Reactions of Steroidal 3,4-Diones (Diosphenols) with Ketalizing Agents[1,2]

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The reaction of 3 4-dioxo steroids (1) with ethylene glycol and *p*-toluenesulfonic acid, under ketalizing conditions, gave steroidal 3,5-dieno[3,4-*b*]dioxanes as well as the 5α- and 5β-4-oxo 3-ethylenedioxy ketals. 2-Mercaptoethanol reacted with 3,4-dioxocholestane (**1a**) to give 3,5-cholestadieno[4,3-*b*]oxathiane as well as four isomeric 4-oxo 3-ethylene monothioketals. Reaction of **1a** with 1,2-ethanedithiol gave 5α- and 5β-4-oxo 3-ethylene dithioketals, but no cholesta-3,5-dieno[3,4-*b*]dithiane was obtained. Base-catalyzed equilibration of the pairs of 4-oxo 3-ethylene monothioketals epimeric at C-5 favored, in each case, the isomer with equatorial oxygen in the monothioketal ring. In the case of the 3(*S*)-ethylene monothioketals of 5α- and 5β-cholestane-3,4-dione, the stability order (A/B trans favored over A/B cis) for cholestan-4-one was inverted, giving predominantly 5β-4-oxocholestane 3(*S*)-ethylene monothioketal.

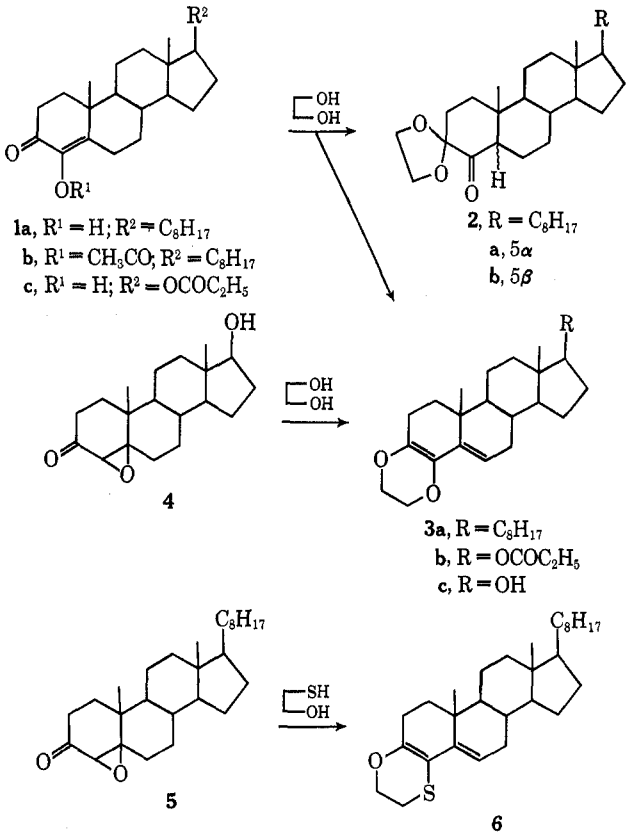
It has been reported[3] that 4,17-diacetoxy-4-androsten-3-one gives 3-ethylenedioxy-4,17-diacetoxyandrost-4-ene under ketalizing conditions (benzene–ethylene glycol–*p*-toluenesulfonic acid). Our need for 4-oxo steroids bearing a protected C-3 oxygen substituent led us to reexamine the above reaction.

We found that both 4-hydroxy-4-cholesten-3-one[4] (**1a**) and the corresponding 4-acetoxy compound[5] **1b** gave 3,5-cholestadieno[3,4-*b*]dioxane (**3a**) in about 30% yield under the standard ketalizing conditions mentioned above, although some ketalization at C-3 also occurred (*vide infra*). The structural assignment for **3a** is supported by analytical and spectroscopic data. Further support comes from analogy with the 2-mercaptoethanol ketalizations to be discussed latter.

Using somewhat different ketalizing conditions (2-methyl-2-ethyl-1,3-dioxolane), we found that 17β-propionoxy-4-hydroxy-4-androsten-3-one (**1c**) gave the analogous [3,4-*b*] dioxane **3b**. The latter compound had spectroscopic properties closely similar to those of compound **3a**, and the mass spectrum of **3b** showed a strong molecular ion peak at *m/e* 386, with a strong fragment peak at *m/e* 358 (probably due to loss of ethylene). Furthermore, reaction of 17β-hydroxy-4,5β-oxidoandrostan-3-one (**4**) with ethylene glycol–benzene–*p*-toluenesulfonic acid gave 17β-hydroxy-3,5-androstadieno[3,4-*b*]dioxane (**3c**). Propionylation at C-17 of the latter compound gave **3b**, identical with the same product obtained from the diosphenol **1c** (see Scheme I).

It is known[6] that 4,5β-oxido-3-oxo steroids react with 2-mercaptoethanol or 1,2-ethanedithiol in polyphosphoric acid to give $\Delta^{3,5}$-dieno[3,4-*b*]oxathianes or dithianes. In these cases, reaction is presumably initiated by oxide protonation and nucleophilic attack on C-4 by sulfur. Indeed, we found that, under our reaction conditions (benzene and *p*-toluenesulfonic acid), 4,5β-oxidocholestan-3-one[7] (**5**) gave, with 2-mercaptoethanol, the known 3,5-cholestadieno[3,4-*b*]-oxathiane (**6**). However, under the same conditions, 4-hydroxy-4-cholesten-3-one (**1a**) gave none of this latter product **6** but instead furnished the *isomeric* 3,5-cholestadieno[4,3-*b*]oxathiane (**7**).

SCHEME I



Analytical data and infrared, nmr, and mass spectra were all consistent with structure **7**, and chemical support came from reduction of compound **7** with Raney nickel to 4-ethoxy-3,5-cholestadiene (**9**). The hitherto undescribed enol ether **9** was readily cleaved by aqueous acetic acid to the known[8] 5-cholesten-4-one (**10**), securing the structure of **9** and hence of the [4,3-*b*]oxathiane **7**.

The acid-catalyzed conversion of α,β-epoxy ketones to diosphenols (*e.g.*, **5** to **1a**) is well documented,[9] and the formation of the $\Delta^{3,5}$-dieno[3,4-*b*]dioxane system

(1) This work was supported in part by U. S. Public Health Service Grant HE-08913 and by GM-16492.

(2) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, Abstracts, O-67.

(3) B. Camerino, D. Catapan, U. Valcavi, and B. Patelli, *Gazz. Chim. Ital.*, **89**, 674, (1959).

(4) A. Butenandt, G. Schramm, A. Wolff, and H. Kudszus, *Chem. Ber.*, **69**, 2779 (1936).

(5) L. F. Fieser and R. Stevenson, *J. Amer. Chem. Soc.*, **76**, 1728 (1954).

(6) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka, and T. Furuta, *Chem. Pharm. Bull.*, **12**, 383 (1964); *Tetrahedron*, **21**, 733 (1965).

