THE REDUCTION OF ENOL ACETATES OF CYCLIC KETONES WITH LITHIUM ALUMINUM HYDRIDE

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Abstract—When 4-t-butylcyclohexanone enol acetate and 3,3,5-trimethylcyclohexanone enol acetates were reduced with LAH the ratio of alcohol to ketone was 67:33 and 63:37 respectively, these ratios being different from those obtained in the previous reduction of some steroid enol acetates. However, the ratio of equatorial to axial 4-t-butylcyclohexanol was practically the same as the ratio of equatorial to axial cholestanol and equatorial to axial coprostanol, which were obtained in the reduction of the corresponding enol acetates. The existing mechanism of this reduction is discussed and a new one is suggested.

INTRODUCTION

It is known[1,2] that enol acetates of different steroids on reduction with LAH give a mixture of equatorial and axial alcohols as well as a ketone; the ketone is a product of reduction and not a result of hydrolysis of unreacted enol acetate. This interesting reaction has been studied in detail by Dauben *et al.*[3–5] Table 1 summarizes their results. These results have been interpreted in the following manner. It is assumed that (similarly to the reduction of "normal" esters) the first step in the reduction is a bimolecular attack by AlH_4^- on the electrophilic carbonyl carbon atom with transfer of a hydride ion, followed by a second hydride attack which displaces the original alkoxide group and gives rise to the anion of a newly formed alcohol. In the reduction of enol acetates the generated enolate anion of the ketone, possibly in the form of the
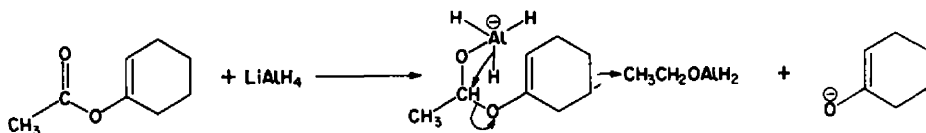
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[1] V. M. Mićović and M. Lj. Mihailović, *Lithium Aluminum Hydride in Organic Chemistry* p. 42. Naučna Knjiga, Belgrade, Yugoslavia (1955).
[2] N. G. Gaylord, *Reduction with Complex Metal Hydrides* p. 533. Interscience, New York (1956).
[3] W. G. Dauben, J. F. Eastham, *J. Amer. Chem. Soc.* **73**, 3260 (1951).
[4] W. G. Dauben, R. A. Micheli, J. F. Eastham, *J. Amer. Chem. Soc.* **74**, 3852 (1952).
[5] W. G. Dauben, J. F. Eastham, *J. Amer. Chem. Soc.* **75**, 1718 (1953).

lithium salt, resists further reduction. The formation of alcohols has been explained[5] as taking place through a cyclic intermediate of the following type:
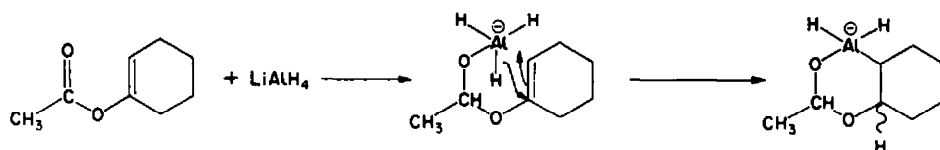
Such a complex could arise by addition of a hydride ion to the unsaturated oxygen-bearing carbon atom with concommitant formation of a carbon–aluminum bond on the adjacent carbon atom. The different ratios of isomeric alcohols have been explained as being due to the fact that the transition state varies markedly, in the stereochemical sense, from that involved in reduction of the corresponding ketones. Deuterium tracer techniques have been used to prove that formation of a carbon–aluminum bond actually takes place during the reduction.[5]

