MeOH to give 88.0 g (44% overall yield from 2) of pure *meso*-azobis(α-phenylethane) [mp 72–73 °C (lit.[2a] mp 72–73 °C)], after being drying to constant weight at 0.5 mmHg. The ^{1}H NMR spectrum was consistent with that reported for 1.[6,13]

Acknowledgment. This work was supported in part by Contract 16-9135 from Sandia National Laboratories, Albuquerque, NM.

Registry No. *meso*-1, 65026-52-0; *dl*-1, 65026-53-1; 2, 729-43-1; *meso*-3, 83587-18-2; *dl*-3, 83587-19-3; acetophenone, 98-86-2; hydrazine, 302-01-2; *dl*-α-phenylethylamine, 618-36-0.

(13) Personal communication from Professor Frederick D. Greene, Department of Chemistry, MIT.

Selectivity in the Hydrogenation of 20(22)-Dehydro Steroids

Grant E. DuBois†

Department of Chemistry, Stanford University, Stanford, California 94305

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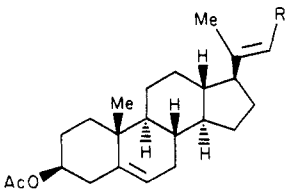
Attachment of the steroid side chain onto tetracyclic steroid starting materials to yield products with the natural C-20(R) configuration has been the subject of investigation by several research groups. The impetus for this work has been provided by a need for synthetic methods for elaboration of the functionalized side chains present in a variety of ecdysones (insect moulting hormones),[1] vitamin D metabolites,[2] and unusual marine sterols.[3] Of all the known methods of side-chain introduction,[4] the Wittig olefination of 20-oxo steroids followed by selective hydrogenation,[4b-d] is one of the simplest and most versatile since it takes advantage of the ready availability of 20-oxo steroids. It has been amply demonstrated, and is now generally accepted, that 20-oxo steroids can be efficiently condensed with Wittig reagents to yield exclusively (*E*)-20(22)-dehydro steroids.[4b-d] The success of this method therefore is dependent only on specific, or at least selective, hydrogenation of the 20(22)-dehydro intermediates. The older literature[5] and even a recent report by Piraux and co-workers[4b] suggest this can be accomplished with complete specificity. More recent reports by McMorris and Schow,[4c,d] however, indicate this to be only a fairly selective process. Other recent work by Uskokovic,[4e] Nes,[6] and their co-workers suggests the near absence of selectivity. In order to resolve this controversy, a study was initiated to determine the effects of experimental parameters on reduction selectivity.

The two 20(22)-dehydro steroids which have been most studied, with regard to hydrogenation selectivity, are 20-(22)-dehydrocholesteryl acetate (1) and 20(22)-dehydro-25-oxo-27-norcholesteryl acetate (2).[7] In this earlier work, the selectivity estimates are in question, due either to the absence of a precise analytical method of quantitation or to the likely possibility of incomplete resolution of all components on gas–liquid phase chromatography (GLC). High-resolution GLC, on wall-coated open tubular (WCOT) columns, was used in the present work to provide rapid and precise estimates of reaction aliquot and product compositions. The results of a study employing authentic samples of 1, and the expected reduction products 3 and 4[8] as well as the tetrahydro compound 5,[9] on commercially available OV-1, SE-54, and SP-2250 WCOT GLC columns showed that only the SP-2250 column is of use in this analysis. Only this medium-polarity column allows complete resolution of diene 1 from cholesteryl acetate (3) such that reduction of 1 to 3 and 4 can be easily followed to the consumption of all 1. The capacity factor (k') and separation factor (α) values were determined as described by Jennings.[10] For the SP-2250 column (10 m, 250 °C), the k' values were as follows: 1, 30.6; 3, 28.9; 4, 25.7; 5, 29.0. The α values were as follows: 1/3, 1.06; 1/4, 1.19; 3/5, 1.00.[11] Analogous results were obtained on GLC analysis



1, R = $CH_2CH_2CH(CH_3)_2$
2, R = $CH_2CH_2COCH_3$

†Correspondence address: Syva Co., 900 Arastradero Road, Palo Alto, CA 94303.