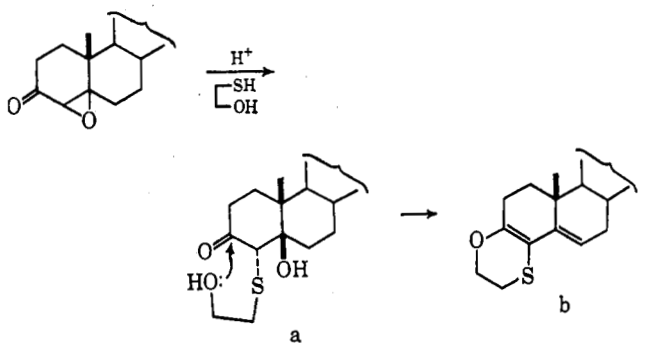
(7) P. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

(8) A. Butenandt and A. Wolff, *Chem. Ber.*, **68**, 2091 (1935).

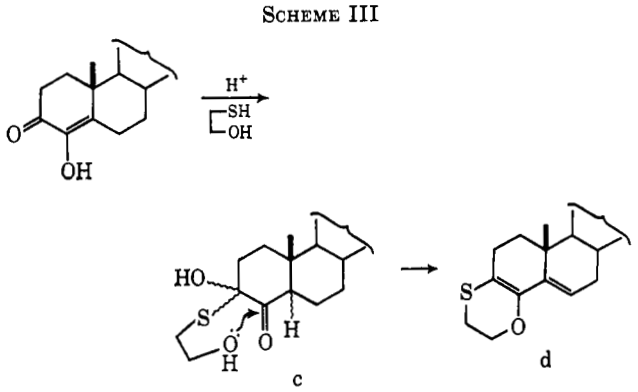
(9) *Cf.* B. Camerino, B. Patelli, and A. Vercellone, *J. Amer. Chem. Soc.*, **78**, 3540 (1956).

(3) from both the diosphenol **1c** and the α,β-epoxy ketone **4** with ethylene glycol and acid might have been so explained. However, the 2-mercaptoethanol experiments which have just been described show that, whereas the α,β-epoxy ketone undergoes nucleophilic attack first at C-4, the diosphenol reacts first at C-3 (see Schemes II and III).

SCHEME II



SCHEME III



Thus, in Scheme II, the adduct a can generate the product b *via* attack of hydroxyl oxygen at C-3, with subsequent acid-catalyzed dehydrations. In Scheme III, attack by sulfur at C-3 with subsequent ketonization of the Δ^4 enol can lead to c. The latter could then form product d by attack of oxygen on the newly formed C-4 carbonyl, with subsequent dehydration.

The reaction of the diosphenol **1a** with 2-mercaptoethanol, which gave the [4,3-*b*]oxathiane (**7**) discussed above, in approximately 10% yield, also furnished four crystalline monothioketals. These are formulated as the four possible isomers (**8a–d**) of cholestane-3,4-dione 3-ethylene monothioketal, for the following reasons.

The analytical data for each compound supported the gross composition, $C_{29}H_{48}O_2S$, and the infrared spectrum of each compound showed absorption attributable to a carbonyl group in a six-membered ring. Two of these compounds, **8b** and **8c**, were further characterized as the sulfones (**15** and **16**, respectively), obtained by oxidation with *m*-chloroperbenzoic acid. The mass spectra of compounds **8a–d** *were indistinguishable* and have been discussed in detail elsewhere.[10] The nmr spectra of compounds **8a–d** were also entirely consistent with the structures assigned and permitted assignment of stereochemistry at C-5. Thus, compounds **8a** and **8b** had resonances at δ 0.72 and 0.73, respectively, for their C-19 methyl groups, whereas compounds **8c** and **8d** each showed the C-19 methyl resonance at δ 1.09. The C-19 methyl protons in 5α-cholestan-4-one appear at δ 0.75, while in 5β-cholestan-4-one the C-19 methyl resonance occurs at δ 1.12, the large difference being attributable to the shielding and deshielding effect, respectively, of the carbonyl group in *trans*- and *cis*-4-oxo steroids. Assuming no serious effects due to the ketal grouping at C-3 in compounds **8a–d**, the above data classify compounds **8a** and **8b** as 5α- and compounds **8c** and **8d** as 5β-4-oxocholestane derivatives. The assumption that the 3-ketal grouping has no substantial perturbing effect was supported by the nmr data for the pairs of 3-ethylenedioxy ketal and 3-ethylene dithioketal derivatives of cholestan-4-one (**2a,b**, and **11a,b**, respectively) whose preparation and properties are discussed later.

Although the nmr data permitted us to conclude that compounds **8a** and **8b** were 5α- and that **8c** and **8d** were 5β-cholestan-4-one derivatives, the stereochemistry at C-3 was still unknown. This problem was attacked by two independent methods, the first of which was ORD and CD measurements. These data allowed conclusive assignment of stereochemistry at C-3 for compounds **8a–d** and have been discussed in detail elsewhere.[11]

The second approach involved reduction of the 5α-cholestan-4-one 3-monothioketals **8a** and **8b** with hydride to give the 4β (axial) alcohols **14a** and **14b**. In one case there should be intramolecular hydrogen bonding between the axial 4β-hydroxyl group and equatorial sulfur at C-3, and in the other the hydrogen bonding would be between the axial 4β-hydroxyl group and equatorial oxygen at C-3. Infrared measurements should then settle the configuration at C-3, given suitable models, which were synthesized as follows.

Reaction of 4-hydroxy-4-cholesten-3-one (**1a**) with 1,2-ethanedithiol in benzene, with *p*-toluenesulfonic acid catalyst, gave both 5α- and 5β-cholestane-3,4-dione 3-ethylene dithioketal (**11a** and **11b**, respectively) which were separated readily by chromatography. When the reaction was monitored by tlc, it became clear that the 5β isomer **11b** is the kinetically controlled product which equilibrates under the acidic reaction conditions to give the more stable 5α isomer **11a**. Interestingly, we could not detect any product with the ultraviolet absorption of a 3,5-cholestadieno[3,4-*b*]dithiane. Equilibration of **11a** and **11b** with base gave a mixture containing preponderantly isomer **11a**.

Fieser and Stevenson had earlier reported[12] the formation of the 5β isomer **11b** by the action of 1,2-ethanedithiol–boron trifluoride on the diosphenol **1a** and had proved the configuration at C-5 by desulfurization to 5β-cholestan-4-one.

Reduction of the 5α isomer **11a** with sodium borohydride gave the expected 4β-hydroxy compound **12** in nearly quantative yield. Elemental analysis and the mass spectrum were consistent with structure **12**, and the nmr spectrum confirmed the equatorial nature of the C-4 hydrogen (width at half height, 5 Hz) and hence the axial nature of the C-4 hydroxyl. Desulfurization of compound **12** gave the known[13] 5α-cholestan-4β-ol providing final proof of structure and stereochemistry.

Similarly, reduction of 5α-cholestane-3,4-dione 3-ethylenedioxy ketal (**2a**) with sodium borohydride gave

(10) C. Fenselau, L. Milewich, and C. H. Robinson, *J. Org. Chem.*, **34**, 1374 (1969).

(11) C. H. Robinson, L. Milewich, G. Snatzke, W. Klyne, and S. R. Wallis, *J. Chem. Soc. C*, 1245 (1968).

(12) R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.*, **78**, 1409 (1956).

