# The Synthesis and Characterization of Ring-B Cholestane 3-Oxetanones[1a]

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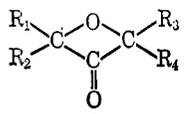
The synthesis of 5,7β-epoxy-6-oxo-5β-cholestanes has been investigated. These compounds, which are examples of highly substituted 3-oxetanone ring systems, were prepared from C-3-substituted 7α-bromo-5β-hydroxy-6-oxocholestanes. When treated with methanolic potassium hydroxide in dimethyl sulfoxide, the bromo ketones bearing 3β substituents (hydroxy, acetoxy, or benzoyloxy) were converted in good yields (>70%) into 3β-hydroxy-5,7β-epoxy-5β-cholestan-6-one (**7a**). The C-3 epimers of the bromo ketones, as well as the 3-desoxybromo ketone (**11b**), were transformed in very poor yields into the corresponding oxetanones under these conditions. The use of aqueous potassium bicarbonate as the base instead of methanolic potassium hydroxide resulted in retention of acyloxy groups but gave lower yields of oxetanones. Speculation is raised concerning the mechanism of the transformation, especially regarding the nature of the conformational change in the A/B steroid ring system that occurs during the reaction. The α-bromo ketones and oxetanones were examined by nmr spectroscopy in order to characterize accurately the structure of starting materials and products. Although entrance into the 3α-substituted oxetanone series was hindred by the poor yields of these compounds that were obtained from the 3α-substituted α-bromo ketones, a simple method of converting the 3β-hydroxyoxetanone (**7a**) into its 3α epimer (**10a**), and also to the 3-desoxyoxetanone **12**, has been developed.

Compounds known as 3-oxetanones (**1**) are of interest because they possess an ether linkage and a carbonyl group in a strained four-membered ring. It has been



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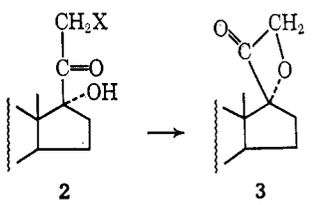
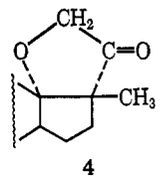
noted[2] that 3-oxetanones undergo normal carbonyl reactions in spite of their strained ring structure; however, literature examples of studies dealing with the preparation and reactions of these compounds are limited in number and scope and generalizations concerning the reactivity of 3-oxetanones cannot be made at this time.

The parent member of this class, 3-oxetanone (**1**, $R_1 = R_2 = R_3 = R_4 = H$), was first characterized as its 2,4-dinitrophenylhydrazone[3a] and has been recently isolated in the pure state.[3b] The syntheses of some alkyl derivatives of 3-oxetanone have been given[4a-e] while earlier inadvertent preparations of substituted 3-oxetanones[4f,5a] have been more recently verified.[4b,5b,c] Few reports on the chemistry of 3-oxetanones are available.[4c,6]

The sole examples of which we are aware where the 3-oxetanone ring system has been prepared as part of more complex structures are in steroids and in each instance the compound was reported to be a 17α,21-oxido-20-one (partial structure **3**). A claim that an oxetanone of this type resulted from the acid-catalyzed hydrolysis of the corresponding ethylene ketal[7a] of partial structure **3** was shown to be erroneous by two groups[7b,c] who demonstrated that the true 17α,21-oxido-20-one underwent rearrangement when treated with acid to give a five-membered oxetanone ring (partial structure **4**). Thus, while the ketal (of partial



**2** **3**



**4**

structure **3**) was represented correctly as a derivative of a 3-oxetanone,[7a] the lability toward acid of the 3-oxetanone itself (resulting from hydrolysis) was demonstrated. All known examples[7] of 17α,21-oxido-20-ones were synthesized by internal displacement reactions (**2** → **3**) involving a 17α-hydroxyl and a common leaving group (mesylate, tosylate, iodide) at C-21, employing basic catalysts (potassium fluoride, silver dihydrogen phosphate, potassium hydroxide) in solvents such as dimethyl sulfoxide, ethanol, or dimethylformamide. The yields of oxetanones under these conditions were low (or not given) and, with the exception of the rearrangement **3** → **4**, little information on the reactivity of the oxetanones was given.

An earlier interest[8] in α-bromo keto steroids has led us to examine the reactions of α-bromo-α′-hydroxy keto steroids with dimethyl sulfoxide (DMSO). Examples of the reactions of DMSO with steroidal α-bromo ke-

(1) (a) This investigation was supported by Public Health Service Research Grant AM-11190-01 from the National Institute of Arthritis and Metabolic Diseases and, in its preliminary stages, by a grant from Research Corporation. Presented at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 2, 1968. (b) To whom inquiries should be directed.

(2) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, Inc., New York, N. Y., 1960, p 46.

(3) (a) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952); (b) G. H. Berezin (E. I. du Pont de Nemours and Co.), U. S. Patent 3,297,719 (Jan 10, 1967).

(4) (a) B. L. Murr, G. B. Hoey, and C. T. Lester, *J. Amer. Chem. Soc.*, **77**, 4430 (1955); (b) J. L. Harper and C. T. Lester, *J. Org. Chem.*, **26**, 1294 (1961); (c) G. B. Hoey, D. O. Dean, and C. T. Lester, *J. Amer. Chem. Soc.*, **77**, 391 (1955); (d) J. K. Crandall and W. H. Machleder, *Tetrahedron Lett.*, 6037 (1966); (e) H. Richet, *Ann. Chim.*, **3**, 317 (1948); *Chem. Abstr.*, **43**, 1393a (1949); (f) D. Vorlander and P. Weinstein, *Ber.*, **56**, 1122 (1923).

(5) (a) W. Langenbeck and H. Langenbeck, *ibid.*, **61B**, 938 (1928); *Chem. Abstr.*, **22**, 2746 (1928); (b) A. Schönberg and A. Sina, *J. Chem. Soc.*, 175 (1947); (c) R. S. Armstrong and R. J. W. LeFèvre, *Aust. J. Chem.*, **10**, 34 (1957); *Chem. Abstr.*, **51**, 10443d (1957).

(6) R. M. Powers and R. A. Day, Jr., *J. Org. Chem.*, **24**, 722 (1959).

(7) (a) W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Amer. Chem. Soc.*, **77**, 4784 (1955); (b) J. E. Herz, J. Fried, P. Grabowich, and E. F. Sabo, *ibid.*, **78**, 4812 (1956); (c) R. Hirschmann, G. A. Bailey, G. I. Poos, R. Walker, and J. M. Chemerda, *ibid.*, **78**, 4814 (1956); (d) M. Heller, R. H. Lenhard, and S. Bernstein, *Steroids*, **5**, 615 (1965); (e) British Patent 869,564 (Upjohn Co.); *Chem. Abstr.*, **56**, 2490d (1962).

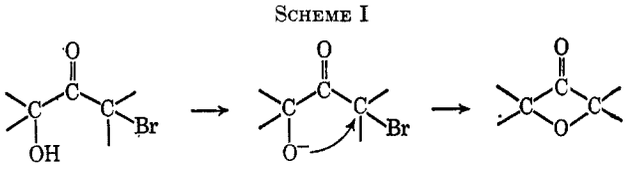
(8) A. T. Rowland, *J. Org. Chem.*, **27**, 1135 (1962).

tones bearing a $\beta$ hydrogen atom are known[9] to yield complex mixtures of products which include $\alpha$-diketones (as diosphenols), $\alpha,\beta$-unsaturated ketones, $\alpha$-hydroxy ketones, and saturated ketones (by reductive elimination of bromide). The product composition obtained from a particular bromo ketone is dependent upon the reaction conditions employed[9b] as well as upon the stereochemistry of, and degree of substitution in, the reactant. To our knowledge the effect of neighboring groups upon the course of reaction of $\alpha$-bromo ketones with DMSO has not been examined and we therefore engaged in a study of the reactivity of DMSO toward ring-B $\alpha$-bromo-$\alpha'$-hydroxy keto steroids. We have found that compounds of this type bearing $3\beta$ substituents are transformed readily into oxetanones.

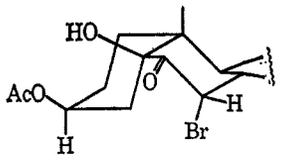
The starting material for the synthesis of the bromo ketones was $3\beta$-acetoxy-5-hydroxy-5$\beta$-cholestan-6-one (**5b**).[8] Bromination of this hydroxy ketone with pyridinium bromide perbromide (PBP)[10] in hot glacial acetic acid gave the $7\alpha$-bromo derivative **6b** in 80% yield. The configuration at C-7 was determined spectroscopically (*vide infra*). The bromo ketone **6b** was easily debrominated by zinc in hot acetic acid to give **5b**. In addition, $3\beta$,5-dihydroxy-$7\alpha$-bromo-5$\beta$-cholestan-6-one (**6a**) and its diacetate **6c** were prepared by PBP bromination of the hydroxy ketones **5a**[8] and **5c**,[11] respectively. The interrelationships of the three $\alpha$-bromo ketones were established as follows: monoacetylation of the diolone bromide **6a** with hot acetic anhydride gave the 3-acetate (**6b**), while diacetylation[11] of **6a** gave **6c** and acetylation[11] of **6b** gave **6c**. The configuration at C-7 was therefore shown to be identical in **6a**, **b**, and **c**.

Treatment of bromo ketone **6b** with DMSO containing suspended sodium bicarbonate[9b] at 100° led to the formation of $3\beta$-acetoxy-5,7$\beta$-epoxy-5$\beta$-cholestan-6-one (**7b**) in 72% yield. The product was identified readily by the characteristic infrared absorption of an oxetanone carbonyl group[7b] at 1815 $cm^{-1}$ (in addition to the acetate carbonyl at 1746 $cm^{-1}$) and the substituted trimethylene oxide ring vibration[12] at 903 $cm^{-1}$. When **6b** was heated in DMSO in the absence of sodium bicarbonate no reaction occurred. Also, treatment of the diacetate **6c** gave no oxetanone under these conditions. These results seemed to indicate that a free hydroxyl group at C-5 must be present in order to give oxetanone and that the reaction presumably proceeds *via* hydrogen abstraction from the hydroxyl group by base, followed by an intramolecular displacement of bromine by the resulting oxy anion (Scheme I).

SCHEME I

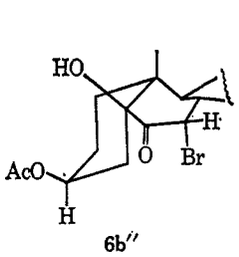


In order for a displacement of this type to occur, the bromine atom at C-7 must be *trans* to the nucleophilic oxy anion, as is the case in bromo ketone **6b**. Inspection of **6b** in perspective form **6b′** indicates clearly that a conformational change in the A/B ring system must

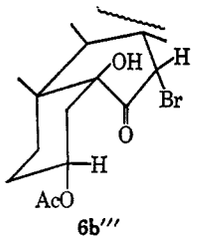


**6b′**

necessarily take place prior to, or during, oxetanone formation in order to position the oxyanion at C-5 properly for the displacement. Such a change might be a minor one involving the B ring only in which this ring adopts a boat form (**6b″**) or, at an extreme, may involve a more



**6b″**



**6b‴**

drastic alteration of both rings A and B, giving a conformation represented by perspective formula **6b‴**. Consideration of **6b‴** as a possible conformer leading to oxetanone formation stems from the relief of the 1,3-diaxial hydroxy–acetoxy interaction[13] found in **6b′** (and **6b″**) and the minimal distance between the C-5 oxygen atom and C-7.