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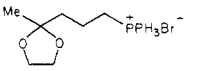
(7) This compound was prepared by modification of the procedure of ref. 4c, which involving Wittig condensation of the ylide derived from phosphonium salt i with pregnenolone. The literature procedure (Crombie, L.; Hemesley, P.; Pattenden, G. *J. Chem. Soc. C* **1969**, 1016) for preparation of i from the corresponding bromide (benzene, 80 °C, 48 h) was found not to be very useful, giving i in only 9% yield. Reaction at 120 °C for 144 h in xylene, however, gave i in 86% yield. Higher temperatures with shorter reaction times resulted in decomposition of i. The condensation of the ylide derived from i with pregnenolone is reported to require a large excess (6–8 equiv) of ylide for high yields of olefin. In the present work, a 71% yield of olefin was obtained from a reaction which employed only 2.2 equiv. of Wittig reagent.



i

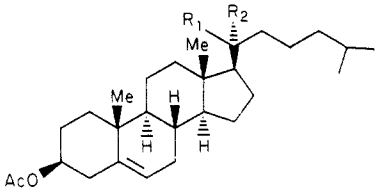
(8) An authentic sample was prepared by acetylation (Ac_2O, pyr) of 20-isocholesterol, a sample of which was generously provided by Dr. M. Tanabe, SRI International.

(9) Reduction of 20(22)-dehydrocholesterol over PtO_2 in dioxane–HOAc has been reported to result in 28% conversion to the C-20 isomeric cholestanol derivatives (see ref 6a).

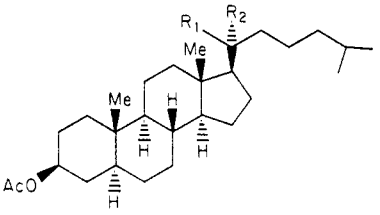
(10) Jennings, W. "Gas Chromatography with Capillary Columns", 2nd ed.; Academic Press: New York, 1980; Chapter 1.

(11) For the OV-1 column (10 m, 240 °C), the k' values were as follows: 1, 12.1; 3, 12.1, 4, 11.0. The α values were as follows: 1/3, 1.00; 1/4, 1.11. For the SE-54 column (15 m, 270 °C), the k' values were as follows: 1, 12.2; 3, 12.2; 4, 11.0; 5, 12.5; 6, 11.2. The α values were as follows: 1/3, 1.00; 1/4, 1.10; 3/5, 1.02; 4/6, 1.02.

0022-3263/82/1947-5035$01.25/0



3, R_1 = H; R_2 = Me
4, R_1 = Me; R_2 = H



5, R_1 = H; R_2 = Me
6, R_1 = Me; R_2 = H

of the free alcohols [i.e., (*E*)-20(22)-dehydrocholesterol, etc.]. Cholestanyl acetate (**5**) when coinjected with **3** gives peak broadening; hence it was assumed that tetrahydro products **5** and **6**, if present in a mixture of **1**, **3**, and **4**, would be integrated with dihydro products **3** and **4**, respectively.[12] Therefore, integration of the **3** and **4** GLC peaks in an (*E*)-20(22)-dehydrocholesteryl acetate (**1**) reduction product mixture should yield an accurate estimate of the hydrogenation selectivity with regard to C-20 configuration.

In view of the quite different selectivities which have been reported for the reduction of diene **1** under comparable conditions, it was considered that these disparities may be due to differences in the PtO_2 catalyst employed. In order to examine this possibility, we investigated the reduction of **1** in the presence of three different PtO_2 catalysts. Two of these were purchased from Alfa Products: one, "catalyst A", ca. 10 years earlier and the other, "catalyst B", very recently. The third, "catalyst C", was freshly prepared by the method of Henze and co-workers.[13] Reduction of **1** over these three catalysts in dioxane–HOAc (98:2) solvent was then carried out under identical experimental conditions.[14] After a 24-h reaction time, aliquots were withdrawn, and the hydrogenation selectivity was determined by GLC. With catalyst A, there was 7% conversion, and the **3**/**4** ratio was 69/31; with catalyst B, there was 20% conversion and a **3**/**4** ratio of 62/38; with catalyst C, there was 29% conversion and a **3**/**4** ratio of 63/37. These results suggest a very modest increase in reaction selectivity with a decrease in catalyst activity. This trend might have been anticipated on the basis of thermodynamic considerations. The highest selectivity observed (69/31 **3**/**4**) is significantly less, however, then the 4:1 result recently reported.[4d]

In an effort to determine the effect of temperature on selectivity in hydrogenation of **1**, reduction was attempted at 0 °C over the most active catalyst (C). No reaction occurred at atmospheric pressure. Under a low pressure (ca. 0.5 psi) of hydrogen, reduction occurred smoothly to yield a 66:34 mixture of **3** and **4**. Thus, major selectivity improvement by temperature adjustment does not seem likely.

