lization from methanol; mixture melting point was undepressed with an authentic sample; infrared spectra were superimposable.

An authentic sample of cholesta-3,5-dien-7-one was obtained from the cholest-5-en-3β-ol-7-one 3-acetate in the manner described by Turner, Meador, and Winkler[17] and had m.p. 112–113°, λ_{max}^{EtOH} 278 mμ (ε 22,400), and R_f 0.66.

Reaction of 7α-Bromo-5α-cholestan-3β-ol-6-one 3-Acetate (XI) with Dimethyl Sulfoxide.—A stream of nitrogen was bubbled for several minutes through a mixture of 500 mg. (0.95 mmole) of the bromo ketone XI, 500 mg. (5.95 mmoles) of sodium bicarbonate, and 10 ml. of dimethyl sulfoxide, and then the mixture was stirred and heated at 125–130° under 1 atm. of nitrogen for 1 hr. The odor of dimethyl sulfide was evident and a yellow color developed. The mixture was then cooled to room temperature, diluted with 250 ml. of cold saturated brine, and extracted with three 25-ml. portions of ether. The extract was washed with ten 20-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to give 400 mg. of a bromine-free, yellow, crystalline residue which gave a deep violet-red color with alcoholic ferric chloride. When the reaction was not carried out under a nitrogen atmosphere, a bromine-containing, dark-red intractible oil was obtained as the only product.

(17) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Am. Chem. Soc.*, **79**, 4122 (1957).

The yellow residue had λ_{max}^{KBr} 2.92, 5.76, 5.98, 6.07, and 8.10 μ, similar to the spectrum of 5α-cholestan-3β-ol-6,7-dione 3-acetate (XII). The ultraviolet spectrum had λ_{max}^{EtOH} 275 mμ (absorbance = 0.69) with a shoulder at 310 mμ (absorbance = 0.13) for a sample obtained by 7:100 dilution of a stock solution containing 18.7 mg. in 25 ml. of ethanol. It was estimated from the absorbance at 275 mμ that the mixture contained 60 ± 5% of the diosphenol XII, corresponding to a yield of about 55%. T.l.c. showed a spot, R_f 0.60, attributed to the diosphenol by comparison with an authentic sample, and spots, R_f 0.65, 0.54, and 0.47, which were not identified.

A 200-mg. sample of the mixture was chromatographed on a column (15 mm. in diameter) of 15 g. of silica gel and elution with 400 ml. of benzene gave 80 mg. of a white solid: λ_{max}^{KBr} 2.92, 5.76, 5.98, 6.08, and 8.10 μ (identical with the spectrum of authentic diosphenol XII); λ_{max}^{EtOH} 273 mμ (ε 7000); R_f 0.61. The material gave a deep violet-red color with alcoholic ferric chloride. Recrystallization from methanol gave white crystals, m.p. 155–157°, undepressed on admixture with authentic material, lit.[5] m.p. 156–157°, λ_{max}^{EtOH} 274 mμ (ε 10,800).

Further elution of the column with more polar solvents gave 60 mg. of a yellow, intractible oil, which by t.l.c. gave three spots, R_f 0.65, 0.53, and 0.46. The oil was not investigated further.

The Reaction of 2α-Bromo-5α-cholestan-3-one with Dimethyl Sulfoxide

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The reaction of 2α-bromo-5α-cholestan-3-one with dimethyl sulfoxide has been shown to give 3-hydroxy-5α-cholest-3-en-2-one, 2,3-seco-5α-cholestane-2,3-dioic acid, 5α-cholestan-3-one, 5α-cholest-1-en-3-one, cholest-4-en-3-one, 2α-hydroxy-5α-cholestan-3-one, dimethyl sulfide, and other, unidentified products. The reaction of 2,2-dibromo-5α-cholestan-3-one with dimethyl sulfoxide gave 2-bromo-5α-cholest-1-en-3-one. The reaction of 2α-bromo-5α-cholestan-3-one with collidine and with lithium chloride in dimethylformamide was reinvestigated.

In recent years a number of reactions have been discovered in which dimethyl sulfoxide, commonly used as a solvent, behaved in an unusual manner as one of the reactants. Among the first of these reactions to be discovered was the conversion of α-bromo ketones to the corresponding α-diketones.[2] It was also found that secondary halides and sulfonate esters of secondary alcohols could be converted to olefins in high yield by dimethyl sulfoxide.[3] The third reaction of interest here is the conversion of primary alkyl halides and sulfonate esters of primary alcohols to the corresponding aldehydes.[4]

It is important to note the distinction between the behavior of the primary and the secondary alkyl derivatives in these reactions, the former reacting to give oxidation products, the corresponding aldehyde, and the latter reacting to give elimination products, olefins, Also of interest is the behavior of the α-halo ketones, which, while secondary halides, were of the type aryl–CO–CHBr–aryl or aryl–CO–CH_2Br where an elimination reaction would be impossible. These compounds also gave oxidation products. The question then arises as to whether α-halo ketones, structurally constituted so as to allow elimination, will give diketones or unsaturated ketones, or both, when allowed to react with dimethyl sulfoxide.

Steroid halo ketones were chosen for a study of this reaction because they were readily available, the conformation of the halogen atom was known, and, in most cases, the expected products were well-characterized compounds. In addition it was hoped that the study would result in the development of good synthetic routes to either α,β-unsaturated ketones or α-diketones in the steroid series.

The first compound chosen for study was 2α-bromo-5α-cholestan-3-one (I). Since this compound contains an equatorial bromine atom and undergoes elimination with difficulty,[5] it was anticipated that the major product would be the diketone, in the form of its diosphenol, 3-hydroxy-5α-cholest-3-en-2-one (II). Infact, when the bromo ketone was heated with dimethyl sulfoxide at 125–130° a complex mixture of products was obtained (Chart I). Sodium bicarbonate was used as an acid acceptor, since it is known that hydrogen bromide reacts with dimethyl sulfoxide to produce

(1) Abstracted from the Ph.D. Thesis of R. N. I., Brown University, 1963. Brown University Fellow, 1959–1961. Holder of the Shell Oil Co. Fundamental Research Grant in Chemistry, 1961–1962.

