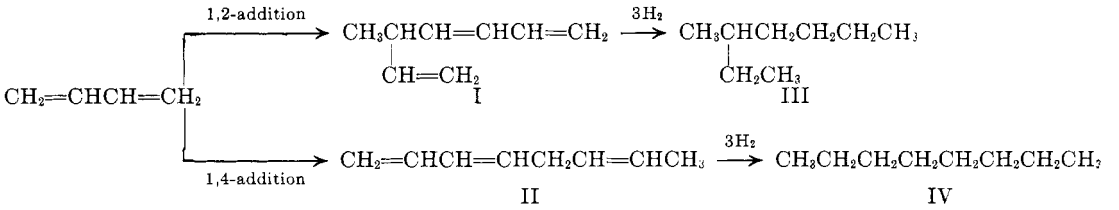
SCHEME I



10 p.s.i.; carrier gas, helium; and flash evaporator temperature, 200°. The first and second chromatographic peaks corresponded to I and II. The amount of II isolated was so small that analytical data, refractive index, and specific gravity of II could not be obtained; only spectroscopic data was obtained.

Hydrogenation of I and a Mixture of I and II.—Hydrogenation at atmospheric pressure of I (2.16 g.) using 100 mg. of platinum black resulted in absorption at 1520 ml. (3 equivalents) of hydrogen. After filtration, saturated hydrocarbon III (2.1 g.) was obtained. The infrared spectrum of this hydrocarbon (III) was identical with that of 3-methylheptane. Similarly on hydrogenation, a mixture of I and II absorbed 3 equiv. of hydrogen, and resulted in a mixture of 3-methylheptane (83%) and *n*-octane (11%). Octane was determined by gas chromatography.

Anal. Calcd. for C_8H_{18}: C, 84.22; H, 15.78. Found: C, 84.15; H, 15.80 (hydrogenated product III).

Anal. Found: C, 84.10; H, 15.75 (hydrogenated product of I and II).

Bromination of a Mixture of I and II.—On bromination, a mixture (10.1 g.) of I and II absorbed 3 equiv. of bromine in carbon tetrachloride (50 ml.). After filtration and evaporation, a white solid (50 g.) was obtained. It was purified by recrystallization from chloroform. The analytical sample melted at 129–130°.

Anal. Calcd. for $C_8H_{12}Br_6$: C, 16.35; H, 2.06; Br, 81.59. Found: C, 16.50; H, 2.20; Br, 81.26.

Acknowledgment.—The authors are indebted to Dr. S. Ito and Dr. K. Takase of Tohoku University, Japan, for the determination and interpretation of the n.m.r. spectra reported in this work.

4-Cholesten-3-one Ethylene Ketal

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Received November 14, 1963

In a study designed to extend our work of comparing the behavior of the cholesteryl and pseudo-cholesteryl systems,[1] the reaction of ethylene glycol and 5-cholesten-7-one (I) was undertaken to resolve the question of whether the pseudocholesteryl system (as I) would exhibit the unusual rearrangement of the double bond reported[2] from the preparation of the ethylene ketal III from 4-cholesten-3-one (II).

5-Cholesten-7-one (I) provided a ketal (IV), the optical rotation of which, in contrast to many other cholestane derivatives, was ambiguous[3] with respect to its use in the prediction of structure (see Table I).

