cyclohexylcarbodiimide (2.06 g., 0 mmoles) and p-nitrobenzyl alcohol (1.56 g., 10 mmoles) were dissolved in dry acetone (5 ml.) containing anhydrous cupric chloride (10 mg.). After 3 hr. at room temperature paper electrophoresis in 1 M acetic acid showed only a trace of neutral ultraviolet-absorbing material remaining, while a heavy spot moved towards the negative pole. The mixture was evaporated to dryness leaving a yellowish-green oil which was partitioned between ether and water. The ether layer was then shaken with 25 ml. of water containing 1 ml. of concentrated hydrochloric acid, whereupon a heavy white precipitate separated. This was removed by filtration, washed with water and ether, and dried giving 3.32 g. of chromatographically and electrophoretically pure product. This was readily crystallized from methanol–ether, giving 3.07 g. (85%) of O-p-nitrobenzyl-N,N'-dicyclohexylisouronium chloride which changed crystal structure at about 120° and melted at 170–190°, depending upon the rate of heating. *Anal.* Calcd. for $C_{20}H_{30}$-ClN_3O_3: C, 60.71; H, 7.64; N, 10.62. Found: C, 60.62; H, 7.77; N, 10.91.

Attempted Oxidation of the Isourea XVII (R = C_6H_{11}; $R^1 = NO_2C_6H_5$). The isourea hydrochloride (396 mg., 1 mmole) was dissolved in methanol (5 ml.), and lithium hydroxide (2 ml. of 1 N) was added. The resulting oil was extracted with ether, dried with sodium sulfate, and evaporated to dryness leaving the free base as a viscous oil which crystallized very slowly. Seven portions (36 mg., 0.1 mmole each) were weighed out and dissolved in DMSO (0.25 ml.) containing the following: (a) 10 μl. of pyridine; (b) 0.05 ml. of 1 M anhydrous phosphoric acid in DMSO; (c) 0.05 ml. of 1 M phosphoric acid in DMSO plus 10 μl. of pyridine; (d) 63 mg. of DCC; (e) 63 mg. of DCC plus 10 μl. of pyridine; (f) 63 mg. of DCC plus 0.05 ml. of 1 M anhydrous phosphoric acid in DMSO; (g) no additions.

After 3 hr. at room temperature aliquots of each reaction were removed, evaporated to dryness on an oil pump, and examined by paper electrophoresis in 1 M acetic acid and by thin layer chromatography. In no case was there more than a trace of neutral, ultraviolet-absorbing material behaving like p-nitrobenzaldehyde. The reactions containing phosphoric acid showed the presence of some p-nitrobenzyl phosphate,[44] and the reaction with both phosphoric acid and pyridine contained quite a strong spot of N-p-nitrobenzylpyridinium ion (independently prepared from pyridine and p-nitrobenzyl chloride), but in general the isouronium compound remained unchanged.

(44) D. L. M. Verheyden, W. E. Wehrli, and J. G. Moffatt, *J. Am. Chem. Soc.*, 87, 2257 (1965).

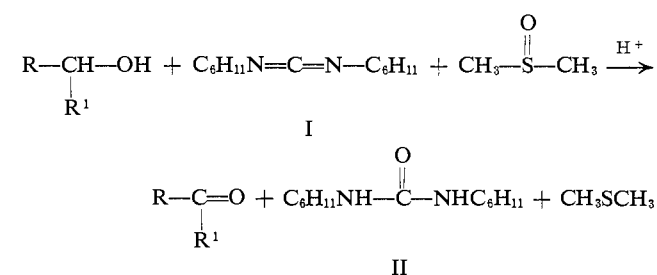# Sulfoxide–Carbodiimide Reactions. II. Scope of the Oxidation Reaction[1]

K. E. Pfitzner[2] and J. G. Moffatt

Contribution No. 28 from the Syntex Institute of Molecular Biology,
Stanford Industrial Park, Palo Alto, California. Received August 18, 1965

Oxidation of many different types of hydroxyl function, particularly in the steroid area, has been carried out through reaction with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of an appropriate acid. Relatively minor differences in rate were apparent during oxidation of epimeric pairs of 3- and 17-hydroxy steroids. On the other hand, the equatorial 11α-hydroxyl group in several steroids was readily oxidized under conditions where the axial epimer was inert. The particular utility of the method for the oxidation of primary alcohols to aldehydes and of sensitive molecules such as homoallylic alcohols is emphasized. In addition, the method has been successfully applied to alkaloids, and an unusual dehydration of a hemiacetal to a vinyl ether is described.

In the accompanying paper[1] we have described the development of a new oxidative reaction which promises to be of considerable synthetic utility. In this reaction an alcohol is treated with dicyclohexylcarbodiimide (DCC, I) and dimethyl sulfoxide (DMSO) in the pres-

ence of a suitable acid according to the following scheme.

$$R-\underset{\underset{R^1}{|}}{C}H-OH + C_6H_{11}N=C=N-C_6H_{11} + CH_3-\overset{\overset{O}{\|}}{S}-CH_3 \xrightarrow{H^+}$$

I

$$R-\underset{\underset{R^1}{|}}{C}=O + C_6H_{11}NH-\overset{\overset{O}{\|}}{C}-NHC_6H_{11} + CH_3SCH_3$$

II

Using the oxidation of testosterone (IIIa) to androst-4-ene-3,17-dione (IIIb) as a model, we have shown that optimal results are obtained upon treatment of the alcohol at room temperature with 0.5 molar equiv. of pyridinium trifluoroacetate (usually in the presence of excess pyridine) and 3 molar equiv. of DCC in anhydrous DMSO or mixtures of DMSO and a suitable inert solvent such as benzene. Under these conditions the reaction remains essentially neutral and should be applicable to the oxidation of both acid- and base-sensitive compounds. Of particular significance is the fact that the oxidation of primary alcohols leads only to aldehydes with no trace of the corresponding acids

being detectable even after prolonged reaction periods. In the present paper we wish to present details of the application of this method to the oxidation of a number of different types of alcohols. Many of these examples involve differently substituted steroidal alcohols and further define the scope and synthetic capability of this general reaction. A preliminary report of some of this work has appeared previously.[3]

Since most of our studies on the determination of optimal conditions were carried out on testosterone (III), we have examined this reaction in detail. Using pyridinium trifluoroacetate as the proton source the oxidation of (IIIa) to androst-4-ene-3,17-dione (IIIb) was quantitative as judged by thin layer chromatography of the crude reaction mixture which showed a single ultraviolet-absorbing product. Following removal by filtration of the insoluble dicyclohexylurea (II), and extraction of the DMSO with water, the crude product is contaminated only by excess DCC and lesser amounts of II. In most cases we have simply isolated the product by chromatography on silicic acid. With compounds that are stable to mild acid, however, it is often convenient to convert the excess DCC to highly insoluble II by addition of oxalic acid which is concomitantly converted to carbon monoxide and carbon dioxide.[4] Following this treatment of the testosterone reaction mixture it was possible to isolate pure IIIb in 92% yield by direct crystallization. As previously mentioned[1] when anhydrous orthophosphoric acid was used as the proton source during oxidation of testosterone, a trace amount (less than 2%) of a by-product moving faster than IIIb on silica thin layer chromatography was obtained. In an effort to identify this material the oxidation of testosterone was carried out on a 20-mmole scale. Following treatment with oxalic acid, pure IIIb (87.5%) was isolated by crystallization and the mother liquors were then separated by column chromatography on silicic acid, which further enriched the unknown material. Final purification was achieved by preparative thin layer chromatography which separated the fast-moving material into two distinct bands which were eluted from the silica and crystallized giving 16 and 9 mg. of the pure products. The faster moving compound was identified as 17-O-(thiomethoxymethyl)testosterone (IV) by elemental analysis and nuclear magnetic resonance (n.m.r.) spectroscopy. The n.m.r. spectrum of IV showed a three-proton singlet (SCH₃) at 126.8 c.p.s. and a two-proton singlet (OCH₂S) at 277.8 c.p.s. in addition to the other typical testosterone signals. The β configuration at C-17 is assigned from the chemical shift of the 18-methyl group (49.1 c.p.s.) as compared with testosterone (47.8 c.p.s.) and 17-epitestosterone (42.5 c.p.s.) and from the appearance of the C-17 proton as a rough triplet centered at 221 c.p.s. The same proton in testosterone is also a triplet centered at 220 c.p.s. while that in epitestosterone is a doublet centered at 226 c.p.s. Mild acid hydrolysis readily converted IV into testosterone and presumably formaldehyde and methyl mercaptan. The n.m.r. spectrum of the slower moving compound showed the presence of a large number of extraneous aliphatic protons. The infrared spectrum showed a sharp NH absorption at

