N-(4-Nitrophenyl)-3-hydroxypiperidine (I).—Fifty grams (0.5 mole) of 3-hydroxypiperidine (Aldrich Chemical Co.) and 39.8 g. (0.25 mole) of *p*-nitrochlorobenzene (Eastman Organic Chemicals) were heated on a steam-bath for 5.5 hr. The material was warmed with 250 ml. of water, cooled, filtered, and again treated with 250 ml. of water. The solid was recrystallized from 100 ml. of 95% ethanol and again from 75 ml. of ethanol; yield of I was 24.6 g. (45%), m.p. 126.5–128.5°. *Anal.* Calcd.: C, 59.7; H, 6.3; N, 12.65. Found: C, 59.6; H, 6.5; N, 12.9.

N-(4-Aminophenyl)-3-hydroxypiperidine Hemisulfate (31).—Reduction of I was carried out using 10% palladium-on-charcoal and absolute alcohol. One equivalent of concentrated sulfuric acid was added to the filtrate, and the solid was filtered and dried in a vacuum desiccator; yield of 31 from 10 g. of I, 8.4 g. Recrystallization of 2 g. of the salt from 95% ethanol gave 1 g. of 31, m.p. >240° with dec. (38.2%). *Anal.* Calcd. : C, 54.75; H, 7.1. Found: C, 55.0; H, 7.1.

Acknowledgment.—The authors wish to express their appreciation to Dr. Arnold Weissberger, of these laboratories, for his helpful discussions and assistance in preparing the manuscript.

ROCHESTER 4, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Reaction of Cholestenolone Acetates with Ethanedithiol

BY LOUIS F. FIESER, CHING YUAN[1] AND TOSHIO GOTO[2]

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Two γ-acetoxy-α,β-unsaturated ketones of the cholestane series were found to react with ethanedithiol in an anomalous fashion to give products other than the normal ethylenethioketals. Structural elucidation of anomalous compounds A-F could not be accomplished by chemical means, and ultraviolet spectroscopy afforded only limited guidance. However, nuclear magnetic resonance spectroscopy provided an unequivocal basis for evaluation of structures and configurations tentatively deduced from considerations of mechanism and led to reasonable solutions of all problems encountered.

In a study of the condensation of ketones with ethanedithiol in the presence of boron fluoride etherate,[3] it was noted that Δ^4-cholestene-6β-ol-3-one, which is easily isomerized by acids to cholestane-3,6-dione,[4] reacts with ethanedithiol to give the same product as this diketone, namely, the bisethylenethioketal **9**, m.p. 220°. The corresponding acetate **1**, however, gave an anomalous isomeric product, m.p. 131°, which we shall designate compound A. Koji Nakanishi found Δ^4-cholestene-3β-ol-6-one acetate to give another product for which no obvious formula was available. In the first phase of the present work (C. Y.), attempts to clarify the issue by condensation of the two α-acetoxy-$\Delta^{\alpha,\beta}$-ketones with ethanedithiol or β-mercaptoethanol under a variety of conditions led, rather, to expansion of the problem by isolation of four more anomalous sulfur compounds. Desulfurization, substantially the only chemical reaction available, afforded little evidence of structure, and ultraviolet absorption characteristics alone did not solve the problem.

Work on the problem was later resumed (T. G.) with guidance from nuclear magnetic resonance spectroscopy. Although the n.m.r. data do not indicate uniquely applicable structures, the combination of n.m.r. and ultraviolet characterization provided useful clues and also afforded a valuable gauge for checking formulas suggested by mechanistic considerations. We shall present first the interpretations eventually arrived at and then report the spectroscopic evidence supporting the structures.

Compound A is regarded as the unsaturated β-mercaptoethylthiomonoketal **5**. The conditions for its formation are about the same as for formation of the 3,6-bisketal **9**, and A is converted into the latter compound on further treatment with ethanedithiol and boron fluoride etherate. Like **9** it yields cholestane on desulfurization, at least on reaction with reactive Raney nickel; saturation of a double bond has been observed in other instances.[3] Compound A is the only one of the six anomalous products which gives a positive test for the sulfhydryl group with sodium azide and iodine.[5] The mechanism suggested involves initial formation of the carbonium ion **2**, and this accommodates the fact that Δ^4-cholestene-6α-ol-3-one acetate likewise yields compound A. The bisketal **9** has also been obtained from 4α-acetoxy-Δ^5-cholestene-3-one **4**.[6] The carbonium ion **3** immediately derived from **4** is destabilized by the adjacent carbonyl group and probably gives place to the more stable conjugated ion **2**, which then affords **6**, **5** and **9** as before.

The second anomalous product derived from **1**, compound B, was obtained with use of one equivalent of ethanedithiol and contains only two atoms of sulfur. An analogous product, compound C, was obtained by reaction of **1** with β-mercaptoethanol. Since C reacts with Raney nickel to form cholestenone (**12**), the oxygen can be placed at C_3 as in **11**, and compound B can be assigned the similar formula (**10**). These formulas account for the dienic ultraviolet absorption, λ266 mμ for C and λ 292 mμ for B. On the assumption that a sulfur atom attached to a double bond has a bathochromic effect of 30 mμ,[7] the values calculated[8] are 264 and 294 mμ. The formation of the S_2-product **10** is accounted for on the supposition

(1) Ph.D. Dissertation, 1956.

