THE SELECTIVE HYDROGENATION OF THE Δ^1 DOUBLE BOND IN 6α-METHYL-$\Delta^{1,4}$-3-KETO STEROIDS

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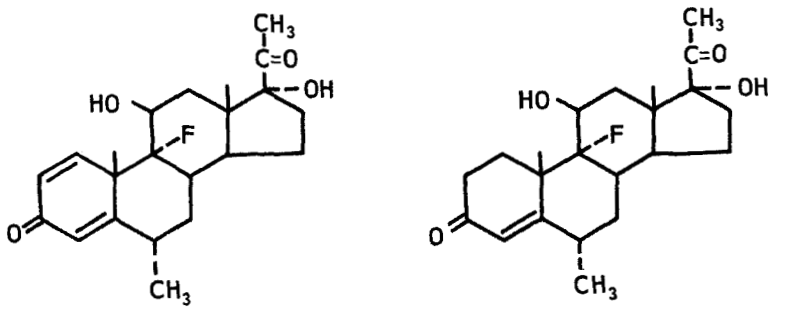
The synthesis of the steroid, Compound II (FIGURE 1), by conventional methods involves a long and difficult sequence of reactions. This compound, however, differs from the commercially available Oxylone® (Compound I) only in that it is saturated in the 1,2-position and, thus, may be considered to be 1,2-dihydro Oxylone. A means of selectively reducing the Δ^1 double bond in Oxylone would, therefore, provide a convenient synthesis of Compound II. Since we needed a large supply of this dihydro Oxylone we began to search for catalytic conditions that would promote the necessary hydrogenation efficiently.

At the time we began our investigation, a number of attempts to carry out such a selective reduction using heterogeneous catalysis had been described in the literature,[1-4] but the results were not promising. Yields of desired Δ^4-3-ketones were low and isolation was difficult. The excellent work of Wilkinson [5, 6] on homogeneous catalysis and its extension to steroids by Djerassi [7] had not yet been published.

We studied two different catalysts, carbon-supported palladium and pre-reduced ruthenium oxide. The results, when used in the hydrogenation of Oxylone, are illustrated graphically in FIGURE 2. Each compound in the crude product is represented as a bar on a scale of R_f values, such as is obtained when the mixture is assayed by thin-layer chromatography. We used silica gel plates developed one or more times in a mixture of 15% acetone and 85% methylene chloride. The height of each bar is proportional to the percentage of the component in the mixture. The starting material, when present, is represented by a white bar, the desired 1,2-dihydro product by a shaded bar, and all by-products by black bars. This convenient means of portraying the number and relative amounts of components has been chosen because of the important relationship between R_f values and ease of isolation of components of a mixture. When a major by-product has an R_f value similar to the product, such as is the case in the uppermost graph, isolation is often difficult. If, on the other hand, no significant by-product approaches the product in R_f value, such as in the lower graph, the product is readily separated, at least by chromatography.

When 5% palladium on carbon is employed in aqueous ethanol for the reduction of Oxylone, and the uptake is interrupted at 1.0 mole equivalent of hydrogen, the reaction mixture contains about equal amounts of starting material, the desired 1,2-dihydro product, and one major by-product as shown in the first graph in FIGURE 2. Upon increasing the uptake to 1.4 equivalents, starting material essentially disappears and the product-to-by-product ratio remains about 1:1. The resulting 40% conversion to the Δ^4-3-keto compound would, on first consideration, appear to offer a reasonably satisfactory synthetic procedure. The difficulty of removing the rather large amount of by-product, however, renders the method impractical. Separation by crystallization



OXYLONE ®

(FLUOROMETHYLONE, UPJOHN)

I

1,2-DIHYDROXY OXYLONE ®

II

FIGURE 1. Oxylone and its 1,2-dihydro reduction product.

is exceedingly poor and, as noted previously, the similarity of R_f values makes separation by chromatography inefficient.

