The Stereochemistry of Reduction of Cholestanone by Complex Metal Hydrides

O. R. VAIL AND D. M. S. WHEELER[1]

Department of Chemistry, University of South Carolina, Columbia, South Carolina, and the Department of Chemistry, University of Nebraska, Lincoln 8, Nebraska

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The effect of changing the reaction conditions on the relative amounts of 3α- and 3β-cholestanols obtained by reduction of 3-cholestanone with metallic hydrides has been studied. The results are discussed in terms of the mechanism of hydride reductions.

Dauben and co-workers[2] have concluded that two factors operate to determine the stereochemistry of an alcohol obtained by hydride reduction of an asymmetric cyclohexanone: the ease of formation of the complex between the carbonyl group and the complex hydride (steric approach control); and the relative energetics of the formation of the products once the initial complex is formed (product development control). They also reported that use of sodium borohydride as a reducing agent gave a greater proportion of the less stable epimeric alcohol than did lithium aluminum hydride. They explained this observation by suggesting that in these reductions sodium borohydride has a greater effective size than lithium aluminum hydride. Recently Wheeler and Huffman[3] criticized this latter suggestion and proposed an alternative theory, which involved differences in the mechanisms by which borohydrides and aluminum hydrides reduce ketones. Wheeler and Huffman supported their ideas with the results of some reductions of Δ^8-lanostenone. However, the scope of this work was not wide; and we thought it of interest to study intensively the effect that changing reagents and conditions would have on the relative amounts of the epimeric alcohols obtained by reduction of steroidal ketones. For the initial study we chose an unhindered ketone, 3-cholestanone.

Previous to our work there had been one similar intensive study of the effect of different reagents and conditions on the products obtained in hydride reductions—that of Beckett and his coworkers[4] on the reduction of tropinone. The use of tropinone introduced two complicating factors: The conformation of tropinone is not fixed; and there is also the possibility of interactions between the nitrogen bridge and the carbonyl group, which might affect the course of the reductions. Neither of these complications is present in our work.

Results.—The reduction of 3-cholestanone has been carried out with four hydrides, lithium aluminum hydride, sodium borohydride, lithium borohydride, and sodium trimethoxyborohydride. The solvents used included ether, tetrahydrofuran, diglyme, methanol, ethanol, isopropyl alcohol, and pyridine. Reactions were run at room-temperature (all solvents), under reflux (tetrahydrofuran, methanol, isopropyl alcohol and pyridine), and on the steam bath (diglyme). As far as possible a uniform procedure was used for all reactions in the hope that at least the relative results would be reliable. Originally we had planned to estimate the relative amounts of the 3α- and 3β-cholestanols by comparing the infrared spectra of the crude reaction products with those of standard mixtures of the alcohols. Although this method had been used successfully by Beckett,[4] we were not able to obtain sufficient accuracy with it, and we abandoned it in favor of direct isolation of the products by chromatography on alumina. The reliability of the method was confirmed by chromatography of some known mixtures. In addition it was shown that neither 3α- nor 3β-cholestanol is epimerized either by lithium aluminum hydride at room temperature or by sodium borohydride in refluxing isopropyl alcohol. These results agree with observations that 11-steroidal alcohols are not epimerized with lithium aluminum hydride[5] and that tropines are not equilibrated by metallic hydrides even at 100°.[4]

The results of our work are summarized in Table I. In general the yields of sterols are 90% or better. In the reactions in which the yields of sterols were low (mainly reactions in which sodium trimethoxyborohydride was the reducing agent), the rest of the material was cholestanone.[6] In the early work the runs were done in triplicate; in later work they were in duplicate. The values "% β" are the mean of each set of runs. The difference between the highest and lowest values of % β in each series of runs is also given. Generally

(1) Present address: Department of Chemistry, University of Nebraska, Lincoln 8, Nebraska.

(2) (a) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); (b) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *ibid.*, **78**, 3752 (1956).

(3) D. M. S. Wheeler and J. W. Huffman, *Experientia*, **16**, 516 (1960).

(4) A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, *Tetrahedron*, **6**, 319 (1959).

(5) S. Bernstein, R. H. Lenhard, and J. H. Williams, *J. Org. Chem.*, **18**, 1166 (1953).

