drolysis rate constant. The values are shown below, and compare quite favorably with those obtained by the titrimetric method shown in Table VII.

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Dimethyl Sulfoxide–Acid Anhydride Mixtures for the Oxidation of Alcohols

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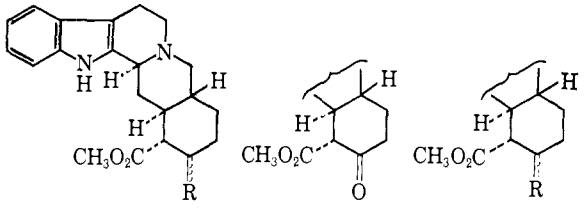
Abstract: Oxidation of alcohols with dimethyl sulfoxide and acetic anhydride is reported. The conversion of secondary hydroxyl functions to ketones in a variety of alkaloids and steroids occurs in moderate to excellent yields. The dimethyl sulfoxide–acetic anhydride oxidation procedure is particularly useful for oxidation of sterically hindered hydroxyl groups and for oxidation of hydroxyl functions in sensitive molecules such as indole alkaloids. The mechanism of oxidation is discussed. By-products often formed are methylthiomethyl ethers of the starting alcohols.

Our continued interest in improved methods for the oxidation of secondary hydroxyl groups of indole alkaloids[1] to ketones led to the discovery of a novel method of oxidation of alcohols to their corresponding carbonyl derivatives with dimethyl sulfoxide (DMSO) and acetic anhydride.[2] Oxidation of alcohols with acetic anhydride–DMSO is a mild oxidative method and is particularly useful with indole alkaloids which are sensitive to nonselective oxidizing reagents. In addition this procedure gives good yields with sterically hindered hydroxyl groups and has been applied to a number of steroids. However, it is obvious that this method will fail in cases where alcohols are rapidly acetylated under the conditions of the reaction, for O-acetylation will then effectively compete with oxidation.

In general, the procedure consists of stirring a solution of the alcohol in a mixture of DMSO and acetic anhydride for 15–24 hr at room temperature. Dimethyl sulfoxide has been used as both solvent and reagent, although there is no reason to believe that an inert diluent is deleterious. In our original experiments a ratio of 20 moles of acetic anhydride to 1 mole of alcohol was employed; however, such a large excess of acetic anhydride is not necessary. Successful oxidations have been carried out with 3–5 moles of anhydride per mole of alcohol.

Optimal conditions for the reaction and variations which could be employed were determined using yohimbine (**1**) as substrate. The reaction of **1** (1 mmole), 3 ml of DMSO, and 2 ml (*ca.* 20 mmoles) of acetic anhydride was followed by periodically removing aliquots and determining the extent of reaction by thin layer chromatography (tlc) on silica gel. In 4–5 hr the reaction was approximately 50% complete and in 12 hr no more starting material remained. Yohimbinone[3] (**3**) was isolated in 80% yield at the end of this time. No reduction in the yield was observed on decreasing the molar ratio of alcohol **1** to acetic anhydride to 1:5.



1, R = –H, ···OH
2, R = –OH, ···H

3

4, R = –H, ···OCH_2SCH_3
5, R = $-OCH_2SCH_3$, ···H

Certain other acid anhydrides can be used in place of acetic anhydride. Benzoic anhydride (17 moles) and yohimbine (1 mole) in DMSO at room temperature for 22 hr afforded 82% of β-keto ester **3**. However trifluoroacetic anhydride and *p*-toluenesulfonic anhydride were not effective. Based on plausible mechanistic considerations (*vide infra*) anhydrides unreactive to DMSO should be unsatisfactory as should overly reactive ones. Phosphorus pentoxide[4] and polyphosphoric acid were studied briefly with the following results. Yohimbine (**1**) (1 mole) and phosphorus pentoxide (1 mole) in DMSO at 65° for 18 hr gave yohimbinone (**3**) in 45% yield. Polyphosphoric acid and **1** at room temperature for 41 hr afforded **3** in 51%

(1) For a previous study of oxidation of alcohols see J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

(2) See J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965), for preliminary communication of this work; for application of this method in the carbohydrate field see W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, **44**, 836 (1966).

(3) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. Soc. Chim. France*, 637 (1961).

(4) The oxidation of alcohols to ketones in the carbohydrate field with DMSO–phosphorus pentoxide has been described recently: K. Onodera, S. Hirano, and N. Kashimura, *J. Am. Chem. Soc.*, **87**, 4651 (1965).

yield. Oxidation of testosterone with polyphosphoric acid and DMSO at room temperature was unsatisfactory as was oxidation of ajmaline with phosphorus pentoxide–DMSO at 65° (multiplicity of products on tlc).

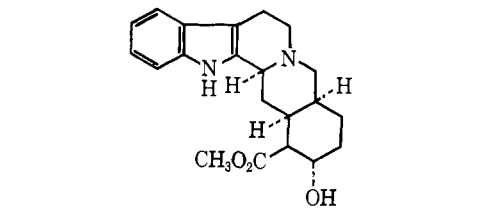
The use of sulfoxides other than DMSO was briefly studied. For example, with tetramethylene sulfoxide, yohimbine (**1**) (1 mole) and acetic anhydride (21 moles) gave yohimbinone (**3**) in 80% yield, while diphenyl sulfoxide gave no oxidation. These limited results showed that only sulfoxides reactive to acid anhydrides[5] will lead to oxidation as anticipated from mechanistic considerations.

Since yohimbine (**1**) undergoes oxidation with DMSO–acetic anhydride to give yohimbinone (**3**) in 80–85% yields, this method constitutes a superior procedure for the preparation of **3**.[6,7] In the oxidation of **1** to **3** a small amount of a second product was observed. From a large-scale oxidation of **1** the minor component was isolated and identified as methyl 17α-[(methylthio)methoxy]yohimban-16α-carboxylate (**4**). The pmr spectrum (in δ) of **4**, with singlets at 2.10 (SCH_3) and 3.73 (OCH_3) and an AB quartet centered at 4.62 (OCH_2S), demonstrated the presence of the methylthiomethoxy group and established the structure.

The application of the DMSO–acetic anhydride oxidative procedure to a variety of substrates was undertaken to further define the utility of the method and to gain information bearing on the mechanism of the reaction. β-Yohimbine (**2**), which differs from **1** only in the configuration of the C-17 hydroxyl group (equatorial in **2** *vs.* axial in **1**), was completely converted to a 50:50 mixture (determined by tlc and integration of pmr signals) of ketone **3** and methylthiomethoxy derivative **5**. Chromatography on silica gel afforded 25% of **3** and 18% of **5**. In a similar manner α-yohimbine (**6**) (equatorial hydroxyl) afforded equal amounts of two components which were separated by chromatography to give 40% of crude methyl 17-hydroxyalloyohimb-16-ene-16-carboxylate[1] (**7**) and 10% of methylthiomethyl ether **8**.

Methyl reserpate (**9**) (equatorial hydroxyl) afforded 33% of methyl ketoreserpate[8] (**10**) and 11% of methyl reserpate methylthiomethyl ether (**11**).