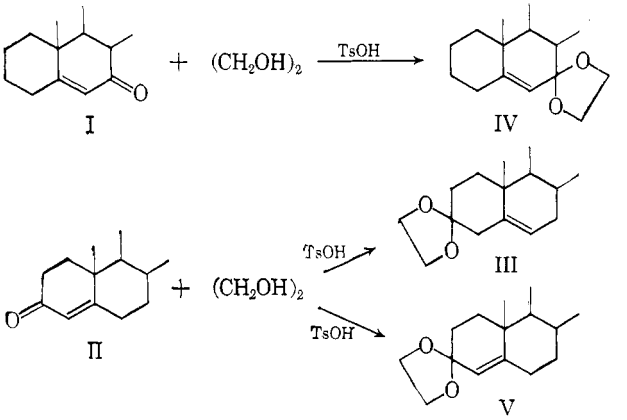
TABLE I

CHOLESTANE DERIVATIVES

Functional group	Hydroxyl position	Reported $[\alpha]_D$	Calculated, $\frac{[\alpha]_D\ \alpha + [\alpha]_D\ \beta}{2}$	Reported $[\alpha]_D$ ethylene ketal
None	3α	+23[a]	+23.5	+21.6[b]
	3β	+24[a]		
5α,6α-Oxido	3α	−44[c,d]	−44.5	−33[f]
	3β	−43[e]		
5β,6β-Oxido	3α	−0.6[c]	+6	+9[f]
	3β	+12[e]		
Δ⁴	3α	+121[g]	+83	+75[o]
	3β	+45[h]		
Δ⁵	3α	−47[i]	−43.5	−28[k]
	3β	−40[j]		
Δ⁴	7α	+45[l]	+67	
	7β	+90[m]		−2.4[o]
Δ⁵	7α	−112[n]	−56	
	7β	±0[n]		

[a] L. F. Fieser and W. Huang, *J. Am. Chem. Soc.*, **75**, 4837 (1953). [b] H. Dauben, Jr., B. Löken, and H. Ringold, *ibid.*, **76**, 1360 (1954). [c] P. Plattner, A. Fürst, F. Koller, and H. Kuhn, *Helv. Chim. Acta*, **37**, 258 (1954). [d] A. Fudge, C. Shoppee, and G. Summers, *J. Chem. Soc.*, 958 (1954). [e] R. Baxter and F. Spring, *ibid.*, 613 (1943). [f] See ref. 8. [g] H. McKennis, Jr. and G. Gaffney, *J. Biol. Chem.*, **175**, 217 (1948). [h] P. Plattner, H. Heusser, and A. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949). [i] P. Plattner and W. Lang, *ibid.*, **27**, 1872 (1944). [j] L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 5421 (1953). [k] See ref. 2a. [l] G. Kent and E. Wallis, *J. Org. Chem.*, **24**, 1235 (1959). [m] See ref. 1b. [n] A. Nickon and J. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961). [o] Details in this paper.

In order to compare the infrared spectrum of this possible α,β-unsaturated ethylene ketal with that of a known β,γ-unsaturated ethylene ketal, the pro-



(1) Q. R. Petersen, *J. Am. Chem. Soc.*, **82**, 3677 (1960); Q. R. Petersen and C. T. Chen, *ibid.*, **77**, 2557 (1955); Q. R. Petersen, *Proc. Indiana Acad. Sci.*, **68**, 118 (1959).

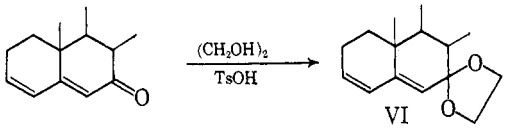
(2) (a) E. Fernholtz, U. S. Patent 2,378,918 (1945); *Chem. Abstr.*, **39**, 5052[3] (1945); (b) H. Koster and H. Inhoffen, German Patent 892,450 (1953); *Chem. Abstr.*, **52**, P18,534*g*, (1958); (c) C. Grob, W. Jundt, and H. Wicki, *Helv. Chim. Acta*, **32**, 2427 (1949); (d) R. Antonucci, S. Bernstein, R. Littell, K. Sax, and J. Williams, *J. Org. Chem.*, **17**, 1341 (1952); (e) H. Koster and H. Inhoffen, U. S. Patent 2,302,636 (1942); *Chem. Abstr.*, **37**, 2388[6] (1943).

(3) For another example of anomalous rotational contribution by the 7-oxygen function, see R. Cremlyn, R. Rees, and C. Shoppee, *J. Chem. Soc.*, 3790 (1954). Compound IV is tentatively assigned the Δ⁵-structure on the basis of its resemblance (in its mode of formation and in its instability toward hydrolysis) to the unrearranged ketals in the cholesteryl system.

cedure of Fernholtz[2a] was applied to the synthesis of the well-described 5-cholesten-3-one ethylene ketal (III). Several attempts to prepare this compound provided, reproducibly, a substance melting at 96° instead of 132° as reported for III. The identity and purity of all starting materials were checked without detection of error. Subsequent synthetic attempts following the procedure of Inhoffen[2b] led to the same result. Extensive chromatography of the crude material from these preparations provided only a little starting material and an apparently homogeneous substance (V), m.p. 96–97°, $[\alpha]_D$ +75°. *None* of the expected product III with the reported[2a] constants, m.p. 132°, $[\alpha]_D$ −28°, was observed.