(6) The relative amounts of the epimeric cholestanols may change as the reaction proceeds; probably the percentage of axial increases as the reaction goes to completion.[7] This should be kept in mind when considering the results from reactions that were incomplete.

(7) W. M. Jones and H. E. Wise, Jr., *J. Am. Chem. Soc.*, **84**, 997 (1962).

TABLE I

Hydride	Solvent	Temperature	Time (Hours)	%β	Number of runs	Difference between highest and lowest values of %β	Average yield of sterols
$LiAlH_4$	Ether	Room temp.	0.5	87.1	4	1.3	95 (7.1)[a]
$LiAlH_4$	Ether	Room temp.	20	87.9	3	2.4	89
$LiAlH_4$	Diglyme	Room temp.	2	90.3	2	0.8	94
$LiAlH_4$	Diglyme	100°	2	87.9	2	1.3	87
$LiAlH_4$	Tetrahydrofuran	Room temp.	2	91.5	2	0.5	95
$LiAlH_4$	Tetrahydrofuran	Reflux	2	90.8	4	0.7	91 (6.3)[a]
$LiAlH_4$	Pyridine	Room temp.	2	89.2	2	0.4	92
$LiAlH_4$[b]	Pyridine	Reflux	2	82.6	2	2.2	90 (5.7)[a]
$LiBH_4$	Ether	Room temp.	4	92.2	3	2.3	99
$LiBH_4$	Tetrahydrofuran	Room temp.	4	93.0	3	2.7	97
$LiBH_4$	Tetrahydrofuran	Reflux	2	91.6	2	0.5	98
$LiBH_4$	Diglyme	Room temp.	4	93.8	3	1.3	95 (7.4)[a]
$LiBH_4$	Diglyme	100°	2	92.2	2	0.0	100
$NaBH_4$	Isopropanol	Room temp.	16	93.2	4	1.2	93
$NaBH_4$	Isopropanol	Reflux	4	90.4	2	3.3	94 (10.7)[a]
$NaBH_4$	Ethanol	Room temp.	16	87.7	3	2.4	94 (5.2)[a]
$NaBH_4$	Methanol	Room temp.	16	86.3	3	1.5	93
$NaBH_4$[b]	Methanol	Room temp.	16	86.6	2	1.3	99
$NaBH_4$	Methanol	Reflux	4	84.1	2	0.5	97
$NaBH_4$	Diglyme	Room temp.	24	90.2	2	0.1	71[c] (5.5)[a]
$NaBH_4$	Diglyme	100°	10	90.4	2	0.6	94
$NaBH_4$	Pyridine	Room temp.	16	94.4	2	0.1	91
$NaBH_4$	Pyridine	Reflux	4	88.3	2	0.7	94
$NaBH(OCH_3)_3$	Ether	Room temp.	4	88.7	2	1.5	59[c]
$NaBH(OCH_3)_3$	Tetrahydrofuran	Room temp.	4	91.0	2	1.7	81[c] (7.3)[a]
$NaBH(OCH_3)_3$	Diglyme	Room temp.	4	87.6	3	0.6	75[c] (9.5)[a]
$NaBH(OCH_3)_3$	Methanol	Room temp.	6	86.7	2	1.0	88[c]
$NaBH(OCH_3)_3$[b]	Methanol	Room temp.	6	86.1	2	0.6	86[c]
$NaBH(OCH_3)_3$	Methanol	Reflux	4	83.9	2	0.0	66[c]
$NaBH(OCH_3)_3$[b]	Methanol	Reflux	4	82.8	2	0.8	83[c]

[a] Figure in brackets represents difference between highest and lowest yields of steroids in the individual runs. The figure is given only if the difference exceeds 5%. [b] Inverse addition used. [c] Balance of material was 3-cholestanone.

this difference is less than 1.5%. Although the differences observed by changing the conditions are small, we believe that the trends shown are significant.