Several additional 5$\beta$-hydroxy-6-oxo-$7\alpha$-bromocholestanes with $3\beta$ and $3\alpha$ acyloxy substituents (**6b**, **9a–c**), along with the 3-desoxy compound (**11b**), were synthesized. This was accomplished with two purposes in mind. (1) Examination of the nmr spectra of the bromo ketones would yield information regarding the environment of the C-3 hydrogen in these compounds. Since the configurations at C-3 in the substituted 5$\beta$-ol-6-ones (**5** and **8**) are known[8,14] the position and $W_{1/2}$ of the C-3 hydrogen signal would indicate whether a conformation such as **6b′** (hydrogen equatorial) or **6b‴** (hydrogen axial) is the major contributor to the ground-state structure of the bromo ketones. (2) If a conformation similar to **6b‴** is necessary for oxetanone formation, then $3\alpha$-substituted bromo ketones might be expected to undergo ring closure to the oxide less readily than the $3\beta$ isomers since the alkyl oxygen of the acyloxy substituent at C-3 (with hydrogen and acyloxy exchanged in formula **6b‴**) would be close to the C-6 carbonyl oxygen, thus introducing an instability factor not present in the $3\beta$-substituted compounds. Also, the absence of a 1,3-diaxial acyloxy–hydroxy interaction in the $3\alpha$-acyloxy bromo ketones (**9**) would not provide a driving force for a conformation change as may occur in the $3\beta$-substituted compounds. If group size at C-3 is important in determining the relative pop-

(9) (a) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967). (b) H. R. Nace and R. N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964); R. N. Iacona, A. T. Rowland, and H. R. Nace, *ibid.*, **29**, 3495 (1964); and references cited in these articles.

(10) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 65.

(11) A. T. Rowland, *J. Org. Chem.*, **29**, 222 (1964).

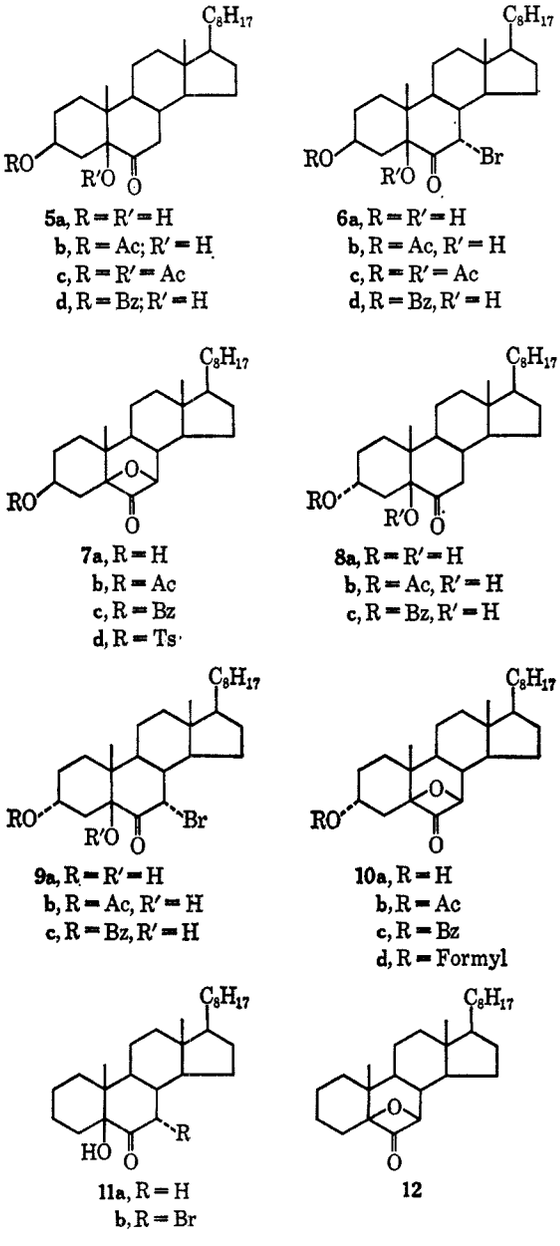
(12) G. M. Barrow and S. Searles, *J. Amer. Chem. Soc.*, **75**, 1175 (1953).

(13) While it is clear that this diaxial orientation is stabilized by hydrogen bonding in $3\beta$-acetoxy-5-hydroxy-5$\beta$-cholestane [A. Nickon, *ibid.*, **79**, 243 (1957)], we have shown that in $3\beta$-acetoxy-5$\beta$-hydroxy-6-oxocholestanes the hydroxy group is hydrogen bonded to the C-6 carbonyl oxygen and not to the alkyl oxygen of the C-3 ester [A. T. Rowland, *Steroids*, **7**, 527 (1966)]. Stabilization by hydrogen bonding of the diaxial interaction in **6b′** or **6b″** should therefore be negligible.

(14) B. W. Sands and A. T. Rowland, *ibid.*, **4**, 175 (1964).

ulation of conformers such as **6b′** and **6b‴**, it would be anticipated that an increase in the size of the 3β substituent would enhance oxetanone formation by increasing the amount of conformer type **6b‴** whereas an increase in the bulk of the 3α substituent would inhibit oxetanone formation by increasing interaction with the C-6 carbonyl oxygen in conformation type **6b‴**.

PBP bromination of the hydroxy ketones **5d**, **8b**, and **8c** gave bromo ketones **6d**, **9b**, and **9c**, respectively. Bromination of 5-hydroxy-5β-cholestan-6-one (**11a**)[14] gave the α-bromo ketone (**11b**) as an oil. Inspection of the uv and ir spectra of the various fractions obtained from column chromatography of the oil indicated that the bulk of the reaction product was the 7α-bromo ketone **11b**. The bromination of the 3α,5β-diol-6-one (**8a**) gave gelatinous products or crystalline material with a wide melting point range. When the bromination of **8a** was conducted in pure tetrahydrofuran at 60°, pyridinium bromide was deposited from the reaction mixture. The steroid product had a uv maximum (311 mμ) consonant with the expected 7α-bromo derivative (**9a**) but column chromatography revealed the presence of numerous compounds, one of which was 3β,5-epoxy-5β-cholestan-6-one (**13**, 16% yield).[13] The fractions obtained from the column whose uv spectra were in agreement with the anticipated bromo ketone **9a** were combined and crystallized, but no pure product could be obtained.[15]




**5a**, R = R′ = H
**b**, R = Ac; R′ = H
**c**, R = R′ = Ac
**d**, R = Bz; R′ = H

**6a**, R = R′ = H
**b**, R = Ac, R′ = H
**c**, R = R′ = Ac
**d**, R = Bz, R′ = H

**7a**, R = H
**b**, R = Ac
**c**, R = Bz
**d**, R = Ts

**8a**, R = R′ = H
**b**, R = Ac, R′ = H
**c**, R = Bz, R′ = H

**9a**, R = R′ = H
**b**, R = Ac, R′ = H
**c**, R = Bz, R′ = H

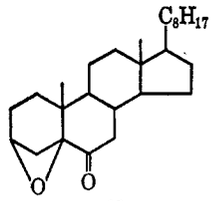
**10a**, R = H
**b**, R = Ac
**c**, R = Bz
**d**, R = Formyl




**11a**, R = H
**b**, R = Br




**12**




**13**

The spectral data (accompanied by molecular rotations) of the α-bromo ketones and the parent ketones reported here are summarized in Table I. The changes noted in $\lambda_{max}$ and $\epsilon_{max}$ of the parent ketones upon bromination and the related minor alterations in the position of the carbonyl stretching frequencies are in full accord with a C-7 axial configuration of bromine in each of the bromo ketones.[16,17]

TABLE I[a]

INFRARED, MOLECULAR ROTATION, AND ULTRAVIOLET DATA OF THE α-HYDROXY KETONES AND THEIR 7α-BROMO DERIVATIVES

| 5β-Cholestane | $\nu_{max}^{C=O}$, cm$^{-1}$ | [φ]D, deg | λmax, mμ (ε) |
|---|---|---|---|
| -5β-ol-6-one (**11a**) | 1706[b] | −69[b] | 283 (54) |
| -7α-bromo-5β-ol-6-one (**11b**) | 1704 | ±0 | 311.5 (114) |
| -3β,5β-diol-6-one (**5a**) | 1711[c] | −21[c] | 284.5 (51) |
| -7α-bromo-3β,5β-diol-6-one (**6a**) | 1706 | +55 | 318 (110) |
| -3β,5β-diol-6-one 3-acetate (**5b**) | 1712[c] | −101[c] | 282.5 (56) |
| -7α-bromo-3β,5β-diol-6-one 3-acetate (**6b**) | 1712 | +49 | 316.5 (110) |
| -3β,5β-diol-6-one 3-benzoate (**5d**) | 1712[c] | +120[c] | *d* |
| -7α-bromo-3β,5β-diol-6-one 3-benzoate (**6d**) | 1712 | +235 | 314.5 (123) |
| -3β,5β-diol-6-one diacetate (**5c**) | 1730[e] | −116[e] | 291 (53) |
| -7α-bromo-3β,5β-diol-6-one diacetate (**6c**) | 1724 | +128 | 317 (90) |
| -3α,5β-diol-6-one (**8a**) | 1708[b] | −59[b] | 282.5 (58) |
| -7α-bromo-3α,5β-diol-6-one (**9a**) | ... | ... | *f* |
| -3α,5β-diol-6-one 3-acetate (**8b**) | 1712[b] | −23[b] | 282 (43) |
| -7α-bromo-3α,5β-diol-6-one 3-acetate (**9b**) | 1712 | +129 | 312 (105) |
| -3α,5β-diol-6-one 3-benzoate (**8c**) | 1712 | −100 | *d* |
| -7α-bromo-3α,5β-diol-6-one 3-benzoate (**9c**) | 1706 | +12 | 314 (95) |

[a] Conditions at which measurements were taken are given in ref 28. [b] Reference 14. [c] Reference 8. [d] $\lambda_{max}$ obscured by aromatic absorptions. [e] Reference 11. [f] Could not be prepared in pure state.

(15) The production of the 3β,5β-epoxy-6-one (**13**) from this reaction is interesting and an attempt was made to determine the mode of its formation. The PBP might be expected to break down into pyridinium bromide and bromine in tetrahydrofuran. The oxide formation almost certainly involves an attack by the C-5 hydroxyl on an electron deficient C-3; this deficiency may be brought about by the action of an acid such as the pyridinium ion or by hydrogen bromide which is generated from the pyridinium bromide or from the bromination reaction itself. When the diolone **8a** was heated under reflux with hydrobromic acid in tetrahydrofuran solution, only starting material was recovered. Treatment of **8a** with suspended pyridinium bromide in boiling tetrahydrofuran gave a mixture of at least four compounds (tlc) but none of the oxide (**13**). The agent responsible for the production of **13** is therefore still unknown.

(16) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 35.

(17) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 170.

