

PART - II

LEAD (IV) ACETATE OXIDATION OF TRITERPENOID

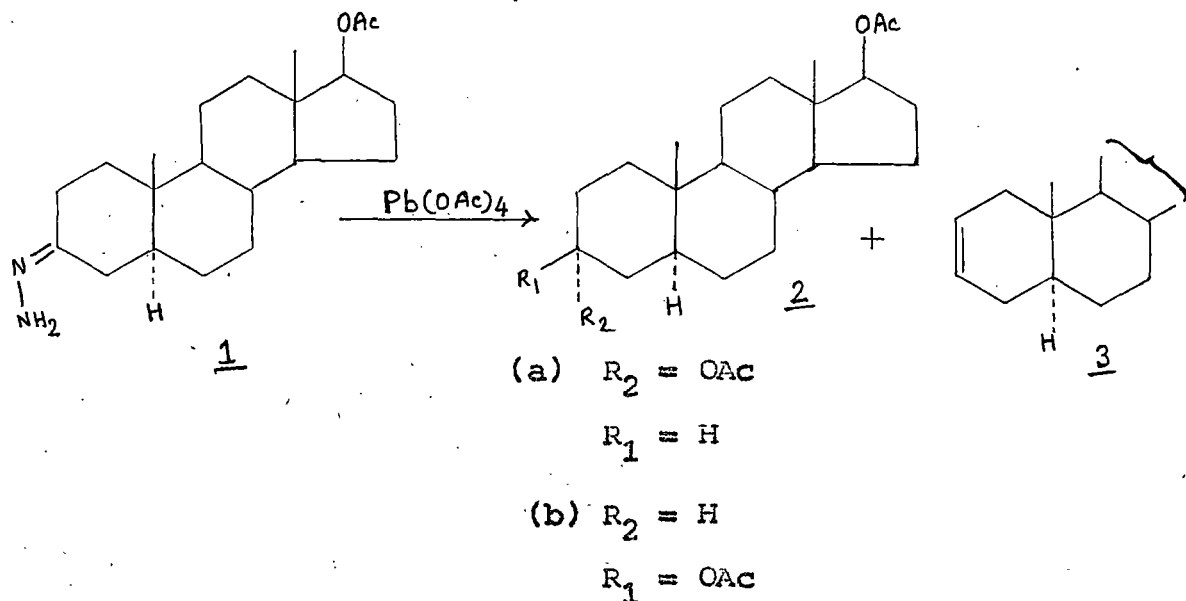
3 - KETOHYDRAZONES

CHAPTER - I

A Short Review on Lead (IV) Acetate Oxidation
of Steroids and Triterpenoid Keto Hydrazones.

Oxidation of 17β -acetoxy- 5α -androstan-3-one by lead
tetraacetate.

M. Debono and R.M. Molloy¹ examined the product formed by lead tetraacetate oxidation of steroidal 3 keto hydrazones. 17β -acetoxy- 5α -androstan-3-one hydrazone 1 gave three major components on oxidation with lead tetra-acetate in CH_2Cl_2 . The



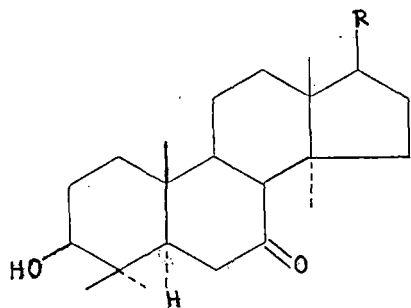
yield of acetate (3α to 3β ca. 2:1) was 52% and of olefin 25%. A predominance of 3α acetate 2a ($R_2 = \text{OAc}$) was in quantitative

agreement with the result obtained by White^{1a} for nitrosoamide decomposition. This reaction required the conversion of the hydrazone into reactive species which could readily lose nitrogen and either reacted with acetic acid formed in the reaction to afford ester product or loss of a proton to give olefin product. The effects brought about by solvent change was studied by them by varying the concentration of acetic acid and also by using pyridine. They noticed that the product ratio remained practically unresponsive to change in condition. However, they did not report detailed mechanistic studies concerning this oxidative reaction.

