Anal. Calcd. for C_5H_5OBrS: Br, 41.39; [R]D 39.53. Found:[20] Br, 42.03; [R]D 38.96.

This compound was then converted to 5-methoxy-2-thenoic acid (III) by stirring overnight 3.60 g. of the halide with 0.90 g. of magnesium and 1 ml. of ethyl bromide. The cloudy mixture was then poured onto a slurry of Dry Ice and ether and the reaction products worked up as usual. There was obtained 0.60 g. (20%) of white needles, m.p. 161–162° (dec.), which did not depress the melting point of authentic III. No other material could be isolated from the mother liquors.

Acylation of 2-Methoxythiophene. A. 5-Methoxy-2-acetothienone.—A solution of 2.0 g. of I in 5 ml. of dry carbon disulfide, cooled to −20°, was added in 3 portions over a 10-minute period to a solution of acetyl chloride (1.2 ml.) and stannic chloride (2.0 ml.) in carbon disulfide (15 ml.) maintained at −20°, and then kept at that temperature for 5 additional minutes. The purple, heterogeneous mixture was then poured on ice (10 g.) and hydrochloric acid (1.0 ml.). The solvent layer was rapidly decanted, washed with water and saturated aqueous sodium bicarbonate. It was dried over sodium carbonate and evaporated, leaving a yellow oil (1.73 g.). The oil was chromatographed over 35.0 g. of alumina. Mixtures of hexane and benzene (9:1 and 4:1) eluted 0.76 g. of material which distilled at 60° (0.001 mm.). The distillate (0.42 g.) crystallized in yellow needles which became colorless and melted at 34–35° after recrystallization from hexane; λ_{max}^{EtOH} 2560 and 3140 Å. (ϵ, respectively, 4,100 and 14,200).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 53.67; H, 5.31.

Its ***p*-nitrophenylhydrazone** crystallized from dilute alcohol in scarlet needles, m.p. 198–199°.

Anal. Calcd. for $C_{13}H_{13}ON_3S$: C, 53.59; H, 4.50. Found: C, 53.54; H, 4.81.

B. **2-Methoxy-3-acetothienone.**—The column of alumina was then washed with benzene–hexane (1:1) and benzene, which eluted 0.155 g. of crystalline material. Two crystallizations from hexane and a sublimation at 85° under high vacuum gave 35 mg. of colorless crystals, m.p. 127–128°; λ_{max}^{EtOH} 2420 and 3030 Å. (ϵ, respectively, 16,300 and 10,200).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 54.07; H, 5.27.

Nitration of 2-Methoxythiophene.—A solution of 0.3 ml. of nitric acid (*d*, 1.50) in 2.0 ml. of acetic anhydride, cooled to −20°, was added in the course of one hour to a solution of 0.5 ml. of I in 3.0 ml. of acetic anhydride, kept at −20°. The purple mixture was then poured onto 20 g. of ice mixed with 8 g. of 50% aqueous sodium hydroxide and extracted with 5 ml. of benzene. Fifty ml. of hexane was then added to the dried organic layer, which precipitated out a certain amount of tar. The solvent was decanted and evaporated. The partially crystalline residue was crystallized from hexane, then sublimed at 80° under high vacuum to give 0.150 g. of colorless needles, m.p. 99–101°. The melting point was not depressed[23] on admixture with authentic **2-methoxy-3-nitrothiophene.**

The mother liquors from the preceding crystallizations were evaporated to dryness and the residue (0.40 g.) distilled in high vacuum (bath temperature 75°). The distillate (0.32 g.) was then chromatographed on 10.2 g. of alumina. The hexane eluate gave, after concentration, recrystallization from the same solvent and sublimation at 55° under high vacuum, 0.25 g. of yellow needles, m.p. 61–63°, which were assumed to be **5-methoxy-2-nitrothiophene.**

Anal. Calcd. for $C_5H_5O_3NS$: C, 37.73; H, 3.17. Found: C, 37.81; H, 3.43.