TABLE II[a]

NMR DATA OF THE BROMO KETONES AND THE EPIMERIC 3-ACETOXY-5β-OL-6-ONES[b]

| 5β-Cholestane | C-7 hydrogen ($J$)[c] | C-3 hydrogen ($W_{1/2}$)[d] | Hydroxyl hydrogen | Acetate methyl | C-4α hydrogen ($J$) | C-19 | C-18 |
|---|---|---|---|---|---|---|---|
| -3β,5β-diol-6-one 3-acetate (**5b**) | ... | 294 (8) | 225.5 | 117.5 | ... | 42 | 40 |
| -3α,5β-diol-6-one 3-acetate (**8b**) | ... | 295 (18) | 229.5 | 116.3 | ... | 41.5 | 40 |
| -7α-bromo-5β-ol-6-one (**11b**) | 257.6 (4.2) | ... | 207.5 | ... | 163[e] | 43 | 41.7 |
| -7α-bromo-3β,5β-diol-6-one (**6a**) | 260.5 (3.0) | 233 (8) | *f* | ... | 176.5 (15)[g] | 46 | 42 |
| -7α-bromo-3β,5β-diol-6-one 3-acetate (**6b**) | 261 (2.5) | 295 (8) | 213.5 | 118.5 | 177 (15.5, 3)[h] | 46 | 42 |
| -7α-bromo-3β,5β-diol-6-one 3-benzoate (**6d**) | 260.3 (2.5) | 315 (8) | 218.5 | ... | 187.5 (16, 4)[h] | 49.5 | 42 |
| -7α-bromo-3β,5β-diol-6-one diacetate (**6c**) | 257 | 306.5 (7) | ... | 115, 123 | 192 (26.5, 17)[h] | 49.5 | 42 |
| -7α-bromo-3α,5β-diol-6-one 3-acetate (**9b**) | 260 (3.0) | 296 (22) | 220.5 | 117 | 167 (12.5, 12)[i] | 44 | 42 |
| -7α-bromo-3α,5β-diol-6-one 3-benzoate (**9c**) | 261.5 (3.0) | 314.5 (22) | 223.5 | ... | 176.5 (12, 12)[i] | 46 | 42 |

[a] Conditions at which measurements were taken are given in ref 28. [b] All chemical shifts are given in cycles per second (cps) downfield relative to tetramethylsilane used as an internal standard. [c] All C-7 hydrogens appeared as doublets except where no $J$ value is given, in which case a single peak was observed. [d] Shifts and half-band widths are approximations owing to broad signal. [e] Broad, low hump. [f] One hydroxyl hydrogen masked by C-3 and C-7 hydrogens each, as shown by integration of spectrum. [g] Doublet. [h] Doublet of doublets. [i] Doublet of doublets with center peaks superimposed.

The nmr spectra of the bromo ketones were obtained (Table II). Included with the bromo ketones are 3β-acetoxy-5-hydroxy-5β-cholestan-6-one (**5b**) and its C-3 epimer **8b**. The importance of the C-3 hydrogens to any conclusion regarding the conformations of the halo ketones may be seen by comparing conformation **6b′**, in which the hydrogen is equatorial, to extreme conformation **6b‴**, where the hydrogen is axial to the A ring. Axial hydrogens generally are less deshielded than equatorial hydrogens in isomeric alcohols[18a] and C-3 axial protons exhibit resonances whose half-band widths ($W_{1/2}$) are over twice as large as the $W_{1/2}$ for the corresponding equatorial hydrogens in epimeric compounds.[18b] Table II shows that the axial C-3 proton in the 3α-acetoxy compound **8b** occurs at 295 Hz which is almost identical with the position (294 Hz) found for the C-3 equatorial hydrogen in the 3β-acetoxy steroid (**5b**). The coincidental signals are not unexpected since the 5β (axial) hydroxy group deshields the 3β (axial) hydrogen in **8b**.[19] The half-band width for the C-3 hydrogens in these isomers indicate that the A ring probably exists in a normal chair conformation.

Inspection of the nmr data for the bromo ketones shows the C-3 hydrogens in the 3β-substituted compounds (**6a–d**) as broad signals with $W_{1/2} \simeq 8$ Hz. The positions of the individual peaks are a reflection of the nature of the substituents (OAc, OBz, OH) at carbons 3 and 5 and are in no way anomalous.[18a] The 3α-acyloxy bromo ketones **9b** and **9c** exhibit C-3 axial hydrogen absorptions at expected positions and have predictable half-band widths ($W_{1/2} \simeq 22$ Hz); the C-3 hydrogens in 5-hydroxy-7α-bromo-5β-cholestan-6-one (**11b**) are not deshielded enough to be shifted from within the methylene envelope of the steroid and cannot be detected. The equatorial C-7 hydrogens all (except in **6c**) appear as doublets with $J$ from 2.5 to 4.2 Hz, indicative of coupling with the C-8 axial proton. Of interest is the deshielding effect of the axial bromine atom at C-7 upon the 4α (axial) hydrogen in these compounds. In the 3β-substituted compounds **6b–d** this axial hydrogen appears as a doublet of doublets due to geminal coupling with the C-4 equatorial proton, with further splitting due to additional coupling with the equatorial proton at C-3.[20] In the 7α-bromo-3β,5β-diol-6-one (**6a**) the C-4 axial proton appears as a doublet with unresolved splitting of the legs. The reason for the large coupling constants in the diacetoxy bromo ketone **6c** is not clear although it may be due to distortion caused by mutual repulsion of the acetoxy groups. The C-4 axial protons of the 3α-acyloxy bromo ketones **9b** and **c** give rise to three peaks (doublet of doublets with center peaks superimposed) with $J = 12$ Hz, indicative of geminal splitting of the proton and further coupling with the C-3 axial hydrogen atom.[20] In the case of the bromo ketone **11b**, the axial C-4 hydrogen signal appears as a broad low hump centered at about 163 Hz. This appearance is not surprising since the lack of a substituent at C-3 would give rise to further couplings with the C-4 axial hydrogen, resulting in a smeared absorption. The deshielding of hydrogen by the halogen in α-halo ketones had been reported previously,[21a] notably in the case of 3β-acetoxy-7α-bromo-5α-cholestan-6-one, where the 5α hydrogen appears as a pair of doublets ($J = 12$ and 3.7 Hz) centered at $\delta$ 3.28.[21b]

The nmr data found for α-bromo ketones **6a–d** and **9b** and **c** and the hydroxy ketones **5b** and **8b** indicate that these compounds exist mainly in ground-state conformations represented by **6b′** and to no significant extent as **6b″** or **6b‴**.

The reactions of some of the α-bromo ketones with sodium bicarbonate–DMSO were investigated. When heated at 100–120° for 19.5 hr, the bromo ketone **9b** gave 3α-acetoxy-5,7β-epoxy-5β-cholestan-6-one (**10b**) in 24% yield. Variations in time, temperature, and the quantity of sodium bicarbonate did not increase the yield of **10b**. Under similar conditions **11b** gave 5,7β-epoxy-5β-cholestan-6-one (**12**) in 21% yield. Saponification of the 3β- and 3α-acetoxy oxetanones (**7b** and **10b**) gave the free hydroxy oxetanones **7a** and **10a**, respectively. Benzoylation of each of the hydroxy oxetanones gave the corresponding benzoates (**7c** and **10c**).

In order to obtain a quantitative measure of the reaction in terms of rate and product composition data, a system was sought which would give oxetanone formation and yet would not cause saponification of ester

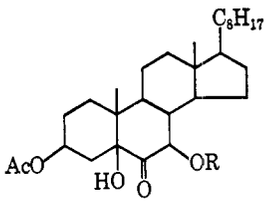
(18) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 77; (b) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).

(19) Examples of deshielding of axial protons by axial hydroxy groups are recorded; see ref 18a, p 186.

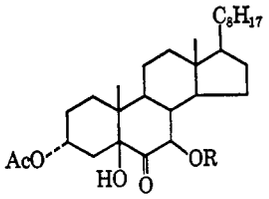
(20) The C-4 axial (α) proton forms the M portion of an AMX system in which X is the C-3 hydrogen and A is the C-4 equatorial (β) hydrogen (which is lost in the methylene envelope).

(21) (a) See ref 18a, p 75; (b) private communication from Professor Alex Nickon, Johns Hopkins University, Dec 1967.

groups at C-3. Treatment at room temperature of a solution of the 3β-substituted bromo ketones (**6a, b**) in DMSO with a standard methanolic potassium hydroxide solution gave *rapid* formation of the hydroxy oxetanone **7a**.[22] The reaction was, however, accompanied by acetate saponification in the case of **6b**; acetylation of the crude reaction products gave the 3β-acetoxy oxetanone (**7b**) as the major product (>70%). In contrast, the 3α-acetoxy oxetanone **10b** was obtained in extremely poor yield (~6%) [along with a low yield of the debrominated hydroxy ketone (**8b**) and a larger amount of an oil whose ir spectrum indicated that it consisted largely of the diacetoxy hydroxy ketone **15b**] when the 7α-bromo ketone **9b** was subjected to the same reaction procedures and the 7α-bromo-5β-ol-6-one **11b** gave a 34% yield of the oxetanone **12**.




**14a**, R = H
**b**, R = Ac

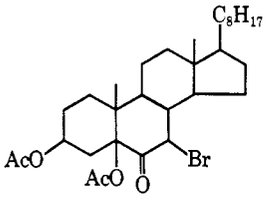



**15a**, R = H
**b**, R = Ac

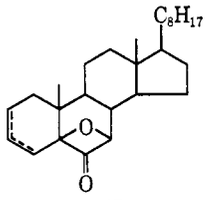
A third system that was employed involved the addition of a calculated amount of a standard aqueous solution of potassium bicarbonate to a DMSO solution of the bromo ketone at ~75°. This gave oxetanones without removal of acyl groups. Yields were reasonably good (50–69%) from the 3β-substituted bromo ketones (**6a, b, d**), low (22%) from the 3-desoxy compound (**11b**), and minute (4–7%) from the 3α-acyloxy bromo ketones (**9b, c**). Attempts at ascertaining relevant rate data in this potassium bicarbonate–DMSO medium were not successful since the potassium bicarbonate started to precipitate immediately after the addition of its aqueous solution to the bromo ketone–DMSO mixture.

The other products produced from the bromo ketone–potassium bicarbonate–DMSO reactions have been investigated in order to determine reaction paths followed as alternatives to oxetanone formation. In addition to the oxetanone (**7b**) obtained from the 3β-acetoxy bromo ketone **6b**, a 6% yield of a compound identified as 3β-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**14a**) was isolated. This material is representative of hydroxy ketones sometimes obtained from treatment of α-halo ketones with base.[8,9b] The 3β-benzoyloxy bromo ketone **6d** gave the oxetanone **7c** (69%) and small amounts of unidentified impure crystalline products. The dihydroxy bromo ketone **6a** gave (after acetylation) a small amount (~5%) of the bromo ketone **6b**, corresponding to acetylated unreacted starting material, and a low yield of another compound best represented as 3β,7β-diacetoxy-5-hydroxy-5β-cholestan-6-one (**14b**). Complete characterization of this compound was impossible owing to an insufficient quantity of material, but the ir and analytical data appear to fit the proposed structure.

