[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

# Derivatives of Sulfenic Acids. XXIX.<sup>1,2</sup> The Characterization of Certain Hydroxysteroids with 2,4-Dinitrobenzenesulfenyl Chloride

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### Received June 12, 1957

The pyridine-catalyzed reactions of 2,4-dinitrobenzenesulfenyl chloride (I) with testosterone, 19-nortestosterone,  $17-\alpha$ -methyltestosterone, and  $11-\alpha$ -hydroxyprogesterone are described. Evidence is presented for the conclusion that the products are sulfenate esters, formed by the reactions of I with the alcohol functions. It is suggested that these reactions, coupled with chromatographic separations of mixtures of the derivatives and regeneration of the hydroxysteroids from the esters, which has been achieved, may prove of value in isolation studies in this field of work. The synthesis of octadecyl 2,4-dinitrobenzene-sulfenate is also reported.

In a previous paper,<sup>3</sup> it was shown that 2,4-dinitrobenzenesulfenyl chloride (I) reacts rapidly and in good yield with cholesterol to form the sul-

$$(\text{NO}_2)_2\text{C}_6\text{H}_3\text{SCl} + \text{C}_{27}\text{H}_{45}\text{OH} + \text{C}_6\text{H}_5\text{N} \longrightarrow$$

$$I$$

$$(\text{NO}_2)_2\text{C}_6\text{H}_3\text{SOC}_{27}\text{H}_{45} + \text{C}_6\text{H}_6\text{N}:\text{HCl}$$

$$II$$

fenate ester, II. Because of the considerable interest in the isolation and characterization of compounds related to the corticosteroids, it was desired to extend this study to representative members of this class of substances. The reactions of I with testosterone, 19-nortestosterone,  $17-\alpha$ -methyltestosterone, and  $11-\alpha$ -hydroxyprogesterone, all of which contain an alcohol function, were therefore examined.

The principal products (Table I) from the reactions of I with the above hydroxysteroids were the sulfenate esters, rather than those which might result by reaction of I at the 4,5-olefin position or at the  $\alpha$ -methylene group of the ketone functions present in some of these molecules.<sup>4</sup> The conclusions as to the structures of the products are based on (1) elementary analyses, (2) previously reported results with simpler alcohols, (3) cleavage of certain of the present products to regenerate the hydroxysteroids, (4) comparisons of the spectra of the products with those of the original hydroxysteroids, and (5) the consideration that the reactions of I and the hydroxysteroids would occur much more rapidly at the alcohol function than at the 4,5-olefin position or the methylene group alpha to the carbonyl function.

The products obtained are listed in Table I. The yields from testosterone, 19-nortestosterone, and cholesterol were reasonably good, considering that the runs were made on a small scale and that the products were subjected to thorough purification. With  $17-\alpha$ -methyltestosterone and  $11-\alpha$ -hydroxyprogesterone, however, the yields were decidedly lower (45% and 22%). Some side reactions, especially with the former, and the known fact that tertiary alcohols give lower yields than primary or secondary ones, in the reaction with I, are the most likely reasons for the lower yields in these cases.<sup>5</sup> Although such complications in the reactions of I with the hydroxysteroids can thus arise, it is nevertheless believed that 2,4-dinitrobenzenesulfenyl chloride may have considerable utility in the characterization of hydroxysteroids. The facts that the products are colored, that they lend themselves well to chromatographic procedures, and that they have definite spectral characteristics are positive features toward the use of I for the characterization of hydroxysteroids. For example, it was shown, in the present study, that mixtures of the hydroxysteroid derivatives can be separated simply by chromatography on alumina, and that the sulfenate esters can be cleaved to regenerate the alcohol component. Such separations, followed by regeneration of the hydroxysteroids, by cleavage of the esters, suggests a potentially valuable technique for separation of hydroxysteroids from complex mixtures.

In the course of this work the octadecyl ester of 2,4-dinitrobenzenesulfenic acid was also prepared, characterized, and cleaved to regenerate the alcohol. This was done to conserve the somewhat limited supplies of the hydroxysteroids while developing the procedure. The octadecyl alcohol derivative was convenient for exploratory work in the chromatographic purifications and for finding suitable conditions for the regeneration of the alcohol by cleavage of the sulfenate ester.

<sup>(1)</sup> This study was conducted under auspices of the Office of Scientific Research, Air Research and Development Command.

<sup>(2)</sup> For preceding papers, cf. J. Org. Chem., 21, 590 (1956); J. Am. Chem. Soc., 78, 2728 (1956) and J. Chem. Ed., 33, 585 (1956); 34, 510 (1957).

<sup>(3)</sup> N. Kharasch, D. P. McQuarrie, and C. M. Buess, J. Am. Chem. Soc., 75, 2658 (1953); cf. also, L. Goodman and N. Kharasch, J. Am. Chem. Soc., 77, 6541 (1955).