TABLE 1. REDUCTION OF ENOL ACETATES OF COPROSTANONE (I), CHOLESTANONE (II) AND CHOLESTENONE (III) WITH LAH[2-5]

| Entry	Enol acetate	Mode of addn.	% ketone	% e-OH	% a-OH	Ratio of e/a	Ref.
1	I	nor.[a]	10	70	13	84/16	4
2	I	inv.[a]	8	63	20	76/24	
3	II	nor.	21	58	17	76/24	4,5
4	II	inv.	10	59	20	75/25	
5[b]	III	nor.	32	34	15	69/35	
6[c]	III	inv.	34	34	16	68/32	3
7[d]	III	nor.	29	32	17	65/35	
8[e]	III	inv.	28	33	6	84/16	

[a] nor. = normal; inv. = inverse. [b] Reduction was carried out at −10° in diethyl ether. [c] Reduction at room temperature in diethyl ether. [d] Reduction in boiling tetrahydrofurane. [e] Reduction in dibutyl ether at 90°.

The given arguments cannot explain why, for example, the yield of ketone obtained in the reduction of cholestanone enol acetate (II) is almost twice as high as the yield of coprostanone obtained in the reduction of coprostanone enol acetate (I), or why the yield of ketone in the reduction of cholestenone enol acetate (III) is three times higher than that observed in the reduction of coprostanone enol acetate.

RESULTS AND DISCUSSION

(a) *Formation of ketones.* If the reduction of steroid enol acetates actually takes place through a cyclic intermediate, then three types of intermediates are possible*:

* Only intermediate of type A could be formed by a *cis*-addition of Al and H to the double bond. The intermediates B and C would be the result of the corresponding *trans*-addition. The fourth intermediate with C—Al and C—O bonds in a *trans*-diaxial configuration cannot exist.
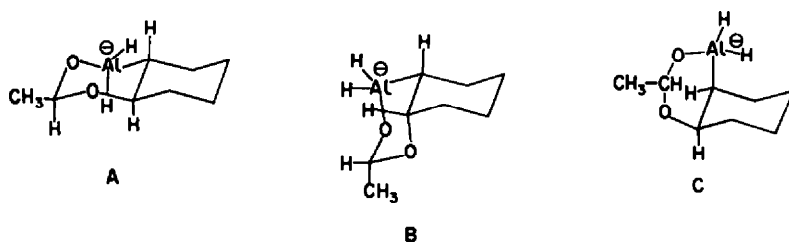
It is necessary to assume that the equatorial alcohols are obtained from the inter-
mediates of type A, in which the equatorial C—O bond already exists, and axial
alcohols are obtained from the intermediates of type B, which have an axial C—O
bond. For steric reasons the ease of formation of the intermediates of type C during
the reduction of the above three enol acetates is III C > II C > I C. On this basis,
the different "yields" of these intermediates should effect the total yield of equatorial
alcohols, and, therefore, also the ratio of equatorial to axial alcohols. It has been
found,[4] however, that the ratio of equatorial to axial alcohols, which were obtained
in the reduction of I and II, is the same. It is obvious, therefore, that during these
reductions the intermediates I C and II C do not contribute to the formation of equa-
torial alcohols. This could mean that the intermediates of type C are not formed
during the reduction, or if formation occurs, they are not able to produce any alcohol.
On the other hand, since the ease of formation of the intermediates of type C (i.e.
III C > II C > I C), during the reduction of the above three enol acetates corresponds
to the yields of ketones which are obtained in these reductions, the formation of ketones
may be envisaged as occurring through intermediates I C, II C and III C.

In another possible mechanism for the reduction of enol acetates the second hyd-
ride attack would also take place on the same carbon atom (which was originally the
carbonyl carbon atom), but with simultaneous breaking of the C—O bond and for-
mation of a C—Al bond. Since formation of a carbon–aluminum bond can occur in
two different ways, the following two types of intermediates (D and E) are possible:
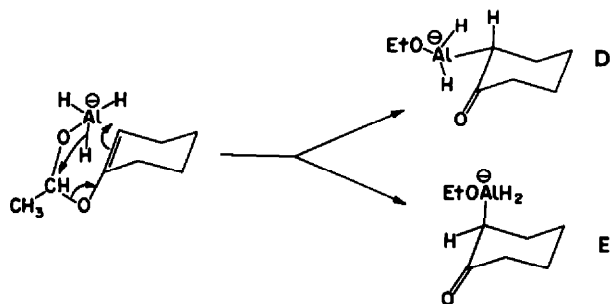
It is obvious that in this mechanism the ratio of the intermediates with the equatorial
and the axial carbon–aluminum bond, D/E, also depends on the number and the size
of syn-axial substituents. Consequently, the ease of formation of intermediates of
type E should follow the same order as above, i.e. III E > II E > I E. The inter-
mediates of type E, from the steric point of view would be less stable than the cor-