(2) (a) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larsen, O. Levand, and W. M. Weaver, *J. Am. Chem. Soc.*, **79**, 6562 (1957). (b) R. T. Major and H. J. Hess, *J. Org. Chem.*, **23**, 1563 (1958); J. M. Tien and I. M. Hunsberger, *Chem. Ind.*, (London), 88 (1959).

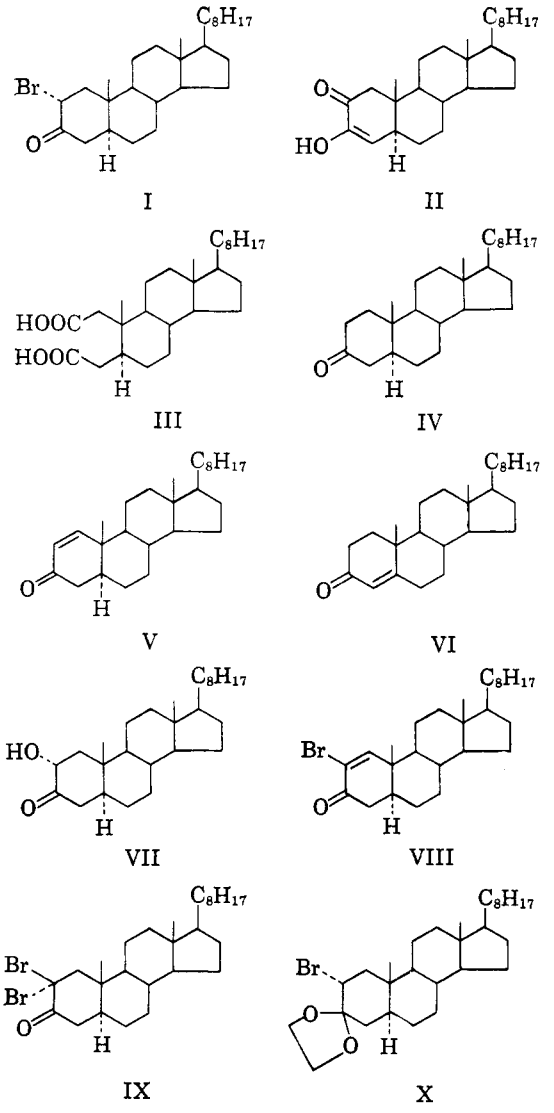
(3) H. R. Nace, *ibid.*, 1629 (1958); H. R. Nace, *J. Am. Chem. Soc.*, **81**, 5428 (1959); H. R. Nace, unpublished results.

(4) H. R. Nace, U. S. Patent 2,888,488 (May 26, 1959); N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959); H. R. Nace and J. J. Monagle, *J. Org. Chem.*, **24**, 1792 (1959).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 280.

CHART I

REACTION OF 2α-BROMO-5α-CHOLESTAN-3-ONE WITH DIMETHYL SULFOXIDE



bromine, which can then react with the other products.[6] Carbon dioxide was evolved during the course of the reaction, as well as small amounts of dimethyl sulfide.[7] The isolation and identification of the products were extremely difficult, and in some instances, the yields given are estimates based on ultraviolet absorption data. Also, in some instances, a compound could not be isolated in pure form, and it was necessary to prove its presence in the product mixture by means of thin layer chromatography (t.l.c.), vapor phase chromatography (v.p.c.), and infrared and ultraviolet spectral analyses, followed by comparison with authentic samples.

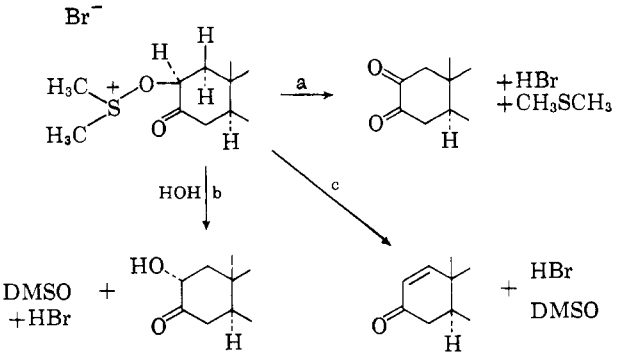
T.l.c. analysis of the crude product mixture revealed the presence of at least seven compounds; six of these were identified. The mixture was first separated into an acidic and a neutral fraction. The acidic fraction contained two compounds, the expected diosphenol II (60–65% yield) and 2,3-seco-5α-cholestane-2,3-dioic acid (III, approximately 4% yield). The diosphenol was extremely difficult to isolate in pure form but was

(6) T. L. Fletcher and H. Pan, *J. Am. Chem. Soc.*, **78**, 4812 (1956).

(7) In the early stages of this work, 1,2-epoxy-3-phenoxypropane was also used as an acid acceptor, but did not appear to offer any special advantage.

CHART II

PROPOSED MECHANISM FOR THE REACTION OF 2α-BROMO-5α-CHOLESTAN-3-ONE WITH DIMETHYL SULFOXIDE



characterized on the basis of spectral properties, quinoxaline derivative, and benzilic acid rearrangement to A-nor-5α-cholestan-2-ol-2-carboxylic acid.[8]

Work-up of the neutral fraction gave a small amount of unreacted bromo ketone, 5α-cholestan-3-one (IV), 5%), 5α-cholest-1-en-3-one (V, about 12%), cholest-4-en-3-one (VI, trace), and 2α-hydroxy-5α-cholestan-3-one (VII, 15%). The remainder of the product mixture consisted of oily materials which could not be identified.

In the early stages of the investigation it was suspected that the 5α-cholestan-3-one was not a reaction product but rather a contaminant in the bromo ketone. However, a careful investigation of the bromo ketone (see below) showed that this was not the case, and that the saturated ketone was indeed a product of the reaction. The formation of the ketone is surprising, since it represents a reduction reaction. Although dimethyl sulfoxide can behave as a mild reducing agent, its role in the present case is not clear.

