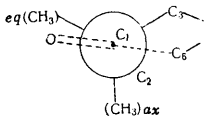
starting ketone. Since the stereochemical course of reactions with t-butyl-substituted cyclohexanones, which have the substituent fixed in the equatorial position, fit into this scheme, it is clear that for reactions of the first group, the addition of the new substituent (H, CN, C≡CH) takes place predominantly into the axial position. With the Grignard reaction, the new substituent enters predominantly in the equatorial position[38]:



In the case of other substituents of smaller volume than tertiary butyl, particularly in the *ortho*-position to the carbonyl group, there are two theoretical conformations with the cyclohexane ring in the "chair"-form, which differ as to whether the substituent is in the equatorial or axial position. Romers[45] studied the actual conformation of the 2-methylcyclohexanone molecule in detail by electron diffraction, and found that in the vapour phase this ketone exists in the "chair"-form, but without an axis of symmetry of the third order, because of distortion of the valency angle at C_1. At the same time, according to Romers' results, the valency angles at the other carbon atoms are still in the range 109.5° ± 2.5°, and the C–C and C–H bonds have length 1.54 ± 0.01 Å and 1.09 ± 0.02 Å respectively. The angle between the C–C bonds at C_1 is 117° ± 3°, and the angle between the C–C and C–O bonds is 121.5° ± 1.5°:



The methyl group occupies exclusively or almost exclusively the equatorial position, but distorted from the normal. Geometrical calculation shows that the angle between the projections of the methyl and carbonyl groups is 15° (105° with the methyl group in the axial position)[46]:



Thus an equatorial *ortho*-substituent occupies a more shielded position with respect to the carbonyl oxygen than the splayed position which occurs in the undeformed cyclohexane molecule. The Raman spectra of the methylcyclohexanones also show that the methyl group in the *ortho*-, *meta*-, and *para*-methylcyclohexanones is predominantly in the equatorial position. This is a further confirmation that *cis*-addition to *ortho*-substituted ketones takes place with axial entry of the substituent, and *trans*-addition with

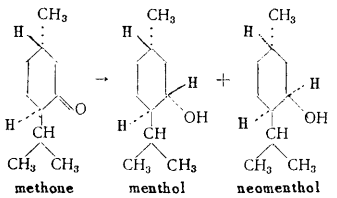
TABLE 2. Stereoselectivity of addition reactions to disubstituted cyclohexanones.

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
2,2-substitution					
2β-Methylcyclohexan-2-ol-1-one	Na + ROH	H	100*	0	47
2β-Ethylcyclohexan-2-ol-1-one	Na + ROH	H	70	30	47
2,6-substitution					
2β,6β-Dimethylcyclohexan-1-one	Na + ROH	H	100*	0	48
2β,6β-Dimethylcyclohexan-1-one	Na in moist ether	H	*xx*	+	48
2,5-substitution					
Menthone (2α, 5β)	$LiAlH_4$	H	71	29	12
Menthone	$NaBH_4$	H	49	51	9
2α-Methyl-5β-isopropylcyclohexan-1-one	$C_6H_5C{\equiv}CMgBr$	$C_6H_5C{\equiv}C$	one isomer (??)	did not agree after hydrogenation	
2α-Methyl-5β-isopropylcyclohexan-1-one	$C_6H_5CH{=}CHMgBr$	$C_6H_5CH{=}CH$	one isomer (??)		39
2,3-substitution					
9β-*trans*-Decalone-1	Na + ROH	H	*xx*	0	49
3-Ethyleneketal-*dl*-18-nor-D-homo-18-androst-5-en-3, 17a-dione	$LiAlH_4$	H	*x*(17*a*)	+	50
9β-*trans*-Decalone-1	$HC{\equiv}CNa$, NH_3	$HC{\equiv}C$	66	33	51
9β-*cis*-Decalone-1	$LiAlH_4$	H	90	10	11
9β-*cis*-Decalone-1	$HC{\equiv}CNa$, NH_3	$HC{\equiv}C$	60*	0	51
3,4-substitution					
9β-*trans*-Decalone-2	Na + ROH	H	99*	0	49
19-norandrostan-17β-ol-3-one	$NaBH_4$	H	85*(3*a*)	0	52
17α-Methyl-19-norandrostan-17β-ol-3-one	$NaBH_4$	H	95*(3*a*)	0	52
17α-Vinyl-19-norandrostan-17β-ol-3-one	$NaBH_4$	H	95*(3*a*)	0	52
17α-Ethyl-19-norandrostan-17β-ol-3-one	$NaBH_4$	H	67*(3*a*)	0	52
9β-*trans*-Decalone-2	$HC{\equiv}CK$	$HC{\equiv}C$	one isomer (??)		53
	$t\text{-}C_5H_{11}OH$				
9β-*cis*-Decalone-2	Na + ROH	H	68	32	11
5β,10β-Oestra-3,17-dione	Na + ROH	H	0	+ (3*a*)	54
17α-Ethyl-5α,10α-oestran-17β-ol-3-one	Na + ROH	H	0	+ (3*a*)	55
9β-*cis*-Decalone-2	$LiAlH_4$	H	90	10	11
5β,10β-Oestra-3,17-dione	$NaBH_4$	H	+ (3*e*)	0	54
17α-Methyl-5α,10α-oestran-17β-ol-3-one	$NaBH_4$	H	+ (3*e*)	0	55

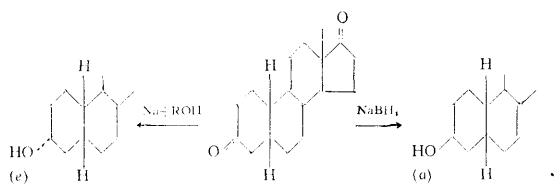
entry of the substituent in the equatorial position. No doubt the ketone can enter into reaction not only in the predominant conformation with an equatorial substituent, but also in the other conformation (with the substituent in the axial position), which may be a partial explanation of the incomplete spatial selectivity.

2. DISUBSTITUTED CYCLOHEXANONES (see Table 2)

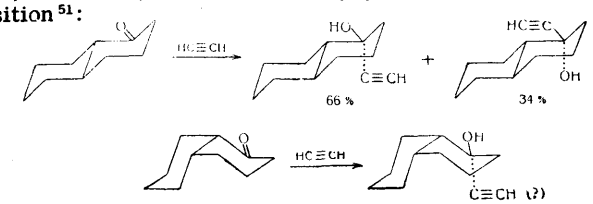
On passing to di- and tri-cyclic disubstituted ketones with more rigid rings, the conformational features of addition to the carbonyl double bond become much clearer. The stereochemistry of addition to such ketones with a cyclohexane ring retains in general features the same tendencies as in the case of monosubstituted cyclohexanones. On reduction with sodium and alcohol, these ketones also form mainly the alcohols in which the hydroxyl group is equatorial[11,47-49,54,55], and the same is found in reduction by means of lithium aluminium hydride[11,12,50]. In a number of cases, however, reduction with sodium borohydride leads predominantly to the formation of alcohols with an axial hydroxyl group (equatorial addition of hydrogen). Thus while Noyce and Denney[12] found that when menthone is reduced with lithium aluminium hydride menthol predominates (71%) in the reaction mixture, Dauben, Fonken, and Noyce[9] observed that neomenthol predominates (51%) in the mixture of alcohols obtained by reduction with sodium borohydride:



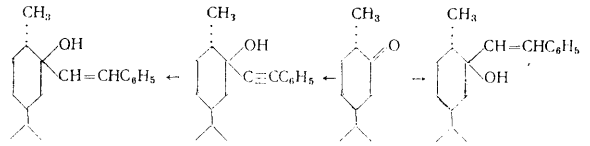
After reducing 5β,10β-oestra-3,17-dione [54] and 17α-methyl-5α,10α-oestran-17β-ol-3-one [55] with sodium in propanol, Rapala and Farkas obtained only products with an equatorial 3-hydroxy group, while by reducing the same ketones with sodium borohydride, they obtained only products with an axial hydroxyl group in the 3-position[55,54]:



The acetylene synthesis on 1-decalones shows interesting differences in the *cis*- and *trans*-compounds. While *trans*-1-decalone reacts with acetylene to form both stereoisomeric alcohols (the isomer with the axial ethynyl group predominating), *cis*-decalone produces only one isomer, apparently that with the ethynyl group in the axial position[51]:



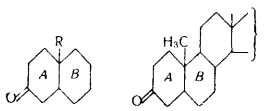
Rupe and Kambli[39] have shown that the condensation of *trans*-2-methylisopropylcyclohexanone with phenylethynylmagnesium bromide and styrylmagnesium bromide gives products with different spatial structures, but their configurations were not established:



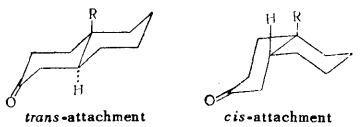
3. TRISUBSTITUTED CYCLOHEXANONES (see Tables 3 and 4)

As distinct from the case of mono- and di-substituted cyclohexanones, the stereochemical data on the reactions of tri- and more highly substituted cyclohexanones relate almost exclusively to rigid systems. This provides more definite results on the composition of the mixtures, particularly in the preparation of secondary alcohols, which isomerise in this case to a lesser extent. On the other hand, the great rigidity of these systems is associated with the appearance of additional factors which influence or might influence the stereoselectivity of the reactions. Because of this, it is considerably more difficult to separate the particular causes underlying the observed stereoselectivity.

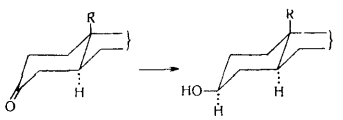
Most data on the stereochemistry of addition to the carbonyl group of trisubstituted cyclohexanones relate to the 3,4,4-trisubstituted compounds: 10-substituted 2-decalones and 3-oxosteroids:



Both types of ketone belong to the angular-substituted decalin systems, and can exist with the rings A and B joined in the *trans*- and *cis*-positions, being thereby divided into two types:



A definite similarity can be observed between the stereochemistry of addition to the carbonyl groups of 3,4,4-trisubstituted cyclohexanones and mono- and di-substituted cyclohexanones. Thus in the series under consideration, as before, reaction takes place, with a few exceptions, with entry of the hydrogen atom mainly in the axial position:



Cholestan-3-one has been the most studied in this series.

