These findings appear to be supported by the study of methylene derivative as intermediates in polar reactions, in which it was found that in buffered solutions the hydrolysis of chloroform is independent of pH.[11]

Experimental

Materials.—The chloroform used in this experiment was purified by successive washings with concentrated sulfuric acid and distilled water and then dried over calcium chloride overnight.[12] The drying agent was removed by filtration and the filtrate distilled through a 30-cm. column, 2 mm. in diameter, packed with glass helices, b.p. 61.0–61.5°, n^{25} 1.4457.

Piperidine was purified by allowing it to stand over potassium hydroxide pellets for 1 week. The pellets were removed by filtration and the filtrate distilled through a 30-cm. column, 2 mm. in diameter, packed with glass helices, b.p. 106°, n^{25} 1.4514.

Commercial anhydrous ether was dried more completely by allowing it to stand over calcium hydride for one week.

Reaction of Piperidine and Chloroform.—Chloroform (11.9 g., 0.1 mole) was added to piperidine (8.5 g., 0.1 mole). The reaction was exothermic. Piperidine hydrochloride was isolated by the addition of anhydrous ether to the reaction mixture after 24 hr., yield 1%. Piperidine hydrochloride was identified by its melting point, 244°, and infrared spectrum. The presence of *N*-formylpiperidine was verified by gas-liquid chromatography using a 3-ft. column of 25% carbowax 20-M on chromosorb 30–60 regular mesh packing, or a 6-ft. column of 25% silicone grease on chromosorb 30–60 regular mesh packing on fluoropak, all at 200° and 145 ml. of helium per min. *N*-Formylpiperidine cannot be obtained by distillation when present in small quantities because of its polar nature and its tendency to decompose when distilled under atmospheric pressure. It may be isolated as its mercuric chloride derivative. This derivative is easily prepared by adding small amounts of solutions believed to contain *N*-formylpiperidine to an aqueous solution of mercuric chloride (5 g. of mercuric chloride in 100 ml. of water). A solid forms immediately, m.p. 145°. The identity of this solid was established by comparing its infrared spectrum to that of an authentic sample of the mercuric chloride derivative of *N*-formylpiperidine. A mixture of the two compounds showed no depression in melting point. The authentic sample of the mercury derivative was prepared according to the directions of Farlow and Adkins[13] from *N*-formylpiperidine which had been obtained from the reaction of chloral and piperidine.[14]

Reaction of Piperidine and Chloroform in the Absence of Air and Light.—In a darkroom, nitrogen was bubbled through chloroform (11.9 g., 0.1 mole) and piperidine (8.5 g., 0.1 mole). Chloroform was added to piperidine and the reaction was exothermic. The mixture was allowed to stand in a pressure bottle, under nitrogen, in the darkroom overnight. To a 10-ml. aliquot of this reaction mixture, 200 ml. of *n*-hexane was added, still in the darkroom. A white solid precipitated, m.p. 242°, yield 1%. The infrared spectrum of this compound agreed with an authentic sample of piperidine hydrochloride. The rest of the reaction mixture was analyzed by gas-liquid chromatography using a 3-ft. column containing 25% carbowax 20-M on chromosorb 30–60 regular mesh packing, at 200° and 145 ml. of helium per minute. Three peaks were obtained. They were attributed to chloroform, piperidine, and *N*-dichloromethylpiperidine, respectively. The last peak had a retention time of 0.78 min. under the above conditions. This peak disappeared upon subsequent hydrolysis of the reaction mixture and a new peak corresponding to *N*-formylpiperidine was observed. The presence of *N*-formylpiperidine was verified by addition of an authentic sample of *N*-formylpiperidine in various amounts to the hydrolyzed reaction mixture.

