17α-Hydroxy-17-[(3-methyl-2-oxazolidinyl)carbonyl]androsta-4-en-3-one (IVb). A soln of 5.0 g (14.5 mmoles) of 17-hydroxy-3,-20-dioxopregna-4-en-21-al (IIIb) and 5.0 ml (72 mmoles) of 2-(*N*-methylamino)ethanol in 170 ml of $CHCl_3$ was heated under reflux for 2 hr. The residue, after evapn under reduced pressure and trituration with cold EtOAc, gave 1.9 g of tan crystals: mp 179–181°. Tlc indicated the presence of a single component, which was more polar than starting material. Recrystn to constant mp from EtOAc afforded 0.5 g of colorless crystals: mp 191–192°; λ_{max} 242 mμ (16,340); ir (cm^{-1}), 3400 (OH); 1730 (C=O); 1653 (C=CC=O); 1605 (C=C); nmr (ppm), 0.69, 0.75 (C_{18}-CH_3); 1.10, 1.20 (C_{19}-CH_3); 2.45, 2.50 (NCH_3); 4.80, 4.90 (C_{21}-H); 5.72 (C_4-H). *Anal.* ($C_{24}H_{35}NO_4$) C, H, N.

17α-Hydroxy-17-[(3-methyl-5-(3,4-dihydroxyphenyl)-2-oxazolidinyl)carbonyl]androsta-1,4-dien-3-one (V). A mixture of 750 mg (1.9 mmoles) of aldehyde IIIa[3] and 750 mg (4.2 mmoles) of (−)-epinephrine in 140 ml of DMF was heated on a hot plate until dissolution occurred and was then maintained at 70° for 1 hr. The dark red soln was evapd to dryness at reduced pressure. Addn of MeOH gave a soln of the product and left behind unreacted epinephrine, which was sepd by filtration. Concn of the filtrate, pptn of the product with saturated NaCl soln, and filtration afforded 940 mg of red crystals: mp 140–145° dec (prior darkening at 130–140°). Recrystn from EtOAc (3 times) and then from 3:2 C_6H_6–EtOAc (2 times) gave light tan crystals which were dried *in vacuo* at room temperature for analysis. The analytical sample exhibited mp 144–146° dec (prior change to dark red), λ_{max} 235 mμ (20,600). *Anal.* Found: C, 66.95; H, 7.16; N, 2.32. Calcd for $C_{30}H_{37}NO_7$: C, 68.83; H, 7.12; N, 2.67. Calcd for V + 1 mole of EtOAc: $C_{34}H_{45}NO_9$: C, 66.75; H, 7.42; N, 2.29.

Reaction of 3,20-Dioxopregn-4-en-21-al (IIIc) and 2-(*N*-Methylamino)ethanol. A soln of 3.0 g (9.5 mmoles) of IIIc (mp 104–105) and 1.5 ml (19 mmoles) of 2-(*N*-methylamino)ethanol in 150 ml of $CHCl_3$ was heated at reflux with constant water sepn for 1.5 hr. Evapn to dryness *in vacuo* gave a yellow oil. Trituration with EtOAc gave 1.1 g of white crystals, mp 104–110°. Recrystn from hexane gave crystals: mp 107–111°; ir (cm^{-1}); 1724, 1704 (C=O) (barely resolved doublet in either KBr or $CHCl_3$ soln); 1667 (C=CC=O); 1610 (C=C); nmr (ppm), 0.75 (C_{18}-CH_3); 1.27, 1.20 (C_{19}-CH_3); 2.44, 2.50 (NCH_3); 5.77 (C_4-H); unassigned peaks at 4.33 and 5.57 (each about one-half proton intensity).

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Novel Anthelmintic Agents. 6. Pyrantel Analogs with Activity against Whipworm

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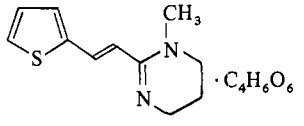
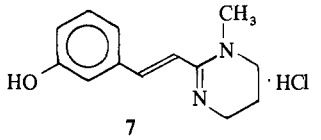
Received October 14, 1971

Although the broad-spectrum anthelmintic agent pyrantel is inactive against adult whipworms (*Trichuris* spp.), a number of its *m*-oxyphenyl analogs are very effective against these refractory helminths. The following compounds exhibit high potency in mice against *T. muris*: *trans*-1,4,5,6-tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine (**7**), *trans*-1-(3-hydroxystyryl)pyridinium bromide (**33**), *trans*-1-(3-benzoyloxystyryl)pyridinium bromide (**34**), *trans*-2-(3-benzyloxystyryl)-1,4,5,6-tetrahydro-1-methylpyrimidine (**12**), and *trans*-3-hydroxy-*N*,*N*-dimethylcinnamamidine (**22**). The methods of preparing these compounds, the technique of evaluating them as whipworm control agents, and structure–activity relationships are discussed.