(13) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

the 4β-ol **13** whose structure followed from analytical, mass spectroscopic, and nmr data and analogy with the reduction of compound **11a**. The 4-oxo 3-ethylenedioxy ketal **2a** had been isolated, along with the 5β isomer **2b**, from the reaction of 4-hydroxy-4-cholesten-3-one (**1a**) with ethylene glycol which gives mainly the [3,4-*b*]dioxane **3a** as already noted. The structures of the ketals **2a** and **2b** were established by analytical and spectroscopic data.

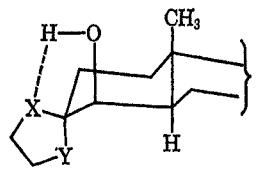
Before preparing the 4β-hydroxy 3-ethylene monothioketals, the hydroxyl stretching frequencies of the model compounds **12** and **13** were measured. The hydroxyl stretching frequency of 5α-cholestan-4β-ol, measured under the same conditions, was used as reference, and the data and $\Delta\nu$ values are given in Table I. Thus, for compound **12** where OH---S intramolecular hydrogen bonding must occur, $\Delta\nu = 86$ cm^{-1}, while for compound **13**, involving OH---O bonding, $\Delta\nu = 37$ cm^{-1}. These figures are in good agreement with data[14,15] from acyclic compounds for OH---S and OH---O intramolecular hydrogen bonding involving a quasi five-membered ring. We therefore set about the preparation of the 4β-hydroxy 3-ethylene monothioketals (**14a** and **14b**), which were readily obtained in nearly quantitative yield by borohydride reduction of the corresponding ketones **8a** and **8b**. The formulation of **14a** and **14b** as 4-hydroxy 3-ketals followed from their mode of preparation, and analytical and mass spectroscopic data, while the configuration at C-4 was assigned on the basis of the nmr spectra. Not only does the width at half height of the C-4 proton resonance confirm its equatorial nature, but the C-19 methyl resonances confirm the presence of a 4β- rather than a 4α-hydroxyl group. Whereas a 4β-hydroxyl substituent causes a marked downfield shift of the C-19 methyl resonance, a 4α-hydroxyl group has little effect.[16,17]

The hydroxyl stretching frequencies of the two monothioketals **14a** and **14b** were measured at high dilution (Table I) and $\Delta\nu$ values of 57 and 36 cm^{-1}, respectively, were recorded.

The latter value corresponds very closely to that for OH---O bonding in compound **13** and the $\Delta\nu$ for compound **14b**, while lower than that seen for OH---S bonding in compound **12**, is still significantly higher than that for the OH---O situation. The C-3 stereochemistry thereby deduced for compounds **14a** and **14b**, and hence for the parent 4-oxo compounds **8a** and **8b**, is in full accord with that established from CD-ORD studies.

Finally, the two remaining 5β-4-oxo 3-monothioketals **8c** and **8d** were matched with the appropriate 5α compounds **8a** and **8b** by equilibration experiments. These equilibrations, using methanolic potassium hydroxide showed that compounds **8a** and **8c** on the one hand, and **8b** and **8d** on the other, constituted pairs differing only in their stereochemistry at C-5. The C-3 stereochemistry thereby deduced for compounds **8c** and **8d** agreed with that assigned on the basis of CD–ORD data. The equilibration studies are of interest, because when epimerization at C-5 occurs in these compounds there is concomitant change from equatorial to axial (or *vice versa*) of the C-3 substituents.

TABLE I
INFRARED DATA[a] FOR 5α-CHOLESTAN-4β-OL 3-ETHYLENE KETALS



Compd	X	Y	νOH, cm^{-1}	$\Delta\nu$, cm^{-1}
5α-Cholestan-4β-ol			3629	
12	S	S	3543	86
14a	S	O	3572	57
13	O	O	3592	37
14b	O	S	3593	36

[a] Obtained for 10^{-3} *M* solutions in CCl_4, with 3-mm cells, using a Perkin-Elmer Model 521 spectrophotometer, calibrated against water vapor.

The equilibration of cholestan-4-one has been found[18] to result in a mixture of 99% of the 5α isomer (A/B trans) and 1% of the 5β isomer (A/B cis) using potassium hydroxide in methanol at 25°. Our equilibrations of the 4-oxo 3-hemithioketals **8a–d** were carried out using 10% potassium hydroxide in methanol at reflux, and we also equilibrated cholestan-4-one under these conditions, obtaining an equilibrium mixture of 83% 5α-cholestan-4-one and 17% 5β-cholestan-4-one. By comparison, the equilibrium between **8a** (X = S; Y = O) and **8c** (X = S; Y = O) (Scheme IV) resulted in *ca.* 87% of the 5β isomer **8c** and *ca.* 13% of the 5α isomer **8a**. On the other hand, compounds **8b** (X = O; Y = S) and **8d** (X = O; Y = S) (Scheme IV) gave an equilibrium mixture containing essentially only the 5α epimer **8b** with no detectable amounts of the 5β compound **8d**.

Equilibration of the 4-oxo 3-ethylenedioxy ketals **2a,b** and the corresponding 3-ethylene dithioketals **11a,b** gave in each case mixtures in which the 5α epimer greatly predominated as shown by tlc. However, these latter experiments were qualitative, and percentage values cannot be assigned.

Although for cholestan-4-one itself equilibrium lies far on the side of the A/B trans isomer, new nonbonded interactions can radically affect the equilibrium position and indeed this is so for 1,4-dioxo steroids.[19] In the latter case, unfavorable C-1, C-11 substituent interactions in the 5α compound are relieved in the 5β (A/B cis) isomer.

Our results with the ethylene monothioketals **8a–d** clearly involve the conformational preferences of the C-3 oxygen and sulfur substituents. Determinations of the effective relative sizes of oxygen and divalent sulfur in substituted cyclohexanes suggest that there should

(14) Dr. L. P. Kuhn (personal communication) has observed a $\Delta\nu$ value of 93 cm^{-1} for intramolecular OH---S bonding in 2-methylmerceptoethanol and of 32 cm^{-1} for intramolecular OH---O bonding in ethylene glycol.

(15) M. Mori, Y. Takahashi, and Y. Tsuzuki, *Bull. Chem. Soc. Jap.*, **40**, 2720 (1967), report a $\Delta\nu$ of 90 cm^{-1} for intramolecular OH---S bonding in 2-ethylmercaptoethanol.

