weight. After 14-16 h, the animals were killed by bleeding from the carotid artery. Peritoneal exudate was collected, and the cavity was washed twice each with 30 mL of physiological saline containing 15 mM potassium phosphate buffer at pH 7.4, 1 mM EDTA, and 15 μM indomethacin. The combined exudate was filtered through four layers of cheesecloth, followed by centrifugation at 500g for 3 min. Cell pellets were suspended in 0.2% sodium chloride solution for 30 s for lysis of contaminating red cells. After centrifugation at 200g for 5 min, the cells were suspended in 50 mM potassium phosphate at pH 7.4 containing 1 mM EDTA and 15 μM indomethacin. The cell suspension (2×10^8 cells/mL) was sonicated at 20 Hz for 30 s, and the sonicate was centrifuged at 105000g for 60 min. The cytosol fraction was concentrated to one-fourth of the original volume by a Diaflo membrane (XM-50). The concentrate (PMNL cytosol) was used as an enzyme throughout this work.

Assay of 5-Lipoxygenase. The standard reaction mixture (0.1 mL) contained 0.1 M potassium phosphate at pH 7.4, 1 mM $CaCl_2$, and enzyme. After preincubation of enzyme for 5 min at 30 °C, [1-^{14}C]arachidonic acid [200000 cpm (5 nmol^{-1} (5 μL of ethanol)$^{-1}$] was added, and the reaction was performed at 30 °C for 5 min. The reaction was terminated by the addition of 0.3 mL of a mixture of ethyl ether/methanol/0.2 M citric acid (30:4:1) precooled at 0-4 °C. The organic layer (50 μL) was applied to a precoated 60 F_{254} glass plate. Arachidonic acid, 5-HETE, and 5,12-diHETE were also placed as a reference. Thin-layer chromatography was carried out with a solvent system of ethyl ether/petroleum ether/acetic acid (85:15:0.1) at 4 °C (R_f values: 15-HETE, 0.32; 5-HETE, 0.23; 5,12-diHETE and LTB_4, 0.03). The measurement of the radioactivity on the silica gel plate was performed as described previously.[12] The PMNL cytosol transformed arachidonic acid to 5-HETE, LTB_4, and 5,12-diHETE. These reaction products were identified by high-performance liquid chromatography and gas chromatography-mass spectrometry. RP-HPLC was performed on a Nucleosil C_{18} (4.6 × 250 mm, 5-μm particles, purchased from Macherey-Nagel Co., Düuran, Germany); solvent MeOH/H_2O/AcOH (75:35:0.01); flow rate 0.9 mL/min, pressure 250 kg/cm^2; monitered by absorbance at 232 or 280 nm. The retention volumes are as follows: 5-(*S*),12(*S*)-diHETE, 2.75; 5(*S*),12(*R*)-diHETE, 3.00; LTB_4, 3.19; 15-HETE, 5.84; 12-HETE, 6.45; 5-HETE, 8.06.

The data of GC-MS spectrometry are in agreement with the published spectra.[14]

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Novel 17α-Chloro-17β-sulfinyl Steroids as Specific Inhibitors of Sebaceous Gland Activity: Potential Antiacne Agents[1]

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The preparation and antisebaceous gland activities of a series of 17α-chloro-17β-sulfinyl steroids are described. They were obtained from the corresponding 17α-sulfides by chlorination and oxidation with iodobenzene dichloride in aqueous pyridine at −40 °C. A single-crystal X-ray structure determination of 17α-chloro-17β-(benzylsulfinyl)-1,4-androstadiene-3,11-dione (**4**) established the absolute configuration at sulfur to be *R*. From an analysis of their CD spectra, some of the other α-chloro sulfoxides were also assigned the same absolute stereochemistry at sulfur. Inhibition of sebaceous gland activity, after topical application of the test compounds, was determined in hamsters and found to reach a maximum with **4**. The 17β-sulfone and 17α-sulfide corresponding to **4** were less potent. Subcutaneous administration of **4** produced no antiandrogenic effects in either hamsters or rats.

Acne vulgaris is a chronic condition involving the pilosebaceous unit, characterized fundamentally by the presence of comedones and secondarily by inflammatory papules, pustules, or cysts. Although the disease has many contributing factors, it has become generally accepted that abnormal sebum production by the sebaceous gland is a major contributor to the etiology of acne.[2-5] Since acne generally appears at puberty, a time when great hormonal changes occur, the possibility that acne is related to hormonal activity was raised[2] as long ago as 1937. Indeed, it was subsequently found that exogenous administration of androgens induced acne in both males and females.[4] Furthermore, both of the potent antiandrogens cyproterone acetate[6,7] and 17α-methyl-*B*-nortestosterone **23**[6,8] were shown to inhibit sebum production in man and were also effective against acne. Side effects,[9] due to their antiandrogenic effects on other tissues, have precluded their clinical use in the control of acne, however.

It is clear then that a close correlation exists between sebaceous gland inhibition and the amelioration of acne. Furthermore, it is apparent that such inhibition can be accomplished by blocking the action of androgens. We therefore set out to identify a compound that would inhibit

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(2) J. B. Hamilton, *Endocrinology*, **21**, 649 (1937).
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[§] Duke University.

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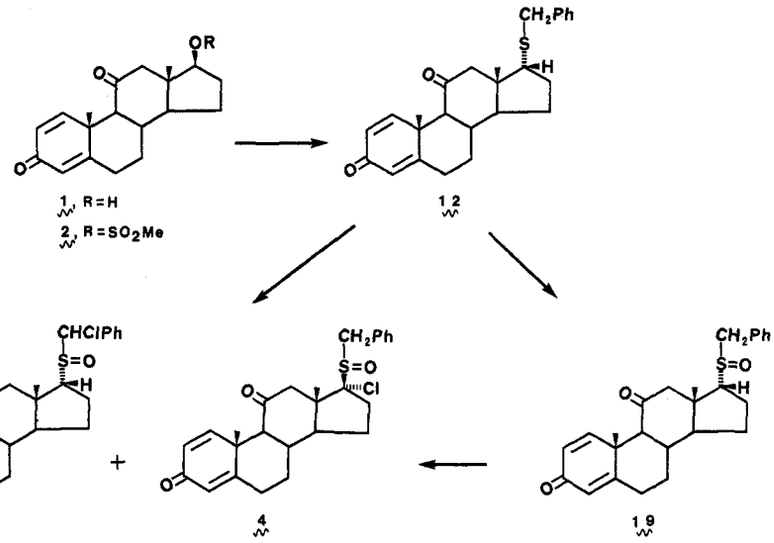
Scheme I



