TABLE III
FLUORIDE DETERMINATION

Sample	Reaction time, min	Total fluoride, 10^{-6} mol	% reaction
1	16.0	3.42	(12.8)
2	30.0	3.53	13.2
3	45.0	4.21	15.8
4	60.2	5.47	20.5
5	75.0	10.8	40.5

3-Iodo-5,5,6,6,7,7,7-heptafluoroheptanenitrile (7).—**11** (30.0 g, 0.10 mol), **16** (3.35 g, 0.05 mol), and **15** (0.25 g, 0.0015 mol) were charged to a Fischer-Porter Aerosol tube, filled with nitrogen, evacuated three times at −78°, and sealed. The tube was heated for 15 hr at 72°. The product was fractionated in a 2-ft platinum spinning-band column. **11** (19.7 g, 0.066 mol) and **16** (1.67 g, 0.025 mol) were recovered, and **7**, bp 60° (0.60 mm), $n^{25}D$ 1.4148, 8.55 g (48% conversion, 98% yield), solidified on cooling to 10°: ir (10% CCl_4) ν CH 2980 and 2950, ν C≡N 2260, δ CH 1450, 1435, 1400, 1380, 1355, and 1340, ν CF 1280–1180, and bands at 1125, 1070, 1010, 990, 965, 950, 900, 845, and 830 cm^{-1}; nmr δ 3.00 (6-line multiplet, 2, J_{HF} = 20, J_{HH} = 7 Hz, CF_2CH_2CH), 3.30 (d, 2, J = 7 Hz, $CHCH_2CN$), 4.50 (5-line multiplet, 1, J = 7 Hz, CH_2CHICH_2).

Anal. Calcd for $C_7F_7H_5NI$: C, 23.15; H, 1.39; I, 34.95. Found: C, 23.34; H, 1.47; I, 35.21.

Hydrolysis of 3-Iodo-5,5,6,6,7,7,7-heptafluoroheptanenitrile (7).—**7** (4.20 g, 0.012 mol) was added to a solution of KOH (0.822 g, 0.0146 mol) in 10.0 ml of 90% aqueous ethanol and kept at 65–70° for 7 hr. Solid separated from the orange, acidic solution in the stoppered flask. Water (10 ml) was added and benzene (three 10-ml portions) and ether (10 ml) was used to extract the organic products. The red color was removed by shaking with a dilute aqueous sodium sulfite solution. Distillation in column A gave product fractions: no. 1, bp 77° (32 mm), $n^{25}D$ 1.3577, 0.80 g; no. 2, bp 82–87° (32 mm), $n^{25}D$ 1.3684, 0.60 g; no. 3, hold-up pumped over, $n^{25}D$ 1.4160, 0.95 g (total 95% recovery). Infrared spectra (KBr plates) showed that no. 1 contained principally 5,6,6,7,7,7-hexafluoro-*trans,trans*-2,4-heptadienenitrile (**17**): ν CH 3090, ν C≡N 2230 (conj), ν C=C 1680 and 1630, δ CH 1455, 1428, 1355, and 1340, and bands at 990, 980, 960, 950, 920, 880, 828, 810, 770, 750, 735, and 725 cm^{-1}. No. 2 contained both **17** and 5,5,6,6,7,7,8,8,8-heptafluoro-*trans*-2-heptenenitrile (**18**): ν CH 3080, 3010, and 2960, ν C≡N 2245 (m, unconj) and 2230 (w), ν C=C 1680 (w) and 1648 (ms), and bands at 982, 970, 960 (s), 920, 890 (w), 810, 800, 765, 760, 755, 730, 655, 635, 545, and 530 cm^{-1}. No. 3 showed only conjugated C=CCN, ν C≡N 2230 (m), ν C=C 1648 (m), and bands at 965 (m), 760 (w), 740 (m), and 730 cm^{-1}. Glpc analysis was done using a 10 ft × 0.25 in. Apiezon M column (20% on Chromosorb W), operated at 160° with 15-psi helium carrier gas. Cut no. 1 eluted 70.3% of **17** at 4.2 min, 6.1% at 5.0 min, and 22.0% of **18** at 5.5 min. Cut no. 2 eluted 28.0% of **17** at 4.2 min, 50.4% of **18** at 5.5 min, and 16.2% of **7** at 17.0 min. Cut no. 3 eluted 2.68% of **17** at 4.2 min, 19.1% of **18** at 5.5 min, and 5 peaks from 17 to 46.8 min. Taken together these results indicate that cut no. 1 was mostly **17** and **18**; cut no. 2 contained some **17**, mostly **18**, and some **7**; and cut no. 3 was a mixture of a little **17**, some **18**, **7**, and several unidentified higher boiling substances.