The column of alumina was then washed with benzene, which eluted some material that was crystallized from hexane; m.p. and m.m.p. with previous material 99–101°, yield 20 mg.

An attempt to prepare 2,4-dinitro-5-methoxythiophene from the mononitro compound with mixed nitric–sulfuric (1:2) acids in chloroform, at −20°, resulted in a 25% recovery of the starting material and tars.

5-Methoxyvaleric Acid.—Methoxythenoic acid (III) (0.80 g.) and sodium bicarbonate (0.42 g.) in water (50 ml.) were shaken at room temperature with 18.0 g. of Raney nickel (Adkins W-7) for 5 hours, then heated at 75° for 30 minutes. The catalyst was separated from the cooled mixture by centrifugation and washed with 0.1 *N* sodium hydroxide. The collected solutions were then concentrated under reduced pressure to 10 ml. and extracted with ether. Evaporation of the dried ether solution left a sirupy residue (0.55 g., 82%). The ***p*-bromophenacyl ester** prepared from 0.25 g. of this material crystallized from dilute ethanol in glistening leaflets (0.23 g., 80%), m.p. 39–41°.

Anal. Calcd. for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.21; Br, 24.28. Found[20]: C, 51.15; H, 5.43; Br, 24.11.

This investigation was supported by grants from the American Cancer Society, as recommended by the Committee on Growth of the National Research Council, and the Jane Coffin Childs Memorial Fund for Medical Research.

(23) Determination kindly performed by Dr. K. L. Kreuz.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE SAMUEL C. HOOKER LABORATORY OF THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Studies in Organic Sulfur Compounds. V.[1] Synthesis of 21-Thiolacetates of Adrenal Cortical Hormones

BY CARL DJERASSI AND A. L. NUSSBAUM[2]

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In order to make available for biological experiments cortical hormone analogs in which the 21-hydroxyl function is replaced by sulfur, the 21-thiolacetate analogs of desoxycorticosterone, Reichstein's substance S and cortisone as well as those of a number of intermediates and model compounds were prepared. The methods of preparation involved either decomposition of the appropriate diazoketone with thioacetic acid or treatment of the steroidal 21-hydroxy-20-ketone with tosyl chloride followed by sodium iodide interchange and reaction with potassium thiolacetate. A characteristic infrared band near 8.8 μ appears to be due to the C–S stretching vibration in thiolacetates.

The biochemical role played by SH-containing substances has been realized for some time,[3] but recent work,[4] particularly with coenzyme A, has indicated that thiolesters also fulfill a very important function in biochemical processes. While the biochemical mechanism by which the steroidal cortical hormones act in the body is not yet understood, it appeared of interest to synthesize certain hormone analogs in which the hydroxyl group of the essential 20-keto-21-hydroxy function is replaced by sulfur and to determine the effect of this structural change upon biological activity. That variations at the C-21 position of the cortical hormones

(1) For earlier papers see: (a) *J. Org. Chem.*, **13**, 848 (1948); (b) THIS JOURNAL, **73**, 1528 (1951); (c) *ibid.*, **73**, 4961 (1951); (d) *J. Org. Chem.*, **17**, 1413 (1952).

(2) U. S. Public Health Service Predoctorate Fellow at Wayne University, 1952–1953.

(3) E. S. Guzman-Barron, *Adv. Enzym.*, **11**, 201 (1951).

(4) L. H. Noda, S. A. Kuby and H. A. Lardy, THIS JOURNAL, **75**, 913 (1953), give most of the leading references.

are not necessarily associated with loss of biological potency is demonstrated by the high biological activity of the C-21 aldehydo derivatives[5] of cortisone and Kendall's Compound F. The corresponding analog of desoxycorticosterone also has been synthesized,[6] because of its possible presence in the "amorphous fraction," and was found to be active.