Reaction of Piperidine and Chloroform in the Presence of Hydroquinone.—Chloroform (11.9 g., 0.1 mole) was added to a piperidine solution (8.5 g., 0.1 mole) containing hydroquinone (1.1 g., 0.01 mole). The reaction was exothermic and the solution turned red within 0.5 hr. The reaction mixture was allowed to stand in a pressure bottle overnight, without attempting to exclude light. The solid which formed was removed by filtration. *n*-Hexane (400 ml.) was added to a 10-ml. aliquot of the reaction mixture and the solid which formed was collected by filtration. The solids were combined and washed with chloroform. The chloroform solution was treated with 400 ml. of *n*-hexane. A solid precipitated and was removed by filtration. This solid was recrystallized from absolute ethanol and anhydrous ether, m.p. 242°, yield 3%.

The remaining reaction mixture was analyzed by gas-liquid chromatography using a 3-ft column of 25% carbowax 20-M on chromosorb 30–60 regular mesh, at 200° and 145 ml. of helium per min. Three peaks were observed which were attributed to chloroform, piperidine, and *N*-dichloromethylpiperidine, the last peak having a retention time of 0.78 min. under the above conditions. After subsequent hydrolysis, the peak occurring at 0.78 min. disappeared and the peak corresponding to *N*-formylpiperidine, having a retention time of 7.38 min., was observed. The proof of the presence of *N*-formylpiperidine was carried out in the same manner as described in the previous experiment.

(11) J. Hine and P. B. Langford, *J. Am. Chem. Soc.*, **80**, 6010 (1958).

(12) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, 1957, p. 283.

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(14) F. F. Blicke and C. J. Lu, *ibid.*, **74**, 3933 (1952).

The Synthesis of Certain 7α- and 21-Methylsulfinyl and Methylsulfonyl Steroid Derivatives

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Our interest in the synthesis of steroid hormone analogs and the availability in our laboratory of a number of steroids substituted at C-7[1] or at C-21[2] with a methylthio group prompted us to investigate the preparation of the corresponding sulfoxide and sulfone derivatives. Several attempts to effect the oxidation of 7α-methylthiocortisone acetate with hydrogen peroxide were unsuccessful and crystalline material could not be isolated.[3] However, treatment of this compound with 1.1 molar equivalents of monoperphthalic acid (MPA) smoothly afforded a 65% yield of the desired sulfoxide. The 7α-methylsulfinyl derivatives of testosterone ace-

(1) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 3915 (1961).

(2) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 1223 (1961).

(3) These experiments utilized a modification of the procedure reported by Ralls, Dodson, and Riegel [*J. Am. Chem. Soc.*, **71**, 3320 (1949)] for the oxidation of 3β-ethylthio-5-cholestenone to the corresponding sulfone.

TABLE I

SULFOXIDES

Compound	Yield, %	M.P. (dec.)	$[\alpha]^{\circ}D$	Concn., Solvent	$\lambda_{max}^{CH_3OH}$, mμ	ε	λ_{max}^{KBr}, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
7α-Methylsulfinyltestosterone acetate[a]														
17β-Acetoxy-7α-methylsulfinyl-androstan-3-one	66	205-207	−80.6	1% in $CHCl_3$	...	....	5.78, 5.83, 8.00, 9.60	$C_{22}H_{34}O_4S$	66.96	66.61	8.69	8.93	8.12	8.01
7α-Methylsulfinylcortisone acetate	65	195	+128	0.2% in dioxane	235	13,100	2.94, 5.69, 5.76, 5.83, 5.95, 6.03, 6.14, 8.10, 9.60	$C_{24}H_{32}O_7S$	62.04	61.44	6.95	7.01	6.90	6.83
7α-Methylsulfinylprogesterone	57	179-180	+76.3	0.5% in $CHCl_3$	242	12,200	5.84, 5.97, 6.17, 9.67	$C_{22}H_{32}O_3S \cdot {}^1/_2H_2O$	68.54	68.89	8.63	8.65	8.32	8.02
21-Methylsulfinylprogesterone	67	130-132	+224	0.4% in $CHCl_3$	239	17,500	5.85, 5.96, 6.16, 9.51	$C_{22}H_{32}O_3S$	70.18	69.98	8.57	8.65	8.52	8.66
21-Methylsulfinyl-21-deoxyhydrocortisone	56	164	+204	0.5% in $CHCl_3$	241	16,300	2.89, 5.83, 5.98, 6.14, 9.72	$C_{22}H_{32}O_5S \cdot {}^1/_4H_2O$	63.98	63.81	7.93	8.21	7.76	7.58
21-Methylsulfinyl-21-deoxy-9α-fluorohydrocortisone	53	212	+126	0.4% in dioxane	238	19,600	3.00, 5.85, 5.97, 6.14, 9.60	$C_{22}H_{31}FO_5S$[b]	61.95	62.20	7.33	7.33	7.52	7.56

