TABLE I

4-ALKYL-3,5-DIPHENYL-4H-1,4-THIAZINE 1,1-DIOXIDES

Compd	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
IIIb	70	228–230[a]	$C_{17}H_{15}NO_2S$				
IIIc	64	252–254	$C_{18}H_{17}NO_2S$	69.42	5.50	69.57	5.57
IIIe	71	205–206	$C_{20}H_{21}NO_2S$	70.76	6.23	70.64	6.49
IIId	48	242–243	$C_{23}H_{19}NO_2S$	73.96	5.13	74.07	5.36
IIIf	75	222–223	$C_{19}H_{17}NO_4S$	64.20	4.82	64.09	4.84

[a] Lit.[4] mp 224–226°.

TABLE II

DERIVATIVES OF PHENACYL SULFIDE AND PHENACYL SULFONE

Compd	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Remarks
Phenacyl sulfide mono-*p*-nitrophenylhydrazone	213–213.5	$C_{22}H_{19}N_3O_3S$	65.16	4.73	64.94	4.69	Yellow needles
Phenacyl sulfone mono-*p*-nitrophenylhydrazone	211.5–212.5	$C_{22}H_{19}N_3O_5S$	60.26	4.37	60.21	4.49	Yellow needles
Phenacyl sulfone monophenylhydrazone	197–198[a]	$C_{22}H_{20}N_2O_3S$	67.34	5.10	67.08	5.36	Colorless needles[a]
Phenacyl sulfone dioxime	217–217.5[b]	$C_{16}H_{16}N_2O_4S$	57.80	4.82	57.82	4.95	

[a] Lit.[5] yellow needles, mp 193°. [b] Lit.[5] mp 204°. Under identical conditions (NaOAc, EtOH, reflux) the previous workers obtained the so-called phenacyl sulfone dioxime anhydride, mp 167°; however, their analytical data varied considerably from theory.

14.2 g (0.1 mole) of CH_3I in 150 ml of absolute ethanol. After 4 hr the reaction mixture was heated to reflux and then allowed to cool to room temperature. The ethanol was partially removed (about two-thirds), and the precipitate was filtered and recrystallized from ethanol yielding 2.5 g (38%), mp 203–204° (lit.[5] mp 178°).

Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49; S, 9.71. Found: C, 65.36; H, 5.41; S, 9.68.

2,6-Dimethyl-3,5-diphenyl-4H-1,4-thiazine 1,1-Dioxide (IV).—A mixture of 1.65 g (0.005 mole) of the foregoing compound and 0.8 g (0.01 mole) of ammonium acetate in 10 ml of glacial acetic acid was heated under reflux 5 hr and cooled. The precipitated solid was filtered, washed with methanol, and recrystallized from ethanol to provide 1.2 g (77%) of colorless needles, mp 260–262°.

Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.42; H, 5.50; N, 4.50; S, 10.30. Found: C, 69.25; H, 5.52; N, 4.40; S, 10.34.

Reaction of Phenacyl Sulfone with Benzylamine.—A mixture of 1.5 g (0.005 mole) of phenacyl sulfone and 0.8 g (0.0075 mole) of benzylamine in 10 ml of xylene was heated under reflux for 3 hr. Cooling afforded 0.15 g (12%) of IIIa. Mixture melting point and infrared spectra confirmed the identity.

Reduction of 4-Methyl-3,5-diphenyl-4H-1,4-thiazine 1,1-Dioxide.—A suspension of 0.5 g of this compound[4] and 0.2 g of $LiAlH_4$ (3:1 ratio) in 25 ml of anhydrous ether was stirred and heated under reflux for 2 hr. The cooled reaction mixture was shaken with 50 g of ice and water, the ethereal layer was separated and dried ($MgSO_4$), and the ether was removed. The infrared spectrum of the residual syrup (0.37 g) did not show the C=C band at 1620 cm^{-1}. The **picrate** of 4-methyl-3,5-diphenyl-thiomorpholine 1,1-dioxide was prepared and recrystallized from ethanol; poor yield, mp 225–226°.