TABLE 3. Stereoselectivity of addition reactions to 3, 4, 4-trisubstituted cyclohexanones.

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
10β-Methyl-*trans*-decalone-2	$LiAlH_4$	H	75*(*a*), 63(*a*)	?,0	56,57
10β-Hydroxymethyl-*trans*-decalone-2 mesylate	$LiAlH_4$	H	>48* (*a*)	?	58
10β-Hydroxymethyl-*trans*-decalone-2 mesylate	$NaBH_4$	H	99* (*a*)	0	58
10β-Carboxy-*trans*-decalone-2	$NaBH_4$NaOH	H	69* (*a*)	0	58
10β-Carbethoxy-*trans*-decalone-2	$NaBH_4$	H	90* (*a*)	0	59
5β-Ethynyl-10β-methyl-5α-hydroxy-*trans*-decalone-2	$NaBH_4$	H	88* (*a*)	0	60
5β-Vinyl-10β-methyl-5α-hydroxy-*trans*-decalone-2	$NaBH_4$	H	83* (*a*)	0	60
5β-Ethyl-10β-methyl-5α-hydroxy-*trans*-decalone-2	$NaBH_4$	H	66* (*a*)	0	60
1-Methoxy-8-oxo-10aβ-methyl-4b, 5, 6, 6aα, 7, 8, 9, 10, 10a, 10b, 11, 12-dodecahydrochrysene	$LiAlH_4$	H	82* (*a*)	0	61
1-Methoxy-8-oxo-10aβ-methyl-4bα, 5, 6, 6aα, 7, 8, 9, 10, 10a, 10bα, 11, 12-dodecahydrochrysene	$LiAlH_4$	H	86* (*a*)	0	62
1-Methoxy-8-oxo-10aβ-methyl-5, 6, 6aα, 7, 8, 9, 10, 10a, 11, 12-decahydrochrysene	$LiAlH_4$	H	76* (*a*)	0	62
3, 6-Dioxoallocholanoic acid	Na+ROH	H	74* (3*a*)	0	63
2-Oxo-6α-hydroxycholanoic acid	Na+ROH	H	40* (*a*)	0	63
Allopregna-3, 11, 20-trione	$LiAlH_4$	H	75* (3*a*)	0	64
Allopregna-17α, 21-diol-3, 11, 20-trione 21-acetate	$LiAlH_4$	H	63* (3*a*)	0	65
Cholestan-3-one	$LiAlH_4$	H	96, 87, 88(*a*)	4, 13, 12(*e*)	66, 67, 68
14-Methylcholestan-3-one	$LiAlH_4$	H	+ (*a*)	0	69
5α, 22a-Spirostan-3, 6-dione	$LiAlH_4$	H	58* (3*a*)	0	70
Solanidan-3-one-18-al	$LiAlH_4$	H	+ (3*a*)	0	71
Androstan-3, 17-dione	$NaBH_4$ in CH_3OH	H	71* (3*a*)	0	72
Androstan-3, 17-dione	$NaBH_4$ in pyridine	H	93(3*a*)	7(3*e*)	72
Allopregna-3, 20-dione	$NaBH_4$	H	86, 76(3*a*)	14, 0	73, 74
Allopregna-3, 11, 20-trione	$NaBH_4$	H	87(3*a*)	13	73
3-Oxoetianic acid methyl ester	$NaBH_4$	H	+ (*a*)	0	75
Cholestan-3-one	$NaBH_4$	H	86, 85(*a*)	14, 15(*e*)	67, 68
Androstan-3-one	CH_3MgI	CH_3	42(*a*)	58(*e*)	76
Cholestan-3-one	CH_3MgI	CH_3	40, 43(*a*)	60, 57(*e*)	77, 78
10β-Methyl-*cis*-decalone-2	Na+ROH	H	0	79* (*a*)	79
10β-Methyl-*cis*-decalone-2	$LiAlH_4$	H	100* (*e*)	0	79
5α-Ethynyl-10β-methyl-5β-hydroxy-*cis*-decalone-2	$NaBH_4$	H	57(*e*)	43(*a*)	60
10β-Hydroxymethyl-*cis*-decalone-2	$NaBH_4$	H	50(*e*)	0	59
10β-Hydroxymethyl-*cis*-decalone-2-tosylate	$NaBH_4$	H	19(*e*)	81(*a*)	56
1-Methoxy-8-oxo-10aβ-methyl-5, 6, 6aβ, 7, 8, 9, 10, 10a, 11, 12-decahydrochrysene	$LiAlH_4$	H	0	76* (*a*)	62
1-Methoxy-8-oxo-10aβ-methyl-4aβ, 5, 6, 6aβ, 7, 8, 9, 10, 10a, 10bβ, 11, 12-dodecahydrochrysene	$LiAlH_4$	H	0	62* (*a*)	62
3-Oxothiobillianic acid trimethyl ester	$NaBH_4$	H	0	50* (*a*)	80
Pregna-3, 16, 20-trione	Na+ROH	H	0	+ (*a*)	81
Testa-3, 17-dione 17-ethyleneketal	$LiAlH_4$	H	0	+ (*a*)	82
Pregna-3, 20-dione 20-ethyleneketal	$LiAlH_4$	H	0	82* (*a*)	82
3-Oxo-bisnorchol-7-enoic acid methyl ester	$LiAlH_4$	H	0	32* (*a*)	82
3-Oxobisnorcholanoic acid methyl ester	$LiAlH_4$	H	0	74* (*a*)	82
3, 11-Dioxobisnorcholanoic acid methyl ester	$LiAlH_4$	H	0	+ (3*a*)	82
Lithocholic acid	$LiAlH_4$	H	0	95* (*a*)	83
9α, 11α-Epoxy-3-oxolithocholanic acid methyl ester	$LiAlH_4$	H	0	80* (*a*)	84
Coprostan-3-one	$LiAlH_4$	H	4, 8, 7(*e*)	96, 92, 93(*a*)	66, 67, 68
Coproergost-22-en-3-one	$LiAlH_4$	H	0	+ (*a*)	82
22-Isospirostan-3-one	$LiAlH_4$	H	0	+ (*a*)	85
22a-Spirost-7-en-3-one	$LiAlH_4$	H	0	90* (*a*)	86
22-Isospirostan-7, 9(11)-dien-3-one	$LiAlH_4$	H	0	69* (*a*)	87
22-Isospirostan-3, 11-dione	$LiAlH_4$	H	0	63* (3*a*)	88
5β-Spirostan-3-on-27-oic acid	$LiAlH_4$	H	0	83* (*a*)	89
Testa-3, 17-dione	$NaBH_4$ in CH_3OH	H	20(3*e*)	80(3*a*)	72
Testa-3, 17-dione	$NaBH_4$ in pyridine	H	0	43* (3*a*)	72
Testan-17β-ol-3-one acetate	$NaBH_4$	H	17(3*e*)	83(3*a*)	72
Pregna-3, 20-dione	$NaBH_4$	H	15, ?	85, 63*(3*a*)	73, 74
Pregnan-11α-ol-3, 20-dione acetate	$NaBH_4$	H	?	63*(3*a*)	74
Pregna-11β, 17α, 21-triol-3, 20-dione 21-acetate	$NaBH_4$	H	0	30* (3*a*)	73
Pregna-3, 11, 20-trione	$NaBH_4$ in C_2H_5OH	H	?	61* (3*a*)	74
Pregna-3, 11, 20-trione	$NaBH_4$ in pyridine	H	0	+ 82* (3*a*)	91, 74
Pregnan-17α-ol-3, 11, 20-trione	$NaBH_4$	H	0.?	78*, 63* (3*a*)	91, 74
Coprostan-3-one	$NaBH_4$	H	17, 13(*e*)	83, 87(*a*)	67, 68
3, 11-Dioxocholanoic acid	$NaBH_4$, NaOH	H	12(*e*)	88(*a*)	92
Digitoxigenone	$NaBH_4$	H	+	72(*a*)	93
Sarsasapogenone	CH_3MgI	CH_3	one isomer	(?) 100*	94

There are no data on the reduction of this ketone with sodium and alcohol, but its reduction with lithium aluminium hydride produces a mixture containing, according to various workers[66-68], from 96 to 88% of cholestan-3β-ol, while sodium borohydride shows a slightly reduced selectivity, producing 86–85% of the 3β-alcohol[67,68]. It is extremely interesting that methylmagnesium iodide reacts with this ketone to form predominantly (although the selectivity is small) 3β-methylcholestan-3α-ol (57–60%)[77,78], *i.e.* the product of equatorial addition of the methyl group:

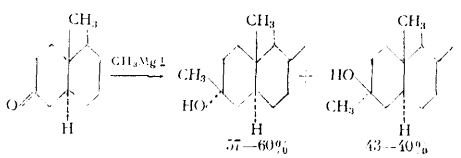
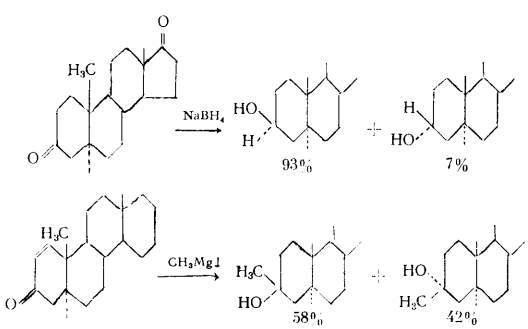


TABLE 4. Stereoselectivity of addition reactions to various trisubstituted cyclohexanones.