[a] See Experimental. [b] %F: Calcd. 4.45; found 4.49.

TABLE II

SULFONES

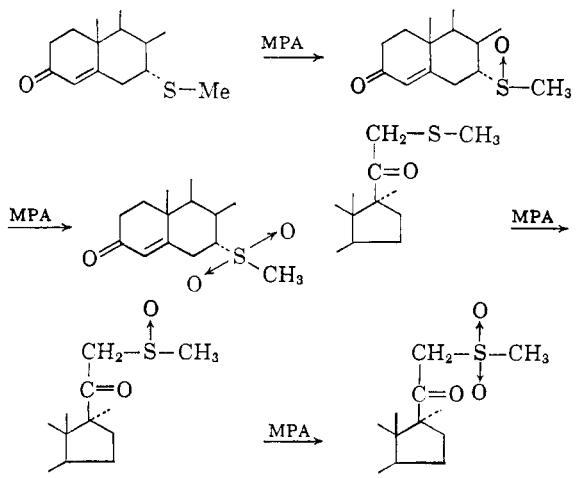
Compound	Yield, %	M.P. (dec.)	$[\alpha]^{\circ}D$	Concn., Solvent	$\lambda_{max}^{CH_3OH}$, mμ	ε	λ_{max}^{KBr}, μ	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
7α-Methylsulfonyltestosterone acetate	65	167-168	+19.7	1.1% in $CHCl_3$	241	15,100	5.77, 6.00, 6.16, 7.33, 8.05, 8.88, 13.00	$C_{22}H_{32}O_5S$	64.68	64.27	7.90	8.25	7.85	8.05
17β-Acetoxy-7α-methylsulfonyl-androstan-3-one	92	265-267	−41.5	0.9% in $CHCl_3$	...	....	5.75, 5.84, 7.73, 8.04, 8.90, 13.04	$C_{22}H_{34}O_5S$	64.35	63.90	8.35	8.58	7.81	7.72
7α-Methylsulfonylcortisone acetate	60	184	+103	0.6% in pyridine	236	18,500	2.86, 5.70, 5.77, 5.86, 5.94, 6.14, 7.68, 7.93, 8.10, 8.87, 13.00	$C_{24}H_{32}O_8S$	59.98	60.31	6.71	6.86	6.67	6.83
21-Methylsulfonylprogesterone	85	197-199	+221	0.9% in $CHCl_3$	242	16,800	5.85, 6.00, 6.15, 7.62, 8.64	$C_{22}H_{32}O_4S$	67.32	67.12	8.22	8.61	8.17	8.61
21-Methylsulfonyl-21-deoxyhydrocortisone	50	196-198	+157	0.9% in CH_3OH	241	15,300	2.81, 5.78, 6.00, 6.15, 7.65, 8.85	$C_{22}H_{32}O_6S$	62.25	62.59	7.60	7.88	7.55	7.85
21-Methylsulfonyl-21-deoxy-9α-fluorohydrocortisone	71	253	+165	0.5% in dioxane	238	19,000	2.84, 2.92, 5.78, 6.01, 6.15, 7.63, 8.78	$C_{22}H_{31}FO_6S$[a]	59.71	59.78	7.06	7.30	7.24	7.33