The optical rotation (see Table I), the infrared spectrum, the elemental analysis, and the ready hydrolysis to 4-cholesten-3-one (II) led to the conclusion that V was, in fact, 4-cholesten-3-one ethylene ketal.

On the basis of the same kinds of evidence plus ultraviolet spectroscopy it was apparent that the ethylene ketal (VI) made from 3,5-cholestadien-7-one (or 5-cholesten-7-on-3β-ol acetate) also had suffered no double bond shift.[4]



VI

The recent paper of Dean and Christiansen[5] reporting the isolation of a Δ^4-ethylene ketal of testosterone[6] and an excellent and thorough examination of the properties of this and related compounds prompts us to terminate our work short of a complete study and present our remarkably similar findings in the cholestane series, reached independently and prior to the publication of their work.

During our study of the nature of V, a successful synthesis of III was achieved following the procedure of Grob.[2c] A re-examination of the experimental descriptions in the procedures used in the preparation of V showed, in common, a curiously inexact instruction in specifying the amount of *p*-toluenesulfonic acid monohydrate catalyst as "a few crystals".[2a,b] Workers[7,8] not supplying specific descriptions have generally referred to their use of the Fernholtz procedure and thus sustained the inexactness. Still other descriptions of the procedure for the formation of these derivatives define the catalyst necessary as "a trace"[9] or "a crystal".[2a]

The quantity "a few crystals" was found to be, in the hands of one of the present authors, 0.004 g. to 0.009 g. and, in the hands of the other, 0.008 g. to 0.015 g. The largest of these amounts was not sufficient to provide, on the scale of our experiments, the Δ^5-ethylene ketal III. On the scale with which we were working, approximately 0.05 g. of catalyst was required for conversion of II to III, and thus our interpretation of the term "a few crystals" was responsible for the anomalous result.

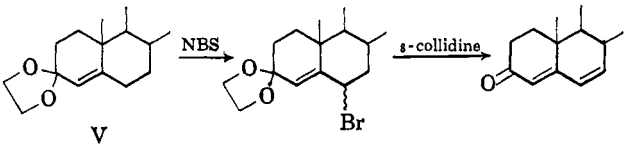
In addition to the similarity of the effect of catalyst concentration on our cholestenone system and on Dean and Christiansen's testosterone system, several other quite parallel observations were made.

(1) The infrared spectra of the Δ^4- and Δ^5-ethylene ketals (V and III) were very similar, the most notable differences being the presence of bands at 1663 (weak), 1175, and 993 cm.$^{-1}$ in the spectrum of the Δ^4-compound which were absent in the Δ^5-isomer. Bands at 1095 and 942 cm.$^{-1}$ were present in the spectra of both compounds.

(2) In our hands the Δ^4-ethylene ketal could not be epoxidized with *m*-chloroperbenzoic acid.

(3) The ethylene ketals prepared without isomerization of the double bonds (IV–VII) were extremely sensitive to hydrolysis and had to be stored over pyridine to remain uncontaminated by the parent ketone for more than a few hours. The ethylene ketals in which the double bond had shifted to the 5-position (III and VIII) proved quite stable and retained their purity over long periods of time without special protection.

(4) The bromination of the Δ^4-ethylene ketal with N-bromsuccinimide (NBS) went readily to give a unique product (VII) which, however, could not be hydrolyzed to an identifiable bromo ketone by any of the experiments carried out prior to the termination of this work. By analogy with the work of Dean and Christiansen, VII would be expected to be the 6α-bromo compound. Treatment of VII with *s*-collidine



V VII

gave an interactable oil; however, its infrared spectrum clearly showed the presence of 4,6-cholestadien-3-one.

In contrast to the testosterone system, preparative isomerization of the Δ^4- to the Δ^5-ethylene ketal was not realized when the former was refluxed in benzene with an excess of catalyst. The reaction was followed by chemical work-up and by periodic infrared spectra over 26 hr. to show an increasingly complex mixture in which only the unsaturated ketone could be positively identified.

6β-Bromo-4-cholesten-3-one provided a Δ^5-ethylene ketal (VIII) with a low catalyst concentration which would have been expected, in the nonhalogenated system, to produce a Δ^4-ketal. Under a still lower catalyst concentration there appeared to be produced a different substance which proved too unstable for purification and analysis. The structure of VIII was shown to be 6-bromo-5-cholesten-3-one ethylene ketal by optical rotation, elemental analysis, and sodium and alcohol reduction to the known ethylene ketal III.