(2) Recipient of a Fulbright travel grant on leave from Nagoya University, Nagoya, Japan.

(3) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).

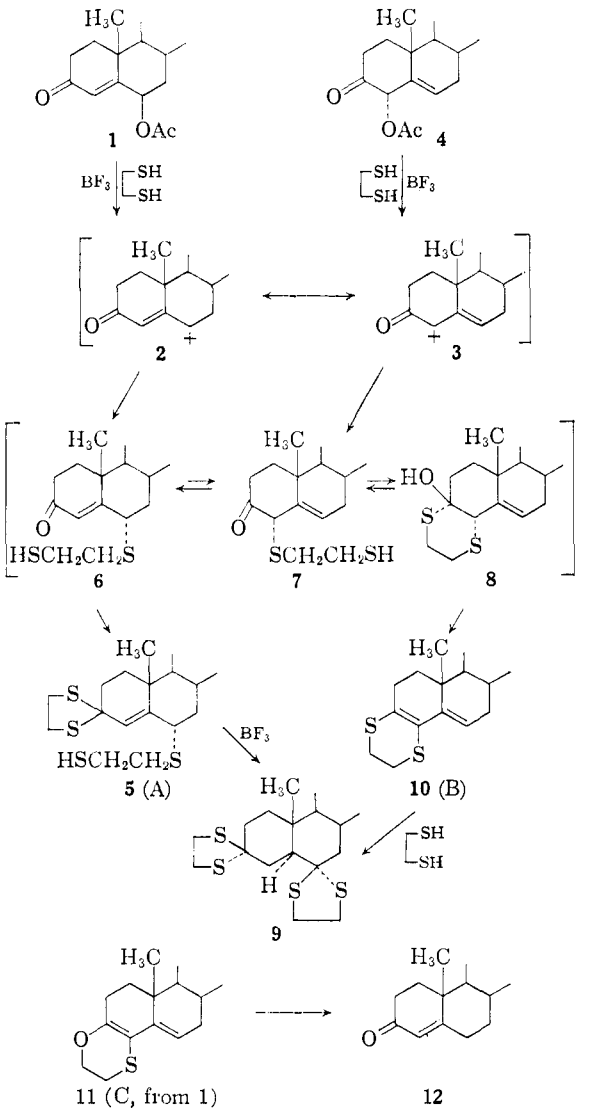
(4) L. F. Fieser, *ibid.*, **76**, 4377 (1953).

(5) F. Feigl, "Spot Tests," Vol. II, Elsevier Press, Houston, Tex., 1954, p. 164.

(6) L. F. Fieser and R. Stevenson, THIS JOURNAL, **76**, 1728 (1954).

(7) J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *ibid.*, **73**, 1528 (1951), report that testosterone 3-benzyl thioenol ether absorbs at 268 mμ; the enol acetate absorbs at 239 mμ.

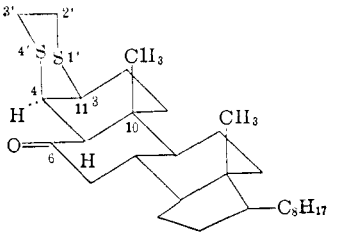
(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 16–18.



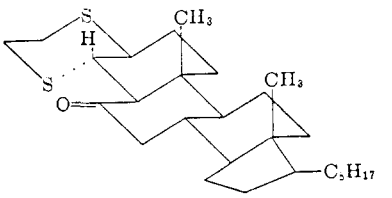
that intermediates **6** and **7** are interconvertible, and that in the absence of excess ethanedithiol the probably less stable form **7** is cyclized to **8,** which undergoes irreversible dehydration to **10.** The hemithio compound **11** can arise by a similar process. The S_2-product **10** on further reaction with ethanedithiol is convertible with some difficulty into the bisketal **9.** It seems likely that the initial reaction is a 1,4-addition of the reagent with linkage of sulfur at C_6, and various sequences can then lead to **9.**

Δ^4-Cholestene-3β-ol-6-one acetate (**13**) on BF_3-catalyzed reaction with ethanedithiol in limited amounts and in excess afforded neither a normal monoketal nor a bisketal but gave instead three abnormal products. That the initial step is the formation of the carbonium ion **14** is indicated by the observation that in the absence of ethanedithiol the enolone acetate **13** is converted by boron fluoride etherate into $\Delta^{2,4}$-cholestadiene-6-one (**16**).[9] In the presence of ethanedithiol, the ion **14** is assumed to form first the mercaptan **15,** in which sulfur is linked to C_3 in the preferential equatorial orientation (β). The sulfhydryl group then attacks C_4 on the β-side to give **18,** and in the presence of excess reagent this structure is stabilized by ketalization at C_6 and formation of the saturated S_4-substance **17,** designated compound D. Compound D, obtainable in high yield, is an isomer of the normal bisthioketal **9,** and like this substance yields cholestane on desulfurization. The abnormal product D may be described as having a 6,6-thioketal group and a 3,4-pseudothioketal group. The latter group is present also in compound B (**10,** above). Reaction of the enolone acetate **13** with one equivalent of ethanedithiol led to isolation in low yield of a ketonic product, compound E (**19**), characterized by desulfurization with deactivated Raney nickel to a product identified as cholestane-6-one. Compound E on treatment with more reagent afforded a third S_4-product, compound F, regarded as the 3,4-pseudoketal-6,6-ketal **20,** stereoisomeric with compound D (**17**). In **17** the six-membered heterocyclic ring has the 3β,4β-orientation, whereas in **20** the junction is 3β,4α. The hypothetical ketonic intermediate **18** is assumed to have the 3β,4β-orientation on mechanistic grounds, but examination of the conformational formula **18a** reveals that **18a** should be less stable than the 3β,4α-form **19a** because of the severe non-bonded interaction of the axial 10-methyl group with the axial sulfur atom (4′) attached to C_4. Isomerization to **19a,** possibly by enolization and bond migration, puts the sulfur atom into the equatorial orientation and relieves excessive steric strain. In the reaction with one equivalent of reagent, the unstable ketone **18** isomerized to **19,** the compound isolated (E). With more reagent, this then affords **20** (F).