[a] %F: Calcd. 4.29; found 4.34.

tate and progesterone were then also prepared by this procedure. Such oxidations were equally applicable in the 21-methylthio series, and the 21-methylsulfinyl derivatives of progesterone, 21-deoxyhydrocortisone and 21-deoxy-9α-fluorohydrocortisone were obtained. The various sulfoxide derivatives are listed in Table I.

Subsequent to the preparation of 7α-methylsulfinyltestosterone acetate, Holmlund and coworkers[4] isolated from a microbiological oxidation of 7α-methylthiotestosterone acetate a product which on acetylation appeared to give the sulfur epimer of the synthetic sulfoxide (epimer A), since further oxidation by monoperphthalic acid of both compounds gave 7α-methylsulfonyltestosterone acetate. In view of this observation we reinvestigated the mother liquor from the synthetic preparation, and indeed were able to isolate a second product (epimer B) which proved to be identical with that obtained by microbiological oxidation. However, in general, we can offer no information concerning the *S*-epimeric purity of the other methylsulfinyl derivatives reported in this paper.

Oxidation of the sulfoxides with 1.1 molar equivalents of monoperphthalic acid then gave the corresponding sulfones in good yield. Again, these oxidations proceeded smoothly and the crystalline products were easily isolated from the reaction mixture. Thus the 7α-methylsulfonyl derivatives of testosterone acetate and cortisone acetate, and the 21-methylsulfonyl derivatives of progesterone, 21-deoxyhydrocortisone and 21-deoxy-9α-fluorohydrocortisone were obtained (Table II).



The α-configuration for the parent 7-methylthio derivatives was assigned on the basis of molecular rotation differences.[1] By the same criterion the α-configuration can be assigned to the various 7-methylsulfinyl and 7-methylsulfonyl derivatives of this investigation (see Table III).

(4) C. E. Holmlund, K. J. Sax, B. E. Nielsen, R. E. Hartman, R. H. Evans, Jr., and R. H. Blank, *J. Org. Chem.*, **27**, 1468 (1962).

TABLE III

CHANGES IN MOLAR ROTATION VALUES RESULTING FROM INTRODUCTION OF 7-METHYLSULFINYL AND 7-METHYLSULFONYL GROUPS

Parent Compound	7-Substituent	MD	ΔMD
Testosterone acetate		+307	
	CH_3SO Epimer A	−138	−445
	Epimer B	+ 44	−263
	CH_3SO_2	+ 80	−227
17β-Acetoxyandrostan-3-one		+ 86	
	CH_3SO	−320	−406
	CH_3SO_2	−170	−256
Cortisone acetate		+745	
	CH_3SO	+594	−151
	CH_3SO_2	+495	−250
Progesterone		+603	
	CH_3SO	+287	−316

Finally, it was of some interest to attempt the base-catalyzed epimerization of the 7α-methylsulfonyl derivatives. However, this did not prove possible since the overriding reaction of a 7α-methylsulfonyl-Δ^4-3-ketone with base is apparently an elimination reaction. Thus, even relatively mild base treatment (0.1% methanolic potassium hydroxide at room temperature) of 7α-methylsulfonyltestosterone acetate gave an 89% yield of 6-dehydrotestosterone acetate. In order to circumvent the elimination reaction, 17β-acetoxy-7α-methylsulfonylandrostan-3-one prepared by the above-described procedures from 17β-acetoxy-7α-methylthioandrostan-3-one,[1] was submitted to the epimerization experiments. However, this compound proved resistant to several attempts at base-catalyzed epimerization—the most vigorous of which was treatment for three hours at reflux temperature with 0.1% methanolic potassium hydroxide. In this last experiment the only isolatable product was starting material (after reacetylation) in about 50% yield.