<sup>(4)</sup> For references to the reaction of I with olefins and ketones, cf., J. Chem. Ed., 33, 585 (1956); 34, 510 (1957).

<sup>(5)</sup> In the tertiary alcohols, competition by water is more serious and leads to the formation of bis(2,4-dinitrophenyl) disulfide and other hydrolysis products; cf., N. Kharasch, W. King, and T. C. Bruice, J. Am. Chem. Soc., 77, 931 (1955).

PRODUCTS FROM THE REACTION OF 2,4-DINITROBENZENESULFENYL CHLORIDE WITH CERTAIN HYDROXYSTEROIDS									
				Analyses					
	Product	Yield,	M.P.,	Calcd.			Found		
Hydroxysteroid	Ar = 2,4-Dinitrophenyl	%	°C.	C	H	S	C	Η	S
Testosterone	0SAr	70	204-205	61.71	6.21	6.59	61.91	5.84	6.70
19-Nortestosterone	OSAr o	60	199–200	61.00	5.95	6.79	60.71	5.78	7.01
$17-\alpha$ -Methyltestosterone	OSAr	45	170–171	62.38	6.44	6.40	62.65	6.56	6.15
$11-\alpha$ -Hydroxyprogesterone	ArSO	32	198–199	61.34	6.10	6.07	61.08	6.21	5.74
$\mathrm{Cholesterol}^a$	ArSo	80	190 -191						
$Octadecanol^b$	CH <sub>3</sub> -(CH <sub>2</sub> ) <sub>17</sub> -O-S-Ar	80	88.0-88.5	${\bf Footnote}^{o}$					

TABLE	I
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<sup>a</sup> Reported in reference (3); m.p., 189-190°C. <sup>b</sup> Not a steroid. <sup>c</sup> N: Calcd. 5.74, found, 6.03.

### EXPERIMENTAL

Starting materials. 2,4-Dinitrobenzenesulfenyl chloride (I), m.p. 95–96°, was prepared by the catalytic chlorinolysis of bis-(2,4-dinitrophenyl) disulfide or obtained from Cyclo Chemical Corp.,<sup>6</sup> m.p. 95–96°. Benzene was A.C.S. grade Baker and Adamson reagent, dried by distillation. Pyridine was also A.C.S. grade Baker and Adamson reagent, distilled from barium oxide and stored over calcium hydride. The hydroxysteroids were supplied by the Upjohn Co., in purities from 95% to 100%.

General Procedure for characterizing hydroxysteroids. To 1.00 g. of the hydroxysteroid, dissolved in 5 ml. of dry benzene, was added 0.5 ml. of dry pyridine, an excess. A solution containing the calculated equivalent amount of I, in 5 ml. of dry benzene, was added to the hydroxysteroid-pyridine mixture at room temperature, with stirring. Completion of the reaction was indicated by a negative starch-iodide test, when I was not used in excess. In most cases the reaction was complete after a few minutes.

The reaction mixture was filtered and the precipitate was extracted with several small portions of hot benzene. To the combined filtrates, at the boiling point, was added twice their volume of hot ethanol. This solution was refrigerated overnight to induce the formation of crystals, which were collected by filtration and air or vacuum dried. The products are listed in Table I. Some variation of the solvent ratios and volumes was necessary to obtain the optimum yields of the various sulfenates. Further purification of the products was obtained by adding them, in benzene solution, to an alumina chromatographic column, prewet with petroleum ether, developing the chromatogram with benzene, and eluting with benzene-methanol (9:1). The purified material was then crystallized as before.

Chromatographic separation of sulfenate esters of hydroxysteroids. A solution of 50 mg. each of cholesteryl 2,4-dinitrobenzenesulfenate and testosteronyl 2,4-dinitrobenzenesulfenate in 1.0 ml. of benzene was added to an alumina chromatographic column, prewet with petroleum ether. Additional benzene was used to develop the chromatogram, followed by benzene-methanol (9:1) for elution. Two distinct bands formed and were readily separated on elution. The melting points of the materials, thus obtained, identified the first fraction as the testosterone derivative, and the other as the cholesterol product.

Recovery of a hydroxysteroid from its sulfenate ester. The recovery of testosterone exemplifies the procedure used. To a solution of about 100 mg. of testosteronyl 2,4-dinitrobenzenesulfenate in 25 ml. of ethanol was added 2.0 ml. of concentrated hydrochloric acid. This mixture was boiled for 5 min. and filtered. The filtrate was refrigerated overnight, yielding a crop of fine, cream colored crystals, m.p. 156-158°. In comparison, the testosterone used to prepare the sulfenate had a melting point of 152-153°, but was rated only 95% pure. On mixing these materials, a melting point of 152-154° was obtained.