The reductive conversion of **1** to **3** and **4** was also examined in other solvents. With catalyst C in hexane, the conversion was 2% (67 h), and the **3**/**4** ratio was 52/48; in benzene, the conversion was 11%, and the **3**/**4** ratio was 66/34; in methanol, the conversion was 35%, and the **3**/**4** ratio was 59/41.[15] Thus, a general increase in reaction rate with solvent polarity was observed, but there was no significant improvement in selectivity. It appears, therefore, that the dioxane–HOAc solvent system, first reported by Hershberg and co-workers[5a] and used by others later,[4b-d,6] has the best properties yet noted, in terms of reduction rate and selectivity, for this reaction.

The hydrogenation of **1** over some other active metal catalysts was also investigated in dioxane–HOAc solvent: over platinum on carbon, 100% conversion within 1 h, 56/44 mixture of **3** and **4**; with palladium on carbon, 47% conversion, ca. 1/1 **3**/**4**; with Raney nickel W-2 at 20 °C, 0% conversion (24 h); with Raney nickel W-2 at 35 °C, 32% conversion (8 h), 42/58 **3**/**4**; with $(Ph_3P)_3RhCl$ in benzene solvent, 0% conversion (24 h).[16] Unfortunately, none of these conditions results in improved selectivity for formation of the natural C-20(*R*) isomer **3**. The palladium and nickel catalysts were observed to form unknown products in addition to **3** and **4**. These are likely due to isomerization[17] of diene **1** with possible subsequent partial or complete saturation to yield a variety of unexpected products. Clearly, in view of the poor results obtained with the above catalysts, PtO_2 represents the best choice as catalyst for selective conversion of **1** and **3**.

In summary, for practical purposes, selective reduction of **1** to provide the natural C-20 stereochemistry may be best achieved over moderately active PtO_2 catalyst in dioxane–HOAc solvent at a slightly elevated pressure. The reaction should be conducted in an apparatus suitable for an on a scale suitable for hydrogen uptake measurement so as to prevent overreduction. The selectivity of natural to unnatural stereochemistry which is possible from such a reaction may approach 70:30 in favor of the natural C-20 stereochemistry.

The reduction of (*E*)-20(22)-dehydro-25-oxo-27-norcholesteryl acetate (**2**) was also examined. Over PtO_2 catalyst C and under low pressure (0.5 psi) of hydrogen, quantitative conversion to a 71/29 mixture of two lower GLC retention time products occurred within 8 h. The major and minor products obtained on hydrogenation of **2** exhibited GLC behavior exactly analogous to that of **3** and **4** obtained from **1** and therefore are presumed to be the natural 20(*R*) and unnatural 20(*S*) isomers, respectively. For a 10-m SP-2250 column (250 °C) the observed k' values were as follows: **2**, 84.0; **7**, 82.3; **8**, 72.7. The α values were as follows: **2**/**7**, 1.02; **2**/**8**, 1.16.

The maximum *R*/*S* selectivities of 69/31 and 71/29 observed in the hydrogenations of **1** and **2**, respectively,

(12) Under conditions of low conversion (i.e., <50%) of **1** to products, as was the case for nearly all reduction reactions described herein, the cholestanol products **5** and **6** were not present in the samples analyzed as determined by GLC on the 15-m SE-54 column.

(13) Frampton, V. L.; Edwards, J. D., Jr.; Henze, H. R. *J. Am. Chem. Soc.* **1951**, *73*, 4432.