Ajmaline (**12**) has two possible sites for oxidation, the C-17 hydroxyl and the C-21 carbinolamine hydroxyl. However, oxidation with DMSO–acetic anhydride, followed by treatment of the product with methanolic sodium hydroxide to hydrolyze O-acetates, gave ajmalidine[9] (**13**) (52% as a glass) and methylthiomethoxy derivative **14** (10%). Difficulties were encountered in crystallizing ajmalidine. From the glass crystalline **13** (4% from **12**) was obtained with the expected spectral



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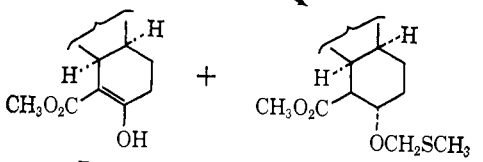
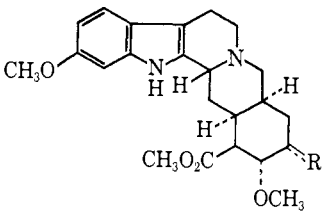
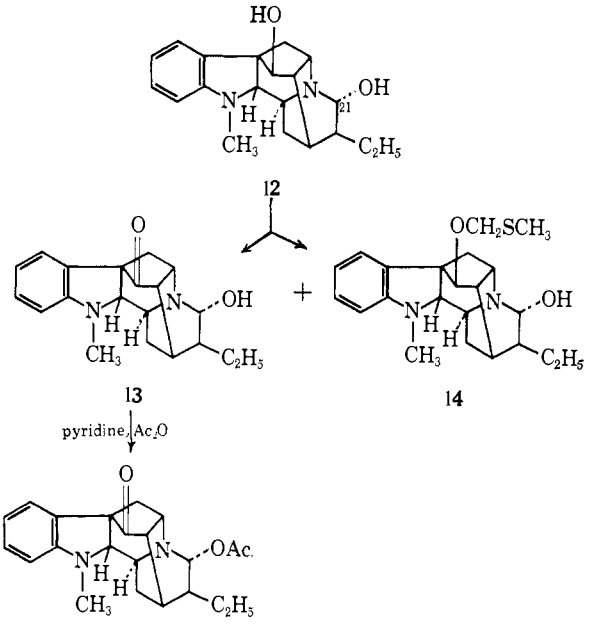


7 **8**



9, R = —OH, ···H
10, R = =O
11, R = —OCH_2SCH_3, ···H



13 **14** **15**

(infrared, ultraviolet, pmr) properties. Thin layer chromatography and pmr spectral data indicated that both the glass and the crystalline material were identical. Furthermore, treatment of the glass with acetic anhydride–pyridine gave, in 68% yield, the same O-acetate **15** as was obtained from crystalline **13**. That ajmalidine O-acetate (**15**) is one of the original products of the oxidation was shown by isolation of **15** when the methanolic base treatment was eliminated from the product work-up. On a larger scale (0.04 mole) oxidation of ajmaline (**12**), crystalline ajmalidine (**13**) was obtained in 25% yield along with 18% of methylthiomethoxy derivative **14**.

(5) For reactivity of sulfoxides to anhydrides (Pummerer rearrangement) see R. Pummerer, *Ber.*, **43**, 1401 (1910); L. Horner and P. Kaiser, *Ann.*, **626**, 19 (1959).

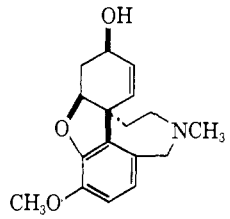
(6) Mild Oppenauer oxidation of yohimbine (**1**) gives yohimbinone (**3**) in 51% yield.[3]

(7) Yohimbine (**1**) was oxidized to **3** (80%) with dicyclohexylcarbodiimide, DMSO, and phosphoric acid.[1]

(8) M. M. Robison, W. G. Pierson, R. A. Lucas, I. Hsu, and R. L. Dziemian, *J. Org. Chem.*, **28**, 768 (1963).

(9) (a) M. Gorman, N. Neuss, C. Djerassi, J. P. Kutney, and P. J. Scheuer, *Tetrahedron*, **1**, 328 (1957); (b) C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney, and S. C. Pakrashi, *J. Am. Chem. Soc.*, **79**, 1217 (1957); (c) C. Djerassi, M. Gorman, S. C. Pakrashi, and R. B. Woodward, *ibid.*, **78**, 1259 (1956); (d) S. C. Pakrashi, C. Djerassi, R. Wasicky, and N. Neuss, *ibid.*, 77, 6687 (1955).

Oxidation[10] of galanthamine (**16**), an allylic alcohol, with DMSO and acetic anhydride gave narwedine[11] (**17**) in moderate yield, while oxidation of codeine to codeinone was unsuccessful.



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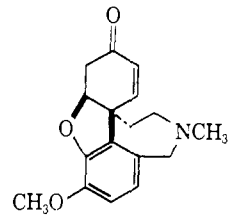
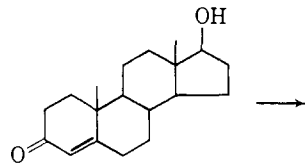
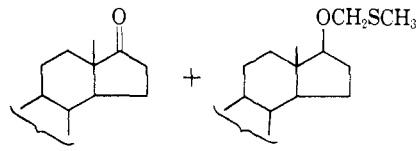


17

The oxidation of a number of steroidal alcohols was studied. Tlc showed that testosterone (**18**) is oxidized with DMSO–acetic anhydride to give approximately 70% of 4-androstene-3,17-dione[12] (**19**) and 30% of



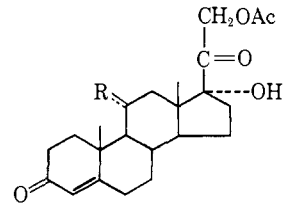
18



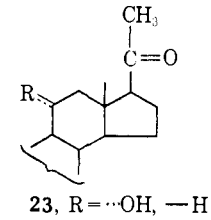
19 20

17β-[(methylthio)methoxy]-4-androsten-3-one[13] (**20**). Chromatography afforded 34% of **19** and 8% of **20**. The effect of the configuration of the hydroxyl group on the product composition was vividly demonstrated by comparison of the oxidation of hydrocortisone 21-acetate (**21**) (axial 11β-hydroxyl) and 11α-hydroxyprogesterone (**23**) (equatorial hydroxyl). The sterically hindered 11β-hydroxyl group of **21** was oxidized smoothly but slowly (92 hr at room temperature) to give cortisone 21-acetate[14] (**22**) (53% by direct crystallization of the product). In contrast, 11α-hydroxyprogesterone (**23**) afforded, after partition chromatography, two major components, the larger of which was a gum (56%) identified by its pmr spectrum as methylthiomethoxy derivative **25**. The second component (30% as glass) was crystallized to give 11-ketoprogesterone[15] (**24**) in 13% yield. It is of interest that oxidation of **23** with dicyclohexylcarbodiimide (DCC), DMSO, and pyridinium trifluoroacetate has been reported by Pfitzner and Moffatt[16] to proceed smooothly while no oxidation was observed with **21**.

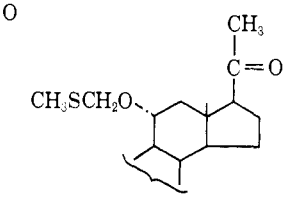
Some conclusions about the mechanism of oxidation of alcohols with DMSO and acid anhydrides can be drawn. Carboxylic acid anhydrides are known to react with sulfoxides to give α-acyloxy sulfides[5,17] and recently carboxylic acids have been shown to react with phosphorus pentoxide and DMSO to give α-acyloxy sulfides.[18] The reaction of thionyl chloride and acid chlorides such as benzoyl chloride with sulfoxides has been shown[19] to give α-chloro sulfides. All these reactions have one feature in common in that they are best visualized as proceeding by reaction of an electrophile on the electronegative oxygen atom of the sulfoxide to give intermediate oxysulfonium salts of type **26**.