Only a limited number of sulfur-containing steroids have been prepared with the aim of examining their biological importance. Aside from the thiazolidines, formed in the reaction[7,8] of saturated 3-ketosteroids with cysteine, for which a possible biochemical significance has been suggested,[8] the only other types appear to be the 21-tosylates of cortical hormones,[9] which presumably are hydrolyzed to the parent hormones, and steroids possessing a mercapto function at C-3[10] in place of the conventional hydroxyl group. Only the analogs of cholesterol,[10a,b,c] provitamin D,[10d,f,g] and dehydroepiandrosterone[10e] were prepared and no biological activity was noted.

The first compound to be investigated in the present work was allopregnane-3,20-dione-21-thiol 21-acetate (Ie) since this served as a model for the more important desoxycorticosterone analog IIId. In order to prepare a sample of proved structure, 3-ketoalloetianic acid (IIa) was converted by the Wilds–Shunk procedure[11] to the diazoketone IId which upon treatment with thioacetic acid yielded the desired 21-thiolacetate Ie. A similar reaction sequence with the Δ^4-unsaturated acid[11] produced the corresponding analog (IIId) of desoxycorticosterone (IIIa). The diazoketone synthesis was employed originally by Reichstein[9,12] for the preparation of various esters of desoxycorticosterone (IIIa) but it is not applicable to the 17α-hydroxy derivatives such as Reichstein's Substance S (VIIa) and cortisone (VIIIa). As a result, it appeared important to develop an alternate procedure for the above described thiolacetates Ie and IIId which could also be employed for cortisone.

The most desirable approach seemed to be that of Chapman and Owen[13] who showed that thiolacetates could be prepared readily by an exchange reaction between potassium thiolacetate and the appropriate tosylate. As applied to the specific cases at hand, such a method has the advantage that the preparation of the sulfur analog requires as the starting material the corresponding hydroxyl-ated parent hormone which is readily available. The preparation of the pure 21-tosylates of cortical hormones is best accomplished by decomposition of the appropriate diazoketone with *p*-toluenesulfonic acid,[9] since the conventional *p*-toluenesulfonyl chloride–pyridine procedure[14] leads to a mixture consisting chiefly of chloride (Ic, IIIb, VIIb, VIIIb) and also tosylate (Id, IIIc, VIIc, VIIIc), accompanied by some pyridinium salt. A model experiment with 21-iodo-Δ^5-pregnen-3β-ol-20-one acetate (IVa)[15] and potassium thiolacetate demonstrated that the 20-keto-21-thiolacetoxy moiety (IVb) could be elaborated very readily by this procedure and it appeared, therefore, that the crude ether-soluble product (the pyridinium salt being insoluble) from the reaction of the appropriate cortical hormone with *p*-toluenesulfonyl chloride could be used directly since upon treatment with sodium iodide in acetone solution this should be converted to the corresponding iodide.[14] This indeed proved to be the case and the 21-thiolacetates in the desoxycorticosterone (Ie, IIId), Reichstein's Substance S (VIId) and cortisone (VIIId) series were prepared in this fashion. In the case of Δ^4-pregnene-3,20-dione-17α-ol-21-thiol 21-acetate (VIId) an alternate procedure was also studied which involved an adaptation of Gallagher's[16] Substance S synthesis for our purpose. Thus, 21-bromopregnane-3,20-dione-17α-ol (Vc)[16] was successively treated with sodium iodide and potassium thiolacetate in acetone solution and the resulting thiolacetate Vd was brominated at C-4 (VI) and dehydrobrominated with semicarbazide, followed by *in situ* cleavage of the semicarbazone with *p*-hydroxybenzaldehyde.[17] The resulting product VIId was identical in all respects with a sample prepared *via* the chloride–tosylate mixture from Reichstein's Substance S (VIIa).

