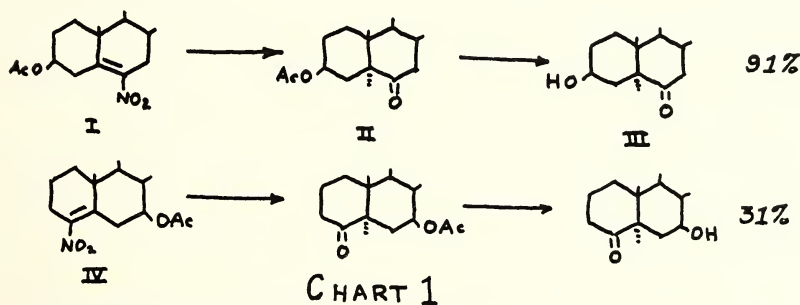


Reductive Preparation of Oximes and the Selective Hydrolysis of their Acetates on Alumina¹

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The reduction of the vinyl nitro compound, 6-nitrocholesteryl acetate (I) has been used since 1903 (1, 2) to prepare 6-ketocholestanol (III) and its acetate (II). More recent work (3, 4, 5) has improved the yield and ease of workup but the synthesis has remained essentially unchanged since that time, zinc and acetic acid remaining the reducing agent. The overall yield of the 6-keto compound (II) from cholesterol—the starting material for the synthesis of all cholestane derivatives—is about 86% following the most recent procedures.

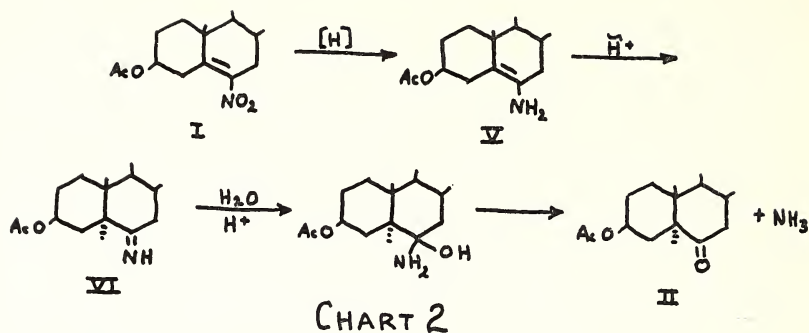
In the course of our work on the synthesis of i-pseudocholesterol (6) we had need of applying this reduction to the analogous vinyl nitro compound, 4-nitro-pseudocholesteryl acetate (IV). Inasmuch as pseudocholesterol had, in general, shown the same reactions as cholesterol (6, 7, 8), it seemed reasonable that such a procedure would work. However, since the pseudocholesteryl acetate starting material was available in only five percent yield from cholesterol, the yields on nitration and reduction were of critical importance and the resulting thirty-one percent yield was not adequate for our synthetic purposes.



Consideration of the reaction path leading to the ketone suggests, as shown in chart 2, that it is a reduction of the nitro group to provide a vinyl amine (V) which suffers a proton shift to provide the imine (VI). Subsequent hydrolysis of the imine would provide the observed product. And, indeed, ammonia is produced as a reaction product (1, 2).

It seemed reasonable that the use of lithium aluminum hydride as a reducing agent instead of zinc and acetic acid might increase the yield of the ketone in the pseudocholesterol series if the vinyl amine (V) or

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imine (VI) produced by the reduction of the nitro compound were removed from the reaction medium by salt formation with lithium in the fashion that other acidic groups form such salts. It would then be predicted that only upon the addition of water would further reaction of the vinyl amine (or imine) take place, and inasmuch as the water would destroy any remaining lithium aluminum hydride, the ketone produced would not be reduced further. It was, of course, expected that the acetoxy would also be reduced by the hydride. 6-Nitrocholesteryl acetate (I) was used as a model compound to study the reaction and its reduction with lithium aluminum hydride provided a good yield of a highly crystalline compound melting at 200° (VII), the elementary analysis of which showed the presence of nitrogen and the infrared spectrum of which showed free hydroxyl. Neither the percentages of nitrogen, carbon and hydrogen, nor the infrared spectrum suggested any specific substance, but clearly production of neither the ketol (III) nor its acetate (II) had obtained.