(3) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3027 (1963).
(4) F. Zetzsche and H. Lindler, *Ber.*, **71B**, 2095 (1938).

3350 cm.$^{-1}$ and the n.m.r., ultraviolet, and infrared spectra all showed the Δ^4-3-ketone system to be intact and unsubstituted. Elemental analysis showed this substance to be an adduct of testosterone and DCC to which we assign structure V, the configuration at C-17 remaining unknown. The isomeric O-substituted isourea structure (VI) is rejected since the compound is electrophoretically neutral at pH 3. We have also prepared VI by the cupric chloride catalyzed addition of testosterone to DCC[5] and isolated the product as the crystalline acetate salt. In this reaction it is interesting to note that no product was obtained using acetone as the solvent[6] whereas an excellent yield resulted using anhydrous DMSO. Other than being somewhat toxic VI showed no pronounced biological activity when tested as an androgenic, antiandrogenic, or antiestrogenic substance.

IIIa, R = β—OH
b, R = O

IV

V

VI
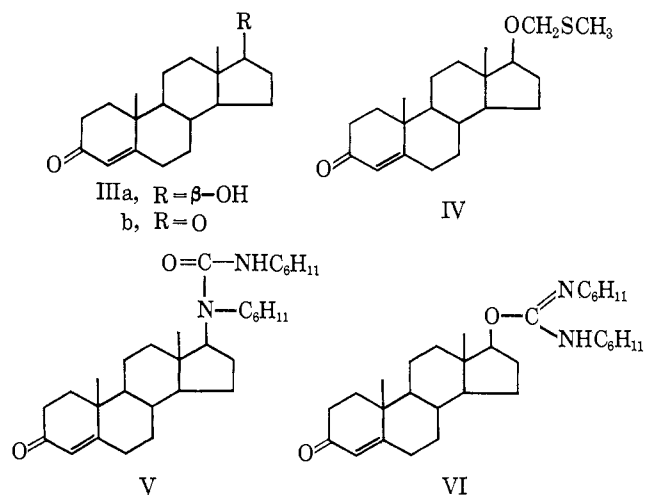
The formation of trace amounts of IV could arise through a rearrangement of the alkoxysulfonium compound VII which we consider to be an intermediate in the oxidation reaction.[1] Ready loss of a proton from VII would give a sulfur d-orbital-stabilized carbanion VIII[7] which could rearrange to IV as follows.

VII VIII IV

$$CH_3\overset{\oplus}{S}=CH_2$$
IX
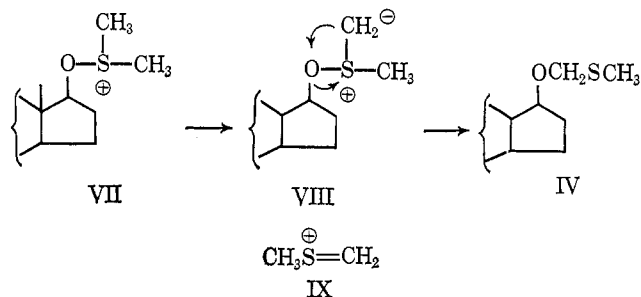
Alternatively, IV might arise through reaction of the 17-hydroxyl group of testosterone with the species IX. We have recently provided some evidence for the presence of minor amounts of such a species in the oxidation reaction.[1] The formation of V is less readily explained but could arise through O → N migration of the isourea adduct VI resulting from addition of testosterone to DCC. There is, however, no evidence that such an adduct is formed under the reaction conditions and

(5) (a) E. Schmidt and F. Moosmuller, *Ann.*, **597**, 235 (1955); (b) E. Schmidt and W. Carl, *ibid.*, **639**, 24 (1961).
(6) See ref. 1 for a similar reaction between *p*-nitrobenzyl alcohol and DCC that proceeded readily in acetone.
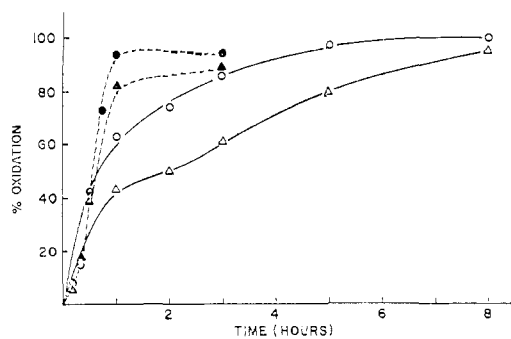(7) G. Cilento, *Chem. Rev.*, **60**, 147 (1960).

Figure 1. Rates of oxidation of testosterone and 17-epitestosterone: ○ and ● are for testosterone; △ and ▲ are for epitestosterone; (--------) is with anhydrous orthophosphoric acid; (———) is with pyridinium phosphate.

independently synthesized VI shows no tendency to undergo such a rearrangement.

The oxidation of cholestanol (Xa) to cholestanone (Xb) has also been examined using both anhydrous orthophosphoric acid and pyridinium trifluoroacetate as the proton source. Using phosphoric acid the yield of crystalline Xb isolated by silicic acid chromatography was 67.4%. Once again a small amount (8%) of a thiomethoxymethyl ether (Xc) was isolated in crystalline form and identified by elemental analysis and nuclear magnetic resonance spectroscopy. Cholestanol consistently gives much larger amounts of this type of product than we have observed with any other alcohol. Using pyridinium trifluoroacetate the yield of the desired ketone rose to 80% while only 1.3% of the ether Xc was formed. A minor disadvantage of the use of pyridinium trifluoroacetate is the formation of some N-trifluoroacetyldicyclohexylurea (XI) which can arise through the well-known O → N rearrangement of an initial O-acyl isourea.[8] Its alternative formation through acylation of dicyclohexylurea[9] by trifluoroacetic anhydride seems less likely since we have never observed the formation of trifluoroacetate esters and, hence, the presence of the anhydride seems unlikely. In general it appears as though the usually rapid reactions of carboxylic acids with carbodiimides are greatly repressed in the presence of a large excess of DMSO. This is consistent with the initial, acid-catalyzed addition of DMSO to DCC which we have proposed as the first step in the mechanism of the oxidation reaction.[2] The formation of some XI generally presents no problem to the work-up of the oxidation reactions since it is extremely soluble in organic solvents and does not separate during crystallization of the desired products from crude reaction mixtures. Also XI separates well on silicic acid columns from most products we have dealt with.

