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MECHANISMS OF DIMETHYLSULFOXIDE OXIDATIONS.

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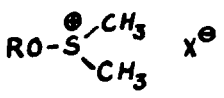
In connection with work on positive halogen compounds[1] new routes to alkoxydimethylsulfonium salts, I, were developed. Until recently few papers[2a-d] have been published on the chemistry of these compounds. Alkoxydimethylsulfonium ions have been postulated as intermediates in the Kornblum oxidation[3a-e] and recent work[4a-e] lends further support to this view. With the isolated intermediates at our disposal we set out to test the suggested mechanistic paths experimentally. The derivate II was chosen for the purpose and exposed to the various oxidation conditions given in the literature. The tetraphenylo- borates form nicely crystalline compounds, are easy to handle and are stable for months in the refrigerator.

The original Kornblum method[3a] recommends heating of a tosylate or a halogenide at 150° for some minutes whereas the novel mild procedures[3d,4c,d] are complete at room temperature within 24 hours or in some cases within a few hours.

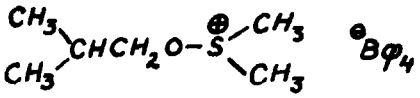
Pyrolysis of II at 140-150° for 8 minutes on a small preparative scale gave ca. 25 percent of iso-butyraldehyde (as crude DNP-derivative). The salt is stable for several days in dimethylsulfoxide at room temperature but the decomposition is complete in less than three minutes at 130°. The yield rises to about 50 percent as determined spectroscopically by infrared technique. The decomposition was also studied by NMR (DMSO,D_6) at 100°. The characteristic peak of the aldehyde proton at δ=9.66 ppm develops rapidly and the integrated curve indicates a yield of ca. 60 percent after 15 min. The sulfonium salt had then completely vanished. An equivalent amount of dimethyl sulfide is formed, which is shown by the appearance of a sharp peak at δ = 2.10 ppm. After 2 h

at 65° only ca. 20 percent of the salt had decomposed. The liberation of dimethylsulfoxide (ca. 25 percent of the intensity of the dimethyl sulfide peak) is due to the formation of olefin (traces) and some hydrolysis but mostly to carbonium ion exchange with the solvent, a reaction comparable with the proton exchange in water. The reaction is completely reversible[1].

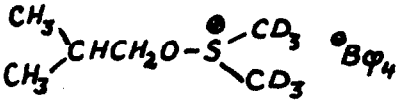
Barton et al. modified the oxidation by treatment of the intermediary sulfonium ion with base. Under these conditions the oxidation is complete within 15 min.[3d] This is verified by our NMR studies,



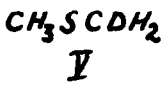
I



II



III



V

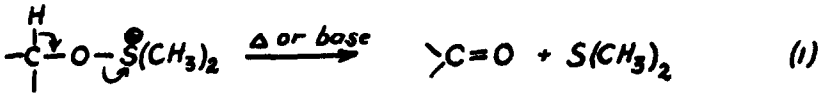
IV

VI

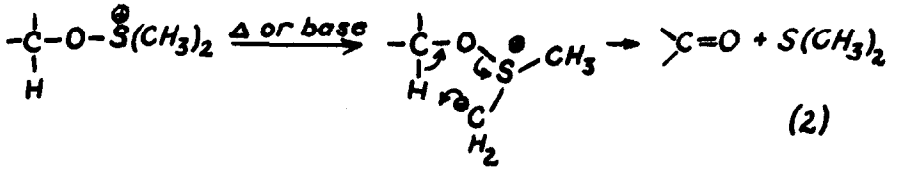
in fact the oxidation of II was almost instantaneous upon addition of triethyl amine. The spectroscopically measured yield was ca. 60 percent.

We are now able to present full evidence that Barton's modification proceeds via a sulfonium ion by precipitation of this intermediate as its tetraphenyloborate in a good yield. Thus, the experiments prove unequivocally that the Kornblum oxidation and Barton's modification proceeds via an intermediary sulfonium ion, which collapses to a carbonyl compound and dimethylsulfide

either by the concerted (or stepwise) reaction (1) or by a cyclic mechanism[4e] (2).



