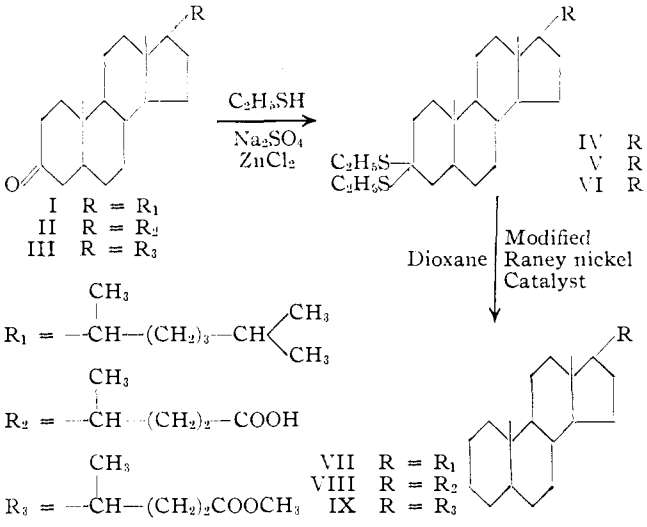
[CONTRIBUTION FROM LEDERLE LABORATORIES, INC.]

Hydrogenolysis of Steroid Thioacetals with Modified Raney Nickel Catalyst

BY SEYMOUR BERNSTEIN AND LOUIS DORFMAN

Wolfrom and Karabinos[1] have recently reported a novel method of converting carbonyl and aldehyde groups to methylene groups. The ketone or aldehyde was converted to the thioacetal which in turn was submitted to hydrogenolysis in dilute ethanol with a modified Raney nickel catalyst to give the corresponding methylene (or desoxo) compound.

It was of interest to us to apply this reaction in the steroid field. Accordingly we have prepared using essentially the same method as Wolfrom and Karabinos cholestanone-3 diethyl thioacetal (IV), 3-ketocholanic acid diethyl thioacetal (V), and methyl 3-ketocholanate diethyl thioacetal (VI) by treating the corresponding ketone with ethyl mercaptan in the presence of sodium sulfate and zinc chloride.



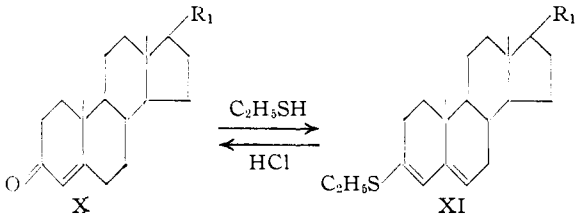
Attempts to prepare by this method the diethyl thioacetals of 7-ketocholestanyl acetate and methyl 3-hydroxy-12-ketocholanate were unsuccessful.

Also it was found that Δ^4-cholestenone-3 (X) reacts with ethyl mercaptan in the presence of sodium sulfate and zinc chloride to give an enol-thioether of probable structure[2] (XI). This enol-thioether on hydrolysis in alcohol with hydrochloric acid gave back X.

The steroid thioacetals were successfully submitted to hydrogenolysis in dioxane solution with a modified Raney nickel catalyst. (IV) gave cholestane (VII), and (VI) gave a low melting methyl cholanate (IX) which on hydrolysis gave

(1) Wolfrom and Karabinos, THIS JOURNAL, **66**, 909 (1944).

(2) See Schwenk, Fleischer and Whitman, THIS JOURNAL, **60**, 1702 (1938), and Schwenk and Whitman, U. S. Patent 2,246,540, for the oxygen analog of this compound.



pure cholanic acid (VIII). It was found that (V) when submitted to hydrogenolysis was "adsorbed" by the catalyst and the product could not be removed with 0.9 *N* sodium hydroxide. However on destroying the catalyst with hydrochloric acid impure (VIII), m. p. 157–159°, was isolated.