We have examined several pairs of epimeric alcohols in order to ascertain any steric preferences of the oxidation reaction. When dealing with relatively unhindered alcohols only minor differences in the rates of oxidation of the epimeric alcohols were observed. Thus the relative rates of oxidation of testosterone (III, R = β-OH) and epitestosterone (III, R = α-OH) using both orthophosphoric acid and pyridinium phosphate are shown in Figure 1. Using phosphoric acid the initial

(8) H. G. Khorana, Chem. Rev., 53, 145 (1953).
(9) M. Smith, J. G. Moffatt, and H. G. Khorana, J. Am. Chem. Soc., 80, 6204 (1958).

rates are very similar but the reaction with epitestosterone appears to slow down somewhat before reaching completion. With pyridinium phosphate the oxidation of testosterone appears to be somewhat faster throughout the course of the reaction. In all cases at least 90% of the desired dione was finally formed, any other products being unreacted starting material and less than 1% of the fast moving by-products IV or V, mentioned above. A similar comparison was made of the relative rates of oxidation of 3α-hydroxy- and 3β-hydroxy-5β-pregn-16-en-20-one (XIIa and XIId). The synthesis of the β-hydroxy compound (XIId) was achieved through treatment of the 3α-tosylate (XIIb) with dimethylformamide essentially according to the general method of Chang and Blickenstaff.[10] Some of the 3β-formate (XIIc) was also obtained in this reaction as well as a small amount of an olefin, presumably 5β-pregna-2,16-dien-20-one. Oxidations of XIIa and XIId using different acids proceeded at quite similar rates. With pyridinium trifluoroacetate the rate curves were almost superimposable while with phosphoric acid the β-alcohol reacted somewhat faster throughout the course of the oxidation. With the latter acid quite appreciable amounts (25% from the 3β-ol and 14% from the 3α-ol) of a fast moving material on thin layer chromatograms were also formed. While this material has not been isolated and characterized it is assumed, once again, to be the Δ²-dehydration product.

Xa, R = β-OH
b, R = O
c, R = β-OCH₂SCH₃

XI

XIIa, R = α-OH
b, R = α-OTs
c, R = β-O-CHO
d, R = β-OH
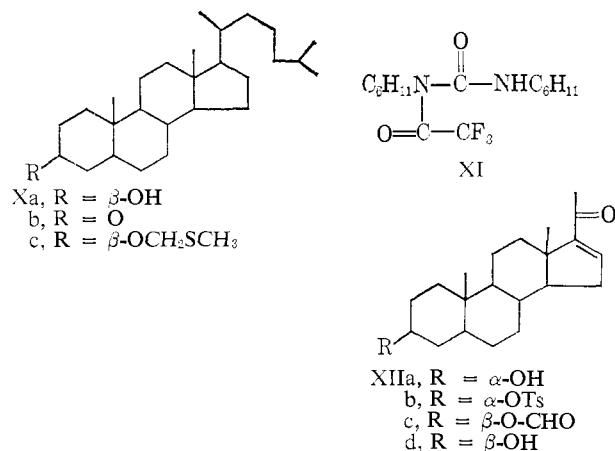
Distinct differences in the course of the reaction were found with the more hindered 11-hydroxy steroids. Thus the equatorial hydroxyl in 11α-hydroxyprogesterone (XIIIa) was smoothly oxidized using either orthophosphoric acid or pyridinium trifluoroacetate and the resulting pregn-4-ene-3,11,20-trione (XIIIb)[11] was isolated almost quantitatively by direct crystallization. On the other hand, the epimeric 11β-hydroxyprogesterone (XIIIc) remained completely unreacted under the usual conditions using pyridinium trifluoroacetate. With phosphoric acid, however, 6% of the 11-ketone (XIIIb) and 20% of the dehydration product pregna-4,9(11)-diene-3,20-dione (XIV)[12] were obtained and identified by thin layer chromatography. In a similar reaction the axial 11β-hydroxyl group of corticosterone-21-acetate (XV) remained inert in the presence of pyridinium trifluoroacetate but was dehydrated giving 23% of 9(11)-dehydrocorticosterone-21-acetate (XVI)[13]

(10) F. C. Chang and R. T. Blickenstaff, ibid., 80, 2906 (1958).
(11) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, ibid., 74, 5933 (1952).
(12) D. E. Ayer, Tetrahedron Letters, 1065 (1962).

when phosphoric acid was used. It is significant that no dehydration whatsoever could be detected upon storage of XV in DMSO containing anhydrous phosphoric acid but in the absence of DCC.

XIIa, R = α-OH
b, R = O
c, R = β-OH

XIV

XV

XVI
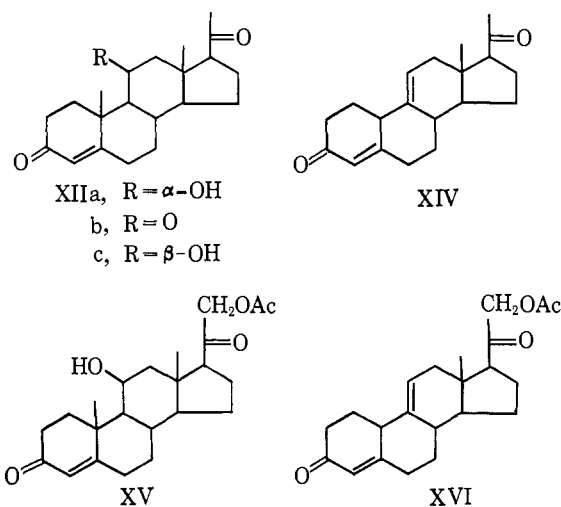
The facile oxidation of equatorial 11α-hydroxyl groups and the relative inertness of the axial epimers is in direct contrast with the results obtained by chromic oxide oxidation.[14] In these cases oxidation of the axial epimer is many times faster than that of the equatorial compound. This stems, in part, from the greater availability of the 11α-hydrogen which must be abstracted from the intermediate chromate ester in the rate-limiting step.[15] In the DMSO–DCC oxidation the rate-limiting step might well be the reaction of the alcohol with the DMSO–DCC adduct (XVII) to form the alkoxysulfonium salt (XVIII) which we have proposed as the active reaction intermediate.[1] In this case the equatorial 11α-hydroxyl will be much less hindered and will react more rapidly.


XVII

XVIII
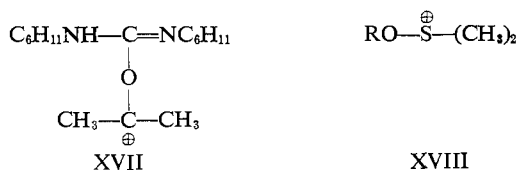
One of the most useful practical features of the DMSO–DCC oxidation reaction lies in its application to primary alcohols. These compounds are converted to aldehydes with no detectable overoxidation to form carboxylic acids, a feature that is notably absent in most other oxidation techniques. The quantitative oxidation of a number of simple aliphatic alcohols to the corresponding aldehydes has been confirmed by thin layer chromatography. Some care must be exercised in isolating such compounds as their dinitrophenylhydrazones since some formaldehyde is usually produced, presumably originating from DMSO. The pure dinitrophenylhydrazone of p-nitrobenzaldehyde was, however, readily isolated in 92% yield following oxidation of p-nitrobenzyl alcohol. Several applica-

(13) R. Casanova, C. W. Shoppee, and G. H. R. Summers, J. Chem. Soc., 2983 (1953).
(14) J. Schreiber and A. Eschenmoser, Helv. Chim. Acta, 38, 1529 (1955), and references cited therein.
(15) F. H. Westheimer and N. Nicolaides, J. Am. Chem. Soc., 71, 25 (1949).

tions have also been made in the steroid series. Thus oxidation of 24-hydroxycholane (XIXa) using pyridinium trifluoroacetate gave crystalline cholane-24-al (XIXb) in 94% yield. Similarly 3β-acetoxyandrost-5-en-19-ol-17-one (XXa) was converted into the 19-aldehyde (XXb) which was isolated in 53% yield, and the related androst-4-en-19-ol-3,17-dione (XXIa) gave 82% of the aldehyde (XXIb).

