obtained by evaporation and crystallization from CH_2Cl_2–ether 75 mg (19%) of IV, mp 160–166°. The analytical sample (positive blue tetrazoleum α-ketol test) had mp 165–166°; $[\alpha]D$ +181°; λ_{max} 239 mμ (ε 15,420); λ 5.87 (s), 6.00 μ (s).

Anal. Calcd for $C_{22}H_{30}O_5S$: C, 65.00; H, 7.44; S, 7.89. Found: C, 64.81; H, 7.80; S, 7.76.

17α,20;20,21-Bismethylenedioxy-3-ethylenedioxy-2α-methylthio-11β-hydroxypregn-5-ene.—A mixture of 762 mg of III, 1.7 ml of ethylene glycol, and 35 mg of *p*-toluenesulfonic acid in 35 ml of benzene was stirred vigorously at reflux for 5 hr. The water formed was removed by means of a Dean–Stark tube. The cooled solution was diluted with benzene and was washed with aqueous $NaHCO_3$, saline, and water, dried, and concentrated to dryness. The resulting solid was triturated with ether and collected to furnish 671 mg (80%) of V, mp 232–240°, which was submitted directly to $NaBH_4$ reduction as follows.

A mixture of 790 mg of V, 18 ml of 2.5% NaOH solution, and 2.56 g of $NaBH_4$ in 65 ml of methanol was heated at reflux for 70 hr. The cooled solution was diluted with 200 ml of CH_2Cl_2 and washed with water, saline solution, and finally with water until neutral, and dried, and the solvent was evaporated. The residue was crystallized with ether–methanol and collected to furnish 586 mg (74%) of mp 200–204°. Recrystallization from methanol containing a drop of pyridine afforded the analytical sample, mp 202–204°, $[\alpha]D$ −59° (0.5%); the material had no significant absorption in the ultraviolet: λ_{max} 2.86, 9.10, 9.25, 10.58 μ.

Anal. Calcd for $C_{26}H_{38}O_5S$: C, 63.13; H, 7.75; S, 6.49. Found: C, 63.17; H, 8.02; S, 6.37.

11β,17α,21-Trihydroxy-2α-methylthiopregn-4-ene-3,20-dione (VI).—A solution of 292 mg of 17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-2α-methylthio-11β-hydroxypregn-5-ene in 20 ml of 50% aqueous acetic acid was heated on the steam bath for 3.5 hr, and then evaporated to dryness. The crude product was partition chromatographed[22] on Celite diatomaceous earth using the heptane–ethyl acetate–methanol–water (60:40:17:4) partition system. The stationary phase was thoroughly mixed (0.5 ml/g) with Celite (200 g) and the mix was packed into a glass column. The reaction product was dissolved in 5 ml of the lower phase, mixed with 10 g of Celite, and packed on top of the column. The HBV was 330 ml and the V_m/V_s ratio was 3.14. The product VI was isolated from the fraction with a peak at 3.5 HBV, and recrystallized from ether to furnish 65 mg (27%); mp 122–124° (gas); $[\alpha]^{25}D$ +125°; λ_{max} 241 mμ (ε 15,000); λ_{max} 2.90, 5.83, 6.02, 6.16 μ.

Anal. Calcd for $C_{22}H_{32}O_5S$: C, 64.68; H, 7.90; S, 7.85. Found: C, 63.97; H, 8.15; S, 7.61.

2α-Methylthioprogesterone (2α-Methylthiopregn-4-ene-3,20-dione, VIII).—To a solution of 2.24 g (5 mmoles if pure) of the ethoxalyl derivative (see VII)[18] of 20-ethylenedioxypregn-4-en-3-one in 10 ml of methanol was added 5 ml of 1 *N* methanolic $NaOCH_3$. The dark red solution was concentrated to dryness at 40° and the residue was reevaporated with 20 ml of dry dioxane. This residue was mixed with 30 ml of dioxane (suspension) and 470 mg of methanesulfenyl chloride. The mixture was allowed to stand at room temperature 30 min. Most of the gel dissolved by the end of this period, but the mixture still gave a strong enol test. It was evaporated and the residue was redissolved in 100 ml of benzene. The solution was washed with water and then portionwise with 1% aqueous KOH until the yellow color was no longer extracted. The combined aqueous washings were acidified with dilute H_2SO_4, and the mixture was extracted ($CHCl_3$). The chloroform extracts were washed with water, dried, and concentrated to dryness to afford 876 mg of a yellow glass which gave a strong enol test. This material was not further investigated. The original benzene solution was washed with water and dried, and the solvent was evaporated. The residue was dissolved in 30 ml of methanol containing 2 g of potassium acetate, and the solution was allowed to reflux for 1 hr and was then concentrated to dryness. The residue was partitioned between water and benzene, and the organic phase was washed several times with KOH and then with water. The dried solution was concentrated to dryness and the partially crystalline residue (1 g) was redissolved in 25 ml of methanol containing 1 ml of 8% H_2SO_4. The solution was heated at reflux for 45 min, and was then cooled and neutralized with Duolite A-4 anion-exchange resin (OH form). The resin was removed by filtration and was washed thoroughly with methanol. The filtrate was evaporated of solvent and the residue was dried by evaporation with $CHCl_3$ to give an orange gum (0.9 g) which was dissolved in ether, treated with decolorizing charcoal, and evaporated.