The reaction of the diacetoxy bromo ketone **6c** with the DMSO–aqueous potassium bicarbonate is of special interest since it had been noted before that this compound did not give oxetanone when treated with sodium bicarbonate in DMSO. In this case, ir analysis of the crude product again demonstrated the lack of oxetanone formation, while chromatography permitted isolation of starting material (21%), the debrominated diacetoxy ketone **5c** (5%),[23] and a bromo ketone which was apparently the C-7 epimer (**16**) of the starting material (**6c**). The ir and uv evidence fit the proposed structure well, as did the elemental analysis for bromine, but the carbon–hydrogen analysis did not correspond to the theoretical values.[24]




**16**




**17**

The by-products isolated from the 7α-bromo-5β-ol-6-one (**11b**) were complex mixtures which could not be separated and identified. The 3α-acetoxy-7α-bromo ketone **9b** gave ~6% of the debrominated hydroxy ketone **8b** and ~12% of 3α-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**15a**). The latter compound was identified on the basis of ir, uv, and analytical data. The only identifiable product (other than the 3α-benzoyloxy oxetanone **10c**) obtained from the 3α-benzoyloxy-7α-bromo ketone (**9c**) was the debrominated hydroxy ketone **8c** (13%).

The inability to obtain rate data for the conversions of the bromo ketones into oxetanones makes speculation concerning the mechanism of the reactions difficult. The yields of oxetanones from 3β-substituted bromo ketones compared with the 3-desoxy and 3α-substituted bromo ketones, however, may be a reflection of the Curtin–Hammett principle. If in **6b**, for example, conformer **6b′** is in rapid equilibrium with **6b″** and **6b‴**, the rate of formation of oxetanone will not depend upon the ground-state population of **6b‴** (which must be extremely small, according to the nmr data previously given) but only upon the differences in the energies of the transition states leading to products from **6b‴** and other conformations. Presumably a 3β substituent serves to raise the energy of pathways competing with oxetanone formation while a 3α substituent would exert an opposite effect, perhaps because of the acyl–$C_6$ oxygen interaction in a conformer such as **6b‴**.

(22) When a solution of **6a** in DMSO was titrated with a standard methanolic potassium hydroxide–DMSO solution in the presence of thymol blue indicator, no indicator color change was noted until slightly more than 1 equiv of base had been added, indicating the rapidity with which the bromo ketone reacts. (A blank run gave color immediately upon addition of 1 drop of base.)

(23) E. W. Warnhoff and D. R. Marshall [*J. Org. Chem.*, **32**, 2000 (1967)] have shown conclusively that α-bromo ketones may undergo reductive debromination with α-disubstituted pyridines when structural features of the bromo ketone prevent or retard displacement or dehydrohalogenation reactions. It appears that a similar path is followed by some of the bromo ketones reported here. While the isolation of debrominated ketones may be ascribed to their presence as impurities from the bromination reactions (*e.g.*, **5b** → **6b**), no unreacted hydroxy ketones could be found in the bromo ketones, each of which was examined by ir, nmr, uv, tlc, and column chromatography. We therefore consider those cases in which the parent hydroxy ketones have been isolated from reactions of the α-bromo ketones with potassium bicarbonate–DMSO as true reaction products.

(24) This may have been due to decomposition during drying of the sample for analysis. See Experimental Section.

TABLE III[a]

INFRARED AND ULTRAVIOLET DATA OF THE OXETANONES

| Oxetanone | $\bar{\nu}_{max}$, cm$^{-1}$ OH | C-6 carbonyl | Ester carbonyl | Oxetanone ring[b] | $\lambda_{max}$, m$\mu$ ($\epsilon$) |
|---|---|---|---|---|---|
| -5,7β-epoxy-6-one (**12**) | ... | 1808 | ... | 907, 896 | 286 (27) |
| -5,7β-epoxy-3β-ol-6-one (**7a**) | 3636,[c] 3460[d] | 1808 | ... | 900 | 285 (42) |
| -5,7β-epoxy-3β-ol-6-one acetate (**7b**) | ... | 1815 | 1746 | 903 | 284.5 (26) |
| -5,7β-epoxy-3β-ol-6-one benzoate (**7c**) | ... | 1812 | 1727 | 905 | *e* |
| -5,7β-epoxy-3β-ol-6-one tosylate (**7d**) | ... | 1806 | ... | 903 | *e* |
| -5,7β-epoxy-3α-ol-6-one (**10a**) | 3546 | 1802 | ... | 904, 894 | 280 (42) |
| -5,7β-epoxy-3α-ol-6-one acetate (**10b**) | ... | 1813 | 1739 | 908, 897 | 285.5 (31) |
| -5,7β-epoxy-3α-ol-6-one benzoate (**10c**) | ... | 1815 | 1718 | 912, 903 | *e* |

[a] Conditions at which measurements were taken are given in ref 28. [b] All absorptions were of medium to strong intensity. [c] Weak absorption. [d] Broad absorption. [e] $\lambda_{max}$ obscured by aromatic absorptions.

TABLE IV[a]

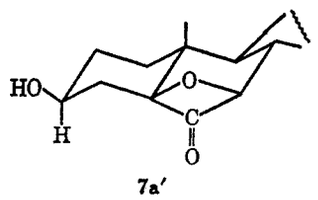
NMR DATA OF THE OXETANONES[b]

| Oxetanone | C-7 hydrogen ($J$)[c] | C-3 hydrogen ($W_{1/2}$)[d] | Hydroxyl hydrogen | Acetate methyl | C-19 | C-18 |
|---|---|---|---|---|---|---|
| -5,7β-epoxy-6-one (**12**) | 277 (1.6) | ... | ... | ... | 61.5 | 44.5 |
| -5,7β-epoxy-3β-ol-6-one (**7a**) | 281.3 (1.5) | 227 (20) | 187.5 | ... | 63 | 44.5 |
| -5,7β-epoxy-3β-ol-6-one acetate (**7b**) | 281 (1.0) | 285 (20) | ... | 117 | 62.5 | 43.5 |
| -5,7β-epoxy-3β-ol-6-one benzoate (**7c**) | 283.5 | 305 (23) | ... | ... | 66 | 44 |
| -5,7β-epoxy-3β-ol-6-one tosylate (**7d**) | 280 | 268 (23) | ... | 147[e] | 60 | 42.1 |
| -5,7β-epoxy-3α-ol-6-one (**10a**) | 282.7 (1.4) | 237.5 (8) | 162.5 | ... | 61.5 | 44.5 |
| -5,7β-epoxy-3α-ol-6-one acetate (**10b**) | 277.6 (1.5) | 295 (7) | ... | 124 | 62.3 | 44 |
| -5,7β-epoxy-3α-ol-6-one benzoate (**10c**) | 279.8 (1.5) | 316.5 (8) | ... | ... | 64 | 44 |

[a] Conditions at which measurements were taken are given in ref 28. [b] All chemical shifts are given in cycles per second (cps) downfield relative to tetramethylsilane which was the internal standard. [c] All C-7 hydrogens appeared as doublets except where no $J$ value is given, in which case a single peak was observed. [d] Shifts and half-band widths are approximations owing to broad signal. [e] Aromatic methyl.

Although the yields of the 3α-substituted and 3-desoxy oxetanones from the corresponding bromo ketones are low,[25] an efficient preparation of these compounds was found in the epimerization technique of Chang and Blickenstaff.[26a] This method involves the displacement, with inversion, of a tosyloxy group from a cyclohexane ring by dimethylformamide yielding a formate ester which may be converted into the free alcohol by saponification. The procedure has recently been used with success on 5,6α-epoxy-5α-cholestan-3β-ol tosylate;[26b] the oxide ring remained intact during the displacement reaction. When 3β-tosyloxy-5,7β-epoxy-5β-cholestan-6-one (**7d**) was heated under reflux in dimethylformamide containing suspended lithium carbonate,[26b] a mixture of the 3α-formate ester **10d** and an unsaturated oxetanone (**17**) was obtained. The mixture was saponified and then acetylated, giving the 3α-acetoxy oxetanone **10b** (64%) and **17** (16%) which were easily separated on alumina. The unsaturated oxetanone **17** may have been the 2- or 3-ene or a mixture of both. Catalytic hydrogenation of **17** gave the desired saturated oxetanone **12** (78%).

The pertinent spectral data of the oxetanones are given in Tables III and IV. All of the oxetanones have ir carbonyl absorptions in the expected range (1802–1815 cm$^{-1}$)[3b,4,7b,c] and in addition show strong ring-absorption at *ca.* 900 cm$^{-1}$.[12] The latter peak appears as a single broad band in the 3β-substituted oxetanones while the absorption is split into two bands in the 3α epimers and in **12** (Table III). The uv spectra are similar to those of other four-membered ring ketones[27] and are in agreement with the only known recorded value for a 3-oxetanone.[3a] Inspection of the nmr data (Table IV) and hydroxyl absorption in the ir (Table III) permits a detailed analysis of the conformation of the A/B ring system in the oxetanones. In most of the compounds, the C-7 hydrogen appears at *ca.* 280 Hz as a doublet due to coupling with the C-8 proton. The position of the C-3 hydrogen varies as expected according to the type of substituent at C-3;[18a] of significance is the half-band width of the signals of these hydrogens. For the 3β-substituted oxetanones **7a–d**, the half-band width ($W_{1/2} \sim 20$ Hz) clearly indicates an axial orientation of hydrogen whereas the half-band width ($W_{1/2} \sim 8$ Hz) for the epimeric oxetanones (**10a–c**) shows the C-3 hydrogens in these compounds to be equatorial on the A ring. Since no configurational change at C-3 is possible during oxetanone formation from the bromo ketones, the reversal in environment of the C-3 hydrogen (*cf.* Table II) with respect to the ring in the oxetanones as compared with the bromohydroxy ketones must be accounted for by a conformational change; the structure of typical oxetanones may therefore be represented by **7a′** and **10a′**. Confirmation




**7a′** **10a′**

(25) The reason for this is still not clear. Any mechanism in operation in bromo ketones does not involve a simple heterolysis of the C-7 to Br bond as the first step in oxetanone formation since bromo ketone **6b** is unreactive to hot DMSO in the absence of base, as noted earlier. Also, **6b** underwent no change when heated at 120° with silver nitrate in DMSO containing a small amount of pyridine or when treated similarly without the addition of silver nitrate.

(26) (a) F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.*, **80**, 2906 (1958); (b) G. A. Selter and K. D. McMichael, *J. Org. Chem.*, **32**, 2546 (1967).

(27) Reference 16, p 29.

comes from the ir spectra (Table III) which show a sharp peak for the intramolecularly bonded C-3 hydroxyl (3546 $cm^{-1}$) in **10a** while the corresponding hydroxyl absorption in **7a** indicates significant intermolecular association.

The ORD curves of the oxetanones all exhibited simple negative Cotton effects with slight inflections on the peaks at lower wavelengths (*ca.* 250 mμ). The molecular amplitudes varied from 5300 to 12,800° but, with the exception of the benzoates **7c** and **10c**, little differences in the amplitudes of the epimeric pairs were noted (see Experimental Section).

In summary, ring-B oxetanones may be easily prepared from the 3β-substituted 5β-hydroxy-6-oxo-7α-bromocholestanes. The 3β oxetanones are readily convertible into their C-3 epimers and to the 3-desoxy compound by the inversion–elimination reaction with dimethylformamide. While the mechanism of oxetanone formation from these α-bromo-α′-hydroxy ketones has not been completely identified, the importance of the substituent at C-3 and the action of a weak base have been shown. Further studies on the mechanism of this conversion and on the chemistry of oxetanones will be reported in the future.