Anal. Calcd for $C_{23}H_{22}N_4O_9S$: C, 52.07; H, 4.18. Found: C, 52.13; H 4.35.

Phenylhydrazones and oximes were prepared in acetic acid solution or in ethanol (Table II).

2,7-Dihydro-3,6-diphenyl,4,5-thiadiazepine (V).—Ten drops of acetic acid were added to a stirred mixture of phenacyl sulfide (1.35 g, 0.005 mole) and 0.25 g (0.0075 mole) of hydrazine in 30 ml of ethanol. The mixture was heated under reflux for 8 hr and then allowed to cool to room temperature. The crude material was filtered and recrystallized from ethanol to provide 1.05 g (79%) of colorless solid: mp 177–177.5° (lit.[6,7] mp 175°); selected infrared maxima ($CHCl_3$), 3050 and 3000 (CH), 1555 (C=N) and 1445 cm^{-1} ($-CH_2$); nmr, doublets centered about δ 3.30 and 3.68 (J = 12.3 cps).

Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.14; H, 5.30. Found: C, 72.35; H, 5.48.

2,7-Dihydro-2,7-dimethyl-3,6-diphenyl-1,4,5-thiadiazepine.—The same procedure as above was employed using 2,2′-thiobispropiophenone instead of phenacyl sulfide. Recrystallization from methanol gave colorless crystals, mp 182–183°, in 55% yield.

Anal. Calcd for $C_{18}H_{18}N_2S$: C, 73.42; H, 6.16. Found: C, 73.50; H, 6.32.

3,6-Diphenyl-2,7-dihydro-1,4,5-thiadiazepine 1,1-Dioxide (VI).—The same procedure as above for V was employed using phenacyl sulfone. Recrystallization from ethanol–benzene gave in 73% yield, fine colorless needles: mp 195–196° dec (lit.[6] mp 196°); selected infrared maxima, 1545 (C=N), 1320 and 1140 (SO_2), and 685 cm^{-1} (C—S). This compound was also obtained by oxidation of V by 2 equiv of *m*-chloroperbenzoic acid in $CHCl_3$. Mixture melting point and infrared spectra confirmed the identity.

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Steroidal 2,3-Epithiospirolactones

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Initial reports[1-3] by Cella and co-workers that steroidal 17-spirolactones possessed antialdosterone activity prompted a continuous stimulus to synthesize and evaluate many related derivatives. This work was in part culminated by the observation of Cella and Tweit,[4] as reported in 1959, that the 7α-acetylthio analog of 3-(17β-hydroxyandrost-4-en-3-on-17α-yl)propionic acid γ-lactone was a highly potent steroidal aldosterone antagonist.

(1) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957).
(2) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).
(3) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).
(4) J. A. Cella and R. C. Tweit, *ibid.*, **24**, 1109 (1959).

Since these earlier findings, several investigators have reported the evaluation of steroidal spirolactones modified in many ways[5] including additional methylation,[6] increased unsaturation,[4] introduction of halogen[7,8] aromatization of the A ring,[9] and removal of the 3-oxygen function.[10] Of these various modifications, the fluoro derivative, 3-(3,11-dioxo-9α-fluoro-17β-hydroxyandrost-4-en-17α-yl)propionic acid γ-lactone,[7] was the most interesting.