(1)



(2)

In order to reach a decision between these possibilities the deuterated compound III was prepared. Provided that only a negligeable hydrogen scrambling occurs in the sulfonium ion before decomposition, the mechanism (1) gives rise to unchanged dimethylsulfide whereas (2) affords a labelled dimethyl sulfide IV which can be detected by NMR. The absorption of the single proton of IV is split by the two deuterons to a quinted (1:2:3:2:1). Figure 1 shows the NMR spectrum of III. A small peak at δ = 3.3 ppm comes from water. Addition of two drops of triethylamine causes an immediate change of the spectrum, Figure 2. The aldehyde proton is visible at δ = 9.66 ppm and the quintet of IV is located at δ = 2.10 ppm, proving that one of the methylene protons of III must have been incorporated in dimethylsulfide via the cyclic mechanism (2). The actual part of the spectrum is

Figure 1. NMR spectrum of $(CH_3)_2CHCH_2OS(CD_3)_2\ ^{\oplus}BF_4^{\ominus}$

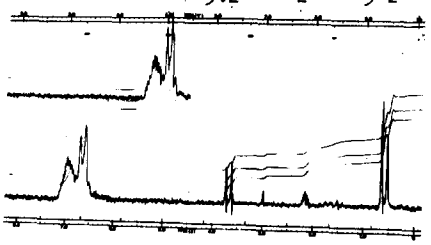
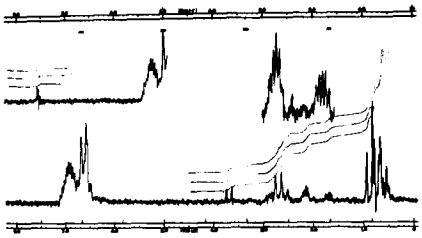


Figure 2. NMR spectrum of $(CH_3)_2CHCH_2O\overset{\oplus}{S}(CD_3)_2\ \overset{\ominus}{B}\varphi_4 + (C_2H_5)_3N$ in DMSO, D_6.



$$RO-\overset{\oplus}{S}\begin{matrix}CH_3\\CH_3\end{matrix} \rightleftharpoons RO-\overset{\oplus}{S}\begin{matrix}CH_3\\\ominus CH_2\end{matrix} + H^{\oplus} \qquad (3)$$

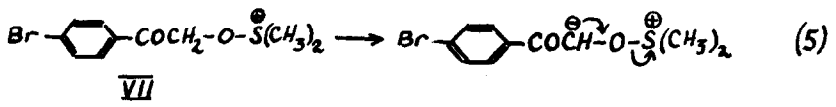
$$CH_3O-\overset{\oplus}{S}(CH_3)_2 + D_2O \rightleftharpoons CH_3OD + (CH_3)_2SO + D^{\oplus} \qquad (4)$$

enlarged in the upper part of Figure 2. The quintet at δ = 2.57 ppm, coincidentally of about the same intensity, comes from protonated dimethylsulfoxide, D_6 (solvent). The triplet at δ = 1.21 ppm and the quartet at δ = 3.11 ppm are due to triethylamine. IV is also formed on direct pyrolysis of III at 100° in DMSO, D_6.

A labelled dimethylsulfoxide can of course arise via (1) combined with a rapid hydrogen exchange (3). An early indication that this route is not the prevailing one was obtained from the observation that I (R = CH_3) with a ten molar excess of deuterium oxide on addition of triethylamine afforded no (or possibly traces of) deuterium labelled dimethylsulfoxide V, e.g. hydrolysis (4) proceeds faster than (3). Finally it was found that oxidation of II in the presence of a ten molar excess of deuterium labelled iso-butanol VI afforded no detectable amounts of V in the NMR spectrum. Alkoxyl exchange has no influence on reactions (1) - (3) in this system.