Oxidation of 3 β -hydroxy lanostan-7-one hydrazone and other related hydrazones by Lead Tetra-acetate.

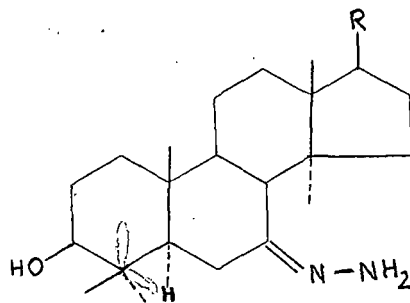
D.H.R. Barton reported² a novel method for the preparation of 7 α -acetoxy derivatives of Lanosterol system via lead tetra-acetate oxidation of the corresponding 7-ketone hydrazones. In a later communication, they also presented³ full report of their investigation of the scope and mechanism of that reaction.

The hydrazone 5a from 3 β -hydroxy lanostan-7-one⁴ 4a, on treatment with lead tetra-acetate in methylene chloride and subsequent acetylation afforded 3 β -acetoxy-lanost-7-ene (20%) 6a and 3 β -7 α -diacetoxy-lanostane (68%) 7a. Similar percentage of products 6b and 7b are obtained from the hydrazone 5b of 3 β -hydroxy lanost-24-ene-7-one 4b on treatment with Pb(OAc)₄ in CH₂Cl₂.