Registry No.—**1** (m = 2; R_F = $CF_3(CF_2)_2$), 29370-66-9; **4** (R_F = $CF_3(CF_2)_2$), 2093-44-9; **4** (R_F = $CF_3(CF_2)_3$), 29260-81-9; **5** (R_F = $CF_3(CF_2)_2$), 29260-82-0; **7** (R_F = $CF_3(CF_2)_2$), 2357-48-4; **8** (R_F' = CF_3CF_2), 29260-84-2; **8** (R_F' = $CF_3(CF_2)_2$), 29260-85-3; **8** (R_F = CF_3CF_2) ethyl ester, 29260-86-4; **9**, 29260-87-5; *cis*-**9**, 29260-88-6; **10**, 29260-89-7; *cis,trans*-**10**, 29370-67-0; **17** (R_F = CF_3CF_2), 29370-68-1; **18** (R_F = $CF_3(CF_2)_2$), 29260-90-0; *cis*-6,6,7,7,8,8,8-heptafluorooct-4-enoic acid, 29260-91-1; *trans*-6,6,7,7,8,8,8-heptafluorooct-4-enoic acid, 29260-92-2.

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Sulfoxide–Carbodiimide Reactions. X.[1] Further Studies on the Mechanism of the Oxidation Reaction

J. G. MOFFATT

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Several new pieces of evidence concerning the course of the DMSO–DCC oxidation reaction have been considered and have led to some modification of the previously proposed mechanism. By nmr studies it has been shown that, in the absence of an alcohol, the initial DMSO–DCC adduct **1** is formed in very low equilibrium concentrations. During oxidation of an alcohol using DMSO-d_6 the resulting dicyclohexylurea is found to contain one atom of deuterium. This had led to the conclusion that the abstraction of the $-SCH_3$ proton leading to the oxysulfonium ylide **3** occurs *via* an intramolecular mechanism involving either an ionic or a tetracovalent sulfur intermediate.

Previous work from this laboratory has demonstrated that efficient oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones can be achieved under mild conditions through reaction with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of an appropriate proton source.[2,3] These same reagents also effect interesting, mechanistically related reactions with phenols,[4] enols,[5] oximes,[6] and a variety of other nucleophilic nitrogenous functional groups.[7]

The mechanism originally proposed[2a] for the oxidation of alcohols is outlined in Scheme I below and both the initial formation of the DMSO–DCC adduct **1** and the intramolecular nature of the proton abstraction step *via* the oxysulfonium ylide **3** have been confirmed by isotope experiments.[8]

(1) For part IX, see U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).

(2) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965); (b) *ibid.*, **87**, 5670 (1965).

(3) For a review, see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, Marcel Dekker, New York, N. Y., in press.

(4) (a) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); (b) *ibid.*, **89**, 4725 (1967).

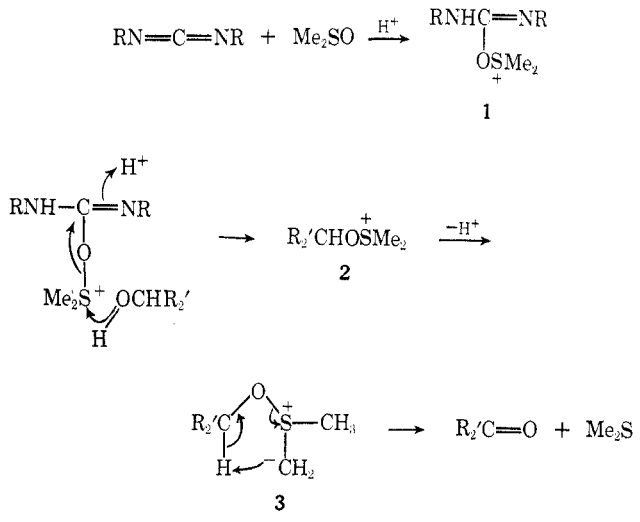
(5) A. F. Cook and J. G. Moffatt, *ibid.*, **90**, 740 (1968).