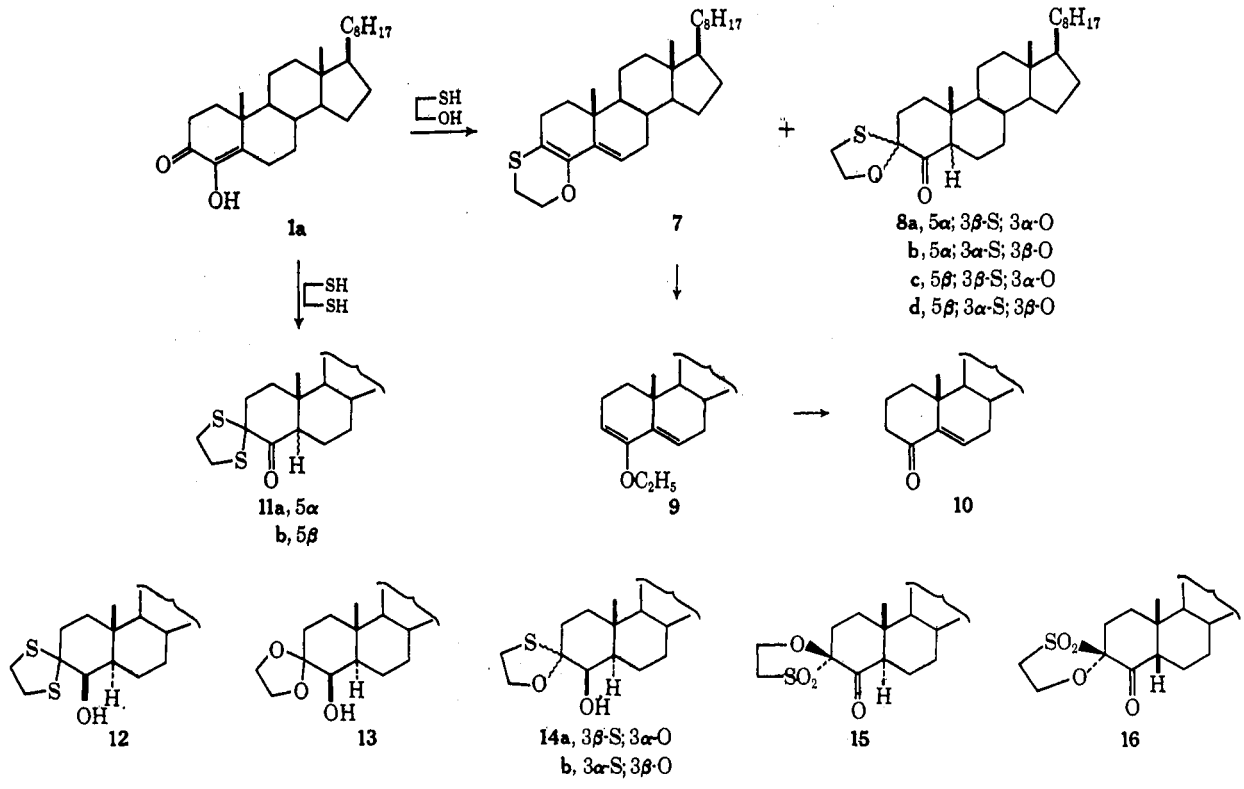
(16) Compare the C-19 methyl resonance for 5α-cholestan-4β-ol (δ 1.04, this paper) with that for 5α-cholestan-4α-ol (δ 0.78) recorded by D. Lavie, S. Greenfield, Y. Kashman, and E. Glotter, *Israel J. Chem.*, **5**, 151 (1967).

(17) Note also the data for the C-19 methyl resonance of 5α-androstan-4β-ol (δ 1.04) *vs.* that for 5α-androstan-4α-ol (δ 0.80), cited in the extensive nmr tabulations of J. E. Bridgeman, P. C. Cherry, A. S. Clegg, J. M. Evans, E. R. H. Jones, A. Kasal, V. Kumar, G. D. Meakins, Y. Morisawa, E. E. Richards, and P. D. Woodgate, *J. Chem. Soc. C*, 250 (1970).

(18) N. L. Allinger, M. A. Darooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961).

(19) D. Lavie, cited in J. E. Bridgeman, P. C. Cherry, E. R. H. Jones, P. W. Lequesne, and G. D. Meakins, *Chem. Commun.*, 561 (1966).

SCHEME IV



be preference for the equatorial orientation of sulfur over oxygen by about 0.2 kcal/mol.[20] This view is supported by the report[21] that equilibration of the propylene monothioketals of 4-*tert*-butylcyclohexanone with boron trifluoride as catalyst generates 55% of the isomer with sulfur equatorial.

On the other hand, equilibrations of the ethylene monothioketals of 4-*tert*-butylcyclohexanone, 3-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, and 3-*tert*-butylcyclohexanone, using boron trifluoride as catalyst, gave[22,23] mixtures favoring, in varying degree, the isomer with equatorial oxygen in each case. However, it was found[22] that equilibrium shifts occurred when the amount of boron trifluoride was varied in the case of 4-*tert*-butylcyclohexanone ethylene monothioketal, suggesting that a complexed intermediate might be involved. More recent work[20] on the boron trifluoride catalyzed equilibration of the ethylene monothioketals of 3,3,5-trimethylcyclohexanone strongly suggests that no significant complexing of catalyst with ketal occurs, in this case at least.

Our equilibration results with the ethylene monothioketals **8a–d** are consistent with equatorial preference for oxygen, and the problem of possible catalyst–ketal complex formation involved in the boron trifluoride equilibrations is, of course, not encountered in these base-catalyzed epimerizations at C-5. The conformational preference of oxygen for the equatorial orientation in these ketals is sufficient to invert the normal stability order of 4-oxo steroids [preponderantly 5α (A/B trans) at equilibrium] giving preponderantly the 5β isomer (A/B cis) in the case of the 3(*S*) isomers **8a** and **8c**.

However, dipole interactions[24] between C-3 equatorial oxygen (or sulfur) and the C-4 carbonyl group are undoubtedly also involved, thus complicating the situation, and further analysis at this time would be quite speculative. Our experiments can, however, be said to provide independent confirmation for the conformational preference of sulfur for the equatorial orientation in cyclohexyl ethylene monothioketals.

In conclusion, we note that monitoring by tlc of the reactions of ethylene glycol, 2-mercaptoethanol, and 1,2-ethanedithiol with the diosphenol **1a** showed that, in each case, 5β-4-oxo 3-ketals predominated initially over the 5α isomers and that acid-catalyzed equilibration at C-5 ensued. In the case of the 2-mercaptoethanol reaction, it was also shown that the [4,3-*b*]oxathiane **7** did not generate the ketals **8a–d** when put back into the ketalizing conditions, nor did the ketals generate discernable quantities of the oxathiane **7** under the reaction conditions.

Experimental Section[25]

3,5-Cholestadieno[3,4-*b*]dioxane (3a) and the Cholestane-3,4-dione 3-Ethylenedioxy Ketals (2a and 2b) from 4-Hydroxy-4-

(20) See M. P. Mertes, H. K. Lee, and R. L. Schowen, *J. Org. Chem.*, **34**, 2080 (1969), and references cited therein for a recent account of this situation.

(21) E. L. Eliel, E. W. Della, and M. Rogic, *ibid.*, **30**, 855 (1965).

(22) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962).

(23) M. P. Mertes, *J. Org. Chem.*, **26**, 2320 (1963).

(24) After completion of the spectroscopically based assignments of configuration to compounds **8a–d**, A. Cooper and D. A. Norton [*ibid.*, **33**, 3537 (1968)] carried out an X-ray crystal structure determination on compound **8b**. Their results, which conclusively confirm the structures of **8b** and hence of the other three isomeric monothioketals, show some distortion of the steroid A ring, probably due (at least in part) to dipole interaction between the equatorial oxygen substituent at C-3 and the C-4 carbonyl group.