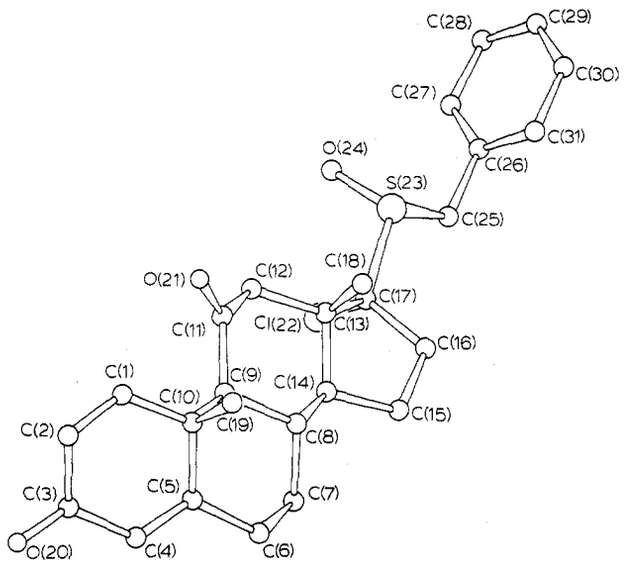
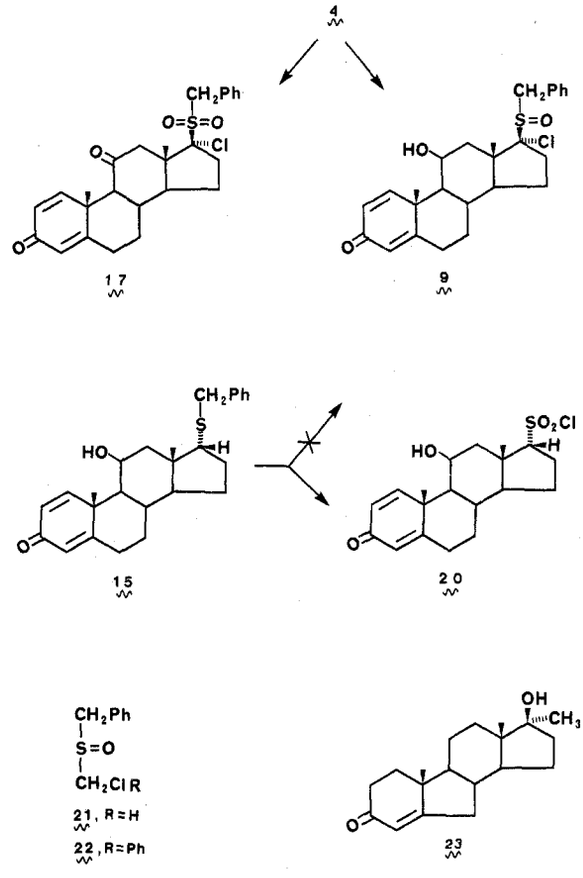


Figure 1. Solid-state conformation and atom numbering scheme in 4.

Scheme II



sebaceous gland function without affecting other androgen-sensitive structures or having other hormonal effects. In this paper we report the synthesis and biological properties of a series of steroidal α-chloro sulfoxides, one of which at least seems to meet these criteria.

Results and Discussion

Chemistry. Selective reduction[10] at C_{17} of 1,4-androstadiene-3,11,17-trione with $NaBH_4$ in MeOH, followed by mesylation, gave **2**. Displacement of the 17β-mesylate with benzyl thiolate ion then gave the 17α-(benzyl thio ether) **12** in 38% yield (Scheme I). Reaction of **12** with iodobenzene dichloride[11] (IBD) in aqueous pyridine at −40 °C gave a crude product from which 17α-chloro 17β-(benzyl sulfoxide) **4** was isolated by crystallization from acetone in approximately 25% yield. Fractional crystallization of the mother liquors gave the isomeric α-chloro sulfoxide **18** (≃1%). TLC examination of the crude reaction product showed that a small amount of the 17α-(benzyl sulfoxide) **19** and several unidentified, unstable products were also produced. Alternatively **4** could be produced stepwise by oxidation of **12** with *m*-chloroperbenzoic acid to give the 17α-sulfoxide **19** (assigned the *R* configuration at sulfur; see later discussion) and subsequent chlorination with IBD in aqueous pyridine.

The structure of **4** was assigned from its elemental analysis, the presence of a sulfoxide absorption at 1070 cm^{-1} in the IR spectrum, and the presence in the NMR

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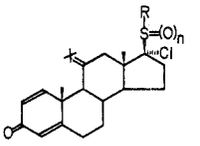
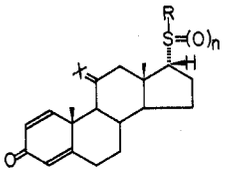
Table I. Physical and Biological Data for the 17α-Chloro 17β-Sulfoxide Steroids and a 17α-Chloro 17β-Sulfone Steroid



Compd	R	X	n	mp (°C)[a]	$[\alpha]_D^{26}$[b]	$UV_{max}\lambda$ nm(ε)[d]	NMR[e] C_{10}-CH_3	NMR[e] C_{13}-CH_3	NMR[e] Other	Inhibition of Lipid Synthesis % (0.1 mg)	Inhibition of Flank Organ Weight % (mg)
3	Ph	O	1	232-6	-108.6[c]	242 (20,300)	1.42	1.28	—	20	
4	CH_2Ph	O	1	266-270	+111.6	223 (21,200)	1.37	1.08	4.01 (CH_2Ph)	70[g]	43 (0.5); 53 (1.0)
5	CH_2 (2′,4′-$Cl_2C_6H_3$)	O	1	238-240	+207	234 (29,200)	1.38	1.09	4.19 (CH_2Ph)		20 (0.5)
6	CH_2(2′-$CH_3C_6H_4$)	O	1	249-251	+135	228 (22,000)	1.39	1.09	4.08 (CH_2Ph)		31 (0.5)
7	CH_2CH_2Ph	O	1	232-5	+65	236 (16,800)	1.36	1.06	—	0	16 (0.25)
8	$(CH_2)_4CH_3$	O	1	196-200	+95.5	236 (16,200)	1.38	1.10	—	29[h]	
9	CH_2Ph	β-OH α-H	1	258-262	+105.1	220 (19,200) 240 (17,000)	1.42	1.40	4.30 (11α-H,m) 4.02 (CH_2Ph)	20[h]	
10	CH_2Ph	H_2	1	260-5	+157.4[c]	220 (19,100) 239 (18,300)	1.23[f]	1.23[f]	4.03 (CH_2Ph)	40[h]	
17	CH_2Ph	O	2	269	+15.1	220 (18,300) 237 (15,400)	1.37	1.08	4.73 (CH_2Ph)	31[h]	
21	—	—	—							14	
22	—	—	—							14	

[a] With decomposition. [b] $CHCl_3$ solution. [c] DMF solution. [d] MeOH solution. [e] $(CD_3)_2SO$ solution. [f] $CDCl_3$ solution. [g] Statistically different from control at $p \leq 0.01$. [h] Statistically different from control at $p \leq 0.1$.

Table II. Physical and Biological Data for the Steroidal 17α-Sulfur Derivatives



Compound	R	X	n	mp °C	$[\alpha]^{26}$[a]	$UV_{max}\lambda$ nm(ε)[c]	NMR[d] C_{10}-CH_3	NMR[d] C_{13}-CH_3	NMR[d] Other	Inhibition of Lipid Synthesis % (0.1 mg)
11	Ph	O	0	177-9	+228.1[b]	249 (19,500)	1.35	0.85		25[f]
12	CH_2Ph	O	0	134-6	+171.4	237 (17,100)	1.37	0.78	3.70 (CH_2Ph)	29[f]
13	CH_2CH_2Ph	O	0	112-5	+237	236 (17,300)	1.37	0.77		
14	$(CH_2)_4CH_3$	O	0	76-8	+117.7	238 (16,200)	1.38	0.80		
15	CH_2Ph	β-OH α-H	0	217-220	+93.1	242 (15,300)	1.40	1.03	4.31 (11α-H) 3.65 (CH_2Ph)	0
16	CH_2Ph	H_2	0	116-8	+61.5[b]	242 (16,000)	1.17	0.81	3.66 (CH_2Ph)	0
18	CHClPh	O	1	135-140		230 (18,200)	1.43[e]	0.98[e]	6.08 (CHClPh)	0
19	CH_2Ph	O	1	182-4	+9.0	230 (19,200)	1.35	0.80	3.80 (CH_2Ph)	28

[a] $CHCl_3$ solution. [b] DMF solution. [c] MeOH solution. [d] $(CD_3)_2SO$ solution. [e] $CDCl_3$ solution. [f] Statistically different from control at $p \leq 0.1$.

spectrum of a benzylic methylene singlet at δ 4.01, which moved downfield to δ 4.73 on oxidation to the sulfone **17**. The stereochemistry at C_{17} was confirmed, and the configuration at sulfur was determined to be *R* by a single-crystal X-ray structure determination (Figure 1).

