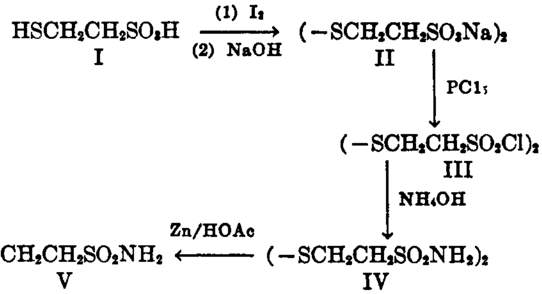
complished by protecting the sulfhydryl group through formation of the disulfide.



EXPERIMENTAL

Disodium-3,4-dithia-1,6-hexanedisulfonate (II). Iodine (39 g., 0.31 equivalent) was added to 250 ml. of a stock solution 2-mercaptoethanesulfonic acid (I) containing 54 g. (0.33 equivalent) of solute based on acidimetric titration.[7] A slight amount of iodine color remained undischarged. The disulfonic acid and the hydriodic acid were neutralized with 25.5 g. of sodium hydroxide (0.64 equivalent) in 25 ml. of water. The solution was then diluted with 380 ml. of methanol and treated with 1200 ml. of acetone. A copious precipitate was filtered, washed with acetone, and dried at 70°. It weighed 56.3 g. Recrystallization of 55.0 g. from 50 ml. of water gave 45 g. of wet crystals (not washed) which dried to 35.2 g. of (II) (65% yield).

Anal. Calcd. for $C_4H_8Na_2O_6S_4$: mol. wt., 326. Found[8]; 328.

3,4-Dithia-1,6-hexanedisulfonyl chloride (III). A dry mixture of 105 g. of II (0.32 mole) and 149 g. of phosphorus pentachloride (0.72 mole) was allowed to stand until it had turned molten and the heat of reaction had dissipated. Fumes were evolved and 24 g. was lost. An additional 93 g. of phosphorus oxychloride was removed by distillation at reduced pressure. The residue, 137 g., was taken up in 300 ml. of benzene, filtered to remove sodium chloride, and stripped to 95 g. of oily crystals. Filtration and washing with petroleum ether (b.p. 90–120°) gave 45 g. of III melting at 64°–72°. Mixing the mother and wash liquors gave more crystals which were dissolved in hot benzene filtered with Norite, and recovered by the addition of petroleum ether. This crop weighed 20 g. (total yield 0.204 mole, 63%) and melted at 68°–72°.

3,4-Dithia-1,6-hexanedisulfonamide (IV). Dithiahexanesulfonyl chloride (III), 20 g., was added to 200 ml. of concd. ammonium hydroxide with cooling to hold the temperature below 25°. The solid dissolved. The solution was concentrated to 100 ml. at reduced pressure, giving a precipitate which was filtered with great difficulty. The very finely divided powder was recrystallized from alcohol with Norite and again from alcohol to give 3.0 g. of crystals (17% yield) melting 146°–151°. Analysis by reduction showed a purity of 99%.

In another preparation the crude powder was recrystallized from water and three times from alcohol, the last time with Norite, to give platelets melting at 152.5°–154°.

Anal. Calcd. for $C_4H_{12}N_2O_4S_4$: S, 45.74. Found: S, 45.89.

2-Mercaptoethanesulfonamide (V). A solution of 7.0 g. (0.025 mole) of disulfonamide (IV) was prepared in a mixture of 50 ml. of water and 40 ml. of acetic acid at 90°. Eleven grams of 20-mesh zinc were added and the reduction mixture held at 90° for 45 min. The zinc was filtered off and the filtrate made up to 100 ml. Titration of an aliquot showed the presence of 50 mequivalents of mercaptan. Ten grams (63 mequivalents) of mercuric acetate in 20 ml. of water were added and the resulting precipitate was filtered and washed with ethanol. It was suspended in water and hydrogen sulfide passed in until the light colored solid had disappeared. Most of the mercuric sulfide suspension was removed by centrifuging and decantation. The rest was filtered on a Seitz K5 asbestos filter.

The solution of 2-mercaptoethanesulfonamide was concentrated at reduced pressure, leaving a small amount of oil. 1-Propanol was added and the solution again concentrated to an oil. Addition of petroleum ether gave 3.0 g. of crystals (yield 43%) which assayed 96% by iodometric titration.[8] A sharp melting point could not be obtained on this product.

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[7] Iodometric titration showed only 0.31 equivalent of mercaptan. The discrepancy is probably due to disulfide formed in the solution by air oxidation.