(25) Melting points were determined on the Kofler hot stage. Optical rotations were measured in chloroform solution, as were infrared spectra, unless otherwise specified. Ultraviolet spectra were recorded using heptane or methanol solutions as noted, and nmr spectra refer to deuteriochloroform solutions with tetramethylsilane as internal reference. The silica gel used for column chromatography was Davison Chemical Co. Grade 923. Preparative thin layer chromatography (tlc) was carried out with 1.0-mm-thick layers of silica gel GF_{254}. Petroleum ether refers to the fraction boiling between 40 and 60°.

cholesten-3-one (1a).—A solution of the diosphenol **1a** (500 mg) in benzene (25 ml) and ethylene glycol (2 ml) together with *p*-toluenesulfonic acid (60 mg) was heated to reflux under a Dean-Stark water separator for 24 hr. The reaction mixture was cooled, washed successively with 10% aqueous sodium carbonate and water, dried (anhydrous solid Na_2CO_3), and evaporated *in vacuo* to give an oil. Chromatography on a Florisil column and elution with petroleum ether (bp 30–60°) gave 3,5-cholestadieno-[3,4-*b*]dioxane (**3a**, 170 mg): mp 77–78° (from methanol containing a trace of pyridine); $[\alpha]D$ −21°; λ_{max}^{MeOH} 258 nm (ε 15,200), shoulders at 250 (13,800) and 267 (10,800); ν_{max} 1631, 1668 cm^{-1}; nmr δ 0.70 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 4.08 (s, 4 H, OCH_2CH_2O), and 5.65 (s, 1 H, C=CH).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.36; H, 11.20.

The Florisil column was then eluted with petroleum ether–ethyl acetate (4:1), and the mixture thereby obtained was separated by preparative tlc (petroleum ether–ethyl acetate, 19:1). This separation gave pure 5β-cholestane-3,4-dione 3-ethylenedioxy ketal (**2b**, 50 mg): mp 121–123° (from methanol); $\nu_{max}^{CCl_4}$ 1725 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.10 (s, 3 H, 19-CH_3), 2.55 (unresolved, 1 H, $W_{1/2}$ = 6.5 Hz, C-5 H), and 3.98 (m, 4 H, OCH_2CH_2O); mass spectrum 444 (M^+), 99 (base peak).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.56; H, 10.74.

There was also isolated the isomeric 5α-cholestane-3,4-dione 3-ethylenedioxy ketal (**2a**, 70 mg) which had mp 131–135° (from methanol). This material was not analytically pure, and the analytical sample was obtained as described in the two experiments immediately below.

4β-Hydroxy-5α-Cholestan-3-one 3-Ethylenedioxy Ketal (13).—To a stirred solution of the 4-oxo 3-ethylenedioxy ketal **2a** (150 mg) in ether (5 ml) was added lithium aluminum hydride (75 mg) in ether (5 ml) at room temperature. After 1.75 hr water was added and the mixture was extracted with chloroform. The chloroform extract was washed with saturated sodium chloride solution and then with water, then dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1) to give the analytically pure 4β-ol **13** (100 mg): mp 167–168° (from methylene chloride–acetone); $[\alpha]D$ +28°; $\nu_{max}^{CCl_4}$ 3592 cm^{-1}; nmr δ 0.66 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 3.38 (s, 1 H, $W_{1/2}$ = 4 Hz, CHOH), and 3.98 (s, 4 H, OCH_2CH_2O); mass spectrum 446 (M^+), 428, 99 (base peak).

Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78.30; H, 11.45.

5α-Cholestane-3,4-dione 3-Ethylene Ketal (2a) from 4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Ketal (13).—A solution of the 4β-ol **13** (80 mg) in acetone (25 ml) was oxidized with Jones reagent[26] in the usual way. The crude product was crystallized from methanol giving the pure 4-oxo compound **2a** (32 mg): mp 136–138°; $\nu_{max}^{CCl_4}$ 1731 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 0.72 (s, 3 H, 19-CH_3), 2.51 (q, 1 H, C-5 H, J_{aa} = 10 Hz, J_{ae} = 4 Hz); mass spectrum 444 (M^+), 99 (base peak).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 77.98; H, 10.68.

Cholesta-3,5-dieno[3,4-*b*]dioxane (3a) from 4-Acetoxy-4-cholesten-3-one (1b).—A mixture of 4-acetoxy-4-cholesten-3-one (**1b**, 400 mg), ethylene glycol (2 ml), benzene (40 ml), and *p*-toluenesulfonic acid (200 mg) was heated to reflux under a Dean-Stark water separator for 24 hr. The reaction mixture was cooled, washed successively with 10% aqueous sodium carbonate and water, dried (solid Na_2SO_4), and evaporated *in vacuo* to give an oil. Chromatography on Florisil and elution with benzene gave pure **3a** (128 mg), mp 77–78° (from methanol containing a trace of pyridine), identical in all respects with the same compound prepared from 4-hydroxy-4-cholesten-3-one (**1a**) as described above.

17β-Hydroxy-3,5-androstadieno[3,4-*b*]dioxane (3c).—A mixture of 4β,5β-oxido-17β-hydroxyandrostan-3-one (**4**, 4.1 g), ethylene glycol (5.0 ml), benzene (100 ml), and *p*-toluenesulfonic acid (220 mg) was heated to reflux under a Dean-Stark water separator for 22 hr. The reaction mixture was worked up exactly as for the other ethylene glycol reactions described above, and the crude product was chromatographed on Florisil. Elution with benzene gave crude **3c**, which was crystallized from methanol containing a trace of pyridine to give pure **3c** (1.67 g): mp 150–175°; $[\alpha]D$ −42°; λ_{max}^{MeOH} 258 nm (13,300), shoulders at 250 (12,000) and 268 (9200); ν_{max} 1632, 1669 cm^{-1}; nmr δ 0.78 (s, 3 H, 18-CH_3), 1.03 (s, 3 H, 19-CH_3), 4.09 (s, 4 H, OCH_2CH_2O), and 5.67 (s, 1 H, >C=CH).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.15.

17β-Propionoxy-3,5-androstadieno[3,4-*b*]dioxane (3b). A. From 17β-Hydroxy-3,5-androstadieno[3,4-*b*]dioxane (3c).—A solution of **3c** (300 mg) in pyridine and propionic anhydride (14 ml, 1:1 mixture) was left for 5 hr at 25°. Water was added, the mixture was filtered, and the solid residue was washed with water, dried, and chromatographed on Florisil. Elution with benzene gave a solid, which was crystallized from methanol to give pure 17β-propionate (**3b**, 100 mg) identical in all respects with material obtained as described in B below.

B. From 17β-Propionoxy-4-hydroxy-4-androsten-3-one (1c).—A solution of **1c** (3.0 g) and *p*-toluenesulfonic acid (100 mg) in 2-methyl-2-ethyl-1,3-dioxolane (100 ml) was distilled slowly through a Vigreux column for 4 hr. Additional amounts of 2-methyl-2-ethyl-1,3-dioxolane (50 ml) and *p*-toluenesulfonic acid (100 mg) were added and the mixture was heated under reflux for 24 hr. The reaction mixture was cooled, and benzene and 10% aqueous sodium carbonate (10 ml) were added. The benzene layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography of the crude product on Florisil gave, on elution with benzene, pure **3b** (400 mg). Crystallization from methanol gave analytically pure **3b** (180 mg): mp 157–174°; λ_{max}^{MeOH} 258 nm (13,400), shoulders at 250 (12,900) and 267 (11,700); ν_{max} 1632, 1669 cm^{-1}; nmr δ 0.83 (s, 3 H, 18-CH_3), 1.03 (s, 3 H, 19-CH_3), 4.09 (s, 4 H, OCH_2CH_2O), and 5.67 (s, 1 H, <C=CH); mass spectrum 386 (M^+), 358.