The other 17α-chloro-17β-sulfinyl steroids shown in Table I, **3**, **5–8** and **10**, were synthesized in low to moderate yields by the combined oxidation/chlorination procedure with IBD. However, in the preparation of **9** by this sequence, treatment of the benzyl thio ether **15** with IBD gave the 17α-(sulfonyl chloride)[12] **20** as the major identifiable product (Scheme II). Thus, **9** was prepared more conveniently by selective reduction of the C-11 ketone function of **4** with $NaBH_4$ in MeOH.[10] The nonsteroidal α-chloro sulfoxides, **21**[11a] and **22**,[11c] were also prepared by the IBD procedure as previously described in the literature.

The absolute configuration at sulfur of some of the 17α-chloro-17β-sulfinyl steroids (**3–10**) have been determined. They all appear to be single isomers, since they showed single C_{13}-CH_3 signals in their NMR spectra, and it was hoped that an analysis of their CD spectra (Table III) would allow an assignment of configuration at sulfur to be made. There is a considerable amount of literature data on the CD and ORD spectra of alkylaryl[13] and dialkyl sulfoxides,[14] which allows the absolute configuration of

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(14) (a) D. N. Jones, M. J. Green, M. A. Saeed, and R. D. Whitehouse, *J. Chem. Soc. C*, 1362 (1968); D. N. Jones, M. J. Green, and R. D. Whitehouse, *ibid.*, 1166 (1969); D. N. Jones, E. Helmy, and A. C. F. Edmonds, *ibid.*, 833 (1970); (b) D. N. Jones, D. Mundy, and R. D., Whitehouse, *ibid.*, 1668 (1969); (c) D. N. Jones and W. Higgins, *ibid.*, 2159 (1969); (d) K. Mislow, M. M. Green, P. Laur, and D. R. Chisholm, *J. Am. Soc.*, **87**, 665 (1965); M. Axelrod, P. Bickert, M. L. Goldstein, M. M. Green, A. Kjaer, and K. Mislow, *Tetrahedron Lett.*, 3249 (1968); (e) U. Folli, F. Montanari, and G. Torre, *ibid.*, 5037 (1966). (f) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *J. Chem. Soc., Chem. Commun.*, 550 (1967); P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967).

Table III. CD Data for α-Chloro Sulfoxide Steroids and Associated Compounds

Compound	CD (MeOH) nm ([θ])		Δ[θ] of Short Wavelength C.E.	Δ[θ] of Long Wavelength C.E.
17β-hydroxy-1,4-androstadiene-3,11-dione	230 (+68,100)	262 (-37,000)	—	—
3	218 (+184,400)	252 (-149,000)	+116,300	-112,000
4	226 (+151,700)	257 (-36,100)	+83,600	+900
7	234 (+33,800)	258 (-43,400)	-34,300	-6,400
8	233 (+39,000)	258 (-37,000)	-29,100	-3,000
19	228 (+151,700)	259 (-59,900)	+83,100	-22,900
11β,17β-dihydroxy-1,4-androstadien-3-one	230 (+19,400)	261 (-19,600)	—	—
9	226 (+108,700)	261 (-7,100)	+89,300	+2,500
17β-hydroxy-1,4-androstadien-3-one	232 (+30,100)	263 (-12,400)	—	—
10	225 (+87,400)	263 (-4,000)	+57,300	+8,400
12	230 (+83,800)	261 (-37,300)	—	—
18	227 (+44,000)	257 (-26,600)	—	—

some of these two classes of sulfoxides to be determined. However, there does not appear to be any related work concerning the assignment of absolute configuration to α-chloro sulfoxides.

The benzyl sulfoxide **4** has the *R* configuration at sulfur, as unequivocally determined by X-ray structure analysis, and shows CD absorption maxima at 226 nm, [θ] +151 700°, and at 257 nm, [θ] 36 100°. These maxima are composites of Cotton effects due to the ring A dienone (225–260 and 220–225 nm absorptions),[15] the 11-ketone (260 nm absorption), and the benzyl sulfoxide moiety (230–235 nm absorption).[14c] If we ignore any possible long-range interactions between these chromophores, then the contributions of the dienone and 11-ketone functions can be approximated by those of 17β-hydroxy-1,4-androstadiene-3,11-dione (Table III). Subtracting these values from those of **4** gives a resultant absorption only at 230 nm of [θ] +83 600° as the contribution of the 17α-chloro 17β(*R*)-(benzyl sulfoxide) grouping. This agrees qualitatively with that reported[14c] for some steroid benzyl sulfoxides assigned the *R* configuration at sulfur ([θ] +37 000° to +69 000°) and indicates that the α-chlorine atom does not drastically affect the chiroptical properties of the sulfoxide chromophore.

By a similar analysis, the 17α-(benzyl sulfoxide) **19** was also assigned the *R* configuration at sulfur, since the contribution of the sulfoxide to the CD absorption at 230 nm was [θ] +83 100°. This was confirmed by its conversion to **4** under conditions that do not affect the configuration at sulfur.[16]

Compound **9** must also have the *R* configuration at sulfur, since it was derived from **4** by $NaBH_4$ reduction, conditions not expected to invert or racemize sulfoxides.[16] Subtracting from its CD maxima those of 11β,17β-dihydroxy-1,4-androstadien-3-one (Table III) leaves the contribution due to the (*R*)-benzyl sulfoxide group of [θ] +89 300° at 230 nm in satisfactory agreement with that found for **4**. The closeness of these three results shows that the neglect of long-range interactions between the dienone and 11-ketone and sulfoxide chromophores is reasonable for our configurational assignments at sulfur. The benzylic sulfoxide **10**, with no oxygen substituent at C_{11}, has a contribution at 230 nm of [θ] +57 300° due to the sulfoxide group and, therefore, is also assigned the *R* configuration at sulfur.

The 17β-(phenyl sulfoxide) **3** is an example of alkylaryl sulfoxides that have another Cotton effect centered at 260–280 nm.[13] This longer-wavelength transition has been studied by several groups,[13] and the association of a strong negative Cotton Effect with the *S* configuration at sulfur has been clearly established. Compound **3** has a [θ] −112 000° contribution due to the sulfoxide in this region (Table III) and therefore must have the same absolute configuration. However, due to the priority rules[17] for assignment of the *R* and *S* notation, this results in the assignment of the *R* configuration at sulfur to the 17α-chloro 17β-(phenyl sulfoxide) **3**. Thus, the α-chloro sulfoxides **3**, **4**, **9**, and **10** all have the same absolute configuration of the sulfoxide group.