## Experimental Section[28,29]

**3β-Acetoxy-5-hydroxy-5β-cholestan-6-one (5b).**—A modification of a given preparation[8] was employed. A suspension of 75 g (140 mmol) of 3β-acetoxy-5-bromo-5α-cholestan-6-one in 650 ml of 1.33 *N* methanolic potassium hydroxide solution[30] was magnetically stirred at room temperature for *ca.* 18 hr. The orange solution (containing precipitated inorganic salts) that resulted was diluted with 1.5 l. of ether and washed twice with saturated salt solutions. The ether layer was dried, filtered, and evaporated, leaving a light brown oil which was covered with 375 ml of acetic anhydride and heated on the hot plate at 110–120° for 4 hr. After remaining at room temperature overnight, crushed ice and 40 ml of 2 *N* hydrochloric acid were added. After standing overnight, the precipitate was collected, washed with water, and recrystallized from methanol, yielding 48 g (72%) of **5b**, mp 138–142°. A further recrystallization from acetone–methanol gave large white plates with mp 142–143° (lit.[8] mp 142.5–144.5°).

**3α-Benzoyloxy-5-hydroxy-5β-cholestan-6-one (8c).**—A solution of 254 mg (0.607 mmol) of the dihydroxy ketone **8a** in 4 ml of pyridine containing 0.75 ml of benzoyl chloride was allowed to remain at room temperature for 23 hr. The standard work-up for benzoylations[8] gave material that crystallized from acetone–methanol, yielding 245 mg (77%) of **8c** as needles: mp 176–178°; $[\alpha]D$ −19° (*c* 1.014); ir, 3484 (w), 1727 (s), 1712 (s, sh) $cm^{-1}$; ir ($CHCl_3$), 3497 (w), 1709 (s) $cm^{-1}$. Recrystallization from ether did not alter the melting point.

*Anal.* Calcd for $C_{34}H_{50}O_4$ (522.74): C, 78.12; H, 9.64. Found: C, 78.12; H, 9.71.

**Preparation of Bromo Ketones. General Procedure.**—A solution of the appropriate ketone in glacial acetic acid was heated to 70–80°, when slightly greater than 1 equiv of pyridinium bromide perbromide was added to the magnetically stirred solution. After 5–15 min the product was precipitated with water, collected, and recrystallized, except for **11b** and **9c**, which were purified by chromatography on alumina. (No homogeneous bromo ketone was obtained from hydroxy ketone **8a**; ketone **5a** was dissolved in tetrahydrofuran prior to addition to the acetic acid.) The following bromo ketones were obtained; % yield, melting points, solvent used for recrystallization, specific rotations, and analytical data were determined. Additional physical data are given in Tables I and II.

**3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a)** was prepared in 63% yield: mp 148.5–150° from aqueous acetone; $[\alpha]D$ +11°.

*Anal.* Calcd for $C_{27}H_{45}BrO_3$ (497.55): C, 65.17; H, 9.11; Br, 16.06. Found: C, 65.35; H, 9.14; Br, 15.87.

**3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b)** was prepared in 80% yield: mp 137–139° from methanol; $[\alpha]D$ +9°.

*Anal.* Calcd for $C_{29}H_{47}BrO_4$ (539.59): C, 64.54; H, 8.77; Br, 14.81. Found: C, 64.31; H, 8.66; Br, 14.99.

**3β,5-Diacetoxy-7α-bromo-5β-cholestan-6-one (6c)** was prepared in 84% yield: mp 151–153° from aqueous acetone; $[\alpha]D$ +22°.

*Anal.* Calcd for $C_{31}H_{49}BrO_5$ (581.62): C, 64.01; H, 8.40; Br, 13.74. Found: C, 64.18; H, 8.51; Br, 13.58.

**3β-Benzoyloxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6d)** was prepared in 82% yield: mp 185.5–187° from acetone; $[\alpha]D$ +39°.

*Anal.* Calcd for $C_{34}H_{49}BrO_4$ (601.65): C, 67.87; H, 8.21; Br, 13.28. Found: C, 67.70; H, 8.17; Br, 13.41.

**5-Hydroxy-7α-bromo-5β-cholestan-6-one (11b)** was prepared in 83% yield as an oil, $[\alpha]D$ ±0°.

*Anal.* Calcd for $C_{27}H_{45}BrO_2$ (481.55): C, 67.34; H, 9.42; Br, 16.60. Found: C, 67.55; H, 9.45; Br, 16.55.

**3α-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (9b)** was prepared in 88% yield: mp 144–146° from acetone–methanol; $[\alpha]D$ +24°.

*Anal.* Calcd for $C_{29}H_{47}BrO_4$ (539.59): C, 64.54; H, 8.77; Br, 14.81. Found: C, 64.69; H, 8.75; Br, 14.92.

**3α-Benzoyloxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (9c)** was prepared in 58% yield: mp 130–131° from chloroform–ethanol; $[\alpha]D$ +2°.

*Anal.* Calcd for $C_{34}H_{49}BrO_4$ (601.65): C, 67.87; H, 8.21; Br, 13.28. Found: C, 68.07; H, 8.37; Br, 13.50.

A 16% yield of 3β,5-epoxy-5β-cholestan-6-one (**13**)[13] was the only identifiable product isolated from the bromination of **9a** conducted in tetrahydrofuran.

**Debromination of 3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b).**—A mixture of 200 mg (0.371 mmol) of **6b** and 1.0 g of zinc dust in 7 ml of glacial acetic acid was heated under reflux for 2 hr. The zinc was removed by filtration and the filtrate was diluted with water. The resulting precipitate (162 mg, mp 140–142°) was collected and recrystallized from methanol to give 134 mg (78%) of **5b** as white plates with mp 142.5–144.5°. No depression in melting point was noted upon admixture with authentic **5b**.[8]

**Interrelationships of the 3β-Substituted α-Bromo Ketones. A. Conversion of 3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a) into Its 3-Acetate (6b).**—A mixture of 52 mg (0.11 mmol) of **6a** and 1 ml of acetic anhydride was heated on the steam bath for 1.33 hr. The hot solution was treated with crushed ice and the precipitated material was recrystallized from methanol, yielding 22 mg (39%) of **6b**, mp 136–138°. Recrystallization from 95% ethanol sharpened the melting point to 137.5–138.5°. The mixture melting point with **6b** prepared from **5b** gave no depression.

**B. Conversion of 3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b) into Its Diacetate (6c).**—A solution of 150 mg (0.278 mmol) of **6b** and 40 mg of *p*-toluenesulfonic acid monohydrate in 2 ml of glacial acetic acid and 2 ml of acetic anhydride was allowed to remain at room temperature for 20.5 hr. The

(28) Melting points were taken in open capillaries on a Mel-Temp apparatus and are uncorrected. Optical rotations were determined in *ca.* 1% chloroform solutions and are accurate to ±2°. Infrared spectra were taken on a Perkin-Elmer Model 21 spectrometer in 5–10% carbon tetrachloride solutions using a sodium chloride prism and 0.1-mm cells; s, m, and w indicate relative intensities of absorption bands, and sh denotes a shoulder. Ultraviolet spectra were determined with a Bausch and Lomb Spectronic 505 spectrophotometer in absolute ethanol solutions. Nmr spectra were determined in carbon tetrachloride solutions (TMS internal standard) on a Varian Model A-60A spectrometer by Sadtler Research Laboratories, Inc., Philadelphia, Pa. ORD measurements were made at 27° on dioxane solutions (*c* ~0.1) using a Cary Model 60 spectropolarimeter. Microanalyses were obtained by Micro-Analysis, Inc., Wilmington, Del. Preliminary examinations of crude reaction products and of column chromatographic fractions were carried out on a Beckman Microspec infrared spectrometer and by tlc on Gelman Type SG sheets using mixtures (generally 1:1) of benzene and cyclohexane as the irrigant, followed by spraying with a 100% (w/v) *p*-toluenesulfonic acid–ethanol solution.[29] "Drying" of solutions was accomplished with anhydrous sodium sulfate. Merck acid-washed alumina was employed for all column separations. Petroleum ether refers to 30–60° solvent. Dimethyl sulfoxide was Baker "analyzed" reagent and was used as purchased since preliminary experiments indicated that redistilled material had no effect upon the reactions.

(29) V. Vlasinich and J. B. Jones, *Steroids*, **3**, 707 (1964).

(30) The use of methanolic potassium hydroxide is favored over the ethanolic potassium hydroxide which was previously used[8] since the latter solution turns yellow soon after its preparation, whereas the methanolic solution remains colorless indefinitely.

reaction flask was then cooled in an ice bath and treated with water. The precipitate was recrystallized from aqueous acetone to give 142 mg (87%) of **6c** as white needles with mp 151.5–153.5°. A further recrystallization from the same solvents gave 125 mg of needles with mp 153–154.5°; no depression occurred upon admixture with **6c** prepared from **5c**.

**C. Conversion of 3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a) into Its Diacetate (6c).**—A solution of 250 mg (0.502 mmol) of **6a** and 51 mg of *p*-toluenesulfonic acid monohydrate in 2.8 ml of glacial acetic acid and 2.8 ml of acetic anhydride was allowed to remain at room temperature for 69 hr. Work-up as in B gave a precipitate which was recrystallized from acetone–methanol, yielding 246 mg (84%) of **6c** as white needles with mp 152.5–154.5°, alone or upon admixture with **6c** prepared from **5c**.

**Reaction of 3α,5-Dihydroxy-5β-cholestan-6-one (8a) with Hydrobromic Acid.**—A solution of 263 mg (0.629 mmol) of **8a** in 15 ml of tetrahydrofuran (redistilled from lithium aluminum hydride) containing 0.50 ml of 48% hydrobromic acid was heated under reflux for 1.5 hr. The cooled solution was diluted with water and the precipitated product was collected, washed with water, and dissolved in chloroform. The dried solution was evaporated, giving material shown to be **8a** by tlc, ir spectroscopy, and recrystallization from acetone–water (203 mg with mp 121–123.5°).

**Reaction of 3α,5-Dihydroxy-5β-cholestan-6-one (8a) with Pyridinium Bromide.**—A solution of 315 mg (0.753 mmol) of **8a** in 15 ml of tetrahydrofuran containing 296 mg (1.85 mmol) of suspended pyridinium bromide was heated under reflux for 3.3 hr. The mixture was diluted with water and extracted twice with chloroform. The extracts were washed with water and dried. The resulting oil had an ir spectrum essentially identical with that of **8a** but tlc of the crystallized product (mp 88–115°) had four spots: $R_f$ 0.52 (weak), 0.43 (weak), 0.28 (intense), and 0.13 (intense). On the same sheet, 3β,5-epoxy-5β-cholestan-6-one (**13**) had $R_f$ 0.75 whereas **8a** had $R_f$ 0.06. Since the absence of oxide **13** was shown by the ir and tlc examinations, no attempt was made to isolate and characterize the components of the mixture.

**3β-Acetoxy-5,7β-epoxy-5β-cholestan-6-one (7b).**—To a solution of 32.0 g (59.3 mmol) of **6b** in 1 l. of dimethyl sulfoxide was added 32.0 g of anhydrous sodium bicarbonate, The mixture was stirred mechanically at 100 ± 3° for 6 hr (tlc indicated complete disappearance of starting material within 2 hr). After cooling to room temperture the mixture was diluted with water and extracted with three 700-ml portions of ether. The combined extracts were washed with two 800-ml portions of water and then dried. The orange oil isolated upon evaporation of the ether was crystallized from aqueous ethanol and then recrystallized twice (aqueous ethanol, then methanol) to give 8.55 g of **7b** as off-white needles, mp 100–102°. The solids obtained from the three mother liquors were combined and chromatographed on 350 g of alumina. Elution with benzene gave an additional 13.0 g of **7b**. Recrystallization from aqueous ethanol gave 10.61 g as white plates with mp 100.5–102°. A further crop (0.462 g, mp 92–96°) was obtained from the mother liquor to give a total yield of 19.62 g (72%) of recrystallized **7b**.