If we examine the results with prereduced ruthenium in the bottom graph of FIGURE 2, we see a somewhat more encouraging picture. Although the conversion to the 1,2-dihydro product is again about 50%, there is little of the troublesome by-product found above. Numerous by-products are formed, but only in minor amounts. In practice, the desired compound may be isolated in about 40% yield even by simple crystallization. This yield is raised to nearly 50% by chromatography. We employed this process successfully to produce

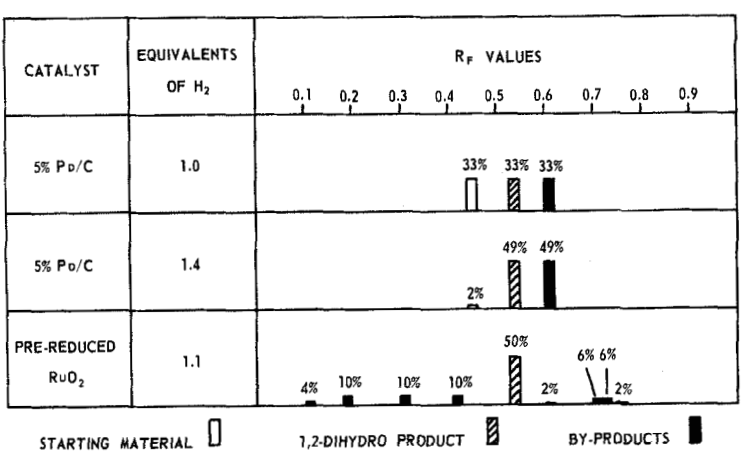
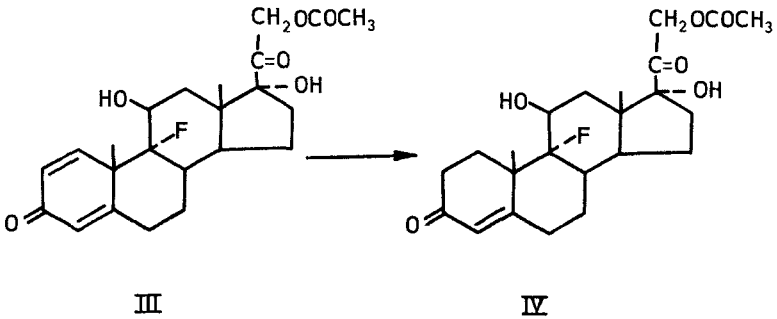


FIGURE 2. Results of the hydrogenation of Oxylone.



III IV

FIGURE 3. Hydrogenation of 9α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione, 21-acetate.

a rather large amount of the Δ^4-3-keto steroid, dihydro Oxylone, which was the original purpose of this investigation.

The striking difference in the nature of the products obtained when using these two catalysts, palladium on carbon and prereduced ruthenium oxide, prompted us to compare them further. At the same time, we chose to study the effect of the 6α-methyl substituent on the selectivity of the reduction of the Δ^1 double bond.

Compound III in FIGURE 3 is a steroid which is very similar to Oxylone except for the absence of the 6α-methyl group. Compound IV is the corresponding 1,2-dihydro derivative. In FIGURE 4, we see again that when this compound is reduced in the presence of palladium on carbon, only one by-product is formed. If the process is interrupted when only a small amount of starting material remains, the ratio of 1,2-dihydro product to by-product is 30:68. In this case, the isolation of pure product is even more difficult than in the case of

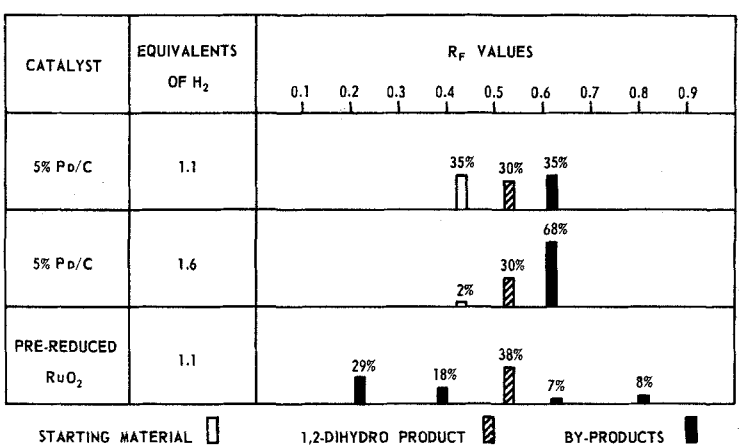


FIGURE 4. Results obtained in the hydrogenation of 9α-fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione, 21-acetate.

