Tetrahedron Letters No.43, pp. 3781-3784, 1969. Pergamon Press. Printed in Great Britain.

MECHANISM OF SULFOXIDE-KETENIMINE AND SULFOXIDE-CARBODIIMIDE OXIDATIONS

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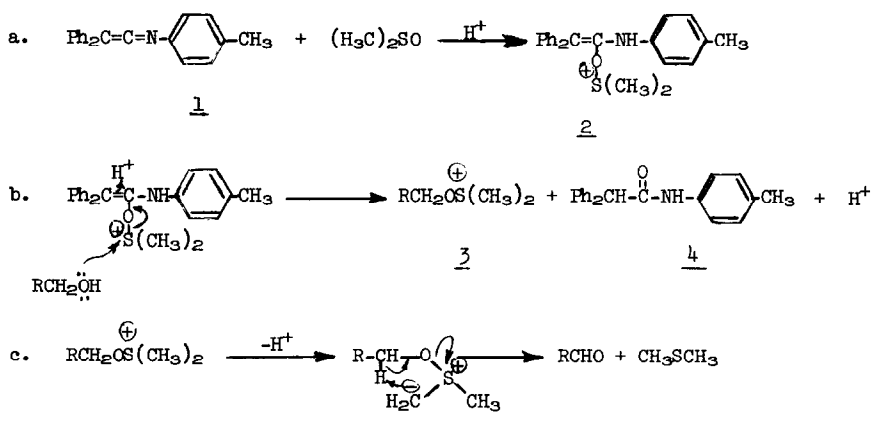
(Received in USA 16 June 1969; received in UK for publication 15 August 1969)

In a recent communication we have described the usefulness of sulfoxide-ketenimine in the oxidation of 2',3'-O-isopropylideneadenosine.[1] We have now extended this new procedure to the oxidation of hydroxy steroids. This is exemplified by the oxidation of testosterone to androst-4-ene-3,17-dione. With the help of hexadeuteriodimethylsulfoxide we have investigated the mechanism of sulfoxide-ketenimine and sulfoxide-carbodiimide oxidations.[2]

Our proposed mechanism for the sulfoxide-ketenimine oxidation is outlined in Scheme I.

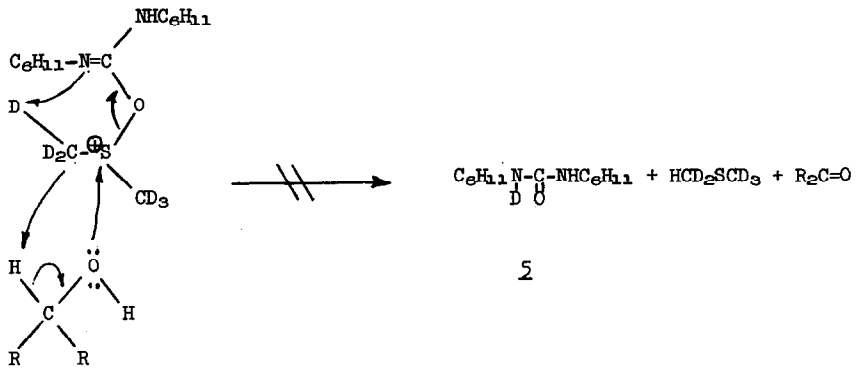
Scheme I.



The initial formation of the diphenylketene-N-p-tolylimine-DMSO adduct (2) was proposed by Lillien.[3] It is also similar to the dicyclohexylcarbodiimide (DCC)-DMSO adduct proposed by Moffatt et al.[2] Apparently, the second step in the mechanism (step b) involves nucleophilic attack by the alcohol on the sulfoxonium ion 2 resulting in the formation of N-(p-tolyl)diphenylacetamide (4) and the alkoxysulfonium ion 3. The final step (step c) involves the abstraction of a proton from the α-carbon of the alkoxy group in 3 and concerted collapse of the resulting intermediate to the carbonyl compound and dimethyl sulfide. These steps are again similar to those proposed by Moffat et al. for the oxidations using DCC-DMSO. Torssell[4]

had proposed a concerted mechanism for the DCC-DMSO oxidation as outlined in Scheme II.

Scheme II.



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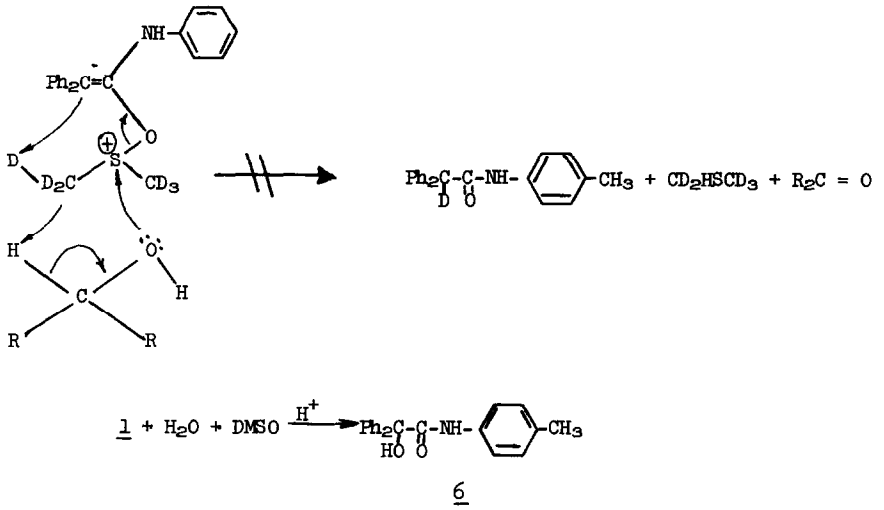
To test the validity of these two mechanisms proposed by Moffatt et al. and Torssell, we conducted the sulfoxide-carbodiimide oxidation of testosterone using hexadeuteriodimethyl sulfoxide (DMSO-d_6) instead of DMSO. The infrared spectrum of the resulting dicyclohexylurea 5 indicated the absence of any N-D stretching absorption around 2475 cm^{-1}. Moreover, treatment of DCC with DMSO-d_6 in the presence of anhydrous orthophosphoric acid for 30 min. also afforded 5 (quantitative yield) which was devoid of N-D stretching vibrations in the infrared spectrum. These results completely ruled out the mechanism proposed by Torssell (Scheme II) and further substantiated Moffatt et al.'s proposed mechanism.