XIXa, R = H,OH
b, R = O

XXa, R = H,OH
b, R = O

XXIa, R = H,OH
b, R = O
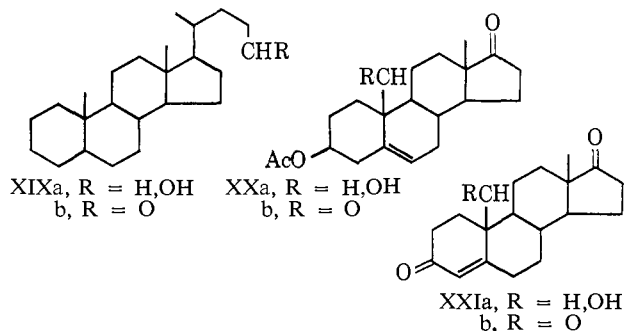
The very mild conditions of the reaction using pyridinium trifluoroacetate as the proton source permit oxidations to be carried out on molecules containing sensitive functional groups. One particularly useful application is in the oxidation of homoallylic alcohols to β,γ-unsaturated carbonyl compounds. The latter compounds rapidly isomerize to the α,β-unsaturated ketones under either mildly acidic or basic conditions and are difficult to obtain by most methods of oxidation. They have been most frequently prepared by rapid titration of the homoallylic alcohol with chromic acid in acetone according to Djerassi, et al.,[16] with quite variable results. The attempted oxidation of androst-5-en-3β-ol-17-one (XXIIa) with DMSO and DCC in the presence of anhydrous phosphoric acid was shown by thin layer chromatography to produce both the desired Δ^5-3-ketone (XXIIb) and the isomerized Δ^4-3-one (IIIb). Using pyridinium trifluoroacetate, however, no more than traces of ultraviolet-absorbing products were formed and by ultraviolet measurements before and after addition of acid it could be shown that at least 90% of the desired product was present. Partial isomerization to the Δ^4-3-one accompanied attempted chromatography on silicic acid, but a 70% yield of pure XXIIb could be obtained by direct crystallization from the crude reaction mixture. As obtained, the product showed only the beginning of end absorption at 240 mμ with ϵ_{240}^{MeOH} 221 which could only correspond to a maximum impurity of 1.4% of the conjugated ketone if all absorption at 240 mμ were due to this impurity. Addition of a trace of concentrated hydrochloric acid led to complete isomerization to IIIb (ϵ_{240}^{MeOH} 16,050) within 7 min. As previously reported,[16] compounds such as XXIIb show broad melting point ranges which vary with the rate of heating. We have confirmed by thin layer chromatography and ultraviolet spectroscopy that a sample of XXIIb was converted into IIIb during determination of its melting point in a Pyrex capillary. A similar oxidation of cholesterol (XXIIIa) using pyridinium trifluoroacetate gave a 66% yield of the chromatographically homogeneous Δ^5-3-ketone (XXIIIb) by direct crystallization. Once again ultraviolet meas-

(16) C. Djerassi, R. R. Engle, and A. Bowers, J. Org. Chem., 21, 1547 (1956).

urements indicate a maximum possible contamination by 2.8% of the conjugated ketone.

XXIIa, R = β-OH
b, R = O

XXIIIa, R = β-OH
b, R = O
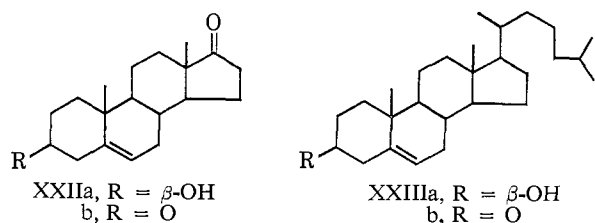
We have also attempted to extend this reaction to the oxidation of thiols and, to our surprise, have found these compounds to be completely inert. Thus parallel reactions using both anhydrous phosphoric acid and pyridinium trifluoroacetate were run on p-chlorobenzyl alcohol and p-chlorobenzyl mercaptan.[17] Thin layer chromatographic examination of the reactions at various times showed that while p-chlorobenzyl alcohol was rapidly and quantitatively converted to p-chlorobenzaldehyde, the corresponding thiol remained completely unchanged even after several days. Identical results were obtained on comparing reactions on octan-1-ol and octan-1-thiol. The reason for this dramatic difference is not clear since one would anticipate that a thiol should react with the DMSO–DCC adduct XVII at least as well as an alcohol. This inertness could prove to be useful in permitting the selective oxidation of the oxygen functions in compounds containing both alcohol and thiol groups.

As mentioned previously[1] the oxidation of alcohols fails completely when a trialkylamine salt of phosphoric, trifluoroacetic, or hydrochloric acid is used in conjunction with DMSO and DCC. This would appear to limit the method if one were to attempt the oxidation of a hydroxyl function in, for example, a relatively basic alkaloid. We have, however, shown that the oxidation of testosterone in the presence of 1 equiv. of triethylamine proceeds well if 1.5 equiv. of phosphoric acid are used rather than the usual 0.5–1 equiv. Under these conditions the oxidation was markedly slower than with phosphoric acid alone in the absence of triethylamine and a notable lag period was observed. The yields of IIIb obtained after 1, 3, 7, and 23 hr. were 7, 16, 86, and 90%, respectively, as determined by quantitative thin layer chromatography. In this way oxidation of the alkaloid spegazzinidine dimethyl ether (XXIVa)[18] in the presence of 1.5 equiv. of anhydrous phosphoric acid gave an 83% yield of 3-dehydrospegazzinidine dimethyl ether (XXIVb) identical with an authentic sample. Very recently Albright and Goldman[19c] have reported the oxidation of a variety of indole alkaloids by the DMSO–DCC method using only 0.5 equiv. of phosphoric acid.

Finally, we have examined the oxidation of the hemiacetal function in the triterpene flindissol (XXV). Using pyridinium trifluoroacetate we obtained a chromatographically fast-moving crystalline compound in 47% yield. Elemental analysis indicated oxidation of

the 3-hydroxyl group to a ketone and loss of 1 mole of water. This product is assigned the structure XXVI on the basis of its analysis and its n.m.r. and infrared spectra. The n.m.r. spectrum clearly showed the presence of a single proton at 363 c.p.s., a region quite compatible with the proton in a vinyl ether. As expected, the product was readily hydrolyzed to a more polar, carbonyl-containing compound by aqueous acid in acetone. The infrared spectrum showed the presence of the 3-ketone (1715 cm.$^{-1}$) and contained a small new peak at 1640 cm.$^{-1}$ for the vinyl ether. No trace of oxidation to the known flindissone lactone was observed. Further studies on other hemiacetals are in progress.