responding intermediates of type D, and they may decompose instantaneously in the following manner:
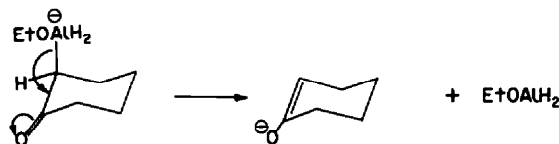
This process would be facilitated by the tendency of the negative charge on the aluminum to be localized on the more electronegative oxygen atom of the CO group, and by the axial orientation of the C—Al bond, since its electron pair has a favourable configuration for the formation of the double bond. A similar transformation of the intermediates of type D, should not take place, because in this case the necessary stereoelectronic conditions for an analogous elimination do not exist. Therefore, the intermediates of type D can react further by an intramolecular hydride shift to afford products which, after hydrolysis, would give equatorial and axial alcohols.

If the above mechanism is correct, then the reduction of enol acetates of 4-t-butylcyclohexanone (IV) and 3,3,5-trimethylcyclohexanone (V and VI), would be expected to give higher yields of ketones, because the formation of the intermediates with an axial C—Al bond (type C or type E), should take place more readily than in the case of I, II and III.

(b) *Reduction of 4-t-butylcyclohexanone enol acetate* (IV) *and 3,3,5-trimethylcyclohexanone enol acetates* (V *and* VI). The reduction of 4-t-butylcyclohexanone enol acetate (IV) was studied under different experimental conditions and results are shown in Table 2.

TABLE 2. REDUCTION OF ENOL ACETATES OF 4-t-BUTYLCYCLOHEXANONE[a] (IV), AND 3,3,5-TRIMETHYLCYCLOHEXANONE[b] (V AND VI) WITH LAH.

Entry	Enol acetate mole	LAH mole	Total yield %	% ketone	% e-OH	% a-OH	e/a	Hydrogen Found mole	Calc. mole
1[c,d]	0·051	0·056	94	39	46·1	14·9	75·6 / 24·4	0·0968	0·0937
2[e]	0·051	0·061	98	33	49·6	17·4	74·1 / 25·9	0·1044	0·1070
3[e,f]	0·0255	0·0145	95	81·4	14·3	4·3	76·0 / 24·0	0·0105	0·0107
4[e,g]	0·0255	0·0275	94·5	33·6	49·9	16·5	75·0 / 25·0		
5[e,g]	0·0255	0·0145	96	82	13·6	4·4	75·5 / 24·5		
6[h]	0·0274	0·0289	97·5	37	32·8	30·2	52·0 / 48·0	0·0457	0·0447

[a] Entries 1–5. [b] Entry 6. [c] Only this experiment has been carried out using a normal addition technique. [d] No precipitate was observed. [e] A precipitate was immediately formed; during the addition of the second half mole of LAH all the precipitate dissolved and further addition of hydride proceeded without apparent reaction. [f] Refluxed 1 hr. [g] Refluxed 6 hr. [h] No precipitate was observed; addition of a second half mole of LAH proceeded with no apparent reaction.

