Stereoselectivity in the Homogeneous Hydrogenation of 3-Oxo-$\Delta^{4,5}$-Steroids

By I. JARDINE and F. J. McQUILLIN*

(*School of Chemistry, The University of Newcastle upon Tyne, Newcastle upon Tyne* NE1 7RU)

Summary Cholestenone, testosterone, progesterone, and methyltestosterone, hydrogenated homogeneously, show the same stereoselectivity as in heterogeneous hydrogenation.

STEREOSELECTIVITY in the heterogeneous reaction: (I) → (II) + (III), has been found[1] to be dependent on the kinetic circumstances and on the nature of the substituents R^1 and R^2. 3-Oxo-$\Delta^{4,5}$-steroids have previously been found rather resistant to homogeneous hydrogenation,[2] but hydrogenation is easily possible by use of the complex[3] [py_2(dmf)-$RhCl_2(BH_4)$]. The Figure compares the selectivity of this

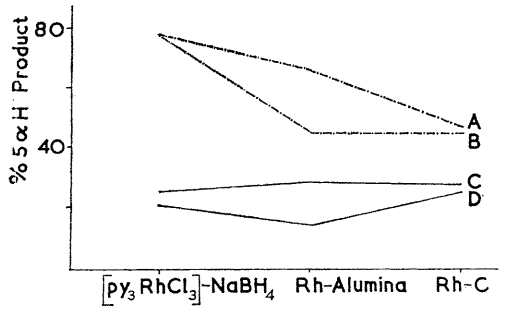
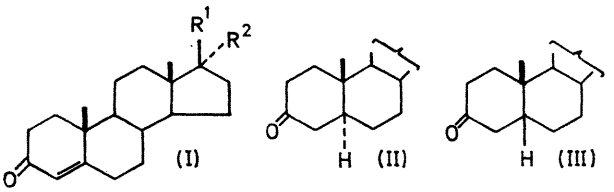


FIGURE. *%5α-H Product* (II) *of hydrogenation of steroids* (100 *mg.*) *with* [py_3RhCl_3] ($7{\cdot}5 \times 10^{-3}$M)–$NaBH_4$ ($17{\cdot}5 \times 10^{-3}$M), *Rh–alumina* (50 *mg.*) *and Rh–charcoal* (50 *mg.*) *in* dmf (15 *c.c.*): (*A*), *progesterone*, (*B*) *testosterone*, (*C*) *methyl testosterone*, *and* (*D*) *cholestenone*

homogeneous reaction with that observed in heterogeneous hydrogenation at a rhodium catalyst. It is evident that the remote substituents, R^1 and R^2, influence both homogeneous and heterogeneous processes in the same sense, and that the effect correlates with substituent bulk rather than the polarity. The substituents fall into two groups: (a) R^1 = OH or COMe and R^2 = H when (III) : (II) ≃ 1 : 3·5 and (b) $R^1 = C_8H_{17}$, R^2 = H, or R^1 = OH, R^2 = Me when (III) : (II) ≃ 3 : 1. The polar hydroxyl group is represented in both groups, and the effective difference between the substituents appears in the axial–equatorial conformational free energy differences,[4] *viz.*: OH, 0·8; COMe, *ca.* 1; CH_3, 1·7; iso-alkyl, > 2 kcal./mole. We have drawn attention to the importance of changes in bond lengths and angles at the site of co-ordination.[1] The relative energy changes for 4,5α- and 4,5β-co-ordination may clearly depend



on the bulk of a remote substituent due to conformational transmission.[5] The 4,5α- and 4,5β- co-ordinated species will not, however, necessarily react with hydrogen at the same rate. We find that although the initial rate of hydrogenation of cholestenone rises linearly with concentration, *i.e.* co-ordination is a rate-limiting factor, the product proportions change somewhat in the higher concentration range, *viz.*:

Cholestenone (M × 10^{-2}) ..	1·73	3·46	8·65
%5β-H product (III) ..	77·7	76·5	73·1

A parallel change, observed in heterogeneous hydrogenation,[1] has been attributed to a higher rate of hydrogenation of 4,5α- adsorbed steroid which becomes more important when hydrogen transfer is rate-limiting. These results are important in offering a practical means of hydrogenation of steroid enones and, in certain cases, a more stereospecific reaction than with a heterogeneous catalyst. We were able to exclude the possibility of sodium borohydride being the reducing agent rather than hydrogen since cholestenone, $8{\cdot}65 \times 10^{-2}$M, was fully hydrogenated by a catalyst solution of sodium borohydride concentration, $1{\cdot}75 \times 10^{-2}$M. In all cases the hydrogen uptake corresponded to the quantity of steroid added.

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