XXIVa, R = H, OH
b, R = O

XXV

XXVI
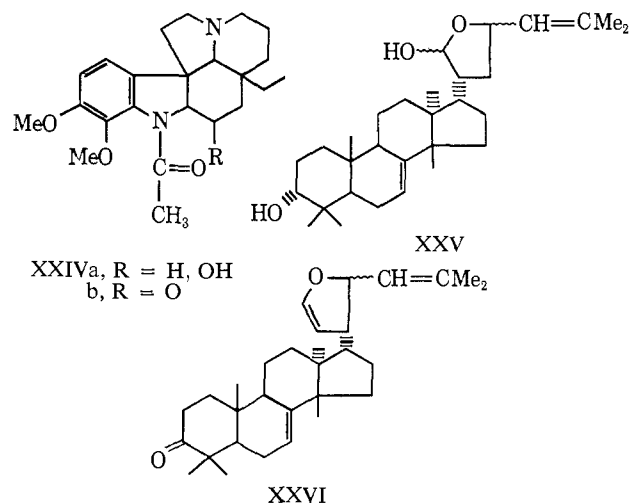
The results reported in this and the accompanying paper[1] indicate that the DMSO–DCC reaction provides one of the mildest methods available for the oxidation of alcohols to carbonyl compounds. Of particular significance is the selective oxidation of primary alcohols to aldehydes without formation of any detectable trace of the corresponding acid. Since preliminary publication of our results[3] a number of other workers have utilized the oxidation reaction with notable success, particularly when dealing with otherwise sensitive compounds. In particular, we draw attention to examples of its use with alkaloids[19] and carbohydrates[20] that have recently appeared. Further studies on the reactions of DMSO and DCC with a variety of other types of compound will be reported shortly.

Experimental Section

General Methods. Thin layer chromatography was performed on Silica-G from Brinkmann Instruments containing 0.05% extracted Radelin GS-115 (Type P-1) phosphor as previously described.[21] Nonultraviolet-absorbing compounds were detected by spraying with 5% ammonium molybdate in 10% sulfuric acid followed by heating at 150°. For quantitative measurements the ultraviolet-absorbing spots were scraped off the plate, and the silica was eluted three times with 1-ml. portions of methanol in a microcentrifuge from Microchemical Specialities, Berkeley, Calif. Samples

(17) The gift of a very pure sample of this compound from Evans Chemetics Inc., New York, N. Y., is gratefully acknowledged.

(18) C. Djerassi, H. W. Brewer, H. Budzikiewicz, O. O. Orazi, and R. A. Corral, *J. Am. Chem. Soc.*, 84, 3480 (1962). We are grateful to Dr. Djerassi for samples of both the alcohol and ketone.

(19) (a) K. S. Brown and C. Djerassi, *ibid.*, 86, 2453 (1964); (b) G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Zeigler, *ibid.*, 87, 2073 (1965); (c) J. D. Albright and L. Goldman, *J. Org. Chem.*, 30, 1107 (1965); (d) R. Arndt and C. Djerassi, *Experientia*, in press.

(20) (a) J. R. Dyer, W. E. McGonigal, and K. C. Rice, *J. Am. Chem. Soc.*, 87, 654 (1965); (b) B. R. Baker and D. H. Buss, *J. Org. Chem.*, 30, 2304, 2308 (1965). We are grateful to Dr. Baker for making these manuscripts available to us prior to publication.

(21) K. E. Pfitzner and J. G. Moffatt, *ibid.*, 29, 1508 (1964).

were read against a silica blank from a comparable plate. Ultraviolet measurements were made on Zeiss PMQ-II and Cary Model 15 spectrophotometers and infrared spectra were obtained from potassium bromide pellets on a Perkin-Elmer Model 237 instrument. Nuclear magnetic resonance spectra were determined in deuteriochloroform with a Varian A-60 instrument, peaks being measured in c.p.s. downfield from a tetramethylsilane standard. Elemental analyses were obtained from Dr. A. Bernhardt, Mülheim, Germany, and from Midwest Microlabs, Indianapolis, Ind. Melting points were determined on a hot-stage microscope built by Dr. J. P. H. Verheyden of this institute.

Androst-4-ene-3,17-dione (IIIb). A. Using Pyridinium Trifluoroacetate. Testosterone (576 mg., 2 mmoles) was dissolved in anhydrous DMSO[22] (3 ml.) and benzene (3 ml.) containing pyridine (0.16 ml., 2 mmoles) and trifluoroacetic acid (0.08 ml., 1 mmole). After addition of DCC (1.24 g., 6 mmoles) the sealed reaction was kept overnight at room temperature. Ether (50 ml.) was added followed by a solution of oxalic acid (540 mg., 6 mmoles) in methanol (5 ml.). After gas evolution had ceased (about 30 min.), water (50 ml.) was added and the insoluble dicyclohexylurea was removed by filtration. The organic phase was then extracted twice with 5% sodium bicarbonate and once with water, dried over sodium sulfate, and evaporated to dryness leaving a crystalline residue (800 mg.) which still contained a little dicyclohexylurea. Direct crystallization from ethanol (5 ml.) gave androst-4-ene-3,17-dione (525 mg., 92%) in two crops, m.p. 169–170° (lit.[23] m.p. 169–170°), and giving an infrared spectrum identical with an authentic sample from the Syntex collection.

B. Using Phosphoric Acid. Testosterone (5.7 g., 20 mmoles) was dissolved in DMSO (20 ml.) and benzene (10 ml.) containing DCC (12.4 g., 60 mmoles). Anhydrous orthophosphoric acid[24] (0.4 ml. of a 5 M solution in DMSO, 2 mmoles[25]) was then added, and the mixture was kept at room temperature for 2 hr. Thin layer chromatography (chloroform–ethyl acetate, 4:1) then showed the presence of very little testosterone. Ethyl acetate (50 ml.) was added followed by a solution of oxalic acid (5 g.) in methanol. After 30 min. the dicyclohexylurea (12.7 g.) was removed by filtration and washed with ethyl acetate. The solution was then extracted with aqueous sodium bicarbonate and water, dried over sodium sulfate, and evaporated to dryness leaving 5.7 g. of an oil which rapidly crystallized. Crystallization from 20 ml. of methanol gave androst-4-ene-3,17-dione (5.0 g., 87.5%), m.p. 169–170°. The mother liquors (0.7 g.) were applied to a column of 100 g. of Merck silica and the column was eluted with chloroform in 15-ml. fractions. Fractions 53–63 contained 360 mg. of a mixture of the dione (IIIb) and about 10% of the faster moving spot. Fractions 64–70 contained a further 60 mg. of pure IIIb and further elution removed some unreacted testosterone. The mixed products were then purified on four 20

X 20 cm. preparative thin layer plates coated with a 1.3-mm. layer of Silica GF using chloroform–ethyl acetate (10:1) as solvent. The dione and two very close running faster bands were eluted with acetone, evaporated to dryness, dissolved in methylene chloride, and filtered from a trace of silica. Evaporation then gave the dione (235 mg., total yield 5.295 g., 92.5%) and the slower and faster moving by-products (21 and 25 mg., respectively). Each was crystallized from a few drops of methanol giving 9 and 16 mg. of chromatographically pure products. (a) The slower product, m.p. 161–163°, showed λ_{max}^{MeOH} 240 mμ (ϵ 16,000); ν_{max} (KBr) 3350, 1735, 1640 cm.$^{-1}$. *Anal.* Calcd. for $C_{32}H_{50}N_2O_2$ (V): C, 77.68; H, 10.19; N, 5.66. Found: C, 78.17; H, 9.83; N, 5.82. (b) The faster product, m.p. 128–129°, showed λ_{max}^{MeOH} 241 mμ and gave n.m.r. singlets (CDCl$_3$) at 126.8 (three protons) and at 277.8 c.p.s. (two protons) as well as other typical testosterone peaks. *Anal.* Calcd. for $C_{21}H_{32}O_2S$ (IV): C, 72.38; H, 9.26. Found: C, 71.65; H, 8.96.