The formation of the acyloin VII in this reaction was also quite interesting, and suggested the possibility that it was the precursor of the diosphenol II and the seco acid III. When a sample of the acyloin was heated in dimethyl sulfoxide with sodium bicarbonate at 125–130°, a 30% conversion to the diosphenol was observed, but no evidence was found for the formation of any seco acid. When the reaction was repeated, but under 1 atm. of nitrogen, only a trace of diosphenol was observed, and the starting material was recovered. However, when the reaction of the bromo ketone was carried out under 1 atm. of nitrogen, no significant change in the composition or yield of the products was observed, indicating that the diosphenol and the acyloin had a common precursor.

The formation of the 5α-cholest-1-en-3-one is undoubtedly the result of the elimination reaction referred to above, and the low yield indicates that the rate of the oxidation reaction is faster, which is not surprising in view of the reluctance of the 2α-bromo ketone to undergo elimination under a variety of conditions. Rearrangement of 5α-cholest-1-en-3-one to cholest-4-en-3-one has also been reported.[9]

Thus the only product whose formation is not readily explained is the seco acid. It could have been formed in at least two different ways. First, acyloins are

(8) H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).

(9) (a) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947); (b) W. G. Dauben, G. A. Boswell, and W. H. Templeton, *ibid.*, **83**, 5006 (1961); (c) M. E. Kuehne, *ibid.*, **83**, 1492 (1961); (d) C. Djerassi and J. J. Beerebohm, *J. Org. Chem.*, **19**, 1196 (1954).

known to undergo air oxidation with carbon–carbon bond cleavage to form acids[10] and, second, the diosphenol is also readily oxidized to the seco acid by dilute alkaline hydrogen peroxide.[11,12] Since the reaction in question was conducted in the presence of air, it is possible that the conditions were proper for oxidation of either of the compounds to the seco acid. No attempt was made, however, to discover the acid's mode of formation.

In order to obtain more information about the reaction, the conditions were varied in several ways. The addition of small amounts of water resulted in a decrease in the amount of diosphenol produced, evidenced by a decrease in the absorption at 272 mμ in the ultraviolet spectrum of the product mixture. In another experiment, the sodium bicarbonate was omitted and lithium bromide was added. In this case the course of the reaction was changed markedly, and the only two products isolated were 2-bromo-5α-cholest-1-en-3-one (VIII, 40%) and 5α-cholest-1-en-3-one (V, 18%). The reaction with lithium bromide was repeated, but this time with sodium bicarbonate. The crude product by t.l.c. showed all of the spots observed when the reaction was run without the lithium bromide and could be separated into an acid and a neutral fraction. The ultraviolet spectrum of the neutral fraction indicated that 5α-cholest-1-en-3-one was produced in 22–25% yield (a 100% increase) and cholest-4-en-3-one was produced in 8–10% yield (another large increase). None of the bromo olefin VIII could be found. A possible interpretation of these results is that the lithium bromide supplied additional bromide ion which could then displace the 2α-equatorial bromine atom by nucleophilic attack and give a 2β-axial bromide. This conformation would be much more favorable for elimination of hydrogen bromide and thus the yield of unsaturated ketones would be increased. When no sodium bicarbonate was present to neutralize the hydrogen bromide, it could then react with the dimethyl sulfoxide to produce bromine, which could then react with the unsaturated ketone. The resulting dibromo ketone would have both bromine atoms axial as a result of diaxial opening of the intermediate bromonium ion, and would also undergo facile elimination to give the bromo olefin VIII. Other α,β-dibromo ketones have been shown to undergo elimination with ease to give α-bromo-α,β-unsaturated ketones.[13] Additional evidence in support of this line of reasoning was obtained from the reaction of 2,2-dibromo-5α-cholestan-3-one (IX) with dimethyl sulfoxide in the presence of sodium bicarbonate. This compound also has a 2α-axial bromine atom, and underwent elimination readily, giving the 2-bromo-5α-cholest-1-en-3-one in 50% yield.

In fact, the elimination reaction of the dibromo compound with dimethyl sulfoxide gave better yields than the collidine method reported previously, or the collidine–dimethylformamide method described in the Experimental section. The bromo olefin is readily debrominated by zinc to 5α-cholest-1-en-3-one, using a procedure developed for the androstane series,[9a] and, since the unsaturated ketone thus obtained is not contaminated by the isomeric 4-en-3-one, the method is a superior one for the preparation of this compound.

In order to obtain some information on the role of the carbonyl group in this reaction, 3,3-(ethylenedioxy)-2α-bromo-5α-cholestane (X) was treated with dimethyl sulfoxide in the presence of sodium bicarbonate at 125° for 1 hr. The bromo ketal was recovered in quantitative yield, indicating that the carbonyl group in some manner activates the halogen atom in these reactions. The bromo ketal was also inert to boiling collidine, boiling alcoholic sodium hydroxide or sodium methoxide, and boiling potassium *t*-butoxide in *t*-butyl alcohol. An attractive mechanism for the reactions with dimethyl sulfoxide described above is based on the work of Winstein and Smith.[14]

They showed that the reaction of methyl iodide with dimethyl sulfoxide gave an O-alkyl salt, which could rearrange reversibly to an S-alkyl salt. Such an O-alkyl salt could give rise to the products obtained here by fission of the O–S bond and loss of a proton from C-2: (a) resulting in oxidation, hydrolysis of the C–O bond; (b) resulting in the acyloin, or proton abstraction from C-1 and C–O fission; (c) to give elimination (Chart II). However, all attempts to isolate such an intermediate from the reactions of the bromo ketone with dimethyl sulfoxide were unsuccessful and such a mechanism for the reaction still awaits proof. It is also possible that the elimination products are a result of direct ionization of the bromine atom and an E1 process, but again no evidence is available.