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.51; H, 8.90.

Reaction of 4-Hydroxy-4-cholesten-3-one (1a) with 2-Mercaptoethanol. A. In Benzene at Reflux.—To a solution of the diosphenol **1a** (5.0 g) in benzene (100 ml) and 2-mercaptoethanol (10 ml) was added *p*-toluenesulfonic acid (1.0 g) and the mixture was heated to reflux under a Dean-Stark water separator for 5 min. The reaction mixture was cooled and neutralized with 10% aqueous sodium carbonate solution, and the benzene layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was dissolved in petroleum ether and chromatographed on Florisil. Elution with petroleum ether gave 3,5-cholestadieno[4,3-*b*]oxathiane (**7**, 484 mg): mp 130–132° (from methanol); $[\alpha]D$ −91°; λ_{max} 279 nm (13,000), 221 (8800); $\nu_{max}^{CCl_4}$ 1610 cm^{-1}; nmr δ 0.70 (s, 3 H, 18-CH_3), 0.99 (s, 3 H, 19-CH_3), 3.02 (m, 2 H, SCH_2), 4.27 (m, 2 H, OCH_2), and 5.86 (s, 1 H, C-6 vinyl H); mass spectrum 442 (M^+), 427 ($M - CH_3$).

Anal. Calcd for $C_{29}H_{46}OS$: C, 78.68; H, 10.47; S, 7.23. Found: C, 78.32; H, 10.19; S, 7.55.

Further elution with petroleum ether gave 5β-cholestane-3,4-dione 3-ethylene monothioketal 3(*S*) isomer (**8c**, 318 mg): mp 125–125.5° (from methanol); ν_{max} 1717 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), 2.58 (m, 1 H, 5β H), 2.99 (t, J = 6 Hz, 2 H, SCH_2), and 4.28 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.94. Found: C, 75.54; H, 10.37; S, 7.16.

Further elution with petroleum ether gave mixtures, from which were separated by preparative tlc (petroleum ether–ethyl acetate, 19:1) the following two compounds. 5β-cholestane-3,4-dione 3-ethylene monothioketal 3(*R*) isomer (**8d**, 21 mg): mp 119–120° (from methanol); $\nu_{max}^{CCl_4}$ 1720 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), 2.68 (m, 1 H, 5β H), 3.02 (m, 2 H, SCH_2), and 2 multiplets centered on 3.68 and 4.17 (2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50. Found: C, 75.15; H, 10.21.

5α-cholestane-3,4-dione 3-ethylene monothioketal 3(*S*) isomer (**8a**, 14 mg): mp 139–140° (from methanol); $\nu_{max}^{CCl_4}$ 1726 cm^{-1}; nmr δ 0.64 (s, 3 H, 18-CH_3), 0.72 (s, 3 H, 19-CH_3) 3.00 (m, 2 H, SCH_2), and 4.19 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.94. Found: C, 75.67; H, 10.64; S, 7.04.

Further elution of the Florisil column with chloroform gave 5α-cholestane-3,4-dione 3-ethylene monothioketal 3(*R*) isomer (**8b**, 827 mg): mp 148.5–150.5°; $\nu_{max}^{CCl_4}$ 1722 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 0.73 (s, 3 H, 19-CH_3), 3.00 (m, 2 H, SCH_2), and 4.20 (m, 2 H, OCH_2).

(26) R. G. Curtis, I. M. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

Anal. Calcd for $C_{29}H_{48}O_2S$: C, 75.60; H, 10.50; S, 6.94. Found: C, 75.55; H, 10.35; S, 7.19.

B. In Benzene at 60°.—To a solution of the diosphenol **1a** (5.0 g) in benzene (750 ml) and 2-mercaptoethanol (50 ml) was added *p*-toluenesulfonic acid (1.0 g) and the mixture was stirred magnetically at 60° for 2 hr. The reaction mixture was worked up exactly as in A above, and the crude product was chromatographed on Florisil. Elution with petroleum ether gave, first, the [4,3-*b*]oxathiane **7** (458 mg) described above, mp 130–132°. Further elution with petroleum ether gave 28 mg of a new compound, possibly a cholestane-3,4-dione bis(ethylene monothioketal): mp 146–147° (from methanol); mass spectrum 520 (M^+), 460, 442.

Anal. Calcd for $C_{31}H_{52}O_2S_2$: C, 71.50; H, 10.07; S, 12.29. Found: C, 71.77; H, 10.28; S, 12.02.

The next petroleum ether fractions provided another new compound (80 mg), possibly another cholestane-3,4-dione bis(ethylene monothioketal): mp 163.5–165° (from methanol); mass spectrum 520 (M^+), 505, 492, 460.

Anal. Calcd for $C_{31}H_{52}O_2S_2$: C, 71.50; H, 10.07. Found: 72.49; H, 10.08.

Further elution with petroleum ether and petroleum ether–ethyl acetate mixtures gave three of the four isomeric cholestane-3,4-dione 3-ethylene monothioketals described in A above, in the following quantities as pure compounds after crystallization from methanol: 5β-cholestane-3,4-dione 3-ethylene monothioketal (**8c**), 348 mg; 5α-cholestane-3,4-dione 3-ethylene monothioketal (**8a**), 169 mg; 5α-cholestane-3,4-dione 3-ethylene monothioketal (**8b**), 893 mg.

Sulfone 15 Derived from 5α-Cholestane-3,4-dione 3-Ethylene Monothioketal (8b).—A solution of the monothioketal **8b** (265 mg) and *m*-chloroperbenzoic acid (625 mg) in chloroform (25 ml) was heated to reflux for 35 min. The solution was cooled, washed successively with 10% aqueous sodium sulfite, 10% aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was chromatographed on silica gel. Elution with chloroform–ethyl acetate (19:1) gave the sulfone **15** (240 mg) which was crystallized from methanol to give analytically pure **15** (193 mg): mp 191–193°; ν_{max} 1717, 1316, 1124 cm^{-1}; nmr δ 0.65 (s, 3 H, 18-CH_3), 0.78 (s, 3 H, 19-CH_3), 3.25 (m, 2 H, SO_2CH_2), and 4.51 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_4S$: C, 70.69; H, 9.82; S, 6.49. Found: C, 70.65; H, 9.58; S, 6.36.

Sulfone 16 Derived from 5β-Cholestane-3,4-dione 3-Ethylene Monothioketal (8c).—A solution of the monothioketal **8c** (258 mg) and *m*-chloroperbenzoic acid (620 mg) in chloroform (25 ml) was heated to reflux for 35 min. The solution was cooled, washed successively with 10% aqueous sodium sulfite, 10% aqueous sodium carbonate, and water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product (248 mg) was crystallized from methanol to give the analytically pure sulfone **16** (204 mg): mp 177–180°; ν_{max} 1712, 1315, 1110 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 1.13 (s, 3 H, 19-CH_3), 2.68 (m, 1 H, 5β H), 3.28 (m, 2 H, $SOCH_2$), and 4.60 (m, 2 H, OCH_2).