The spectroscopic data for our steroidal thiolacetates are in excellent agreement with those reported recently[4] for simple thiolacetates. Thus the saturated allopregnane-3,20-dione-21-thiolacetate (Ie) exhibited an ultraviolet absorption maximum at 230.5 mμ (log ϵ 3.54) which coincides with that observed for simple thiol esters.[4,18] As a result, the extinction coefficients of the ultraviolet maxima of the various Δ^4-3-keto thiolacetates (IIId, VIId, VIIId) are appreciably higher (log ϵ *ca.* 4.35) than those observed for their corresponding oxygen counterparts. In contrast to the characteristic infrared band of acetates at 8.0 μ[19] due to the C–O stretching vibration, the presently described thiolacetates exhibit a very characteristic band near 8.8 μ, which appears to be associated with the stretching vibration of the C–S linkage and which has also been observed recently[4] in simple thiolacetates.

Biological tests of the presently described cortical hormone thiolacetates are now under investigation and the results will be reported elsewhere.

(5) E. F. Rogers, W. J. Leanza, J. P. Conbere and K. Pfister, THIS JOURNAL, **74**, 2947 (1952).

(6) T. Reichstein and H. Reich, *Helv. Chim. Acta*, **22**, 1124 (1939).

(7) S. Lieberman, *Experientia*, **2**, 411 (1946).

(8) S. Lieberman, P. Brazeau and L. B. Hariton, THIS JOURNAL, **70**, 3094 (1948).

(9) T. Reichstein and W. Schindler, *Helv. Chim. Acta*, **23**, 669 (1940).

(10) *Inter al.*: (a) T. Wagner-Jauregg and T. Lennartz, *Ber.*, **74**, 27 (1941); (b) L. C. King, R. M. Dodson and L. A. Subluskey, THIS JOURNAL, **70**, 1176 (1948); (c) J. Strating and H. J. Backer, *Rec. trav. chim.*, **69**, 638 (1950); (d) J. Strating and H. J. Backer, *ibid.*, **69**, 909 (1950); (e) S. Bernstein and K. Sax, *J. Org. Chem.*, **16**, 679 (1951); (f) S. Bernstein and K. Sax, *ibid.*, **16**, 685 (1951); (g) J. A. K. Buisman and P. Westerhof, *Rec. trav. chim.*, **71**, 925 (1952).

(11) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948).

(12) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).

(13) H. J. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950).

(14) T. Reichstein and H. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

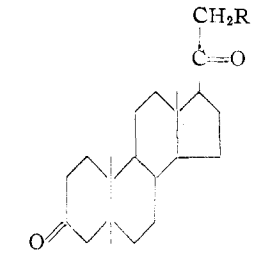
(15) C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953).

(16) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 189 (1951).

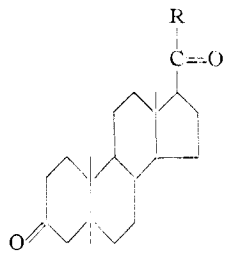
(17) V. R. Mattox, E. L. Woroch, G. A. Fleischer and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

(18) B. Sjöberg, *Z. physik. Chem.*, **52B**, 209 (1942)

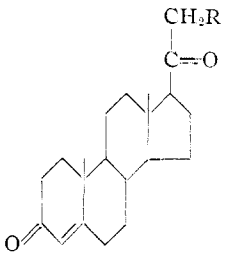
(19) R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, THIS JOURNAL, **70**, 2024 (1948).



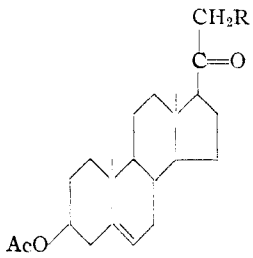
Ia, R = OAc
b, R = OH
c, R = Cl
d, R = $OSO_2C_6H_4CH_3$-*p*
e, R = $SCOCH_3$



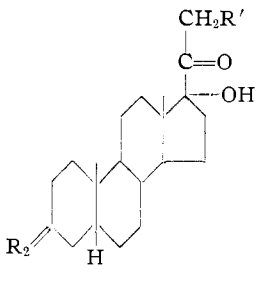
IIa, R = OH
b, R = ONa
c, R = Cl
d, R = CHN_2