Recrystallization of a sample from methanol gave mp 101–102°; $[\alpha]_D$ −49° (*c* 1.315); ORD, $[\phi]_{310}$ −4500° (trough), $[\phi]_{290}$ 0°, $[\phi]_{270}$ +3300° (peak).

*Anal.* Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.93; H, 10.11. Found: C, 75.92; H, 9.99.

**3α-Acetoxy-5,7β-epoxy-5β-cholestan-6-one (10b).**—A solution of 5.077 g (9.41 mmol) of bromo ketone **9b** in 170 ml of DMSO containing 5.08 g of suspended sodium bicarbonate was stirred mechanically at 120 ± 5° under a nitrogen atmosphere. After 1 hr the mixture had turned a dark brown with much frothing; the temperature was lowered to 100° and the nitrogen stream was removed. After stirring a further 19.5 hr, the mixture was worked up as given in the previous procedure. Chromatography on 100 g of alumina and elution with benzene gave 1.17 g of a white solid. Recrystallization from acetone–methanol afforded 1.056 g (24.5%) of the 3α-acetoxy oxetanone (**10b**) as small white needles: mp 145–147°; $[\alpha]_D$ −28° (*c* 0.96); ORD, $[\phi]_{310}$ −4100° (trough), $[\phi]_{291}$ 0°, $[\phi]_{267}$ +3750° (peak).

*Anal.* Calcd for $C_{29}H_{46}O_4$ (458.66): C, 75.93; H, 10.11. Found: C, 75.96; H, 9.97.

**5,7β-Epoxy-5β-cholestan-6-one (12).**—A solution of 570 mg (1.18 mmol) of bromo ketone **11b** in 25 ml of DMSO containing 2.0 g of sodium bicarbonate was mechanically stirred at 105 ± 3° for 6.5 hr. After remaining at room temperature overnight, the usual work-up was employed. The oil (455 mg) obtained was chromatographed on 10 g of alumina. The semicrystalline material (106 mg) eluted with 14% benzene–petroleum ether (bp 30–60°) mixtures was crystallized from acetone-methanol, giving 39 mg of the oxetanone **12**, mp 92–94°. Concentration of the mother liquor gave two additional crops of **12**: 51 mg, mp 93–94°, and 9 mg, mp 90.5–93° (total yield, 21%). Recrystallization gave the oxetanone as white needles: mp 93–94°; $[\alpha]_D$ −61° (*c* 1.077); ORD, $[\phi]_{310}$ −3650° (trough), $[\phi]_{288}$ 0°, $[\phi]_{270}$ +1650° (peak).

*Anal.* Calcd for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.84; H, 10.89.

Further elution of the column with benzene–petroleum ether mixtures gave mainly starting material (ir spectroscopy).

**3β-Hydroxy-5,7β-epoxy-5β-cholestan-6-one (7a).**—A solution of 334 mg (0.729 mmol) of the 3β-acetoxy oxetanone **7b** in 15 ml of 0.13 *N* methanolic potassium hydroxide containing 1 ml of water was boiled on the steam bath for 40 min. The clear, colorless solution was cooled and diluted with 1 ml of 2 *N* hydrochloric acid and water. The precipitate that formed was collected and recrystallized from aqueous ethanol to give 266 mg (88%) of **7a** as small white needles with mp 119–120°. Another recrystallization gave mp 119.5–120.5°; $[\alpha]_D$ −58° (*c* 1.112); ORD, $[\phi]_{310}$ −4500° (trough), $[\phi]_{288}$ 0°, $[\phi]_{270}$ +2500° (peak).

*Anal.* Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.64. Found: C, 77.81; H, 10.63.

**3α-Hydroxy-5,7β-epoxy-5β-cholestan-6-one (10a).**—A suspension of 424 mg (0.925 mmol) of the 3α-acetoxy oxetanone **10b** in 3 ml of 1.33 *N* methanolic potassium hydroxide and 7 ml of methanol was boiled gently on the steam bath. The steroid dissolved completely within 5 min and the volume of the solution was reduced to about 5 ml over a total reaction time of 30 min. The solution was cooled, acidified with 2 ml of 2 *N* hydrochloric acid, and diluted with water. The amorphous product was extracted twice with chloroform and the combined extracts were washed once with water, dried, and evaporated yielding 383 mg (99%) of **10a** as a colorless oil that could not be crystallized but which was shown to be homogeneous by column chromatography; the 3α-hydroxy oxetanone (**10a**) had $[\alpha]_D$ −63° (*c* 1.09); ORD, $[\phi]_{307}$ −4150° (trough), $[\phi]_{285}$ 0°, $[\phi]_{265}$ +2700° (peak).

*Anal.* Calcd for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.64. Found: C, 77.54; H, 10.55.

**3β-Benzoyloxy-5,7β-epoxy-5β-cholestan-6-one (7c).**—A solution of 400 mg (0.960 mmol) of the 3β-hydroxy oxetanone (**7a**) and 1 ml of benzoyl chloride in 6 ml of pyridine was allowed to remain at room temperature for 22 hr. The usual work-up of benzoylations[8] yielded a yellow oil that crystallized from acetone–methanol, giving 333 mg of **7c** as needles with mp 146.5–148°. Recrystallization of the solid obtained from the mother liquor from acetone–methanol gave an additional 79 mg of **7c** as needles, mp 146–147.5° (total yield, 82%). A sample recrystallized from the same solvents gave long white needles: mp 147–148°; $[\alpha]_D$ −33° (*c* 1.013); ORD, $[\phi]_{310}$ −4100° (trough), $[\phi]_{292}$ 0°, $[\phi]_{266}$ +4300° (peak).

*Anal.* Calcd for $C_{34}H_{48}O_4$ (520.72): C, 78.42; H, 9.29. Found: C, 78.26; H, 9.32.

**3α-Benzoyloxy-5,7β-epoxy-5β-cholestan-6-one (10c).**—A solution of 64 mg (0.15 mmol) of the 3α-hydroxy oxetanone (**10a**) and 0.25 ml of benzoyl chloride in 2 ml of pyridine was allowed to remain at room temperature for 21 hr. The usual work-up,[8] followed by crystallization of the product from acetone–methanol, yielded 60.5 mg (76%) of **10C**: mp 147.5–148.5°; $[\alpha]_D$ −73° (*c* 0.908); ORD, $[\phi]_{310}$ −6800° (trough), $[\phi]_{288}$ 0°, $[\phi]_{265}$ +6000° (peak). Recrystallization from acetone–methanol raised the melting point to 148–149.5°.

*Anal.* Calcd for $C_{34}H_{48}O_4$ (520.72): C, 78.42; H, 9.29. Found: C, 78.61; H, 9.35.

**Reactions of Bromo Ketones with Methanolic Potassium Hydroxide in Dimethyl Sulfoxide (DMSO).**—The work-up used in each case was as follows: after the indicated heating period the reaction vessel was cooled under the tap and its contents were then poured onto crushed ice contained in a separatory funnel. Sodium chloride and water were added and the mixture was extracted twice with ether. The combined extracts were washed once with water, dried, and evaporated.

**A. 3β,5-Dihydroxy-7α-bromo-5β-cholestan-6-one (6a).**—A suspension of 1.029 g (2.067 mmol) of **6a** in 30 ml of DMSO was stirred magnetically at room temperature as 2.65 ml of 1.126 *N* methanolic potassium hydroxide solution was added in one por-

tion. The steroid dissolved rapidly and the resulting yellow solution was worked up after 9 min. The oil thus obtained was acetylated with 5 ml of acetic anhydride in 5 ml of pyridine for 18.5 hr at room temperature. Crushed ice and 5 ml of concentrated hydrochloric acid were added and the precipitated product was collected, washed with water, and taken up in chloroform. The dried solution was evaporated and the residue was chromatographed on 30 g of alumina. Elution with 80% benzene–petroleum ether gave 822 mg of crystalline material which was recrystallized from aqueous ethanol, yielding 682 mg (72%) of the 3β-acetoxy oxetanone **7b** as white needles with mp 100–101.5°. Dilution of the mother liquor with water gave a further 67 mg of less pure **7b**, mp 92–97°. Three fractions totaling 49 mg of oil were eluted from the column with 20% ether–benzene mixtures. Infrared analysis indicated that these oils were complex mixtures of oxetanone, unsaturated ketones, and other compounds; the oils were not investigated further.

**B. 3β-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (6b).**—A suspension of 1.023 g (1.899 mmol) of **6b** in 30 ml of DMSO was stirred magnetically at room temperature as 2.50 ml of 1.126 *N* methanolic potassium hydroxide was added in one portion. After 5 min the deep yellow solution was worked up; tlc indicated that the reaction oil consisted largely of the 3β-hydroxy oxetanone **7a**. Acetylation of this product was accomplished as in part A. Chromatography on 30 g of alumina and elution with 80% benzene–petroleum ether yielded 727 mg of oil which, when crystallized from aqueous ethanol, gave 640 mg (73.5%) of the 3β-acetoxy oxetanone (**7b**) as needles, mp 100.5–102°. Dilution of the mother liquor with water produced an additional 34 mg of **7b**, mp 95–99°. Further elution of the column with 20% ether–benzene mixtures gave several fractions of oils (45 mg total) whose ir spectra indicated mixtures similar to those obtained in part A.

When carried out on a larger scale, 68.1 g (126 mmol) of the bromo ketone (**6b**) gave 43.5 g (75%) of the oxetanone **7b**, mp 100.5–102°.

**C. 3α-Acetoxy-5-hydroxy-7α-bromo-5β-cholestan-6-one (9b).**—A suspension of 410 mg (0.760 mmol) of **9b** in 13 ml of DMSO was magnetically stirred at room temperature as 1.00 ml of 1.126 *N* methanolic potassium hydroxide was added. After 15 min the bright yellow solution was subjected to the usual work-up. Tlc of the reaction oil showed several compounds and the ir spectrum exhibited intense hydroxyl absorption, a weak oxetanone carbonyl band, and no acetate absorptions. The oil was dissolved in 3 ml of pyridine and treated with 3 ml of acetic anhydride at room temperature for 18 hr. Crushed ice and 3 ml of concentrated hydrochloric acid were added. The amorphous material that separated was extracted into ether (two portions) and the combined ether extracts were washed twice with water, dried, filtered, and evaporated. The residue was chromatographed on 10 g of alumina. Elution with benzene gave 73 mg in two initial fractions. Crystallization from acetone–methanol produced 23 mg (6.6%) of impure 3α-acetoxy oxetanone **10b**, mp 139–143° (softened at 135°). Recrystallization from methanol gave 17 mg of **10b** as white needles, mp 143–145°.

The next three benzene fractions contained 31 mg of oil which crystallized from methanol, yielding 11 mg (3.1%) of 3α-acetoxy-5-hydroxy-5β-cholestan-6-one (**8b**) as needles with mp 120–122.5°. This material did not depress the melting point of authentic **8b** upon admixture.