Experimental[5]

General Procedure for the Preparation of Steroidal C-7 and C-21 Methyl Sulfoxides.—The steroidal C-7[1] or C-21[2] methylthio compound was dissolved or suspended in 75 ml. of methylene chloride per 0.01 mole of steroid and 1.1 mole equivalents of ethereal monoperphthalic acid was then added. The reaction mixture, protected from moisture, was allowed to stand at room temperature for 24 hr., during which period phthalic acid separated. The solution showed a negative test with 20% aqueous potassium iodide solution. The phthalic acid was collected by filtration. The filtrate was washed with dilute sodium carbonate solution, water, dried with anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The residue was recrystallized from acetone or petroleum ether (b.p. 60–70°)–acetone and collected by filtration. For analysis, the product was recrystallized from acetone or acetone–petroleum ether. The results obtained by this general procedure are shown in Table I.

(5) All melting points were determined in an open capillary tube and are uncorrected. The ultraviolet spectra were obtained on a Cary recording spectrophotometer and the infrared spectra were determined with a Perkin-Elmer spectrophotometer (Model 21). Optical rotations were measured in a 1-dm. semi-micro tube.

7α-Methylsulfinyltestosterone Acetate. Isolation of Two Epimers. Epimer A.—7α-Methylthiotestosterone acetate (1 g.) was treated with monoperphthalic acid by the general procedure for sulfoxide preparations described above. Evaporation of the methylene chloride solvent gave a solid which was dissolved in hot acetone. To the refluxing acetone solution petroleum ether (b.p. 60–70°) was added to the point of crystal formation. The mixture was then chilled and the solid was filtered to give 418 mg. (40%) of product with m.p. 148–150° (gas). (The mother liquor was further investigated; see below.) This product was recrystallized once from methylene chloride–ether and then three times from acetone–petroleum ether (b.p. 60–70°) to a constant m.p. at 142–145°; $[\alpha]^{25}D$ −36.2° (0.6% in chloroform); $\lambda_{max}^{CH_3OH}$ 248 mμ (ε 12,800); λ_{max}^{KBr} 5.75, 6.00, 6.16, 8.0–8.06, 9.55, 9.63 μ, also weak bands at 7.71 and 8.84 μ indicating the presence of some sulfone; $R_f^6 = 0.42$.

Anal. Calcd. for $C_{22}H_{32}O_4S$: C, 67.32; H, 8.22; S, 8.17; O, 16.31. Found: C, 66.85; H, 8.31; S, 7.87; O, 16.64.

Similar material prepared in another experiment with 0.75 molar equivalents of monoperphthalic acid (37% yield) had m.p. 149–151°; $[\alpha]^{25}D$ −6.8° (1.0% in chloroform); $R_f^6 = 0.42$; $\lambda_{max}^{CH_3OH}$ 247 mμ (ε 11,000); infrared spectrum was essentially the same as that above except that the sulfone bands were almost absent. This product was different (mixture melting point and papergram mobility comparisons) from the 7α-methylthiosulfinyltestosterone acetate obtained by Holmlund and co-workers[4] by a microbiological procedure.

Epimer B.—The acetone–petroleum ether mother liquor from the 418-mg. preparation (above) gave, after partial evaporation, a second product (202 mg., 20%) with m.p. 171–173° (gas). Recrystallization from acetone–petroleum ether (b.p. 60–70°) three times to constant melting point gave material with m.p. 175–176° (gas); $[\alpha]^{25}D$ +15.5° (0.6% in chloroform). Further purification of this product was accomplished by partition chromatography on Celite[7] diatomaceous earth using the solvent system cyclohexane–dioxane–water (60:40:8) according to a procedure developed by C. Pidacks and described previously.[8] In the second holdback volume a small amount of 7α-methylsulfonyltestosterone acetate was obtained and in the fourth holdback volume the desired 7α-methylsulfinyltestosterone acetate which was identical by mixed melting point and paper chromatographic comparisons with the microbiological product of Holmlund and co-workers[4] (presumed epimer B) was obtained. This material had the following constants: m.p. 170–171° (gas), $[\alpha]^{25}D$ +11.3° (0.97% in chloroform). $R_f^6 = 0.56$; $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 10,800); λ_{max}^{KBr} 5.75, 5.97, 6.18, 8.05, 9.78 μ (no sulfone bands).

