[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., MEXICO, D. F., MEX.]

Steroids. CXXXVIII.[1] Hydrogenolysis of Hydroxyl Groups in the 3-Phenylcholestanol Series[2]

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Hydroxyl group hydrogenolysis in both 3α-phenylcholestane-3β-ol and 3β-phenylcholestane-3α-ol has been shown to provide 3β-phenylcholestane. This result indicates that in certain cases hydroxyl group hydrogenolysis may occur with inversion of configuration.

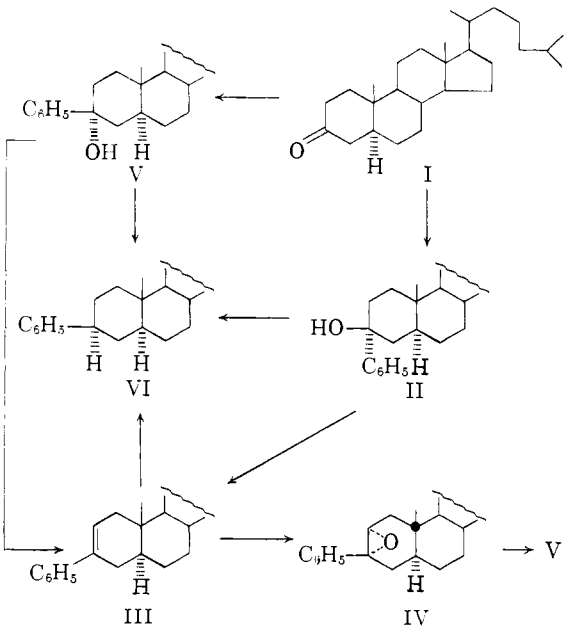
Aside from the work of Bonner and his associates concerning Raney nickel catalyzed hydrogenolyses of acyclic asymmetrically situated sulfur,[3] hydroxyl,[4] methoxyl[5] and certain types of methylol[6] groups, little has been reported concerning the optical course of such reactions in cyclic systems. On the basis of the results obtained by these workers in the atrolactic acid series it was ascertained that sulfone desulfuration[3] occurred with inversion of configuration as contrasted to sulfide desulfurization[3] (complete racemization) and hydroxyl group hydrogenolysis,[4] where a highly stereospecific retention of configuration was obtained.

In contrast to the above results concerning the desulfuration of an acyclically situated sulfone, van Tamelen and Grant[7] have recently reported that in the cyclic 3-methyl 3-mercaptocyclohexanol system, sulfone desulfurization may proceed by means other than those requiring complete inversion. Now from the present work, evidence also has been obtained demonstrating that hydroxyl group hydrogenolysis may occur by a route other than that requiring retention of configuration.

During a non-related investigation in these laboratories it was observed that 16α-hydroxy-17-ethylenemercaptals undergo desulfurization with partial hydrogenolysis of the hydroxyl group at C-16.[8] Since Bonners'[4] work indicated that hydrogenolysis of hydroxyl groups occurred only with retention of configuration, this seemed to demand that the leaving hydroxyl group and the catalyst surface bearing the entering hydrogen should be adsorbed face to face, *i.e.*, that both participating groups be on the same side of the molecule. On this basis we were led to wonder if the observed partial hydrogenolysis of the 16α-hydroxyl was not solely a consequence of its alpha orientation coupled with alpha face adsorption of the entire steroid molecule to the catalyst surface. Such a hypothesis would thus fulfill all the prerequisites for hydrogenolysis if it was further assumed that the adjacent sulfur groups provided a strong bonding between the molecule and the catalyst surface thereby bringing the hydroxyl group very close to the Raney nickel surface.

With these points in mind we chose to study more closely the steric course of dehydroxylation in a simplified benzylic alcohol model,[4] namely the 3-phenylcholestanol system, wherein it was originally thought that the 3α-phenyl-3β-ol isomer might be less susceptible to hydrogenolysis due to the β-orientation of the hydroxyl group. As will be apparent from the sequel this proved not to be the case.