21, R = —OH, ···H
22, R = =O



23, R = ···OH, —H
24, R = =O



25

$$(CH_3)_2S{=}O \xrightarrow{ROX} (CH_3)_2S^{\oplus}ORX^{\ominus}$$

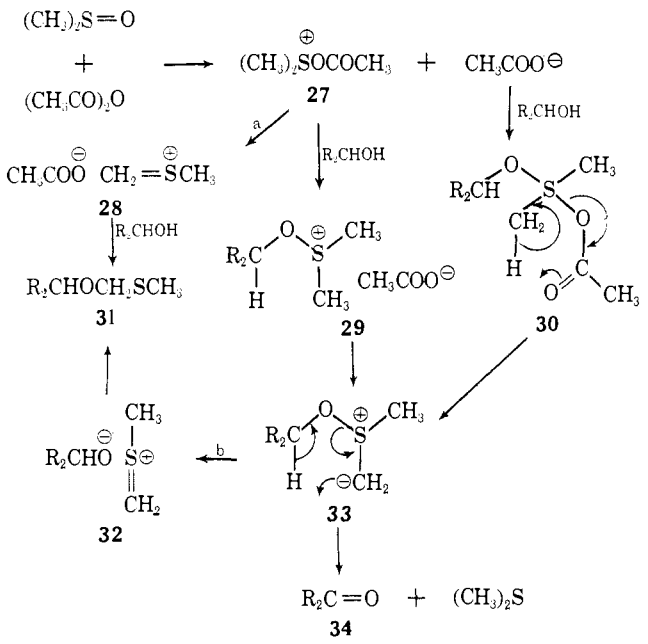
26

a, R = $COCH_3$; X = $OCOCH_3$
b, R = COC_6H_5; X = Cl
c, R = SOCl; X = Cl

We were led to consider an oxidation sequence involving activation of DMSO to give an intermediate of type **26** by the evidence for such intermediates and by reasoning that they might react with an alcohol *in situ*. Such SN2 displacements with alkoxysulfonium salts[20] have been demonstrated recently. Alkoxysulfonium salt **26** (wherein R = alkyl or cycloalkyl) could be reasonably expected to collapse in the presence of a base to give carbonyl products. The oxidation of α-bromoketones and alkyl tosylates with DMSO and base is based on similar mechanistic principles.[21] The sequence of reactions in Chart I can be considered for the oxidation of alcohols with DMSO–acetic anhydride. The acyloxysulfonium salt **27** is first formed, and nucleophilic attack of an alcohol on the positively charged sulfur atom of **27** with back-side displacement of acetate ion occurs to give alkoxysulfonium salt **29**. Base-promoted removal of a proton from the methyl group of **29**[22] then gives the sulfur stabilized ylid **33** which, through a cyclic transition state, collapses to give

(10) Experiment carried out by E. Benz of these laboratories.
(11) D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 806 (1962).
(12) E. S. Wallis and E. Fernholz, *J. Am. Chem. Soc.*, **57**, 1511 (1935).
(13) Compound **20** has also been isolated in the oxidation of **19** with dicyclohexylcarbodiimide, DMSO, and phosphoric acid: K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5670 (1965); J. B. Jones and D. C. Wigfield, *Tetrahedron Letters*, 4103 (1965), have also isolated methylthiomethoxy derivatives in oxidations with DCC and DMSO.
(14) T. Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937).
(15) D. H. Peterson, H. C. Murray, S. H. Eppstein, L. M. Reineke, A. Weintraub, P. D. Meister, and H. M. Leigh, *J. Am. Chem. Soc.*, **74**, 5933 (1952).
(16) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **85**, 3027 (1963); **87**, 5670 (1965).
(17) S. Oak, T. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, **19**, 317 (1963); W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **28**, 2686 (1963); W. E. Parham and S. H. Groen, *ibid.*, **30**, 728 (1965).
(18) K. Onodera, S. Hirano, N. Kashimura, and T. Yajima, *Tetrahedron Letters*, 4327 (1965).
(19) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, 77, 572 (1955).
(20) C. R. Johnson, *ibid.*, **85**, 1020 (1963); C. R. Johnson and W. G. Phillips, *Tetrahedron Letters*, 2101 (1965).
(21) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959); N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Zevand, and W. M. Weaver, *ibid.*, **79**, 6562 (1957).
(22) See ref 20 for the reactions of alkoxysulfonium salts with alkoxides.

Chart I



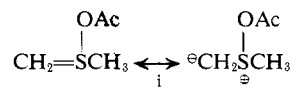
carbonyl derivative **34** and dimethyl sulfide. Fenselau and Moffatt[23] have recently demonstrated that, in oxidations of alcohols with sulfoxides and carbodiimides, sulfur ylid **33** is an intermediate and showed that proton abstraction is intramolecular.

If an alkoxysulfonium salt **29** is an intermediate in oxidations with DMSO–acetic anhydride, acetate anion must be serving as the base to remove a proton from alkoxysulfonium salt **29** to give ylid **33**. That acetate is a strong enough base for this step is expected, since it is known that protons of methyl groups attached to sulfur in trimethylsulfonium and trimethyloxosulfonium salts **35** and **36** are readily exchanged[24] with D_2O.

$(CH_3)_3\overset{\oplus}{S}X^{\ominus}$ **35** $\qquad$ $(CH_3)_3\overset{\oplus}{S}{=}O\,X^{\ominus}$ **36**

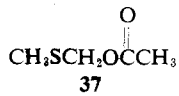
The possibility that an alkoxysulfonium salt **29** is not an intermediate in oxidations with DMSO–acetic anhydride must be considered. Thus, nucleophilic attack of an alcohol on acyloxysulfonium salt **27** without displacement of acetate ion would give a neutral tetrasubstituted sulfur intermediate **30**. Collapse of **30** in a cyclic mechanism (loss of acetic acid) would give the ylid **33** directly without the intermediacy of alkoxysulfonium salt **29**. The recent report[25] that isobutoxydimethylsulfonium tetraphenylborate gave only traces of carbonyl compounds under DMSO–acetic anhydride oxidative conditions would appear to indicate that alkoxysulfonium salts **29** are not intermediates. However, these results do not definitively rule out intermediate **29**. In DMSO–acetic anhydride oxidations, 1 mole of acetate anion is produced for each mole of alkoxysulfonium ion formed. In the absence of an alcohol acetic anhydride and DMSO produce intermediate **27** which undergoes Pummerer rearrangement to acetoxymethyl methyl sulfide (**37**) and acetic acid. Thus acetate anion is not available for removal of a proton from the preformed alkoxydimethylsulfonium tetraphenylborate to give ylid **33**. It would be instructive to know whether addition of potassium acetate would promote the conversion of alkoxysulfonium salts to carbonyl products.

Several pathways for formation of methylthiomethyl ethers are possible, either through an independent competitive reaction *via* intermediate **28** (path a) or by rearrangement of ylid **33** (path b). If methylthiomethyl ether **31** is, indeed, formed by rearrangement of ylid **33**, it is difficult to reconcile the greater yields of methylthiomethoxy derivative **31** in oxidations with DMSO and acetic anhydride than with carbodimides and DMSO.[16] With the same intermediate ylid[23] involved in both oxidations, similar amounts of rearrangement product would be expected, and this is not observed. Therefore, it appears unlikely that rearrangement of ylid **33** is the sole source of methylthiomethoxy derivative. If, however, a competitive reaction is occurring involving intermediate **28**[26] a greater amount of ether



31 in oxidations involving DMSO–acetic anhydride than in oxidations with carbodiimides may be expected, for a solvated form of **28**, or more likely an ion pair with acetate anion, may be an intermediate in this reaction as well as in the Pummerer rearrangement[5] reaction. With DMSO–acetic anhydride the Pummerer rearrangement and oxidation are occurring concurrently.