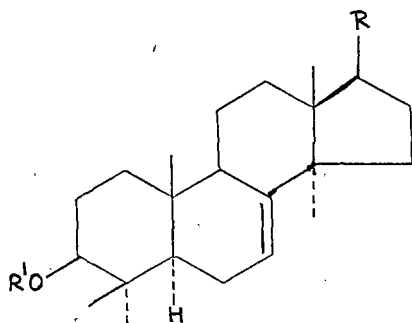
4 a $R = C_8H_{17}$

b $R = C_8H_{15}$



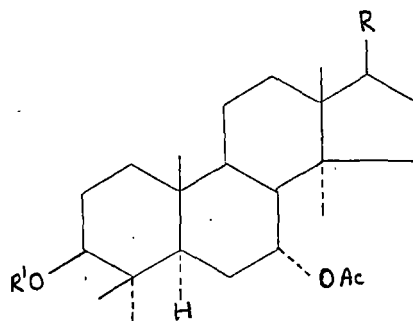
5 a $R = C_8H_{17}$

b $R = C_8H_{15}$



6 a $R = C_8H_{17}$, $R' = Ac$

b $R = C_8H_{15}$, $R' = H$



7 a $R = C_8H_{17}$
 $R' = Ac$

b $R = C_8H_{15}$

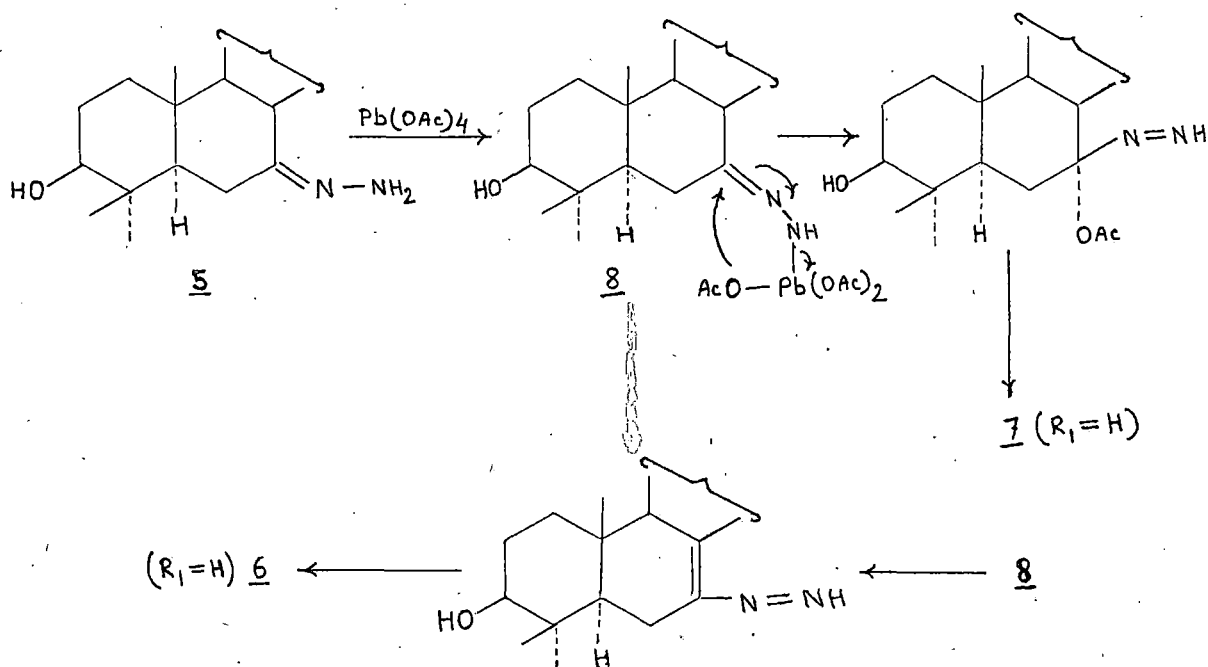
$R' = H$

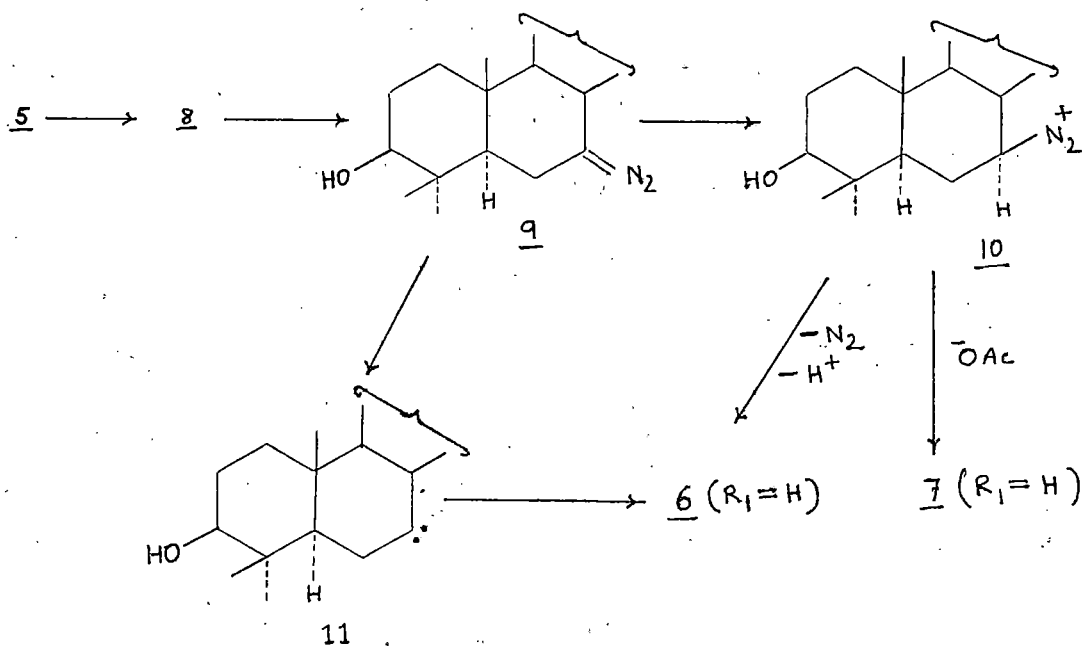
There was no remarkable variation in yields of the olefin and acetate in different solvents like acetic acid, benzene, methylene

chloride, light petroleum etc. except methanol in which case 3-methoxy derivative was also obtained.