To substantiate the proposed mechanism for the sulfoxide-ketenimine oxidation (Scheme I), we first extended this new oxidation procedure to the oxidation of hydroxy steroids. Thus, the oxidation of testosterone afforded 82% yield of androst-4-ene-3,17-dione, whose identity was confirmed by comparison with an authentic sample. Next, the oxidation of testosterone was conducted using the ketenimine 1[5] and DMSO-d_6 in the presence of anhydrous orthophosphoric acid. The infrared spectrum of the resulting amide 4 showed no C-D absorption, and its nuclear magnetic resonance spectrum (DMSO-d_6) indicated the presence of C-H (s, 1, 5.1 ppm.) and NH (s, 1, 9.85 ppm.) absorptions. A mixture of benzene and the labeled dimethylsulfide was isolated from the reaction mixture. The nmr spectrum of this mixture indicated a quintet at δ 2.10 ppm., characteristic of pentadeuteriodimethylsulfide.[4] Furthermore, the reaction of ketenimine 1 with DMSO-d_6 in the presence of orthophosphoric acid (30 min.) and characterization of the resulting amide 4 afforded similar results. These results tend to rule out the

possibility of the three-body concerted mechanism (similar to Torssell's proposed mechanism for DCC-DMSO oxidation, Scheme II) as shown in Scheme III and support the mechanism proposed in Scheme I. Finally, to illustrate that in the first step (step a, Scheme I) of the sulfoxide-ketenimine oxidation, the protonation takes place on the nitrogen rather than on the carbon, the ketenimine 1 was treated with DMSO in the presence of orthophosphoric acid and water. This afforded a quantitative yield of N-(p-tolyl-α-hydroxydiphenylacetamide (6) whose physical constants were in agreement with the literature values.[3]

Scheme III.



In summary, the mechanism of sulfoxide-ketenimine oxidations is similar to the mechanism of sulfoxide-carbodiimide oxidations as proposed by Moffatt et al. The possibility of a three-body concerted mechanism for these oxidations as proposed by Torssell has been refuted.

Experimental

The melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the infrared spectra. The nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Diphenylketene-N-p-tolylimine (1) was prepared according to the procedure of Stevens et al.[5] The oxidation of testosterone using DCC and DMSO-d_6 in the presence of anhydrous orthophosphoric acid was conducted according to the procedure reported by Moffat et al.[2] Similar procedure was used for the reaction of DCC with DMSO-d_6 in the presence of anhydrous orthophosphoric acid.

Sulfoxide-ketenimine oxidation of testorterone. -To a solution containing diphenylketene-

N-p-tolyl-imine (1, 4.24 g, 20mmole), dry dimethylsulfoxide (5 ml), dry benzene (3 ml), and some molecular sieves (4a, 1/16) was added testosterone (1.35 g, 5 mmole) with stirring. The reaction mixture was stirred at room temperature for two days. The oxidation was followed by thin-layer chromatography using chloroform-ethylacetate (4:1) as the developing solvent system. The reaction mixture was diluted with benzene (200 ml) and the organic layer was washed successively with a solution of sodium hydrogen carbonate (10%) and water and dried. The organic layer was concentrated under diminished pressure and chromatographed over a column of Silica Gel G. Elution with chloroform-ethylacetate (4:1) afforded colorless crystals (1.3 g), m.p. 138-140°. Recrystallization from acetone gave (1.1 g, 82%) colorless crystals of androst-4-ene-3,17-dione, m.p. 141-143°. A mixture melting point of the crystals with an authentic sample of androst-4-ene-3,17-dione (m.p. 141-143°) showed no depression and the infrared spectra (KBr) of the two samples were superimposable.

The reaction of ketenimine 1 with DMSO-d_6 in the presence of orthophosphoric acid was done according to the above procedure except that the labeled dimethylsulfide liberated during the course of the reaction was trapped by condensation at -70° and the remaining labeled dimethylsulfide was isolated by flash distillation of the reaction mixture at 50°.

N-(p-tolyl)-α-hydroxydiphenylacetamide (6). -To a solution of the ketenimine 1 (0.45 g) in DMSO (20 ml) was added dropwise concentrated orthophosphoric acid until the yellow color disappeared. The mixture was stirred for 15 min. and then poured into ice-water (600 ml) with stirring. The resulting white precipitate was filtered, washed with water, and dried. Crystallization from absolute ethanol afforded colorless crystals (0.4 g, 80%) of 6, m.p. 185-190° (lit.[3] m.p. 189-190°). The nuclear magnetic resonance spectrum of 6 (DMSO-d_6) was consistent with the structure proposed.

Acknowledgement. -This work was supported by Grant No. CA-06140 from the National Cancer Institute.

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