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THE OCCURENCE OF 1,4-ADDITION IN THE REDUCTION OF α , β- UNSATURATED KETOSTEROIDS WITH RECOIL TRITIATED LITHIUM ALUMINIUM COMPLEX-HYDRIDES(1)

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Saturation of a double bond conjugated to a carbonyl was observed for borohydride reductions, where saturated alcohols were obtained (2) with the expected unsaturated alcohols. Similar saturations have also been recorded for several reductions with $LiAlH_4$ (3).

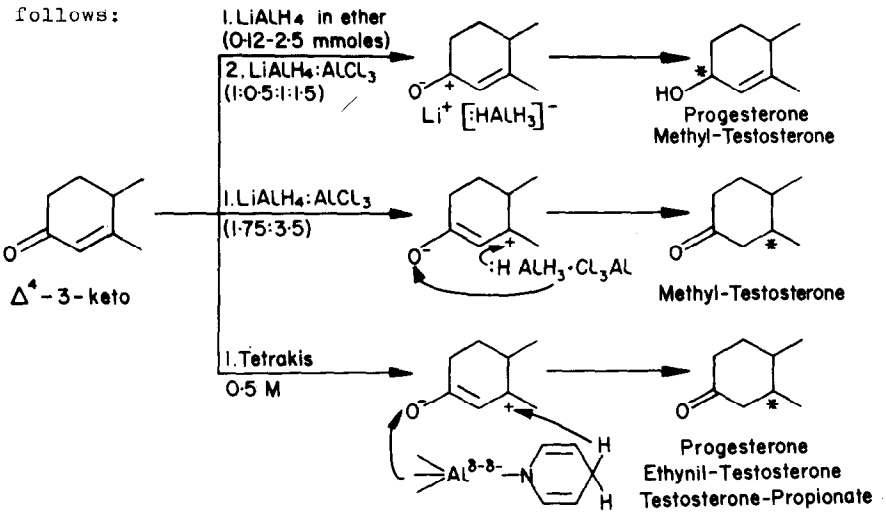
Unlike $LiAlH_4$ which can lead also to 1,4 addition, the complex reagent $LiAlH_4$:$AlCl_3$ in ether was reported to reduce α,β unsaturated ketones always to the corresponding olefine (4-7).

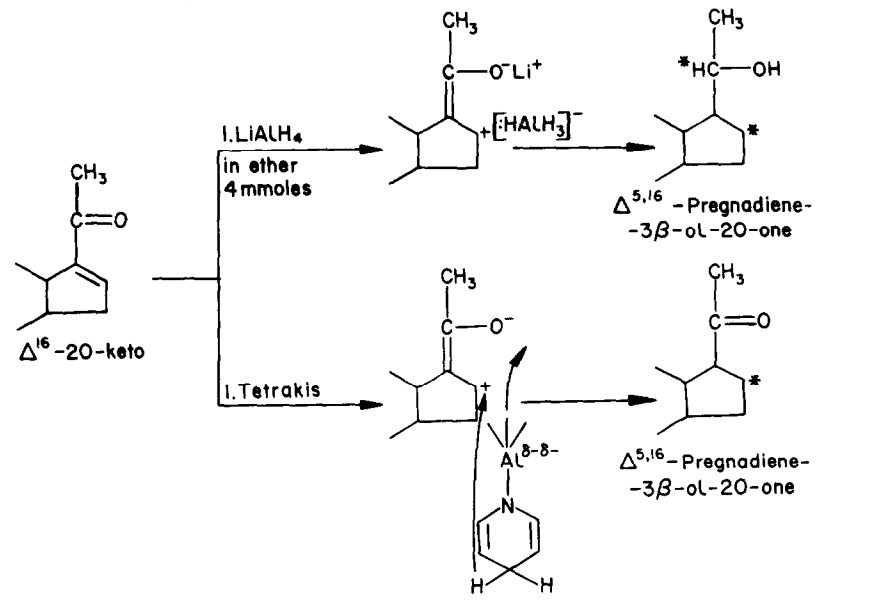
Lithium tetrakis-(N-dihydropyridyl)-aluminate (8) paralleled other dihydropyridine derivatives in giving large amounts of saturated carbinols.

In the experiments reported here, performed with recoil tritiated reagents in certain ratios, in order to obtain tritiated sterol that is $LiAlH_4$-t:substrate (1:4 mmoles); $LiAlH_4$-t:$AlCl_3$:substrate(1:2:1 mmoles) and Lithium-Tetrakis-(N-dihydropyridyl)-aluminate:substrate (1:1 mmoles) the 1,4 addition was often observed leading to the saturated ketones. In a certain case the 1,4 addition followed by the 1,2

addition resulting the saturated carbinol also occured.

The α , β unsaturated ketosteroids reduced with the above mentioned reagents and the reaction paths are as follows:





As it may be seen the Δ^4-3 keto and $\Delta^{5.16}$-20-keto systems of α, β unsaturated ketosteroids were studied. The excess $LiAlH_4$-t reduced $\Delta^{5.16}$pregnadiene-3β-ol-20-one to the saturated carbinol, Δ^5-pregnene-3-20-diol in 95% chemical yield, by addition to the β-carbon giving the enol of the corresponding saturated ketones, which was further reduced to the saturated alcohol. It must be underlined that this reaction was performed practically in one step. The saturation of the double bond with $LiAlH_4$-t occured only in the $^{5.16}$-20-one reduction, the Δ^4-3-one giving only the allylic alcohol.

The reduction with $LiAlH_4$-t:$AlCl_3$ of the 17α-methyl-androsten-17β-ol-3-one gave the saturated ketone by the stabilization of the enol obtained at the 1,4 addition.

There was a great difference between the reduction of the Δ^4-3-ones and $\Delta^{5.16}$-20-one in the reduction with tritiated lithium-tetrakis-(N-dihydropyridyl)-aluminate. While the Δ^4-3-one in 17α-methyl-Δ^4 androstene-3-one-17β-ol and Δ^4-androstene 17α-ol-3-one were totally inactive towards this reagent, from the $\Delta^{5.16}$-pregnadiene-3β-ol-20-one only the Δ^5-pregnene-3β-ol-20-one was obtained in 73% yield. On the other hand the Δ^4-3-one system in Δ^4-pregnene-3-20-dione in 17β-propionyloxy-Δ^4-androstene-3-one and in etynyl-testosterone was also reduced to the saturated ketone.

Though the Δ^4-3-ketogroup is least hindered sterically and therefore should be most reactive, its lower reactivity in certain compounds has been attributed to resonance interactions (9) or may also be regarded as being sterically hindered towards certain bulky reagents which have no room

like lithium tetrakis-(N-dihydro-pyridyl) aluminate.

There is however a delicate balance of steric and polar factors and a slight modification in the magnitude of each will tend to affect the course of the reaction (1).

The 1,4 addition and/or not followed by the 1,2 addition in the reduction of α,β unsaturated ketosteroids with tritiated complex hydrides afforded tritiated saturated ketosteroids or sterols not only to the weak α C-H bond but also to the stronger β C-H bond.

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1. Details concerning the preparation of tritiated reagents, and the experimental conditions of the reduction reactions, as well as the methods of purification and identification of the products are to be appeared in J. Labelled Compounds.

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