Two different pathways which could explain the formation of the products, were considered by them. Iffland and co-workers reported that the cyclic mechanism established the formation of products ^{from} substituted hydrazones. By analogy it was conceivable that in the reaction of 3 β -hydroxy lanostan-7-one hydrazone with $Pb(OAc)_4$ both the olefin 6a and the acetate 7a were formed via pathway A. The attack on the α -face of the sterol molecule coupled with the large steric requirements of the intermediate 8 would explain the formation of the 7 α -acetoxy-derivatives.

Mechanism A



Mechanism B

An alternative mechanism involved initial oxidation of the hydrazone to the diazo-compound 9 followed by reaction of the diazo-compound with acetic acid formed in the primary oxidation step. This could lead to formation of either the acetate or the olefin shown in pathway B.

Protonation of the diazo-compound on the carbon atom from the α -side would be expected to give an intermediate 10 identical with that obtained in the diazotization of the corresponding 'equatorial' 7β amine. This diazotization gave the product with retention of configuration⁶. But 7β -acetate was not found with substantial quantity. This fact alone was insufficient to ignore this route as a reasonable reaction mechanism. Loss of nitrogen from the diazo-compound would yield a carbene 11, from which the olefin would form

via 1,2 hydrogen shift. Alternatively, loss of nitrogen from the diazonium ion 10 would give olefin via carbonium ion.

To distinguish between these two mechanisms the lead tetra-acetate oxidation of benzophenone hydrazone was investigated. Benzophenone hydrazone rapidly oxidised to diphenyldiazomethane, followed by a slower step in which the diazo-compound is partitioned between reaction with acetic acid to give, after hydrolysis, benzhydrol, and reaction with lead tetra-acetate to give, ultimately benzophenone and was consistent with pathway B. Confirmation that all the hydrazone was oxidised to the diazo-compound was established from a trapping experiment. To get an insight into the mechanism for the triterpenoid hydrazone, dicyclohexyl ketone was taken. The compound dicyclohexyl ketone gave the similar result to those obtained in the corresponding reactions of 3β -hydroxy lanostan-7-one hydrazone with lead tetraacetate. Even under conditions of high lead tetra-acetate concentration the yield of dicyclohexyl ketone was negligible and no ketone could be detected for 3β -hydroxy lanostan-7-one. The results obtained with both 3β -hydroxylanostan-7-one hydrazone and dicyclohexyl ketone hydrazone are compatible with the cyclic mechanism depicted in pathway A, since it would be predicted that changes in concentration of lead tetra-acetate, acetic acid, or acetate ion would have no effect upon the product distribution from such a reaction mechanism.

However, the compound dicyclohexyldiazomethane with acetic acid in methylene chloride gave the olefin to acetate ratio 1.18:1 and 14% ketone. The identity of the ratios of olefin to acetate in the reaction of the hydrazone with lead tetra-acetate and in that of the diazo-compound with acetic acid support a mechanism involving primary oxidation of the hydrazone to the diazo-compound (mechanism B).

So, at first the results indicated that the oxidation of benzophenone hydrazone proceeded by a mechanism different from that of dicyclohexyl ketone hydrazone or 3β -hydroxylanostan-7-one hydrazone, but latter the results established ^{that} ~~the~~ mechanism in all cases involved preliminary oxidation of the hydrazone to the diazo-compound (mechanism B). Next they carried out mechanistic work to resolve whether the olefinic precursor was the carbene or the corresponding carbonium ion. In accordance with the classical work of Meerwein on the mercury (II) oxide oxidation of camphor hydrazone⁷, the formation of tricyclene via carbene intermediate has been well established. On the other hand, the formation of the carbonium ion would yield camphene by a Wagner-Meerwein rearrangement.

Oxidation of camphor hydrazone with lead tetra-acetate afforded a mixture of camphene (60%) and isoborneol and borneol acetates. No tricyclene could be detected. The olefin was thus formed via a carbonium ion. The application of perbenzoic acid on hydrazone also confirmed the mechanism of the product obtained via a carbonium ion.