Another pathway for the formation of methylthiomethoxy derivatives was also considered. It is conceivable that under the mildly acidic conditions of the reaction, acetoxymethyl methyl sulfide (**37**) and an alcohol might give ether **31**, for acetoxymethyl methyl sulfide (**37**)[5] is an acetylated hemithioacetal of formaldehyde. This possibility was eliminated when it was found that acetoxymethyl methyl sulfide (**37**) and alcohols such as



yohimbine and β-yohimbine do not give methylthiomethoxy derivatives under the conditions of the oxidation either in the presence or absence of acetic acid.

Some qualitative information about the rate of reaction of acetic anhydride and DMSO was obtained by the observation that a mixture of acetic anhydride and DMSO (slight excess) still contained unreacted acetic anhydride after standing at room temperature for 1 month. This aged mixture converted β-yohimbine (**2**) to yohimbinone (**3**) and methylthiomethoxy derivative **5** very slowly at room temperature, but heating at 65–70° for 7 hr gave complete conversion to β-keto ester **3** (50%) and ether **5** (50%). Yohimbine, on heating with the 1 month aged DMSO–acetic anhydride mixture for 9 hr at 65–70° was converted to a 50:50 mixture of ketone **3** and ether **4**. The increase in methylthiomethoxy derivative from yohimbine on oxidation in aged DMSO–acetic anhydride is due to the presence of acetic acid. The use of acetic acid as solvent in the oxidation of testosterone with equimolar

(23) A. H. Fenselau and J. G. Moffatt, *J. Am. Chem. Soc.*, **88**, 1762 (1966).

(24) W. von E. Doering and A. H. Hoffman, *ibid.*, 77, 521 (1955); G. S. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

(25) K. Torssell, *Tetrahedron Letters*, 4445 (1966).

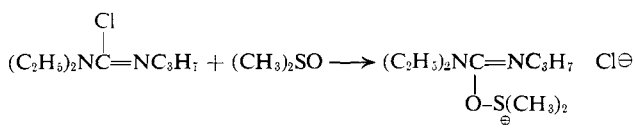
(26) It is conceivable that ylid i is the reactive intermediate in formation of ether **31** although this possibility appears unlikely.

amounts of acetic anhydride and DMSO leads to *ca.* 65% of methylthiomethoxy derivative **20** after 6 days at room temperature. In addition, testosterone O-acetate and 4-androstene-3,17-dione (**19**) were formed as evidenced by tlc.

The difference in product composition observed between compounds with an axial or equatorial hydroxyl group deserves further comment. The increased amounts of methylthiomethoxy derivative with compounds having an equatorial hydroxyl group may be explained on the basis of two independent pathways, one for oxidation (*via* intermediates **29** or **30** and ylid **33**) and one for methyl thiomethyl ether formation (*via* ion pair **28**). It is then necessary to postulate that the less hindered equatorial alcohol reacts sufficiently faster with ion pair **28** than an axial alcohol due to steric factors. If ylid **33** is the intermediate for both oxidation and ether formation and the rate-determining steps are collapse of ylid with abstraction of the hydrogen on the carbinol carbon and rearrangement, a faster rate of oxidation of sterically hindered hydroxyl groups (steric assistance) would explain the fact that axial alcohols give more ketone and less ether derivative. A faster rate of oxidation of sterically hindered hydroxyl groups has been observed in chromic acid oxidations of steroidal alcohols[27] and these results were rationalized in terms of steric assistance.[27]

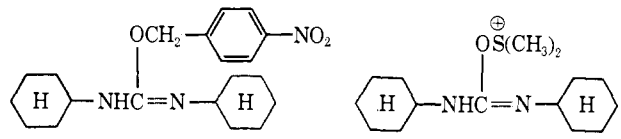
Without definitive rate data no conclusive choice between alternative mechanisms can be made. However, we believe methylthiomethoxy derivatives **31** are formed in a pathway independent of the oxidative sequence rather than by rearrangement of ylid **33** (*via* ion pair **32**). This belief rests mainly on the fact that little rearrangement of ylids of type **33** is observed in oxidations with DMSO, DCC, and phosphoric acid.[1,13,16,23]

The fact that trifluoroacetic anhydride and *p*-toluenesulfonic anhydride were unsatisfactory was mentioned previously and is readily understood on the basis of mechanistic considerations. For successful oxidations the intermediate acyloxysulfonium salt must be stable enough and present in sufficient concentration to allow nucleophilic attack by an alcohol to occur. With a very reactive anhydride, the acyloxysulfonium salt will rearrange (Pummerer reaction) too rapidly to allow subsequent reactions with it. Experimentally trifluoroacetic anhydride reacts violently with DMSO at room temperature. Probably for similar reasons a mixture of 1-chloro-N,N-diethyl-N′-propylformamidine[28] (**39**) and DMSO failed to oxidize testosterone. Alcohols react rapidly with chloroformamidine **38** and, therefore, intermediate **39** must be preformed. However, **39** may go on to other products too rapidly for subsequent reaction with an alcohol.



38 39

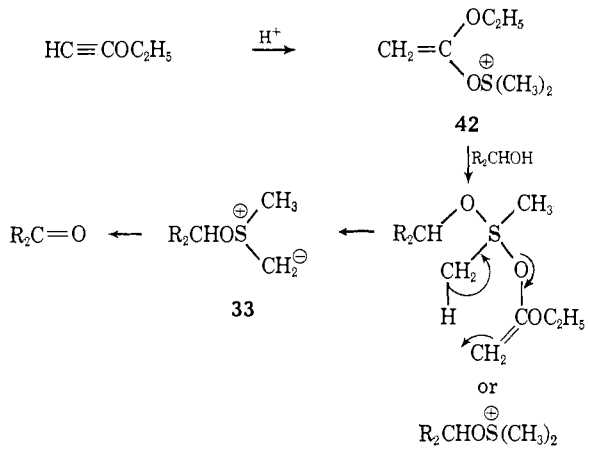
Further evidence that oxidations of alcohols by reagents prepared from mixtures of DMSO and suitable electrophiles proceeds *via* oxysulfonium salts, and that this is a general phenomenon was provided by experiments with ^{18}O-labeled alcohols. Oxidation of benzhydrol-^{18}O (4.8% ^{18}O) with DCC, DMSO, and phosphoric acid gave unlabeled N,N′-dicyclohexylurea and 42% of the ^{18}O was found in the benzophenone isolated.[29] Oxidation of ethanol-^{18}O (1.9% ^{18}O) afforded N,N′-dicyclohexylurea with only 16% of ^{18}O label.[30] In addition pseudourea **40**[31] was unaffected by the oxidizing reagent. These results indicate that DCC and DMSO interact to give sulfonium salt **41** which reacts



40 41

with alcohols to give alkoxysulfonium salts. Similar conclusions have been reached by Fenselau and Moffatt.[23]

Testosterone was found to be oxidized to 4-androstene-3,17-dione by a mixture of ethoxyacetylene, DMSO, pyridine, and phosphoric acid. Mechanistically the reaction may be illustrated as follows.



Protonation of ethoxyacetylene followed by reaction with DMSO gives intermediate **42** which then reacts with an alcohol. Tlc demonstrated that no testosterone O-acetate was formed in the reaction.