Discussion.—The most striking features of the results are that the equatorial alcohol is always the predominant epimer,[8] and that changes in conditions do not have a large effect on the relative amounts of the epimers formed. Thus the % β varies from 82.6 (lithium aluminum hydride in refluxing pyridine, inverse addition) to 94.4 (sodium borohydride in pyridine at room temperature). As pointed out by Dauben,[2b,9a] more marked differences are expected and found with 2-cholestanone. In view of the small differences that we report, it is important to stress that many of the tendencies which we have observed have also been noted by other workers using different compounds.[4,7,9] In addition Dauben[9a] has also obtained from 3-cholestanone a higher yield of axial alcohol by using lithium aluminum hydride than by use of sodium borohydride in isopropyl alcohol.

In general for reactions at room temperature changing the solvent with a given hydride makes little difference (up to 4.4%) in the product compositions. The reactions of sodium borohydride in alcohols are an exception to this and show an increase in the amount of axial alcohol produced as the solvent is changed from isopropyl alcohol to ethanol to methanol. This effect, which was first observed by Beckett,[4] is confirmed by work with other compounds,[9] and will be discussed below.

Increasing the reaction temperature for a given solvent and hydride usually causes a small increase (1–3%) in the amount of axial alcohol formed. The effect is the expected one for a reaction which can take two possible paths that differ slightly in activation energy. The temperature effect for pyridine (over 6%) is larger than that for the other solvents. The use of pyridine as a solvent will be discussed later.

The conditions that favor the maximum formation of equatorial alcohol are use, at room temperature, of lithium borohydride in tetrahydrofuran or diglyme or sodium borohydride in pyridine. The yield of axial alcohol is largest when sodium borohydride or sodium trimethoxyborohydride in refluxing methanol or lithium aluminum hydride in refluxing pyridine is used. Sodium borohydride in pyridine at reflux also tended to increase the amount of axial alcohol. Thus, the conditions for

(8) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(9) (a) W. G. Dauben, unpublished work. (b) W. S. Johnson, unpublished work. We thank Professors Dauben and Johnson for informing us of their results.

sodium borohydride reductions used by Dauben[2] in his original work were, by chance, those which particularly favored formation of the axial alcohol to a greater extent than is usual with that reagent. The results for diglyme, the only solvent that was used with the four reagents, show that at room temperature the percentage of axial alcohol increases in the order lithium borohydride (6.2), lithium aluminum hydride (9.7), sodium borohydride (9.8), sodium trimethoxyborohydride (12.4). Jones[7] also found that with diglyme as solvent lithium borohydride gave more equatorial alcohol than sodium borohydride.

Before analyzing some of our results in detail, we wish to summarize our present view on the course of reductions of ketones by metallic hydrides. Any reduction involves the formation of two new bonds: one between a hydride from the reagent and the carbon of the carbonyl; the second between the metal of the hydride and the oxygen of the carbonyl group[10,11] (Figure 1).

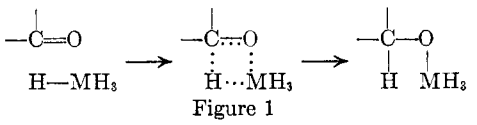

Figure 1

If, in the transition state, the hydride transfer is the more important of bond formations then steric approach control is the dominant factor; when the bond to the oxygen atom is the more important, then product development control is the major factor. Usually both formations are involved to a greater or lesser extent in forming the transition state. In general reagents will be less hindered if they attack a cyclohexanone along a line perpendicular to the plane of the carbonyl group and from a direction that will yield an axial alcohol. (Figure 2,a) (This is sometimes loosely referred to as equatorial attack.[13])

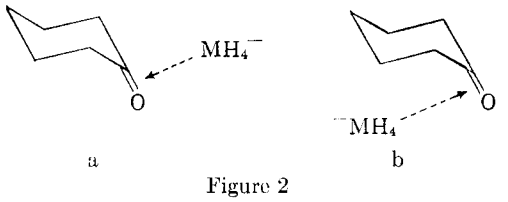

Figure 2

The alternative mode of attack, axial attack (Figure 2,b) will give the equatorial alcohol. Usually, increasing the size of the reagent will increase the amount of equatorial attack and hence the amount of axial alcohol formed. This tendency is shown in the present study in the increase of the axial alcohol formed at room temperature in diglyme as the reagent was changed from lithium borohydride to lithium aluminum hydride to sodium trimethoxyborohydride. However, the size factor is not the only one because sodium borohydride should then be similar to lithium borohydride. We attribute the difference between these reagents to the greater ionic character of sodium borohydride. Wheeler and Huffman[3] have already suggested why increasing ionic character in the reagent should increase the importance of the hydride transfer in the transition state of the reduction, and why increasing covalent character of the reagent should increase the contribution of the oxygen–metal bond formation in the transition state. The explanation of the latter point involved the suggestion that a covalent hydride AMH_4 can dissociate homolytically:

$$AMH_4 \longrightarrow AH + MH_3$$

The metallic hydride (MH_3) can then complex with the oxygen of the carbonyl; and in the subsequent reduction step the presence of the bulky group attached to the oxygen favors the formation of the equatorial alcohol.[14] An alternative, and perhaps better, explanation is based on the fact that increased covalent character of the hydride is associated with greater hydrogen bridging (Figure 3).[15] This increases the electrophilic character of the metal atom and so favors the attack of oxygen on that atom early in the reaction (Figure 4). Jones[7] suggests that the increase of

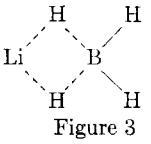

Figure 3

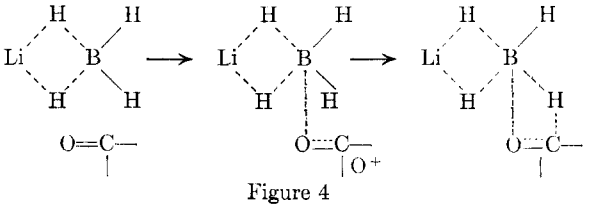

Figure 4

equatorial alcohol obtained with lithium borohydride as compared with sodium borohydride is due to an increased polarization of the carbonyl group. This explanation is similar to ours.

As was mentioned above, we observed that with sodium borohydride as reagent the amount of the axial product increases as the solvent is changed from isopropyl alcohol (6.8%) to ethanol (12.3%) to methanol (13.7%). Beckett[4] explained this

(10) It is possible that two hydride molecules are involved in each reduction step (one supplying the hydride, the other accepting the oxygen); however, this does not affect our argument.

(11) We do not exclude a rapid formation of a complex before the reduction step.[12]

(12) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).

(13) For cases in which equatorial attack is not less hindered see D. M. S. Wheeler and M. Wheeler, *Chem. Ind. (London)*, 463 (1961) and W. H. Castine, D. M. S. Wheeler, and M. Wheeler, *Chem. Ind. (London)*, 1832 (1961).

(14) *Cf.* A similar explanation by N. L. Paddock, *Chem. Ind., (London)*, 63 (1953).

(15) W. C. Price, *J. Chem. Physics* **17**, 1044 (1949); W. C. Price, H. C. Longuet-Higgins, B. Rice, and T. F. Young, *ibid.*, 217.

effect by suggesting that reactions of sodium borohydride with ethanol and especially methanol lead to alkoxyborohydrides and that these species being larger than borohydride favor formation of the axial alcohol. In agreement with this theory we found that sodium trimethoxyborohydride in methanol gives almost the same amount of the axial alcohol as sodium borohydride in methanol. In addition, Jones[7] has recently shown that in the reaction of a ketone with sodium borohydride, the initial stage of the reduction, which involves sodium borohydride, gives less axial alcohol than the subsequent stages, which probably involve alkoxyborohydrides. These results support Beckett's ideas.

Although the theory is plausible, there are difficulties associated with it. Inverse addition of borohydride to cholestanone in methanol makes no difference to the product composition which suggests that the solvent–reagent reaction is much faster than the reagent–ketone reaction. It has been established that, when sodium borohydride reacts, the transfer of its first hydride is slower than that of the other three. This applies both to the reduction of ketones[12,16] and to the reaction with methanol.[17] If Beckett's theory is correct, it is not clear why the ketone should be able to compete successfully with the methanol for all the hydrides other than the first.

