[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Some New Reactions of Methanesulfenyl Chloride[1]

IRWIN B. DOUGLASS

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Methanesulfenyl chloride (I) has been found to react with methyl thiolacetate to form acetyl chloride and methyl disulfide (II). I also reacts with methyl methanethiolsulfonate (III) in an analogous manner to form II and methanesulfonyl chloride (IV). With ethyl ethanesulfinate (V), I reacts to form ethyl chloride, ethanesulfonyl chloride, and II. With methanol the reaction products are hydrogen chloride, methyl chloride, II, and III. Toward water, I reacts more slowly to form hydrogen chloride, II, and III. These reactions are readily explained if one assumes that I behaves as an electrophilic reagent.

Sulfenyl chlorides have been found to attack a wide variety of reagents. Most of these reactions have appeared to involve simple addition to double bonds, replacement of active hydrogens, or rupture of strained rings. More recently reactions have been found which require a less simple explanation. Sulfenyl chlorides, for example, have been found to react with trialkyl phosphites to form monothiophosphate esters and alkyl chlorides.[2]

$$RSCl + R'OP(OR')_2 \longrightarrow R'Cl + RSP(OR')_2 \quad (1)$$

Morrison[3] has described this reaction as one involving nucleophilic displacement of chloride accompanied by elimination of alkyl chloride. Considered from the standpoint of the sulfenyl chloride as the attacking reagent, this reaction can also be described as an electrophilic attack on phosphorus accompanied by elimination of alkyl chloride.

Indeed, if one examines most of the well known reactions of the sulfenyl chlorides the concept of electrophilic attack is useful in explaining reaction mechanisms. The concept also helps to explain the results observed when methanesulfenyl chloride (I) reacts with methyl thiolacetate, methyl methanethiolsulfonate, ethyl ethanesulfinate, methanol, and water.

Methanesulfenyl chloride (I) reacts readily with methyl thiolacetate with the formation of methyl disulfide (II) and acetyl chloride. The reaction can be explained as an electrophilic attack on sulfur with elimination of acetyl chloride.

$$\underset{\text{I}}{CH_3SCl} + CH_3COSCH_3 \longrightarrow CH_3COCl + \underset{\text{II}}{CH_3SSCH_3} \quad (2)$$

When I reacts with methyl methanethiolsulfonate (III) an analogous but much slower reaction takes place forming methanesulfonyl chloride (IV) and II.

$$\underset{\text{I}}{CH_3SCl} + \underset{\text{III}}{CH_3SO_2SCH_3} \longrightarrow \underset{\text{IV}}{CH_3SO_2Cl} + \underset{\text{II}}{CH_3SSCH_3} \quad (3)$$

With ethyl ethanesulfinate (V), I reacts to form ethyl chloride, ethanesulfonyl chloride (VI), and II. Before attempting this reaction, compound V was considered to be analogous to the dialkyl phosphonous esters, which have an unshared electron pair on the phosphorus atom and which react with sulfenyl chlorides to form thiophosphonate esters.[4] By analogy it was expected that compounds I and V would react to form methyl ethanethiolsulfonate, $C_2H_5SO_2SCH_3$ (VII). Instead, however, the reaction took place as indicated in Equation 4 with no trace of thiolsulfonate ester being found among the products.

$$2\underset{\text{I}}{CH_3SCl} + \underset{\text{V}}{C_2H_5SOC_2H_5} \longrightarrow \underset{\text{VI}}{C_2H_5SO_2Cl} + C_2H_5Cl + \underset{\text{II}}{CH_3SSCH_3} \quad (4)$$

The absence of thiolsulfonate ester and the presence of VI and II among the products first suggested that the expected methyl ethanethiolsulfonate (VII) had reacted with excess I as soon as it had been formed. On further thought, however, this view did not seem tenable in consideration of the fact that Equation 3 is slow, being only 10% complete in one hour, 26% in 6 hours, and only 45% in 24 hours. Likewise, there was evidence for the formation of only a 40% yield of VI when VII and I stood in contact for 2 weeks.