(6) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(7) U. Lerch and J. G. Moffatt, unpublished results.

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

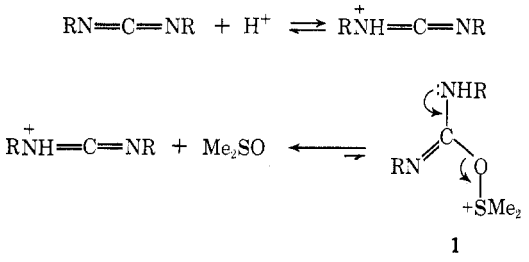
SCHEME I



While formation of the adduct **1** was unequivocally demonstrated[8] by the isolation of ^{18}O-dicyclohexylurea from an oxidation reaction using ^{18}O-DMSO, we have been unable to demonstrate the accumulation of this intermediate by nmr spectroscopy. Thus, the nmr spectrum of a solution of diisopropylcarbodiimide[9] (0.3 mmol) and DMSO (0.6 mmol) in deuteriochloroform shows only the expected signals of the individual compounds, the isopropyl groups appearing as a 6-proton doublet (J = 6 Hz) at 1.20 ppm and a 1-proton quintet (J = 6 Hz) at 3.55 ppm and the DMSO as a singlet at 2.62 ppm. Upon addition of 0.06 mmol of dichloroacetic acid there were essentially no changes in the spectrum scanned at intervals during 10 min except for the formation of small amounts of diisopropylurea (1.10 ppm, d, J = 6 Hz) and *N*-dichloroacetyl-*N*,*N*′-diisopropropylurea (1.47 ppm, d, J = 6 Hz). There was no observable change in the $-SCH_3$ resonance of the DMSO and no signal was observed in the 3.3-ppm region where oxysulfonium salts are known to appear.[10] Subsequent addition of *p*-nitrobenzyl alcohol (0.1 mmol) led to rapid oxidation to *p*-nitrobenzaldehyde, once again with no observable oxysulfonium intermediate in the 3.3-ppm range.

The lack of any observable accumulation of an oxysulfonium intermediate such as **1** upon mixing DMSO, DCC, and dichloroacetic acid in the absence of an alcohol suggests that this is a reversible process with the equilibrium lying far on the side of starting materials as in Scheme II. Such an equilibrium might well

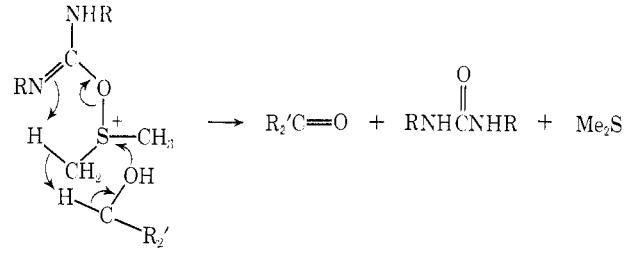
SCHEME II



be expected since the inductive effect of the positively charged sulfur in **1** would act as a driving force leading toward regeneration of DMSO and protonated carbodiimide. Since subsequent addition of an alcohol leads rapidly to oxidation without accumulation of any oxysulfonium intermediates, the formation and collapse of species such as **2** and **3** must be rapid.