Studies[14a,b,f] have shown that dialkyl sulfoxides exhibit two optically active transitions at ca. 210 and 230 nm. The short-wavelength Cotton effect dominates the CD spectra of simple methyl sulfoxides, and a negative sign has been associated with the *R* configuration at sulfur,[14d] although exceptions have also been reported.[14b] With increasing bulk of the alkyl groups, the Cotton effect at 230 nm assumes greater importance in the CD spectrum. This has been attributed[14a,b] to asymmetric perturbation of the sulfoxide chromophore as a result of restricted rotation; therefore, this transition cannot be used for configurational assignments. The dialkyl sulfoxides **7** and **8** would be expected to have severely restricted rotation about the quaternary C_{17}-S bond and, indeed, their CD spectra show the expected strong absorptions at 230 nm due to the sulfoxide group. The negative signs of these absorptions indicate that **7** and **8** probably have the same absolute configuration at sulfur but do not allow an assignment to be made.

X-ray Crystal Structure Analysis of 4. The crystal structure of **4** was solved by direct methods.[18] Full-matrix least-squares refinement of atomic positional and thermal parameters converged at $R = 0.052$[19] over 1145 statistically significant reflections. A view of the solid-state conformation of **4**, with the atom numbering scheme, is shown in Figure 1: the absolute configuration at sulfur is *R*.[17] Non-hydrogen atom positional parameters are in Table V.[20] Bond lengths and angles, presented in Figure 3,[20] are

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(17) R. S. Cahn, *J. Chem. Educ.*, 41, 116 (1964).
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(19) $R = \sum||F_o| - |F_c||/\sum|F_o|$.

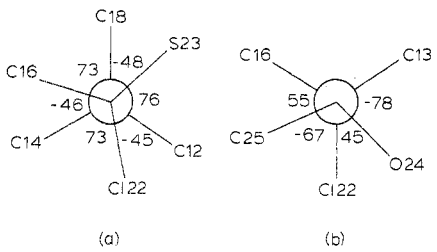

Figure 2. Newman projections along (a) the C_{13}–C_{17} bond and (b) the C_{17}–S_{23} bond in **4**.

normal, except in the phenyl ring where apparent variations between chemically equivalent bonds may be ascribed to some orientational disordering of this group in the crystal as reflected in the relatively high thermal parameters of the phenyl-ring carbon atoms (Table VI).[20] A complete list of torsion angles[21] and deviations of selected atoms from various least-squares planes are in Table VII and VIII,[20] respectively. The arrangement of molecules of **4** in the crystal is illustrated in Figure 4.[20]

The atoms comprising ring A are approximately coplanar (root mean square displacement 0.029 Å), as would be expected for maximum delocalization, and the substituent atoms C_6 and O_{20} (Δ = −0.063 and 0.025 Å, respectively) lie close to the least-squares plane through atoms C_1–C_5, C_{10}. The dihedral angle between the ring A plane and the least-squares plane through atoms C_5–C_{17} of the steroid skeleton is 35.3°, with an associated 2.028-Å displacement of O_{20} from the latter. Although similar degrees of ring A bowing to the α side have been associated elsewhere[22] with relatively high antiinflammatory activity, **4** is considerably weaker in this regard than hydrocortisone (see Biology), presumably as a consequence of the C_{17} substituents. Rings B and C both adopt chair conformations, somewhat flattened owing to the presence of sp^2-hybridized carbon centers at C_5 and C_{11}.

Newman projections along the C_{13}–C_{17} and C_{17}–S_{23} bonds in **4** are shown in Figure 2. Nonbonded interactions between the C_{18}-methyl group and the 17β-sulfoxide substituent appear to dictate not only the cyclopentane ring D conformation but also the conformation around the C_{17}–C_{23} bond. Thus, adoption of a C_{13} β-envelope conformation[23] by ring D serves to minimize repulsive nonbonded β-face interactions between the C_{18}-methyl group and the sulfoxide substituent at C_{17}, since any pseudorotation of ring D toward, for example, a C_{13}-β/C_{14}-α half-chair form would require closure of the endocyclic C_{14}–C_{13}–C_{17}–C_{16} torsion angle and concomitant reduction in the C_{18}–C_{13}–C_{17}–S_{23} torsion angle with its attendant overcrowding of the C_{18}-methyl group. Minimization of nonbonded interactions in addition to preferred dipole orientation is achieved by the conformation adopted about the C_{17}–S_{23} bond. In this case, the three possible staggered conformations about the C_{17}–S_{23} bond would have associated with them a quasi-1,3-diaxial relationship involving the C_{18}-methyl group and either the sulfur lone pair, the sulfoxide oxygen, or the C_{25}-methylene group when each of these is oriented in turn anti to Cl_{22}. However, of these conformations, that with the C_{25}-methylene group anti to Cl_{22} would be the least favored both on steric and polar grounds. Of the other two conformations, which would appear to be equally probable on polar grounds, that which results in the least amount of steric crowding, i.e., that with the sulfur long pair anti to Cl_{22}, is preferred.

Table IV. Effect of **4** and 17α-Methyl-*B*-nortestosterone (**23**) on Selected Organs of Male Hamsters

Application		Organ Weights (mg)	
Topical[a]		Treated Flank	Seminal Vesicles
Control		38.9 ± 1.5	343 ± 16
4	-0.375 μg	29.5 ± 0.6[c]	351 ± 6
	-0.75 μg	23.7 ± 1.2[c]	358 ± 20
17α-Methyl-B-Nortestosterone	-0.375 μg	15.6 ± 0.9[c]	316 ± 34
	-0.75 μg	13.7 ± 0.9[c]	283 ± 33[d]
S.C.[b]			
Control		30.5 ± 2.1	126 ± 5
4	-1 mg	21.5 ± 1.6[c]	138 ± 3
	-5 mg	19.5 ± 1.7[c]	128 ± 6
17α-Methyl-B-Nortestosterone	-1 mg	22.5 ± 1.0[d]	121 ± 6
	-5 mg	22.1 ± 0.9[c]	94 ± 10[d]

[a] Six animals per group; compounds dissolved in $CHCl_3$ and applied topically to flank gland for 14 days. [b] Five animals per group; compounds suspended in CMC and injected subcutaneously once daily for 14 days. [c] Significantly different from control at $p \leq 0.01$. [d] Significantly different from control at $p \leq 0.05$.

Biology. Studies have shown that the sebaceous glands of rats,[24] rabbits,[25] and hamsters[26] are under androgen control just as they are in man. In the rat it was found that not only did androgen administration stimulate sebum secretion[27] but also antiandrogens [cyproterone acetate[28] and 17α-methyl-*B*-nortestosterone (**23**)[29]] reduced sebum secretion, again paralleling such effects found in man.[6] Similar results have also been reported for the flank glands (costovertebral glands) of hamsters with the nonsteroid antiandrogen flutamide.[30] Indeed, the hamster flank gland, which contains primarily sebaceous cells, appears to be well suited as an assay system for evaluating compounds with sebaceous gland inhibiting activity, particularly those with potential topical activity. We have used two such assays based upon the hamster flank gland to evaluate the steroidal sulfoxides, sulfides, and the sulfone shown in Tables I and II.