As stated above, the bromo ketone used in these experiments was free of unbrominated 5α-cholestan-3-one. Warnhoff[15] showed, after this work was completed, that the bromo ketone, prepared by the usual procedure, was contaminated by as much as 10% of unbrominated ketone, but he did not report the preparation of the pure bromo ketone. It can be obtained pure in 73% yield by chromatography of the crude product on silica gel.

Since the bromo ketone was available pure for the first time, several previously reported reactions were reinvestigated. The first was the reaction with collidine, which has been reported[16] to yield the 1-en-3-one V, the 4-en-3-one VI, and 5α-cholestan-3-one (IV) in varying amounts. Warnhoff, using bromo ketone known to be contaminated with cholestan-3-one, reported formation of the 1-en-3-one V (38%), the 4-en-3-one VI (25%), and the 3-one IV (37%), the yields being based on t.l.c. and ultraviolet spectroscopy. The yield of the saturated ketone was obtained by difference, since it could not be resolved by t.l.c., and allowance was made for the amount present in the starting material. In our hands, using pure bromo ketone, the reaction gave the 1-en-3-one (65%), the 4-en-3-one (13%), and less than 2% of the 3-one. The yields are based on v.p.c., in which the 3-one is well resolved from the other two components. These results indicate that the reduction reaction is not significant in the reaction of bromo ketones with collidine.

(10) M. Stoll and J. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815 (1947).
(11) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).
(12) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957).
(13) Ref. 5, p. 285.
(14) S. Winstein and S. G. Smith, *Tetrahedron*, **3**, 317 (1958). See also D. N. Jones and M. A. Saeed, *J. Chem. Soc.*, 4657 (1963).
(15) E. W. Warnhoff, *J. Org. Chem.*, **27**, 4587 (1962).
(16) See ref. 15 for an excellent critical review of the previous work.

The reaction of the bromo ketone with lithium chloride and dimethylformamide was also carried out,[17] and the 1-en-3-one (77–84%) and the 4-en-3-one, (14–20%) were obtained.

Finally, since pure bromo ketone was now available, it was used to prepare the 1-en-3-one, uncontaminated by the 3-one. Reaction of the bromo ketone with 2,4-dinitrophenylhydrazine gave the derivative of the 1-en-3-one, as described by Djerassi.[18] This was hydrolyzed to the pure 1-en-3-one, uncontaminated by the 3-one.

In conclusion, the reaction of 2α-bromo-5α-cholestan-3-one with dimethyl sulfoxide gave, contrary to expectations, a complex mixture of products, representing oxidation, elimination, reduction, and rearrangement reactions. Although the reaction with this bromo ketone is of little synthetic value, other steroid bromo ketones react with dimethyl sulfoxide in a more straightforward manner, as described in the accompanying paper.[19]

Experimental[20]

2α-Bromo-5α-cholestan-3-one (I).—To a solution of 5.0 g. (13.0 mmoles) of 5α-cholestan-3-one in 135 ml. of glacial acetic acid, 13.0 ml. of a 1.0 *M* solution of bromine in glacial acetic acid was added dropwise with stirring at room temperature. After about three-fourths of the bromine solution had been added, the product began to precipitate from solution. The product was collected, washed with glacial acetic acid, and air dried to give 4.2 g. An additional 0.6 g. was obtained from the filtrate for a total yield of 80%. Two recrystallizations from glacial acetic acid gave 3.2 g. of bromo ketone: m.p. 168–169°, $[\alpha]_D$ +42°; lit. m.p. 167.5–168°, $[\alpha]_D$ +41°,[9a] and m.p. 168–169°, $[\alpha]_D$ +46°.[21] T.l.c. gave two spots, R_f 0.80 (bromo ketone) and 0.67 (cholestan-3-one).

A solution of 5.7 g. of the bromo ketone in 200 ml. of 3:1 petroleum ether (b.p. 30–60°)–benzene was chromatographed on a column (36 mm. in diameter) of 200 g. of silica gel. Elution with 4:6 petroleum ether–benzene gave 5.2 g. (73%) of pure bromo ketone, one spot on t.l.c. Two recrystallizations from 95% ethanol gave 3.5 g., m.p. 174–174.5°, $[\alpha]_D$ +46°.

Elution of the column with ether gave 0.4 g. of 5α-cholestan-3-one, homogeneous on t.l.c. Recrystallization from 95% ethanol gave powdery white crystals, m.p. 128–129°, undepressed on admixture with an authentic sample.

Reaction of 2α-Bromo-5α-cholestan-3-one with Dimethyl Sulfoxide. A. In Air.—A mixture of 1.0 g. (2.15 mmoles) of 2α-bromo-5α-cholestan-3-one, 1.0 g. (11.9 mmoles) of sodium bicarbonate, and 15 ml. of dimethyl sulfoxide was heated at 125–130° for 30 min. with stirring. The reaction mixture foamed vigorously and developed a yellow color during the first 15 min. and the odor of dimethyl sulfide was apparent. The reaction mixture was cooled to room temperature, diluted with 200 ml. of water, and extracted with four 40-ml. portions of ether. The ether extract was washed with water, dried, and evaporated to give 815 mg. of a white crystalline solid. The solid had λ_{max}^{KBr} 2.90, 5.82, and 5.98 μ. By v.p.c. this compound showed two broad, poorly resolved peaks of nearly equal height, T_r 1.00 and 1.14. It also showed λ_{max}^{EtOH} 272 mμ (*A* 0.69) and 230 mμ (*A* 0.32) for a sample obtained by 1:10 dilution of a stock solution containing 19.4 mg. of product mixture in 25 ml. of ethanol. From the absorbance values it was estimated that the mixture contained 65 ± 5% of 3-hydroxy-5α-cholest-3-en-2-one (II) and 15 ± 5% of 5α-cholest-1-en-3-one (V), for a 60–65 and 12–18% yield, respectively. However, t.l.c. showed the product to be a complex mixture, R_f 0.84 ,0.80, 0.76, 0.68, 0.62, 0.32, and a long streak, 0.58. By comparison with authentic samples the following spots were identified: bromo ketone I, 0.80; 5α-cholest-1-en-3-one (V), 0.68; 2α-hydroxy-5α-cholestan-3-one (VII), 0.32; and 3-hydroxy-5α-cholest-3-en-2-one (II), 0.58.