In the course of his studies on the chemistry of oxysulfonium salts, Torssell[10,11] has considered the role of these compounds as intermediates in the oxidation reaction. In these studies pure samples of independently prepared isobutyloxysulfonium tetraphenylborate were reacted with DMSO, DCC, and pyridinium trifluoroacetate under conditions similar to those used successfully for oxidation of the free alcohol to the aldehyde. Examination of the reaction mixture by gas–liquid chromatography showed the presence of isobutyraldehyde and isobutyl alcohol in a ratio of 1:2 but the aldehyde could be isolated as its dinitrophenylhydrazone in only 10% yield. Attempts to isolate an oxysulfonium salt from the reaction mixture during oxidation of the alcohol were unsuccessful and, on the basis of these observations, Torssell has concluded that free oxysulfonium salts cannot be intermediates in the oxidation pathway. In order to accommodate this conclusion, Torssell has proposed a "three-body mechanism" as shown in Scheme III in which attack

SCHEME III



of the alcohol upon the DMSO–DCC adduct is accompanied by abstraction of a proton from the $S-CH_3$ group by the incipient dicyclohexylurea nitrogen and leads directly to products without intervention of the oxysulfonium salt **2**.

As proposed by Torssell[10,11] this mechanism, which involves nucleophilic attack, two proton abstractions, and collapse to products, is considered to be a concerted process and this has been criticized by Capon *et al.*,[12] on electronic grounds. There is also some doubt that the experiment using pre-formed alkoxysulfonium tetraphenylborates as described by Torssell is an entirely valid one. Our earlier work has clearly shown that the oxidation reaction is extremely sensitive to the nature of the proton source used, with neither very strong (*e.g.*, trifluoroacetic or mineral acids) or very weak (*e.g.*, acetic acid) acids being suitable. The pyridine salts of some acids give excellent results but in other cases the reactions are slow and incomplete. Since tetraphenylboric acid, while unknown as a free compound, is considered to be a strong acid,[13] it is not at all certain that the reduced yield of isobutyral-

(9) This compound is generally as good as DCC in oxidation reactions but offers the advantages of a much sharper nmr signal and a more soluble urea product.

(10) K. Torssell, *Acta Chem. Scand.*, **21**, 1 (1967).

(11) K. Torssell, *Tetrahedron Lett.*, 4445 (1966).

(12) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms 1967," Interscience, New York, N. Y., 1968, p 426.

(13) J. N. Cooper and R. E. Powell, *J. Amer. Chem. Soc.*, **85**, 1590 (1963).

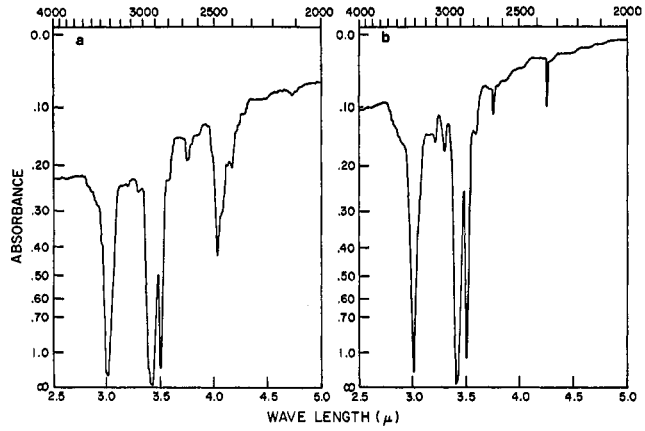


Figure 1.—Infrared spectra of dicyclohexylurea as KBr pellets: (a) dicyclohexylurea obtained following oxidation of testosterone in DMSO-d_6 (see Experimental Section); (b) unlabeled dicyclohexylurea.

dehyde is sufficiently meaningful to draw mechanistic conclusions.

The intramolecular proton abstraction from the S–CH_3 group is, however, an attractive feature of the Torssell mechanism that is amenable to experimental verification. This question appeared to be answered when Harmon and Zenarosa[14] briefly reported that an oxidation reaction using DMSO-d_6 led to the isolation of monodeuteriodicyclohexylurea thus supporting an intramolecular proton abstraction similar to that of Scheme III. Subsequently, however, these same authors, without reference to their earlier work, have reported that a similar experiment gives dicyclohexylurea which contains no deuterium.[15] The absence of deuterium appears to be based solely upon the infrared spectrum of the product and no experimental details are given as to how the reaction was worked up in order to avoid deuterium–proton exchange of the reactive N–D bond. On the basis of this latter result, Harmon, *et al.*,[15] have ruled out the Torssell mechanism (Scheme III) and favored our original proposal (Scheme I).