N,N'-Dicyclohexyl-O-(androst-4-en-3-one-17-yl)isouronium Acetate (VI). Testosterone (576 mg., 2 mmoles) was dissolved in anhydrous DMSO (10 ml.) containing DCC (824 mg., 4 mmoles) and anhydrous cupric chloride (25 mg.) and stored at 37° for 2 days. Paper electrophoresis in 1 M acetic acid then showed nearly all the ultraviolet-absorbing material moving towards the negative pole. Ether (50 ml.) was added and the mixture was extracted twice with 0.3 M ammonium hydroxide (50 ml., to remove copper ions) and then with water. The ether solution was then extracted four times with 15-ml. portions of 1 M acetic acid, and the extracts were evaporated to dryness. After several evaporations with acetone a dry residue remained which was crystallized from acetone giving the acetate salt of VI (1.06 g., 95%), m.p. 136–139° after drying *in vacuo* at 65°, λ_{max}^{MeOH} 237 mμ (ϵ 15,500). *Anal.* Calcd. for $C_{34}H_{54}N_4O_2$: C, 73.60; H, 9.81; N, 5.05. Found: C, 73.21; H, 10.03; N, 5.15.

Oxidation of Cholestanol. A. Cholestanol (1.167 g., 3 mmoles) was dissolved in DMSO (5 ml.) and benzene (10 ml.) containing DCC (1.85 g., 9 mmoles) and pyridine (0.24 ml., 3 mmoles). Trifluoroacetic acid (0.12 ml., 1.5 mmoles) was added, and the mixture was stored overnight at room temperature. Ethyl acetate (25 ml.) was added and dicyclohexylurea (700 mg., m.p. 234°) was removed by filtration. The ethyl acetate solution was extracted three times with water (50 ml.), dried, and evaporated. Chromatography on 100 g. of Merck silica with benzene gave 12 mg. (1.3%) of crystalline O-(thiomethoxymethyl)cholestanol (Xc, see below) followed by 615 mg. (80%) of chromatographically pure cholestanone (Xb, m.p. 128.5–130°) which was indistinguishable from an authentic sample (m.p. 129°) by mixture melting point and infrared spectrum.

B. An identical reaction, except that anhydrous orthophosphoric acid (1.5 ml. of a 1 M solution in DMSO) was used in place of pyridine and trifluoroacetic acid, was chromatographed in the same way. Elution with benzene gave 107 mg. (8%) of a crystalline compound that could be recrystallized from methanol giving 85 mg. of O-(thiomethoxymethyl)cholestanol (Xc), m.p. 82–83°. It showed n.m.r. singlets at 281

(22) Dried by distillation *in vacuo* and stored over Linde Molecular Sieve Type 4A from the Linde Co., Los Angeles, Calif.
(23) P. N. Rao, *J. Org. Chem.*, **26**, 2149 (1961).
(24) A product of Fulka A.G. obtained through the International Chemical and Nuclear Corp., City of Industry, Calif.
(25) These conditions were selected in order to maximize the yields of the faster moving products.

(OCH₂S) and at 129 (SCH₃) and a broad, one-proton signal at 210 c.p.s. (axial C-3–H). Treatment with 0.8 N hydrochloric acid in acetone at 37° for 2 hr. resulted in complete hydrolysis to cholestanol as shown by thin layer chromatography using benzene–chloroform (1:2). *Anal.* Calcd. for $C_{29}H_{52}OS$: C, 77.61; H, 11.68; S, 7.14. Found: C, 77.21; H, 11.50; S, 7.09.

Continued elution with benzene gave 781 mg. (67%) of cholestanone identical with that above.

Relative Rates of Oxidation of Testosterone and Isotestosterone. Identical experiments were set up containing the appropriate steroid (29 mg., 0.1 mmole), DCC (103 mg., 0.5 mmole), and anhydrous phosphoric acid (0.05 ml. of a 1 M solution in DMSO) in anhydrous DMSO (0.5 ml.). After 10, 20, 30, 45, 60, and 180 min. 20-µl. aliquots were removed and rapidly evaporated to dryness under high vacuum. The residues were dissolved in methanol (0.1 ml.) and 10–15 µl. was chromatographed on thin layer silica plates containing extracted P-1 phosphor[21] using chloroform–ethyl acetate (5:1). The ultraviolet-absorbing spots (starting material and product plus a maximum of 1% faster moving material) were scraped off, and the silica was eluted twice with 1-ml. portions of methanol. The eluates were read at 242 mµ against a silica blank, and the results are shown in Figure 1.

A second pair of experiments included pyridine (15 µl., 0.2 mmole) in addition to the above reagents and aliquots were examined after 1, 2, 3, 5, and 8 hr. (see Figure 1).

3α-Tosyloxy-5-β-pregn-16-en-20-one (XIIb). 3-α-Hydroxy-5-β-pregn-16-en-20-one (XIIa, 500 mg., m.p. 194–197°,[26] obtained by hydrolysis of the 3α-acetate from the Syntex collection) and p-toluenesulfonyl chloride (900 mg.) were stored overnight at room temperature in pyridine (5 ml.). The mixture was poured onto ice, extracted into chloroform, washed with water, and evaporated. Cystallization from methanol gave the 3-α-tosylate (640 mg., 86%), m.p. 152–154°. *Anal.* Calcd. for $C_{28}H_{38}O_4S$: C, 71.40; H, 8.14; S, 6.81. Found: C, 71.69; H, 8.22; S, 6.65.

3β-Hydroxy-5β-pregn-16-en-20-one (XIId). The tosylate (XIIb, 550 mg.) was dissolved in dimethylformamide (6 ml.) and heated at 80° for 4 days,[10] the reaction being followed by thin layer chromatography in chloroform. The solvent was evaporated and the residual oil was treated with methanolic ammonium hydroxide at room temperature. The solvent was evaporated and the residue was dissolved in benzene–chloroform (3:1) leaving insoluble ammonium p-toluenesulfonate. The solution was chromatographed on silica giving 45 mg. of a fast-moving olefin, presumably 5β-pregna-2,16-diene-20-one (m.p. 107–112° and not further purified) and 120 mg. of the desired 3β-hydroxy compound (XIId), m.p. 186–188°, mixture melting point 155–158° with the 3α-hydroxy compound (lit.[26] m.p. 188–190°). This was chromatographically homogeneous and moved just ahead of the 3α-epimer in chloroform. In addition a small amount of the corresponding 3β-formate (XIIc, ν_{max} 1725, 1190 cm.⁻¹), m.p. 115–116°, was isolated and hydrolyzed to the 3β-alcohol identical with that above.

Relative Rates of Oxidation of 3α- and 3β-Hydroxy-5β-pregn-16-en-20-one. Reactions of the appropriate alcohol (32 mg., 0.1 mmole) with DCC (63 mg., 0.3 mmole) and phosphoric acid (0.05 mmole) in DMSO (0.5 ml.) and benzene (0.2 ml.) were followed by quantitative thin layer chromatography as above, using chloroform–ethyl acetate (5:1). In addition to starting material and the 3-ketone, which was chromatographically identical with an authentic sample, lesser amounts (up to 25% with the α-ol and 13% with the β-ol) of a compound moving identically to the presumed 2,16-diene above was formed. An identical pair of reactions was run using pyridine (10 µl.) and trifluoroacetic acid (5 µl.) in place of phosphoric acid. With both epimers the rates of oxidation were very similar but olefin formation was less (5% with both epimers) than when using phosphoric acid.