The synthesis of the required isomers was effected by the conversion of cholestan-3-one (I) to a mixture of 3α-phenylcholestan-3β-ol (II) and 3β-phenylcholestan-3α-ol (V) by the action of phenylmagnesium bromide. The nature of the two compounds was readily apparent since neither any longer possessed carbonyl bands in the infrared and their analytical data showed them to be isomeric. A separation was easily carried out by column chromatography whereby the axial alcohol isomer V was eluted first.[9]



It is interesting to note that Barton and his coworkers[10] have observed that the action of methylmagnesium bromide on cholestanone produces both the 3α-methyl-3β-ol and 3β-methyl-3α-ol isomers in *ca.* a 60:40 ratio, respectively. Since in the

(1) Paper CXXXVII, J. S. Mills, A. Bowers, C. Djerassi and H. J. Ringold, THIS JOURNAL, **82**, 3399 (1960).

(2) Taken in part from the professional thesis submitted by M. E. C. R. to the Facultad de Química, Universidad Nacional Autónoma de México.

(3) W. A. Bonner, THIS JOURNAL, **74**, 1034 (1952).

(4) W. A. Bonner, J. A. Zderic and G. A. Casaletto, *ibid.*, **74**, 5086 (1952).

(5) W. A. Bonner and J. A. Zderic, *ibid.*, **78**, 3218 (1956).

(6) W. A. Bonner and T. W. Greenlee, *ibid.*, **81**, 3336 (1959).

(7) E. E. van Tamelen and E. A. Grant, *ibid.*, **81**, 2160 (1959).

(8) J. Fajkos and F. Sorm, *Chem. Listy.*, **49**, 723 (1955), report only completely hydrogenolyzed material in this series. A more detailed report concerning this reaction may be found in J. A. Zderic and A. Bowers, *Ciencia*, **20**, 23 (1960).

(9) In general, axial alcohols are known to be less polar than their equatorial isomers; see K. Savard, *J. Biol. Chem.*, **202**, 457 (1953).

(10) D. H. R. Barton, A. da J. Campos-Neves and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

present work only a slightly different ratio of isomers has been observed, the results suggest that there is essentially little difference in the effective bulk of phenyl and methyl Grignard reagents.

In order to provide a definition of the stereochemistry for the isomers II and V the following approach was undertaken. Thionyl chloride–pyridine dehydration of either pure II or V provided the same styrene derivative, Δ^2-3-phenyl-cholestene (III), which could then be epoxidized to yield as the sole product $2\alpha,3\alpha$-oxido-3-phenylcholestane (IV).[11] The assignment of the double bond in III to the Δ^2- rather than the Δ^3-position was made on the basis of the known stability of double bonds in this position in 5α-steroids,[12] whereas the configuration of the epoxide IV rests on analogy with the epoxidation of Δ^2-cholestene which is known[13] to provide almost exclusively the α-epoxide.

The epoxide IV proved somewhat resistant to fission with lithium aluminum hydride but produced 3β-phenylcholestane-3α-ol (V)[11] in moderate yield after 20 hours under reflux in tetrahydrofuran. The configuration assignment for V follows from the known preference of epoxides for diaxial opening[14] as well as the fact that epoxystyrene provides exclusively phenylmethylcarbinol under these reaction conditions.[15] In addition to these theoretical considerations it was experimentally demonstrated that V contained a *tertiary* hydroxyl since the material could be recovered unchanged after attempted oxidation with the pyridine–chromium trioxide complex.[16]

Treatment of the isomers II and V with excess W-4 Raney nickel[17] in boiling ethanol was conducted in two simultaneous experiments which employed Raney nickel obtained from the same parent batch. From each of the experiments there was obtained in *ca.* 50% yield the same hydrocarbon to which we assign the structure of 3β-phenylcholestane (VI). The analytical data support this gross structure, whereas the configurational assignment rests on two facts. First of all, catalytic reduction of Δ^2-3-phenylcholestene (III) provided 3β-phenylcholestane (VI) in good yield. Such a steric result would be expected on the basis of the rule of rear attack.[18] Secondly, it was observed that VI was also produced in high yield by reduction of III with lithium metal in liquid ammonia and reactions of this type are known usually to afford the thermodynamically more stable isomer[19] which in the present case is represented by the 3β-position.