A 600-mg. sample of the mixture was dissolved in 75 ml. of ether; the solution was cooled to 0° and extracted with three 20-ml. portions of 20% potassium hydroxide solution. The pale yellow precipitate which formed at the interface each time was combined with the aqueous layers; the extract was acidified with dilute hydrochloric acid and extracted with three 30-ml. portions of ether. The ether extract was then washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to give 280 mg. of pale yellow solid, the "acid fraction." The original ether solution was washed with water and saturated brine, dried over anhydrous sodium sulfate, and evaporated to give 400 mg. of white, semicrystalline material, the "neutral fraction."

The acid fraction had λ_{max}^{EtOH} 273 mμ (ε 4900), λ_{max}^{KBr} 2.92, 5.83, 6.00, 7.10, and 8.20 μ, practically identical with the infrared spectrum of 3-hydroxy-5α-cholest-3-en-2-one (II). A solution of 200 mg. in 20 ml. of ether was extracted with two 5-ml. portions of saturated potassium bicarbonate solution, and the extract was acidified with dilute hydrochloric acid and then extracted with ether. The ether extract yielded 20 mg. (4%) of semisolid which on recrystallization from aqueous acetic acid gave 2,3-seco-5α-cholestane-2,3-dioic acid (III), m.p. 180–186°, lit.[12] m.p. 195–196°; the infrared spectrum was superimposable on that of an authentic sample.

A sample of the acid fraction from another experiment was recrystallized from petroleum ether (b.p. 60–70°) and gave powdery crystals which had m.p. 120–130° and gave a deep violet-red color with alcoholic ferric chloride. 3-Hydroxy-5α-cholest-3-en-2-one had lit. m.p. 144–145.5°; $\lambda_{max}^{CCl_4}$ 2.82, 5.86, and 5.98 μ; $\lambda_{max}^{CHCl_3}$ 274 mμ (ε 6166)[8]; λ_{max}^{EtOH} 272 mμ (ε 5012).[22]

Another 90-mg. sample of the acid fraction was boiled under reflux for 1 hr. with 110 mg. of *o*-phenylenediamine. The quinoxaline derivative of the diosphenol crystallized from the solution as orange plates, m.p. 167–171°. Two recrystallizations from acetone (charcoal) gave nearly white scales, m.p. 177–178°, lit.[22] m.p. 179–180°.

Another sample, 120 mg., of the acid fraction and 1.0 g. of potassium hydroxide were dissolved in 12 ml. of 1-propanol and 2 ml. of water and the solution was boiled under reflux to rearrange the diosphenol to A-nor-5α-cholestan-2-ol-2-carboxylic acid, as described previously.[8] A light yellow solid, 115 mg., was obtained, whose infrared spectrum was identical with that of the hydroxy acid. Recrystallization from acetone gave white crystals, m.p. 235–250°, unchanged on admixture with authentic material.

The neutral fraction by t.l.c. showed all of the spots which were present in the original mixture except the streak for the acidic diosphenol II. It also had λ_{max}^{EtOH} 268 (*A* 0.32) and 230 mμ (*A* 0.29) for a sample obtained by 1:10 dilution of a stock solution containing 15.6 mg. in 25 ml. of ethanol. The absorption at 230 mμ was attributed to 5α-cholest-1-ene-3-one (V), estimated to amount to 20 ± 5% of the neutral fraction. The compound absorbing at 268 mμ was not identified.

A 200-mg. sample of the neutral fraction in 15 ml. of 4:1 petroleum ether–benzene was chromatographed on a column (15 mm. in diameter) of 25 g. of Florisil. Nothing was eluted with 150 ml. of petroleum ether or 150 ml. of 3:1 petroleum ether–

(17) Essentially the conditions described for the corresponding chloro compound (ref. 9d) were used.

(18) C. Djerassi, *J. Am. Chem. Soc.*, **71**, 1003 (1949).

(19) R. N. Iacona, A. T. Rowland, and H. R. Nace, *J. Org. Chem.*, **29**, 3495 (1964).

(20) Melting points are corrected and were obtained with a Hershberg apparatus using Anshutz thermometers. The analytical samples were recrystallized to constant melting point. Analyses were by Dr. S. M. Nagy and associates, Microchemical Laboratories, Massachusetts Institute of Technology. Optical rotations were determined on approximately 1% chloroform solutions. Column chromatographic separations were carried out using alumina (Merck & Co., Inc.), silica gel (J. T. Baker Chemical Co., 80–200-mesh powder), or Florisil (Floridin Co., 100–120 mesh). The benzene and petroleum ether used for chromatography were washed with concentrated sulfuric acid, dried, and distilled. Anhydrous ether (Mallinkrodt analytical reagent grade) was used directly.

For vapor phase chromatography an F and M Model 500 gas chromatograph, equipped with a 4-ft. column containing 1% Dow-Corning FS-1265 fluid on Gas-Chrom Z (Applied Science Laboratories) was used. Relative retention times, T_r, are given. Cholestan-3-one was the standard compound.

Thin layer chromatography was performed on layers of 500 μ of silica gel G (Desaga-Brinkman) using 3:1 benzene–ether (anhydrous solvents). The plates were developed by spraying with a solution of 5 g. of 2,4-dinitrophenylhydrazine in 60 ml. of 85% phosphoric acid and 40 ml. of 95% ethanol.

The dimethyl sulfoxide was purified by distillation from barium oxide under reduced pressure, or by filtration through Linde Type 4A Molecular Sieves, followed by distillation under reduced pressure.

(21) H. R. Nace and B. B. Smith, *J. Am. Chem. Soc.*, **76**, 6119 (1954).