[8] Samples of 100 mg. were dissolved in 20 ml. of water and 5 ml. of sulfuric acid. Titration showed the absence of mercaptan. One-half gram of powdered zinc was added and the reaction allowed to proceed for 30 min. (Similar results were obtained after 20 min. or 40 min.) The metallic zinc was removed, and the solutions were titrated with standard tenth normal iodine.

Oxidation of Dialkyl Sulfides with Nitric Acid

DAVID W. GOHEEN AND CLIFTON F. BENNETT

Received June 27, 1960

Many articles in the literature describe the oxidation of organic sulfides and sulfoxides to the corresponding sulfones. Oxidizing agents which are cited[1] are hydrogen peroxide, organic peroxides, per acids, potassium permanganate, sodium hypochlorite, hypochlorous acid, aqueous chlorine, chromic acid, oxygen, ozone, oxides of nitrogen, fuming nitric acid, ruthenium tetroxide,[2] and potassium persulfate.[3] Anodic oxidation also has been used.

For commercial processes, the above oxidizing agents are relatively costly and thus a search for an inexpensive oxidizing agent was undertaken. Nitric acid offers the advantage of economy over most of the other oxidants. Not only is the initial cost low but also the recovery of nitrogen oxides produced during oxidation and passage through a nitric acid tower assures very high recovery of the acid for re-use.

The oxidation of sulfides to corresponding sulfoxides with nitric acid[4,5] has been known to proceed smoothly and in good yield for many years. However, oxidation in high yield of the resulting sulfoxides to sulfones with nitric acid has heretofore not been realized at ordinary pressures.[6,7,8]

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[1] C. M. Suter, *The Organic Chemistry of Sulfur,* John Wiley, New York, 1944, pp. 660–667.

[2] C. Djerassi and R. R. Engle, *J. Am. Chem. Soc.,* 75, 3838 (1953).

[3] E. Howard, Jr., and L. S. Levitt, *J. Am. Chem. Soc.,* 75, 6170 (1953).

[4] T. P. Hilditch, *J. Chem. Soc.,* 1618 (1908).

[5] E. Fromm, *Ann.,* 396, 75 (1913).

[6] G. W. Fenton and C. K. Ingold, *J. Chem. Soc.,* 3127 (1928).

[7] O. Beckmann, *J. Prakt. Chem.,* (2), 17, 471 (1878).

[8] F. Beilstein and A. Kurbatow, *Ann.,* 197, 75 (1879).

TABLE I

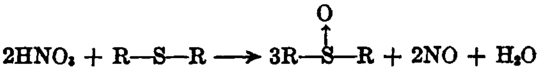
Oxidation with Nitric Acid

Material Oxidized	Quantity Oxidized, Mole	Quantity Nitric Acid, Moles	Reaction Temp.	Reaction Time, Min.	Sulfone Produced	M.P.	Yield, %
Dimethyl sulfide	1.00	3.0	122–148	85	Dimethyl	109	88
Diethyl sulfide	0.45	0.96	140	120	Diethyl	74	77
Di-*n*-propyl sulfide	.33	1.33	115–150	45	Di-*n*-propyl	26	97
Di-*n*-butyl sulfide	.33	1.33	96–120	60	Di-*n*-butyl	43	69
Di-*n*-octyl sulfide	.33	1.33	125–176	12	Di-*n*-octyl	73	83
Dimethyl sulfoxide	.42	0.64	120–150	240	Dimethyl	109	86

In the early literature there are several references to the use of nitric acid for oxidation of sulfides.[9–12] In all cases, ordinary nitric acid resulted in the formation of only the sulfoxide. In order to obtain the sulfone it was necessary to use fuming nitric acid or sealed tubes and long heating periods. Reaction details in these references are very sketchy and conversions to the sulfone were not complete.

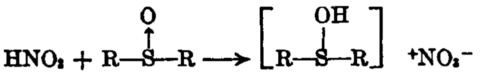
In contrast to these earlier methods, the procedure used in the present investigation gave high yields using ordinary concentrated nitric acid. The dialkyl sulfides and dialkyl sulfoxides which were examined in the present study were converted to the sulfones in yields approaching theoretical in many cases.