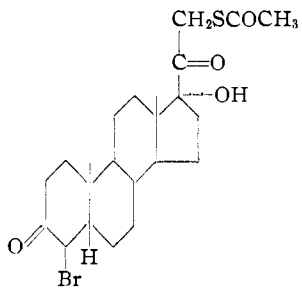
IIIa, R = OH
b, R = Cl
c, R = $OSO_2C_6H_4CH_3$-*p*
d, R = $SCOCH_3$



IVa, R = I
b, R = $SCOCH_3$



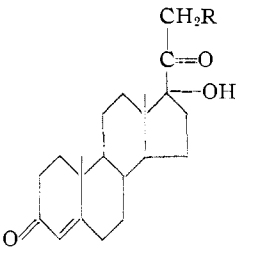
Va, R_2 = ; R′ = Br



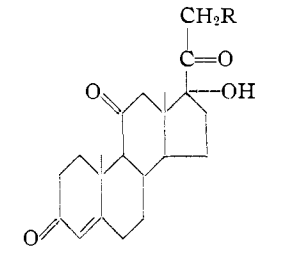
VI

b, R_2 = ; R′ = $SCOCH_3$

c, R_2 = O; R′ = Br
d, R_2 = O; R′ = $SCOCH_3$



VIIa, R = OH
b, R = Cl
c, R = $OSO_2C_6H_4CH_3$-*p*
d, R = $SCOCH_3$



VIIIa, R = OH
b, R = Cl
c, R = $OSO_2C_6H_4CH_3$-*p*
d, R = $SCOCH_3$

Acknowledgment.—We are indebted to the U. S. Public Health Service for support in the form of a predoctorate fellowship and to Syntex, S.A., Mexico City, D.F., for a generous gift of various steroid hormones and intermediates.

Experimental[20]

Allopregnane-3,20-dione-21-ol Acetate (Ia).—Since the Wilds–Shunk method[11] has not yet been described for the conversion of 3-ketoalloetianic acid (IIa) to the ketol acetate Ia, it was first carried out as a model for the thiolacetate synthesis described below.

A solution of 0.63 g. of 3-ketoalloetianic acid (IIa)[21] in 20 cc. of ethanol containing 0.08 g. of sodium hydroxide was evaporated to dryness and dried at 100° and 0.1 mm. for 18 hours. The sodium salt IIb was powdered under 15 cc. of dry benzene, cooled in ice, treated with 3 drops of pyridine and 2.5 cc. of oxalyl chloride and left at 15° for 10 minutes. The colorless solution was evaporated to dryness at 15° *in vacuo*, benzene was added and again evaporated. After repeating this process once, the residue containing the acid chloride IIc was mixed with benzene, filtered and the filtrate was added to an ethereal solution of diazomethane prepared from 6 g. of nitrosomethylurea and allowed to stand at 0° for 1 hour. Evaporation to dryness afforded the yellowish, crystalline diazoketone IId (m.p. 164–166° with gas evolution) which was added in portions to hot acetic acid as described by Wilds and Shunk[11] for the preparation of desoxycorticosterone. Evaporation to dryness under reduced pressure and crystallization from acetone afforded 0.35 g. of colorless needles of the desired acetate Ia with m.p. 194–195°, $[\alpha]^{20}D$ +119°; reported[22] m.p. 197–199°, $[\alpha]D$ +115°.

Allopregnane-3,20-dione-21-thiol Acetate (Ie). (a) From 21-Diazoallopregnane-3,20-dione.—3-Ketoalloetianic acid (1.55 g.) was converted into the diazoketone IId as described above and then refluxed with 25 cc. of thioacetic acid for 30 minutes. Evaporation of the solution to dryness *in vacuo* and recrystallization of the solid residue (m.p. 165–175°) from methylene chloride–hexane afforded 0.68 g. of the thiolacetate Id with m.p. 184–186°, undepressed upon admixture with a specimen prepared according to (b). The infrared absorption spectra were identical.