(22) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938). This value of ϵ_{max} was used to calculate the yield of II.

benzene, but the first 25-ml. fraction from 1:1 petroleum ether–benzene gave 10 mg. of bromo ketone I: λ_{max}^{KBr} 5.79 μ; t.l.c., R_f 0.80. The next fraction, eluted with the same solvent, gave 20 mg. of white solid which was mainly 5α-cholestan-3-one (IV): λ_{max}^{KBr} 5.83, 5.98, 6.12 and 12.80 μ. V.p.c. showed a major peak with T_r 1.00 (87% relative abundance) for 5α-cholestan-3-one and a shoulder, 1.15 (13% relative abundance) for 5α-cholest-1-en-3-one. The yield of the 5α-cholestan-3-one was about 5%.

The next three fractions gave 30 mg. of 5α-cholest-1-en-3-one: λ_{max}^{KBr} 5.95, 6.12, and 12.80 μ; v.p.c., one peak, with T_r 1.17; λ_{max}^{EtOH} 230 mμ (ϵ 9000), corresponding to 95 ± 5% of unsaturated ketone. The yield was about 12%.

Nothing was eluted with 1:1 or 1:3 petroleum ether–benzene but the first 25 ml. of 1:6 petroleum ether–benzene gave 10 mg. of a yellow oil which was shown to be a mixture of three components. The oil had λ_{max}^{KBr} 2.92, 5.83, and 5.95 μ, and v.p.c. gave two peaks, which were nearly equal in area, T_r 1.17 and 1.53, corresponding to 5α-cholest-1-en-3-one and cholest-4-en-3-one. T.l.c. gave three spots, R_f 0.68, 0.55, and 0.33, corresponding to the two ketones and to 2-α-hydroxy-5α-cholestan-3-one, respectively. The fraction contained about 30% of each component.

The next 150 ml. eluted 40 mg. (15%) of 2α-hydroxy-5α-cholestan-3-one (VII): λ_{max}^{KBr} 2.90 and 5.84 μ; the spectrum was superimposable on that of an authentic sample[12]; t.l.c. gave a single spot, R_f 0.33. This material was not purified or characterized further. Further elution with more polar solvents gave additional material which could not be characterized.

B.—Under Nitrogen.—The reaction was carried out as described above except that a slow stream of nitrogen was bubbled through the reaction mixture. The ultraviolet spectrum and t.l.c. showed that the composition of the product mixture was essentially the same as that obtained when the reaction was run in air.

C.—With Moist Dimethyl Sulfoxide.—To 5 ml. of dimethyl sulfoxide containing 5 micro drops of water was added 160 mg. of bromo ketone and 160 mg. of sodium bicarbonate and the mixture was heated under nitrogen as described above. The only difference observed in the products was a decrease in the amount of diosphenol produced, evidenced by a decrease in the absorption at 272 mμ in the ultraviolet spectrum.

D.—In the Presence of Lithium Bromide.—A slurry of 200 mg. (2.41 mmoles) of lithium bromide (dried at 120° for 24 hr.) and 5 ml. of dimethyl sulfoxide was added to 200 mg. (0.43 mmole) of bromo ketone and the mixture was heated at 125–130° for 20 min. The solid dissolved quickly, the solution developed a red-brown color, and the odor of dimethyl sulfide was evident. The solution was cooled to room temperature, diluted with 250 ml. of cold, saturated brine, and extracted with three 25-ml. portions of ether. The extract was washed with ten 20-ml. portions of water, dried over anhydrous sodium sulfate, and evaporated to give 145 mg. of a dark orange, bromine-containing, semicrystalline residue. T.l.c. gave two major spots, R_f 0.78 and 0.68, which were attributed to 2-bromo-5α-cholest-1-en-3-one (VIII) and 5α-cholest-1-en-3-one (V), respectively, by comparison with authentic samples. In addition, two faint spots, R_f 0.73 and 0.62, were observed, but were not identified. The solid had λ_{max}^{KBr} 5.77, 5.94, 6.02, and 6.30 μ, λ_{max}^{EtOH} 255 mμ (A 0.98) and 300 mμ (A 0.15), for a sample obtained by 2:25 dilution of a stock solution containing 19.5 mg. in 25 ml. of ethanol, indicating that the mixture contained 75 ± 5% of 2-bromo-5α-cholest-1-en-3-one (VIII), or a yield of 55%.

The solid was dissolved in 10 ml. of petroleum ether and chromatographed on a column (15 mm. in diameter) of 15 g. of silica gel. Elution with 1:1 petroleum ether–benzene gave 80 mg. (40%) of the unsaturated bromo compound, VIII: λ_{max}^{EtOH} 256 mμ (ϵ 7500); infrared spectrum was identical with that of an authentic sample; t.l.c. showed one spot, R_f 0.78. After recrystallization from methanol it had m.p. 106.5–107°, undepressed on admixture with an authentic sample.

Elution with benzene (100 ml.) and 1% ether in benzene (100 ml.) gave 30 mg. (18%) of a yellow oil. Recrystallization from methanol gave white needles of 5α-cholest-1-en-3-one (V): λ_{max}^{KBr} 5.95 and 12.8 μ, λ_{max}^{EtOH} 230 mμ, R_f 0.68.

Continued elution with more polar solvents gave small amounts of yellow oily material which was not investigated.

E.—In the Presence of Lithium Bromide and Sodium Bicarbonate.—The reaction was carried out as in D above but with the addition of 300 mg. of sodium bicarbonate and heating for 30 min. The reaction was worked up as in A above and gave 55 mg. of an acid fraction and 110 mg. of neutral material. T.l.c. gave all of the spots observed in A above and the ultraviolet spectrum indicated that the 1-en-3-one and the 4-en-3-one were produced in yields of 22–25 and 8–10%, respectively.