The reaction of nitric acid, as is the case with many other oxidizing agents, with sulfides proceeds in two steps, *viz.*,



$$2HNO_3 + R{-}S{-}R \longrightarrow 3R{-}\overset{\overset{\displaystyle O}{\uparrow}}{S}{-}R + 2NO + H_2O \qquad (1)$$

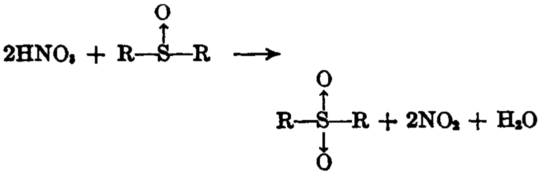
The sulfoxide formed immediately reacts with any excess nitric acid to form the hydroxy sulfonium nitrate,



$$HNO_3 + R{-}\overset{\overset{\displaystyle O}{\uparrow}}{S}{-}R \longrightarrow \left[R{-}\overset{\overset{\displaystyle OH}{|}}{S}{-}R\right]^{+}NO_3^{-} \qquad (1a)$$

The oxidation proceeds so readily with most oxidizing agents that one must assume a low activation energy exists for the conversion of a sulfide to sulfoxide.

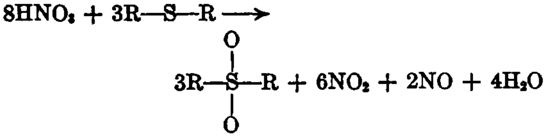
The second step of the oxidation, although in most cases is accompanied by a larger heat of reaction, proceeds with much greater difficulty:



$$2HNO_3 + R{-}\overset{\overset{\displaystyle O}{\uparrow}}{S}{-}R \longrightarrow R{-}\underset{\underset{\displaystyle O}{\downarrow}}{\overset{\overset{\displaystyle O}{\uparrow}}{S}}{-}R + 2NO_2 + H_2O \qquad (2)$$

and thus the activation energy for the oxidation of sulfoxides to sulfones is probably very high.

It has been found that reaction (2) starts at about 120° and proceeds readily only at temperatures above 130° and then only with continuous application of heat. One must be dealing, in this case, with a large activation energy. The failure of previous investigators satisfactorily to oxidize sulfides to sulfones resulted because reaction temperatures were too low to overcome readily the high activation energies. It is fortunate that sulfoxides readily form the conjugate acid with nitric acid, as this allows the use of high temperatures at ordinary pressures without undue loss of nitric acid. The overall reaction of nitric acid with sulfides can best be summarized by adding equations (1) and (2) to give (3):



$$8HNO_3 + 3R{-}S{-}R \longrightarrow 3R{-}\underset{\underset{\displaystyle O}{\downarrow}}{\overset{\overset{\displaystyle O}{|}}{S}}{-}R + 6NO_2 + 2NO + 4H_2O \qquad (3)$$

This is, of course, an oversimplification but most closely explains the stoichiometry which has been observed. In reaction (1), it has been found experimentally that most of the nitric acid is reduced to nitric oxide although a small amount of nitrogen dioxide is formed, and conversely, in reaction (2), the major part of the nitric acid is reduced to nitrogen dioxide with only a small portion appearing as nitric oxide.

The results obtained in this investigation demonstrate that sulfones can be readily prepared by an inexpensive oxidation and thus may become available commercially. High cost has, until now, been a large factor in retarding their commercial utilization. The oxidative process is especially adaptable to recovery and re-use of the nitric acid. The nitrogen oxides can be recovered and regenerated to nitric acid with at least 95% efficiency.

EXPERIMENTAL

Nitric acid, of any desired concentration, was combined with the sulfide in a molar ratio between 2.00 nitric acid:1.00 sulfide and 6.00 nitric acid:1.00 sulfide, and the mixture was heated at atmospheric pressure to a temperature of 120 to 180° until red-brown fumes ceased to evolve. Any water originally present in the acid was driven off during the heating. The addition of the nitric acid to the sulfide, or

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(9) A. Saytzeff, *Ann.*, 139, 354 (1866).
(10) A. Von Oefele, *Ann.*, 127, 370 (1863).
(11) A. Saytzeff, *Ann.*, 144, 148 (1867).
(12) N. Grabowsky, *Ann.*, 175, 348 (1875).

vice versa, was found to be possible at any temperature between 0° and the boiling point of the higher boiling component.

Dialkyl sulfoxide was oxidized to the sulfone by combining it with nitric acid of any desired concentration at any temperature between 0° and the boiling point of the higher boiling component, and heating at atmospheric pressure until cessation of red fumes signified completion of the reaction.

The various oxidations are summarized in Table I.