Experimental Section

All melting points were taken on a Mel-Temp apparatus and are uncorrected. Samples for analysis were dried *in vacuo* over phosphorus pentoxide at 100° for 18–24 hr. Ultraviolet absorption spectra were measured on a Cary recording spectrophotometer. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Pmr spectra were determined with a Varian Model A-60 spectrometer in deuterated chloroform or deuterated dimethyl sulfoxide; chemical shifts (δ) are in parts per million

(27) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955); E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 289.

(28) Prepared by R. B. Conrow of these laboratories from N,N-diethyl-N′-propylurea and phosgene.

(29) Per cent ^{18}O was determined by mass spectral analysis. Partial loss of label in the benzophenone probably resulted from exchange with solvent during aqueous acidic work-up.

(30) If ethanol were adding to the DCC the N,N′-dicyclohexylurea should have been extensively labeled with ^{18}O. The small incorporation of label may have occurred from reaction of DCC with water-^{18}O produced by aldol condensation of the acetaldehyde-^{18}O formed in the oxidation.

(31) Prepared by the method of E. Schmidt and F. Moosmüller, *Ann.*, **597**, 235 (1955); E. Schmidt and W. Carl, *ibid.*, **639**, 24 (1961).

relative to internal tetramethylsilane. Concentrations were carried out *in vacuo*. Dimethyl sulfoxide was dried over Molecular Sieves (Type 4A, Fisher). Per cent ^{18}O in labeled compounds was determined by mass spectral analysis. The ^{18}O labeled water was purchased from Yeda Research and Development Co., Ltd. (affiliated with Weizmann Institute of Science), Rehovoth, Israel.

Oxidation of Yohimbine (1) to Yohimbinone (3). A. With DMSO and Acetic Anhydride. To a mixture of 886 g of yohimbine (**1**) and 7.55 l. of dry dimethyl sulfoxide was added 5.05 l. of acetic anhydride. The mixture was stirred at room temperature for 18 hr. The mixture was diluted with 16.8 l. of ethanol, stirred for 1 hr, and diluted with 4.2 l. of water. Concentrated ammonium hydroxide (11 l.) was added while maintaining the temperature at 15–30° by cooling and the mixture was then diluted with 16.8 l. of water. Filtration gave a solid which was washed with water and dried to give 818 g (93%) of tan crystals, mp 248–250° dec. This was slurried twice with 4 l. of ethanol and filtered to give 742 g (84%) of **3**, mp 253–254° dec; lit.[3] mp 243–249°.

The filtrate from the first slurry with 4 l. of ethanol was concentrated to give a dark colored gum. The gum was dissolved in chloroform–acetone–ethanol (6:3:1) and filtered through synthetic magnesia silica gel, the filter cake was washed with acetone, and the combined filtrates were concentrated to give 40 g of dark gum. The gum (20 g) was chromatographed on a column of 300 g of silica gel using chloroform–ethanol (99.3:0.7) as eluting solvent and 250-ml cuts were collected. Evaporation of cuts 5–11 gave the product as a glass. The combined glass from two column purifications was crystallized from methanol to give 6.95 g (0.7%) of methyl 17α-[(methylthio)methoxy]yohimban-16α-carboxylate (**4**) as tan crystals, mp 195–198°. On standing the mother liquors gave a second crop (2.7 g, 0.3%) of yellow crystals, mp 195–198°. Recrystallization of 2.0 g from 20 ml of methanol gave 1.2 g of off-white crystals of **4**, mp 198–200°; $[\alpha]^{25}D$ −164° (*c* 1.03, pyridine); pmr ($CDCl_3$) singlets at δ 2.10 (SCH_3) and 3.73 (OCH_3); AB quartet centered at δ 4.62 (J_{AB} = 12 cps) (OCH_2S); ν_{max}^{KBr} 1724 (s), 1156 (s), 1041 cm^{-1} (s).

Anal. Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.6; H, 7.30; N, 6.76; S, 7.74. Found: C, 66.8; H, 6.99; N, 6.89; S, 7.74.

B. With DMSO and Benzoic Anhydride. A mixture of 2.12 g (0.0060 mole) of **1**, 22.6 g (0.10 mole) of benzoic anhydride, and 20 ml of dry dimethyl sulfoxide was allowed to stand at room temperature for 22 hr. The mixture was diluted with 10 ml of water and 50 ml of ethanol and allowed to stand 30 min. The mixture was chilled by means of an ice bath and made basic with concentrated ammonium hydroxide. After diluting with 75 ml of water, the solid was collected by filtration and washed with water and with ether to give 1.73 g (82%) of **3** as light tan needles, mp 253–256° dec.

C. With Tetramethylene Sulfoxide and Acetic Anhydride. A mixture of 0.708 g (0.0020 mole) of **1**, 10 ml of tetramethylene sulfoxide, and 4 ml of acetic anhydride was allowed to stand at room temperature for 21 hr. The solution was poured into 20 ml of ethanol, chilled, and made basic with concentrated ammonium hydroxide. The mixture was diluted with 25 ml of water and filtered to give 0.57 g (80%) of **3** as tan crystals, mp 250–253° dec.

D. With DMSO and Polyphosphoric Acid. A mixture of 1.8 g of polyphosphoric acid (Matheson Coleman and Bell, 82–84% P_2O_5), 0.708 g of **1**, and 6 ml of dry dimethyl sulfoxide was warmed on a steam bath until the solid dissolved, and the solution was then stirred at room temperature for 41 hr. The resulting solution was diluted with 25 ml of ethanol and 5 ml of water, chilled, and made basic with concentrated ammonium hydroxide. The chilled mixture was diluted with 30 ml of water and filtered, and the precipitate was washed twice with 25-ml portions of water. The solid was then washed with ether to give 0.36 g (51%) of **3** as tan crystals, mp 239–243° dec. Recrystallization from ethanol–chloroform gave the product as tan crystals, mp 250–253° dec.

E. With DMSO and Phosphorus Pentoxide. To a solution of 1.06 g (0.0030 mole) of **1** in 10 ml of dry dimethyl sulfoxide was added 0.425 g (0.0030 mole) of phosphorus pentoxide. The solution was heated at 65° for 18 hr under nitrogen. The mixture was poured onto ice and made basic with concentrated ammonium hydroxide, and the resulting solid was removed by filtration and washed with water. The partially dried solid was dissolved in chloroform–ethanol (6:4) and filtered through Florisil. The filter cake was washed with chloroform–ethanol (9:1), and the filtrate was concentrated. The residue was triturated with ethanol, and the crystals were removed by filtration and washed with ether to give 0.48 g (45%) of **3** as yellow crystals, mp 240–243° dec.

Oxidation of β-Yohimbine (2) to Yohimbinone (3). A mixture of 5.30 g of **2**, 45 ml of dry dimethyl sulfoxide, and 30 ml of acetic anhydride was allowed to stand at room temperature for 19.5 hr under an atmosphere of nitrogen. The solution was diluted with 100 ml of ethanol and 10 ml of water, chilled, and made basic with concentrated ammonium hydroxide. The chilled mixture was diluted with 125 ml of water and filtered; the precipitate was washed with water to give 4.35 g of tan crystals. Chromatography of the product over silica gel gave, on elution with chloroform–methanol (99.5:0.5), a glass which was crystallized from methanol to yield 1.1 g (18%) of methyl 17β-[(methylthio)methoxy]-yohimban-16α-carboxylate (**5**) as colorless crystals, mp 167–169°. Recrystallization from methanol gave 0.7 g of **5**, mp 189–190°; $[\alpha]^{25}D$ −80° (*c* 1.0, pyridine); pmr ($CDCl_3$) singlets at δ 2.10 (SCH_3), 3.78 (OCH_3), and 4.62 (OCH_2S); ν_{max}^{KBr} 1736 (s), 1064 (s), and 1047 cm^{-1} (s) (sh).