When the reduction was carried out in the normal way by mixing the reactants, the reaction was vigorous but no formation of a precipitate was observed. When the inverse addition technique was used a heavy white precipitate was immediately formed; during the addition of the second half mole of LAH all the precipitate dissolved, and further addition of LAH proceeded with no apparent reaction. Entry No. 1 shows the data which were obtained in a normal reduction and by using equimolar amounts of enol acetates and LAH. The total yield of products (calculated on the basis of sample wt after removing all low boiling fractions) was 94%. Gas chromatographic analysis showed 39% of 4-t-butylcyclohexanone and 61% of alcohols. During the decomposition of the reaction mixture with water, 0·0937 mole of hydrogen was collected, and the calculated value (taking in account that for each mole of ketone obtained two mole of hydrogen and for each mole of alcohol one mole of hydrogen should be liberated), was 0·0968 mole. Using the inverse addition technique and equimolar amounts of reactants (entry No. 2) 33% of ketone and 67% of alcohols was obtained. In this case 0·1044 mole of hydrogen was evolved, while the calculated value was 0·1070 mole. When the inverse reduction was carried out with half a mole of LAH (entry No. 3), 81·4% of ketone was obtained and the yield of alcohols amounted to 18·6%; 0·0105 mole of hydrogen was collected, the calculated value being 0·0107 mole. The ratio between the products was unchanged, even when the reduction time was extended to 6 hr (entries No. 4 and No. 5).
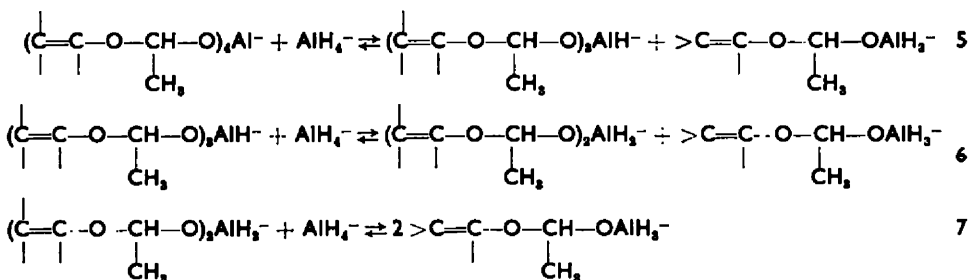
In the reduction of 3,3,5-trimethylcyclohexanone enol acetates (V and VI), using the inverse technique and equimolar amount of reactants (entry No. 6), the yield of ketone was 37% and that of alcohols 63%. The liberated amount of hydrogen was 0·0457 mole and the calculated one 0·0447 mole.

Consequently, as expected, the reduction of 4-t-butylcyclohexanone enol acetate and 3,3,5-trimethylcyclohexanone enol acetates gave the lowest ratios of alcohols to ketone.

(c) *Stoichiometry of reaction*. The stoichiometric results can best be explained in the following way. During the addition of LAH solution to the solution of enol acetate a very fast reaction takes place. The product of the first stage of this reaction is a monoalkoxyaluminohydride anion. This anion, because of a large excess of enol acetate, reacts immediately to give a tetraalkoxide, which is insoluble in ether because of its large mol. wt.

$$>C{=}C{-}O{-}COCH_3 + AlH_4^- \rightarrow \;>C{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}OAlH_3^- \qquad 1$$

$$>C{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}OAlH_3^- + \;>C{=}C{-}OAc \rightarrow (>C{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}O)_2AlH_2^- \qquad 2$$

$$(\underset{|}{C}{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}O)_2AlH_2^- + \;>C{=}C{-}OAc \rightarrow (\underset{|}{C}{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}O)_3AlH^- \qquad 3$$

$$(\underset{|}{C}{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}O)_3AlH^- + \;>C{=}C{-}OAc \rightarrow (\underset{|}{C}{=}C{-}O{-}\underset{\underset{CH_3}{|}}{CH}{-}O)_4Al^- \qquad 4$$
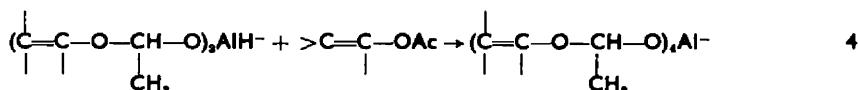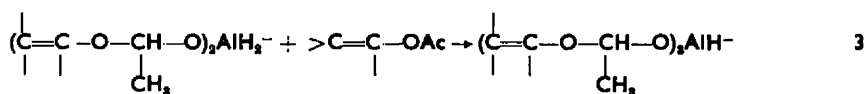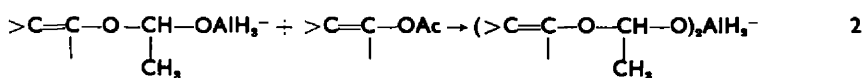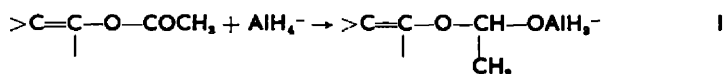
This means that the first quarter mole of LAH is almost entirely used for the formation of the insoluble tetraalkoxide.* With excess of AlH_4^- ions the following reactions occur:

$$(\overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_4Al^- + AlH_4^- \rightleftarrows (\overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_3AlH^- + >C{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}OAlH_3^- \quad 5$$

where CH_3 groups are attached to the indicated carbons.

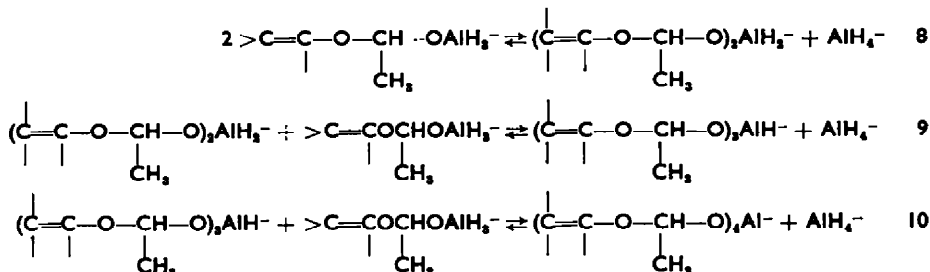$$(\overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_3AlH^- + AlH_4^- \rightleftarrows (\overset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_2AlH_2^- + >C{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}OAlH_3^- \quad 6$$

$$(\overset{|}{\underset{|}{C}}{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_2AlH_2^- + AlH_4^- \rightleftarrows 2 >C{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}OAlH_3^- \quad 7$$

The last anion, $\overset{\displaystyle CH_3}{\underset{|}{\underset{|}{C}}{=}\overset{|}{\underset{|}{C}}{-}O{-}\overset{|}{CH}{-}OAlH_3^-}$, is, of course, the same anion that is formed in the first stage of the reduction, regardless of the order of addition of reactants. Now, however, further reaction (reaction 2 or 8) is prevented, just as in the case of the normal addition, because of the presence of AlH_4^- ions. Therefore, the primary alkoxy-aluminohydride anion has now enough time for the future transformations. It can react in either of two possible ways:

$$+ \; EtOAlH_2 \quad 11$$

$$12$$
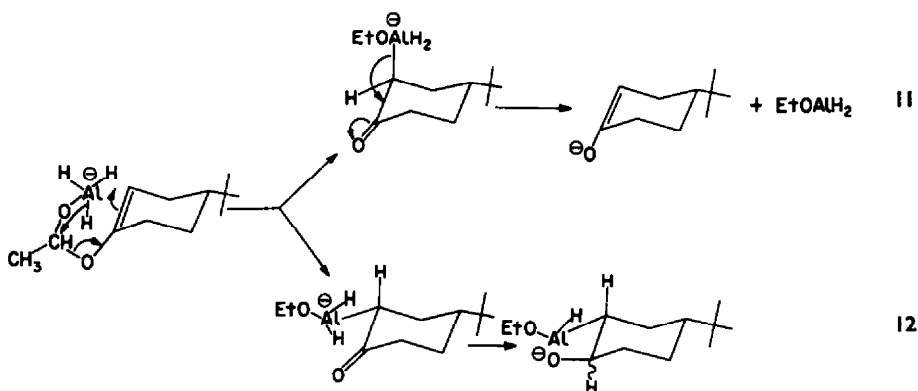
* The formation of insoluble tetraalkoxide may also be envisaged as a series of very rapid disproportionations starting from the monoalkoxyaluminohydride:[6]

$$2 >C{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}\cdot OAlH_3^- \rightleftarrows (\overset{|}{\underset{|}{C}}{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_2AlH_2^- + AlH_4^- \quad 8$$