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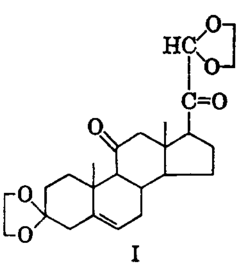
Steroidal Cyclic Ketals. XXII.[1] By-Products of the Ketalization of Cortisone and 11-Epihydrocortisone

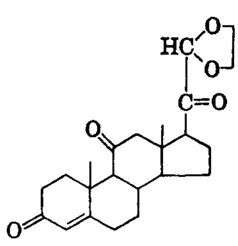
SEYMOUR BERNSTEIN, MILTON HELLER, AND WILLIAM S. ALLEN

Recieved June 16, 1960

In view of the recent comment of Evans and co-workers[2] that a nonhydroxylic by-product was formed in substantial yield during the ketalization of 5α-dihydrocortisone, we wish to disclose certain similar experiences in the preparation of cortisone 3,20-bisethylene ketal[3] and 11-epihydrocortisone 3,20-bisethylene ketal.[4]

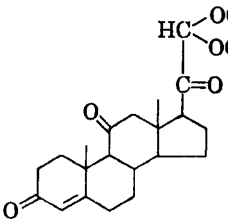
The combined mother liquors for several preparations of cortisone-3,20-bisethylene ketal[3] were evaporated and after crystallization from ethanol and then acetone, gave a new compound (I) whose elemental analyses indicated an empirical formula of $C_{25}H_{34}O_6$. There was no selective ultraviolet absorption. The infrared absorption spectrum, however, indicated the presence of two carbonyl functions, at least one ethylene ketal moiety, and a Δ^5-double bond, but no hydroxyl function. Treatment of I with sulfuric acid in methanol gave a new compound II, which obviously, from the ultraviolet and infrared absorption spectra and elemental analyses, was the result of removal of the 3-ethylene ketal group to form a Δ^4-3-one. This latter compound, moreover, still did not contain a hydroxyl group. The most convenient rationale for the by-product I was to assume it was the product of ordinary ketalization at the C3-one with a concomitant Mattox rearrangement[5] of the side chain. Since the only alcohol present in the reaction was ethylene glycol, this would necessitate that the final formulation of I would be 3,21-bisethylenedioxy-5-pregnene-11,20-dione, while II would be 21-ethylenedioxy-4-pregnene-3,11,20-trione (II).

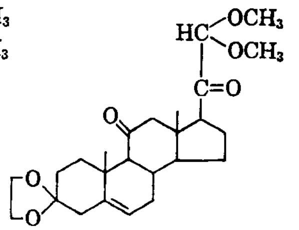

I


II

It was interesting to note the difficulty in removing the C21-ketal group in I which may be ascribed to the influence of the C11-carbonyl group. A similar influence has been previously found in the hydrolysis of a C20-ketal group in an 11-ketosteroid.[3,6-8] Also, the infrared absorption spectrum of I revealed the presence of carbonyl functions at 1712 and 1738 cm.$^{-1}$. The former band has been assigned to the C11-carbonyl group.[9] The assignment of the 1738 cm.$^{-1}$ band to the C20-carbonyl function implies that the band is markedly displaced from the normal 1706–1710 cm.$^{-1}$ region associated with such a group.[9,10] It would appear, then, that there is some interaction between the C20-carbonyl and the C21-ethylenedioxy groups analogous to the interaction in the 21-acetoxy-20-ketosteroids.[10]

It was thought that further confirmation of the postulated structure for I might be achieved by ketalization of 21,21-dimethoxy-4-pregnene-3,11,20-trione (III)[5] with an exchange reaction taking place at C21. Apparently no exchange reaction occurred at C21 since a new compound was obtained, presumably, 3-ethylenedioxy-21,21-dimethoxy-5-pregnene-11,20-dione (IV).


III


IV

When the mother liquors from the preparation of 11-epihydrocortisone-3,20-bisethylene ketal[4] were

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[1] Paper XXI, W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 3223 (1956).

[2] R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Phillips, *J. Chem. Soc.*, 1529 (1958).

[3] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

[4] W. S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

[5] V. R. Mattox, *J. Am. Chem. Soc.*, **74**, 4340 (1952).

[6] W. S. Allen, S. Bernstein, M. Heller, and R. Littell, *J. Am. Chem. Soc.*, **77**, 4784 (1954).

[7] J. A. Zderic and D. C. Limon, *J. Am. Chem. Soc.*, **81**, 4570 (1959).

[8] K. Tsuda, N. Ikekawa, and S. Nozoe, *Chem. and Pharm. Bull.* (Tokyo), **1**, 519 (1959), have recently illustrated the same sort of ketalization and Mattox rearrangement[5] while performing an exchange dioxolanation reaction on Reichstein's substance S. In this case where a C11-carbonyl group is not present, the C21-ketal group was easily hydrolyzed with dilute acid.

[9] R. N. Jones, P. Humphries, and K. Dobriner, *J. Am. Chem. Soc.*, **72**, 956 (1950).

[10] R. N. Jones, V. Z. Williams, M. J. Whalen, and K. Dobriner, *J. Am. Chem. Soc.*, **70**, 2024 (1948).