(b) From Allopregnane-3,20-dione-21-ol (Ib).—Allopregnane-3,20-dione-21-ol acetate (Ia) (1.0 g.) was hydrolyzed in chloroform solution with methanolic hydrochloric acid at room temperature for 48 hours exactly as described for cortisone acetate.[23] Recrystallization from acetone–hexane yielded 0.6–0.7 g. of the **free alcohol Ib** with m.p. 154–156° which was used below. Further recrystallization produced the analytical sample with m.p. 157–159°, $[\alpha]^{20}D$ +100°, $\lambda_{max}^{CHCl_3}$ 2.87 and 5.86 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.81; H, 9.92.

The above alcohol Ib (1.5 g.), dissolved in 8.5 cc. of a 10% solution of pyridine in chloroform, was treated at 0° in portions with 1.8 g. of *p*-toluenesulfonyl chloride and kept at room temperature for 14 hours. The mixture was worked up as described for the analogous reaction with desoxycorticosterone[14] and the crude product, which still contained some tosyl chloride, was chromatographed on 100 g. of ethyl acetate-washed alumina. The combined pentane–benzene and benzene eluates were evaporated and recrystallized from hexane–acetone furnishing 0.80–0.83 g. of the **21-chloro-20-ketone Ic** with m.p. 180–184° which was used in the next step. The analytical sample was obtained from the same solvent pair; m.p. 185–188°, $[\alpha]^{20}D$ +179°, $\lambda_{max}^{CHCl_3}$ 5.80 (inflection) and 5.86 μ.

Anal. Calcd. for $C_{21}H_{31}O_2Cl$: C, 71.87; H, 8.90. Found: C, 72.10; H, 8.83.

A mixture of 206 mg. of the chloroketone Ic, 150 mg. of sodium iodide and 20 cc. of acetone was refluxed for 1 hour in an atmosphere of nitrogen and then filtered directly into

(20) All melting points are uncorrected and were determined on the Fisher–Johns block. Rotations (10 mg. in 2 cc., 1 dcm. tube) were measured in chloroform and ultraviolet absorption spectra in ethanol solution. The infrared absorption spectra were obtained with a Baird Associates double beam recording infrared spectrophotometer. We are indebted to Messrs. R. Mullins and M. Papo (Wayne University) and Mr. Joseph F. Alicino (Metuchen, New Jersey) for the microanalyses.

(21) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1040 (1937).

(22) A. Wettstein and F. Hunziker, *ibid.*, **23**, 764 (1940).

(23) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1952).

a suspension of 162 mg. of potassium thiolacetate (freshly washed with acetone) in 20 cc. of acetone. After refluxing for an additional 2 hours in a nitrogen atmosphere, the solution was concentrated, diluted with water and the precipitate was collected. Recrystallization from acetone–hexane yielded 0.18 g. of the pure **thiolacetate Ie** with m.p. 186–188°, $[\alpha]^{20}D$ +142°, λ_{max}^{EtOH} 230.5 mμ, log ε 3.54, $\lambda_{max}^{CHCl_3}$ 5.86 and 8.81 μ; the 5.72 μ band found in the acetate Ia was not present.

Anal. Calcd. for $C_{23}H_{34}O_3S$: C, 70.73; H, 8.77. Found: C, 71.04; H, 8.76.

Δ⁴-Pregnene-3,20-dione-21-thiol Acetate (IIId).—Desoxycorticosterone (IIIa) (3.0 g.) was treated with tosyl chloride exactly as described by Reichstein and Fuchs[14] including purification by chromatography. The resulting mixture (1.1 g., m.p. 184–193°) of chloroketone IIIb and tosylate IIIc was used directly in the next step (reported:[14] chloroketone m.p. 206°, tosylate m.p. 168°). The above mixture (200 mg.) was treated in acetone solution with potassium thiolacetate exactly as described above for the dihydro analog Ie; recrystallization from methylene chloride–hexane led to 170 mg. of thiolacetate with m.p. 163.5–165°, $[\alpha]^{20}D$ +193°, λ_{max}^{EtOH} 239 mμ, log ε 4.35, $\lambda_{max}^{CHCl_3}$ 5.85 (ill-resolved shoulder), 5.91, 6.01, 6.18 (double bond) and 8.80 μ. Desoxycorticosterone acetate shows well-resolved bands at 5.73 (acetate) and 5.82 μ (20-ketone) indicating that the carbonyl peak of the thiolacetate moiety appears at a slightly higher wave length than that of the acetate.