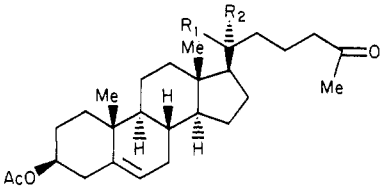
(14) All reactions were carried out simultaneously at 20 °C while connected to the same atmospheric pressure hydrogenation apparatus. Catalysts were prereduced, and the reaction solvent containing **1** was pretreated with recently prepared Raney nickel W-2.

(15) All reactions were carried out as described in ref 14 except that the catalyst was reduced in the presence of **1** by application of a low pressure (0.5 psi) of H_2 for 15 min, and the Raney nickel pretreatment of **1** was omitted.

(16) All reactions were carried out as described in ref 14, omitting only the catalyst prereduction. In reduction of **1** over palladium on carbon, expected products **3** and **4** comprised only ca. 50% of the product, the remainder being made up of two unknown products (k' = 25.5 and 27.5) which were present in approximately equal amounts. In reduction of **1** over Raney nickel at 35 °C, at least five unknown minor products were formed in addition to an approximately 50% conversion to **3** and **4**.

(17) Relative to platinum hydrogenation catalysts, palladium and nickel catalysts are known to have much greater olefin migration promoting activity. See: Rylander, P. N. "Catalytic Hydrogenation in Organic Syntheses"; Academic Press: New York, 1979; pp 36–38 and references cited therein.

are better than some[4e,6] but poorer than others which have been reported in the literature.[4b-d,5] Of all the earlier work, however, only the recent works of McMorris[4c,d] and Nes[6] report product analysis by GLC. In the present work, which employed highly efficient WCOT GLC columns, the separation factors $\alpha(1/3)$ and $\alpha(2/7)$, for resolution of starting materials 1 and 2 from the desired 20(*R*) products 3 and 7, were found to be rather small, especially for the



7, R_1 = H; R_2 = Me
8, R_1 = Me; R_2 = H

2/7 separation. Since such small 1/3 and 2/7 separations were observed in the above-described experiments, it is likely that the resolution observed on the lower efficiency columns employed for earlier work must have been significantly lower. This lack of 1/3 and 2/7 resolution would render it difficult, if not impossible, to follow the reductions (i.e., 1 → 3 + 4 and 2 → 7 + 8) to the consumption of all starting materials. Thus some of the *R*/*S* selectivity values reported for reduction of 1 and 2[4c,d] are high, probably due to the presence of significant amounts of starting materials in the integration of the assumed product GLC peaks. These arguments are especially valid for the 2 → 7 + 8 reaction were the 2/7 separation is very small.

In summary, it has been found, for the cases of the two (*E*)-20(22)-dehydrosterols studied, that hydrogenation results in a significant bias (ca. 2:1) for formation of the products with the natural C-20(*R*) stereochemistry. These results are intermediate between those of Uskokovic,[4e] Nes,[6] and their co-workers, which suggest no selectivity (i.e., ca. 1:1 ratios of C-20 isomers), and those of Piraux,[4b] McMorris,[4c,d] and their co-workers, which suggest selectivities ranging from 4:1 to complete. It is possible that a small part of this disparity may be due to differences in activity of the PtO_2 catalyst employed by the different workers. However, it is probable that the major portion of the inconsistencies in previously reported results is due to lack of consistently accurate methods for determination of hydrogenation product composition.

Experimental Section

Authentic samples of cholesteryl acetate and cholestanyl acetate were obtained by acetylation (Ac_2O/pyr) of cholesterol and cholestanol which in turn were obtained from Aldrich Chemical Co. The pregnenolone used for the preparation of 20(22)-dehydro steroids 1 and 2 was obtained by saponification of pregnenolone acetate.[18] The commercial platinum oxide (PtO_2), 5% platinum on carbon (Pt/C), and tris(triphenylphosphine)chlororhodium ($(Ph_3P)_3RhCl$) hydrogenation catalysts were purchased from Alfa Products while 5% palladium on carbon (Pd/C) was obtained from Englehard Minerals and Chemical Corp. Raney nickel W-2 was prepared from nickel–aluminum alloy (W. R. Grace Chemical Co.) by the method described in the literature.[19] The catalyst was dried by azeotropic distillation with dioxane after which it was stored as an approximately 1:1 (v/v) mixture of dioxane over catalyst. The solvents used were reagent grade and were obtained from either J. T. Baker Chemical Co. or Fisher Scientific Co. Dioxane was additionally purified by distillation from freshly prepared Raney nickel W-2. The benzene and methanol used as hydrogenation solvents were rendered anhydrous before use by drying them over sodium ribbon and over activated (400 °C, 3 h) molecular sieves (Type 3 Å, J. T. Baker Chemical Co.), respectively. A stock solution of dioxane–glacial acetic acid (98:2) was prepared and used for all hydrogenation reactions employing this solvent system.