$$(\overset{|}{\underset{|}{C}}{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_2AlH_2^- + >C{=}COCHOAlH_3^- \rightleftarrows (\overset{|}{\underset{|}{C}}{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_3AlH^- + AlH_4^- \quad 9$$

$$(\overset{|}{\underset{|}{C}}{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_3AlH^- + >C{=}COCHOAlH_3^- \rightleftarrows (\overset{|}{\underset{|}{C}}{=}C{-}O{-}\underset{|}{\overset{|}{CH}}{-}O)_4Al^- + AlH_4^- \quad 10$$

[6] See, for example, H. Haubenstock, E. L. Eliel, *J. Amer. Chem. Soc.* **84**, 2363 (1962).

Therefore, during the reduction of 4-t-butylcyclohexanone enol acetate with half a mole of LAH one should expect to obtain, as the stoichiometry of Eq. 5 requires, ketone and alcohols in the ratio 75:25. However, because of contribution of reaction 11, this ratio should be larger. If the proposed mechanism is correct, then in this case one would expect to obtain the ketone in 83% yield and the alcohols in 17% yield.* Furthermore, on hydrolysis, for each mole of alcohol one should obtain one mole of hydrogen and for each mole of ketone the corresponding amount of hydrogen (1/3 mole of hydrogen according to Eq. 5, and two moles of hydrogen for each mole of ketone which is formed by Eq. 11). In this reduction (Table 2, entry No. 3), 81·4% of ketone and 18·6% of alcohols were obtained, and 0·0105 mole of hydrogen was collected, while the calculated value was 0·0107 mole.

(d) *Formation of alcohols.* On the basis of the above discussion the data obtained for the reduction of coprostanone enol acetate,[4] cholestanone enol acetate,[4] cholestenone enol acetate,[3] 4-t-butylcyclohexanone enol acetate and 3,3,5-trimethylcyclohexanone enol acetates concerning the formation of corresponding ketones, can be explained by either of the two mechanisms.

From the data in Table 1 (entries 2–4), as well as from entries 1–5 in Table 2, the ratio of equatorial to axial alcohol is practically constant. According to the first mechanism, in the reduction of coprostanone enol acetate the formation of intermediate of type A should take place as readily as the formation of the corresponding intermediates in the reduction of cholestanone enol acetate and 4-t-butylcyclohexanone enol acetate, respectively, because the stereochemical factors which are responsible for the ease of formation of the intermediates of type A are identical in all three enol acetates. The situation is similar in connection with the formation of intermediates of type B. However, the intermediate B derived from cholestenone enol acetate should be formed much more easily than the corresponding intermediates in the reductions of I, II and IV, since in this case the *syn*-axial hydrogen at C_5 is absent and therefore the C—O bond is sterically less hindered. (This is in accordance with the experimental results, Table 1, entries 5–7.) Consequently, it would be normal to expect that the formation of cyclic intermediates of type B in the case of enol acetates of 3,3,5-trimethylcyclohexanone (V and VI),† occurs less easily than the formation of the corresponding intermediates of I, II, IV and III (because the axial C—O bond in the former should be under the greater strain); therefore, in this case the ratio between the equatorial and axial alcohol should be the highest. However, in the reduction of these enol acetates the ratio of equatorial to axial alcohol was 52:48, and, therefore, the prediction of ease of formation of cyclic intermediates of type B is not fulfilled.

The possibility that equatorial and axial alcohols, which are obtained in reduction of enol acetates, are formed in an intermolecular reaction of the intermediates of type

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* When the reduction was carried out with equimolar amounts of reactants the total yield of ketone was 33%; this means that only 33% of anions, $>C=C-O-CHOAlH_3^-$ (Eq. 7), reacted
$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad | \quad\quad\quad\quad |$
$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad CH_3$
via reaction 11 to give a ketone. In the reduction with half a mole of LAH the same anion is formed in an amount which is only 25% (Eq. 5) of that when one mole of hydride is used; therefore 33% of these anions react through Eq. 11 to afford 8% of ketone. This gives 83% of total ketone yield. On the other hand, for the same reasons, the total yield of alcohol should be 17%.