Anal. Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.6; H, 7.30; N, 6.76; S, 7.74. Found: C, 66.5; H, 7.47; N, 6.71; S, 7.36.

Further elution of the column with chloroform–methanol (99.5:0.5) afforded, after recrystallization from acetone–chloroform (80:20), 1.4 g (25%) of **3**, mp 255–258°.

Oxidation of α-Yohimbine (6) to Methyl 17-Hydroxyalloyohimb-16-ene-16-carboxylate (7). A mixture of 2.12 g of **6**, 25 ml of dry dimethyl sulfoxide, and 4.0 ml of acetic anhydride was stirred at room temperature for 21 hr. The mixture was poured onto 60 g of ice and 10 ml of water and made basic with concentrated ammonium hydroxide. The solid which separated was removed by filtration and washed with water. The dry solid was dissolved in ether and filtered through 10 g of synthetic magnesia silica gel. The filter cake was washed with ether and the combined filtrates were concentrated to give 2.10 g of a pale orange glass. Chromatography of 4.1 g of the glass over 200 g of silica gel gave in the first fractions, on elution with chloroform–ethanol (99.5:0.5), a glass which was crystallized from methanol to yield 0.48 g (10%) of methyl 17α-[(methylthio)methoxy]alloyohimban-16β-carboxylate (**8**) as tan crystals; melting point changes above 92° to a viscous mass which slowly liquifies. Recrystallization from methanol gave colorless crystals of **8** hemihydrate, melting point changes to viscous mass above 100° which slowly liquifies; $[\alpha]^{25}D$ +25° (*c* 1.0, pyridine); pmr ($CDCl_3$) singlets at δ 2.10 (SCH_3), 3.76 ($C(=O)OCH_3$), and 4.62 (OCH_2S); ν_{max}^{KBr} 1724 (s) and 1064 cm^{-1} (s).

Anal. Calcd for $C_{23}H_{30}N_2O_3S \cdot 0.5H_2O$: C, 65.2; H, 7.38; N, 6.61; S, 7.57. Found: C, 65.5, 65.0; H, 7.76, 7.05; N, 6.74; S, 7.62.

Further elution of the column with chloroform–ethanol (99.5:0.5) afforded 1.8 g (40%) of **7** as a glass which was crystallized from methanol to give 0.67 g of tan crystals, mp 176–179° dec; lit.[1] mp 185–188° dec.

Oxidation of Methyl Reserpate (9) to Methyl Ketoreserpate (10). A mixture of 8.29 g of **9**, 60 ml of dry dimethyl sulfoxide, and 40 ml of acetic anhydride was stirred at room temperature for 20 hr. The mixture was poured onto 350 g of ice and made basic with 10 *N* sodium hydroxide. The mixture was extracted with 250 ml and with two 100-ml portions of dichloromethane. The combined extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was suspended in ethanol and concentrated nearly to dryness. The residue was triturated with ether and filtered to give 5.17 g of off-white crystals. The ether filtrate was concentrated, and the residue was triturated with ether and filtered to give 2.2 g of solid. Trituration with 15 ml of hot ethanol and filtration afforded 1.81 g (22%) of **10** as tan crystals, mp 229–231° dec; lit.[8] mp 241–242° dec.

The 5.17 g of solid from above was chromatographed over 250 g of silica gel with chloroform–ethanol (96:4). The first fractions afforded 1.45 g (15%) of methyl reserpate methylthiomethyl ether (**11**) which was recrystallized from methanol to give 1.0 g (11%) as off-white crystals, mp 248–252° dec; $[\alpha]^{25}D$ −81° (*c* 1.1, pyridine); pmr ($CDCl_3$–DMSO-d_6) singlets at δ 2.15 (SCH_3), 3.53 (OCH_3), 3.78 (two OCH_3), and 4.73 (OCH_2S); ν_{max}^{KBr} 1736 (s), 1151 (s), 1058 cm^{-1} (s).

Anal. Calcd for $C_{25}H_{34}N_2O_5S$: C, 63.3; H, 7.22; N, 5.90; S, 6.76. Found: C, 63.1; H, 7.28; N, 6.18; S, 6.74.

The latter fractions from the column afforded an additional 0.65 g (11%) of **10** as off-white crystals, mp 229–231° dec.

Oxidation of Ajmaline (12) to Ajmalidine (13). A. A mixture of 7.17 g of **12**, 60 ml of dry dimethyl sulfoxide, and 40 ml of acetic anhydride was allowed to stand at room temperature for 18 hr. The solution was poured onto 250 g of ice, and the chilled mixture was made basic with concentrated ammonium hydroxide and extracted with dichloromethane. The extract was washed with water,

dried over magnesium sulfate, and concentrated to give a gum. The gum was dissolved in 50 ml of hot ethanol, and the solution was diluted with 10 ml of water and 2.5 ml of 10 *N* sodium hydroxide. The solution was heated on a steam bath for 45 min, and the solvent was then removed under reduced pressure. Ethanol was added, and the solvent was again removed. The residue was triturated with water and filtered to give 6.1 g of solid. Chromatography of the solid over silica gel with chloroform–methanol (98:2) as eluent gave 3.4 g (52%) of **13** as a colorless glass which was crystallized from acetone to give 0.26 g (4%) of colorless crystals, mp 240–243°; lit.[9d] mp 241–242°; $[\alpha]^{25}D$ −80° (*c* 1.0, acetic acid); ν_{max}^{KBr} 1742 (s) and 1616 cm^{-1} (m).

Anal. Calcd for $C_{29}H_{23}N_2O_2$: C, 74.0; H, 7.46; N, 8.64. Found: C, 73.7; H, 7.76; N, 8.63.

The mother liquors from crystalline **13** were evaporated to a glass which was acetylated in the next experiment.

Further elution of the column with chloroform–methanol (98:2) gave 0.80 g (10%) of 17β-[(methylthio)methoxy]-21α-ajmalaninol (**14**) as colorless crystals, mp 145–147°. Recrystallization from methanol afforded 0.45 g of colorless crystals, mp 148–150°; $[\alpha]^{25}D$ −9.8° (*c* 1.0, pyridine); pmr ($CDCl_3$) singlets at δ 2.20 (SCH_3) and 2.77 (NCH_3); AB quartet at δ 4.73 (J_{AB} = 12 cps) (OCH_2S); ν_{max}^{KBr} 1605 (m) and 1047 cm^{-1} (s).

Anal. Calcd for $C_{22}H_{30}N_2O_2S \cdot 0.25H_2O$: C, 67.6; H, 7.86; N, 7.16; S, 8.20. Found: C, 67.3; H, 8.04; N, 7.00; S, 7.97.

B. In a similar manner 14.34 g (0.040 mole) of **12** was oxidized and the product chromatographed over 350 g of silica gel (200-ml cuts) with the eluents chloroform–ethanol (99.3:0.7) (5.2 l.), chloroform–ethanol (98.3:1.7) (1 l.), and chloroform–ethanol (97:3) (3 l.). The solid from fractions 13–33 was crystallized from methanol to give 3.5 g (25%) of **13** as colorless crystals, mp 240–243°. The solid from fractions 40–50 were crystallized from methanol to give 2.3 g (15%) of **14**, mp 147–150°.

In another oxidation of **12** the crude product, extracted with dichloromethane from the basified (with ammonium hydroxide) reaction mixture, gave crystals of ajmalidine O-acetate (**15**), mp 209–211°.