Acetylation of the compound provided, by chromatographic workup, a substance also melting at 200° (VIII) but showing both acetate and free hydroxyl in the infrared. When, however, workup was by crystallization alone a substance melting at 130° (IX), showing no free hydroxyl in the infrared was isolated as the sole product. In spite of almost identical melting points, the former acetate (VIII) was clearly distinct from the starting material (VII) and the latter acetate (IX) clearly distinct from the expected product 6-ketocholesteryl acetate (II). Both acetates provided, upon basic hydrolysis, the starting material (VII).

During the preparation of an analytical sample of the 130° acetate (IX) it was chromatographed on alumina and the sole product eluted proved to be the 200° acetate (VIII) in a very pure form. When this acetate was treated with acetic anhydride, the 130° acetate (IX) was resynthesized. Elemental analyses on these derivatives proved more meaningful and the identity of the reduction product was established as the oxime of 6-ketocholesterol (VII) and the derivatives as the mono (IX) and diacetates (XIII) of that substance, alumina chromatography having been capable of effecting hydrolysis of the oxime acetate selectively. The structures were verified by independent synthesis (9) from the known ketol (III) and its acetate (II) as shown on chart 3.

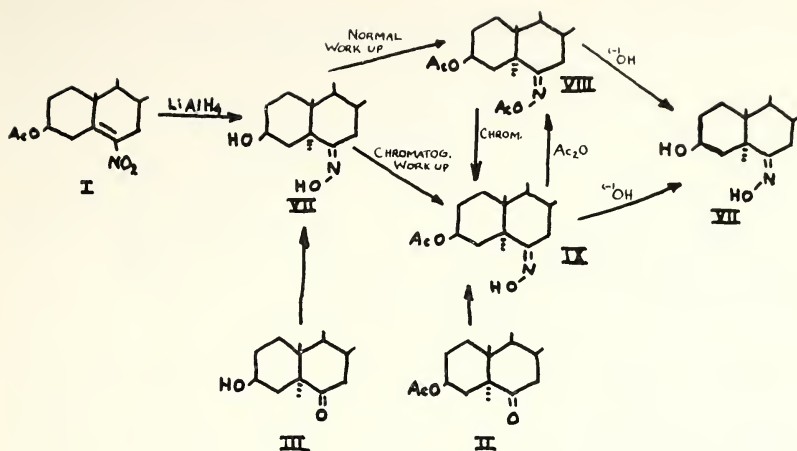


CHART 3

Thus, in contrast to the zinc and acetic acid reduction, the reduction with lithium aluminum hydride had stopped short of the vinyl amine (V) stage and, as shown in chart 4 might be considered to have proceeded through the vinyl nitroso compound (X) and the vinyl hydroxylamine (XI) at which point the reduction ceases with the hydroxyl group of (XI) presumably removed by salt formation. Hydrolysis of the salt and subsequent acid catalyzed rearrangement to the oxime would complete the reaction.

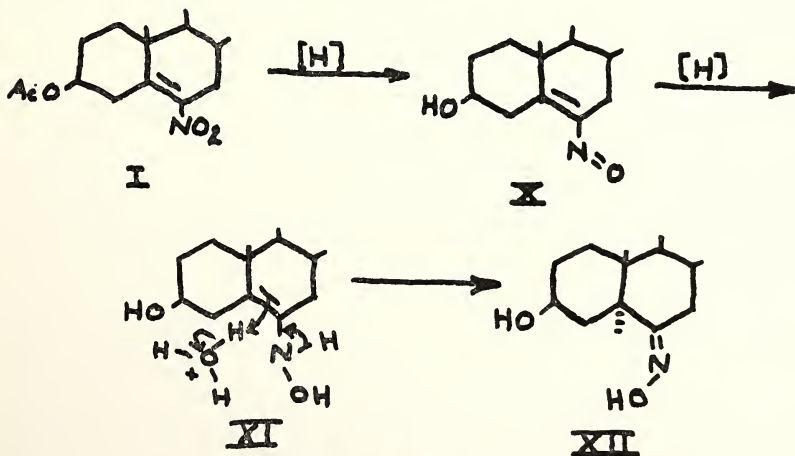
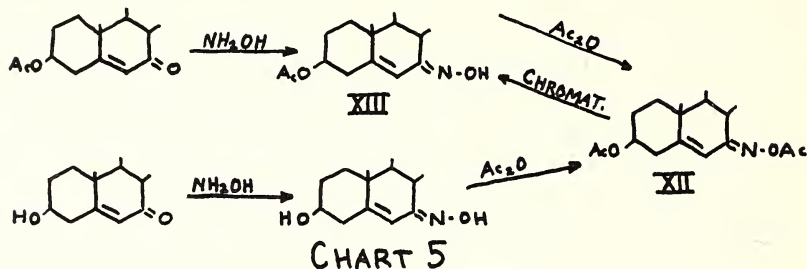


CHART 4

In order to generalize the behavior of the alcohol-oxime diacetate, 7-ketocholesterol oxime diacetate (XII) was synthesized and found to be converted essentially quantitatively to 7-ketocholesteryl acetate

oxime (XIII) upon passage over an alumina column in a fashion identical to the behavior of the 6-keto oxime diacetate (IX).