The following alternative mechanism is tentatively advanced to explain the results observed (Equations 5a and 5b). The electrophilic sulfenyl chloride (I) first attacks the oxygen of the alkoxy group in V with elimination of ethyl chloride and the formation of an unstable sulfinic - sulfenic anhydride (VIII) with which additional I reacts by electrophilic attack on sulfur followed by elimination of ethanesulfonyl chloride (VI).

(1) Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) E. E. Gilbert and C. J. McGough, U. S. Patents **2,690,450** and **2,690,451**, issued Sept. 28, 1954.

(3) D. C. Morrison, *J. Am. Chem. Soc.*, **77**, 181 (1955).

(4) D. C. Morrison, *J. Org. Chem.*, **21**, 705 (1956).

$$\underset{\text{I}}{CH_3SCl} + \underset{\text{V}}{C_2H_5S\ddot{O}C_2H_5} \longrightarrow \left[\underset{\text{(VIII)}}{C_2H_5S{-}OSCH_3}\right] + C_2H_5Cl \quad (5a)$$

$$\underset{\text{VIII}}{} + \underset{\text{I}}{CH_3SCl} \longrightarrow \underset{\text{VI}}{C_2H_5SCl} + \underset{\text{II}}{CH_3SSCH_3} \quad (5b)$$

The reaction between methanol and I is rapid, forming methyl chloride, methyl methanethiolsulfonate (III), methyl disulfide (II), and hydrogen chloride. The sequence of reactions would appear to involve first the formation of methyl methanesulfenate (IX) with which I then reacts by electrophilic attack on sulfur with elimination of methyl chloride and the formation of methyl methanethiolsulfinate (X). This latter compound then disproportionates to III and II.

$$\underset{\text{I}}{CH_3SCl} + CH_3OH \longrightarrow \underset{\text{IX}}{CH_3SOCH_3} + HCl \quad (6a)$$

$$\text{I} + \text{IX} \longrightarrow \underset{\text{X}}{CH_3SSCH_3} + CH_3Cl \quad (6b)$$

$$2\text{X} \xrightarrow{\text{Disproportionation}} \underset{\text{III}}{CH_3SO_2SCH_3} + \underset{\text{II}}{CH_3SSCH_3} \quad (6c)$$

Sulfenate esters are stable derivatives of 2,4-dinitrobenzenesulfenyl chloride,[5] but alkyl esters derived from alkanesulfenyl chlorides have not been reported. The aliphatic thiolsulfinate esters have been prepared by the oxidation of disulfides but they are reported to be unstable.[6] Likewise, the addition of a mercaptan to an aliphatic sulfinyl chloride, a reaction which might be expected to produce a thiolsulfinate ester, produces instead a thiolsulfonate ester and a disulfide.[7]

Additional work on the reaction between methanol and I, now in progress, suggests that other products are formed, in addition to those indicated, but the results are consistent with the chemical behavior of I described in this paper.

The reaction of I with water is slower than that with methanol but it follows a somewhat similar course. The products formed are II, III, and hydrogen chloride. The proposed mechanism involves the electrophilic attack of I on water to form methanesulfenic acid (XI) which then reacts with additional I to form methyl methanethiolsulfinate (X) which undergoes disproportionation as already described.

$$\underset{\text{I}}{CH_3SCl} + HOH \longrightarrow \underset{\text{XI}}{CH_3SOH} + HCl \quad (7a)$$

$$\text{I} + \text{XI} \longrightarrow \underset{\text{X}}{CH_3SOSCH_3} + HCl \quad (7b)$$

$$2\text{X} \xrightarrow{\text{Disproportionation}} \underset{\text{III}}{CH_3SO_2SCH_3} + \underset{\text{II}}{CH_3SSCH_3} \quad (7c)$$

The first part of this proposed mechanism is supported by the recent findings of Vinkler and Klevényi that the "sulfenic anhydrides" formed by the reaction of aromatic sulfenyl chlorides with water actually have the thiolsulfinate structure.[8]

EXPERIMENTAL

Preparation of methanesulfenyl chloride (I). A weighed quantity of liquid chlorine was allowed to evaporate into slightly more than the calculated quantity of pure methyl disulfide maintained at −10° to −20° during the reaction. When the last of the chlorine had been added, the reaction mixture was shaken to bring unchanged methyl disulfide in contact with the solid methylsulfur trichloride which had been formed to convert both to the desired sulfenyl chloride. The product was considered ready for use when the solid had disappeared. Best results were obtained when the desired quantity was prepared immediately before use.