Reaction of 2α-Bromo-5α-cholestan-3-one with Collidine.—A solution of 500 mg. (1.08 mmoles) of chromatographically pure bromo ketone in 10 ml. of collidine (freshly distilled, b.p. 32–33° at 0.5 mm.) was boiled under reflux for 12 hr. The precipitated collidine hydrobromide was removed by filtration and 50 ml. of ether was added to the filtrate. This solution was washed successively with three 20-ml. portions of dilute sulfuric acid, saturated brine, and water, and then dried over anhydrous sodium sulfate in the presence of decolorizing charcoal. The solvent was then evaporated to give 335 mg. of a bromine-free, pale yellow, semicrystalline residue. T.l.c. gave two spots, R_f 0.70 (1-en-3-one V) and 0.53 (4-en-3-one VI). V.p.c. gave two peaks, which had T_r 1.18 (1-en-3-one, 80% relative abundance, 65% yield) and 1.50 (4-en-3-one, 15% relative abundance, 12% yield), and a small shoulder, 1.00, at the base of the 1.18 peak, corresponding to about 2% relative abundance of cholestan-3-one. (In other experiments, using bromo ketone known to contain 5–8% of the saturated ketone, the peak at 1.00 was clearly resolved.) The crude product had λ_{max}^{KBr} 5.95, 5.83 (shoulder), 6.19, 11.50, and 12.80 μ, λ_{max}^{EtOH} 235 mμ (A 0.66 at 230 mμ, and 0.61 at 242 mμ), indicating that the product contained 65 ± 5% of 1-en-3-one and 25 ± 5% of 4-en-3-one. Alumina chromatography did not give a good separation of the mixture.

Reaction of 2α-Bromo-5α-cholestan-3-one with Lithium Chloride and Dimethylformamide.—A solution of 500 mg. (1.08 mmoles) of pure bromo ketone and 500 mg. of anhydrous lithium chloride in 10 ml. of dimethylformamide was boiled under reflux for 2.5 hr. The solution was then cooled to room temperature, diluted with 250 ml. of cold, saturated brine, and extracted with three 30-ml. portions of ether. The extract was washed with five 20-ml. portions of water, dried over anhydrous sodium sulfate, and evaporated to yield 405 mg. of pale yellow solid, λ_{max}^{KBr} 5.95, 6.19, 11.50, and 12.80 μ, λ_{max}^{EtOH} 233 mμ (A 0.79 at 230 mμ, and 0.70 at 242 mμ), at a concentration of 7.9×10^{-5} M, indicating that the composition of the crude product was 79 ± 5% of the 1-en-3-one and 20 ± 5% of the 4-en-3-one. T.l.c. gave two spots, R_f 0.69 (1-en-3-one) and 0.54 (4-en-3-one), and v.p.c. gave only two peaks, T_r 1.17 (1-en-3-one, 86% relative abundance) and 1.50 (4-en-3-one, 14% relative abundance). The yields were 77–84% of 1-en-3-one and 13.5–19.5% of 4-en-3-one.

Reaction of 2α-Hydroxy-5α-cholestan-3-one (VII) with Dimethyl Sulfoxide. A. In Air.—A mixture of 75 mg. (0.19 mmole) of 2α-hydroxy-5α-cholestan-3-one, 75 mg. of sodium bicarbonate, and 3 ml. of dimethyl sulfoxide was stirred and heated at 125–130° for 30 min., then cooled to room temperature, diluted with cold, saturated brine, and extracted with ether. The ether extract gave 75 mg. of a yellow solid which gave a deep violet color with alcoholic ferric chloride (the ketol gave no color) and two spots, R_f 0.33 (ketol) and 0.57 (diosphenol II). The solid had λ_{max}^{EtOH} 2.70 mμ (A 0.35) for a 2.05×10^{-4} M solution, indicating about 30% conversion to the diosphenol.

B. Under Nitrogen.—When the reaction was carried out as in A but under a nitrogen atmosphere, starting material was recovered, which contained only a trace of diosphenol, on the basis of t.l.c.

Reaction of 2,2-Dibromo-5α-cholestan-3-one (IX) with Dimethyl Sulfoxide.—A mixture of 500 mg. (1.08 mmoles) of the dibromo ketone IX, 500 mg. (5.95 mmoles) of sodium bicarbonate, and 15 ml. of dimethyl sulfoxide was stirred and heated at 125° for 20 min., then cooled to room temperature, diluted with 250 ml. of cold, saturated brine, and extracted with three 30-ml. portions of ether. The ether extract was washed with four 20-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to give 385 mg. of a yellow solid. A 360-mg. sample in 10 ml. of petroleum ether was chromatographed on a column (20 mm. in diameter) of 30 g. of silica gel. Elution with 4:1 and 3:1 petroleum ether–benzene (150 ml. each) gave 20 mg. of a yellow oil, identified as starting material by t.l.c., R_f 0.85. Elution with 1:1 petroleum ether–benzene gave 210 mg. (50%) of 2-bromo-5α-cholest-1-en-3-one (VIII): one spot on t.l.c., R_f 0.80. Recrystallization from methanol gave white scales, m.p. 107–107.5°, $[\alpha]_D$ +44°; the infrared spectrum was superimposable on that of an authentic sample. The melting point

was undepressed on admixture with an authentic sample (see below).

2-Bromo-5α-cholest-1-en-3-one (VIII).—A solution of 1.80 g. (3.32 mmoles) of crude 2,2-dibromo-5α-cholestan-3-one[23] in 8 ml. of collidine (freshly distilled) and 15 ml. of dimethylformamide was boiled under reflux for 2.5 hr. under a nitrogen atmosphere. Then the solution was cooled to room temperature and 200 ml. of ether was added, which precipitated 610 mg. of collidine hydrobromide, collected by filtration. The filtrate was washed with three 30-ml. portions of dilute sulphuric acid, then with 20-ml. portions of water until the wash was neutral, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The residue was dissolved in 10 ml. of petroleum ether and chromatographed on a column (22 mm. in diameter) of 60 g. of silica gel. Elution with 1:1 petroleum ether–benzene yielded 735 mg. (47.6%) of 2-bromo-5α-cholest-1-en-3-one, which was recrystallized from methanol and then had m.p. 105–107°, $[\alpha]_D$ +44°, λ_{max}^{EtOH} 256 mμ (ε 9400), λ_{max}^{KBr} 5.92 and 6.28 μ, R_f 0.78; lit.[9a] m.p. 91.5–92.5°, $[\alpha]_D$ +37.4°, λ_{max}^{EtOH} 256 mμ (ε 8500).