Prior to the appearance of the second paper from Harmon,[15] we too have examined the oxidation of an alcohol in DMSO-d_6 taking pains to exclude as much as possible the probability of exchange reactions. Thus, we have oxidized testosterone in a mixture of DMSO-d_6 and benzene using DCC and a small amount (0.24 molar equiv) of dichloroacetic acid. After 10 min the mixture was diluted with benzene and the resulting crystalline dicyclohexylurea was removed by filtration and washed carefully with dry benzene. The yield of dicyclohexylurea was, as is usually the case, somewhat in excess of theory, and thin layer chromatography of the filtrate showed that quantitative oxidation of testosterone to androst-4-ene-3,17-dione had taken place. The infrared spectrum of the dicyclohexylurea (Figure 1a) showed a fairly intense peak at 2475 cm^{-1} characteristic of an N–D stretching frequency[16] that is not present in unlabeled dicyclohexylurea (Figure 1b).

(14) R. E. Harmon and C. V. Zenarosa, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, No. D3.

(15) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Tetrahedron Lett.*, 3781 (1969).

(16) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 207.

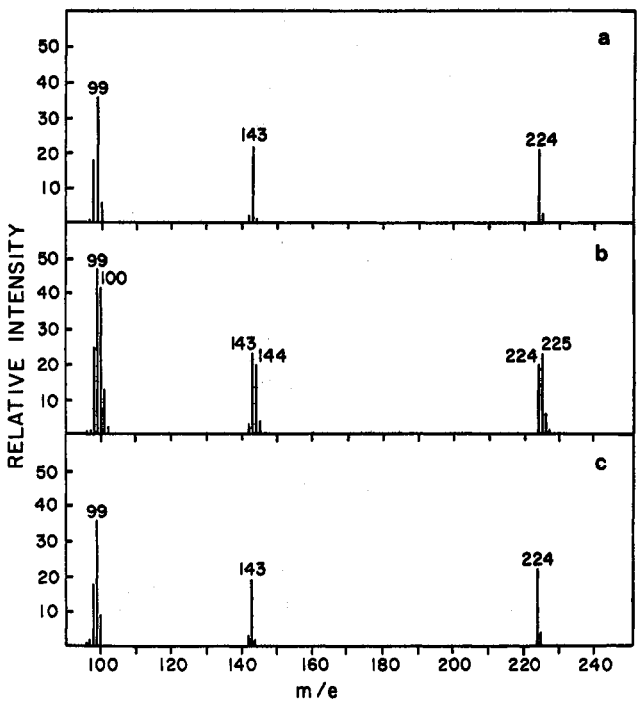


Figure 2.—Mass spectra (70 eV) of dicyclohexylurea: (a) unlabeled dicyclohexylurea; (b) dicyclohexylurea obtained following oxidation of testosterone in DMSO-d_6 (see Experimental Section); (c) dicyclohexylurea obtained from a control reaction with out an added alcohol (see Experimental Section).

More compelling evidence for the incorporation of deuterium was obtained by mass spectrometry. The mass spectrum (70 eV) of unlabeled dicyclohexylurea (Figure 2a) shows a molecular ion at *m/e* 224 with a small natural abundance isotope peak (roughly 14% as intense) at *m/e* 225. The spectrum, under identical conditions, of the dicyclohexylurea isolated from the oxidation reaction is shown in Figure 2b which clearly indicates that the predominant molecular ion is now at *m/e* 225 indicating the incorporation of a single deuterium atom. The presence of a very small peak at *m/e* 227 suggests that even a trace of a dideuterio species might be present and, after correction for natural isotope abundance, the mondeuterio and nondeuterated species were estimated to be present in a ratio of 1.1:1. The incorporation of a single deuterium atom can also be seen in the fragments at *m/e* 144 ($M^+ - C_6H_9$) and *m/e* 100 $[C_6H_{11}NDH]\cdot^+$.