These results clearly indicate the following three points: (1) that both isomers readily undergo hydrogenolysis; (2) that 3β-phenylcholestan-3α-ol underwent hydrogenolysis with retention of configuration; (3) that hydrogenolysis of 3α-phenylcholestan-3β-ol proceeded with inversion of configuration.

While it is not impossible that this configurational inversion resulted from a SN2 type displacement, molecular models would not seem to support such a conclusion due to the inaccessibility of the back side of C-3. A more feasible explanation may be that catalyst adsorption occurs principally on one face of the benzene ring with the plane of the steroid molecule being suspended perpendicularly to the surface of the catalyst. This adsorbed intermediate could then undergo dehydroxylation to produce an adsorbed reactive species which would ordinarily lead to a reaction product maintaining the original configuration.[4] In lieu of the results, however, we are led to speculate that once the reactive species has been formed, the adsorption energy[3] binding it to the surface of the catalyst is less than the energies involved in the 1:3 non-bonded interactions of the axial 3α-phenyl group. For these reasons then the reactive species is desorbed from the catalyst surface, whereupon the 3α-phenyl group becomes free to assume the thermodynamically more stable 3β-equatorial position. The process is finally completed by the addition of a hydrogen species obtained either from the solvent or by readsorption to the catalyst surface. It should be noted that this hypothesis offers no suggestions concerning the ionic or radical nature of the reactive species involved.

Experimental[20]

Action of Phenylmagnesium Bromide on Cholestan-3-one (I).—To 100 ml. of anhydrous tetrahydrofuran containing 1.0 g. of magnesium turnings was added 7.0 g. of bromobenzene in 20 ml. of tetrahydrofuran. Upon completion of Grignard reagent formation, 2.5 g. of cholestan-3-one (I) dissolved in 50 ml. of tetrahydrofuran was added. After being heated at reflux temperature for 5 hours the mixture was allowed to stand overnight at room temperature. Following decomposition with 50 ml. of saturated aqueous ammonium chloride the resulting solution was extracted 5 times with 75-ml. portions of ethyl acetate. The combined extracts were washed to neutrality with water, dried over sodium sulfate and evaporated to dryness. Chromatography of the resulting residue on 50 g. of neutral alumina then provided in the hexane eluates 1.2 g. of crystals, m.p. 157–159°. Recrystallization from acetone then provided pure **3β-phenylcholestan-3α-ol** (V), m.p. 163–165°, $[\alpha]_D$ +26°; λ_{max}^{EtOH} 252, 258 and 264 mμ; log ϵ 2.18, 2.17 and 2.15.

Anal. Calcd. for $C_{33}H_{52}O$: C, 85.28; H, 11.28; O, 3.44. Found: C, 85.27; H, 11.23; O, 3.76.

Upon further elution of the column there was obtained in the hexane–benzene (7:3) fractions 1.3 g. of crystals, m.p. 60–63°. Several recrystallizations then yielded **3α-phenylcholestan-3β-ol** (II), m.p. 76–78°, resolidifying with m.p. 100–103°, $[\alpha]_D$ +35°; λ_{max}^{EtOH} 252, 258 and 264 mμ; log ϵ 2.10, 2.18 and 2.06.

(11) During an early part of this investigation a brief communication appeared, R. C. Cookson and J. Hudec, *Proc. Chem. Soc.*, 24 (1957), describing certain reactions of the epoxide IV and alcohol V in connection with another problem. We are pleased to acknowledge Dr. Cookson's kind coöperation in carrying out confirmatory comparisons of IV and V with his authentic samples. A complete description of their work is now being prepared.

(12) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 276–279, for discussion and leading reference; see also ref. 10 where the Δ^2-position was rigorously proved.