Anal. Calcd for $C_{29}H_{48}O_4S$: C, 70.69; H, 9.82; S, 6.49. Found: C, 70.76; H, 9.62; S, 6.41.

4-Ethoxy-3,5-cholestadiene (9).—3,5-cholestadieno[4,3-*b*]oxathiane (**7**, 500 mg) was desulfurized by stirring with Raney nickel (2 teaspoons; W-2) in benzene (50 ml) for 75 min. The mixture was filtered and evaporated *in vacuo* and the residue was crystallized twice from ether–methanol, giving the enol ether **9** (150 mg): mp 71–75°; $[\alpha]_D$ −19°; $\lambda_{max}^{heptane}$ 243 nm (12,000); ν_{max} 1650, 1618 cm^{-1}; nmr δ 0.67 (s, 3, 18-CH_3), 0.94 (s, 3, 19-CH_3), 1.28 (t, 3 H, J = 7 Hz, CH_3 of ethoxyl group), 3.66 (q, 2 H, J = 7 Hz, CH_2 of ethoxy group), 4.64 (s, 1, C-3 vinyl hydrogen), and 6.02 (s, 1, C-6 vinyl hydrogen); mass spectrum 412 (M^+), 397.

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.24; H, 11.28.

5-Cholesten-4-one (10) from 4-Ethoxy-3,5-cholestadiene (9).—The enol ether **9** (110 mg) was dissolved in a mixture of ethanol (22 ml), water (2 ml), and glacial acetic acid (2 ml), and the solution was heated on the steam bath for 3 min and then left at 25° for 30 min. The reaction mixture was then concentrated to about 15 ml *in vacuo*, diluted with water, and extracted with chloroform. The chloroform extract was washed with water and evaporated *in vacuo* to an oily residue which was chromatographed on silica gel (6 g). Elution with petroleum ether–ethyl acetate (19:1) gave crystalline 5-cholesten-4-one (**10**, 80 mg): mp 112–114° (from methylene chloride–methanol); $[\alpha]_D$ −31° (lit.[8] mp 112°; $[\alpha]_D$ −32°).

5α- and 5β-Cholestane-3,4-dione 3-Ethylene Dithioketal (11a and 11b).—A mixture of 4-hydroxy-4-cholesten-3-one (**1a**, 500 mg), 1,2-ethanedithiol (1.0 ml), and benzene (40 ml) containing *p*-toluenesulfonic acid (110 mg) was heated to reflux under a Dean-Stark water separator for 20 min. The mixture was cooled, washed successively with 10% aqueous Na_2CO_3 solution and water, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was dissolved in petroleum ether and chromatographed on Florisil. Elution with petroleum ether gave the 5β-dithioketal (**11b**) which was recrystallized from methanol to give pure **11b** (70 mg): mp 131.5–132°; $[\alpha]_D$ +109° (lit.[12] mp 128°, $[\alpha]_D$ +126°); $\nu_{max}^{CCl_4}$ 1712 cm^{-1}; nmr δ 0.64 (s, 3 H, 18-CH_3), 1.09 (s, 3 H, 19-CH_3), and 3.29 (m, 4 H, SCH_2CH_2S).

Anal. Calcd for $C_{29}H_{48}OS_2$: C, 73.07; H, 10.15; S, 13.42. Found: C, 73.36; H, 10.26; S, 13.28.

Further elution with petroleum ether–ethyl acetate (19:1) gave the 5α-dithioketal **11a** which was crystallized from methanol to give the analytical sample (60 mg): mp 143–144°; $[\alpha]_D$ 0°; $\nu_{max}^{CCl_4}$ 1716 cm^{-1}; nmr δ 0.65 (s, 3 H, 18-CH_3) 0.73 (s, 3 H, 19-CH_3), and 3.27 (s, 4 H, SCH_2CH_2S).

Anal. Calcd for $C_{29}H_{48}OS_2$: C, 73.07; H, 10.15; S, 13.42. Found: C, 73.53; H, 10.33; S, 13.25.

4β-Hydroxy-5α-Cholestan-3-one 3-Ethylene Dithioketal (12).—To a solution of the 4-oxo compound **11a** (300 mg) in dioxane (54 ml) and water (6 ml) was added sodium borohydride (300 mg), and the solution was stirred at room temperature for 72 hr. The crude product (isolated by precipitation with water and filtration) was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1) to give the analytically pure 4β-hydroxy compound **12** (202 mg): mp 174–175° (from methylene chloride–methanol); $[\alpha]_D$ +24°; $\nu_{max}^{CCl_4}$ 3453 cm^{-1}; nmr δ 0.65 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 3.27 (s, H, SCH_2CH_2S); and 3.50 (s, 1 H, $W_{1/2}$ = 2.5 Hz, CHOH); mass spectrum 478 (M^+), 460.

Anal. Calcd for $C_{29}H_{50}OS_2$: C, 72.76; H, 10.53; S, 13.37. Found: C, 72.82; H, 10.84; S, 13.09.

In addition, a minor product (9 mg) was isolated from the preparative tlc. This compound had mp 176–177° (from methanol), mass spectrum 478 (M^+), 460, and is tentatively formulated as 5α-cholestan-4α-ol-3-one 3-ethylene dithioketal. Lack of material precluded further characterization.

5α-Cholestan-4β-ol from 4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Dithioketal (12).—The 4β-hydroxy compound **12** (65 mg) was desulfurized by treatment with W-2 Raney nickel in ethanol under reflux for 1.5 hr. Preparative tlc (petroleum ether–ethyl acetate, 9:1) of the crude product gave 5α-cholestan-4β-ol (20 mg), mp 135–136° (from methanol), identical with an authentic specimen as judged by tlc, melting point, and infrared comparison. In addition, there was isolated from the preparative tlc plate 19 mg of pure 5α-cholestan-4-one, identified by tlc, melting point, and infrared comparison.

4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Monothioketal [14b, 3(*R*) Isomer].—To a solution of the 4-ketone **8b** (200 mg) in dioxane (36 ml) was added sodium borohydride (200 mg) in water (4 ml) and the mixture was left at 25° for 66 hr. The crude product (obtained by dilution of the reaction mixture with water and extraction with chloroform) was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1). The analytically pure 4β-hydroxy steroid **14b** (112 mg) had mp 157–158° (from methanol); $[\alpha]_D$ +26°; $\nu_{max}^{CCl_4}$ 3593 cm^{-1}; nmr spectrum δ 0.62 (s, 3 H, 18-CH_3), 1.01 (s, 3 H, 19-CH_3), 2.94 (t, J = 5.5 Hz, 2 H, SCH_2), 3.58 (s, $W_{1/2}$ = 3 Hz, 1 H, CHOH), and 4.02 (m, 2 H, OCH_2); mass spectrum 462 (M^+), 444, 115 (base peak).

Anal. Calcd for $C_{29}H_{50}O_2S$: C, 75.28; H, 10.89; S, 6.92. Found: C, 75.29; H, 10.60; S, 6.82.