Reaction of I with methyl thiolacetate. Methyl thiolacetate (0.2 mol.) was added slowly to well stirred methanesulfenyl chloride (0.2 mol.) in a flask cooled to −10°. Reaction occurred readily to give a colorless reaction mixture. Distillation gave an 85% yield of acetyl chloride and 75% yield of methyl disulfide. Both products were identified by boiling point and density determinations.

Reaction of I with methyl methanethiolsulfonate (III). Methyl methanethiolsulfonate (III) (0.8 mol.) and methanesulfenyl chloride (I) (0.4 mol.) were mixed at room temperature and stirred for 1 hr. but there was no evidence of reaction. The mixture was heated to 75° for 2 hr. but there was still no apparent change in color. Finally, the mixture was allowed to stand two weeks. During this period hydrogen chloride was evolved but the color did not change appreciably. On distilling the mixture, 15.0 g. of purified methyl disulfide (40% yield) and 10 g. of methanesulfonyl chloride (21.8%) were obtained. The methyl disulfide recovered had the same boiling point and refractive index as an authentic sample. The methanesulfonyl chloride was identified by conversion to the *p*-toluidide which melted at 103–104° and unchanged when mixed with an authentic sample.

In a second experiment, 0.1 mol. of methyl methanethiolsulfonate (III) and 0.087 mol. of methanesulfenyl chloride (I) were added to each of three tubes and allowed to stand at room temperature. At different times each tube in turn was treated as follows: Acetone was added to react with excess I, then the reaction mixture was diluted with ether, treated with *p*-toluidine in presence of sodium bicarbonate and, after standing several hours, was extracted with 10% sodium hydroxide. On acidifying, the alkaline extract, methanesulfon-*p*-toluidide, separated.

Tube	Time of Standing, Hr.	Wt. Methanesulfon-*p*-toluidide	Corresponding Yield of Methanesulfonyl Chloride
1	1	1.61 g.	10%
2	6	4.29	26.5%
3	24	7.17	45%

(5) N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Am. Chem. Soc.*, **75**, 2658 (1953).

(6) V. D. Small, N. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, **69**, 1710 (1947).

(7) J. v. Braun and K. Weisbach, *Ber.*, **63B**, 2836 (1930) and unpublished work in this laboratory.

(8) E. Vinkler and F. Klevényi, *Acta, Chim. Acad. Sci. Hung.*, **11**, 15 (1957).

Reaction of I with methyl ethanethiolsulfonate (VII). To 0.2 mol. of I, 0.2 mol. of VII was added, and the mixture was allowed to stand at room temperature for two weeks. There was no change in color. The mixture was then distilled yielding 5.27 g. of methyl disulfide (58% recovery) and 1.39 g. of a fraction boiling 57–63° (12 mm.). The latter was diluted with ether and caused to react with *p*-toluidine and yielded 15.7 g. of ethanesulfon-*p*-toluidide, corresponding to a 40% yield of ethanesulfonyl chloride.

Reaction of I with ethyl ethanesulfinate (V). Ethyl ethanesulfinate, $C_2H_5S(=O)OC_2H_5$ (V) (0.2 mol.), was added dropwise to 0.2 mol. of I at −20°. The mixture gradually faded in color and was nearly colorless by the time it had warmed to room temperature. It was heated to 90° to drive off volatile matter and was then cooled to await distillation.

The volatile portion after purification consisted of ethyl chloride (3.0 g., 23%). Molecular wt.: Calcd., 64.52; found, 66. Boiling pt.: Reported, 12.3°; found, 12–13°.

Distillation of the residual reaction mixture yielded 8.5 g. of methyl disulfide, identified by boiling point and refractive index and 12.4 g. of ethanesulfonyl chloride (VI). The latter was identified by conversion to the *p*-toluidide which melted at 81° and unchanged when mixed with an authentic sample.

More than 20% of the original V was recovered unchanged.