Compounds were initially screened for their ability to inhibit lipid synthesis in hamster flank glands. The procedure used,[31] a modification of that developed by Lutsky et al.,[32] measured the incorporation of labeled acetate by

(20) Supplementary material, see paragraph at end of paper.
(21) Endocyclic torsion angles, ω_{ij} (degrees), about the bonds between atoms C_i and C_j in the steroid skeleton are as follows: $\omega_{1,2}$ −6, $\omega_{2,3}$ 4, $\omega_{3,4}$ −1, $\omega_{4,5}$ 0, $\omega_{5,10}$ −2, $\omega_{10,1}$ 4 for ring A; $\omega_{5,6}$ −52, $\omega_{6,7}$ 50, $\omega_{7,8}$ −53, $\omega_{8,9}$ 58, $\omega_{9,10}$ −57, $\omega_{10,5}$ 55 for ring B; $\omega_{8,9}$ −46, $\omega_{9,11}$ 51, $\omega_{11,12}$ −57, $\omega_{12,13}$ 60, $\omega_{13,14}$ −62, $\omega_{14,8}$ 54 for ring C; $\omega_{13,14}$ 45, $\omega_{14,15}$ −27, $\omega_{15,16}$ −2, $\omega_{16,17}$ 30, $\omega_{17,13}$ −46 for ring D.
(22) C. M. Weeks, W. L. Duax, and M. E. Wolff, *J. Am. Chem. Soc.*, **95**, 2865 (1973); J. Albertsson, A. Oskarsson, and C. Svensson, *Acta Crystallogr., Sect B*, **B34**, 3027, (1978) and references therein.
(23) Pseudorotation parameters for **4** at Δ = +36°, ϕ_{max} = 47.3°, are not significantly different from the standard ring D values, Δ = +36°, ϕ_{max} = 46.7°, for a C_{13} β-envelope form: C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, **24**, 13 (1968).
(24) F. J. Ebling, *J. Endocrinol.*, **5**, 297 (1948).
(25) W. Montagna and P. Kenyon, *Anat. Rec.*, **103**, 365 (1949).
(26) J. B. Hamilton and W. Montagna, *Am. J. Anat.*, **86**, 191 (1950).
(27) A. Archibald and S. Shuster, *J. Endocrinol.*, **37**, xxii (1967); A. Archibald and S. Shuster, *Proc. R. Soc. Med.*, **62**, 887 (1969); F. J. Ebling, E. Ebling, and J. Skinner, *J. Endocrinol.*, **45**, 245 (1969).
(28) F. J. Ebling, *Proc. R. Soc. Med.*, **62**, 890 (1969).
(29) F. J. Ebling, *J. Endocrinol.*, **38**, 181 (1967).
(30) B. N. Lutsky, M. Budak, P. Koziol, M. Monahan, and R. O. Neri, *J. Invest. Dermatol.*, **64**, 412 (1975).
(31) T. T. Kung, B. N. Lutsky, R. O. Neri, P. Koziol, J. S. Massenberg, and A. S. Watnick, *J. Invest. Dermatol.*, **76**, 327 (1981).

androgen-stimulated flank glands after two daily topical applications of the test compound. The results for the compounds under study (Tables I and II) show that inhibition of lipid synthesis reaches a maximum with the 17α-chloro 17β-(benzyl sulfoxide) **4**. Changing the group attached to the sulfoxide to either a phenyl or to a phenylethyl group resulted in reduced potency, as did oxidation of **4** to the sulfone **17**. The purely aliphatic sulfoxide **8** was also less active, and none of the 17α-sulfides tested showed activity comparable to that of **4** in this assay.

The two nonsteroidal α-chloro benzyl sulfoxides, **21** and **22**, were inactive, indicating that the steroid portion of **4** plays an important role in the activity of these compounds. It also appears that this role is more than that of a lipophilic carrier, since the isomeric α-chloro sulfoxide **18** was inactive. Also, minor changes in the structure of the steroid group produced large changes in activity; for example, both the 11-deoxy and the 11β-hydroxy analogues exhibited reduced potency.

Compound **4** and the two phenyl-substituted derivatives, **5** and **6**, were then tested for their effect on androgen-stimulated female hamster flank glands (Table I). After 10 daily topical applications, **4** again showed the highest inhibition of the increase in flank organ weight and was selected for further evaluation.

The effects of **4** in the male hamster are shown in Table IV, along with the antiandrogen 17α-methyl-*B*-nortestosterone (**23**). Both compounds caused a decrease in flank organ weight, but only 17α-methyl-*B*-nortestosterone (**23**) had any effect upon the androgen-sensitive seminal vesicles. The lack of antiandrogenic activity of **4** was also shown in the rat where no changes in testes, seminal vesicle, ventral prostate, adrenal, or thymus weights were seen after sc administration of **4** at 25 mg/kg for 20 days.[33] Specific assays also showed that **4** lacked any uterotrophic, antiuterotrophic, or progestational activity[33] and possessed only very slight topical antiinflammatory activity (0.004 – 0.02 × hydrocortisone).[34] It therefore appears that **4** can effectively reduce sebaceous gland function in animals without hormonal or antihormonal side effects. This activity may be due to specific antagonism of androgen action on the sebaceous gland androgen receptor, and experiments are underway to investigate this possibility.

Experimental Section

Melting points were taken on a Fisher-Johns hot-stage melting-point apparatus and are uncorrected. NMR spectra were obtained at 60 or 100 MHz on either a Varian A60-A or an XL-100-15 spectrometer, and chemical shifts are reported in parts per million downfield from an internal $Si(CH_3)_4$ standard. Mass spectra were recorded on a Varian MAT CH5 spectrometer using a 70-eV source, and Circular dichroism spectra were measured on a Cary Model 61 CD spectropolarimeter. Silica gel preparative (1000 μm) and analytical (250 μm) thin-layer chromatography (TLC) plates were obtained from Analtech, Inc., and the silica gel used for column chromatography was the TLC grade (silica gel G type 60) supplied by E. Merck.

17β-Hydroxy-1,4-androstadiene-3,11-dione (1). To a solution of 1,4-androstadiene-3,11,17-trione (50 g, 0.168 mol) in MeOH (2.5 L) at 0–5 °C was added $NaBH_4$ (3.75 g, 0.1 mol) in one portion. After 15 min at 0–5 °C, AcOH (25 mL) was added dropwise so as to maintain the temperature below 5 °C. The reaction mixture was poured into ice–water (1.2 L), and the product was extracted into $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to a solid residue. Crystallization from $CHCl_3$/hexane gave 1[35] (41 g, 82%): UV λ_{max} (MeOH) 238 nm (ε 15 000).

17β-(Methanesulfonyloxy)-1,4-androstadiene-3,11-dione (2). A solution of **1** (100 g, 0.336 mol) and methanesulfonyl chloride (100 mL) in pyridine (1 L) was stirred at room temperature for 1 h and then poured into 3.5 N H_2SO_4 (12 L). The precipitate was filtered off, washed with water, and dried in vacuo to constant weight at room temperature to give **2**, which was used without purification for the preparation of the 17α-sulfides.