4β-Hydroxy-5α-cholestan-3-one 3-Ethylene Monothioketal [14a, 3(*S*) Isomer].—A solution of the 4-oxo compound **8a** (140 mg) in dioxane (25 ml) and water (2.8 ml) was treated with sodium borohydride (140 mg) and left at room temperature for 48 hr. The crude product was purified by preparative tlc (petroleum ether–ethyl acetate, 9:1), and the analytically pure **14a** (73 mg) had mp 160–161° (from methylene chloride–methanol); $\nu_{max}^{CCl_4}$ 3572 cm^{-1}; nmr δ 0.63 (s, 3 H, 18-CH_3), 0.98 (s, 3 H, 19-CH_3), 2.92 (t, J = 5.5 Hz, 2 H, SCH_2), 3.30 (s, $W_{1/2}$ = 5 Hz, 1 H, CHOH), and 4.08 (t, J = 5.5 Hz, 2 H, OCH_2); mass spectrum 462 (M^+), 444, 115 (base peak).

Anal. Calcd for $C_{29}H_{50}O_2S$: C, 75.28; H, 10.89; S, 6.92. Found: C, 74.88; H, 10.95; S, 7.16.

Equilibration of 5β-Cholestan-4-one Using Methanolic Potassium Hydroxide.—A solution of 5β-cholestan-4-one (66 mg) in 10% methanolic potassium hydroxide solution was heated to reflux for 18 hr. The crude product was isolated by extraction with ether (3 times), and evaporation of the ethereal extract after washing with water and drying (Na_2SO_4). Preparative tlc (petroleum ether–ethyl acetate, 9:1) gave pure 5α-cholestan-4-one (53 mg) and pure 5β-cholestan-4-one (11 mg), by elution of the scraped out zones with ethyl acetate. The products were identified by tlc, infrared comparison, and melting point, and mixture melting point determination.

Equilibration of Cholestan-4-one 3-Ethylene Monothioketals 8b and 8d with Potassium Hydroxide in Methanol. A.—The 5α-cholestan-4-one derivative **8b** (10 mg) was dissolved in 10% methanolic potassium hydroxide solution (5 ml) and the solution was heated under reflux for 4 hr. Monitoring of the reaction solution by tlc (petroleum ether–ethyl acetate, 19:1) showed no change, and the reaction mixture was worked up by dilution with water, extraction with ether, and evaporation of the dried (Na_2SO_4) ethereal extract. The crude residue (9.3 mg) was unchanged **8b** as shown by tlc, infrared comparison, and melting point, and mixture melting point determination.

B.—The 5β-cholestan-4-one derivative **8d** (6 mg) was dissolved in 10% methanolic potassium hydroxide solution (4 ml) and the solution was heated under reflux. Monitoring of the reaction solution by tlc (petroleum ether–ethyl acetate, 19:1) showed that no **8d** was present after 2 hr, but that a new compound was present with an R_F identical with that of the 5α compound **8b**. After 3 hr the situation was unchanged, and work-up of the reaction mixture as for A above gave crude product (5.5 mg) which proved identical with compound **8b** as shown by tlc, infrared comparison, and melting point, and mixture melting point determination.

Equilibration of Cholestan-4-one 3-Ethylene Monothioketals 8a and 8c with Potassium Hydroxide in Methanol. A.—A solution of the 3-monothioketal **8a** (9 mg) in 10% methanolic potassium hydroxide solution (5 ml) was heated under reflux for 2.5 hr. Monitoring of the reaction solution by tlc (petroleum ether–ethyl acetate, 19:1) had shown that no further change occurred after 2-hr reflux. Work-up as for the previous equilibration and preparative tlc of the crude product (8 mg) gave pure starting material **8a** (1.0 mg) and pure compound **8c** (6.0 mg), identified in the former case by tlc, melting point, and mixture melting point determination, and in the latter case by the above criteria and also by infrared comparison.

B.—A solution of the 3-monothioketal (**8c**, 100 mg) in 10% methanolic potassium hydroxide solution (50 ml) was heated under reflux for 2.5 hr. Work-up as for the previous equilibrations gave crude product (95 mg) which was separated by preparative tlc into pure starting material **8c** (78 mg) and pure compound **8a** (12 mg). Identification in each case was by tlc, infrared comparison, melting point, and mixture melting point determination.

Registry No.—**2a**, 18897-72-8; **2b**, 18897-73-9; **3a**, 28876-03-1; **3b**, 28876-04-2; **3c**, 28876-05-3; **7**, 28876-06-4; **8a**, 18897-78-4; **8b**, 17021-85-1; **8c**, 18897-79-5; **8d**, 18897-77-3; **9**, 28856-58-8; **11a**, 18897-74-0; **11b**, 18897-75-1; **12**, 28856-61-3; **13**, 28856-62-4; **14a**, 18897-83-1; **14b**, 18897-82-0; **15**, 18897-80-8; **16**, 18897-81-9; 5α-cholestan-4β-ol, 566-50-7; cholestane-3,4-dione bis(ethylene monothioketal), 28856-67-9.

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β-Carbonylamides in Peptide Chemistry. Synthesis of Optically Active Peptides from *N*-Acetoacetylamino Acids *via* 2-Acetonylidenoxazolidin-5-ones[1]

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N-Acetoacetylamino acids react with dicyclohexylcarbodiimide yielding 2-acetonylidenoxazolidin-5-ones. These condense in turn with nucleophiles producing amides and peptides with retention of configuration.

In contrast to the widespread tendency of activated *N*-acylamino acids to racemize under conditions suitable for peptide synthesis,[2] we recently found that *N*-acetoacetylamino acids (AcA-aa) (**1**) yield optically pure peptide derivatives under certain conditions;[3] furthermore, the acetoacetyl protecting group can be selectively cleaved with hydroxylamine under very mild conditions.[3,4]

To explore the reasons for this retention of configuration, we examined the behavior of some AcA-aa when treated with dicyclohexylcarbodiimide (DCCI) and isolated reactive acylating agents that we regard as 2-acetonylidenoxazolidin-5-ones. Their optical stability and tendency to condense with nucleophiles have been compared with similar properties of some related azlactones (**2**).

Representative *N*-AcA-aa (**1**) were reacted with DCCI under the conditions used in peptide synthesis but omitting a nucleophilic partner. A molar amount of dicyclohexylurea (DCU) was formed, while the optical activities of the solutions shifted to higher positive values. Prompt lyophylization of the solutions yielded solid, frequently crystalline products.

The uv spectra exhibited a strongly conjugated chromophore [$\lambda_{max}^{dioxane}$ near 285 nm (ε *ca.* 10,000)] ruling out the formation of anhydrides;[5] in the ir spectra, a strong absorption at 1835–1840 cm^{-1} accounted for the presence of a carbonyl group in a strained lactone ring. Finally, the nmr spectra showed absorptions that could more satisfactorily be ascribed to 2-acetonylidenoxazolidin-5-ones (**3**) than to 2-acetonyl-2-oxazolin-5-ones (**2′** and possible tautomers **2″**, **2‴**), as might be expected since β-aminoenones are more stable than the isomeric β-imino ketones.[6] Furthermore, evidence has been obtained that β-aminoenones

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