(4) G. Fonken [*J. Org. Chem.*, **26**, 2549 (1961)] has demonstrated the nonrearrangement in the isomeric 4,6-cholestadien-3-one which we have verified.

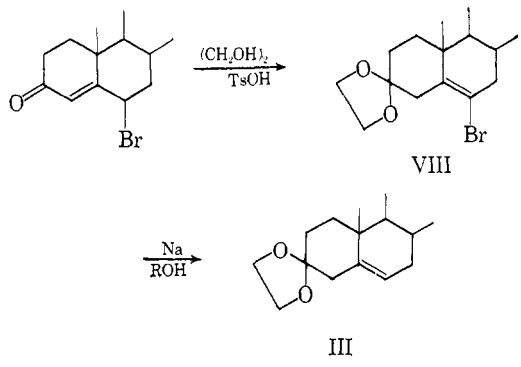
(5) J. W. Dean and R. G. Christiansen, *ibid.*, **28**, 2110 (1963).

(6) This compound was previously reported by J. Brown, R. Lenhand, and S. Bernstein [*Experientia*, **18**, 310 (1962)], but no physical constants or experimental details were given.

(7) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(8) G. Cooley, B. Ellis, D. Kirk, and V. Petrow, *J. Chem. Soc.*, 4112 (1957).

(9) E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953).



Experimental[10]

5(4?)-Cholesten-7-one Ethylene Ketal (IV).—A solution of 1.0 g. of 5-cholesten-7-one in 100 ml. of benzene was mixed with 2.0 ml. of ethylene glycol and refluxed with a Dean–Stark water take-off in place. After 5 min., a "few crystals" of *p*-toluenesulfonic acid monohydrate were added, and the mixture refluxed for 24 hr. The benzene layer was decanted from the excess ethylene glycol and, after the addition of a drop of pyridine, evaporated under an air stream to provide a solid residue. Crystallization from methanol (pyridine) gave a fibrous, gel-like solid, m.p. 90°. Chromatography on alumina provided 0.97 g. of crystalline fractions melting variously from 100.5–102.5° to 93–101°. This substance was extremely unstable, decomposing to a significant extent if exposed to the atmosphere for 1 hr. The analytical sample showed m.p. 95–102°, $[\alpha]_D$ −2.4°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3. Found: C, 81.18; H, 11.52

The infrared spectrum showed no carbonyl adsorption and several peaks in the 900–1200-cm.$^{-1}$ region.

An acetone solution of IV when treated with a drop of concentrated hydrochloric acid and permitted to stand overnight gave, upon evaporation, pure 5-cholesten-7-one.

4-Cholesten-3-one Ethylene Ketal (V).—A solution of 1.02 g. of 4-cholesten-3-one in 100 ml. of benzene was mixed with 2.0 ml. of ethylene glycol and refluxed for 40 min. with a Dean–Stark water take-off in place. At the end of this time 0.0052 g. of *p*-toluenesulfonic monohydrate acid was added; the reflux was continued for 7 hr. The resulting mixture was washed three times with 2 *N* potassium bicarbonate and once with water. The benzene solution was filtered through anhydrous sodium sulfate and, after addition of a drop of pyridine, evaporated to a yellow oil which crystallized. The sample was recrystallized from 30 ml. of ethanol (pyridine) to provide 0.89 g. of powdery white solid, m.p. 103–104°, with some individual crystals melting between 92 and 96°. When the same was recrystallized from methanol (pyridine), it gave chunky needles, m.p. 95–97°, $[\alpha]_D$ +75°.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3. Found: C, 81.05; H, 11.55.

Eight separate preparations of this compound were carried out, in each case the catalyst–steroid ratio ranging between that described above and three times that ratio. In every case the same product was obtained and none of the Δ^5-isomer was observed either by chromatographic separation or spectroscopic examination.

The ketal V apparently held some solvent under normal conditions. Fresh chromatographic fractions occasionally had a m.p. of 102° which declined to 95–97° on short standing in air, in a pyridine–air atmosphere, or upon crystallization from methanol (pyridine). The compound showed adsorption in the infrared as described in the discussion portion of this contribution.