17α-(Phenylthio)-1,4-androstadiene-3,11-dione (11). Sodium (5.44 g, 0.237 mol) was dissolved in EtOH (420 mL), and after cooling to room temperature, thiophenol (19.6 mL, 0.178 mol) and **2** (8 g, 0.021 mol) were added. The reaction mixture was refluxed for 48 h, cooled, and poured into 5% aqueous NaOH. The precipitate was filtered off, dried in vacuo, taken up in a minimum of $CHCl_3$, and filtered through a small column of silica gel. The $CHCl_3$ eluates were evaporated to dryness to give crude **11** (6.5 g), which was crystallized from Me_2CO/hexane to give **11** (3.9 g, 45%), mp 177–179 °C. Anal. ($C_{25}H_{28}O_2S$) C, H, S.

17α-(Benzylthio)-1,4-androstadiene-3,11-dione (12). Sodium (13.8 g, 0.6 mol) was dissolved in EtOH (1 L) under N_2. The resulting solution was cooled to room temperature, and benzyl mercaptan (47 mL, 0.4 mol) was added, followed by **2** (21 g, 0.056 mol). After refluxing for 3 days, the solution was cooled, and a small quantity of insoluble material was filtered off. The solution was concentrated under reduced pressure and then poured into water (1.5 L) containing 5% NaOCl (150 mL), and the product was extracted into $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4), and concentrated to a viscous oil. This oil was taken up in $CHCl_3$ and filtered through a column of silica gel (300 g); elution with $CHCl_3$/hexane (1:1) removed nonpolar, evil smelling material, and elution with $CHCl_3$/hexane/EtOAc (9:9:1) gave **12**, which was crystallized from EtOAc/hexane to give pure **12** (8.5 g, 38%), mp 134–136 °C. Anal. ($C_{26}H_{30}O_2S$) C, H, S.

17α-[(β-Phenylethyl)thio]-1,4-androstadiene-3,11-dione (13). Compound **2** (3 g, 0.0079 mol) in a solution of sodium (2.25 g, 0.098 mol), EtOH (180 mL), and β-phenylethyl mercaptan (8 mL, 0.059 mol) was refluxed for 2 days. Workup as for **12** and chromatography on silica gel (300 g, elution with $CHCl_3$/EtOAc, 2:1) gave **13**, which crystallized from Et_2O/hexane to give **13** (0.74 g, 22%), mp 112–115 °C. Anal. ($C_{27}H_{32}O_2S$) C, H, S.

17α-(*n*-Pentylthio)-1,4-androstadiene-3,11-dione (14). Similar treatment of **2** (5 g, 0.013 mol) with a solution of sodium (3.75 g, 0.163 mol) and *n*-pentyl mercaptan (15 mL) in EtOH (300 mL) gave, after workup, crude **14** as an oil, which was chromatographed on a column of silica gel (500 g). Elution with EtOAc/$CHCl_3$ (1:9) gave **14** (2.4 g, 45%), which would not crystallize. A portion (1.2 g) of this material was filtered through another column of silica gel (100 g) with $CHCl_3$ to give **14**, which crystallized from Et_2O/hexane, mp 76–78 °C. Anal. ($C_{24}H_{34}O_2S$) C, H, S.

17α-(Benzylthio)-1,4-androstadien-3-one (16). 17β-Hydroxy-1,4-androstadien-3-one (10 g, 0.0278 mol) and methanesulfonyl chloride (10 mL) in pyridine (100 mL) was kept at room temperature for 1 h and then poured into 10% aqueous H_2SO_4. The precipitate was filtered off, washed well with H_2O, and dried in vacuo to give 17β-(methanesulfonyloxy)-1,4-androstadien-3-one (12 g). This product (10.4 g) was added to a solution of sodium (6.9 g, 0.3 mol) and benzyl mercaptan (12 mL, 0.088 mol) in EtOH (540 mL). After refluxing for 5 days, it was cooled and poured into 5% aqueous NaOH. The product was extracted into $CHCl_3$, and the organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated to an oil (9 g), which was purified on a column of silica gel. Elution with $CHCl_3$/EtOAc (97:3) gave first nonpolar material and then **16** (4.8 g, 42%), mp 116–118 °C after crystallization from Me_2CO/hexane. Anal. ($C_{26}H_{32}OS$) C, H, S.

17α-(Benzylthio)-11β-hydroxy-1,4-androstadien-3-one (15). A solution of **12** (0.35 g, 0.766 mmol) in THF (20 mL) was treated

(32) B. N. Lutsky, C. Casmer, and P. Koziol, *Lipids*, **9**, 43 (1974).
(33) Unpublished data from these Laboratories by R. O. Neri, T. T. Kung, and C. Casmer.
(34) Determined by Dr. B. N. Lutsky in a modified Tonelli mouse croton oil ear assay as described in B. N. Lutsky, J. Berkenkopf, X. Fernandez, M. Monohan, and A. S. Watnick, *Arzneim.*-Forsch., **29**, 992 (1979).
(35) L. Lorenc, M. Miljkovic, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **49**, 1183 (1966).

with $LiAl(t\text{-}BuO)_3H$ (1.4 g, 5.51 mmol) for 18 h at room temperature. The reaction mixture was then poured into 10% aqueous HCl, and the product was extracted into EtOAc. The organic extract was washed with H_2O, dried (Na_2SO_4), and concentrated to a solid residue. Crystallization from Me_2CO/hexane gave pure **15** (0.145 g, 41%), mp 217–220 °C. Anal. ($C_{28}H_{32}O_2S$) C, H, S.

17α(*R*)-(Benzylsulfinyl)-1,4-androstadiene-3,11-dione (19). A solution of **12** (1.014 g, 2.5 mmol) and *m*-chloroperbenzoic acid (0.526 g, 80% pure, 1.53 mmol) in benzene (10 mL) was stirred at room temperature. After 0.5 h it was diluted with EtOAc, washed with $NaHCO_3$ solution and water, dried (Na_2SO_4), and concentrated to a solid residue under reduced pressure. This material was chromatographed on silica gel (50 g); elution with $CHCl_3$/EtOAc (1:1) gave **19** (0.65 g), which was crystallized from EtOAc to give pure **19** (0.4 g, 39%): mp 182–184 °C. Anal. ($C_{26}H_{30}O_3S$), C, H, S.

17β(*R*)-(Benzylsulfinyl)-17α-chloro-1,4-androstadiene-3,11-dione (4). Method A. To **12** (8 g, 19.6 mmol) in pyridine (192 mL) and water (48 mL) at −40 °C was added iodobenzene dichloride (16.8 g, 61 mmol). After standing for 18 h at −40 °C, the reaction mixture was diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to an oil. Crystallization from Me_2CO gave **4** in two crops (2 g, 22%), mp 266–270 °C. Anal. ($C_{26}H_{29}O_3SCl$) C, H, S, Cl. Fractional crystallization of the mother liquors from MeOH gave the isomeric α-chloro sulfoxide **18** (95 mg, 1%). Anal. ($C_{26}H_{29}O_3SCl$) C, H, Cl.

Method B. A solution of **19** (0.18 g, 0.43 mmol) in pyridine/water (4:1; 6 mL) at −40 °C was treated with iodobenzene dichloride (0.33 g, 1.2 mmol). After 18 h the reaction mixture was diluted with $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to an oil. Purification of this product by preparative TLC (development solvent $CHCl_3$/EtOAc, 2:1) gave **4** (0.09 g, 46%) identical with **4** produced in method A by TLC, NMR, CD, and MS spectra.