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
2,2,3-substitution					
Cholestan-1-one	$Na+C_2H_5OH$	H	64 (a)	36 (e)	95
Cholestan-1-one	$Na+n\text{-}C_3H_7OH$	H	91 (a)	9 (e)	96
D-Homotestan-3α-ol-11, 17a-dione acetate	$LiAlH_4$	H	+ (17aa)	0	97
Cholestan-1-one	$LiAlH_4$	H	35 (a)	65 (e)	96
D-Homotestan-3α-ol-11, 17a-dione acetate	$NaBH_4$	H	94 (17aa)	6 (17ae)	97
D-Homoepiandrostenone acetate	$NaBH_4$	H	85 * (17aa)	0	98
D-Homoandrost-5-en-3β-ol-17a-one	HC≡CH	C≡H	x (17aa)	+ (17ae)	99
D-Homotestan-3α-ol-11, 17a-dione	HC≡CK, t-C_4H_9OH	C≡H	86 (17aa)	14 (17ae)	100
D-Homotesta-3α, 11β-diol-17a-one acetate	HC≡CK, t-C_4H_9OH	C≡H	50 * (17aa)	0	100
D-Homotesta-3α, 11α-diol-17a-one 3, 11-diacetate	HC≡CK, t-C_4H_9OH	C≡H	85 * (17aa)	0	100
D-Homoandrosten-3-ol-17a-one	CH_3MgI	CH_3	0	90 * (17ae)	101
D-Homotestan-3α-ol-11, 17a-dione 3-acetate	CH_3MgI	CH_3	0	65 * (17ae)	100
3,3,4-substitution					
Cholestan-2-one	Na+ROH	H	0	+ (a)	102
Cholestan-2-one	$LiAlH_4$	H	58 (e)	42 (a)	103
Cholestan-2-one	$NaBH_4$	H	82 (e)	18 (a)	103
2,3,3-substitution					
Cholestan-4-one	Na+ROH	H	0	+ (a)	104
Cholestan-4-one	$LiAlH_4$	H	92 (e)	8 (a)	105
3,4,5-substitution					
1α-Methyl-19-norandrostan-17β-ol-3-one	$NaBH_4$	H	70 * (3a)	0	32
2,4,5-substitution					
2α-Hydroxy-*cis*-9β, 10β-decalone-3	$LiAlH_4$	H	27	73 (e)	106
2β-Hydroxy-*cis*-9β, 10β-decalone-3 acetate	$LiAlH_4$	H	30	70 (e)	106

A similar effect is observed with other ketones of this series. Thus androstan-3,17-dione, on reduction with sodium borohydride, provides androstan-3β,17-diol in 93% yield, the 3α-isomer being produced in a very small amount, while androstan-3-one, like cholestan-3-one, with methylmagnesium iodide, gives a mixture containing 58% of 3β-methylandrostan-3α-ol [76]:



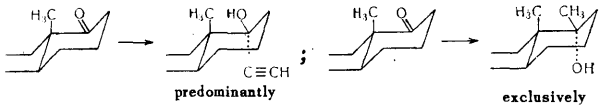
Such directivity has already been mentioned in respect of the monosubstituted cyclohexanones, where it was shown that the Grignard reaction takes place with stereoselectivity opposite to that found with reduction or the acetylene synthesis.

The steric course of the reduction of the ketones (axial addition of hydrogen) in the 3,4,4-trisubstituted cyclohexanones is also retained in respect of *cis*-fusion of rings A and B. The only exception is the reduction of 10β-methyl- and 10β-hydroxymethyl-*cis*-2-decalone with lithium aluminium hydride or sodium borohydride [50,79], where the results (predominantly equatorial addition of hydrogen) agree with those of the reduction of *cis*-2-decalones. These facts have not yet been explained. There are very few reliable data on the quantitative determination of the relative proportions of isomers in the products of addition to 3,4,4-trisubstituted cyclohexanones. Most workers give only the amount of the one isomer which they have separated, and the yield is sometimes less than 50% of the theoretical; no further information on the composition of the reaction product is usually given. However, a few results of the accurate separation of these mixtures (from cholestan-3-one [66-68,77,78], androstan-3-one [76], coprostan-3-one [66-68], testane-3,17--dione [72], and 3,11-dioxocholanoic acid [92]) show that the reduction of these ketones with lithium aluminium hydride is apparently somewhat more selective (87–96% of one isomer) than reduction with sodium borohydride (80–88% of the same isomer).

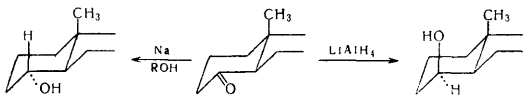
It is very interesting to compare the data on the stereochemistry of addition to 2,2,3-trisubstituted cyclohexanones. Representative of such ketones are the 1-oxosteroids and 17a-oxo-D-homosteroids. The reduction of cholestan-1--one with sodium and alcohol produces mainly alcohols with an equatorial hydroxyl group (64–91%) [95,96], and the same is found in the reduction of 17a-oxo-D-homosteroids with sodium borohydride (94%) [97]. However, according to Henbest's results [95], reduction of cholestan-1-one with lithium aluminium hydride gives predominantly cholestan--1α-ol with an axial hydroxyl group.

Studies by Dodson *et al.* [99] and Clinton *et al.* [100] have shown that the addition of acetylene to 17a-oxo-D-homosteroids proceeds mainly with the formation of an axial ethynyl group (86%). while the Grignard reagent adds exclusively in the equatorial position [100,101]. Exclusively axial addition apparently also occurs in the acetylene synthesis on 10β-methyl-6-methoxy-Δ⁶-*cis*-1-octalone [107].

In this instance, therefore, the difference in the directivity of these two reactions is greater than with 4-t-butylcyclohexanone and the 3-oxosteroids:



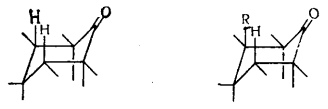
The 3,3,4- and 2,3,3-trisubstituted cyclohexanones such as cholestan-2-one and cholestan-4-one differ greatly in the directivity of their addition reactions. In both cases only reduction of the keto-group with sodium and alcohol produces alcohols with an equatorial hydroxyl group[102-104]; reduction with lithium aluminium hydride[103,105] or sodium borohydride[103] takes place mainly with addition of hydrogen in the equatorial position:



Such a sharp difference in the directivity of the reactions can only be due to the presence of the axial methyl group in the *meta*-position to the carbonyl group, which greatly hinders the approach of the reagent from one direction. However, this steric hindrance apparently does not affect the directivity in the case of sodium and alcohol, since only one isomer, with an equatorial hydroxyl group, has been obtained from the reduction products[102,104], although there are no quantitative data in the literature.

4. TETRASUBSTITUTED CYCLOHEXANONES (see Table 5)

In respect of the spatial specificity of addition reactions to the carbonyl group, the ketones of the tetrasubstituted cyclohexane series can be divided into two groups, the reactions of which correspond in general features with those already described. The first group comprises those compounds which do not contain other axial substituents, other than hydrogen atoms, in the *meta*-position to the carbonyl group, *i.e.* the tetrasubstituted cyclohexanones which are unsubstituted or monosubstituted in the 3- and 5-positions. The directivity of addition reactions to the carbonyl group of such ketones is in general features the same as in the case of mono-, di-, and tri-substituted cyclohexanones, other than the 2,3,3- and 3,3,4-trisubstituted cyclohexanones. The second group, which corresponds to these last compounds, includes the tetrasubstituted cyclohexanones which are geminally substituted in the 3- or 5-positions. A review of the available factual data confirms such a division:



First group
2,2,3,4-substitution
2,3,4,5-substitution
2,4,4,5-substitution
2,3,4,4-substitution

Second group
2,3,3,4-substitution
2,4,5,5-substitution
2,2,5,5-substitution

Thus ketones of the first group (2,3,4,5-, 2,4,4,5-, and 2,3,4,4-substitution) on reduction with sodium and alcohol or complex metal hydrides give predominantly, as a rule, alcohols with an equatorial hydroxyl group, the selectivity being apparently somewhat higher with lithium aluminium hydride[109-111,114-116,119] and reducing when using sodium borohydride[108,112,113].

A very interesting example, which is a connecting link between the first and second groups, is the sodium borohydride reduction of the methyl ester of 1β-hydroxy-3-oxoetianic acid (3,4,4,5-substitution), described by Schlegel and Tamm[121]. This compound contains an axial substituent in the *meta*-position to the carbonyl group — the

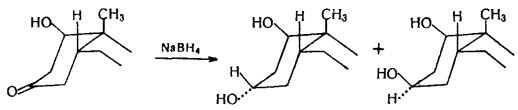
TABLE 5. Stereoselecticity of addition reactions to tetrasubstituted cyclohexanones.

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
	2,2,3,4-substitution				
4,4-Dimethyl-19-norandrostan-17β-ol-3-one	$NaBH_4$	H	78 *(4a)	0	108
4,4,17α-Trimethyl-19-norandrostan-17β-ol-3-one	$NaBH_4$		80* (4a)	0	108
	2,2,4,5-substitution				
2,2,17α-Trimethyl-19-norandrostan-17β-ol-3-one	$NaBH_4$	H	90 * (a)	0	108
	2,4,4,5-substitution				
5α,22a-Spirostan-2α-ol-3-one acetate	$LiAlH_4$	H	81 * (a)	0	109
5α,22a-Spirostan-2β-ol-3-one acetate	$LiAlH_4$	H	58 * (a)	0	109
2α-Bromocholestan-3-one	$LiAlH_4$	H	87 * (a)	0	110
2α-Methylcholestan-3-one	$LiAlH_4$	H	87 * (a)	0	111
2α-Bromocholestan-3-one	$NaBH_4$	H	68,61 (a)	32,39	112, 113
2β-Methylcoprostanone	$LiAlH_4$	H	0	82 * (a)	111
	2,3,4,4-substitution				
α-Methylcholest-7-en-3-one	Na+ROH	H	83 * (a)	0	114
4α-Methylcholestan-3-one	$LiAlH_4$	H	87 * (a)	0	111
4α-Methylstigmastan-3-one	$LiAlH_4$	H	81 * (a)	0	115
4α-Methylcholest-7-en-3-one	$LiAlH_4$	H	85 *, 62 * (a)	0	114, 116
3-Oxo-5α,11α(H),4α,6β(H)-eudesman-6;13-olide	KBH_4	H	78 * (3a)	0	117
1α-(2′α-Hydroxyethyl)-7,7,10β-trimethyl-*trans*-decalone-2	CH_3MgI	CH_3	52 (2a?)	48 (2e?)	118
4β-Methylcoprostan-3-one	$LiAlH_4$	H	0	46 * (a)	111
3-Oxo-11α(H),4β,5β,6β(H)-eudesman-6:13-olide	KBH_4	H	0	76 * (3a)	117
6α-Hydroxy-3-oxo-4α(H),5β(H)-eudesmanoic acid	KBH_4. KOH	H	66 (3e)	0	117

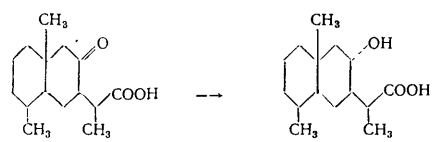
TABLE 5 (contd.)