When an acetone solution of V was treated with a few drops of 3 *N* hydrochloric acid and permitted to stand overnight it reverted completely to 4-cholesten-3-one.

(10) Melting points were determined on the hot stage of a polarizing microscope and are corrected to ±1°. Rotations were taken in pyridine at room temperature. Infrared spectra were determined in carbon tetrachloride with a Perkin-Elmer 21 instrument. Ultraviolet spectra were determined in methanol with a Beckman DU instrument. Recrystallizations from solvents containing a drop of pyridine are indicated as "methanol (pyridine)." Microanalyses were by Midwest Microlab Inc., Indianapolis, Ind.

Oxidation of the ketal according to the procedure of Poos, *et al.*,[7] provided, after work-up of the product, only unchanged ketal starting material and its hydrolysis product II.

The ketal also proved to be refractory to catalytic hydrogenation. In two attempts, 1.0 g. of the ketal was shaken with 0.093 g. of 12% palladium on charcoal in a 1% solution of potassium hydroxide in absolute ethanol under positive hydrogen pressure to give no reaction after 12 hr. The starting material was recovered quantitatively from the reaction mixture.

3,5-Cholestadien-7-one Ethylene Ketal (VI).—Using the same general techniques described for the previous experiments, 2.0 g. of 3,5-cholestadien-7-one provided 2.0 g. of an oily product which, upon chromatography on alumina, gave several crystalline fractions which could be recrystallized from methanol (pyridine) as long colorless needles, m.p. 102.5–103.5°, $[\alpha]_D$ −100°, λ_{max} 236 mμ.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.8; H, 10.8. Found: C, 81.34; H, 10.95.

This compound was also obtained each time the preparation of the ethylene ketal of 5-cholesten-7-on-3-ol acetate was attempted using the procedures described above.

6ξ-Bromo-4-cholesten-3-one Ethylene Ketal (VII).—A dry mixture of 0.27 g. of V and 0.13 g. of N-bromsuccinimide was added to 20 ml. of dry carbon tetrachloride, and the mixture refluxed under a spotlight for 2 min. The mixture was filtered and evaporated under an air stream to a semisolid which was crystallized from acetone to give rosettes, m.p. 120–122°. The mixture melting point with 4,6-cholestadien-3-one ethylene ketal[11] was depressed to 100°; the analysis of VII was not satisfactory.

Anal. Calcd. for $C_{29}H_{47}BrO_2$: C, 68.6; H, 9.3. Found: C, 67.47; H, 8.98.

6-Bromo-5-cholesten-3-one Ethylene Ketal (VIII).—Following the same procedure described for the preparation of V above, 2.0 g. of freshly recrystallized 6β-bromo-4-cholesten-3-one provided 1.5 g. of white needles, m.p. 136°. Samples of this material turned pasty on standing in a pyridine atmosphere, but either the paste or the crude crystals readily recrystallized from acetone to long needles, m.p. 145–146°, $[\alpha]_D$ −35.5°.

Anal. Calcd. for $C_{29}H_{47}BrO_2$: C, 68.6; H, 9.3. Found: C, 69.44; H, 9.21.

A sample of 0.15 g. of VIII was treated with 30 ml. of hot isopropyl alcohol and 2.0 g. of sodium metal was added. After the reaction was complete (15 min.), the mixture was worked up to produce 0.11 g. of III, m.p. 129–132°, shown to be authentic by mixture melting point and infrared spectrum.

When ketalization of 1.0 g. of the bromo ketone was attempted using 0.005 g. of catalyst, a portion of opaque rosettes, m.p. 105 dec., was obtained. This material showed an infrared spectrum different from either VII or VIII, but all purification attempts led to decomposition of the product.

Acknowledgment.—The authors express their appreciation for a grant from the Wolcott Gibbs Fund of the National Academy of Sciences and for a generous gift of 4-cholesten-3-one from the Schering Corporation.

(11) We find this compound (see ref. 4) to show m.p. 122°, $[\alpha]_D$ +63°.

The Synthesis of O-Acetylhydroxy-α-amino Acids

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Received November 1, 1963

O-Acetylhydroxy-α-amino acids are conveniently used as starting materials for the synthesis of peptides and polyhydroxy-α-amino acids.[1] A number of

(1) J. Kurtz, G. D. Fasman, A. Berger, and E. Katchalski, *J. Am. Chem. Soc.*, **80**, 393 (1958).