Ajmalidine O-Acetate (15). Ajmalidine (**13**) (1.8 g of glass obtained from mother liquors of crystalline **13**; see part A of preceding experiment) was dissolved in 5 ml of dry pyridine and 2 ml of acetic anhydride. The solution was allowed to stand for 19 hr at room temperature and then poured onto 35 g of ice. After standing 2 hr the mixture was made slightly basic with concentrated ammonium hydroxide and filtered. The solid was washed thoroughly with water and dried to give 1.4 g (68%) of **15** as off-white crystals, mp 208–213°. Recrystallization from ethanol gave 0.80 g of **15** as colorless needles, mp 218–220°; $[\alpha]^{25}D$ +242° (*c* 1.0, pyridine); pmr ($CDCl_3$) singlets at δ 2.12 ($OCOCH_3$), 2.78 (NCH_3), and 5.35 (>CHOCO), one proton doublet at 3.77 (C-2 H), and one proton multiplet at 3.23 (C-16 H); ν_{max}^{KBr} 1739 (s), 1613 (m), and 1244 cm^{-1} (s).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.1; H, 7.15; N, 7.65. Found: C, 72.1; H, 6.96; N, 7.81.

In a similar experiment crystalline ajmalidine afforded the same O-acetate as colorless crystals, mp 218–219°.

Oxidation of (−)-Galanthamine (16) to Narwedine (17). A mixture of 1.00 g of **16**, 10.5 ml of dimethyl sulfoxide, and 6.98 ml of acetic anhydride was stirred at room temperature for 18 hr. The solution was poured into 200 ml of ice–water and made alkaline with concentrated ammonium hydroxide. The mixture was extracted with dichloromethane and the extract was washed with water, dried over magnesium sulfate, and concentrated. Trituration of the residual yellow gum with ether and filtration gave 0.38 g (38%) of **17** as a yellow solid, mp 167–180° dec. Recrystallization from acetone gave 0.20 g of colorless crystals, mp 184–188°; lit.[11] mp 187–190°.

Oxidation of Testosterone (18) to 4-Androstene-3,17-dione (19).

A. With DMSO and Acetic Anhydride. To a solution of 1.15 g of **18** in 12 ml of dry dimethyl sulfoxide was added 8 ml of acetic anhydride. The solution was stirred for 13 hr at room temperature and poured onto 125 g of ice. The mixture was made basic with 10 *N* sodium hydroxide, and the resulting precipitate was removed by filtration and washed thoroughly with water to give 1.10 g of white crystals. Recrystallization from ether gave 0.70 g (60%) of **19** as white crystals, mp 160–162°. Concentration of the mother liquors gave 0.25 g of crystals which were partitioned on a column of 640 g of Celite diatomaceous earth (stationary phase: 2-methoxyethanol saturated with heptane). The column was developed with heptane and the fraction which was collected at 3.8–5.8 hold-back volumes (HBV) gave, on evaporation, 0.090 g (8%) of **19**, mp 168–170°; lit.[12] mp 170°.

The fraction collected at 1.0–1.5 HBV was concentrated and the solid was recrystallized from petroleum ether (bp 30–60°) to give 0.117 g (8%) of 17β-[(methylthio)methoxy]-4-androsten-3-one (**20**) as colorless needles, mp 123–124°; lit.[13] mp 128–129°; $[\alpha]^{25}D$ +113° (*c* 1.1, $CHCl_3$); pmr ($CDCl_3$) singlets at δ 0.82 (CH_3), 1.20 (CH_3), 2.12 (SCH_3), 4.60 (OCH_2S), 5.70 (>C=C(CO)H); ν_{max}^{KBr} 1675 (s), 1626 (m), 1075 (s), and 1062 cm^{-1} (s).

Anal. Calcd for $C_{23}H_{32}O_2S$: C, 72.4; H, 9.26; S, 9.20. Found: C, 71.9; H, 9.37; S, 9.07.

B. With DMSO, Phosphoric Acid, Pyridine, and Ethoxyacetylene. To a chilled mixture of 4.0 ml of dry dimethyl sulfoxide, 0.98 g (0.010 mole) of crystalline phosphoric acid, 0.577 g (0.0020 mole) of **18**, and 0.95 ml (0.012 mole) of dry pyridine was added 1.0 ml of redistilled ethoxyacetylene. The mixture was allowed to warm to room temperature and stand at room temperature for 23 hr. The mixture was poured into 25 ml of ice–water and ten drops of acetic acid was added. The mixture was extracted with four 25-ml portions of dichloromethane; the combined extracts were washed with two 25-ml portions of water, dried over magnesium sulfate, and concentrated to a gum. Ether was added several times, and the solvent was removed *in vacuo* after each addition. Ether and heptane were added, and the solvent was evaporated to give 0.5 g of off-white crystals. Tlc on silica gel [solvent: cyclohexane–ethyl acetate (7:3)] showed the presence of three components: *ca.* 25% 4-androstene-3,17-dione, *ca.* 70% testosterone, and *ca.* 5% of a fast moving component [probably 17β-(methylthiomethoxy)-4-androsten-3-one]: the infrared spectrum showed a ketone band at 1747 cm^{-1}. No testosterone O-acetate was present as determined by tlc comparison with an authentic sample.

17β-(Methylthiomethoxy)-4-androsten-3-one (20). To a mixture of 11.5 g (0.040 mole) of testosterone, 35 ml of dimethyl sulfoxide, and 40 ml of acetic anhydride was added 40 ml of glacial acetic acid. The mixture was chilled briefly and then allowed to stand at room temperature for 6 days. The solution was poured onto 500 g of ice and, after standing for 2 hr, was made basic with concentrated ammonium hydroxide. A gummy solid separated, and the liquid was decanted. The gummy solid was triturated with methanol and filtered to give 9.2 g of colorless crystals. Recrystallization from hot methanol gave 6.9 g (49%) of **20** as colorless crystals, mp 126–127°. Recrystallization from methanol afforded 5.35 g (38%) of colorless crystals, mp 127–128°; lit.[13] mp 128–129°.

Oxidation of Hydrocortisone 21-Acetate (21) to Cortisone 21-Acetate (22). A mixture of 0.404 g (0.0010 mole) of **21**, 3 ml of dry dimethyl sulfoxide, and 2 ml of acetic anhydride was allowed to stand at room temperature for 56 hr. The mixture was poured into a mixture of 50 g of ice and 10 ml of water, and the resulting gummy precipitate was triturated while the pH of the mixture was adjusted to 7 by addition of concentrated ammonium hydroxide. Filtration gave 0.400 g of white crystals. Recrystallization from acetone gave 0.15 g (37%) of **22**, mp 237–239°; $[\alpha]^{25}D$ +236° (*c* 0.63, $CHCl_3$); lit.[14] mp 239–241°.

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.6; H, 7.51. Found: C, 69.0; H, 7.45.

In a similar run with 0.606 g (0.0015 mole) of **21** carried out for 92 hr, 0.57 g (94%) of product was obtained. Recrystallization from acetone–petroleum ether (bp 30–60°) afforded 0.31 g (53%) of **22** as colorless crystals, mp 236–239°.