A further difficulty with the theory is that Brown[18] has shown that sodium trimethoxyborohydride disproportionates in aprotic solvents to sodium borohydride and sodium tetramethoxyborohydride. The possibility that this happens in methanol is particularly relevant in view of recent work by Eliel.[19] He shows that in reductions with lithium aluminum hydride the reducing species is always aluminum hydride ion. He suggests that alkoxyaluminum hydride ions formed in the reduction disproportionate to tetraalkoxyaluminum hydride and aluminum hydride ions so that alkoxyaluminumhydrides are not involved in reduction steps. While his results do not necessarily apply to the borohydride series (*cf.* ref. 7), they are to some extent not compatible with Beckett's ideas.

It is possible that the solvent effects observed with alcohols are due partly to differences in the polarity of these solvents. Thus the ionization of the reagent is most favored in methanol and so the highest amount of axial alcohol is obtained in this solvent. However, Beckett's results[4] for aqueous solutions indicated that this factor, even if present, is not the only one.

In reductions with sodium borohydride in methanol the reaction between borohydride and methanol is so fast[17,20] and the ratio of methanol to ketone in the reaction system is usually so large that it is puzzling that ketones can be fully reduced in methanol. Davis[17] has recently pointed out that the purity of the borohydride is an important factor in determining its rate of reaction with methanol. In particular the presence of methoxide ion will slow the reaction down. In our studies we have used hydride marked as 98%+, which was at least 95% pure when used. The manufacturer's specification lists the methoxide content as 0.3%. On the basis of this and Davis's results we do not think there was sufficient methoxide in our borohydride to reduce the rate of the methanol–borohydride reaction greatly.

It has been noted already that the temperature effect with pyridine is larger than that with the other solvents. Lansbury[21] has recently started a study of reductions by lithium aluminum hydride in pyridine. He has found that when direct addition is used to an aged solution of lithium aluminum hydride and pyridine, the reducing species is lithium N-dihydropyridylaluminum hydride, which only reduces highly electrophilic carbonyl groups. In agreement with Lansbury's work we found that lithium aluminum hydride reduces cholestanone in pyridine at room temperature by the direct addition; but if the direct addition is used at reflux temperature, most of the ketone is not reduced. This is because the dihydropyridyl compound, which forms very rapidly in refluxing pyridine, does not reduce dialkyl ketones. When we used the inverse addition at reflux, the reduction took place and gave our largest yield of axial alcohol.[22] Our results confirm Lansbury's view that a simple dialkyl ketone is only reduced with difficulty by dihydropyridylaluminum hydride.

It is not entirely certain to what the marked temperature effect in pyridine should be attributed. The reductions in refluxing pyridine were done at a higher temperature than the other reductions and on this basis it is perhaps not surprising that the difference between the product distribution at room temperature and that at reflux is larger than for any other solvent. However, we believe another factor may be involved.

Our final conclusions are that, in agreement with Dauben,[2] we think that the size of the reagent is an important factor in determining the stereochemistry of the hydride reduction. We suggest that the covalent or ionic character of the reagent is also significant. Further work is needed to clarify fully the problems involved. As has been emphasized

(16) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953).

(17) R. E. Davis and J. A. Gottbrath, *ibid.*, **84**, 895 (1962).

(18) H. C. Brown, E. J. Mead, and P. A. Tierney, *ibid.*, **79**, 5400 (1957).

(19) E. L. Eliel and H. Haubenstock, Abstracts of Papers at A.C.S. Meeting, Washington, 1962 11-O.

(20) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).

(21) P. T. Lansbury and J. O. Petersen, *ibid.*, **83**, 3537 (1961), *ibid.*, **84**, 1756 (1962), and *Chem. Eng. News*, **39**, No. 37, 59 (1961).

(22) Addition of lithium aluminum hydride to refluxing pyridine may result in fires.

by Jones[7] and Davis,[17] it is most important to determine the nature of the various intermediate species involved in the reductions.