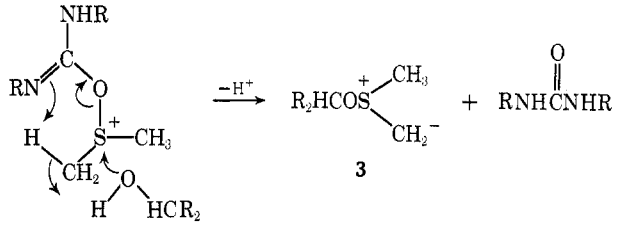
As a control for any possible exchange reactions that could lead to deuterium incorporation independent of the oxidation reaction, a similar reaction was set up without addition of any testosterone. Under these conditions only a small amount of dicyclohexylurea crystallized from the reaction mixture and after 40 min it was collected and washed with benzene as above. The mass spectrum of this material (Figure 2c) was essentially identical with that of the nondeuterated reference sample (Figure 2a) and suggested the presence of only a trace of deuterium. The fact that only about one-half of the isolated dicyclohexylurea contained deuterium suggests that decomposition of DCC to the urea can also take place through simple acid-catalyzed reactions quite independent of oxidation. This is confirmed by the isolation of the unlabeled urea in the absence of an alcohol and leads to the con-

clusion that the oxidation reaction is probably accompanied by a stoichiometric transfer of deuterium.

The experiments above quite conclusively show that the abstraction of a $(CH_3)_2S^+OR$ proton leading to the oxysulfonium ylide **3** is indeed facilitated by the nitrogen of the incipient dicyclohexylurea as suggested by Torssell and are in contrast with the conclusions of Harmon, *et al.*[15]

These observations can be accommodated into the overall mechanism of the oxidation reaction in two ways that both lead directly to the oxysulfonium ylide **3** that we have previously shown to be the direct precursor of the carbonyl compound.[8] The first of these (Scheme IV) is a concerted, ionic process that

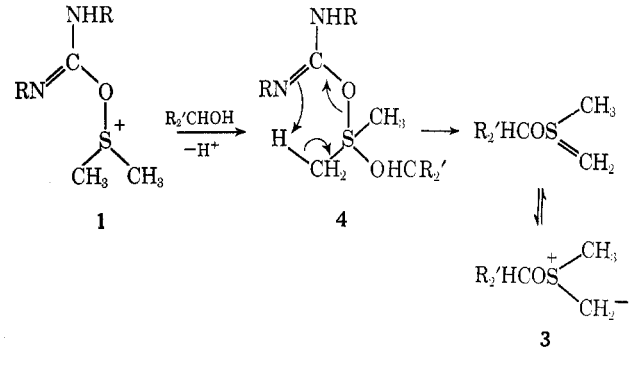
SCHEME IV



is closely related to a portion of the more complex Torssell mechanism (Scheme III).

The second involves addition of the alcohol to the DMSO–DCC adduct **1** with formation of a tetracovalent sulfur intermediate **4** which can then collapse *via* a cyclic process to the oxysulfonium ylide **3** and dicyclohexylurea (Scheme V). A similar tetracovalent

SCHEME V



intermediate was also considered in our earlier work on the reactions of phenols with DMSO and DCC.[4b]

The latter process has the particular advantage that formation of the neutral intermediate **4** removes the positive charge on sulfur that acted as a driving force in the maintenance of very low equilibrium concentrations of the adduct **1** (Scheme II). Loss of this driving force then allows a complete reversal of the electron flow leading, once again, directly to the ylide **3**.

The mechanism which now appears to best represent the overall oxidation reaction is thus a combination of Scheme II with either Scheme IV or V giving the oxysulfonium ylide **3** which can then collapse *via* a cyclic mechanism to the carbonyl compound and dimethyl sulfide as in Scheme I. This does not represent any major deviation from the pathway originally proposed[2a,8] and only differs basically in the manner in which the oxysulfonium proton is abstracted. It is, however, undoubtedly a more correct representation of this useful reaction sequence and will be used in the future in explaining the reactions of DMSO and DCC with other nucleophilic functional groups.