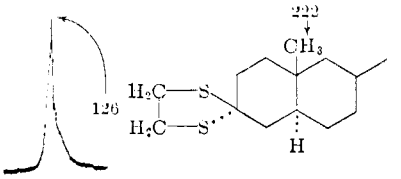
(9) H. Reich, F. E. Walker and R. W. Collins, *J. Org. Chem.*, **16**, 1753 (1957).



18a

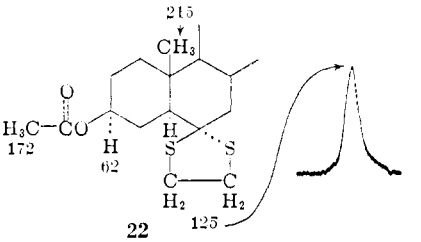


19a



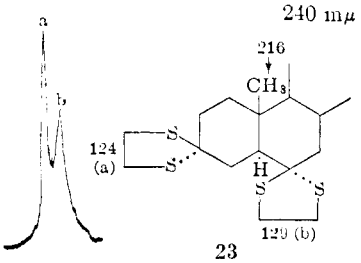
21

240 mμ (275)



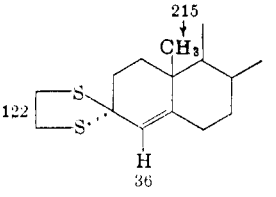
22

240 mμ (358)



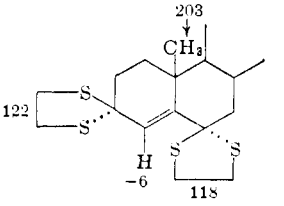
23

241 mμ (725)



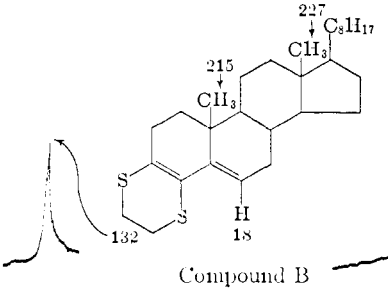
24

213 mμ (10,200)

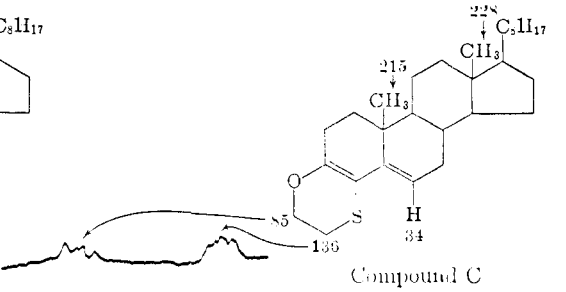


25

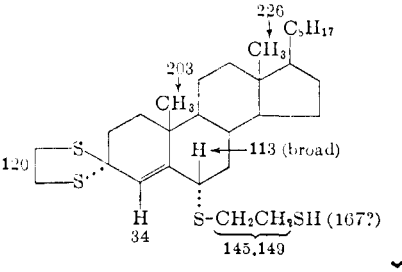
211, 230, 255 mμ
(10,700; 7,440; 2,890)



Compound B

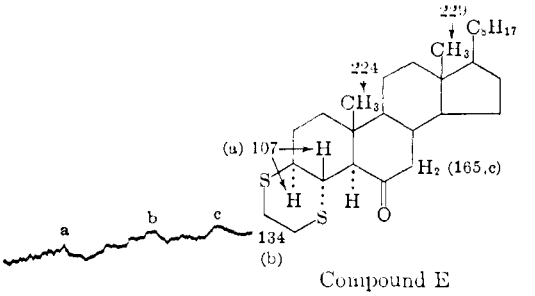


Compound C



Compound A

212, 255 mμ (13,000; 2,280)