Oxidation of 11α-Hydroxyprogesterone. 11α-Hydroxyprogesterone (1.0 g., 3 mmoles) was reacted overnight in DMSO (5 ml.) and benzene (5 ml.) with DCC (1.85 g., 9 mmoles), pyridine (0.24 ml.), and trifluoroacetic acid (0.12 ml.). Ether (25 ml.) and a saturated methanol solution of oxalic acid (1.23 g.) was added, and after 30 min. the urea precipitate (1.8 g.) was removed. The ether solution was extracted once with 5% sodium bicarbonate and twice with water, dried, and evaporated leaving 1.30 g. of white, crystalline residue. Recrystallization from methanol gave 1.02 g. of needles melting at 168–171° which were chromatographically free of any steroidal by-products and contaminated only by a trace of dicyclohexylurea (ν_{max} 3325 cm.⁻¹). An analytical sample purified by preparative thin layer chromatography (chloroform–ethyl acetate, 3:2) and crystallization from methanol had m.p. 175–177° (lit.[11] m.p. 172–175°); λ_{max}^{MeOH} 237 mµ (ϵ 16,100); ν_{max} (KBr) 1715, 1670 cm.⁻¹. *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.68; H, 8.59.

Oxidation of 11β-Hydroxyprogesterone (XIIIc). The reaction of 11β-hydroxyprogesterone (11 mg., 0.033 mmole) in DMSO (0.3 ml.) with DCC (31 mg., 0.15 mmole) was studied in the presence of both anhydrous phosphoric acid (0.02 mmole) and pyridine trifluoroacetate (4 µl. of pyridine and 2 µl. of trifluoroactic acid). After 15 hr. both reactions were evaporated to dryness and examined by quantitative thin layer chromatography in chloroform–ethyl acetate (1:1). The reaction with pyridinium trifluoroacetate contained virtually no ultraviolet-absorbing products other than starting material. The phosphoric acid reaction contained 74% unreacted XIIIc, 6.2% pregn-4-ene-3,11,20-trione(XIIIb) and 20% of a compound chromatographically identical with pregna-4,9(11)-diene-3,20-dione (XIV).[12] Insufficient starting material did not permit a preparative reaction.

Oxidation of Corticosterone 21-Acetate (XV). Corticosterone 21-acetate[27] (388 mg., 1 mmole) was treated overnight in DMSO (3 ml.) with DCC (618 mg., 3 mmoles) and anhydrous phosphoric acid (0.5 mmole). After the usual work-up with ether and oxalic acid the material was chromatographed on a column of silicic acid (50 g.). Elution with chloroform–benzene (3:1) gave 85 mg. (23%) of 9(11)-dehydrocorticosterone 21-

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(26) R. E. Marker, *J. Am. Chem. Soc.*, 62, 3350 (1940), reports m.p. 194–196°.

(27) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, 26, 1316 (1943).

acetate (XVI), m.p. 157–158° after recrystallization from ethyl acetate–hexane. The reported[13] melting point of XVI is 159°. *Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.48; H, 8.07.

Further elution gave only unreacted XV and thin layer chromatography of the crude reaction mixture with ethyl acetate–chloroform (1:1) showed the presence of no other products.

A similar reaction using pyridinium trifluoroacetate in place of phosphoric acid gave only 1–2% of XVI in addition to starting material.

p-Nitrobenzaldehyde. *p*-Nitrobenzyl alcohol (153 mg., 1 mmole) was reacted for 1 hr. with DCC (618 mg., 3 mmoles) and anhydrous phosphoric acid (0.5 mmole) in DMSO (5 ml.). After removal of excess DCC with oxalic acid and extraction of the DMSO the crude aldehyde was evaporated to dryness and dissolved in ethanol. Addition of an excess of 2,4-dinitrophenyl-hydrazine in aqueous ethanol and sulfuric acid[28] gave an immediate precipitate that was thoroughly washed with ether and crystallized from hot ethyl acetate giving *p*-nitrobenzaldehyde dinitrophenylhydrazone (307 mg., 92%), m.p. 316–317° (lit.[28] m.p. 320°).

Cholan-24-al (XIXb). Cholan-24-ol[29] (XIXa, 1.033 g., 3.0 mmoles) was reacted overnight in DMSO (10 ml.) and benzene (10 ml.) containing DCC (1.85 g., 9 mmoles), pyridine (0.24 ml., 3 mmoles), and tri-fluoroacetic acid (0.16 ml., 1.5 mmoles). Benzene (50 ml.) was added and the dicyclohexylurea was removed by filtration. The benzene solution was extracted three times with water (50 ml.), dried with sodium sulfate, and evaporated. The partially crystal-line residue was chromatographed on 125 g. of Merck silica using benzene–hexane (1:1). The product was located (thin layer chromatography with benzene) in fractions 5–8 (125 ml. each) and immediately crystallized upon evaporation giving 870 mg. (85%) of cholan-24-ol (XIXb), m.p. 102–104°. Recrystallization from 5 ml. of hot acetone only raised the melting point to 103–104° with excellent recovery.[30] *Anal.* Calcd. for $C_{24}H_{40}O$: C, 83.65; H, 11.70. Found: C, 83.74; H, 11.73.

The product gave a crystalline dinitrophenylhydra-zone, m.p. 163–164°. *Anal.* Calcd. for $C_{30}H_{44}N_4O_4$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.81; H, 8.54; N, 10.80. A semicarbazone, m.p. 194–196°, also resulted.

3β-Acetoxyandrost-5-en-19-al-17-one (XXb). 3β-Acetoxyandrost-5-en-19-ol (1.035 g., 3 mmoles) was reacted overnight in DMSO (6 ml.) and benzene (3 ml.) with DCC (1.85 g.), pyridine (0.24 ml.), and tri-fluoroacetic acid (0.12 ml.). Ether (50 ml.) was added followed by oxalic acid (750 mg.) in methanol. After 30 min. dicyclohexylurea was removed and the solution was extracted with bicarbonate and then water. The solution was dried and evaporated giving a semi-crystalline residue that was chromatographed on 100 g. of Merck silica with chloroform–benzene (3:1). N-Trifluoroacetyl-N,N'-dicyclohexylurea (XI, 246 mg.) was eluted first and crystallized from aqueous methanol

(28) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

(29) Aldrich Chemical Co., Milwaukee, Wis.

(30) Crystallization from aqueous ethanol gave a hydrate, m.p. 95°.

giving m.p. 138–138.5°; ν_{max} (KBr) at 3340, 1720, 1690, 1540 cm.$^{-1}$. *Anal.* Calcd. for $C_{15}H_{23}N_2O_2F_3$: C, 56.22; H, 7.23; N, 8.74. Found: C, 56.62; H, 7.21; N, 9.00.

Continued elution gave 542 mg. (53%) of chromato-graphically pure 3β-acetoxyandrost-5-en-19-al-17-one (XXb) which was crystallized from ethyl acetate–hexane as cubes, m.p. 141–143°; ν_{max} (KBr) 1740, 1715 cm.$^{-1}$). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.36; H, 8.21.

Subsequent fractions from the column contained addi-tional XXb contaminated with dicyclohexylurea but were not further purified.