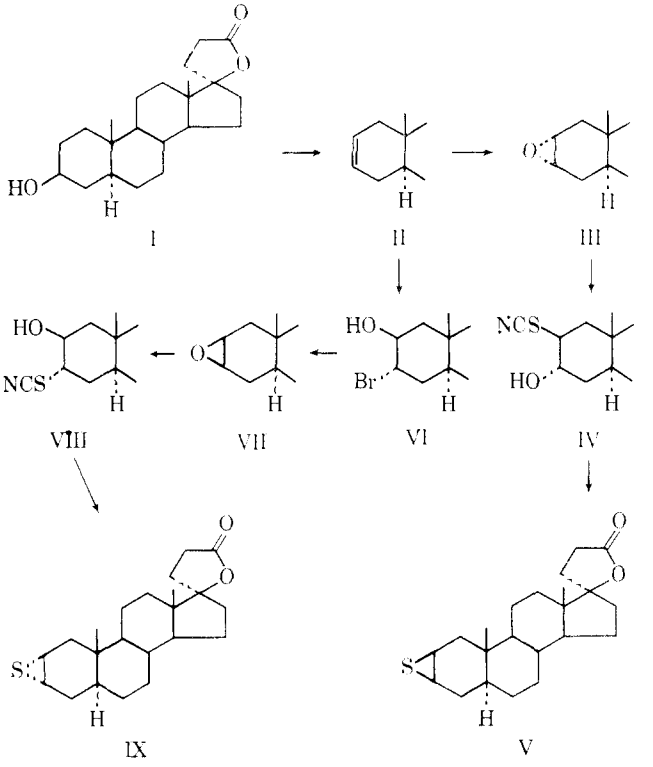
In a recent publication,[11] we reported the synthesis and potent anabolic activity of some 2,3-epithioandrostane derivatives. Because of this surprising observation, it was deemed desirable to investigate the antialdosterone activity of compounds possessing the 2,3-epithio function and the 17-spirolactone system in the same steroidal molecule. To this end, both the 2,3α- and 2,3β-epithioandrostane-17-spirolactone analogs were synthesized and evaluated biologically.

The starting material utilized in these experiments for the epithiospirolactones V and IX was 3-(3β,17β-dihydroxy-5α-androstan-17α-yl)propionic acid γ-lactone (I).[3] This substance was converted into the 3-tosylate ester and then smoothly transformed into 3-(17β-hydroxy-5α-androst-2-en-17α-yl)propionic acid γ-lactone (II)[10,12] upon heating in refluxing collidine. The 2,3α-epoxide III was prepared by the treatment of II with *m*-chloroperbenzoic acid. On the other hand, reaction of the olefin II with hypobromous acid followed by treatment with base afforded the 2,3β-epoxy isomer VII in good yield.

The scheme outlined in Chart I which is analogous to that used in the androstane[11] and pregnane[13] series, was utilized to prepare the episulfides V and IX. Briefly, treatment of either epoxide III or VII with thiocyanic acid formed the corresponding thiocyanohydrins IV and VIII. Subsequent reaction with methanolic potassium hydroxide[14] afforded the episulfides V and IX, respectively, in moderate yields. The configuration of the episulfides was based on the analogous route of formation of the thirane ring system in the androstane series.[11] The homogeneity of the product was evaluated by thin layer chromatography (tlc).

Biological Results.[15]—The episulfides V and IX as well as all of the intermediates included in this paper were evaluated in the adrenolectomized male rat by subcutaneous injection with deoxycorticosterone acetate (DOCA) and a saline solution. Anti-DOCA activity is indicated by some degree of reversal of the urinary Na^+/K^+ ratio produced by the DOCA. Unfortunately, none of the substances tested produced any measurable effect on the typical potassium excreting–sodium retaining effects of DOCA at the 2.4-mg/kg screening dosage. Any response here would have been indicative of antialdosterone activity.

CHART I



Experimental Section[16]

3-(17β-Hydroxy-5α-androst-2-en-17α-yl)propionic Acid γ-Lactone (II).—A solution of I[3] (50 g) and *p*-toluenesulfonic acid monohydrate (50 g) in pyridine (500 ml) was allowed to stand at room temperature for 16 hr. The reaction mixture was poured into ice and water (4.5 l.). The precipitate was collected, washed with H_2O, and dried at 80° *in vacuo*. The crude product was dissolved in ethyl acetate, washed with H_2O, and dried (Na_2SO_4 containing Darco). Solvent removal *in vacuo* afforded an oil which was suitable for the following elimination reaction as determined by infrared spectroscopy.