Compound E

N.m.r. and Ultraviolet Spectra.—Nuclear magnetic resonance spectra were determined in $CDCl_3$ at 40 megacycles/sec. with benzene resonance as the standard of reference. Data for five cholestane or cholestene thioketals of unequivocal structure are reported in formulas **21–25** by citation of the cycles per second of peaks associated with specific hydrogen atoms. Cholestane-3-one-ethylenethioketal (**21**)[3] gives rise to a very strong, sharp peak at 126 c.p.s. attributable to resonance of the four equivalent methylene hydrogens of the five-membered heterocyclic ring attached to C_3; the fact that no splitting occurs shows that the four hydrogens of the ethylene group are in very nearly the same electronic environment. The 6-ketal group of **22** gives rise to a somewhat broader peak at a slightly lower field (125 c.p.s.). The 3,6-bisketal **23** gives rise to two peaks in the same region and the sharper peak at 124 c.p.s. is assigned to the hydrogens of the 3-ketal group even though it is at a lower

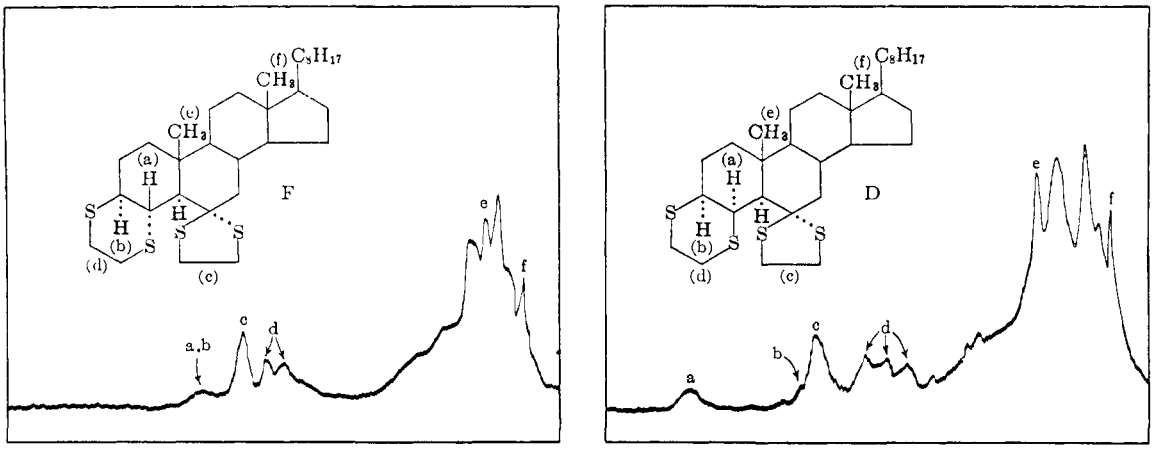


Fig. 1.—N.m.r. spectra, cycles per sec. Compound F (**20**): a,b, 102 (axial 3α-H and 4β-H); c, 120 (6-ketal ethylene hydrogens); d, 130, 140 (pseudoketal ethylene hydrogens); e, 212 (10-CH_3); f, 228 (13-CH_3). Compound D (**17**): a, 72 (equatorial 4α-H); b, broad band centering at 115 (axial 3α-H); c, 120 (6-ketal ethylene hydrogens); d, three bands centering at 146 (pseudoketal ethylene hydrogens); e, 200 (10-CH_3); f, 227 (13-CH_3).

field than the peak at 129 c.p.s. Comparison of the unsaturated 3-ketal **24** with the parent compound **21** shows that the double bond produces a slight shift (4 c.p.s.) in the sharp ethylene hydrogen peak for the 3-ketal group. The unsaturated bisketal **25** resembles the parent **23** in that the sharper peak is that of the 3-ketal group, but this is at a higher rather than lower field than the 6-ketal peak. It is apparent that five-membered ketal rings are recognizable from strong resonance peaks in the range 118–129 c.p.s. The acetate **22** gives a broad band centering at 62 c.p.s. attributable to the axial 3α-hydrogen. The spectra of compounds **24** and **25** show sharp bands characteristic of olefinic hydrogens, and the shift from 36 to −6 c.p.s. reflects the effect of the sulfur atoms at C_6. The figures recorded for the position of the 10-methyl peak show that substituents in rings A and B affect the electronic environment of the 10-methyl hydrogens. In contrast, the peaks for the 13-methyl group are all in the range 225–229 c.p.s.

Reference compounds **21** and **22** show weak ultraviolet absorption characteristic of a five-membered thioketal ring; the bisketal **23** has a band at the same position but of twice the intensity. In compound **24** the ketal ring is conjugated with a double bond and the absorption is almost comparable to that of a diene. The second ketal group of **25** extends the conjugation and gives rise to absorption (shoulders) at longer wave length. The absorption characteristics reveal that the unsaturated bisketal **25** has a conjugated system somewhat analogous to that of Δ^4-cholestene-3,6-dione, and the analogy helps account for the surprising observation that the substance is reduced to **23** by ethanedithiol in the presence of boron fluoride etherate at room temperature. Zinc and acetic acid, which constitutes a specific means for reduction of the Δ^4-ene-3,6-dione, caused no noticeable conversion of the unsaturated to the saturated bisketal. The unsaturated monoketal **24** is not similarly reduced by ethanedithiol, and Δ^4-cholestene-3-one is stable to zinc and acetic acid.