The bulk of the material (139 mg) was eluted from the column with 15–40% ether–benzene mixtures. The ir spectrum of this oil was consistent with the diacetoxy hydroxy ketone **15b**, but no crystallization could be induced. Rechromatography and tlc of the fractions indicated that this oil was a mixture of at least three components, none of which could be isolated and identified.

**D. 5-Hydroxy-7α-bromo-5β-cholestan-6-one (11b)** (379 mg, 0.787 mmol) was covered with 45 ml of a 0.0178 *N* solution of methanolic potassium hydroxide in DMSO. The mixture was stirred magnetically overnight, during which time the oily bromo ketone dissolved very slowly. Work-up yielded 308 mg of a yellow oil which was chromatographed on 8 g of alumina. The solid (142 mg) eluted with 20% benzene–petroleum ether was recrystallized from acetone–methanol, giving 107.7 mg (34%) of 5.7β-epoxy-5β-cholestan-6-one (**12**), mp 91–93°. Recrystallization of a sample from acetone–methanol gave **12** as white needles with mp 93–94°.

The bulk of the remaining material (oil) eluted from the column was starting material, according to ir evidence and Beilstein tests.

**Reactions of Bromo Ketones with Aqueous Potassium Bicarbonate Solution in DMSO. General Procedure.**—A suspension of the bromo ketone in DMSO was heated in an oil bath (80–85°) until solution was complete. To the hot (*ca.* $1.1 \times 10^{-2}$ *M*) solution was added a calculated volume of 0.403 *M* aqueous potassium bicarbonate solution to give a 3:1 molar ratio of base to steroid. The reaction flask was shaken periodically and the cloudy solution that resulted from the bicarbonate addition gradually cleared, accompanied by the deposition of small amounts of inorganic salts. After the indicated reaction time the product was isolated in the same manner employed in the bromo ketone–methanolic potassium hydroxide–DMSO reations.

**A. Bromo Ketone 6b.**—A solution of 614 mg (1.14 mmol) of **6b** in 104 ml of DMSO was heated until the internal temperature reached 75°, at which time 8.50 ml of the bicarbonate solution was added. After a reaction time of 25 min (tlc indicated reaction almost complete within 5 min) the product was isolated and chromatographed on 20 g of alumina. Elution with 80% benzene–petroleum ether gave 384 mg of the 3β-acetoxy oxetanone (**7b**) which crystallized from aqueous ethanol as 341 mg (65%) of white needles with mp 101–102°. An additional 20 mg of impure **7b**, mp 89–97°, was obtained by dilution of the mother liquor with water.

Elution with 25% ether–benzene gave 35 mg of an oil shown by tlc to consist of at least two compounds. This oil was not investigated further.

The 50% ether–benzene fractions yielded 39 mg of a solid that was recrystallized from petroleum ether giving 32.6 mg (6%) of a compound formulated as 3β-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**14a**): mp 150–152°; ir, 3509 (m, sharp with broad base), 1736 (s, acetate C=O), 1704 (s, $C_6$=O) $cm^{-1}$. Recrystallization from petroleum ether led to the recovery of 23 mg of **14a**: mp 150–152°; $uv_{max}$ 278.5 mμ (ε 83).

*Anal.* Calcd for $C_{29}H_{48}O_5$ (476.67): C, 73.07; H, 10.15. Found: C, 73.06, 73.25; H, 10.07, 9.92.

**B. Bromo Ketone 6a.**—A solution of 608 mg (1.22 mmol) of **6a** in 112 ml of DMSO was heated at 73–76° (internal temperature) with 9.0 ml of the bicarbonate solution for 47 min. The product was isolated in the usual manner and then acetylated with 4 ml of acetic anhydride in 4 ml of pyridine for 16.7 hr at room temperature. The addition of crushed ice and 4 ml of concentrated hydrochloric acid gave amorphous material which was extracted with two portions of ether. The combined extracts were washed twice with water, dried, filtered, and evaporated. The resulting oil was chromatographed on 25 g of alumina. Elution with 50% benzene–petroleum ether gave 329 mg of crystalline material. Recrystallization from aqueous ethanol yielded 280 mg (50%) of the 3β-acetoxy oxetanone (**7b**) as needles, mp 101–102°.

Crystalline material (49 mg) eluted with 75% benzene–petroleum ether and with benzene was recrystallized from methanol to give 36.3 mg (5.5%) of the bromo ketone **6b**, mp 137–138.5°. No depression in melting point was observed upon admixture with authentic **6b**.

Eluted with 20% ether–benzene was 99 mg of a semicrystalline product. Recrystallization from methanol gave 48.8 mg (7.6%) of a white powder, mp 159–163° (37 mg was precipitated with water from the mother liquor, mp 125–145° with much previous softening). Recrystallization from methanol containing a little water afforded 27.7 mg of small white needles: mp 162–164°; ir, 3497 (w, *t*-hydroxyl), 1739 (s, with sh at higher and lower frequency) $cm^{-1}$; $\lambda_{max}$ ~248 mμ (with inflection at longer wavelengths) (ε 178).

*Anal.* Calcd for $C_{31}H_{50}O_6 \cdot {}^1/_2H_2O$ (527.72): C, 70.55; H, 9.72. Found: C, 70.18, 70.48; H, 9.53, 9.53.

This compound is presumed to be 3β,7β-diacetoxy-5-hydroxy-5β-cholestan-6-one (**14b**) on the basis of the ir absorptions.

**C. Bromo Ketone 6d.**—A suspension of 605 mg (1.01 mmol) of **6d** in 92 ml of DMSO was heated to an internal temperature of 77–78°; the steroid had not dissolved at this point. An additional 20 ml of DMSO was added and heating was continued for a further 0.5 hr at 78°. At this point some steroid remained undissolved; 7.50 ml of the bicarbonate solution was added to the mixture. After 1.5 hr of treatment with the base, the reaction mixture was worked up and the semicrystalline residue was chromatographed on 30 g of alumina. The first fraction eluted with 80% benzene–petroleum ether gave 384 mg of a white solid. Recrystallization from acetone–methanol yielded 362 mg (69%) of the 3β-benzoyloxy oxetanone **7c** as beautiful white needles,

mp 147–148.5°. A second 80% benzene–petroleum ether fraction contained 21 mg of an oil which, when crystallized twice from methanol, gave an additional (impure) 7.5 mg of **7c** as needles with mp 142–147° (soften 135°). Further fractions of the benzene–petroleum ether mixture gave 25 mg of an oil that crystallized from aqueous acetone, giving 18 mg of material with mp 138–160°. Recrystallization from methanol produced 8 mg (mp 140–148°) of an unidentified mixture.

Elution with 25% ether–benzene gave 49 mg of an oil that crystallized from petroleum ether, giving 24 mg of tiny white needles which had a double melting point (79.5–81° and 163–165°). Recrystallization from the same solvent returned 3 mg, mp 88° and 164–166°. Lack of material precluded further investigation.

**D. Bromo Ketone 6c.**—A solution of 404 mg (0.694 mmol) of **6c** in 64 ml of DMSO was heated to 76°, when 5.10 ml of the bicarbonate solution was added. After 1.35 hr the product (no oxetanone was observed *via* ir spectroscopy) was isolated from the colorless reaction mixture and chromatographed on 20 g of alumina. Elution with 50–70% benzene–petroleum ether mixtures yielded 197 mg of oil that crystallized from aqueous acetone: 85 mg (21%) of starting material (**6c**) precipitated as white needles, mp 151.5–153.5° (*ca.* 210° dec) Elution with benzene produced an oil (108 mg) that crystallized from methanol, mp 175–177.5° (dec pt 185°). Recrystallization from methanol afforded 56 mg (14%) of **16** (positive Beilstein test) with mp 176.5–178.5° (dec pt 182°); $uv_{max}$ 286 mμ (ε 49); ir, 1739 (s, with strong sh at 1754 and 1761) $cm^{-1}$. When a sample for analysis was recrystallized from methanol and dried at 80° (1 mm) for 3.2 hr, the melting point dropped to 152–154° (dec pt 175°).

*Anal.* Calcd for $C_{31}H_{49}BrO_5$ (581.62): C, 64.01; H, 8.40; Br, 13.74. Found: C, 65.60; H, 8.83; Br, 13.42.

Finally, elution of the column with 30% ether–benzene gave 56 mg of 3β,5-diacetoxy-5β-cholestan-6-one (**5c**) that crystallized from methanol (with seeding) as 17 mg (5%) of little prisms, mp 189–193°, some previous softening (lit.[11] mp 192–193.5°).

**E. Bromo Ketone 11b.**—A solution of 179 mg (0.371 mmol) of **11b** in 10 ml of anhydrous ether was added, in portions, to 34 ml of DMSO which had been preheated to 72°. After 10 min 2.80 ml of the potassium bicarbonate solution was added and the reaction was allowed to proceed at 75–77° for 2 hr. The work-up gave product containing little oxetanone (ir). Chromatography on 4 g of alumina gave 43 mg of oil from 20% benzene–petroleum ether fractions. Crystallization from acetone–methanol afforded 33 mg (22%) of 5,7β-epoxy-5β-cholestan-6-one (**12**) as white needles with mp 93–94°.

The remaining oils (61 mg) eluted with increasingly polar solvent mixtures were examined by uv spectroscopy. The maxima varied from *ca.* 274 to 314 mμ and most showed shoulders indicative of complex mixtures. None of the oils was investigated further.

**F. Bromo Ketone 9b.**—A solution of 319 mg (0.592 mmol) of **9b** in 55 ml of DMSO was heated to 81°; 4.40 ml of the bicarbonate solution was then added. The reaction product was chromatographed on 8 g of alumina. Eluted with 50% benzene–petroleum ether was 17 mg of an oil that crystallized from methanol, yielding 11.6 mg (4.3%) of the 3α-acetoxy oxetanone (**10b**), mp 146–147.5°. The 70% benzene–petroleum ether and benzene fractions yielded 58 mg of semicrystalline material. Crystallization from methanol gave 17.5 mg (6.4%) of 3α-acetoxy-5-hydroxy-5β-cholestan-6-one (**8b**) as white needles, mp 120–122.5°. No depression in melting point occurred upon admixture with authentic **8b** and the ir spectra were identical.

Elution with 15–25% ether–benzene mixtures gave 86 mg of semicrystalline material. Crystallization from ethanol gave 33 mg (11.7%) of a compound formulated as 3α-acetoxy-5,7β-dihydroxy-5β-cholestan-6-one (**15a**) (negative Beilstein test): mp 141–142.5°; ir, 3521 (m), 1744 (s), 1709 (s) $cm^{-1}$; $\lambda_{max}$ 286 mμ (ε 393).

*Anal.* Calcd for $C_{29}H_{48}O_5$ (476.67): C, 73.07; H, 10.15. Found: C, 72.93, 72.78; H, 10.19, 10.20.

**G. Bromo Ketone 9c.**—To a solution of 217 mg (0.361 mmol) of **9c** in 34 ml of DMSO at 76° was added 2.70 ml of the potassium bicarbonate solution. After 1.67 hr the product was isolated and chromatographed on 5 g of alumina. The 60% benzene–petroleum ether eluates gave 16 mg of crystalline material that was recrystallized from methanol, giving 14 mg (7.5%) of the 3α-benzoyloxy oxetanone (**10c**) as white plates, mp 148–149°.