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′ α-form	R′ β-form	
2,3,4,5-substitution					
1-Methoxy-8β-hydroxy-11-oxo-10aβ-methyl-4bβ, 5, 6, 6aα, 7, 8, 9, 10, 10a, 10bβ, 11, 12-dodecahydrochrysene	$LiAlH_4$	H	0	83 * (11*a*)	119
2,2,3,6-substitution					
1, 1, 6α, 10β-Tetramethyl-2β-hydroxy-*trans*-decalone-5 benzoate	$CH{\equiv}CNa$, NH_3	C≡CH	92 * (5*a*)	0	120
3,4,4,5-substitution					
1β-Hydroxy-3-oxoetianic acid methyl ester	$NaBH_4$	H	50 (*a*)	50 (3*e*)	121
2,3,3,4-substitution					
Friedelin	Na+ROH	H	0	75 *, 50 * (*a*)	122, 123
Friedelin	$LiAlH_4$	H	+	0	123
2,4,5,5-substitution					
Cholestan-3β-ol-2-one tosylate	$NaBH_4$	H	0	90 * (*e*)	124
Cholestan-3β-ol-2-one acetate	$NaBH_4$	H	0	84 * (*e*)	124
7-Oxotetrahydroalantolic acid	Na+ROH	H	0	75* (7*a*)	125
7-Oxotetrahydroalantolic acid	$NaBH_4$	H	68 * (7*e*)	0	126
2,2,5,5-substitution					
2, 2, 5, 5-Tetramethylcyclohexa-1, 3-dione	$LiAlH_4$	H	35 (α, β)	65 (β, β)	127

1β-hydroxy group — but a hydroxyl group has a smaller volume than a methyl group, and so screens one side of the carbonyl group to a substantially lesser extent than an axial methyl group. The reduction of the methyl ester of 1β-hydroxy-3-oxoetianic acid with sodium borohydride therefore produces a mixture of equal quantities of both isomers:



Tetrasubstituted ketones of the second group are reduced by all methods, except sodium and alcohol[122,123,125], to form mainly or exclusively alcohols with an axial hydroxyl group[123,124,126,127]. However, the examples of 7-oxotetrahydroalantolic acid, which by reduction with sodium and isopropanol gives the corresponding α-alcohol in 75% yield[125]



7-oxotetrahydroalantolic acid — 7α-hydroxytetrahydroalantolic acid

and friedelin, which under the same conditions gives friedelan-3β-ol in 50–75% yield[122,123], show that reduction with sodium and alcohol takes place with the same stereoselectivity as in the case of less substituted ketones. This is possibly due to polar influence of the carboxyl group.

5. PENTASUBSTITUTED CYCLOHEXANONES (see Table 6)

The existing material on the stereochemistry of addition to the pentasubstituted ketones can be divided into nine groups of variously substituted cyclohexanes (2,2,3,4,4-, 2,2,4,4,5-, 2,3,4,4,5-. 2,2,3,4,5-, 2,2,3,6,6-, 2,2,4,5,6-, 2,3,3,4,5-, 2,3,3,6,6-, and 2,3,4,5,5-substitution). The first six of these do not possess the geminal substitution in the *meta*-position to the carbonyl group which exists in the last three. However, spatial hindrance exerts an effect in the pentasubstituted ketones, even when these do not possess large axial 3- or 5-substituents. While the 2,2,3,4,4-pentasubstituted ketones, mostly 4,4-dimethyl-3-oxotriterpenoids, are reduced by complex metal hydrides mainly to alcohols with equatorial hydroxyl[128–141], the 2,3,4,5-pentasubstituted ketones (7-oxosteroids)[103,147] and 2,2,3,4,5-pentasubstituted cyclohexanones (12-oxosteroids)[151,153] are converted by reduction with sodium borohydride predominantly into alcohols with an axial hydroxyl group. There are indications that even the reduction of 7-oxosteroids with sodium and alcohol (3β-hydroxyergost-22-en-7,11-dione)[144] and with lithium aluminium hydride (cholestan-3β-ol-7-one acetate)[103,146] leads predominantly to 7α-alcohols with an axial hydroxyl group.

The reduction of hecogenin with sodium and ethanol has produced only rockogenin[148] (12β-equatorial hydroxyl group, 57%), while with lithium aluminium hydride[149], both isomers are formed, and reduction of hecogenin acetate with lithium aluminium hydride produces 54–82% rockogenin and 18–46% 12-epirockogenin (12α-axial hydroxyl group)[150,151]:

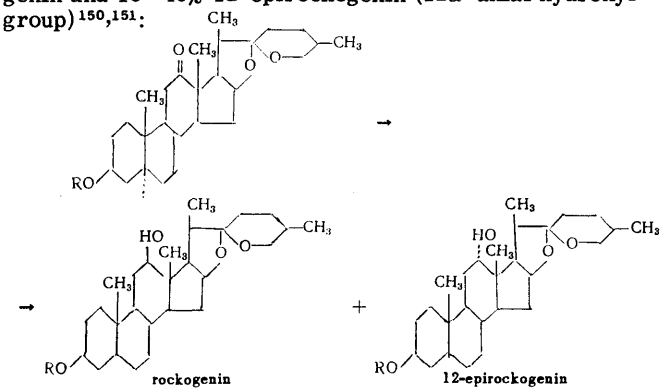


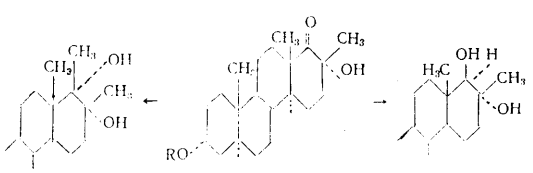
TABLE 6. Stereoselectivity of addition reactions to pentasubstituted cyclohexanones.