The structures deduced above for the abnormal reaction products F (**20**) and D(**17**) represent these substances as C_4-epimers, and the n.m.r. spectra reproduced in Fig. 1 substantiate the assignment. Both spectra contain a prominent but rather broad band (c) at 120 c.p.s. which is clearly attributable to resonance of the four hydrogens of the 6-ketal group. The six-membered pseudoketal ring is less strained than the five-membered ring and hence it is reasonable to attribute bands (d), in the region of about 130–150 c.p.s. to the four ethylene hydrogens of the ring extending to C_3 and C_4. Compound F is formulated as having axial 3α- and 4β-hydrogens, and the band labeled (a, b) at 102 c.p.s. is indeed consistent with the presence of two equivalent axial hydrogens on sulfur-bearing carbon atoms. With compound D, however, only a small band (b) appears at a corresponding position (115 c.p.s.), and the companion band (a) is shifted to a much lower field (72 c.p.s.). In the case of a carbon carrying a hydroxyl or acetoxyl group an equatorial hydrogen usually gives a peak at a frequency about 20–25 c.p.s. lower than an axial hydrogen. In compound D, furthermore, the equatorial 4α-hydrogen should be shifted to still lower frequency because of its proximity to the β-sulfur atom at C_6, and hence the peak at 72 c.p.s is fully consistent with the configuration assigned. A further check is that the 10-methyl peak for compound F appears at 212 c.p.s. but in D it is shifted to 200 c.p.s.; the model shows that in D the 4β-sulfur atom is very close to the 10-methyl group and hence in a position to dampen the resonance.

The positions of the principal n.m.r. peaks for the other four anomalous products are reported in the formulas. Compounds B and C give olefinic hydrogen peaks consistent with the presence of hydrogen at C_6, a 13-methyl peak at the normal position, and a 10-methyl peak shifted from the normal position at 222 c.p.s. by the heterocyclic 3,4-ring. In compound B the four hydrogens in the heterocyclic ring evidently are electronically equivalent for they give rise to a single strong, sharp peak at 132 c.p.s. Compound C presents a different pattern, since the methylene group linked to oxygen differs in environment from that linked to sulfur. Since the two groups are coupled, each

band is split into several peaks. One group of bands centered at 136 c.p.s. can be assigned to the S-linked methylene hydrogens, as in compound B, and another group centered at 85 c.p.s. is thus associated with the O-linked group.

The spectrum of compound A contains a strong, sharp peak at 120 c.p.s. attributable to a Δ^4-ene-3-ketal grouping (compare **24**, above). Peaks at 145 and 149 c.p.s. are evidently due to the S-linked methylene groups, comparable to those of the (unstrained) pseudoketals F and D. A sharp peak at 34 c.p.s. identifies the olefinic hydrogen at C_4 and a broad band centering at 113 c.p.s. is attributed to the axial 6β-hydrogen attached to a sulfur-linked carbon. A peak at 167 c.p.s. is tentatively assigned to the sulfhydryl hydrogen. Compound A shows ultraviolet absorption intermediate between reference compounds **24** and **25**. The n.m.r. spectrum of compound E shows one series of bands centering at 107 c.p.s. attributable to the axial 3α- and 4β-hydrogens and another series at 134 c.p.s. associated with the pseudoketal hydrogens; similar characteristics were noted with compound F. The hydrogens at C_7 seem responsible for a broad band at 165 c.p.s. Compound E shows no absorption at 240 mμ and therefore contains no five-membered ketal grouping; it gives rise merely to a shoulder at about 230 mμ (780).

Acknowledgments.—This investigation was supported by grants from the National Cancer Institute of the National Institutes of Health (CY 1696, Endo), the National Science Foundation, Research Corporation, and the Higgins Fund of Harvard University. We are indebted to Professor Koji Nakanishi for brief participation in the work in 1952.

Experimental (C. Y.)

Compound A (5).—In a repetition of the experiment reported,[3] Δ^4-cholestene-6β-ol-3-one acetate (1) on treatment with ethanedithiol and boron fluoride etherate yielded both compound A and **cholestane-3,6-dione bisethylenethioketal** (9). The preparation of A is facilitated by use of acetic acid as solvent, for in this case the formation of **9** was not observed. Thus addition of 1 ml. each of ethanedithiol and boron fluoride etherate to a solution of 0.6 g. of the acetate 1 in 10 ml. of acetic acid caused prompt separation of a paste of product. After two days methanol was added and the product collected. Purification by solution in chloroform and precipitation with methanol gave 0.5 g. of A as an amorphous powder, m.p. 130–131°. Repetition of the process raised the m.p. to 131–132°, α_D +66° Chf, positive sodium azide–iodine test.[5]

Treatment of 0.2 g. of the acetate 1 with 1 ml. each of ethanedithiol and catalyst for 8 hr. at 25° afforded the bisketal **9**, m.p. 217–219° Chf. Treatment of 50 mg. of A in the same way for 6 hr. and crystallization of the product gave 20 mg. of **9**, m.p. 217–221°, α_D +35° Chf.

For desulfurization, 0.6 g. of A was refluxed with 6 g. of Raney nickel in 70 ml. of absolute ethanol for 9 hr. The mixture was filtered through Supercel and addition of water to the filtrate precipitated a solid which on crystallization from methanol formed small plates (0.3 g.), m.p. 67–69°. Chromatography raised the m.p. to 74–75° and the sample gave a negative tetranitromethane test and did not depress the m.p. of **cholestane**.