† From 3,3,5-trimethylcyclohexanone a mixture of the two isomeric enol acetates, V and VI, in an approximate ratio of 1:1 was obtained.

D and E with LAH itself, is not in accordance with the fact that in the reduction of 4-t-butylcyclohexanone enol acetate with half a mole of LAH only 18% of alcohols was obtained and that further reduction with the second half a mole of LAH occurred without apparent reaction (see above).

CONCLUSION

In conclusion it may be said that the ratio between equatorial and axial alcohols, which are obtained in these reductions, can be explained by assuming that the reduction occurs through the intermediates of type D and E, and not *via* the corresponding intermediates of the cyclic type A, B and C. Only the stable intermediates of type D can further react to give, by an intramolecular hydride shift the corresponding products from which, on hydrolysis, the epimeric alcohols are formed. The differences in yields of equatorial and axial alcohols are probably due to the energy differences between transition states leading to products, from which alcohols are obtained.

The intermediate of type E should be formed in different "yields", which are directly dependent on the stereochemical structure of the enol acetate, and because of their instability they decompose to give the enolate ion of the corresponding ketone, which is resistant to further reduction.

EXPERIMENTAL

4-t-Butylcyclohexanone enol acetate (IV). A mixture of 48 g (0·31 mole) 4-t-butylcyclohexanone, 35 g (0·35 mole) isopropenyl acetate and 0·15 g *p*-toluenesulphonic acid was placed in a 250 ml flask equipped with a 30 cm Vigreux column and heated. When 23 ml (0·32 mole) of acetone had distilled the reaction mixture was transfered in a separatory funnel and 200 ml ether added. The ether solution was washed twice with a sat. $NaHCO_3$ aq, salt solution, and dried over anhydrous $MgSO_4$. The ether was removed *in vacuo* and the remaining liquid was distilled through the same Vigreux column. Only one fraction was obtained, b.p. 85–86°/2·5–3 mm, $n_D^{20} = 1·4640$, reported[7] b.p. 87°/3 mm, $n_D^{20} = 1·4641$; IR spectrum (neat) 1755 cm^{-1}, yield 59 g (97%).

3,3,5-Trimethylcyclohexanone enol acetates (V *and* VI). These enol acetates were prepared using the same procedure as above and 50 g (0·355 mole) 3,3,5-trimethylcyclohexanone, 45 g (0·45 mole) isopropenyl acetate and 0·5 g *p*-toluenesulphonic acid. Enol acetates V and VI were obtained boiling at 70–71°/2·5–3 mm, 60 g (92·5%); IR spectrum (neat) 1755 cm^{-1}. (Found C, 72·17; H, 9·87. $C_{11}H_{18}O_2$ requires: C, 72·49; H, 9·95%.) A gas chromatographic analysis, using a 10 ft. Carbowax 20 M column at 160°, indicated a mixture of the two isomers in an approximate ratio 1:1.

Lithium aluminum hydride reduction of enol acetates

Inverse addition. A solution of LAH in ether (about 1·2 molar) was added dropwise to a stirred solution of enol acetate in ether in a 250 ml 3-neck flask. After the addition was complete, the reaction mixture was stirred and heated under reflux for 30 min. Water and 10% H_2SO_4 was added to the reaction mixture and the H_2 liberated was measured as a check on the stoichiometry. The ether layer was separated and the aqueous layer extracted with ether. The combined ether solution was washed with sat. $NaHCO_3$ aq, salt solution, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* leaving a clear, colourless residue. This residue was analysed directly by gas chromatography on a 10 ft. Carbowax 20 M column at 160°. Relative ratios of components were determined by peak-high-half-width measurement of peak.[8]

Direct addition was carried out in the usual manner and the workup was essentially the same. Experimental results are summarized in Table 2.

[7] I. V. Machinskaya, *Zh. Obsh. Khim.* **23**, 569 (1953); *Chem. Abstr.* **48**, 6383 (1954).