Comparison with Lanostenone Series.—The results obtained in the present work are not those which would have been predicted from the lanostenone studies.[3] In particular the yields of axial alcohols obtained with borohydrides are less than those obtained with lanostenone. The differences are, however, not surprising when recent studies on the conformation of ring A in 4,4-dimethyl-3-oxo steroids and in 3-oxo triterpenoids are considered. Although the actual conformations of these rings are still in dispute,[23] it seems clear they are not in a simple chair form; the repulsion which the 10-methyl group and the 6β-hydrogen exert on the 4β-methyl group forces the latter outward from the ring with the result that carbon three is pushed upward. (The extent of this upward displacement is not yet settled.) As carbon 3 is moved up, the direction of the carbon–oxygen bond in the ketone is changed; it no longer points toward the α-side as in the ordinary chair form, but is either in the same plane as carbon atoms 1, 2, 4, and 5 or points upwards in the β direction (if the ring is in a skewed-boat form). The conclusions summarized here have been drawn[23] for 4,4-dimethyl-3-keto compounds, which have no double bond at 8,9. Studies with Dreiding models indicate that the conformation of Δ^8-lanostenone should be similar to that of the saturated compounds.[24]

On the basis of these considerations, there are three factors affecting the reduction of lanostenone with metallic hydrides which are not present in the reduction of cholestanone. (a) The twisting-up of ring A makes it more difficult for hydrides to approach from the β side. Presumably lithium aluminum hydride and lithium tritertiarybutoxyaluminum hydride are more affected by this than sodium or lithium borohydrides. (b) The 4α-methyl group is below the plane of ring A and so will hinder the approach of reagents from the α side. (c) The reaction path leading to the development of the 3β-alcohol will involve an O—MH_3 group on the β side of the ring. This group will be seriously hindered by the 10-methyl group; and during the reaction the ring must change its conformation to the chair form. (It has been demonstrated by X-ray crystallography that in 3β-lanostenyl iodoacetate ring A is a chair.[26]) These three conflicting factors may be the reason that borohydride gives more 3α-alcohol with lanostenone, than with cholestanone, but in any case it is not surprising that different results are obtained in the two series. Thus, consideration of the results of the two series indicates that changing the conformation of the ketone (as one does in going from lanostenone to cholestanone) probably affects the stereochemistry of hydride reduction more than the factors which have been studied in this paper.

(23) (a) J. S. E. Holker and W. B. Whalley, *Proc. Chem. Soc.*, 464 (1961); (b) N. L. Allinger and M. A. DaRooge, *Tetrahedron Letters*, No. 19, 676 (1961); (c) J. Lehn, J. Levisalles, and G. Ourisson, *ibid.*, 682.

(24) Although the differences in conformation between the saturated and unsaturated compounds are small, they may be sufficient to produce marked changes in reactivity because of the conformational transmission effect.[25]

(25) D. H. R. Barton, A. J. Head, and P. J. May, *J. Chem. Soc.*, 935 (1957); D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *ibid.*, 1297 (1960).

(26) J. Fridrichsons and A. McL. Mathieson, *ibid.*, 2159 (1953).

Experimental

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 Recording Spectrophotometer. The distillations of ether, benzene and hexane were carried out on a column 70 cm. × 25 mm. packed with helices; all other distillations were on a Vigreux column (20 cm. × 25 mm.)

Materials.—3-Cholestanone[27] had melting point 129–130°. Lithium aluminum hydride, sodium borohydride, lithium borohydride, and sodium trimethoxyborohydride were obtained from Metal Hydrides, Inc. The alumina used was Alcoa-F20. The isopropyl alcohol (reagent), ethanol (100% USP), and methanol (reagent) were all distilled before use. The b.p.'s were isopropyl alcohol 82°; ethanol 78°; and methanol 65°. Hexane (reagent) and ether (reagent) were passed through alumina and distilled from phosphorus pentoxide. The ether (b.p. 35°) was stored over sodium; the hexane had b.p. 69°. Benzene (reagent) was passed through alumina, distilled from sodium wire (b.p. 80°), and kept over sodium wire. The pyridine (reagent) was distilled from potassium hydroxide and had b.p. 114°. Bis(2-methoxyethyl) ether (diglyme, practical) was first distilled from potassium hydroxide, and then from lithium aluminum hydride, b.p. 95°/40 mm. Tetrahydrofuran (industrial grade) was kept over potassium hydroxide overnight, then passed through alumina, distilled from sodium, and finally distilled from lithium aluminum hydride (b.p. 66°). It was kept over sodium wire.