Anal. Calcd. for $C_{27}H_{48}$ (372.64): C, 87.02; H, 12.98. Found: C, 87.15; H, 13.00.

Compound B (10).—A solution of 1.6 g. of Δ^4-cholestene-6β-ol-3-one acetate (m.p. 103°) in 10 ml. of acetic acid was treated at 25° with 0.29 ml. (**1** equiv.) of ethanedithiol in 3 ml. of acetic acid, followed by 6 ml. of boron fluoride etherate. The solution turned orange and at once set to a white paste. After 20 min. methanol was added for thinning and the amorphous white solid was collected (1.25 g.). Attempted crystallization from chloroform–methanol, acetic acid, acetone or hexane gave only fluffy, amorphous solid, m.p. 152–157°. Some purification was accomplished by elution from Woelm alumina (grade 1) with 3:2 petroleum ether–benzene; the substance then separated from a solution in methylene chloride–methanol as an amorphous powder, and repetition of the process gave slightly yellowish material, m.p. 165°, α_D −121° Chf; λ^{EtOH} 239, 292 mμ (10,700, 13,200); brown color with tetranitromethane in chloroform.

Anal. Calcd. for $C_{29}H_{46}S_2$ (458.66): C, 75.94; H, 10.11. Found: C, 75.91; H, 10.25.

A solution of 0.15 g. of B in 1 ml. of ethanedithiol on addition of 1 ml. of boron fluoride etherate slowly deposited a reddish solid. After 24 hr. the paste was thinned with methanol and the resulting white solid was collected and crystallized twice from chloroform–methanol to give needles of **cholestane-3,6-dione bisethylenethioketal**, m.p. 215–217°, α_D +28°.

Compound C(11).—A solution of 1 g. of Δ^4-cholestene-6β-ol-3-one acetate in 4 ml. of acetic acid was treated with 0.18 g. (1 equivl) of β-mercaptoethanol in 2 ml. of acetic acid and 1 ml. of boron fluoride etherate, and after 20 min. the resulting paste was thinned with methanol and the product collected: 0.63 g., m.p. 151–153°, λ^{Chf} 6.13, 6.20 μ. Crystallization from ether–ethanol or from acetone gave glistening needles or cylindrical prisms, m.p. 154–155°, α_D −122°, λ^{EtOH} 266 mμ (9,340), brown color with tetranitromethane.

Anal. Calcd. for $C_{29}H_{46}OS$ (442.72): C, 78.68; H, 10.47; S, 7.28. Found: C, 78.69, 78.94; H, 10.53, 10.58; S, 7.15; mol. wt. (Rast), 417.

A run made in the same way but with excess β-mercaptoethanol (0.4 ml.) and conducted overnight afforded the same monohemithio derivative (0.74 g., m.p. 154–155°).

Desulfurization was accomplished by refluxing 1 g. of C with 4 g. of Raney nickel in 100 ml. of acetone for 5 hr. The product was recovered in the usual way and on chromatography (0.2 g., m.p. 78–80°) and crystallization from ether–ethanol gave needles of **Δ^4-cholestene-3-one**, m.p. 80–81°, α_D + 89°, λ^{Chf} 6.01, 6.21 μ, undepressed by admixture with an authentic sample; thioketal derivative, m.p. 112–113°, α_D +110°.

Compound D (17) was prepared for the first time by K. Nakanishi by allowing a mixture of 440 mg. of Δ^4-cholestene-3β-ol-6-one acetate (**13**), 500 mg. of freshly fused zinc chloride, 500 mg. of sodium sulfate and 0.45 ml. of ethanedithiol to stand at room temperature for 84 hr. The mixture was extracted with chloroform, and addition of ethanol to the extract caused separation of fine needles. Recrystallization in the same way gave 350 mg. of needles, m.p. 279.5–280.5°, α_D +39° Chf. An identical sample was later obtained (C. Y.) by letting a mixture of 0.2 g. of **13** in 0.5 ml. each of ethanedithiol and boron fluoride etherate stand overnight and adding methanol; crystallization from chloroform–methanol gave 0.18 g. of fine needles, m.p. 280–281°.

Anal. Calcd. for $C_{31}H_{52}S_4$ (552.94): C, 67.36; H, 9.48; S, 23.19. Found: C, 66.98, 67.21; H, 9.42, 9.51; S, 24.45, 23.69; mol. wt. (Rast), 561.

Desulfurization of 200 mg. of **17** (K. N.) with excess Raney nickel in refluxing ethanol (8 hr.) gave 100 mg. of **cholestane**, m.p. 80–81°.

Anal. Calcd. for $C_{12}H_{48}$ (372.64); C, 87.02; H, 12.98. Found: C, 86.75; H, 12.88.