Crystallization and recrystallization from ether afforded 162 mg (9%) of solid (VIII), mp 176–180°. The analytical sample, obtained in a similar experiment and recrystallized from ethyl acetate, had mp 180–183°; $[\alpha]D$ +202° (0.41%); λ_{max} 240 mμ (ε 12,060); λ 5.87 (s), 5.99 (s), 6.13 μ (m).

Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.29; H, 8.95; S, 8.45. Found: C, 73.22; H, 9.14; S, 8.76.

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Steroidal γ-Lactones. The Claisen Condensation of 17α-Acetate with 17β-Acetyl

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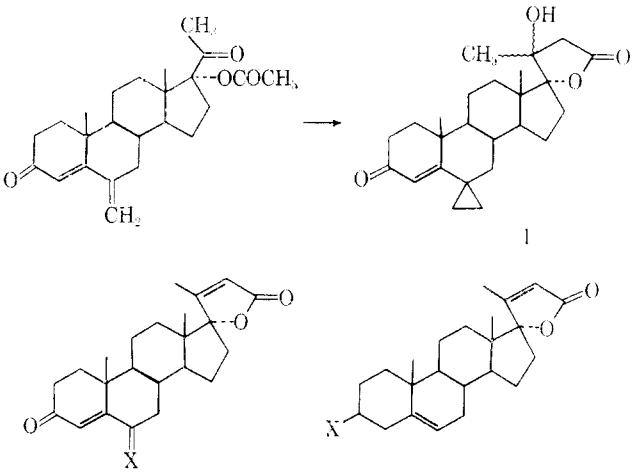
In attempting to prepare a 6-spirocyclopropyl steroid by the reaction of dimethylsulfoxonium methylide in the presence of excess sodium hydride with 6-methylene-17α-acetoxypregn-4-ene-3,20-dione,[1] the product was shown by analysis and determination of spectra to be 17α,20-dihydroxy-3-oxo-6-spirocyclopropyl-23-norchol-4-enic acid γ-lactone (I).



I

II, X = H, H
V, X =

III, X = HO
IV, X = CH_3COO

It appears that two reactions occurred, the 6-spiro cyclopropane formation by addition of dimethylsulfoxonium methylide to the conjugated unsaturation and the base-catalyzed condensation of the α position of the ester with the ketone of C-20.

Further examples, which limited the reaction only to the lactone formation, yielded the $\Delta^{20(22)}$-lactones (see Tables I and II). Thus the 17α-acetoxypregnene-20-

(1) D. Boro, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kick, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron*, **20**, 597 (1961).

TABLE I

STEROIDAL γ-LACTONES

Compd	% yield	Crystn solvent	Mp, °C[a]	λ_{max},[b] mμ	ε	$[\alpha]D$,[c] deg	Formula	Calcd, % C	Calcd, % H	Found,[d] % C	Found,[d] % H
I	69	Benzene–hexane	235–238	249	12,300	+145[g]	$C_{25}H_{34}O_4 \cdot 0.5H_2O$	73.68	8.66	73.94	8.61
		Acetone–benzene	232–234				$C_{25}H_{34}O_4 \cdot 0.5C_3H_6O$	74.50	8.72	74.61	8.46
II	49	Benzene–hexane	217–219	221	15,000	−38[h]	$C_{23}H_{30}O_3$	77.92	8.53	77.46	8.49
III	100	Methanol–water	248–255[e]	220	10,600	−133	$C_{23}H_{32}O_3$	77.49	9.05	77.48	9.21
IV	66	Ether	252–253	219	8,650	−129	$C_{25}H_{34}O_4 \cdot 0.5H_2O$	73.68	8.66	73.93	8.44
V	40	$CHCl_3$–ether	260–263	223	13,800	+102	$C_{25}H_{32}O_3 \cdot H_2O$	75.34	8.60	75.60	8.34
				248[f]							

[a] Capillary tube, corrected. [b] In methanol. [c] At 24–26° and 1% in $CHCl_3$ except as indicated. [d] Microanalyses are by Mr. C. E. E. Childs (Ann Arbor) and by Mr. F. H. Oliver (Hounslow). [e] Lit.[2] mp 257–259°. [f] Inflection. [g] 0.72% in acetone. [h] 0.75% in $CHCl_3$.