The crude tosylate (~70 g) was refluxed with collidine (700 ml, freshly distilled) for 10 hr. The reaction mixture was cooled to room temperature and poured into ice and H_2O (4 l.) containing concentrated H_2SO_4 (300 ml). The product was collected by filtration, washed with a large quantity of H_2O, and air dried. The crude product was dissolved in ether, washed with aqueous 5% HCl followed by 5% aqueous $NaHCO_3$ solution, and dried (Na_2SO_4, Darco). Solvent removal *in vacuo* left an oil which solidified. Recrystallization from hexane afforded pure II (28 g): mp 136.5–138°; $[\alpha]D$ +12.5°; nmr[17] signals, 240 (2- and 3-vinyl protons), 150 (C-21 methylene), 56.5 (C-19 methyl), and 46.5 cps (C-18 methyl); lit.[10] mp 134–136°, $[\alpha]D$ +17°.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.59; H, 9.89.

The mother liquors were chromatographed over silica gel and eluted with benzene–ethyl acetate (9:1) to give after recrystal-

(5) For a partial review of some of the modifications see R. R. Burtner, "Hormonal Steroids, Biochemistry, Pharmacology, and Therapeutics: Proceedings of the First International Congress on Hormonal Steroids," Vol. 2, L. Martini and A. Pecile, Ed., Academic Press Inc., New York, N. Y., 1965, p 31.

(6) N. W. Atwater, R. H. Bible, E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *J. Org. Chem.*, **26**, 3077 (1961).

(7) E. A. Brown, R. D. Muir, and J. A. Cella, *ibid.*, **25**, 96 (1960).

(8) E. A. Brown and R. R. Burtner, *J. Med. Chem.*, **6**, 732 (1963).

(9) W. F. Johns and E. A. Brown, *J. Org. Chem.*, **31**, 2099 (1966).

(10) P. Crabbé, J. Revilla, and A. Bowers, *J. Med. Chem.*, **6**, 182 (1963).

(11) P. D. Klimstra, E. F. Nutting, and R. E. Counsell, *ibid.*, **9**, 693 (1966).

(12) This substance was first prepared by Mr. E. A. Brown of our laboratories.

(13) P. D. Klimstra, *J. Med. Chem.*, **9**, 781 (1966).

(14) It is interesting to note that under these basic conditions none of the open-chain hydroxy acid was isolated.

(15) The author thanks Dr. L. Hofmann and Mr. R. Jacobs of these laboratories for furnishing this biological information.

(16) The elemental analyses and optical rotations at 1% in $CHCl_3$ at ambient temperatures were furnished by Mr. E. Zielinski and Mr. J. Damascus of our analytical department under the supervision of Dr. R. T. Dillon. The melting points were obtained on a Fisher-Johns apparatus and are corrected. The nmr spectrum was obtained with a Varian A-60 spectrometer.

(17) The nmr data were furnished by Mr. E. A. Brown of our laboratories.

lization from hexane an additional 8.2 g of II, mp 129–131°, identical with that obtained above (total yield, 78.6%) as determined by tlc and infrared spectra.

3-(3α-Bromo-2β,17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (VI).—To a cooled and stirred solution of II (16 g) in dioxane (250 ml, purified) was added dropwise a mixture of N-bromosuccinimide (9.6 g), H_2O (105 ml), and 60% $HClO_4$ (8.34 g) over 15 min. The reaction was stirred for 3 hr at room temperature and poured into H_2O. The oily product was extracted with ethyl acetate and the extract washed with aqueous HCl (5%) followed by $NaHCO_3$ (5%, aqueous) and water. After drying (Na_2SO_4, Darco), the solvent was removed *in vacuo* to leave a white solid. Recrystallization from methanol–H_2O afforded VI (15.7 g, 75.5%), mp 204–207°. Further recrystallization from methanol produced an analytical sample, mp 220–220°, $[\alpha]_D$ +33°.