17β(*R*)-[(β-Phenylethyl)sulfinyl]-17α-chloro-1,4-androstadiene-3,11-dione (7). Treatment of **13** (0.42 g, 1 mmol) as in method A above with iodobenzene dichloride (0.822 g, 3 mmol) gave **7** (0.11 g, 23%), mp 230–235 °C, after crystallization from $CHCl_3$/hexane. Recrystallization from $CHCl_3$/hexane gave the analytical sample, mp 232–235 °C dec. Anal. ($C_{27}H_{31}O_3SCl$) C, H, S, Cl.

17β-(*n*-Pentylsulfinyl)-17α-chloro-1,4-androstadiene-3,11-dione (8). Reaction of **14** (0.81 g, 2.1 mmol) with iodobenzene dichloride (1.7 g, 6.3 mmol) in the same manner gave a crude product, which was chromatographed on silica gel (100 g). Elution with EtOAc/$CHCl_3$ (1:4) gave fractions containing **8**, which, after crystallization from Me_2CO/hexane, gave a product (0.35 g) that still contained a less polar impurity (TLC). Further purification of this material on preparative TLC (development solvent EtOAc/$CHCl_3$, 1:3) gave **8** (0.128 g, 14%), mp 196–200 °C, after crystallization from $CHCl_3$/hexane. Anal. ($C_{24}H_{33}O_3SCl$) C, H, S; Cl: calcd, 8.11; found, 8.52.

17β(*R*)-(Phenylsulfinyl)-17α-chloro-1,4-androstadiene-3,11-dione (3). Similar treatment of **11** (1.176 g, 2.98 mmol) with iodobenzene dichloride (2.75 g, 9.0 mmol) in pyridine/water (4:1; 30 mL) gave crude **3** (0.7 g), which was crystallized twice from Me_2CO/hexane to give pure **3** (0.4 g, 30%), mp 232–236 °C dec. Anal. ($C_{25}H_{27}O_3SCl$) C, H, S, Cl.

17β-[(2,4-Dichlorobenzyl)sulfinyl]-17α-chloro-1,4-androstadiene-3,11-dione (5). Compound **2** (0.15 g, 4 mmol) was dissolved in a solution of sodium (1.06 g, 45 mmol) and 2,4-dichlorobenzyl mercaptan (5.55 mL, 45 mmol) in EtOH (80 mL). After refluxing for 48 h, the reaction mixture was poured into 5% aqueous NaOH, and the product was extracted into $CHCl_3$. The organic extract was washed with 2% NaOCl solution and water, dried (Na_2SO_4), and concentrated under reduced pressure to an oil, which was purified on a column of silica gel. Elution with petroleum ether removed nonpolar impurities, and elution with petroleum ether/ether (4:1) gave 17α-[(2,4-dichlorobenzyl)thio]-1,4-androstadiene-3,11-dione (1.6 g), which was used directly for the next step. Treatment of this product (0.476 g) with iodobenzene dichloride (0.822 g) in pyridine/water (4:1) at −10 °C for 18 h gave, after workup, crude **5**. Stirring with ether and crystallization of the solids from CH_2Cl_2/Et_2O gave **5** (88 mg), mp 238–240 °C dec. Anal. ($C_{26}H_{27}O_3SCl_3$) H; C: calcd, 59.37; found, 58.82; Cl: calcd, 20.23; found, 19.77.

17β-[(2-Methylbenzyl)sulfinyl]-17α-chloro-1,4-androstadiene-3,11-dione (6). Compound **2** (1.5 g, 4.5 mmol) was dissolved in a solution of sodium (1.04 g) in EtOH (80 mL) and 2-methylbenzyl mercaptan (5.55 mL). After refluxing for 36 h, the reaction mixture was concentrated and then poured into aqueous 10% NaOH. The product was extracted into $CHCl_3$ and washed with 5% aqueous NaOCl and water, dried (Na_2SO_4), and concentrated to an oil, which was purified on a column of silica gel. Elution with petroleum ether/ether (4:1) gave 17α-[(2-methylbenzyl)thio]-1,4-androstadiene-3,11-dione as an oil (1.13 g). Treatment of this material (0.946 g) with iodobenzene dichloride (1.6 g) in the same manner as for **5** gave a semisolid residue. Slurrying with EtOAc/Et_2O gave **6** (0.18 g), mp 249–252 °C dec. Anal. ($C_{27}H_{31}O_3SCl$) C, H, S, Cl.

17β(*R*)-(Benzylsulfinyl)-17α-chloro-1,4-androstadien-3-one (10). Reaction of **16** (0.579 g, 1.5 mmol) with iodobenzene dichloride (1.24 g, 4.5 mmol) gave a crude product, which was purified on preparative TLC (development solvent EtOAc/$CHCl_3$, 1:9) to give **10** (0.3 g). Crystallization from Me_2CO/hexane gave **10** (0.25 g, 40%), mp >260 °C dec. Anal. ($C_{26}H_{31}O_2SCl$) C, H, S, Cl.

17β(*R*)-(Benzylsulfinyl)-17α-chloro-11β-hydroxy-1,4-androstadien-3-one (9). $NaBH_4$ (0.3 g, 7.9 mmol) was added to a solution of **4** (1.1 g, 2.4 mmol) in MeOH (100 mL). After stirring for 15 min at room temperature, the reaction mixture was acidified with 1 N HCl and then poured into ice–water. The precipitate was filtered off, washed with H_2O, dried in vacuo, and crystalled from $CHCl_3$/hexane to give **9** (0.6 g, 55%), mp 258–262 °C. Anal. ($C_{26}H_{31}O_3SCl$) C, H, S, Cl.

Attempted Preparation of 9 from 15. Iodobenzene dichloride (0.8 g, 2.91 mmol) was added to a solution of **15** (0.408 g, 1 mmol) in pyridine/water (4:1, 15 mL) at −40 °C. After 18 h at −40 °C, the reaction mixture was diluted with $CHCl_3$, washed with H_2O, and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a solid product (0.4 g). Purification of this material by preparative TLC (development solvent $CHCl_3$/EtOAc, 3:1) gave as the major product **20** (0.082 g): ^1H NMR (Me_2SO-d_6) δ 1.20 (C_{13} CH_3, s), 1.38 (C_{10} CH_3, s), 4.30 (11α H and 17β H, m), 5.96 (C_4 H, s), 6.20 (C_2 H, dd, $J \approx 10$ and 2 Hz), 7.35 (C_1 H, d, $J = 10$ Hz). Anal. ($C_{19}H_{25}O_4SCl$) H, S; C: calcd, 59.28; found, 58.02. TLC examination of the crude product showed the presence of **15** as a minor product.

17β-(Benzylsulfonyl)-17α-chloro-1,4-androstadiene-3,11-dione (17). Compound **4** (0.25 g, 0.55 mmol) in $CHCl_3$ (2.5 mL) was treated with *m*-chloroperbenzoic acid (0.125 g, 80% pure, 0.58 mmol) for 2 h at room temperature. The reaction mixture was diluted with $CHCl_3$, washed with saturated $NaHCO_3$ and H_2O, and dried ($MgSO_4$), and the solvent was evaporated to give crude **17**. Crystallization from $CHCl_3$/hexane and recrystallization from CH_2Cl_2/MeOH gave pure **17** (0.173 g, 69%), mp 269 °C dec. Anal. ($C_{26}H_{29}O_4SCl$) C, H, S, Cl.