Anal. Calcd. for $C_{22}H_{32}O_4S$: C, 67.32; H, 8.22; S, 8.17. Found: C, 66.97; H, 8.36; S, 8.24.

General Procedure for the Preparation of Steroidal C-7 and C-21 Methyl Sulfones.—The steroidal C-7 or C-21 methyl sulfoxide was dissolved or suspended in 75 ml. of methylene chloride per 0.01 mole of steroid and treated with 1.1 mole equivalents of ethereal monoperphthalic acid according to the procedure described above for the preparation of the steroidal sulfoxides, except that the reaction time was extended to 48 hr. The product obtained was recrystallized from the same solvents described above. The compounds thus prepared by this general procedure are shown in Table II.

Treatment of 17β-Acetoxy-7α-methylsulfonyl-4-androsten-3-one with 0.5% Methanolic Potassium Hydroxide to Give 6-Dehydrotestosterone Acetate.—A suspension of 56 mg. of 17β-acetoxy-7α-methylsulfonyl-4-androsten-3-one in 5 cc. of 0.5% methanolic potassium hydroxide was stirred under nitrogen for 3 min. when solution was completed. After an additional 1 min., the solution was acidified with acetic acid. Dilution with water and filtration afforded 40 mg. (89%) of 6-dehydrotestosterone acetate,[9] m.p. 137–140°. Admixture with an authentic sample did not depress the melting point. The infrared spectra for the two samples were identical.

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the spectral and polarimetric determinations.

(6) The solvent system used was benzene, acetic acid, petroleum ether (b.p. 90–100°), water in the volume ratio 13:16:7:4. We thank Dr. Holmlund and his colleagues for these determinations.

(7) Celite is the trademark of Johns Manville Corp. for diatomaceous earth.

(8) W. S. Allen, C. C. Pidacks, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.*, **26**, 5046 (1961).

(9) C. Djerassi, G. Rosencranz, J. Romo, St. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

Formation and Oxidation of 2-(9′-Fluorenyl)-fluorene[1]

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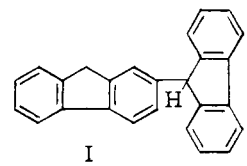
In an earlier paper it was reported that reaction of fluorene and sodium amide yielded two products which were isomers of 9,9′,9′,9″-terfluorene since more than two moles of fluorenone were obtained by oxidation of these products.[2] In the present work, the preparation and oxidation of a related compound, 2-(9′-fluorenyl)fluorene (I) are described. I was isolated as a by-product in the Clemmensen reduction of 9-fluorenol in toluene, was also produced when 9-fluorenol was boiled with fluorene in acetic acid in the presence of sulfuric acid, or was obtained by Friedel-Crafts reaction between fluorene and 9-bromofluorene in carbon disulfide.



I

On oxidation with sodium dichromate in acetic acid, I gave *o*-(fluorenone-2-carbonyl)benzoic acid and 13*H*-indeno[1,2-*b*]anthracene-6,11,13-trione (*lin*-phthaloylfluorenone), but no fluorenone, indicating that two molecules of fluorene were condensed at the 2- and 9- positions, respectively. I gave fluorene by zinc dust distillation, and its ultraviolet absorption spectrum differed from those of dibiphenyleneethane,[3] tribiphenylenepropane,[3] and 2,2′-difluorenyl.[4]

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