Anal. Calcd for $C_{22}H_{33}BrO_3$: C, 62.11; H, 7.82. Found: C, 62.54; H, 7.82.

3-(2,3α-Epoxy-17β-hydroxy-5α-andostan-17α-yl)propionic Acid γ-Lactone (III).—A solution of II (9 g) and *m*-chloroperbenzoic acid in benzene (1.2 *N*, 275 ml) was allowed to stand at 7° for 16 hr. The mixture was allowed to warm to room temperature and washed repeatedly with aqueous Na_2CO_3 solution (5%) followed by H_2O and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded an oil which gradually solidified. Recrystallization from methanol gave III (6.5 g, 68.8%), mp 164–166°, $[\alpha]_D$ −9°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.46; H, 9.08.

3-(2,3β-Epoxy-17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (VII).—A solution of VI (6.0 g) in DMF (100 ml) was heated with K_2CO_3 (2.0 g) in H_2O (10 ml) in a steam cabinet (40–60°) for 16 hr. The reaction was cooled and poured into ice and water. A precipitate formed and was collected, washed with H_2O, and air dried. Recrystallization from methanol afforded VII (3.0 g, 47.6%), mp 178.5–180.5°, $[\alpha]_D$ +1.5°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.22; H, 9.02.

3-(3α,17β-Dihydroxy-2β-thiocyano-5α-androstan-17α-yl)propionic Acid γ-Lactone (IV).—To a mixture of KSCN (44 g) in ice-cold H_2O (21.6 ml) and ether (180 ml) in a separatory funnel was added with shaking H_3PO_4 (66.4 g) in small portions. The pink organic layer was separated, washed with two small portions of H_2O, and dried briefly (Na_2SO_4). The solution of HSCN in ether was decanted into a stirred slurry of III (4.0 g) in ether (30 ml). The mixture was allowed to stand at room temperature for 2 days. The homogeneous reaction was washed with 10% aqueous Na_2CO_3 until neutral. After washing with several portions of H_2O and drying (Na_2SO_4, Darco), the solvent was removed *in vacuo*. The remaining semisolid was recrystallized from methanol to give IV (2.2 g, 52.8%). Further recrystallization from the same solvent gave an analytical sample, mp 216–217.5°, $[\alpha]_D$ −9°.

Anal. Calcd for $C_{23}H_{33}NSO_3$: C, 68.45; H, 8.24. Found: C, 68.87; H, 8.23.

3-(2β,17β-Dihydroxy-3α-thiocyano-5α-androstan-17α-yl)propionic Acid γ-Lactone (VIII).—A solution of VII (2.5 g) in ether (50 ml) was treated with HSCN in ether as described above. Rectification as above and recrystallization from methanol–H_2O afforded VIII (2.15 g, 73.5%), mp 239–240°, $[\alpha]_D$ +20.0°.

Anal. Calcd for $C_{23}H_{33}NO_3S$: C, 68.45; H, 8.24. Found: C, 68.78; H, 8.23.

3-(2,3β-Epithio-17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (V).—To a stirred solution of IV (1.2 g) in methanol (40 ml) was added KOH (0.6 g) in methanol (10 ml). The reaction mixture was allowed to stand at room temperature for 2 hr. Water (25 ml) was added and the solution was cooled in the refrigerator. The precipitate which formed was collected and recrystallized from methanol–H_2O to give V (0.4 g, 37.4%), mp 158.5–160°, $[\alpha]_D$ −10.0°.

Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.95. Found: C, 73.12; H, 8.85.