Inhibition of Sebaceous Gland Function. Hamster: 2-Day Assay. Female hamsters were injected subcutaneously with testosterone propionate (200 μg) in sesame oil once daily for 2 days. The test compounds (0.1 mg) in chloroform solution were applied topically to the left flank gland for 2 days; 24 h following the last treatment, the animals were sacrificied, and the flank glands were excised, weighed, trimmed, and incubated with 5 μCi of [^{14}C]acetate (New England Nuclear) for 3 h at 37 °C in Krebs–Ringer phosphate buffer (pH 7.4). The tissues were digested with 15% ethanolic KOH for 30 min at 70 °C, the solution was acidified to pH 1.0 with 12 N HCl, and the lipids were extracted into hexane. Incorporation of radioactivity into this lipid fraction was determined by standard liquid scintillation techniques.

Hamster: 14-Day Assay. Female hamsters (100–110 g) were injected subcutaneously once daily with testosterone propionate (125 μg) for 14 days. The compounds (0.5 mg), dissolved in chloroform, were applied topically to the left flank gland once daily for 14 days, while the right flank received only chloroform. The flank glands were excised and weighed at necropsy on day 15.

Inhibition of Flank Gland Weight in Male Hamsters. For topical administration, compounds in chloroform solution (10 μL)

were applied to the left flank gland of male hamsters (80 g) once daily for 15 days. Chloroform only was similarly applied to the right flank. For subcutaneous administration, the compounds, as aqueous carboxymethylcellulose suspensions, were injected once daily for 14 days. On the day following the last treatment, the animals were sacrificed, and the flank glands, seminal vesicles, adrenals, and thymuses were removed and weighed.

Crystal Data. $C_{26}H_{29}ClO_3S$ (4), mol wt 457.0, orthorhombic, a = 13.056 (7) Å, b = 21.541 (10) Å, c = 8.323 (4) Å, U = 2341 Å^3, Z = 4, d_{calcd} = 1.297 g cm^{-3}. Absorption coefficient for Cu $K\alpha$ radiation (λ = 1.5418 Å), μ = 24 cm^{-1}. Space group $P2_12_12_1$ (D_2^4) uniquely established from the systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k = 2n$, $00l$ when $l \neq 2n$.

Crystallographic Measurements. A crystal of dimensions ca. 0.06 × 0.08 × 1.00 mm was oriented on the end of a glass fiber. Preliminary unit-cell constants and space group information were obtained from oscillation and Weissenberg photographs taken with Cu $K\alpha$ radiation. The crystal was then transferred to an Enraf–Nonius CAD-3 automated diffractometer (Ni-filtered Cu $K\alpha$ radiation) where one octant of reciprocal space to θ = 67° was surveyed by the θ–2θ scanning procedure as described in detail elsewhere.[36] Refined unit-cell parameters were derived by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space. From a total of 2283 independent intensity measurements, only those 1145 for which $I > 2.0\sigma(I)$ [$\sigma^2(I)$ = scan count + total background count] were considered observed and used in the structure analysis after the usual Lorentz and polarization corrections had been applied.

Structure Analysis. The structure was solved by use of MULTAN.[18] Approximate positions for 24 non-hydrogen atoms were obtained from E-map, and the remaining 7 were located in a F_0 Fourier synthesis phased by this group of atoms. Full-matrix least-squares refinement, at first with isotropic, and subsequently with anisotropic, thermal parameters reduced R[19] to 0.100 from its value of 0.265 for the initial model. Hydrogen atoms were then included at their calculated positions and, after several further rounds of least-squares adjustment of non-hydrogen atom parameters, the refinement converged at R = 0.052. Final atomic positional parameters are in Table V. Anisotropic thermal parameters and calculated hydrogen atom positional parameters are in Tables VI and IX. Observed and calculated structure amplitudes are listed in Table X.

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In all structure-factor calculations, the atomic scattering factor for hydrogen was taken from ref 37, and the atomic scattering factors for carbon, chlorine, oxygen, and sulfur were taken from ref 38, with those for chlorine and sulfur corrected for anomalous dispersion.[39] In the least-squares iterations, $\sum w\Delta^2(\Delta = ||F_o| - |F_c||)$ was minimized with weights, w, assigned according to the following scheme: $w^{1/2} = 1$ when $|F_o| \leq 30.0$ and $w^{1/2} = 35.0/|F_o|$ when $|F_o| > 30.0$.

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Registry No. **1**, 5885-11-0; **2**, 73038-49-0; **3**, 83220-36-4; **4**, 73024-18-7; **5**, 73024-23-4; **6**, 73024-26-7; **7**, 73024-19-8; **8**, 73024-20-1; **9**, 73024-29-0; **10**, 83289-27-4; **11**, 83220-37-5; **12**, 73024-08-5; **13**, 73024-09-6; **14**, 73024-10-9; **15**, 83220-38-6; **16**, 73024-17-6; **17**, 73024-33-6; **18**, 83220-39-7; **19**, 83220-40-0; **20**, 83220-41-1; **21**, 24824-97-3; **22**, 18086-90-3; **23**, 3570-10-3; IBD, 932-72-9; 1,4-androstadiene-3,11,17-trione, 7738-93-4; thiophenol, 108-98-5; benzyl mercaptan, 100-53-8; β-phenylethyl mercaptan, 4410-99-5; pentyl mercaptan, 110-66-7; 17β-hydroxy-1,4-androstadien-3-one, 846-48-0; 17β-(methanesulfonyloxy)-1,4-androstadien-3-one, 63015-07-6; m-chloroperbenzoic acid, 937-14-4; 2,4-dichlorobenzyl mercaptan, 59293-67-3; 17α-[(2,4-dichlorobenzyl)thio]-1,4-androstadiene-3,11-dione, 73024-13-2; 2-methylbenzyl mercaptan, 7341-24-4; 17α-[(2-methylbenzyl)thio]-1,4-androstadiene-3,11-dione, 73024-25-6.

Supplementary Material Available: Figures showing interatomic distances and bond angles (Figure 3) and crystal packing arrangement (Figure 4) and tables of non-hydrogen atom fractional coordinates (Table V), anisotropic thermal parameters (Table VI), torsion angles (Table VII), least-squares planes (Table VIII), hydrogen atom parameters (Table IX), and observed and calculated structure amplitudes (Table X) (20 pages). Ordering information is given on any current masthead page.

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Acute Effects of Alkylating Agents on Canine Renal Function: Specifically Designed Synthetic Maleimides

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Maleimidohippurates and maleimidobenzoates were synthesized that possess a carboxy group for active uptake into renal proximal tubular cells and a reactive maleimide moiety to covalently bond with proximal tubular components. The reactivity of the maleimide moiety in each series was progressively reduced by substitution of methyl groups in place of the vinyl hydrogens. In contrast to *N*-ethylmaleimide (NEM), the resulting maleimidohippurates and maleimidobenzoates did not possess significant diuretic activity in the dog following renal arterial administration. However, as predicted, the nephrotoxicity of the maleimidohippurates paralleled their in vitro alkylating ability and was quite specifically located in the proximal portion of the canine renal tubule.

Recently we demonstrated that *N*-ethylmaleimide (NEM) is diuretic, as well as potentially nephrotoxic, in the dog following renal arterial, but not intravenous administration.[1] Although the anatomical sites at which NEM acts to induce a diuresis or a nephrotoxic response have not as yet been thoroughly delineated, we felt that

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