GLC analyses were carried out on a Hewlett-Packard Model 5710A gas chromatograph equipped with a Hewlett-Parckard Model 3380S integrator–recorder. Determinations were carried on either 10-m OV-1 (Supelco Inc.), 15-m SE-54 (J and W Scientific Co.), or 10-m SP-2250 (Supelco Inc.) WCOT columns. Capacity factors (k') and separation factors (α) were calculated from the relationships $k' = t - t_0)/t_0$ and $\alpha = (t_b - t_0)/(t_a - t_0)$, respectively, as has been discussed by Jennings.[10]

Hydrogenation reactions were carried out at atmospheric pressure in an apparatus constructed as described by Vogel.[20] This system was fitted with a four-way stopcock such that three reactions could be carried out simultaneously under identical reaction conditions. In order to ensure maximum hydrogenation reaction rates, through the removal of catalyst poisons and/or deactivators,[21] for reactions employing the dioxane–HOAc solvent system, we pretreated (30 min) the solvent (1.5 mL) and the 20(22)-dehydrosteroid to be reduced (15 μmol) with 0.1 mL of Raney nickel–dioxane slurry.

General Hydrogenation Procedure. Dioxane–HOAc stock solution (0.5 mL) was added to 5.0 mg of PtO_2 catalyst in a 25-mL two-necked flask. The flask was then connected to the atmospheric pressure hydrogenation apparatus and the catalyst reduced by application (15 min) of a low pressure (0.5 psi) of hydrogen. A solution of the 20(22)-dehydrosteroid (15 μmol) in 0.8 mL of dioxane–HOAc was then added to the vigorously stirring Pt black suspension after which hydrogenation was conducted at atmospheric pressure. Aliquots (0.1 mL) were withdrawn at various time intervals, filtered with EtOAc through Fluorisil, and analyzed by GLC. For reactions employing Pt/C, Pd/C, Raney nickel W-2, and $(Ph_3P)_3$ RhCl hydrogenation catalysts, the catalyst reduction step was omitted. The hydrogenation substrate/catalyst/solvent ratios employed for these latter reductions were 15 μmol/25 mg/1.5 mL for Pt/C, 15 μmol/5 mg/1.5 mL for Pd/C, 15 μmol/0.1 mL/1.5 mL for Raney nickel, and 15 μmol/5 mg/1.0 mL (benzene) for $(Ph_3P)_3RhCl$.

Acknowledgment. I am grateful to Professor W. S. Johnson for many useful discussions during the course of this work and for the use of the facilities in which this work was carried out. Thanks are also due to Dr. M. Tanabe (SRI International) for providing an authentic sample of 20-isocholesterol and to the National Institutes of Health for financial support of this work (Grants No. AM 03787-21 and AM 03787-22).

Registry No. 1, 54548-85-5; 2, 53139-44-9; 3, 604-35-3; 4, 38774-63-9; 5, 1255-88-5; 6, 83648-90-2; 7, 7548-94-9; 8, 55122-55-9; i, 5944-33-2; pregnenolone, 145-13-1.

(18) Provided by Professor W. S. Johnson, Stanford University.

(19) Horning, E. C., Ed. "Organic Syntheses; Wiley: New York, 1955; Collect. Vol. III, pp 181–183.

(20) Vogel, A. "Textbook of Practical Organic Chemistry"; 4th ed.; Longman: New York, 1978; pp 65–67.

(21) Treatment of hydrogenation substrates with Raney nickel is a procedure which has been recommended for removing catalyst poisons. See: Adkins, H. "Reactions of Hydrogen"; The University of Wisconsin Press: Madison, WI, 1937; p 28. Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 727.