(13) A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949); see also ref. 10.

(14) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954).

(15) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3738 (1948).

(16) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(17) (a) H. Adkins and A. A. Pavlic, *ibid.*, **69**, 3039 (1947); (b) A. A. Pavlic and H. Adkins, *ibid.*, **68**, 1471 (1946).

(18) L. F. Fieser, *Experientia*, **6**, 312 (1950); T. F. Gallagher and T. H. Kritchevsky, THIS JOURNAL, **72**, 882 (1950).

(19) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(20) All melting points are uncorrected and the rotations were determined in chloroform. We wish to thank Dr. L. J. Throop and staff for the determination of all rotations and spectral data.

Anal. Calcd. for $C_{33}H_{52}O$: C, 85.28; H, 11.28; O, 3.44. Found: C, 85.50; H, 11.28; O, 3.59.

Δ^2-3-Phenylcholestene (III).—A mixture of 1.0 g. of pure II, 10 ml. of pyridine and 1.3 ml. of thionyl chloride was maintained at ice-bath temperature for 3 minutes. Following dilution with water (30 ml.) the solution was extracted three times with 50 ml. of chloroform. After being washed with dilute acid, aqueous sodium bicarbonate and finally with water, the extract was dried and evaporated. By these means there was obtained 0.80 g. of oily crystals which following several recrystallizations from acetone yielded 0.50 g. of III, m.p. 126–127°, $[\alpha]D$ +53°, λ_{max}^{EtOH} 248–250 mμ, log ϵ 4.04.

Anal. Calcd. for $C_{33}H_{50}$: C, 88.72; H, 11.28. Found: C, 88.98; H, 11.20.

In exactly the same manner there was obtained from 1.1 g. of pure V, 0.35 g. of III, m.p. 125–126°, identical in all respects with that material isolated above.

2α,3α-Oxido-3β-phenylcholestane (IV).—A solution of chloroform (100 ml.) and 1.3 g. of Δ^2-3-phenylcholestene (III) was cooled to 0° and then treated with 275 ml. of 0.5 *N* ethereal monoperphthalic acid. The resulting mixture was maintained at 5° overnight whereafter it was washed consecutively with 5% aqueous sodium bicarbonate and water. After drying and evaporation there was obtained 1.2 g. of crystals, m.p. 113–115°, which were readily recrystallized from acetone to a constant melting point, m.p. 133–135°, $[\alpha]D$ +63°; λ_{max}^{EtOH} 252–254 and 258–260 mμ, log ϵ 2.40 and 2.40.

Anal. Calcd. for $C_{33}H_{50}O$: C, 85.65; H, 10.89; O, 3.46. Found: C, 85.31; H, 11.05; O, 3.63.

3β-Phenylcholestane-3α-ol (V).—Tetrahydrofuran (60 ml.) containing 0.61 g. of epoxide IV and 1.0 g. of lithium aluminum hydride was heated at reflux temperature for 20 hours with constant stirring. The mixture was then decomposed by the cautious addition of saturated aqueous sodium sulfate followed by solid sodium sulfate. Filtration and evaporation provided a non-crystalline residue which was then chromatographed over 20 g. of alumina. Elution with hexane provided material (0.32 g.) which after several recrystallizations from acetone yielded authentic V, m.p. 161–163°, identical in all respects with V obtained by the action of phenylmagnesium bromide on cholestan-3-one (I); *vide supra*.

3β-Phenylcholestane (VI). A. By the Action of Raney Nickel on 3α-Phenylcholestan-3β-ol (II).— A mixture of 0.20 g. of II and 3 g. of Raney nickel in 25 ml. of ethanol was heated for 3 hours at reflux temperature. After this period the solution was filtered through Celite and the filter cake was copiously washed with hot ethanol. Evaporation of the combined filtrates provided a residue which crystallized from acetone to provide 90 mg. of crystalline VI, m.p. 105–109°, obtained pure following one recrystallization from the same solvent; m.p. 113–114°, $[\alpha]D$ +31°, λ_{max}^{EtOH} 254, 258–260 and 268 mμ; log ϵ 2.28, 2.33 and 2.22.