Oxidation of 11α-Hydroxyprogesterone (23) to 11-Ketoprogesterone (24). A mixture of 0.330 g of **23**, 3 ml of dry dimethyl sulfoxide, and 2 ml of acetic anhydride was allowed to stand at room temperature for 25 hr. The solution was poured onto a mixture of 20 g of ice and 10 ml of water, made basic with concentrated ammonium hydroxide, and diluted with 25 ml of water. The mixture was extracted with chloroform, and the extracts were dried over magnesium sulfate and concentrated to give 300 mg of a gum. This material was chromatographed on a column of 440 g of Celite diatomaceous earth (stationary phase: methanol saturated with heptane) with a hold-back volume (HBV) of 600 ml, using heptane saturated with methanol as solvent. The fraction collected from 6.0–7.6 HBV was concentrated under reduced pressure to yield 0.100 g (30%) of **24** as a colorless glass. Crystallization from acetone–petroleum ether (bp 30–60°) gave 0.044 g (13%) of **24** as colorless crystals, mp 171–172°; lit.[15] mp 172–175°; ν_{max}^{KBr} 1709 (s), 1667 (s), and 1613 cm^{-1} (m).

The fraction collected at 2.77–4.1 HBV was concentrated to give 0.220 g (56%) of methylthiomethoxy derivative **25** as a pale yellow gum which could not be induced to crystallize; pmr ($CDCl_3$) singlets at δ 0.72 (CH_3), 1.35 (CH_3), 2.15 and 2.23 ($COCH_3$, SCH_3), 4.72

(OCH_2S), 5.77 (>C=C(CO)H); ν_{max}^{KBr} 1709 (s), 1667 (s), 1613 (m), and 1042 cm^{-1} (s).

Oxidation of *p*-Nitrobenzyl Alcohol to *p*-Nitrobenzaldehyde. A mixture of 1.53 g of *p*-nitrobenzyl alcohol, 30 ml of dry dimethyl sulfoxide, and 10 ml of acetic anhydride was allowed to stand at room temperature for 20 hr. The solution was poured onto 75 g of ice and allowed to stand for 1 hr. The chilled mixture was made basic with cold 10 *N* sodium hydroxide and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and concentrated. The residue was triturated with ether and filtered, and the precipitate was recrystallized from ether to give 0.47 g (31%) of *p*-nitrobenzaldehyde as pale yellow crystals, mp 102–103° (infrared spectrum identical with an authentic sample).

The mother liquors were combined and concentrated to give 0.95 g of crystals which were recrystallized from ether to yield 0.55 g of crystals. The pmr spectrum ($CDCl_3$) showed the latter crystals were a mixture composed of two-thirds *p*-nitrobenzaldehyde and one-third *p*-nitrobenzyl alcohol O-acetate: singlets at δ 2.13 ($C(=O)CH_3$), 5.20 (CH_2O), and 10.1 (CHO) with intensities of 1.5:1:1.

Oxidation of Ethanol-^{18}O with DMSO, Phosphoric Acid, and DCC. To a mixture of 4.09 g (0.020 mole) of DCC and 5 ml of dry DMSO under nitrogen was added 0.300 g of crystalline phosphoric acid. The mixture became warm and was cooled. After standing for 15 min, 0.39 ml (0.0067 mole) of ethanol (containing 1.9% ^{18}O) was added. The temperature was kept below 20° by cooling and, after stirring for 1.33 hr, 10 ml of dry dichloromethane was added, and the mixture was filtered. The solid was washed with 200 ml of dichloromethane, two 20-ml portions of dry acetone, and finally with ethanol and water to give, after drying, 1.83 g of N,N'-dicyclohexylurea, mp 228–229°. Analysis by mass spectral measurements for ^{18}O content showed a maximum of 0.3% ^{18}O. In a similar run the solid which precipitated during the reaction was removed by filtration and washed with dichloromethane and ethanol. The solid was extracted with 250 ml of hot acetone, and the acetone extract was chilled and filtered to give 0.30 g of N,N'-dicyclohexylurea, mp 231–232°. Mass spectral analysis showed a maximum of 0.26% ^{18}O.

Benzyhydrol-^{18}O. A mixture of 4.04 g (0.020 mole) of benzhydryl chloride, 25 ml of dry acetone, and 5.0 ml of water labeled with 10% ^{18}O was allowed to stand at room temperature for 7 days. The solution was concentrated and filtered to give 3.3 g of colorless crystals. These crystals were washed with 10 ml of ethanol, and the ethanol wash was diluted with water. The resulting crystals were removed by filtration. The filtrate was concentrated, chilled, and filtered to give colorless crystals which were recrystallized from petroleum ether (bp 60–90°) to yield 0.53 g of benzhydrol as white needles, mp 64–65°. Mass spectral analysis showed the benzhydrol to contain 4.8% ^{18}O.

Oxidation of Benzhydrol-^{18}O with DMSO, Phosphoric Acid, and DCC. A mixture of 0.184 g (0.001 mole) of benzhydrol-^{18}O (4.8% ^{18}O), 0.613 g (0.003 mole) of DCC, 0.050 g of phosphoric acid, and 1 ml of DMSO was allowed to stand at room temperature for 16 hr. The mixture was diluted with 8 ml of dry ether and filtered to remove solid A. To the filtrate was added 5 ml of water and several drops of acetic acid. After standing 6 hr, the mixture was filtered, and the solid was washed with ether. The ether was separated from the aqueous layer of the filtrate, and the aqueous layer was extracted with ether. The combined ether extracts were dried over magnesium sulfate and concentrated. The residue was extracted with petroleum ether (bp 60–90°) and the petroleum ether extract was concentrated to a gum. Mass spectral analysis of the crude benzophenone showed the presence of 2.0% ^{18}O (42% of the original label).

Solid A was washed with ether and with water to yield 0.39 g of white crystals. Recrystallization from acetone gave 0.31 g (0.00138 mole) of N,N'-dicyclohexylurea, mp 227°; no ^{18}O above natural abundance was found by mass spectral analysis.

1,3-Dicyclohexyl-2-*p*-nitrobenzylpseudourea (40). To a solution of 7.66 g (0.050 mole) of *p*-nitrobenzyl alcohol and 10.2 g (0.050 mole) of DCC in 150 ml of acetone was added 10 mg of anhydrous cupric chloride. The mixture was stirred at room temperature for 70 hr, and the solvent was then removed. The oil was dissolved in 30 ml of petroleum ether (bp 30–60°) and 30 ml of acetone and 1.0 g of *p*-nitrobenzyl alcohol and 10 mg of cupric chloride were added. After 70 hr the solvent was removed and a solution of the residual oil in ether was filtered through neutral alumina (Woelm, activity I). The first 250 ml of filtrate was concentrated to a pale yellow oil which crystallized on chilling [12.2 g (66%), mp 48–52°]. A portion (8.6 g) was recrystallized from petroleum ether (bp 30–60°) to give 7.1 g (38%) of **40** as nearly colorless crystals, mp 55–57°.

Anal. Calcd for $C_{20}H_{29}N_3O_3$: C, 66.8; H, 8.13; N, 11.7. Found: C, 66.3; H, 8.32; N, 11.9.

Reaction of 1,3-Dicyclohexyl-2-*p*-nitrobenzylpseudourea (40) with DMSO and Phosphoric Acid. A mixture of 3.61 g (0.010 mole) of **40**, 0.40 g of crystalline phosphoric acid, and 12 ml of dry dimethyl sulfoxide was stirred at room temperature for 18 hr. The mixture was poured onto 50 g of ice and allowed to stand. The mixture was made basic with 10 *N* sodium hydroxide and extracted with ether. The ether extracts were concentrated, and the residue was diluted with water and extracted with petroleum ether (bp 30–60°). Concentration of the extract gave a pale yellow oil which crystallized. Chilling and filtering gave 2.2 g (61%) of starting material, mp 48–50°.

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