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
2,2,3,4,4-substitution					
Elemadien-3-onic acid methyl ester	$LiAlH_4$	H	+ (*a*)	0	128
Masticadien-3-onic acid	$LiAlH_4$	H	+ (*a*)	0	129
Dihydromasticadien-3-onic acid methyl ester	$LiAlH_4$	H	+ (*a*)	0	129
Dihydroisomasticadien-3-onic acid	$LiAlH_4$	H	+ (*a*)	0	130
β-Amyren-3-one	$LiAlH_4$	H	55* (*a*)	0	131
Lupen-3-one	$LiAlH_4$	H	60* (*a*)	0	131
Taraxerone-3	$LiAlH_4$	H	+ (*a*)	0	132
20α, 21α-Epoxy-19α(H)-taraxastan-3-one	$LiAlH_4$	H	50* (*a*)	0	133
β-Boswellonic acid methyl ester	$LiAlH_4$	H	+ (*a*)	0	134
Betulonic lactone	$LiAlH_4$	H	85* (3*a*)	0	135
4,4-Dimethylandrostan-17β-ol-3-one	$NaBH_4$	H	88* (*a*)	0	136
4,4,17α-Trimethylandrostan-17β-ol-3-one	$NaBH_4$	H	87* (*a*)	0	136
20-Isoeburico-7,9(11)-dien-16β-ol-3-on-21-oic acid lactone	$NaBH_4$	H	76* (*a*)	0	137
Thurberogen-3-one	$NaBH_4$	H	60* (*a*)	0	138
Masticadien-3-onic acid	$NaBH_4$	H	+ (*a*)	0	129
Dihydromasticadien-3-onic acid	$NaBH_4$	H	+ (*a*)	0	129
Dioxoechinocystic acid methyl ester	$NaBH_4$	H	75* (3*a*)	0	139
Olean-12-en-3-on-28,30-dioic acid dimethyl ester	$NaBH_4$	H	92* (*a*)	0	140
11-Desoxy-β-glycyrrhetinic acid methyl ester	$NaBH_4$	H	71* (*a*)	0	141
β-Boswellonic acid methyl ester	$NaBH_4$	H	+ (*a*)	0	134
2,2,4,4,5-substitution					
2,2-Dimethylcholestan-3-one	$LiAlH_4$	H	85* (*a*)	0	111
2,3,4,4,5-substitution					
Cholestan-7-one	Na+ROH	H	+ (*a*)	0	142
Cholestan-3β-ol-7-one acetate	Na+ROH	H	78 (*a*)	22 (*e*)	143
3-Hydroxyergost-22-en-7,11-dione	Na+ROH	H	45 (7*a*)	55 (7*e*)	144
Lanostan-3β-ol-7-one acetate	Na+ROH	H	70* (*a*)	0	145
Cholestan-7-one	$LiAlH_4$	H	67 (*a*)	33 (*e*)	142
Cholestan-3-ol-7-one acetate	$LiAlH_4$	H	50,43—35 (*a*)	50,57—65 (*e*)	146, 103
Lanostan-3β-ol-7-one acetate	$LiAlH_4$	H	70* (*a*)	0	145
Cholestan-3-ol-7-one acetate	$NaBH_4$	H	27 (*a*)	73 (*e*)	103
7-Oxocholanoic acid	$NaBH_4$	H	9 (*a*)	91 (*e*)	147
2,2,3,4,5-substitution					
Hecogenin	Na+ROH	H	57* (*a*)	0	148
Manogenin diacetate	Na+ROH	H	25* (*a*)	0	148
Mexogenin diacetate	Na+ROH	H	+ (*a*)	0	148
Hecogenin	$LiAlH_4$	H	+ (*a*)	+ (*e*)	149
Hecogenin acetate	$LiAlH_4$	H	54,82 (*a*)	46,18 (*e*)	150, 151
12-Oxo-13β-ursan-3β-ol acetate	$LiAlH_4$	H	90 (*a*)	10 (*e*)	152
Allopregna-3β,17β-diol-12,20-dione	$NaBH_4$	H	?	+ (*e*)	153
Allopregna-3β,17α,21-triol-12,20-dione 21-acetate	$NaBH_4$	H	?	+ (*e*)	153
Hecogenin acetate	$NaBH_4$	H	+ (*a*)	*x* (*e*)	151
2,2,3,6,6-substitution					
17β-Methyl-D-homotesta-3α,17α-diol-11,17a-dione diacetate	Na+ROH	H	17* (*aa*)	0	154
17β-Methyl-D-homotesta-3α,17α-diol-11,17a-dione diacetate	$LiAlH_4$	H	22* (17*aa*)	0	154
17β-Methyl-D-homotesta-3α,17α-diol-11,17a-dione acetate	CH_3MgI	CH_3	0	+17 (*ae*)	155
2,2,4,5,6-substitution					
2β,4b-Dimethyl-2-allyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthren-4β-ol-1-one	$NaBH_4$	H	80* (*a*)	0	156
2β,4b-Dimethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,5,6,7,8,10,10aβ-dodecahydrophenanthren-1,4-dione	$C_2H_5OC{\equiv}CMgBr$	$C{\equiv}COC_2H_5$	88 (1*a*)	12 (1*e*)	157
dl-Δ⁸-4β-Hydroxy-2β-formyl-2α-(3′-hydroxypropyl)-4bβ,7-dimethoxy-4aα,10aβ-dodecahydrophenanthren-1-on-dilactol(4→2←3)-3-methyl ester	$C_2H_5OC{\equiv}CLi$	$C{\equiv}COC_2H_5$	68 (1*a*)	32 (1*e*)	158
dl-Δ⁸-1-Oxo-4β-hydroxy-2α-(3′-dimethoxypropyl)-4bβ-methyl-7-ethylenedioxy-4aα,10aβ-dodecahydrophenanthrene 2β-carboxylic acid	$C_2H_5OC{\equiv}CLi$	$C{\equiv}COC_2H_5$	89—63 (*a*)	11—37 (1*e*)	148
2,3,3,4,5-substitution					
2,3-Secocholestan-6-on-2,3-dioic acid	Na+ROH	H	0	90* (*a*)	159
Cholest-2-en-6-one	Na+ROH	H	0	+ (*a*)	159
Cholestan-6-one	Na+ROH	H	0	50* (*a*)	160
Cholestan-3α-ol-6-one	Na+ROH	H	0	93* (*a*)	161
Cholest-2-en-6-one	$LiAlH_4$	H	96 (*e*)	4 (*a*)	159
Cholestan-6-one	$LiAlH_4$	H	95 (*e*)	5 (*a*)	162
Cholestan-3α-ol-6-one	$LiAlH_4$	H	84* (*e*)	0	163
Cholestan-3β-ol-6-one	$LiAlH_4$	H	90* (*e*)	+	161
3α-Chlorocholestan-6-one	$LiAlH_4$	H	97*, 91* (*e*)	0	161, 164
3α-Bromocholestan-6-one	$LiAlH_4$	H	100* (*e*)	0	164
3α-Iodocholestan-6-one	$LiAlH_4$	H	100* (*e*)	0	164
6-Oxocholestan-3-acetic acid methyl ester	$LiAlH_4$	H	47* (*e*)	0	165
N-Benzyl-3-aminocholestan-6-one	$LiAlH_4$	H	75* (*e*)	0	166
5α,22a-Spirostan-3,6-dione	$LiAlH_4$	H	58* (6*e*)	+	70
2,3-Secocholestan-6-on-2,3-dioic acid dimethyl ester	$NaBH_4$	H	0	80* (*a*)	167
2,3-Secocholestan-6-on-2,3-dioic acid 2-methyl,3-ethyl ester	$NaBH_4$	H	0	75* (*a*)	167
Androsta-3,6,17-trione 3-ethyleneketal	$NaBH_4$	H	56* (6*e*)	+	168
Cholestan-3β-ol-6-one 3-tosylate	$NaBH_4$	H	+ (*e*)	0	169
Androsta-3β,17β-diol-6-one 3,17-diacetate	CH_3MgI	CH_3	+ (*e*)	0	170
Androstan-3β-ol-6,17-dione 3-acetate	CH_3MgI	CH_3	+ (6*e*)	0	170
17α,20;20,21-Bis-methylenedioxy-3-ethylenedioxyallopregna-6,11-dione	CH_3MgJ	CH_3	79* (6*e*)	0	171
Cholestan-6-one	CH_3MgI	CH_3	60* (*e*)	0	172
Cholestan-3β-ol-6-one	C_2H_5MgJ	C_2H_5	92* (*e*)	0	173, 174
5α,25D-Spirostan-3β-ol-6-one 3-acetate	CH_3MgI	CH_3	+ (*e*)	0	175
2,3,3,6,6-substitution					
19-Oxo-18-iso-β-amyranol	$LiAlH_4$	H	+ (*e*)	0	176
19-Oxo-18-iso-β-amyranolic acid	$LiAlH_4$	H	+ (*e*)	0	177

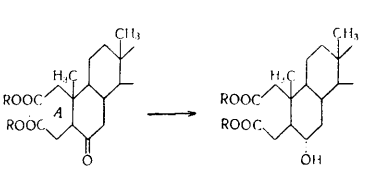
TABLE 6 (contd.)

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
2,3,4,5,5-substitution					
Testan-3α-ol-11, 17-dione	N+ROH	H	0	99* (11*a*)	178
D-Homotesta-3α, 17aβ-diol-11-one	N+ROH	H	0	+ (*a*)	97
dl-Pregn-5-en-3, 11, 16, 20-tetrone 3-ethyleneketal	N+ROH	H	0	16* (11*a*)	179
Ergost-22-en-3β-ol-11-one acetate	$Na+C_3H_5OH$	H	0	66* (*a*)	180
Ergost-22-en-3β-ol-11-one acetate	$Na+n\text{-}C_3H_7OH$	H	0	100* (*a*)	181
11-Oxotigogenin acetate	Na+ROH	H	0	87* (*a*)	182
Adrenosterone	$LiAlH_4$	H	62* (11*e*)	0	183
Androst-5-en-3, 11, 17-trione 3, 17-bisethyleneketal	$LiAlH_4$	H	83* (*e*)	0	184
Androsta-3, 5-dien-3-ol-11, 17-dione 3-benzoate	$LiAlH_4$	H	64* (11*e*)	0	184
Testan-3α-ol-11, 17-dione cyanohydrin acetate	$LiAlH_4$	H	+ (11*e*)	0	185
D-Homotestan-3α-ol-11, 17a-dione acetate	$LiAlH_4$	H	+ (11*e*)	0	97
17, 20; 20, 21-Bis-methylenedioxy-A-norpregna-2, 5-diol-11-on-2-oic acid	$LiAlH_4$	H	68* (*e*)	32 (*a*)	186
Pregna-3α, 20α-diol-11-one diacetate	$LiAlH_4$	H	83* (*e*)	0	187
Pregna-3α, 17α, 20β, 21-tetrol-11-one 20, 21-acetonide	$LiAlH_4$	H	53* (*e*)	0	188
17α, 20β-Epoxypregna-3α, 20α-diol-11-one diacetate	$LiAlH_4$	H	90 (*e*)	10 (*a*)	189
Pregnan-3α-ol-11, 20-dione acetate 20-ethyleneketal	$LiAlH_4$	H	92* (11*e*)	0	190
Allopregnan-3β-ol-11, 20-dione acetate 20-hemithioketal	$LiAlH_4$	H	88* (11*e*)	0	191
Pregna-3α, 17α-diol-11, 20-dione 20-ethyleneketal	$LiAlH_4$	H	76 (11*e*)	24 (11*a*)	192
Allopregna-3, 11, 20-trione	$LiAlH_4$	H	75* (11*e*)	0	64
Pregn-5-en-17α-ol-3, 11, 20-trione 3-ethyleneketal	$LiAlH_4$	H	79 (11*e*)	21 (11*a*)	193
4-Chloropregnan-17α-ol-3, 11, 20-trione 3, 20-bis-ethyleneketal	$LiAlH_4$	H	90* (11*e*)	+ (11*a*)	192
Pregn-4-en-3, 11, 20-trione 3, 20-bis-ethyleneketal	$LiAlH_4$	H	94 (11*e*)	6 (11*a*)	194
Allopregna-17α, 21-diol-3, 11, 20-trione 21-acetate	$LiAlH_4$	H	63* (11*e*)	0	65
Pregn-5-en-17α, 21-diol-3, 11, 20-trione 3, 20-bis-ethyleneketal	$LiAlH_4$	H	88 (*e*)	12 (*a*)	195
Cortisone 3, 20-bis-ethyleneketal	$LiAlH_4$	H	90 (*e*)	10 (*a*)	196
Pregna-1, 4-dien-17α, 21-diol-3, 11, 20-trione 3, 20-bis-semicarbazone 21-acetate	$LiAlH_4$	H	90* (11*e*)	0	197
16-Isopropoxypregna-5, 16-dien-3, 11, 20-trione 3-ethyleneketal	$LiAlH_4$	H	41* (11*e*)	0	179
11-Oxolanost-24-enol acetate	$LiAlH_4$	H	+ (*e*)	0	198
Lanostan-3β-ol-11-one acetate	$LiAlH_4$	H	93* (*e*)	0	199
Lanostan-3β-ol-7, 11-dione acetate	$LiAlH_4$	H	100* (11*e*)	0	199
Ergost-22-en-3β-ol-11-one acetate	$LiAlH_4$	H	90* (*e*)	0	180, 181
22-Isospirostan-3, 11-dione	$LiAlH_4$	H	63* (11*e*)	0	200
11-Oxotigogenin acetate	$LiAlH_4$	H	75* (*e*)	+	182
Pregn-5-en-17α, 21-diol-3, 11, 20-trione 3, 20-bis-semicarbazone	KBH_4	H	99* (11*e*)	0	201
Pregna-1, 4-dien-17α, 21-diol-3, 11, 20-trione 3, 20-bis-semicarbazone	KBH_4	H	85* (11*e*)	0	202
7-Methylpregn-4-en-17α, 21-diol-3, 11, 20-trione 3, 20-bis-semicarbazone 21-acetate	KBH_4	H	54* (11*e*)	0	203
3α-Hydroxy-11-oxoetianic acid acetate	$NaBH_4$+NaOH	H	74* (*e*)	0	204
3, 11-Dioxoetianic acid 3-ethyleneketal	$NaBH_4$+NaOH	H	90* (*e*)	0	205
Pregnan-3α-ol-11, 20-dione	$NaBH_4$	H	85* (11*e*)	0	206
Pregnan-3α-ol-11, 20-dione 20-ethyleneketal	$NaBH_4$	H	87* (11*e*)	0	207
Pregna-3α, 17α-diol-11, 20-dione 20-ethyleneketal	$NaBH_4$	H	100* (11*e*)	0	207
Pregna-3α, 17α-diol-11, 20-dione	$NaBH_4$	H	74 (11*e*)	0	208
3-Diethoxy-20-cyanopregn-17-en-21-ol-11-one	$NaBH_4$	H	+ (*e*)	0	209
Pregna-3, 11, 20-trione 3, 20-bis-ethyleneketal	$NaBH_4$	H	91* (11*e*)	0	207
Pregnan-17α-ol-3, 11, 20-trione 3, 20-bis-ethyleneketal	$NaBH_4$	H	96* (11*e*)	0	207
20-Isopropoxypregna-5, 17(20)-dien-3, 11, 16-trione 3-ethyleneketal	$NaBH_4$	H	50* (11*e*)	0	179
5α-Pregna-17α, 21-diol-3, 11, 20-trione 3, 20-bis-ethyleneketal	$NaBH_4$	H	67* (11*e*)	0	210
3α-Hydroxy-11-oxocholanoic acid	$NaBH_4$+NaOH	H	80* (*e*)	0	92
3β-Hydroxyergostan-11-one	$NaBH_4$	H	84* (*e*)	0	210
5β-Pregnan-3α-ol-11, 20-dione 20-ethyleneketal	CH_3Li	CH_3	50* (11*e*)	0	211
5β-Pregna-3, 11, 20-trione 3, 20-bis-ethyleneketal	CH_3Li	CH_3	65* (11*e*)	0	211
5α-Pregna-3, 11, 20-trione 3, 20-bis-ethyleneketal	CH_3Li	CH_3	82* (11*e*)	0	211
18-Benzylidene-14-iso-17-isoallopregnan-3β-ol-11, 20-dione	$LiAlH_4$	H	75* (11*e*)	0	212
9β-Ergostan-3β-ol-11-one acetate	$LiAlH_4$	H	0	+ (11*a*)	213