Compound E (19).—A solution of 4 g. of the acetate **13** and 0.95 g. of ethanedithiol (1 equiv. = 0.87 g.) in 150 ml. of acetic acid was treated with 16 ml. of boron fluoride etherate. The solution turned purple, with gradual separation of a solid. The product was recovered by extraction with chloroform and chromatographed. Elution with 1:1 petroleum ether–benzene and then with benzene gave material which on crystallization from ethyl acetate–ethanol or chloroform–ethanol (Norit) gave 0.9 g. of needles, m.p. 183–185°. On two more crystallizations the sample melted at 185–186°, α_D −76° Clf, λ^{Chf} 5.85 μ.

Anal. Calcd. for $C_{29}H_{48}OS_2$ (476.67): C, 73.07; H, 10.15; S, 13.54. Found: C, 72.76; H, 10.15; S, 13.47.

When technical grade ether was used for crystallization, E was gradually transformed into the **disulfoxide**. An

identical product resulted on heating E (100 mg.) in dioxane (15 ml.) with 30% hydrogen peroxide (1 ml.) on the steam-bath for 5 min.[10] The substance crystallized from ethanol in needles having a glistening metallic luster, m.p. 270–275° dec., α_D −188° Chf; λ^{Chf} 5.83, 9.72 μ.

Anal. Calcd. for $C_{29}H_{48}O_3S_2$ (508.67); C, 68.47; H, 9.51. Found: C, 68.38; H, 9.36.

One gram of compound E was refluxed with 8 g. of deactivated Raney nickel in 70 ml. of dioxane for 7 hr. and the oily product (0.8 g.) was chromatographed. Crystallization afforded crude **cholestane-6-one**, m.p. 84–88°, and two more crystallizations raised the m.p. only to 91–94°. The sample did not depress the m.p. of authentic cholestane-6-one, m.p. 96–98°, and the infrared spectrum was identical except for the presence of a low-intensity peak at 15.09 μ. However, conversion of a 50-mg. sample to the oxime[11] (44 mg.) and two crystallizations from ethanol afforded needles of satisfactory cholestane-6-one oxime, m.p. 195–196° (Reich, *et al.*,[8] report 194–196°).

Anal. Calcd. for $C_{27}H_{47}ON$ (401.65): C, 80.73; H, 11.80. Found: C, 80.79; H, 11.69.

Compound F (20).—On addition of 0.5 ml. of boron fluoride etherate to a solution of 45 mg. of compound E (m.p. 186°) in 0.5 ml. of ethanedithiol a stiff paste soon resulted and did not change in color on standing. Crystallization of the product from acetone gave 40 mg. of slender needles, m.p. 233–234°. After two more crystallizations the sample melted at 234°, α_D −20° Chf.

Anal. Calcd. for $C_{31}H_{52}S_4$ (552.94): C, 67.36; H, 9.48; S, 23.19. Found: C, 67.19; H, 9.47; S, 23.15.

$\Delta^{2,4}$-Cholestadiene-6-one (16).—After addition of 1 ml. of boron fluoride etherate to an orange-yellow solution of 1 g. of Δ^4-cholestene-3β-ol-6-one acetate (1) in 15 ml. of acetic acid the solution was allowed to stand overnight and the deep reddish-brown mixture was diluted with water and extracted with benzene. After adsorption on alumina, 7:3 petroleum ether–benzene eluted a series of crystalline fractions and crystallization of early fractions from ethanol afforded the dienone in 15% yield as needles, m.p. 125–126°, λ^{EtOH} 317 mμ; λ^{Chf} 5.98, 6.13, 6.40, 6.60 μ. The constants agree with those reported by Tarlton.[12] Later fractions afforded 40% of starting material (1).

3β-Acetoxycholestane-6-one ethylenethioketal (22), obtained by reaction of the ketone with ethanedithiol and boron fluoride etherate, on two crystallizations from acetone melted at 156–157°.

Anal. Calcd. for $C_{31}H_{52}S_2O_2$ (520.85): C, 71.48; H, 10.06. Found: C, 71.72; H, 9.86.

Desulfurization of 300 mg. of material with 3 g. of Raney nickel in refluxing dioxane (25 ml., 5 hr.) and crystallization from ethanol gave 170 mg. of **cholestanyl acetate**, needles, m.p. 107–109°, identified by mixed m.p. determination.

Reduction of Δ^4-Cholestene-3,6-dione Bisethylenethioketal (25) by Ethanedithiol.—A solution of 0.91 g. of **25** (m.p. 207°) in 3 ml. of chloroform was treated with 1.5 ml. each of ethanedithiol and boron fluoride etherate and let stand at room temperature. The solution turned red and a precipitate separated and later redissolved. After 24 hr. addition of methanol precipitated 0.73 g. of a white solid, m.p. 217°, and a sample recrystallized from chloroform–methanol, m.p. 218–219°, α_D + 34°, was identical with **cholestane-3,6-dione bisethyleneketal (23)**. Reduction of **25** to **23** was effected also with ethanedithiol and boron fluoride etherate and no further solvent. No reduction was observed in the absence of boron fluoride etherate. Δ^4-Cholestene-3-one ethylenethioketal was recovered unchanged under conditions suitable for the reduction of **25**.