Anal. Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found: C, 70.80; H, 8.61; S, 8.27.

Diazoprogesterone was prepared from 0.9 g. of Δ⁴-3-ketoetienic acid according to the procedure of Wilds and Shunk[11] and decomposed with thioacetic acid. The thiolacetate IIId was obtained in 19% over-all yield, m.p. 161–163°, undepressed when mixed with the above sample and further identified by its infrared absorption spectrum. No attempts were made to improve the yield in this instance.

Δ⁵-Pregnen-3β-ol-20-one-21-thiol Diacetate (IVb).—A mixture of 0.21 g. of 21-iodo-Δ⁵-pregnen-3β-ol-20-one acetate (IVa),[15] 125 mg. of potassium thiolacetate and 40 cc. of acetone was refluxed for 2 hours in a nitrogen atmosphere. The usual work-up produced 160 mg. of thiolacetate with m.p. 124–128° which upon further recrystallization from acetone–hexane led to the analytical sample with m.p. 128.5–130°; $[\alpha]^{20}D$ +63°, $\lambda_{max}^{CHCl_3}$ 5.82, 5.91, 8.00 (acetate) and 8.82 μ (thiolacetate).

Anal. Calcd. for $C_{25}H_{36}O_4S$: C, 69.42; H, 8.39; S, 7.41. Found: C, 69.66; H, 8.08; S, 7.52.

Pregnane-3α,17α-diol-20-one-21-thiol 21-Acetate (Vb).—21-Bromopregnane-3α,17α-diol-20-one (Va)[16] (1.20 g., m.p. 200–204°) dissolved in 120 cc. of acetone, was refluxed with 0.9 g. of sodium iodide for 1 hour in an atmosphere of nitrogen and then filtered directly into a suspension of 0.68 g. of potassium thiolacetate in 120 cc. of acetone. After refluxing for an additional 2 hours, the reaction mixture was worked up as in the preceding examples and there was isolated 1.1 g. of colorless crystals with m.p. 187–193°. The analytical sample (70% over-all yield) was obtained from ethyl acetate–hexane with m.p. 194–195°, $[\alpha]^{20}D$ +89°, $\lambda_{max}^{CHCl_3}$ 2.75 (plateau to 2.89 μ), 5.84 (shoulder), 5.91 and 8.83 μ.

Anal. Calcd. for $C_{23}H_{36}O_4S$: C, 67.61; H, 8.88; S, 7.85. Found: C, 68.05; H, 8.99; S, 7.34.

Pregnane-3,20-dione-17α-ol-21-thiol 21-Acetate (Vd).—The reaction of potassium thiolacetate with 21-bromopregnane-3,20-dione-17α-ol (Vc) was carried out exactly as described in the preceding example and yielded 72% of the thiolacetate Vd with m.p. 166–168°, $[\alpha]^{20}D$ +74°, $\lambda_{max}^{CHCl_3}$ 2.87, 5.86 and 8.82 μ.

Anal. Calcd. for $C_{23}H_{34}O_4S$: C, 67.94; H, 8.43. Found: C, 68.08; H, 8.65.

Δ⁴-Pregnene-3,20-dione-17α-ol-21-thiol Acetate (VIId).