Experimental

Cholestanone-3 Diethyl Thioacetal (IV).—To a mixture of 0.5 g. of cholestanone-3, 1 g. of anhydrous sodium sulfate, and 0.5 g. of freshly fused zinc chloride there was added 10 cc. of ethyl mercaptan. The reaction mixture was placed in the refrigerator (3–5°) overnight. The excess ethyl mercaptan was evaporated *in vacuo*, and this gave a solid residue. Water was added and the product was taken up in ether. The ether extract was washed successively with water, dilute sodium hydroxide and water. It was dried with anhydrous sodium sulfate and on evaporation *in vacuo* a solid residue was obtained. On recrystallization from acetone–alcohol 0.5 g. of thioacetal was obtained m. p. 51–55°. A sample of this material was recrystallized from dilute acetone, and at no time was the solvent permitted to become warmer than 50°, m. p. 80–82°.

Anal. Calcd. for $C_{31}H_{54}S_2$: S, 13.1. Found: S, 13.6.

3-Ketocholanic Acid Diethyl Thioacetal (V).—Five hundred milligrams of 3-ketocholanic acid in the same manner gave 0.6 g. of crude thioacetal, m. p. 106–112°, with effervescence. The product was recrystallized from dilute alcohol, m. p. 138–144° with effervescence.

Anal. Calcd. for $C_{28}H_{48}O_2S_2$: S, 13.3. Found: S, 13.1.

Methyl 3-Ketocholanate Diethyl Thioacetal (VI).—Six hundred milligrams of methyl 3-ketocholanate in the same manner gave 0.61 g. of an oil. Attempts to crystallize the oil from ether–methanol and from acetone were unsuccessful.

Δ^4-Cholestenone-3 Enol Ethyl Thioether (XI).—One gram of (X) in the same manner gave 1.17 g. of a yellow viscous oil which crystallized on standing. On recrystallization from acetone 570 mg. of crude product was obtained which melted at 95–98°. It was taken up in ether and filtered to free it of some insoluble material, and on further recrystallization from acetone 435 mg. of pure enol-thioether were obtained, m. p. 98–99.5°. It gave a positive Rosenheim test.

Anal. Calcd. for $C_{29}H_{50}S$: C, 80.9; H, 11.7; S, 7.4. Found: C, 81.2, 81.1; H, 10.9, 11.0; S, 7.4.

A solution of 1 g. of the enol-thioether, 10 cc. of 6 *N* hydrochloric acid and 40 cc. of alcohol was refluxed for

six hours. The solution was cooled and a white solid separated, m. p. 84–86°.[3] On recrystallization from acetone pure (X) was obtained, m. p. 81–82°. A mixed melting point determination with an authentic sample of (X) gave no depression of melting point.

Modified Raney Nickel Catalyst.[4]—The catalyst was prepared in the usual manner except that after the addition of the alloy the reaction mixture was allowed to stand at room temperature overnight.

Hydrogenolysis of (IV).—A mixture of 100 mg. of cholestanone-3 thioacetal in 15 cc. of dioxane and 1.5 g. of modified Raney nickel catalyst was heated on the steam-bath for seventeen hours. The cooled mixture was filtered through Celite and the recovered catalyst was washed with dioxane and ether. The filtrate on evaporation gave an oil which on working with methanol solidified. The solid cholestane was collected by filtration and washed with methanol, m. p. 73–74.5°, wt. 67 mg. An additional milligram of material was obtained from the mother liquor. All-told the yield of impure cholestane was 91%. On recrystallization from acetone–methanol pure cholestane was obtained, m. p. 78.5–79°. It gave a negative nitroprusside test for the presence of sulfur and a negative Liebermann test.

Hydrogenolysis of (V).—To a solution of 0.1 g. of 3-ketocholanic acid thioacetal in 15 cc. dioxane there was added 1.5 g. of modified Raney nickel catalyst, and the mixture was heated on the steam-bath for six hours. It was filtered through Celite and gave a water-white filtrate which on evaporation gave an extremely small amount of solid which was insoluble in cold alcohol.

The recovered catalyst was leached with 0.9 *N* sodium hydroxide which when acidified gave only a slight turbidity. The catalyst was treated with hydrochloric acid. The insoluble material was collected by filtration and was washed well with water. It was then washed successively with hot alcohol, chloroform and acetone. The organic washings were evaporated and this gave a slightly yellow oil which solidified on the addition of alcohol. Water was added and the solid was collected by filtration, wt. 50 mg., m. p. 115–129°. This material gave a negative nitroprusside test for sulfur, was soluble in chloroform and became electrified on rubbing similar to cholanic acid. After three recrystallizations from dilute alcohol low melting cholanic acid was obtained, m. p. 157–159°.