Reductions.—The experimental procedure for the reduction of 3-cholestanone was made as uniform as possible for all hydrides and solvents. When solvents miscible with water were used, some variation was required in the amounts of water and ether added after hydrolysis of the reaction mixture, in order to cause separation into two phases.

In the general procedure, 5α-cholestan-3-one (100 mg. 0.26 mmole) was reduced with the hydride (1.3 or 1.4 mmoles) in 40 ml. of solvent. Usually the direct mode of addition was used. The reaction mixture, which was protected from the atmosphere by a drying tube, was stirred for the appropriate time, and then N hydrochloric acid (25 ml.) was added cautiously. The products were isolated through extraction with ether. If the yield of crude products (after drying for some hours at 60° *in vacuo*) were less than 95 mg. or greater than 106 mg., the run was usually discarded.[28] The crude products in ether (5 ml.) were chromatographed on alumina (38 g. packed in hexane in a column 50 cm. long and 12 mm. in diameter). The following amounts of solvents were passed through and 10-ml. fractions were taken: hexane (50 ml.); 1:1 hexane–benzene (80 ml.); 8:1 benzene–ether (90 ml.); and ether (until no further material was eluted). Usually any unreduced cholestanone was eluted in fractions 1–14; 5α-cholestan-3α-ol was eluted in fractions 17–24; and 5α-cholestan-3β-ol was eluted in fractions 26–36.

(27) Mann Research Laboratories, New York 6, New York.

(28) In the three exceptional cases smaller yields (92, 93, and 94.8 mg.) were used.

The yield of each material was estimated by combining its separate fractions[29].

The materials were identified by m.p. or in doubtful cases by infrared spectra. 3α-Cholestanol (lit. m.p. 181–182°) from the column usually had a m.p. 183–185° but m.p.'s up to 187–189° were frequent. 3β-Cholestanol (lit. m.p. 141–142°) usually had m.p. 143–144° but m.p.'s from 141–143° to 145–147° were observed. 3-Cholestanone (lit. m.p. 128–129°) had m.p.'s ranging from 118–120° to 129–130°. Most were 124–126° or higher.

The following is a typical run: A solution of 3-cholestanone (100 mg.) in tetrahydrofuran (10 ml.) was added in one portion to a stirred solution of lithium borohydride (33 mg.) in tetrahydrofuran (30 ml.) at room temperature. After 4 hr. hydrochloric acid (25 ml., *N*) was added cautiously, and then the mixture was extracted with ether (25 ml.). The aqueous layer was washed with three further lots (each 10 ml.) of ether. The combined ethereal layers were washed with water, aqueous sodium hydrogen carbonate, and again with water, and the solution was dried (Na_2SO_4). The solvent was evaporated and the crude product (102 mg. after drying for some hours at 60° *in vacuo*) was chromatographed on alumina. 3α-Cholestanol (6.6 mg. m.p. 182–185°) was eluted in benzene–ether and the first three ether fractions; 3β-cholestanol (92.4 mg. m.p. 143–144°) was eluted in the 5th–10th ethereal fractions. Yield of α-isomer 6.7%; yield of β-isomer 93.3%; total yield of sterols 98%.

The general procedure was modified slightly for reactions run above room temperature. In these cases the solvent was brought to the desired temperature, the hydride was added, and then as quickly as possible the ketone was introduced. In reactions involving inverse addition the order of the latter two steps was reversed.[22]

When pyridine was used as solvent, the method of work-up of the reaction was changed. After the reaction was complete, aqueous sodium hydroxide (25 ml., *N*) was added cautiously and the stirring of the mixture was continued for 1 hr. Water (25 ml.) was added and the product extracted with ether (75 ml.). The aqueous layer was then extracted with three further lots of ether (15 ml. each). The combined ethereal solutions were washed with water, hydrochloric acid (*N*), and water and were dried (Na_2SO_4). The crude product was obtained on evaporation of the ether.

The results of all these experiments are summarized in Table I.