(a) From Pregnane-3,20-dione-17α-ol-21-thiol Acetate (Vd).—The above dione Vd (0.3 g.) in 10 cc. of glacial acetic acid was treated in one portion with 0.5 cc. of a solution of 1.4 g. of bromine in 50 cc. of acetic acid. After decolorization, an additional 4.49 cc. of this bromine solution containing 66 mg. of anhydrous sodium acetate was added dropwise over a period of 30 minutes and the colorless solution was diluted with ice-water. The precipitated 4-bromo-3,20-dione VI was collected, washed well with water and dried in a vacuum desiccator: yield 0.36 g., m.p. 173–175°. Washing with ether raised the m.p. to 177–179° (dec.) but this was not necessary for the next step.

The bromoketone VI (0.25 g.) in 26 cc. of glacial acetic acid was mixed with a solution of 0.19 g. of semicarbazide hydrochloride and 0.14 g. of anhydrous sodium acetate in 28 cc. of 96% acetic acid and left at room temperature in an atmosphere of nitrogen. After 4 hours, a solution of 0.063 g. of semicarbazide hydrochloride and 0.046 g. of anhydrous sodium acetate in 11 cc. of 96% acetic acid was added and this was followed after 2 hours by a suspension of 1.34 g. of *p*-hydroxybenzaldehyde and 0.046 g. of sodium acetate in 17 cc. of water. The reaction mixture was diluted with chloroform after having stood at room temperature for 15 hours and was washed with sodium carbonate solution, water, bisulfite solution, water, dried and evaporated. Trituration of the residue with ether followed by recrystallization from ethyl acetate furnished 0.1 g. with m.p. 210–215°, raised on further recrystallization to 222–223°, $[\alpha]^{20}D$ +195°, λ_{max}^{EtOH} 239 mμ, log ε 4.35, $\lambda_{max}^{CHCl_3}$ 2.87, 5.80 (shoulder), 5,84, 5.93 (shoulder), 6.01 and 8.84 μ.

Anal. Calcd. for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.93. Found: C, 68.55; H, 8.17; S, 7.77.

(b) From Reichstein's Substance S (VIIa).—One gram of Reichstein's Substance S (VIIa) was treated with 7.8 cc. of a 10% solution of pyridine in chloroform and 1.23 g. of tosyl chloride exactly as described for Ib except that chromatography was carried out on silica gel; yield 0.4–0.46 g., m.p. 160–162°, which appears to be chiefly the chloroketone VIIb (Beilstein test strongly positive). This material, dissolved in acetone solution, was treated successively with sodium iodide and potassium thiolacetate exactly as described for Vb and afforded 68–72% of colorless crystals with m.p. 213–216°. Further recrystallization raised the m.p. to 219–221° and identity with a sample prepared according to (a) was established by a mixture melting point and comparison of the infrared spectra.

Δ⁴-Pregnene-3,11,20-trione-17α-ol-21-thiol-21 Acetate (VIIId).—A suspension of 277 mg. of cortisone (VIIIa) in 2.3 cc. of a 10% solution of pyridine in chloroform was mixed with 350 mg. of tosyl chloride at 0° and then left at room temperature for 5 hours. At this point 1.5 cc. of dioxane was added to dissolve any remaining steroid and after an additional 12 hours at room temperature, the mixture was extracted with chloroform, washed until neutral, dried, concentrated to a small volume and diluted with ether; yield 180 mg. of a solid with an indefinite melting point (210–280°), probably containing some pyridinium salt in addition to chloroketone (VIIIb) and tosylate (VIIIc). This material was treated in the standard manner with sodium iodide and potassium thiolacetate and the residue from the reaction on trituration with ether yielded 160 mg. of crude thiolacetate with m.p. 196–203°. Two recrystallizations from chloroform–methanol afforded 90 mg. of the analytical sample with m.p. 219–220°, $[\alpha]^{20}D$ +218°, λ_{max}^{EtOH} 236 mμ, log ε 4.39, $\lambda_{max}^{CHCl_3}$ 2.88–2.95, 5.86, 6.01 and 8.85 μ.

Anal. Calcd. for $C_{23}H_{30}O_5S$: C, 65.99; H, 7.23; S, 7.66. Found: C, 65.92; H, 7.14; S, 7.49.

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