Cholestane-3,6-dione Bispropylenethioketal.—A mixture of 0.97 g. of the dione with 1 ml. each of 1,3-propanedithiol and boron fluoride etherate was let stand for 8 hr., when a red oil had separated, and on addition of methanol a white product separated (1.2 g., 165–178°). Chromatography and crystallization from acetone and then from chloroform–methanol gave material melting at 180–181°, α_D +80° Chf, λ^{EtOH} 248 mμ (2,090).[13]

Anal. Calcd. for $C_{33}H_{56}S_4$ (580.78): C, 68.24; H, 9.72. Found: C, 68.04; H, 9.73.

An attempt to prepare a comparable derivative from Δ^4-cholestene-3,6-dione afforded only oily products.

Experiments by Koji Nakanishi

6-Ethoxy-$\Delta^{4,6}$-cholestadiene-3β-ol (26).—A solution of 7.3 g. of Δ^4-cholestene-3,6-dione enol ethyl ether (m.p. 164–165°) in 300 ml. of absolute ether was refluxed for 2 hr. with 350 mg. of pulverized lithium aluminum hydride, excess reagent was decomposed with ethyl acetate and water, and an ethereal extract was dried and evaporated. Two crystallizations of the product from petroleum ether gave 4.3 g. of fine needles, m.p. 96.5–97.5°, α_D −52.9° Chf., λ^{EtOH} 250 mμ (13,800).

Anal. Cacd. for $C_{29}H_{48}O_2$ (428.67): C, 81.25; H, 11.29. Found: C, 81.19; H, 11.26.

Δ^4-Cholestene-3β-ol-6-one (27).—A solution of 200 mg. of the ethoxy alcohol **26** and 400 mg. of tartaric acid in 20 ml. of 80% ethanol was left overnight at room temperature. Gradual addition of water caused separation of crystalline material and the sample was recrystallized by addition of water to a solution in ethanol at room temperature. The product (170 mg.), m.p. 151.5–152.5°, α_D −11.8°, gave no depression on admixture with a sample prepared from cholestane-3β-ol-6-one according to Heilbron, Jones and Spring.[14] Acetylation of **27** with acetic anhydride and pyridine at room tmperature afforded **Δ^4-cholestene-3β-ol-6-one acetate (13)**, m.p. 109–110°, λ^{EtOH} 236 mμ (6,300), identical with authentic material.[14]

Δ^4-Cholestene-3α-ol-6-one Acetate (28).—The method developed for obtaining this compound is based on the observation that refluxing the 3β-acetoxy compound **13** in 80% acetic acid effects partial epimerization at C_3 to give a mixture of **13** and **28**, along with some of the 3,6-dione. The epimers **13** and **28** form a 1:1 complex which can be isolated by fractional crystallization. Saponification and processing with digitonin then effects separation of the α,β-mixture. One of the various procedures studied is as follows.

A solution of 2 g. of the ethoxy alcohol **26** in 45 ml. of 80% acetic acid was refluxed for 2.5 hr. and the product was extracted with ether and acetylated with acetic anhydride and pyridine at 25°. The crude product was chromatographed and submitted to 7-stage, diamond-type fractional crystallization from methanol, which afforded 20 mg. of Δ^4-cholestene-3β-ol-6-one acetate and 440 mg. of the 1:1 complex, m.p. 106–107°, α_D +23° Chf. A solution of 200 mg. of this complex in 15 ml. of methanol was treated with a solution of 45 mg. of anhydrous potassium carbonate in 1 ml. of water and let stand overnight. Addition of water and one drop of acetic acid precipitated a white powder, 175 mg., m.p. 137–138°. A solution of 160 mg. of the powder in 32 ml. of 90% ethanol was treated with 460 mg. of digitonin in 7 ml. of 90% ethanol. After standing overnight the digitonide was collected (329 mg.) and the filtrate was evaporated in a current of air. The residue was extracted repeatedly with cold ether and the material recovered from the ether was acetylated (Ac_2O–Py) and chromatographed. Elution with 1:1 petroleum ether–ether gave a colorless oil which crystallized from aqueous methanol to give 34 mg. of the Δ^4-cholestene-3α-ol-6-one acetate, m.p. 90–91°, α_D +93.9° Chf, λ^{EtOH} 237 μ (7,390).

Anal. Calcd. for $C_{29}H_{46}O_3$ (442.66): C, 78.68; H, 10.48. Found: C, 78.52; H, 10.51.

Like the 3β-epimer **13**, the 3α-acetate on reaction with excess ethanedithiol afforded compound D.

Δ^4-Cholestene-3α-ol-6-one (29).—A solution of 25 mg. of **28** in 2 ml. of methanol was treated with a solution of 6 mg. of potassium carbonate in 0.2 ml. of water and left overnight at room temperature. Water was added, and crystallization of the precipitate from aqueous methanol gave 14 mg. of **29**, m.p. 124–125°, α_D +62° Chf, λ^{EtOH} 239 mμ (7,260).

Anal. Calcd. for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.71; H, 10.90.

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(10) Method of Romo, *et al.*[7]

(11) A. Windaus, *Ber.*, **53**, 488 (1920).

(12) E. J. Tarlton, Dissertation, Harvard, 1953.

(13) The extinction coefficient is much higher than observed for ethylenethioketals; comparable values are reported by D. J. Cram and M. Cordon, THIS JOURNAL, **77**, 1810 (1955).

(14) I. M. Heilbron, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 801 (1937).