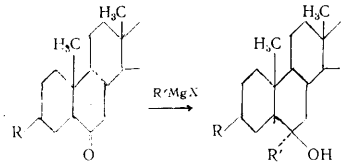
The sodium borohydride reduction of hecogenin acetate produces 12-epirockogenin in greater amount[151]. The reduction of 17β-methyl-D-homoetiocholan-3α,17α-diol-11,17α-dione with sodium in isopropanol or with lithium aluminium hydride gives the 17aβ-alcohol, possessing an equatorial hydroxyl group, in low yield[154]. On the other hand, the action of methylmagnesium iodide on 17β-methyl-D-homoetiocholan-3α,17α-diol-11,17a-dione acetate produces only 17β,17aβ-dimethyl-D-homoetiocholan-3α,17α,17aα-triol-11-one acetate, which is formed by addition of the methyl group in the equatorial position[155]:



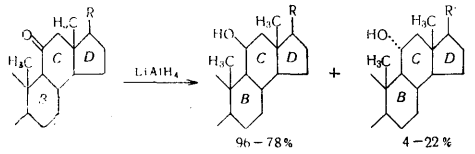
The literature on the stereochemistry of addition to the carbonyl group of 6-oxosteroids (2,3,3,4,5-substitution) indicates considerable steric hindrance. Here, as would be expected from the presence of the axial methyl group in the *meta*-position, only with sodium and alcohol does reduction of the carbonyl group take place predominantly with addition of hydrogen in the axial position[159-161]. Reduction with lithium aluminium hydride[159-166] or particularly with sodium borohydride[167-169] produces the 6β-alcohol with an axial hydroxyl group as the predominant product. The esters of 2,3-secocholestane-6-one-2,3-dioic acid are exceptions[167]; this is apparently due to the loss of rigidity of ring A and the possible polar influence of the acid side chains:



The Grignard reaction on 6-oxosteroids leads exclusively to 6α-methyl-6β-hydroxy-compounds[170-175].



The considerable literature on the stereochemistry of addition reactions to 2,3,4,5,5-pentasubstituted ketones with a cyclohexane ring relate only to 11-oxosteroids. The data can be collated into a few rules which can be deduced from the published material. 11-Oxosteroids with an axial methyl group in the *meta*-position show considerable steric hindrance to the approach of a reactant from the direction of this group, so that only reduction with sodium and alcohol produces 11α-hydroxysteroids formed by the axial addition of hydrogen[97,178-182]. In all the other cases described in the literature, the reactions take place predominantly with addition of the substituent in the equatorial position. It was earlier thought[188] that all these reactions are strictly stereospecific, forming 11β-hydroxy-compounds exclusively, but the studies of Bernstein *et al.*[195,196], Brooks *et al.*[182], Poos[193], and several others[189,192,194] showed that when 11-oxosteroids are reduced with lithium aluminium hydride a small quantity of the 11α-hydroxysteroid (4–22%) is formed in addition to the main product, 11β-hydroxysteroid:



There is nothing in the literature on the formation of 11α-hydroxy-compounds by the reduction of 11-oxosteroids with sodium or potassium borohydride.

Fonken[211] has shown that 11-oxosteroids condense with methyllithium to form, as would be expected, 11α-methyl--11β-hydroxy-compounds. Interesting results have been obtained in the lithium aluminium hydride reduction of 11-oxo-compounds in which the B and C or C and D rings are *cis*-fused. Thus the reduction of 18-benzylidene-14--iso-17-isoallopregnan-3β-ol-11,20-dione with lithium aluminium hydride gave 18-benzylidene-14-iso-17-isoallopregnan-3β,11β,20-triol in 75% yield[212], while from the reduction products of 9β-ergosten-3β-ol-11-one acetate only 9β-ergosten-3β,11α-diol, which has an equatorial hydroxyl group that can be acetylated, was obtained[213]. The same product is obtained in the reduction of this steroid with lithium and methanol in liquid ammonia[213].

6. HEXASUBSTITUTED CYCLOHEXANONES (see Table 7)

The compounds of this type for which the literature contains data on the stereochemistry of addition to the carbonyl group either carry halogen or oxygen as a substituent, or are 6-oxo-3,5-cyclosteroids. The existing material shows that for compounds of the first class, the spatial directivity of the reactions is greatly dependent on the conformational position of the non-alkyl substituent *ortho* to the carbonyl group. Thus 6-bromocholestan-3β-ol-7-one acetate, in which the bromine atom has the axial conformation (6β-configuration) is reduced by lithium aluminium hydride to form only the 7β-hydroxy-compound[110] (axial addition of hydrogen), while the ketone with equatorial bromine (6α-configuration) is reduced to a mixture of the two epimers, containing 56% of the 7α-hydroxy- and only 14% of the 7β-hydroxy-steroid[110]:

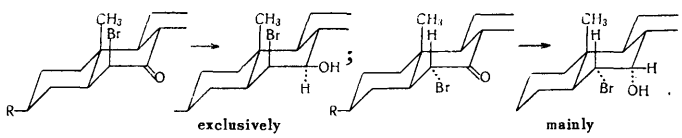
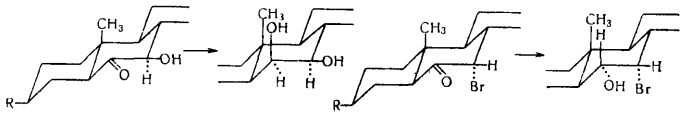


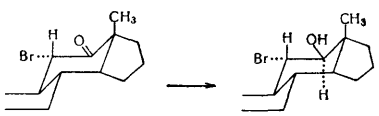
TABLE 7. Stereoselectivity of addition reactions to hexasubstituted cyclohexanones.

Ketone	Reagent	R′	Content in resulting mixture, %		Reference
			R′α-form	R′β-form	
2,3,4,4,5,6-substitution					
6β-Bromocholestan-3β-ol-7-one acetate	$LiAlH_4$	H	60*(a)	0	110
6α-Bromocholestan-3β-ol-7-one acetate	$LiAlH_4$	H	44(a)	56(e)	110
2,3,4,5,6,6-substitution					
23a-Bromo-5α, 25D-spirostan-3β, 11β-diol-12-one 3-acetate	$LiAlH_4$	H	+(a)	+(e)	214
23a-Bromo-5α, 25D-spirostan-3β, 11β-diol-12-one 3, 11-diacetate	$LiAlH_4$	H	46*(a)	0	214
11α, 23ξ-Dibromo-5α, 22a-spirostan-3β-ol-12-one acetate	$NaBH_4$+$NaHCO_3$	H	72(a)	28(e)	215
2,2,3,3,4,5-substitution					
Cholestan-5-ol-6-one	Na+ROH	H	0	+(a)	105
Cholesta-3β, 5α-diol-6-one	Na+ROH	H	0	60*(a)	216
3, 5-Cyclocholestan-6-one	Na+ROH	H	0	40*(a)	162
Cholestan-5α-ol-6-one	$LiAlH_4$	H	+(e)	0	105
Cholesta-3β, 5α-diol-6-one	$LiAlH_4$	H	82*(e)	0	216
Cholesta-3β, 5α-diol-6-one acetate	$LiAlH_4$	H	60*(e)	0	217
3, 5-Cycloandrostan-6-one	$LiAlH_4$	H	80*(e)	0	218
3, 5-Cycloandrosta-6, 17-dione	$LiAlH_4$	H	90*(e)	0	218
3, 5-Cyclocholestan-6-one	$LiAlH_4$	H	86*.0.13(e)	0.78*.77(a)	218, 219, 162
5-Bromocholestan-3β-ol-6-one acetate	$NaBH_4$	H	+(e)	+(a)	220
3, 5-Cyclocholestan-6-one	CH_3MgJ	CH_3	96*(e)	0	221
2,2,3,4,5,5-substitution					
Pregna-5α, 9α, 17α, 21-tetrol-3, 11, 20-trione 3, 20-bis-ethyleneketal	$LiAlH_4$	H	68(11e)	+	222
17, 20; 20, 21-Bis-methylenedioxy-3-ethylenedioxy-9α--methylpregn-5-en-11-one	$LiAlH_4$	H	+(e)	0	223
3α, 9α-Dihydroxy-11-oxocholanoic acid	$NaBH_4$+NaOH	H	78*(e)	0	92
3β, 9α-Dihydroxy-11-oxocholanoic acid methyl ester acetate	$NaBH_4$	H	98(e)	0	92
2,3,3,4,5,6-substitution					
3α, 7β-Dihydroxy-6-oxoallocholanoic acid	$NaBH_4$	H	90(e)	0	224
7α-Bromocholestan-3β-ol-6-one acetate	$NaBH_4$	H	47(e)	53(a)	220
7α-Bromocholestan-6-one	$NaBH_4$	H	44(e)	56(a)	225
2,3,4,5,5,6-substitution					
22-Isoallospirostan-3β, 12β-diol--11-one	$LiAlH_4$	H	94*(e)	0	226
5α, 22a-Spirostan-3β, 12β-diol--11-one 3-acetate 12-tosylate	$LiAlH_4$	H	40*(e)	0	227
12α-Bromo-11-dehydrocortisone acetate	$LiBH_4$	H	(e)	0	228
Pregn-4-en-21-ol-3, 11, 20-trione 3, 20-bis-semicarbazone 21-acetate	$LiBH_4$	H	91*(e)	0	229
2,3,3,4,4,5-substitution					
11-Oxo-oleanolic acid methyl ester acetate	$LiAlH_4$	H	+(e)	0	230