Experimental Section

General Methods.—Thin layer chromatography was conducted using 0.25-mm layers of Merck silica gel GF and products were detected by either their ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate followed by brief heating at 150°. Nuclear magnetic resonance (nmr) spectra were obtained using a Varian A-60 spectrometer and are recorded in parts per million downfield of an internal standard of tetramethylsilane. Mass spectra were obtained at an ionizing voltage of 70 eV using an Atlas CH-4 instrument fitted with a direct inlet system. Infrared spectra were obtained using potassium bromide pellets and a Perkin-Elmer 237 instrument.

Nuclear Magnetic Resonance Studies.—A solution of diisopropylcarbodiimide (0.046 ml, 0.3 mmol) and DMSO-d_6 (0.042 ml, 0.6 mmol) in $CDCl_3$ (0.45 ml) containing 1% tetramethylsilane was placed in a conventional nmr cell and the spectrum was recorded (see text). Dichloroacetic acid (5 μl, 0.06 mmol) was then added and the spectrum was recorded after 1.5 and 10 min. There was no significant change in the spectra except for the appearance of small doublets at 1.10 and 1.47 ppm corresponding to the isopropyl resonances of diisopropylurea and of *N*-dichloroacetyl-*N*,*N*′-diisopropylurea, respectively. Subsequent addition of *p*-nitrobenzyl alcohol (15 mg, 0.1 mmol) led to the rapid formation of *p*-nitrobenzaldehyde that could be detected by tlc using chloroform. Once again, there was no detectable change in the $-SCH_3$ resonances during this phase of the reaction.

***N*-Dichloroacetyl-*N*,*N*′-diisopropylurea.**—Dichloroacetic acid (1.29 g, 10 mmol) and diisopropylcarbodiimide (1.26 g, 10 mmol) were dissolved in dry pyridine (10 ml) and kept overnight at 23°. The brown solution was evaporated to dryness and the residue coevaporated several times with ethanol. The residue was crystallized from ether giving 1.50 g of beige needles that were recrystallized from ether after decolorization with charcoal giving 1.20 g (47%) of colorless needles. An analytical sample had mp 115–116° from isopropyl alcohol: λ_{max}^{MeOH} 208 mμ (ϵ 5800); nmr ($CDCl_3$) 1.25 and 1.42 (d, 1, J = 6 Hz, $CH(CH_3)_2$), 3.97 and 4.51 (quint, 1, J = 6 Hz, $CH(CH_3)_2$), 6.45 ppm (s, 1, $CHCl_2$).

Anal. Calcd for $C_9H_{16}N_2O_2Cl_2$: C, 42.35; H, 6.32; N, 10.97. Found: C, 42.37; H, 6.36; N, 11.07.

Oxidation of Testosterone in DMSO-d_6. A.—Dichloroacetic acid (2 μl, 0.024 mmol) was added to a solution of testosterone (30 mg, 0.1 mmol) and DCC (62 mg, 0.3 mmol) in anhydrous (molecular sieve) DMSO-d_6 (0.1 ml) and benzene (0.2 ml). After 10 min at room temperature the mixture was diluted with anhydrous benzene (0.5 ml) and the crystalline dicyclohexylurea was removed by filtration, washed thoroughly with anhydrous benzene, and dried *in vacuo*. The yield was 30 mg while the theoretical yield for 1 equiv was 22 mg. The infrared spectrum is shown as Figure 1a and the mass spectrum as Figure 2b.

Examination of the filtrate by tlc using chloroform–ethyl acetate (4:1) showed that complete oxidation of the testosterone to androst-4-ene-3,17-dione had occurred. Some further dicyclohexylurea could also be shown to be present in the filtrate.

B. Control Reaction without Alcohol.—A reaction was set up exactly as above except that testosterone was omitted. Separation of dicyclohexylurea was, in this case, slow and incomplete but after 40 min the reaction was diluted with benzene and treated exactly as in A. The yield of dicyclohexylurea was only 5 mg and the mass spectrum of this material is shown as Figure 2c.

Registry No.—**1**, 29474-72-2; *N*-dichloroacetyl-*N*,*N*′-diisopropylurea, 29474-73-3.

Acknowledgment.—Sincere thanks are due to Drs. M. L. Maddox and L. Tokes for their kind assistance with nmr and mass spectrometry, respectively.