Anal. Calcd. for $C_{33}H_{50}$: C, 88.72; H, 11.28. Found: C, 88.62; H, 11.53.

B. By the Action of Raney Nickel on 3β-Phenylcholestan-3α-ol (V).—In an experiment conducted exactly as above in A, 0.20 g. of V led to the isolation of 80 mg. of slightly impure VI, m.p. 108–111°. A single recrystallization from acetone then yielded material identical in all respects to that isolated in A.

C. By Catalytic Reduction of Δ^2-3-Phenylcholestene (III).—To 10 ml. of ethyl acetate containing 10 mg. of prereduced 5% palladium-on-charcoal was added 26 mg. of III in 10 ml. of ethyl acetate. The hydrogen uptake was not measured but after 2 hours of stirring in a hydrogen atmosphere the mixture was filtered. Evaporation to dryness followed by a single crystallization from acetone provided 12 mg. of VI, m.p. 112–113°, identical with the material isolated in part A.

D. By Li/NH_3 Reduction of Δ^2-3-Phenylcholestene (III).—Tetrahydrofuran (2 ml.) containing 75 mg. of III was added with stirring to a solution of 0.10 g. of lithium in 20 ml. of liquid ammonia. After 1 minute of stirring the blue color of the solution was discharged by the addition of a few drops of methanol. Following evaporation to dryness the residue was triturated with hexane and the hexane was then passed through 2 g. of alumina. From the first fractions there was obtained 60 mg. of crystals, m.p. 103–106°, which after one recrystallization from acetone provided 28 mg. of VI, m.p. 113–114°, identical in all respects with the material isolated above in A.

Treatment of 3β-Phenylcholestane-3α-ol (V) with Pyridine–Chromium Trioxide.—To 0.6 ml. of pyridine containing 33 mg. chromium trioxide was added 33 mg. of V. After 20 hours at room temperature the mixture was diluted with ethyl acetate (3 ml.) and filtered through 2 g. of alumina. Elution of the column with ethyl acetate provided in the first fraction *ca.* 20 mg. of a slightly colored crystalline residue. Following three triturations with 0.3 ml. of acetone there was obtained 15 mg. of colorless crystals, m.p. 161–163°. A mixed melting point with authentic 3β-phenylcholestane-3α-ol (V) of the same melting point was not depressed.

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Cyclopropene. V. Some Reactions of Cyclopropene[1]

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A number of the reactions of cyclopropene, including the addition of bromine, iodine and similar reagents, the thermal rearrangement, polymerization, formation of argentic complex, addition of diazo compounds and reaction with dienes are discussed. An estimate of the heat of formation is made, and is used in interpreting the results of the investigation.

Because of the interesting structure of cyclopropene and our interest in the effects of bond angle deformation on the reactions and properties of organic compounds, we have examined a number of the reactions and properties of cyclopropene. The ones to be discussed here are those which bear on the thermodynamic destabilization of cyclopropene as compared to cyclopropane.

Thermal Rearrangement.—One of the more informative reactions of cyclopropene is the thermal isomerization to methylacetylene. When a stream of cyclopropene mixed with helium is passed through a glass tube packed with glass helices at 325° (600°K.), rearrangement proceeds slowly. At 425°, the rearrangement is fairly rapid.[2] In a typical experiment, the effluent gas contained methylacetylene and cyclopropene in the ratio of 5:1. Under the same conditions, methylacetylene did not give a detectable amount of cyclopropene. Thus, the equilibrium constant for the reaction is at least 30,[3] and the free energy of isomerization is less than −4.7 kcal./mole.

(1) This work was supported by the Office of Ordnance Research, U. S. Army.

(2) This rearrangement has also been observed by Dr. F. P. Lossing, National Research Council, Canada.

(3) One per cent. of cyclopropene in the mixture could be detected and 3% could easily be seen in the infrared spectrum.