The infrared spectra of most of the compounds discussed were measured both in the solid state and in carbon tetrachloride solution. One unanticipated observation made on the spectra obtained by either technique was that when comparing pairs of compounds from the two series—that is, the saturated 3-hydroxy-6-oxime and the unsaturated 3-hydroxy-7-oxime—similarly substituted hydroxyl groups showed essentially identical adsorption frequencies. For example, the $\text{C}=\text{N}$ stretching frequency (9, 10) at 1638 cm^{-1} in the saturated oxime diacetate (IX) is identical to that in the unsaturated system (XII). In view of the conjugation of the latter, this was certainly not anticipated.

The adsorption frequencies of the $=\text{N}-\text{OAc}$ do not appear to have been reported and were found to differ significantly from those of the $\text{C}-\text{O}-\text{Ac}$ but to resemble, not surprisingly, those of an enol ester (11), the carbonyl stretching frequency being elevated by 31 cm^{-1} in both series and the $\text{N}-\text{O}-\text{C}$ band was 28 cm^{-1} lower than the $\text{C}-\text{O}-\text{C}$ band in both series.

Experimental

6-Ketocholestanol oxime (VII)

To a slurry of 2.0 g. of lithium aluminum hydride in 200 ml. of ether was added over 30 min. a solution of 7.0 g. of 6-nitrocholesteryl acetate (I) in 50 ml. of ether. A vigorous reaction took place upon each addition of solution and toward the end of the addition a precipitate formed at the surface, dissolving as the initial reaction subsided. After addition was complete the mixture was heated for 10 min. and decomposed with 2 N sulfuric acid. After standing overnight the ether layer was filtered from a white precipitate (which possessed a definite ammonia odor) and evaporated to give 5.5 g. of a taffy-like solid which was crystallized from methanol to provide 4.0 g. of 6-ketocholestanol oxime, m.p. $180-190^\circ$. This material was recrystallized once from methanol to give needles, m.p. $206-208^\circ$, undepressed upon admixture with authentic 6-ketocholestanol oxime prepared from 6-ketocholestanol (4).

6-Ketocholestanol oxime diacetate (IX)

A solution of 0.7 g. of VII in 20 ml of acetic anhydride was refluxed for one hour, cooled to room temperature, and poured into 50 ml of cold water. After 20 hours the yellow, semicrystalline product was

removed and crystallized from acetone-water to a yellow granular solid. This solid recrystallized well from methanol to provide white needles, m.p. 130-131°. Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.31; H, 10.24; N, 2.79. Found: C, 74.29; H, 10.34; N, 2.64. Treatment of VIII with acetic anhydride also provided this compound.

6-Ketocholestanol acetate oxime (VIII)

A solution of 0.2 g. of the diacetate IX in petroleum ether was passed over a 1 x 14 cm. column of alumina and then eluted with benzene. Evaporation of the benzene fractions provided 0.18 g of directly pure 6-ketocholestanol acetate oxime m.p. 202-204°. Recrystallization from acetone provided magnificent square plates of the same m.p., undepressed upon admixture with an authentic sample (12) prepared from 6-ketocholestanol acetate.

7-Ketocholesterol oxime diacetate (XII)

One tenth gram of 7-ketocholesterol oxime was dissolved in 10 ml. of acetic anhydride and refluxed for one hour. The resulting pale yellow solution was poured into water and after hydrolysis was complete a yellow mat of needles was filtered off. Two washes with cold methanol provided 0.09 g. of white needles m.p. 180-183°. Recrystallization from methanol gave 0.06 g. m.p. 183-186°. Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.45; H, 9.87. Found: C, 74.39; H, 9.87.

7-Ketocholesteryl acetate oxime (XIII)

The diacetate XII, when treated with alumina in a fashion identical to that described for the diacetate IX provided 7-ketocholesteryl acetate oxime, m.p. 191-192, undepressed upon admixture of an authentic sample (13) prepared from 7-ketocholesteryl acetate.

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