TABLE II

INFRARED[a] AND NMR DATA[b]

	Infrared, cm⁻¹						Nmr, δ							
Compd	OH	Lactone	Ketone	Δ^{20}	Δ^4	Ester	Cyclopropyl	18-Me	19-Me	21-Me	C-4	C-6	C-22	C-3
I	3440	1776	1653		1608		0.38	1.11	1.13	1.62	5.85			
II		1744	1665	1632	1618			0.95	1.19	2.15	5.44		5.87	
III	3530, 3480	1743		1634				0.94	1.02	2.15		5.38	5.87	3.50
IV		1750		1632		1730, 1249		0.96	1.04	2.15		5.43	5.88	4.54
V		1745	1658	1635	1604		0.46	1.00	1.26	2.17	5.66		5.87	

[a] Infrared determinations were made by Mr. E. Schoeb (Ann Arbor) using a Beckman Model IR-9. KBr disks were used except for II which was run in $CHCl_3$ solution. [b] Nmr spectra were obtained by Mr. R. B. Scott (Ann Arbor) using a Varian A-60. Except for I, which was run in pyridine, solutions in $CDCl_3$ were used.

TABLE III

PROPORTIONS OF REACTANTS

Product	Me_3SOI, mmoles	NaH, mmoles	DMSO, ml	Steroid, mmoles
I	5	5.3	90	4.75
II		5.6	100	5.6
III		5.3	100	5.3
IV	4.5	4.5	150	4.3[a]
V		5	55	2.4[b]

[a] 3β,17α-Diacetoxypregn-5-en-20-one, mp 174–177°, from pyridine–acetic anhydride acetylation of 17α-acetoxypregnenolone. [b] G. D. Searle & Co., South African Patent 65/4327 (Feb 14, 1966).

ones yielded the corresponding $\Delta^{20(22)}$-lactones:[2] 17α-hydroxy-3-oxo-23-norchola-4,20(22)-dienic acid γ-lactone (II), 3β,17α-dihydroxy-23-norchola-5,20(22)-dienic acid γ-lactone (III), 3β-acetoxy-17α-hydroxy-23-norchola-5,20(22)-dienic acid γ-lactone (IV), and 17α-hydroxy-3-oxo-6-spirocyclopropyl-23-norchola-4,20-(22)-dienic acid γ-lactone (V), when run with sodium hydride in dimethyl sulfoxide. Our work has not permitted the assignment of configuration to the C-20 position.

Compounds I and II were tested for biological activity. Compound II failed to prevent litters being born when fed to mice at 10 mg/kg/day. Neither compound antagonized 1 μg of aldosterone in the salt-loaded rat at dose levels of 30–50 mg/kg. Neither compound showed any progestational effect in the McPhail assay in rabbits at a dose level of 20 times progesterone by subcutaneous and 100 times norethindrone by oral administration.

(2) H. G. Lehmann, *Angew. Chem.*, **77**, 808 (1965), has since reported that the reaction leads to the unsaturated lactone (III) in the presence of equimolar amounts of NaH while catalytic amounts of NaOH for short reaction times allow isolation of the hydroxylactone. Also N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Letters*, 1841 (1966), have reported the conversion of 17α-acetoxypregna-4,6-diene-3,20-dione to the corresponding unsaturated lactone by NaH in DMSO.

Experimental Section

General Procedure.—Sodium hydride was added to dimethyl sulfoxide (DMSO) under nitrogen and stirred at room temperature for about 1 hr. A solution of trimethylsulfoxonium iodide in DMSO was added and stirred for 15–30 min. The steroid was suspended in DMSO and added in one portion. The mixture was then stirred overnight and worked up by pouring into ice–water, separating, and crystallizing. When trimethylsulfoxonium iodide was not used, the remainder of the procedure was unchanged. In two of the preparations, II and V, the reaction mixture was acidified with 3 *N* HCl after being quenched in ice–water. The reactant proportions are given in Table III.

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The Synthesis of Some Aryl Nitrogen Mustard Derivatives of Estrogens[1]

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The synthesis of several new steroidal compounds has been accomplished from the corresponding intermediates 4-aminoestrone 3-methyl ether (I) and 2-aminoestrone 3-methyl ether (II). These mustards were prepared because the literature describes no previous attempts to study aryl nitrogen mustards of steroids and also because of their potential as anticancer agents.

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(2) The data published here are taken from a thesis submitted by Charles R. Walk in partial fulfillment for the degree of Master of Science.

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