Determination and evaluation of spectra. Infrared absorption spectra were obtained from carbon disulfide solutions of testosterone, 19-nortestosterone, testosteronyl 2,4-dinitrobenzenesulfenate, and 19-nortestosteronyl 2,4-dinitro-

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benzenesulfenate. Both hydroxysteroids had absorption bands in the hydroxyl region, near 3625 cm.<sup>-1</sup> These absorption bands were not present in the spectra of either derivative, indicating that the reaction occurred at the hydroxyl group, rather than at some other point in the hydroxysteroid molecule.

Acknowledgment. We are indebted to the Upjohn

Co., Kalamazoo, Mich., for a generous supply of the hydroxysteroids and to Mr. D. M. Frankel of the Stauffer Chemical Co., Torrance, Calif., for assistance with the infrared spectra.

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## **Thiocarboxylic Esters and Related Compounds**<sup>1</sup>

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### Received October 25, 1956

The reaction of unsaturated acid chlorides with lead mercaptides gave the corresponding thiolesters. Polymerization of thiolacrylates and thiolmethacrylates yielded glasslike materials, comparable in properties to the corresponding ester polymers. Attempts to prepare thionoacrylates by dehydrohalogenation of halothionopropionates failed. The stability of the intermediate halo- and dihalopropionimidates to decomposition was found to decrease markedly with increasing halogen substitution. The reaction of unsaturated acid chlorides with sodium sulfhydrate yielded polymeric material, equivalent in analytical composition to the corresponding thioacids.

In spite of the abundant literature published in recent years on lower unsaturated acids and esters, unsaturated thioacid derivatives received remarkably little attention. Previous work in this field was in fact limited to the investigations of Reppe<sup>3</sup> and Jacobs.<sup>4</sup>

In the present study, a number of new thiolesters and thionoesters were prepared, and their physical and chemical properties determined and evaluated. Since this work was completed, Jacobs<sup>4</sup> made a series of thiolacrylates by debromination of dibromothiolpropionates. His attempts to obtain thiolacrylates directly from acrylyl chloride and a mercaptan in presence of sodium carbonate were not successful, due presumably to the addition of the mercaptan to the double bond and the formation of a mercapto thiolpropionate.

In the present work, thiolesters of unsaturated carboxylic acids were prepared directly from the corresponding acid chloride and lead mercaptide, by a modification of the method first described by Obermeyer,<sup>5</sup> which is based on the reaction:

 $2 \operatorname{RCOCl} + \operatorname{Pb}(\operatorname{SR}')_2 \longrightarrow 2 \operatorname{RCOSR}' + \operatorname{PbCl}_2$ 

Attempts to prepare ethyl thiolmethacrylate from methacrylyl chloride and lead ethyl mercaptide by Obermeyer's method without a solvent resulted in a violet, exothermic reaction and the formation of a dark, polymerized product. This difficulty was overcome by using anhydrous ether, in which the lead mercaptide was slurried up initially, and by adding the acid chloride gradually with good agitation and cooling. An excess of lead mercaptide (10%) was used to avoid the troublesome separation of unreacted acid chloride.

Properties and analyses of a number of unsaturated thiolesters made by this procedure are listed in Table I.

Samples of the thiolesters were heated in bulk, or in a solvent, or irradiated with ultraviolet light to obtain polymers. As could be expected by analogy with the corresponding esters, only thiolacrylates and thiolmethacrylates were found to polymerize under the conditions employed, yielding transparent, colorless materials.

Saturated thionoesters have been made by Matsui<sup>6</sup> and by Sacurada<sup>7</sup> from an iminoester and hydrogen sulfide:

 $RC(OR')NH + 2 H_2S \longrightarrow RCSOR' + NH_3$ 

Unsaturated thionoesters have not been described before, and it was an object of this work to attempt their preparation by dehydrohalogenation of halothionopropionates.

A modification of Matsui's method was used for the preparation of a series of halothionopropionates from the corresponding halopropionimidates. The analyses and physical properties of these new compounds are listed in Table II.

Dichloro- and dibromothionopropionates intended for dehalogenation trials, could not be prepared from the corresponding iminoesters, as dihalopropionimidates are not sufficiently stable for reaction with hydrogen sulfide.

(6) M. Matsui, Mem. Coll. Sci. Kyoto, 1, 285 (1908); 3, 247 (1912).

(7) Y. Sacurada, Mem. Coll. Sci. Kyoto, 9, 237 (1925/26).

<sup>(1)</sup> Includes some data from "Unsaturated Thioacids and Derivatives" by G. Braude and T. Lieser (Doctoral Dissertation), University of Halle.

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<sup>(3)</sup> W. Reppe, Ann., 582, 1 (1939). German Patent 856,293, July 8, 1949.

<sup>(4)</sup> L. Jacobs, "Thioacrylic Esters," Doctoral Dissertation, University of Illinois, 1955.

<sup>(5)</sup> J. Obermeyer, Ber., 20, 2920 (1887).