Control Experiments.—The following standard mixtures of 3-cholestanol epimers were made up and chromatographed on alumina: 70% β- and 30% α- (on chromatography gave 70.7% β-, m.p. 142–143°, and 29.3% α-, m.p. 183–184°); 76% β- and 24% α- (on chromatography gave 74.5% β-, m.p. 143–144°, and 25.5% α-, m.p. 187–188°)[30]; and 90% β- and 10% α- (on chromatography gave 89.8% β-, m.p. 143–144°, and 10.2% α-, m.p. 184–186°).

These results indicate that chromatography on alumina is a satisfactory method for estimating the isomers.

A number of experiments were done to confirm that the cholestanols are not epimerized under the reaction conditions.

A mixture of 3β-cholestanol (20 mg.) and lithium aluminum hydride (10 mg.) in ether (20 ml.) was stirred at room temperature for 2 hr. The mixture was worked up by the general procedure. The yield of product was 20.4 mg., m.p. 142–143°, infrared spectrum identical with starting material.

A mixture of 3α-cholestanol (10 mg.) and lithium aluminum hydride (5 mg.) in ether (20 ml.) was stirred for 2 hr. On work-up the mixture yielded 9.7 mg. of product, m.p. 185–188°, infrared spectrum identical with starting material.

A mixture of 3β-cholestanol (100.4 mg.) and sodium borohydride (52.1 mg.) in isopropyl alcohol was refluxed for 4 hr. The mixture on the usual work-up gave 95.6 mg. crude product which was chromatographed on alumina. Only one fraction (89.6 mg. m.p. 143–145°) could be obtained. There was no trace of the α-epimer. An earlier experiment on a 20-mg. scale had given a product m.p. *ca.* 120° with infrared spectrum identical with starting material.[31]

A mixture of 3α-cholestanol (10 mg.) and sodium borohydride (5 mg.) was refluxed in isopropyl alcohol for 4 hr. The m.p. of the product was 183–186°. Its infrared spectrum was the same as the starting material.

Attempted Estimation of Isomers by Infrared Spectra.—Standard solutions (50 mg. in 5 ml. of CCl_4) of 3α- and 3β-cholestanol were made up. The compositions varied from 6–50% of the α-isomer. The infrared spectra were determined and the peaks at 9.65 μ and 9.32 μ were studied as a basis for analyzing mixtures of the 3-cholestanol epimers. The peak at 9.65 μ appeared to be the more suitable. However, repetition of the spectra (even after the instrument had been serviced) showed small changes in the % transmission at 9.65 μ. As these changes could introduce uncertainties of up to 8% in the estimations, the method was not used.

(29) In one run of the lithium aluminum hydride–ether 0.5 hr. series the weight of the β-isomer was estimated from the separate weights of the individual fractions.

(30) The poorness of this result is due probably to the fact that the amounts of the isomers were determined by adding the weights of individual fractions instead of the usual procedure of weighing the combined fractions of each isomer.

(31) 3β-Cholestanol has a double m.p., 125° and 141–142°.

Benzo[*b*]thiophene. III.[1] Synthesis of Hydroxylated Diphenylalkanes from Anisyl Derivatives of Benzo[*b*]thiophene

RENÉ ROYER, PIERRE DEMERSEMAN, JEAN-PIERRE LECHARTIER, AND ANDRÉE CHEUTIN

The Organic Chemical Laboratory of the Institut du Radium—Fondation Curie, Paris 5, France

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The desulfurization with Raney nickel W4 of benzo[*b*]thiophene derivatives substituted by an anisyl group gives methoxylated diphenylalkanes which can be demethylated by means of pyridinium chloride. The anisoylation of 2,3-diethylbenzo[*b*]thiophene occurs mainly in the 6-position, secondarily in the 5-position.

After being discovered by Bougault, Cattelain, and Chabrier,[2] the desulfurizing reduction with Raney nickel of cyclic sulfur compounds was applied several times in the benzo[*b*]thiophene series in order to establish structures.[1a,3]

We have been using this procedure as a preparative method for some hydroxylated diphenyl-

(1) Our former publications in this series are (a) Part I: *Bull. soc. chim. France*, 1534 (1961); (b) Part II: *Compt. rend.*, **254**, 2605 (1962).

(2) *Bull. soc. chim. France*, 1699 (1938); 34 (1939); 780 (1940).