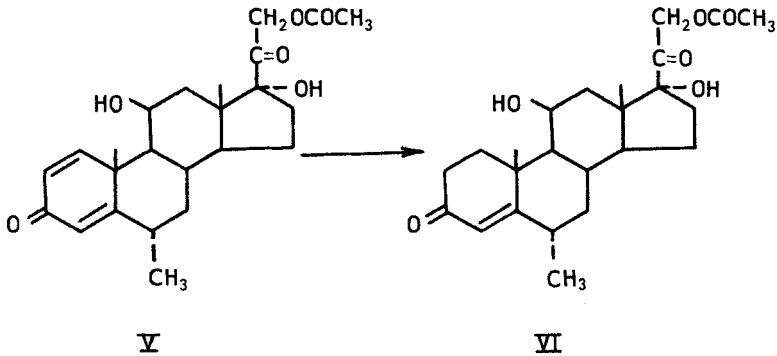


FIGURE 5. Hydrogenation of Medrol acetate.

Oxylone because the large amount of by-product literally overwhelms the product. On the other hand, when prereduced ruthenium oxide is employed, separation of the 1,2-dihydro compound is reasonably satisfactory, even though the actual conversion is still only about 38%. By chromatography, a 28% yield of isolated product may be obtained. There are several by-products, but they are either present in small amounts or are well separated in polarity.

For a second example of a 6α-methyl substituted $\Delta^{1,4}$-3-keto steroid we chose Medrol® acetate (Compound V, FIGURE 5), which is shown with its dihydro reduction product, 6α-methylhydrocortisone acetate, Compound VI. The performance of palladium on carbon with Medrol acetate is very poor. It can be seen in the first graph in FIGURE 6 that when 1.0 equivalent of hydrogen has been absorbed, the reaction mixture contains only about 16% of the 1,2-dihydro compound, with 42% of the starting material remaining and an equal amount of by-product being formed. The yield is not improved by allow-

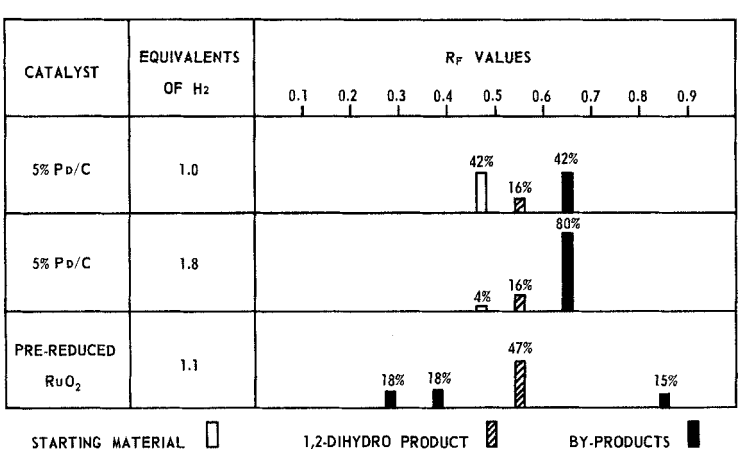


FIGURE 6. Results of the hydrogenation of Medrol acetate.

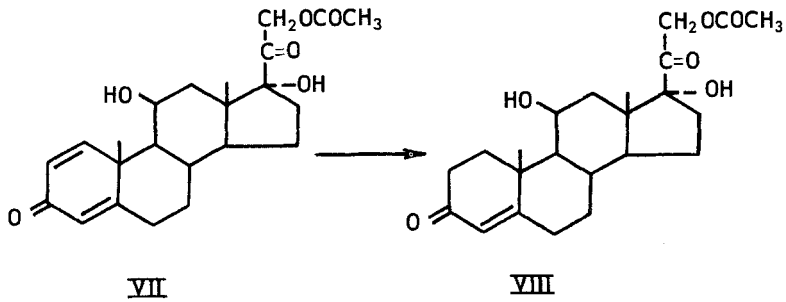


FIGURE 7. Hydrogenation of Deltasone acetate.

ing the reaction to proceed nearly to completion as shown in the graph below. The desired product remains at about 16%; only the by-product increases as the starting material is consumed. If, instead, prereduced ruthenium oxide is used, the process becomes a useful synthetic method. As seen in the lowest graph, the conversion to Δ^4-3-ketone is improved to about 47%. This compound becomes the major component of the reaction mixture and is readily separated from the lesser components which have widely differing R_f values.