Reaction of I with methanol. In an attempt to prepare methyl methanesulfenate, $CH_3S—O—CH_3$ (IX), 0.6 mol. of I was added slowly to 1.2 mol. of well stirred methanol at −20°. The resulting colorless reaction mixture was then distilled but no product with the properties expected of IX was found. There was obtained, however, 12.5 g. of III or 66% yield on the basis of the postulated reactions described above.

The reaction was repeated using 1.6 mol. I and 0.8 mol. of methanol under conditions which would insure the recovery of any methyl chloride and methyl disulfide formed. A 55% yield of methyl chloride, identified by boiling point and molecular weight, was obtained. Methyl disulfide, having properties identical to an authentic sample, was recovered in 70% yield.

Reaction of I with water. Water (0.25 mol.) was added dropwise to well stirred I (0.25 mol.) at −20°. At first there was little evidence of reaction but gradually the evolution of hydrogen chloride became apparent and when the last of the water had been added the mixture was only faintly yellow. After warming slowly to room temperature, the reaction mixture was distilled and yielded 8.0 g. of methyl disulfide and 12.0 g. of III. The yields were 64% and 72%, respectively, based on the reactions outlined above. Both products proved identical to authentic samples.

ORONO, ME.

[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE UNIVERSITY OF PENNSYLVANIA]

Investigations on Steroids. XXX. New Transformation Products of Strophanthidin: 19-Hydroxytestosterone, 19-Hydroxy-1-dehydrotestosterone Diacetate and Estradiol-17β[1-3]

MAXIMILIAN EHRENSTEIN AND KLAUS OTTO[4,5]

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Improvements in the synthesis from strophanthidin of 19-hydroxy-Δ⁴-androstene-3,17-dione (II) are presented. The role of II as a possible key intermediate in the metabolic transformation of androgens into estrogens is pointed out. Under specific conditions, reduction of II with sodium borohydride gave mainly 19-hydroxytestosterone (IV) and, as a by-product, Δ⁴-androstene-3β,17β,19-triol (VI). By treatment with selenium dioxide, 19-hydroxytestosterone diacetate (V) was converted into 19-hydroxy-1-dehydrotestosterone diacetate (IX). Even under mild alkaline conditions, it was not possible to saponify IX to the free 19-hydroxy-1-dehydrotestosterone (VIII). By the action of mild alkali, IX is rapidly transformed into the 17-monoacetate of estradiol-17β (XI), whereas with stronger alkali, free estradiol-17β (X) is obtained. The physiological activities of IV and IX are discussed.

The synthesis from strophanthidin of analogs of steroid hormones oxygenated in the 19- position was reported from this laboratory some time ago.[6–10] A number of such products were subsequently isolated from various biological systems. Thus, several 19-hydroxy steroids have been isolated from adrenocortical extracts.[11] Hydroxyl groups have been introduced into the 19- position either by incubation with beef adrenal homogenates

(1) This paper is dedicated to the memory of Lyndon F. Small, former editor of this journal.

(2) This investigation was supported by research grants (CY757-C5 and CY757-C6) from the National Cancer Institute of the National Institutes of Health, Public Health Service. A part of the K-Strophanthin used in this investigation was kindly donated by S. B. Penick & Co., New York, N. Y.

(3) The essential findings of this paper were presented on September 5, 1958, at the 4th International Congress of Biochemistry in Vienna (*cf.* Maximilian Ehrenstein: Biochemistry of the Corticoids, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 (Symposium: Biochemistry of Steroids), Pergamon Press, p. 259 (1959).

(4) Dr. Klaus Otto was the recipient of a Fulbright Travel Grant and was on leave of absence from the Physiologisch-chemisches Institut der Universität Bonn, West Germany.

(5) In collaboration with G. Winston Barber.

(6) G. W. Barber and M. Ehrenstein, *J. Am. Chem. Soc.*, **76**, 2026 (1954).

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(9) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, 21, 774 (1956).

(10) M. Ehrenstein and M. Dünnenberger, *J. Org. Chem.*, 21, 783 (1956).

(11) *Cf. e.g.*, Albert Wettstein: Biochemie der Corticoide, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 (Symposium: Biochemistry of Steroids), Pergamon Press, p. 233 (1959).