(3) See Barton and Jones, *J. Chem. Soc.*, 391 (1942), for the higher melting form of (X).

(4) See Bougault, Cattelain and Chabrier, *Bull. soc. chim.*, [5] **5**, 1699 (1938), and Mozingo, *et al.*, THIS JOURNAL, **65**, 1013 (1943), for the preparation of similar modified Raney nickel catalysts.

Hydrogenolysis of (VI).—A mixture of 0.61 g. of VI, 9 g. of modified Raney nickel catalyst and 40 cc. of dioxane was refluxed for eleven hours. It was filtered and the recovered catalyst was washed thoroughly with ether. The filtrate was evaporated *in vacuo* and gave a slightly yellow viscous oil which on working with methanol solidified. The solid was collected by filtration and was washed with cold methanol, m. p. 76–78°, wt. 0.245 g. From the mother liquor 77 mg. more of material was isolated, m. p. 71–75°. The yield of crude methyl cholanate was 0.322 g. (69.7%). The main fraction of crystals was recrystallized from acetone–methanol, m. p. 78.5–79.5°. Two more recrystallizations did not improve the melting point and the material analyzed as follows:

Anal. Calcd. for $C_{25}H_{42}O_2$: C, 80.2; H, 11.3. Found: C, 80.3; 80.2; H, 11.5, 11.4.

The melting point in the literature for methyl cholanate is 86–87°.[5] The material was therefore hydrolyzed in the usual manner and gave pure cholanic acid, m. p. 162–162.5°.

Acknowledgment.—The microanalyses were carried out by Dr. J. A. Kuck of the Stamford Laboratories of the American Cyanamid Co., and by Mr. Philip Weiss of this laboratory.

Summary

1. The diethyl thioacetals of cholestanone-3, 3-ketocholanic acid and methyl 3-ketocholanate have been prepared.

2. The enol ethyl thioether of Δ^4-cholestenone-3 has been prepared. Hydrolysis of this compound with alcoholic hydrochloric acid gave back Δ^4-cholestenone-3.

3. Hydrogenolysis of cholestanone-3 thioacetal with a modified Raney nickel catalyst in dioxane gave cholestane.

4. Hydrogenolysis of methyl 3-ketocholanate thioacetal with a modified Raney nickel catalyst in dioxane gave a low-melting methyl cholanate from which on hydrolysis pure cholanic acid was obtained.

(5) Reichstein and Alther, *Helv. Chim. Acta*, **25**, 805 (1942).

PEARL RIVER, N. Y. RECEIVED SEPTEMBER 19, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Synthesis of Arylpropylamines. III. From Nuclear Nitration[1]

BY T. M. PATRICK, JR.,[2] E. T. MCBEE AND H. B. HASS

Many of the more important arylpropylamines which have shown sympathomimetic activity are distinguished by hydroxy, methoxy, or methylenedioxy substituents in nuclear positions. On the other hand, little has been published concerning the synthesis or physiological activity of the corresponding nitro and amino derivatives.

In addition to their potential use as pharmaceuticals *per se*, the nitrated phenylpropylamines can serve as intermediates for synthesis of other derivatives not readily prepared by other methods. Thus, Hoover[3] reported that 1-(*p*-aminophenyl)-2-propylamine can be selectively diazotized and hydrolyzed to 1-(*p*-hydroxyphenyl)-2-propylamine (known commercially as Paredrine). Other nuclear amino derivatives should likewise undergo selective diazotization and accordingly several different substituents could conceivably replace the amino group by known methods.

1-Nitro-3-phenylpropane, 2-chloro-1-(*p*-chloro-

(1) Based upon a thesis submitted by T. M. Patrick, Jr., to the Faculty of Purdue University in partial fulfillment of the requirements for the Degree of Doctor of Philosophy, April, 1943.

(2) Abbott Laboratories Fellow, 1941–1942. Present address: Monsanto Chemical Co., Dayton 7, Ohio.

(3) Hoover, Ph.D. Thesis, Purdue University, 1941.