3-(2,3α-Epithio-17β-hydroxy-5α-androstan-17α-yl)propionic Acid γ-Lactone (IX).—A warm solution of VIII (1.5 g) in methanol (80 ml) was treated with methanolic KOH as above. Rectification and recrystallization from acetone–H_2O afforded IX (0.85 g, 63.5%), mp 175–177°, $[\alpha]_D$ +26.5°.

Anal. Calcd for $C_{22}H_{32}O_2S$: C, 73.28; H, 8.95. Found: C, 73.36; H, 8.98.

3,4-Dihydro-1,3-oxazines from Dicyclohexylcarbodiimide

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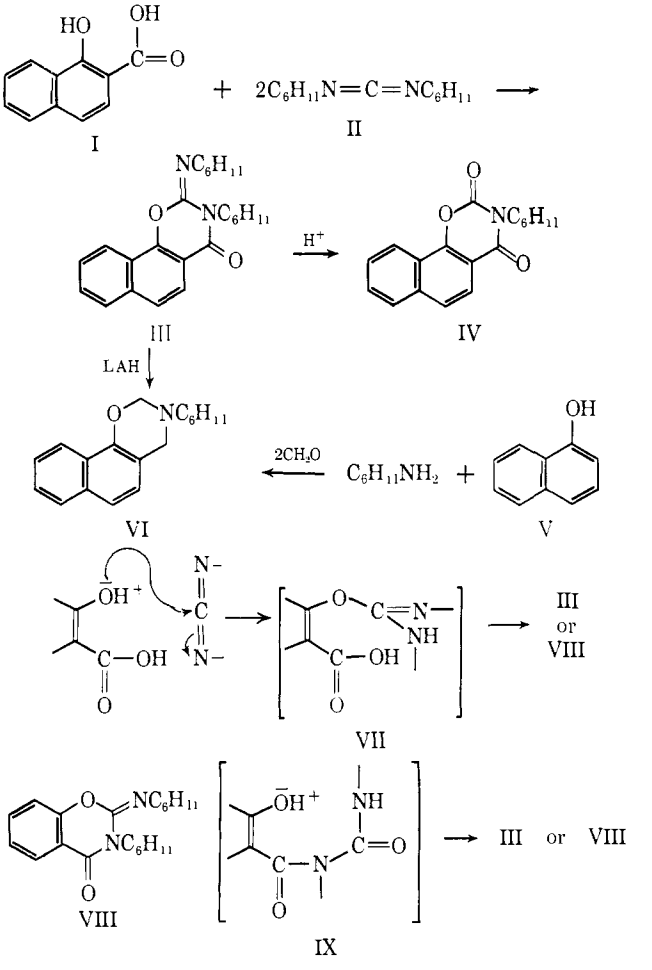
Several years ago, we attempted to prepare amides of 1-hydroxy-2-naphthalenecarboxylic acid (I) by the carbodiimide method using dry tetrahydrofuran (THF) as the solvent. Instead of the expected amides, a product containing the combined components of the two reagents minus the elements of H_2O was isolated whether or not an amine was used. 1,3-Dicyclohexylurea was also obtained in 70–80% yield. Analytical, infrared, and nmr data left little doubt that this product was 3-cyclohexyl-2-cyclohexylimino-3,4-dihydro-4-oxo-2H-naphth[2,1-*e*]-1,3-oxazine (III).

Compound III was essentially unchanged by refluxing (3 hr), alcoholic KOH. It was also resistant to hydrogenation with PtO_2, but $LiAlH_4$ effected hydrogenolysis of the cyclohexylimino and carbonyl groups, producing 3-cyclohexyl-3,4-dihydro-2H-naphth[2,1-*e*]-1,3-oxazine (VI), isolated in 20–40% yields as the hydrochloride salt[1] (see Scheme I). It proved to be identical with VI obtained by synthesis from 1-naphthol.

SCHEME I



(1) Also detected was N,N′-dicyclohexylformamidine providing evidence of some ring rupture.