The corresponding steroid without the 6α-methyl group is Deltasone® acetate (compound VII, FIGURE 7). Its 1,2-dihydro derivative is hydrocortisone acetate, Compound VIII. Rather surprisingly, carbon-supported palladium made a slightly better showing here. The first graph in FIGURE 8 shows the results obtained when the process was interrupted at an uptake of 1.0 equivalent of hydrogen. The conversion to the 1,2-dihydro compound was about 20%, the amount of starting material and by-product each being about 40%. As in the case with Medrol acetate, permitting the process to go nearly to completion did not improve the yield of 1,2-dihydro compound. The only effect was to

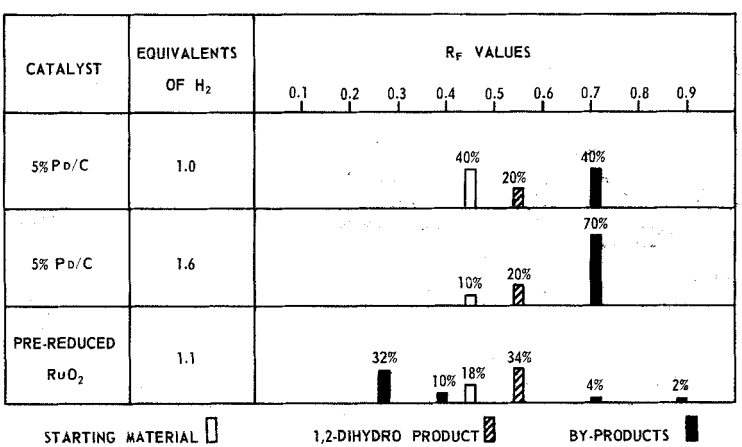
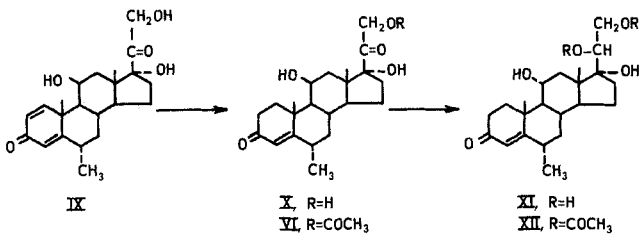


FIGURE 8. Results of the hydrogenation of Deltasone acetate.

produce more by-product, as shown by the bar representing 70% in the next graph. The lowest graph shows that, again, the use of prereduced ruthenium oxide for the catalyst makes selective reduction of the Δ^1 bond practicable. The conversion to the 1,2-dihydro compound in the particular run shown is about 34%, even though the reaction was interrupted when 18% of the starting material still remained. Although one by-product is formed in nearly equal amount, it is somewhat more polar and is readily separated.

We also studied the Medrol molecule itself without the 21-acetate substituent (Compound IX, FIGURE 9) and found that the presence of the acetate group played an important role in the course of the reduction over prereduced ruthenium. The product we intended to form is 6α-methylhydrocortisone, Compound X. A look at the graph at the bottom of FIGURE 9, which shows the



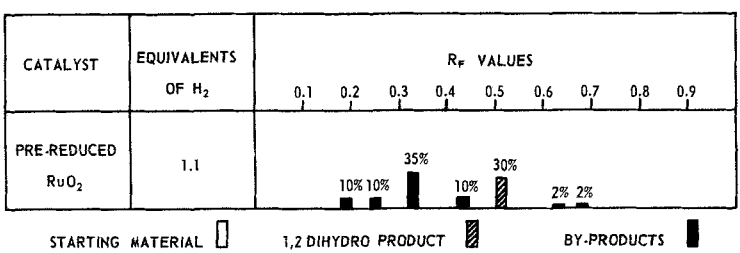


FIGURE 9. Hydrogenation of Medrol.

spectrum of products obtained, reveals that although the intended methylhydrocortisone is present to the extent of about 30%, another more polar component represents an even larger portion of the mixture. In fact, it was the latter compound which we isolated first. This particular reaction mixture proved to be one which did not separate well by chromatography. The solid which separated from the principal chromatography fractions was obviously not pure. It was acetylated and rechromatographed. The crystallized solid from the major fractions thus obtained was not the expected 6α-methylhydrocortisone acetate (Compound VI) but was, instead, found to be identical to the known diacetate (Compound XII) of the tetrahydroxy derivative. In this case, the starting $\Delta^{1,4}$-3-keto compound has first added hydrogen to the 1,2-double bond, and then part of the resulting Δ^4-3-ketone has been reduced further at the

20-keto position to the corresponding hydroxy compound. Since no equivalent product was found in significant amount in the reduction of Medrol acetate (Compound V, FIGURE 5), it seems apparent that the presence of the 21-acetate group affords a certain degree of protection for the 20-ketone against attack by hydrogen in the presence of ruthenium catalyst.