It should be pointed out in this connection that this investigation concerns the oxidation mechanism of inactivated alcohols. In their first paper on dimethylsulfoxide oxidations Kornblum et al.[5] describe the facile dicarbonyl formation from α-bromoketones, which proceeds at room temperature. The inter-

mediate sulfonium salt VII from phenacyl bromide contains enolizable protons and in this case it is conceivable that mechanism (1) = (5) is working. In fact, when we dissolved p-bromophenacyl bromide in DMSO, D_6 and heated the solution for two



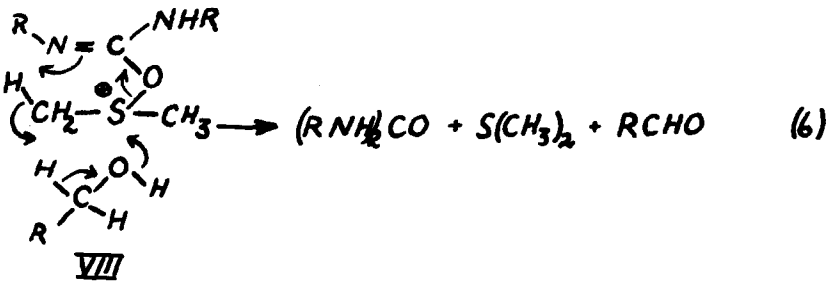
VII (5)

hours at 70° all of the starting material had disappeared. The glyoxal was formed but no labelled dimethyl sulfide V could be detected by the NMR spectrum proving that the cyclic mechanism is not working in this case. We can conclude, therefore, that the oxidation mechanism follows equation (2) but if the α-proton is activated as in VII mechanism (1) is working.

We then investigated the action of the novel mild oxidation media according to Pfitzner and Moffat[4d] and Albright and Goldman[4c] on the alkoxysulfonium salts. We found unexpectedly that the yield of the carbonyl compounds was very low. One mmole of II oxidized according to the first method afforded ca.10 percent of a crude DNP derivative, whereas the latter method only gave traces of carbonyl compounds. The experiments were repeated and the products analyzed by gas chromatography with the same result. Oxidation of isobutyl alcohol, trans-2-bromocyclohexanol and cyclohexanol according to the acetic anhydride method [4c] met with little success. Some carbonyl compounds was obtained but the main product was the acetate and the starting material. Addition of triethylamine to the reaction mixture increased the yield of the acetate. The authors point out that this method is particularly suited for the oxidation of sterically hindered hydroxyl groups. The gas chromatogram of the products from the acetic anhydride oxidation of II revealed the presence of iso-butanol but only small amounts of aldehyde and no iso-butyl acetate. This does not necessarily mean that alkoxysulfonium salts are not intermediates in the oxidation but rather

that these simple unhindered alcohols and salts are stable in the medium.

Oxidation of iso-butanol and trans-2-bromocyclohexanol by the dicyclocarbodiimide method[4d] proceeded in good yields (41 and 63 percent). The yield of iso-butyraldehyde from II in the same reaction was distinctly lower and considerable amounts of iso-butanol in the workup were detected by gas-chromatography. As a consequence we can not accept a free alkoxysulfonium ion as an intermediate here as suggested by Pfitzner and Moffat.[4d,e] This can be circumvented by the following threebody mechanistic scheme (6).



VIII

At the very moment the alcohol displaces the urea, a strong base is formed, which abstracts a proton from the S-methyl group as in VIII and thus creates the cyclic intermediate. This explains why the oxidation proceeds in a weak acid medium in which the sulfonium ion is stable, and also why the DCC method is sensitive to change of pH. We were not successful in trapping the ionic carbodiimide-DMSO intermediate of VIII with sodium tetraphenyloborate. In their last paper Fenselau and Moffat[4e] studied the mechanism by ^{18}O labelling and NMR techniques. They proved the cyclic mechanism (2) in general agreement with our results but with the reservation above for scheme (6).

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