Androst-4-en-19-al-3,17-dione (XXIb). Androst-4-en-19-ol-3,17-dione (XXIa, 1.51 g., 5 mmoles) was reacted in DMSO (5 ml.) and benzene (5 ml.) with DCC (3.09 g., 15 mmoles), pyridine (0.40 ml.), and trifluoro-acetic acid (0.20 ml.) for 3 hr. at room temperature. Ethyl acetate (25 ml.) was added followed by oxalic acid (1.9 g.) in methanol (7 ml.). After 15 min. the dicyclohexylurea (3.0 g.) was removed, and the filtrate was extracted with aqueous bicarbonate and water. The organic phase was dried and evaporated leaving 1.94 g. of dry solid that was crystallized from ether giving 1.235 g. (82%) of chromatographically homo-geneous (chloroform–ethyl acetate, 4:1) androst-4-en-19-al-3,17-dione (XXIb), m.p. 129–131°. Further recrystallization raised the melting point to 131–132.5°; λ_{max}^{MeOH} 244 mμ (ε 12,500); ν_{max} (KBr) 1740, 1670 cm.$^{-1}$. *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.90; H, 7.95.

Androst-5-ene-3,17-dione (XXIIb). Androst-5-en-3β-ol-17-one (1.152 g., 4 mmoles) was reacted overnight in DMSO (10 ml.) with DCC (2.47 g., 12 mmoles), pyridine (0.32 ml.), and trifluoroacetic acid (0.15 ml.). Ether (40 ml.) was added and after removal of dicyclo-hexylurea the solution was extracted twice with 0.2 *M* phosphate buffer, pH 7.2, and twice with water. The ether was evaporated *in vacuo*, and the residue was leached four times with 5-ml. portions of ice-cold pentane to remove excess DCC. The dry residue (1.37 g.) was directly crystallized from methanol (8 ml.) giving 800 mg. (70%) of chromatographically homo-geneous (chloroform–ethyl acetate, 5:1) androst-5-ene-3,17-dione (XXIIb) which melted between 136 and 145° depending upon the rate of heating[31]; λ_{max}^{MeOH} 290 mμ (ε 96) and end absorption starting at 268 mμ (ε(240 mμ) 221 corresponding to a max-imum of 1.4% Δ⁴-3-ketone). Addition of 5 μl. of con-centrated hydrochloric acid to 1 ml. of a solution of XXIIb in methanol gave, after 7 min. at room tempera-ture, λ_{max} 240 mμ (ε 16,050); ν_{max} (KBr) 1715 cm.$^{-1}$. *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.90; H, 9.35.

Cholest-5-en-3-one (XXIIIb). The oxidation of cholesterol (1.16 g., 3 mmoles) in DMSO (5 ml.) and benzene (10 ml.) containing DCC (1.85 g.), pyridine (0.24 ml.), and trifluoroacetic acid (0.12 ml.) was

(31) C. Djerassi, *et al.*,[16] and W. R. Nes, E. Loeser, R. Kirdani, and J. Marsh, *Tetrahedron*, **19**, 299 (1963), have reported m.p. 119–125° for this compound. A. Butenandt and J. Schmidt-Thomé reported m.p. 158°. On one occasion[3] we have obtained pure material melting at 167–169°, but in several subsequent reactions only product melting as described above has been obtained. Chromatographic and spectral examination of material that has been melted in a Pyrex capillary shows it to have isomerized to the Δ⁴-3-ketone, m.p. 169–170°.

carried out overnight at room temperature. Worked up with ethyl acetate and pH 7.2 phosphate buffer, as above with XXIIb, this gave a crude product that was directly crystallized from methanol (20 ml.) giving chromatographically homogeneous cholest-5-en-3-one (760 mg., 66%), m.p. 121–123°. An analytical sample after two further crystallizations had m.p. 123–125° provided that the apparatus was preheated to 115°.[32] The ultraviolet spectrum in methanol showed only end absorption below 260 mμ (ϵ(242 mμ) 466) and on adding 5 μl. of concentrated hydrochloric acid λ_{max} 242 mμ (ϵ 17,000); ν_{max} (KBr) 1725 cm.$^{-1}$; [α]D −2°. *Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.20; H, 11.34.

Reactions with p-Chlorobenzyl Alcohol and p-Chlorobenzylthiol. Parallel reactions were set up containing p-chlorobenzyl alcohol (29 mg., 0.2 mmole) or p-chlorobenzylthiol[17] (32 mg., 0.2 mmole) in DMSO (0.5 ml.) containing DCC (124 mg., 0.6 mmole) and either anhydrous orthophosphoric acid (0.1 mmole) or pyridine (15 μl.) and trifluoroacetic acid (8 μl.). Aliquots of each reaction were removed, partitioned between water and methylene chloride, and the organic phase was examined by thin layer chromatography (benzene for the alcohol and benzene–heptane 2:3 for the thiol) after 18 hr. With either acid the alcohol was quantitatively converted to p-chlorobenzaldehyde while the thiol remained completely unchanged even after 3 days of reaction. Similar results were obtained with n-octanol and octane-1-thiol.

3-Dehydrospegazzinidine Dimethyl Ether (XXIVb). Spegazzinidine dimethyl ether[18] (XXIVa, 25 mg., 0.06 mmole) was dissolved in DMSO (0.1 ml.) containing DCC (63 mg.) and anhydrous phosphoric acid (0.1 ml. of a 1 M solution in DMSO). After 18 hr. water (5

ml.), 0.1 mmole of phosphoric acid, and ether (5 ml.) were added, and dicyclohexylurea was filtered off. The water layer was extracted once more with ether, made alkaline with lithium hydroxide, and extracted several times with ether. The ether extracts were evaporated leaving 27 mg. of a white solid which was purified by preparative thin layer chromatography (ethyl acetate). The ultraviolet absorbing band (λ_{max} 223 and 285 mμ) was eluted with methanol, evaporated to dryness, and redissolved in methylene chloride to remove a trace of silica. Evaporation of the solvent led to immediate crystallization of XXIVb (20 mg., 80%) which was identical with an authentic sample[18] by thin layer chromatography and by ultraviolet and infrared spectra.

Oxidation of Flindissol (XXV).[33] Flindissol (410 mg., 0.90 mmole) was reacted overnight in DMSO (2.5 ml.) and benzene (2.5 ml.) containing DCC (560 mg., 2.7 mmoles), pyridine (0.08 ml.), and trifluoroacetic acid (0.04 ml.). Ethyl acetate (20 ml.) was added and dicyclohexylurea removed. The solution was extracted three times with water, dried, and evaporated leaving a semicrystalline residue that was chromatographed on 50 g. of Merck silica with chloroform–benzene (1:1). The main product (226 mg.) was contaminated with a little dicyclohexylurea but crystallization from methanol and then benzene gave chromatographically pure material (183 mg., 47%), m.p. 146–147°. The infrared spectra showed ν_{max} (KBr) 1715 and a small peak at 1640 cm.$^{-1}$. The ultraviolet spectrum in dioxane showed only end absorption below 250 mμ, and the n.m.r. spectrum showed two vinyl protons as multiplets between 305 and 325 c.p.s. and a single proton as a barely resolved doublet at 363 c.p.s. *Anal.* Calcd. for $C_{30}H_{44}O_2$: C, 82.51; H, 10.16; O, 7.33. Found: C, 82.35; H, 10.30; O, 7.85.

(32) L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, 20, 244 (1937), have reported m.p. 119–120° while L. F. Fieser, *J. Am. Chem. Soc.*, 75, 4377 (1953), reports m.p. 127–128° for material prepared by bromination, oxidation, and debromination of cholesterol.

(33) We are very grateful to Dr. A. J. Birch for a generous gift of flindissol and flindissone lactone: see A. J. Birch, D. J. Collins, S. Muhammad, and J. P. Turnbull, *J. Chem. Soc.*, 2763 (1963).