Anal. Calcd. for $C_{27}H_{43}BrO$: C, 69.96; H, 9.35. Found: C, 70.16; H, 9.34.

5α-Cholest-1-en-3-one 2,4-Dinitrophenylhydrazone.—Pure bromo ketone I was converted to the 2,4-dinitrophenylhydrazone of 5α-cholest-1-en-3-one in almost quantitative yield by the procedure of Djerassi.[18] Recrystallization from 1:1 benzene–ethanol gave brilliant orange-red scales: m.p. 228–230°, $\lambda_{max}^{CHCl_3}$ 384 mμ (ε 30,800); lit. m.p. 219–221°,[18] 232–233°,[24] $\lambda_{max}^{CHCl_3}$ 384 mμ (ε 27,200).[25]

5α-Cholest-1-en-3-one (V). A. By Hydrolysis of the 2,4-Dinitrophenylhydrazone.—The acid-catalyzed hydrolysis of the 2,4-dinitrophenylhydrazone was carried out in acetone according to the procedure of DeMaecker and Martin[24] and gave the the 1-en-3-one V in 75% yield, m.p. 98–101°, homogeneous by t.l.c. and v.p.c. Two recrystallizations from methanol gave an analytical sample: m.p. 100.5–101.5°, $[\alpha]_D$ +62°, λ_{max}^{KBr} 5.95 and 12.80 μ, λ_{max}^{EtOH} 230 mμ (ε 9650) and 242 mμ (ε 7000); lit.[9a] m.p. 98–100°, λ_{max} 231 mμ (ε 9950).

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.18; H, 11.29.

B. By Debromination of 2-Bromo-5α-cholest-1-en-3-one (VIII).—A mixture of 415 mg. (0.90 mmole) of bromo ketone VIII, 4.0 g. of zinc dust, and 35 ml. of absolute ethanol was boiled under reflux with stirring for 12 hr. The zinc, removed by centrifuging, was washed with hot ethanol, and the combined ethanol solutions were evaporated under reduced pressure to give a bromine-free oil which crystallized from methanol to yield 175 mg. (51%) of the 1-en-3-one V, m.p. 93–97°. Two more recrystallizations from methanol gave m.p. 98.5–99°, $[\alpha]_D$ +68°, λ_{max}^{KBr} 5.95 and 12.80 μ, λ_{max}^{EtOH} 230 mμ (ε 9400), homogeneous by v.p.c. with T_r 1.15, and t.l.c., R_f 0.69.

3,3-(Ethylenedioxy)-2α-bromo-5α-cholestane (X).—To a solution of 3.00 g. (7.00 mmoles) of 3,3-(ethylenedioxy)-5α-cholestane in 20 ml. of tetrahydrofuran (dried over potassium hydroxide and distilled from lithium aluminum hydride) was added 2.45 g. (7.70 mmoles) of pyridinium bromide perbromide.[26] After 30 min. at room temperature, 100 ml. of 5% sodium bicarbonate solution was added and the mixture was extracted with three 30-ml. portions of methylene chloride. The extract was washed with five 20-ml. portions of water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give a pale yellow solid. This was dissolved in 60 ml. of petroleum ether and chromatographed on a column (25 mm. in diameter) of 75 g. of Florisil. Elution with 280 ml. of petroleum ether gave 2.32 g. (65%) of the bromo ketal X, the infrared spectrum being identical with that of an authentic sample, prepared as reported previously.[27] Recrystallization from methanol gave fluffy needles, m.p. 161–162.5°, which changed to small rods, m.p. 158–160°, if allowed to stand in contact with the mother liquor.

Elution with 60 ml. of benzene gave 775 mg. of a white solid which was recrystallized from methanol and then had m.p. 135–138°; λ_{max}^{KBr} 7.55, 8.60, 8.93, 10.15, and 10.45–10.60 μ (doublet); positive Beilstein test. When a sample of this material was heated (steam bath) in 80% acetic acid containing a few drops of concentrated sulfuric acid a 75% yield of 2α-bromo-5α-cholestan-3-one was obtained. Another sample was recovered unchanged after boiling under reflux for 3 hr. with collidine. No further attempt was made to identify this material.

Attempted Reaction of 3,3-(Ethylenedioxy)-2α-bromo-5α-Cholestane (X) with Dimethyl Sulfoxide.—A mixture of 595 mg. (7.08 mmoles) of sodium bicarbonate, 595 mg. (1.17 mmoles) of the bromo ketal X, and 15 ml. of dimethyl sulfoxide was stirred and heated at 125° for 60 min., and then cooled to room temperature. The white crystals which formed were collected, washed with water, and dried over calcium chloride to give 595 mg. which had an infrared spectrum identical with that of the starting material. T.l.c. showed only one spot, R_f 0.82, corresponding to starting material.

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The Formation of Cyclopentadienones[1]

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Cyclopentadienone and 2-chlorocyclopentadienone have been generated in ether solution at room temperature. Once formed, these dienones dimerize extremely readily. The structure of the dimer from chlorocyclopentadienone has been determined by nuclear magnetic double resonance. Cyclopentadienone has been trapped with cyclopentadiene, but all attempts to trap it as a diene, using maleic anhydride and a wide variety of dienophiles, were unsuccessful.

Cyclopentadienone (I) is a potentially interesting but highly elusive molecule whose chemistry is almost completely unknown. Some time ago, we began a study of the chemistry of unsaturated derivatives of cyclopentanone, and a number of the results of the published portion of that study, dealing with cyclopentene-3,5-dione and related compounds, had a direct bearing on the stability and formation of cyclopentadienone.[4] In the following, we deal more directly with the parent dienone and of a simple monochloro derivative.

It has been known for a long time that attempts to generate simply substituted cyclopentadienones lead, invariably, to the formation of dimeric products.

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