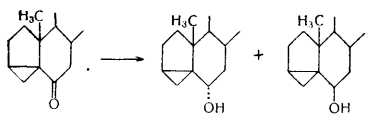
An analogous effect is found with 7-substituted 6-oxosteroids. For example, 3α,7β-dihydroxy-6-oxoallocholanoic acid is reduced by sodium borohydride to form only the 6β-hydroxy-isomer with an axial hydroxyl group[224], while 7α-bromocholestan-3β-ol-6-one acetate is reduced by the same reagent to a mixture containing 53% of the 6α-hydroxy- and 47% of the 6β-hydroxy-compound[220], *i.e.* the addition of hydrogen takes place also from the direction screened by the angular methyl group:



An interesting effect is found in the reduction of 11α,23ξ-dibromo-5α,22α-spirostan-3β-ol-12-one acetate, with an equatorial bromine atom, by means of sodium borohydride[215]. While the sodium borohydride reduction of 12-oxo-compounds leads mainly to the formation of products of addition of hydrogen in the equatorial position[151,153], the introduction of the 11α-bromine atom directs this reaction towards predominantly axial entry of hydrogen[215]:



In its general features, the reduction of 6-oxo-3,5-cyclosteroids obeys the same rules as in the case of ketones with an axial *meta*-substituent. Reduction of 3,5-cyclocholestan-6-one with sodium and alcohol produced only the 6α-alcohol with an equatorial hydroxyl group[162]. Reduction with lithium aluminium hydride gives the 6β-alcohols with axial hydroxyl in dominant amount[162,218,219]:

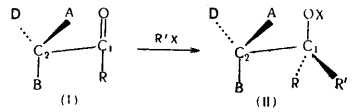


However, the existing literature on this subject are somewhat contradictory. Thus Wagner, Wolff and Wallis[218] show that the lithium aluminium hydride reduction of 3,5-cyclocholestan-6-one produces only 3,5-cyclocholestan-6β-ol (in 86% yield), while in the same reaction, Shoppee and Summers[162] and Kosower and Winstein[219] obtained 3,5 cyclocholestan-6α-ol in considerably predominant amount.

7. ATTEMPTED GENERALISATION OF THE RESULTS ON THE STEREOCHEMISTRY OF NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP

Tiffeneau[231] suggested that addition to a carbonyl group in ketones with an asymmetric carbon atom adjacent to the keto group takes place under the influence of this asymmetric centre. This theory found its widest development in the so-called "Cram rule", deduced by Cram and Abd El Hafez[232] from a study of the stereochemistry of addition to optically active ketones and aldehydes. Although Cram himself related this rule only to aliphatic compounds, later workers attempted to apply it to cyclic ketones.

According to the Cram rule, addition of a nucleophilic reagent to a ketone (or aldehyde) takes place from the less screened side of the carbonyl double bond in conformation (I), where this bond lies between substituents A and D of smallest volume (A < D < B) attached to the adjacent asymmetric centre:

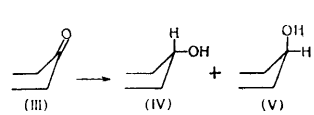


It is thus assumed that in the initial conformation the oxygen atom occupies a position between the smallest substituents on C_2 (A and D), and the substituent on C_1 (R) occupies a shielded position with respect to the largest substituent on C_2 (B). However, the conformation which exists in *ortho*-substituted ketones with a six-membered ring is nearer that in which the carbonyl oxygen and the equatorial *ortho*-substituent are in the shielded position with respect to one another, since the angle of projection between them is 15°.[46] Existing data show that the Cram rule cannot apparently be applied to the cyclohexane series. According to this rule, which was deduced from the Grignard reaction and reduction with lithium aluminium hydride, the addition to 2-methylcyclohexanone of the methyl group in the first case and hydrogen in the second must take place from the same direction. In practice, however, these two reactions show opposite selectivity[13,19]. Moreover, the selective course of nucleophilic addition reactions depend, according to the Cram rule, on the presence of an asymmetric centre adjacent to the carbonyl group[232], but in the cyclohexane series even ketones without asymmetric centres, such as 4-t-butylcyclohexanone, show a spatial selectivity in these reactions[29,30,36].

Other attempts at generalisation in the literature relate exclusively to the reduction of cyclic ketones.

In 1919 Skita[233] considered that the reduction of cyclic ketones with sodium and alcohol always gives *trans*-alcohols as the main product (*cis*-addition of hydrogen). This was developed by Vavon[234], who, on the basis of a number of examples, proposed the rule that *trans*-alcohols are predominantly formed when cyclic ketones are reduced in alkaline medium, and by Hückel[235], who extended Skita's suggestion to include the reduction of oximes. However, after the actual configuration of 3-substituted cyclohexanols had been proved[41], it became clear that 3-substituted cyclohexanones are reduced by sodium and alcohol to form not the *trans*-, but the *cis*-alcohols (*trans*-addition of hydrogen).

Finally, in 1953 Barton[236] formulated a rule for the stereoselectivity in the ionic reduction of ketones (with sodium and alcohol, complex metal hydrides, etc.), according to which such reduction of ketones not sterically hindered (III) produces as the main product the thermodynamically more stable isomer with an equatorial hydroxyl group (IV):



Barton was led to his rule from the fact that the composition of the mixture of alcohols (IV) and (V) formed in

such a reduction is close to that of the mixture obtained when either of the stereoisomers (IV) or (V) is isomerised under the action of alkaline reducing agents. It was considered that the composition of the equilibrium mixture depends only on the relative thermodynamic stability of the two isomers (IV) and (V). The equilibrium position in this case is independent of the method by which it is attained. However, Hückel[11] recently showed that the composition of the equilibrium mixture of the alcohols (IV) and (V) is different when different isomerising agents are used (sodium, lithium aluminium hydride, sodium borohydride, etc.). On the other hand, Hückel and Naab[237] and later Doering and Aschner[238] showed that the isomerisation of secondary alcohols from one form into the other under the action of alkaline agents is an oxidation-reduction process in which the ketone (III) is an intermediate. The equilibrium in such processes will only depend on the relative thermodynamic stabilities of the components (or more correctly, on the energies of activation) only with symmetrical (ideally dynamically homologous) systems[239]. The systems under consideration are clearly not of this type, and therefore the composition of the equilibrium mixtures obtained in the reduction of the ketones is not determined by the relative thermodynamic stabilities of the isomers (IV) and (V), but primarily by the kinetics of the competing reactions (III) → (IV) and (III) → (V). This agrees completely with Hückel's deduction[239] that "the quantitative relationship between the components in competing reactions is determined primarily not by their thermodynamic stabilities, but mainly by the relative rates of the reactions taking place in the various possible directions".

The suggestion that the equilibrium depends on the kinetics of the reduction reactions finds confirmation in the following facts: (1) the use of different reducing agents gives mixtures of alcohols of different composition[11]; (2) the addition of aluminium bromide to the lithium aluminium hydride can completely change the directivity of the reduction,[11], because of attack by the larger ion $AlBr_3H^-$ instead of AlH_4^-; (3) increasing the temperature of the lithium aluminium hydride reduction from -60° to +35° increases the quantity of the conformationally less stable isomer with the axial hydroxyl group[11]; and (4) reduction of lanostan-3,11-dione[181] and cholesta-3β,5α-diol-6-one[216] with sodium and alcohol produces the alcohols with an equatorial hydroxyl group (11α, 6α), while reduction with lithium aluminium hydride gives the alcohols with axial hydroxyl (11β, 6β), which are not isomerised to the former alcohols by the action of sodium. Quite recently, Beckett, Harper, Balon, and Watts[240] also apparently came to the conclusion that the stereochemistry of the reduction of tropinone depends primarily on kinetic and not thermodynamic factors.