The limited amount of work presented here represents only a preliminary investigation, and broad generalizations are not warranted. It is tempting, however, to point out some interesting observations. First, although carbonyl groups are very much more resistant than olefinic double bonds toward reduction in the presence of palladium, this appears not to be the case when ruthenium is used. It is beyond the scope of this paper to fully characterize all the by-products produced. Nevertheless, we did study the infrared spectra of many of the by-products obtained over ruthenium and found that in a number of them one or more carbonyls had been reduced. Furthermore, in the case of the hydrogenation of unacetylated Medrol, we have shown that the 20-ketone competes with the Δ^1 double bond to such an extent that even though most of the starting material is converted to the Δ^4-3-ketone, about half of this is also reduced to the 20-hydroxy derivative. This vulnerability of the carbonyl groups as well as the ethylenic double bonds to the addition of hydrogen accounts in part for the greater number of by-products obtained over ruthenium and their wider variation in polarity that aids in their separation.

It also appears that steric hindrance has a greater effect in hydrogenation over ruthenium than over palladium. As we have seen in FIGURE 6, the data obtained on the hydrogenation of Medrol acetate reveal that in the presence of palladium the major component of the final mixture is a by-product. This is known to have a saturated A-ring. It is evident that there is not much difference in the ease with which hydrogen adds to the Δ^1 and the Δ^4 double bonds. Indeed, addition to the second double bond follows the first so closely that comparatively little intermediate dihydro compound is permitted to accumulate. In the presence of ruthenium, on the other hand, it would seem that the Δ^4 bond is somewhat more resistant to attack by hydrogen since the dihydro compound accumulates to the extent of nearly 50%. It is interesting that no saturated A-ring product is found in the final mixture. If any significant amount is formed, it must be unusually susceptible to further change when ruthenium is present.

The standard procedure for hydrogenation over ruthenium catalyst was as follows: an amount of ruthenium oxide about equal to the amount of steroid to be reduced was suspended in a 15:1 mixture of acetic acid and water and this suspension was treated with hydrogen overnight for prereduction. The steroid was then added and treatment with hydrogen resumed at 1–2 atmospheres and room temperature, usually until about 1.1 mole equivalents of hydrogen was absorbed.

We found a great variability in catalyst preparations despite the fact that they were all obtained from the same manufacturer, Engelhard Industries, and the manufacturer's specifications revealed no appreciable differences among them. Lot Nos. 9507 and 9369 were readily activated by prereduction at 1–2 atm and room temperature. Lot No. 9226, on the other hand, was activated only after treatment with hydrogen at 1000 psig and 50° C, whereas Lot Nos. Ru32 and 29BX could not be activated even at high pressures.

In summary, we would like to submit that, from a practical point of view, hydrogenation over prereduced ruthenium oxide affords a reasonably satis-

factory means of obtaining Δ^4-3-keto derivatives from the corresponding $\Delta^{1,4}$-3-keto steroids, especially if they possess a 6α-methyl substituent. Although the reaction mixture may contain only 35–50% product, the by-products tend to be of sufficiently different polarity to be readily removed, at least by chromatography.

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Discussion of the Paper

UNIDENTIFIED SPEAKER: I have an obvious question. Have you since tried Wilkinson's catalyst on this?

DR. TIFFANY: No, we haven't.

SAME SPEAKER: I think you ought to.

DR. TIFFANY: We accomplished our purpose, and that is about all the time we could spend on this.

DR. JONES: I have a question, or rather, a comment on this. We have observed the same sort of variability in activity of catalysts prepared by ruthenium dioxide, but we find that if you use the supported catalyst, five percent on carbon, this obviates the difficulty. I wonder if you tried this?

DR. TIFFANY: We didn't do much with that. Again, we accomplished our purpose and did very little beyond it.