The 30% ether–benzene fractions gave 28 mg of an oil which crystallized from methanol as white needles (25 mg, 13%) of 3α-benzoyloxy-5-hydroxy-5β-cholestan-6-one (**8c**), mp 173–175°.

No other fractions contained significant amounts of material.

**3β-Tosyloxy-5,7β-epoxy-5β-cholestan-6-one (7d).**—The 3β-acetoxy oxetanone **7b** (10.018 g, 21.90 mmol) was saponified with methanolic potassium hydroxide. The resulting 3β-hydroxy oxetanone (**7a**) was dissolved without prior recrystallization in 60 ml of pyridine and treated with 10.732 g (56.40 mmol) of recrystallized *p*-toluenesulfonyl chloride for 43.3 hr at room temperature. Crushed ice and 60 ml of concentrated hydrochloric acid were added to the vigorously swirled solution. After 2 hr, the precipitated product was collected, washed well with water, and dissolved in chloroform. The dried solution was evaporated and the residue was recrystallized from petroleum ether containing a small amount of chloroform, yielding 10.499 g of tosylate **7d** as a mat of white needles, mp 142.5–143.5° with dec at 185°. Concentration of the mother liquor yielded a further 1.715 g of product with mp 142–143.5° (total yield, 96.5%). Recrystallization of a 170-mg sample from chloroform–petroleum ether gave 148 mg of needles with mp 142–143.5° (dec 183°); $[\alpha]_D$ −16° (*c* 0.857); ir, 1806 (s, oxetanone C=O), 1600 (w, aromatic ring), 1188 and 1176 (s, tosylate), 903 (s, oxetanone ring) $cm^{-1}$.

*Anal.* Calcd for $C_{34}H_{50}O_5S$ (570.81): C, 71.54; H, 8.83; S, 5.62. Found: C, 71.33; H, 8.66; S, 5.81.

**Reaction of Tosylate 7d with Lithium Carbonate–Dimethylformamide.**—To a solution of 7.073 g (12.39 mmol) of tosylate **7d** in 350 ml of dimethylformamide (Baker "analyzed") was added 7.180 g of lithium carbonate.[26b] The mixture was heated under reflux for 2.25 hr, during which time moderate bumping occurred. The mixture was cooled to 35° under the tap, diluted with ether, and filtered with suction to remove suspended salts. The filtrate was washed three times with water, dried, and evaporated to yield an orange oil whose ir spectrum [3534 (w, OH), 1808 and 1799 (s, oxetanone C=O), 1727 (s, H—C=O), 1189, 1186, and 1160 (m, O—CH=O), 903 (m, oxetanone ring) $cm^{-1}$] was consistent[26b] with a mixture consisting mainly of a formyloxy oxetanone (**10d**). A solution of the oil in 300 ml of 0.112 *N* methanolic potassium hydroxide was boiled for 20 min. The solution was cooled, acidified with 20 ml of 2 *N* hydrochloric acid, diluted with water, and extracted twice with chloroform. The combined extracts were washed once with water, dried, and evaporated. The resulting oil [ir 3534 (m, OH), 1802 (s, oxetanone C=O), 903 (m, oxetanone ring) $cm^{-1}$] was dissolved in 50 ml of pyridine and 50 ml of acetic anhydride and allowed to remain at room temperature for 41.5 hr. Crushed ice and 50 ml of conc hydrochloric acid were added and the crystalline precipitate that formed was collected, washed with water, and taken up in chloroform.

The dried solution was evaporated and the residue {ir, 1812 (s, oxetanone C=O), 1739 (s, acetate C=O), 1650 (very w, C=C), 1241 [s, O—C(CH$_3$)=O], 907 and 897 (m, oxetanone ring) $cm^{-1}$} was chromatographed on 175 g of alumina. Elution with 20% benzene in petroleum ether gave 900 mg of a colorless oil that crystallized from methanol as a mat of white needles (330 mg) with mp 91–93° (previous softening). The mother liquor was evaporated to dryness and the residue was recrystallized from aqueous ethanol, yielding an additional 477 mg of needles, mp 88–90° (previous softening). The ir spectrum of this material was identical with that of the first crop of crystals. The total yield was 16.3%. The first crop was recrystallized from aqueous ethanol to give 277 mg of needles with mp 91.5–94.5°, softened at 85°; $[\alpha]_D$ −91° (*c* 1.48); ir, 3049 (w, H—C=C—H), 1808 (s, oxetanone C=O), 1661 (very w, C=C), 907 and 895 (m, oxetanone ring) $cm^{-1}$; $\lambda_{max}$ 286 mμ (ε 56). The spectral results, taken with the melting point behavior, indicated that this material was probably a mixture of 5,7β-epoxy-6-oxo-5β-cholest-2- and -3-enes (**17**) as the half-hydrate.

*Anal.* Calcd for $C_{27}H_{42}O_2 \cdot {}^1/_2H_2O$ (407.62): C, 79.55; H, 10.63. Found: C, 79.87, 80.17; H, 10.38, 10.60.

Elution of the column with 40 to 55% benzene–petroleum ether mixtures and with pure benzene gave 3.705 g of crystalline residue which, when recrystallized from acetone–methanol, gave 3.257 g of the 3α-acetoxy oxetanone **10b**, mp 145.5–147°. A further 214 mg of the oxetanone (mp 144–146°) was obtained from the mother liquor. Elution of the column with ether gave an additional 159 mg of **10b**, which had mp 145.5–147° after recrystallization from methanol. The total yield of crystalline oxetanone **10b** was 64%.

**Hydrogenation of the Unsaturated Oxetanone (17).**—A solution of 477 mg (1.20 mmol) of **17** in 35 ml of ethyl acetate was hydrogenated in the presence of a Pd–C catalyst until uptake of the gas ceased. The catalyst was removed by suction filtration through magnesium sulfate and the filtrate was evaporated to dryness. Crystallization of the residue from acetone–methanol gave 309 mg of 5,7β-epoxy-5β-cholestan-6-one (**12**) as long white needles, mp 91–93.5°. The mixture melting point with starting material was 76–90°. A second recrystallization from the same solvents yielded 248 mg with mp 92.5–94°. The ir spectrum of this product was identical with that of **12** prepared from the bromo ketone **11b** and no depression in melting point was noted upon admixture of the two samples.

Dilution of the first mother liquor with water gave an additional 65 mg of **12**, mp 92–93°, softened at 87°, which brought the total yield to 78%.

**Registry No.**—**5a**, 16526-63-9; **5b**, 14956-13-9; **5c**, 6579-84-6; **6a**, 16526-66-2; **6b**, 16526-67-3; **6c**, 16525-96-5; **6d**, 16525-97-6; **7a**, 16525-98-7; **7b**, 16525-99-8; **7c**, 16526-00-4; **7d**, 16526-01-5; **8a**, 6580-08-1; **8b**, 6580-09-2; **8c**, 16564-29-7; **9b**, 16526-04-8; **9c**, 16526-05-9; **10a**, 16526-06-0; **10b**, 16526-07-1; **10c**, 16526-08-2; **11a**, 16526-09-3; **11b**, 16526-10-6; **12**, 16526-11-7; **14a**, 16526-12-8; **14b**, 16526-13-9; **15a**, 16526-14-0; **16**, 16526-15-1; **17** (2-ene), 16526-16-2; **17** (3-ene), 16526-17-3.

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# A New Type of Steroid Dimer

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The cyclic ethylene hemithioketals of saturated steroidal ketones react with *p*-toluenesulfonic acid and acetic anhydride to form enol ether dimers. The reaction proceeds through the monomer enol ether formed by preferential acylative cleavage of the carbon–sulfur bond. It is shown that 3,3-dialkyl ketals and $\Delta^2$- and $\Delta^3$-enol ethers form similar dimers in yields of 40–90%. Hydrolysis of the enol ether dimers gives dimer β,γ-monoketones of the type obtained from cholestanone and dihydrotestosterone acetate by aldol condensation in highly acidic media.

It might be expected that polymers of steroidal ketones (or ketone derivatives) would readily be formed in reaction media of high acidity or basicity. There seems, however, to be only two instances of an aldol type of product having been isolated in sufficient quantity and purity to have merited reporting in the literature. Corey and Young[1] found that cholestanone is converted by hydrogen bromide in acetic acid into 2α-(2′-cholesten-3′-yl)-3-cholestanone (IIIa). What is presumed to be the same dimer, in less pure form, has recently been isolated from the products of oxidation of cholestanol with chromium trioxide–acetic acid.[2]

This report describes a new type of steroid dimer: enol ethers related to the Corey–Young type of 2,3′-β,γ-unsaturated ketone. Each of the cyclic ethylene hemithioketals of 5α-cholestanone[3] reacted readily at 25° with *p*-toluenesulfonic acid in acetic anhydride (but *not* in benzene), yielding 85% of a crystalline product whose infrared spectrum displayed typical bands of an acetylthio group (5.88 and 8.79 μ) and an ultraviolet absorption maximum at 230 mμ. Mild acid hydrolysis converted this presumed diene into a ketone identical with the dimer of Corey and Young, which for comparison was resynthesized in 10% yield by heating cholestanone in a 5% solution of anhydrous *p*-toluenesulfonic acid in benzene. Clearly, the hemithioketals Ia and Ia′ had been acetylatively cleaved at the carbon–sulfur bond and dimerized to the acetylthioethyl enol ether of structure IIa, which was then hydrolyzed to dimer ketone IIIa.

For further study, the isomeric 3-ethylene hemithioketals (Ib and Ib′) of 5α-dihydrotestosterone acetate[4] were prepared. Each of these reacted with toluenesulfonic acid in acetic anhydride to yield 60% of an acetylthioethyl enol ether (IIb) which could not be crystallized nor adequately purified by chromatography. Acid hydrolysis afforded 40–50% (over-all from hemithioketals) of dimer keto diacetate IIIb. By-products of this reaction sequence were dihydrotestosterone acetate and probably Wagner–Meerwein rearrangement products of the D ring.[5]

The dimer IIIb was also formed in low yield on heating dihydrotestosterone acetate in toluenesulfonic acid–benzene solution, but was extremely difficult to purify. Its N-acetyloxime was shown to be identical with the same derivative of the dimer ketone from IIb.

The Corey and Young structure for dimers of type III was supported by the nmr spectrum of IIIb, in which a one-proton quartet centered at δ 2.90 ppm is

(1) E. J. Corey and R. L. Young, *J. Amer. Chem. Soc.*, **77**, 1672 (1955).

(2) C. W. Shoppee, R. E. Lack, S. C. Sharma, and L. R. Smith, *J. Chem. Soc.*, 1155 (1967).

(3) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962); (b) E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965), describe the stereoisomeric hemithioketals **Ia** and **Ia′**. (c) Also, for isomer **Ia**, see C. Djerassi and M. Gorman, *J. Amer. Chem. Soc.*, **75**, 3704 (1953); (d) L. F. Fieser, *ibid.*, **76**, 1945 (1954); (e) C. Djerassi, M. Shamma, and T. Y. Kan, *ibid.*, **80**, 4723 (1958).

(4) For mixture of hemithioketals **Ib** and **Ib**, see (a) J. Romo, G. Rosenkranz, and C. Djerassi, *ibid.*, **73**, 4961 (1951); (b) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961). See Experimental Section for the individual isomers. The trivial name, 5α-dihydrotestosterone, is used throughout this report in referring to 5α-androstan-17β-ol-3-one.

(5) (a) A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935); (b) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963).