In 1956 Dauben, Fonken, and Noyce[9] put forward the suggestion that the stereoselectivity of the reduction of cyclic ketones with complex metal hydrides is determined by two factors, the first, which they called "steric approach control", comprising screening of one or other side of the molecule, and the second ("product development control") comprising the energetic effect, which depends on the relative stabilities of the resultant reaction products. The reduction of menthone with lithium aluminium hydride, which gives predominantly axial addition of hydrogen with the formation of the more stable equatorial hydroxyl group, they attributed to the influence of the second factor, and the reduction with sodium borohydride, which leads mainly to equatorial addition of hydrogen, to screening of the carbonyl bond by the 2-isopropyl group and to the larger size of sodium borohydride as compared with lithium aluminium hydride. However, the radius of the boron ion (B^{3+} = 0.2 Å) is less than that of the aluminium ion (Al^{3+} = 0.57 Å)[241,242], so that only the solvated ion $BH(OR)_3^-$ can have a larger volume, and this is confirmed by the identity in the stereoselectivity in reduction with sodium borohydride in methanol and with the complex $NaBH(OCH_3)_3$. The steric hindrance in the ketone molecule is ascribed by Dauben, Fonken, and Noyce[9] to the presence of axial alkyl groups in the *meta*-position to the carbonyl group. The influence of the second factor, in their opinion, is shown by the complex hydride ion so orientating itself in the reaction mixture that when it decomposes, the product is the more stable alcohol isomer with the equatorial hydroxyl group. Here again, therefore, the relative thermodynamic stabilities of the end products are largely responsible for the stereoselectivity of the reaction. The existence of steric hindrance because of axial *meta*-substituents is well known[1,243]. It is also known that an axial substituent in the cyclohexane ring enters into steric reaction even with axial hydrogen atoms in the *meta*-position. According to Angial and Mills[244], the distance between the 1a- and 3a-hydrogen atoms in the undistorted chair form of cyclohexane is 2.51 Å, which is only slightly greater than the sum of the van der Waals' radii for two hydrogen atoms (2.34–2.4 Å)[241,242]. When the hydrogen is replaced by any other axial substituent, the sum of the van der Waals' radii for this substituent and the axial hydrogen atom becomes greater than 2.51 Å, causing strong mutual repulsion. Thus for an axial hydroxyl group, with a van der Waals' radius for oxygen of 1.36–1.4 Å[241], this sum becomes 2.6 Å. The cyano- and ethynyl-groups are linear, and their axis is approximately parallel to the axial carbon–hydrogen bond, so that any reaction between these substituents and *meta*-hydrogen atoms will depend only on the van der Waals' radius of triply-bonded carbon (1.7–1.8 Å)[241], and the sum of the two van der Waals' radii (1a, 3a) will be 2.9 Å. The methyl group, being branched, has large dimensions in the 1a–carbon–3a–hydrogen direction (2.05 Å)[241,242]. Even these rough calculations show: (1) that not only axial carbon-containing *meta*-substituents, but even axial *meta*-hydrogen atoms, cause spatial screening of one side of the carbonyl group, and (2) that this screening effect increases with increasing size of the entering substituent.

The steric hindrance therefore depends on the number and size of the axial substituents (including hydrogen atoms) in the *meta*-position to the keto-group, and on the size of the entering substituent (or attacking complex).

The experimental material given above shows that with increase in the size of the entering substituent (from hydrogen to methyl) with the same ketone, or with increased steric hindrance in the ketone (for the same reaction), there is an increase in the yield of isomer formed by entry of the substituent in the equatorial position. This can only be due to the influence of the steric hindrance factor. On the other hand, decreasing the size of the attacking agent and the number and size of the axial *meta*-substituents in the ketone molecule leads to the formation of an increased quantity of the isomer formed by axial addition. This cannot be explained by a simple comparison of the relative thermodynamic stabilities of the two isomers, as follows from the Barton rule[236].

In fact, in the reduction of ketones of low steric hindrance, when the entering substituent (H) is small in comparison to the hydroxyl group, the secondary alcohol with the equatorial hydroxyl group which is the main product is

conformationally more stable, as is seen by calculation and from experiments[1,242] independent of alkaline isomerisation. However, the isomer which is the main product in the cyanohydrin and acetylene syntheses has in the axial position a cyano- or ethynyl-group, which have a greater effective volume than the hydroxyl group. Comparison of the van der Waals' radii and the generalised Auwers-Skita rule[1,242] both show that an axial cyano- or ethynyl-group in combination with an equatorial hydroxyl group is apparently conformationally less favourable than the reverse. Some attempts can be made to explain these facts. The Arrhenius equation for the velocity constant of a reaction, $K = \alpha e^{-q/RT}$, contains two terms, of which one ($e^{-q/RT}$) depends on the energy of activation, and the other (the frequency factor α) is related to non-thermodynamic quantities: the frequency of collisions, the size of the molecules, the size of the "sensitive region", and other steric factors.

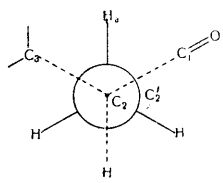
According to Hückel[239], all organic reactions can be divided into two groups: (1) reactions whose rates depend mainly on differences in the energies of activation, and (2) reactions whose rates are mainly determined by the frequency factor.

The high velocity of reactions in which the carbonyl group takes part indicates its comparatively low energy of activation (10–13 kcal mole^{-1}), and the considerable complexity of molecules of cyclic ketones must inevitably lead to a small frequency factor. It can thus be assumed that these reactions belong to the second group.

The stereoselectivity of nucleophilic addition to the carbonyl group of cyclic six-membered ketones is apparently therefore determined by two opposing factors: one which directs the entering substituent into the axial position, and one which depends on steric hindrance and directs the substituent into the equatorial position.

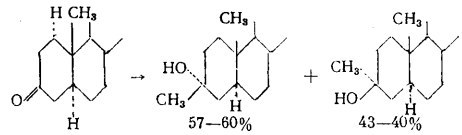
It seems probable that the first factor is determined mainly by the orientation taken up by the charged nucleophilic (anion) attacking agent under the influence of polar forces, and not the thermodynamic stability of the end products. This orientation is closely bound up with the actual mechanism of the nucleophilic reaction, and may be due to the difference in the electrostatic fields originating from the upper and lower ends of the carbonyl double bond, produced, for example, by the non-compensated dipole moments of the carbon–hydrogen bonds.

In comparing the stereochemical data on the nucleophilic addition, the Grignard reaction with 2-methylcyclohexanone[19] is clearly more stereoselective than the reaction with 3-methylcyclohexanone[38], the first producing 75% equatorial addition, and the second only 60%. A molecular model of 2-methylcyclohexanone shows that a methyl group in the equatorial position will be most stable when the hydrogen atoms are in angular positions with respect to the substituents at C_2.

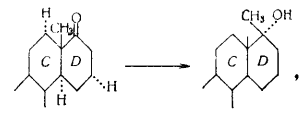


In this case the hydrogen atom H will be the same distance from the carbon atom C_1 as the axial *meta*-hydrogen atoms, *i.e.* it will act as a third axial *meta*-hydrogen atom, causing additional steric hindrance. The existence of considerable steric hindrance in 2-methylcyclohexanone in comparison with 3-methylcyclohexanone is additional confirmation that these ketones enter into these reactions predominantly in the conformation with an equatorial methyl group. In fact, if with the methyl group in this position there is more hindrance with 2-methylcyclohexanone, there would be considerably more screening of one side of the molecule with an axial methyl group in the case of 3-methylcyclohexanone.

It is very interesting to compare the stereochemistry of the Grignard reaction in the cyclohexane and steroid series. 3-Oxosteroids, which like 3-methylcyclohexanone possess two axial *meta*-hydrogen atoms, react with methylmagnesium iodide to form a mixture containing 57–60% of the product of equatorial addition of the methyl group[76-78].



However, 17a-oxo-D-homosteroids, which have three axial *meta*-hydrogen atoms in a rigid system (at C_{12}, C_{14}, and C_{16}), form only the equatorial addition product[100,101]:



and Clinton, Christiansen, Neumann, and Laskowski[100] explained this as being due to these hydrogen atoms. The difference in the stereoselectivity of the reactions of 17a-oxo-D-homosteroids (with a rigid skeleton) and 2-methylcyclohexanone shows that the latter clearly reacts partly in the conformation with an axial methyl group.

We have attempted to systematise the existing data on the stereochemistry of these nucleophilic addition reactions from the point of view of increasing steric hindrance in the ketone molecule, using average compositions of the mixtures formed from variously substituted ketones with the cyclohexane ring (Table 8). The steric hindrance is considered as being due to hydrogen atoms and methyl groups in the *meta*-position to the carbonyl group in the ring or in a side chain, and possessing, in the most stable conformation, an axial disposition.

TABLE 8. Content in the mixture (%) of the isomer with axial disposition of the entering substituent.

Reagent	Hindering axial groups and disposition of substituents				
	2H 3-, 4-, 3, 4, 4	3H 2-; 2,2-; 2,5-; 2,3-, 2,2,3-2,3, 4,4-; 2,3,4,4,5-; 2,2,3,4,5	1CH$_3$, 1H 3,3,4-	1CH$_3$, 2H 2,3,3-; 2,3 3,4,5-; 2,2,3,3,4,5	2CH$_3$, 1—2H 2,3,4,4,5-;2,3, 4,5,5,6-, 2,3,3, 4,4,5
Na in alcohol	78	80	main product	main product	main product
HCN	75	73	?	?	?
HC≡CH and KOH	86	73	?	?	?
LiAlH$_4$	82	61	42	23	14
NaBH$_4$	77	55	18	low ?	0
CH$_3$MgI	38	26	?	0	0

Table 8 shows that increasing the number and size of the axial substituents in the *meta*-position to the keto-group causes a regular increase in the quantity of isomer formed by equatorial entry of the substituent.

It cannot at present be stated definitely whether the volume of the incoming substituent or the size of the attacking complex as a whole plays a large part in the stereoselectivity of the reaction.

Summarising what has been set out above, despite the limited quantity of material, it appears that the spatial directivity of nucleophilic addition reactions (which may be the result of definite orientations of molecules in the reaction mass) depends on two factors — polar orientation (polar factor) and steric hindrance (steric factor).

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LIGNIN

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I. INTRODUCTION

The study of the structure of natural lignin and the conditions under which it is formed in the plant cell, and also the search for methods of utilising the enormous amount of lignin wastes from the modern paper and hydrolytic industries, are tasks of great scientific and economic importance.

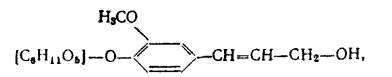
Lignin constitutes about 30% of the plant resources which are annually renewed on a hugh scale on the earth. It is the most important natural aromatic polymer, and is thus potentially a rich source of phenolic products, which are widely used in modern industrial organic synthesis.

During the past decade a great deal of research has been done on the chemistry and the biogenesis of lignin, which to a large extent enables us to understand and to explain the structure of this interesting natural polymer.

II. PATHWAYS OF LIGNIN BIOSYNTHESIS IN PLANTS

Study of plant evolution shows that lignin has a protective function, since the start of biosynthesis of lignin in plants is associated with the transition to life on land. Botanists consider that lignin first appeared in the Pteridophyta. No lignin is present in algae, liverworts, or mosses. It is contained in small amounts in horsetails, and definitely occurs in ferns[1].

The process of lignification and lignin formation in the plant cell must be regarded as part of normal metabolism. Manskaya[1] showed that cambium and wood of the new annual layer of pine contain β-glucosidase and the oxidising enzymes peroxidase and polyphenol-oxidase. Coniferin (a glucoside)



found in the cambium of conifers, serves as a substrate