Pyrantel is a highly effective broad spectrum nematocide, but as with many other commercially important anthelmintics, it is of no practical value against adult whipworms.



pyrantel tartrate (**25**)



7

In the course of exploiting this series of compounds,[1-4] it was discovered that *trans*-1,4,5,6-tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine hydrochloride (**7**) is highly effective against the adult whipworms of mice (*Trichuris muris*),[5] and dogs (*T. vulpis*).[5] There are 2 surprising features in this discovery: (1) although **7** is highly potent against *T. muris*, it is active only at high doses (125 mg/kg) against our primary screening organism, *Nematospiroides dubius;* pyrantel has no practical effect on adult *T. muris*, but is highly potent against *N. dubius;* (2) the structure–activity relationships developed previously in this series[1,6] would suggest that **7** should not be active, meta substitution and OH substituents in the aryl rings being usually unfavorable for activity.

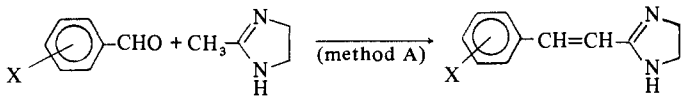
Because **7** is at least 10 times more potent that dichlorvos, the leading agent for the control of whipworms in dogs and swine,[7] it seemed logical to pursue this compound as a structure lead.

Although several analogs were discovered to have activity against *T. muris*, none were more potent than **7** itself. The results of these studies are given in this report. The compounds prepared and their activities against *T. muris* are summarized in Tables I–IV. The activities of some related compounds are given in Tables V and VI.

Chemistry. The general methods for preparing the new compounds mentioned in Tables I–IV have been described previously;[1,3] specific details for the preparation of typical entities are given in the Experimental Section. The use of formate esters as water scavengers[8] in the condensation of hydroxybenzaldehydes with 2-methyl cyclic amidines was decisive to the success of this research. Attempts to effect these reactions by distilling the by-product H_2O were often unsatisfactory.

The stereochemistry of **7** was established by nmr spec-

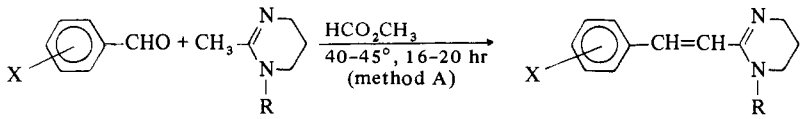
Table I



No.	X	Reaction conditions: hr	Reaction conditions: Solvent	Reaction conditions: °C[a]	Salt	Recrystn solvent	Mp, °C	Formula	Analyses	ED_{90} mg/kg
1	2-OH	18	HCO_2Me	43	HCl	EtOH	234-236	$C_{11}H_{13}ClN_2O$	C, H, N	>200
2	3-OH	48	HCO_2Et	75	Tartaric	H_2O	211-214	$C_{15}H_{18}N_2O_7$	C, H, N	>200
3	4-OH	18	HCO_2Bu	120	$HCl \cdot 0.5H_2O$	H_2O	223-225	$C_{11}H_{14}ClN_2O_{1.5}$	H, N; C[b]	>100
4	3-OCH_3	18	HCO_2Me	43	HPF_6	EtOH-2-PrOH	181-183	$C_{12}H_{15}F_6N_2OP$	C, H, N	>200

[a]Bath temp. [b]C: calcd, 56.5; found, 56.0.

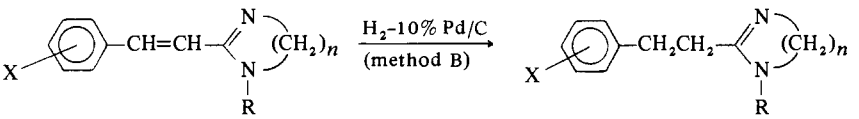
Table II



No.	X	R	Salt	Recrystn solvent	Mp, °C	Formula	Analyses	ED_{90}, mg/kg
5	2-OH	CH_3	Fumaric	*c*	*c*	*c*	*c*	>625
6[a]	3-OH	H	Tartaric	H_2O	200-202	$C_{16}H_{20}N_2O_7$	C, H, N	100
7	3-OH	CH_3	HCl	EtOH	207-208	$C_{13}H_{17}ClN_2O$	C, H, N	2
8	4-OH	CH_3	Tartaric	*c*	*c*	*c*	*c*	>250
9	3-OCH_3	H	HPF_6	2-PrOH	137-138	$C_{13}H_{17}F_6N_2OP$	C, H, N	>200
10	3-OCH_3	CH_3	H_2CO_3	*c*	*c*	*c*	*c*	25
11	3-OC_2H_5	CH_3	Fumaric	EtOH	172-175	$C_{19}H_{24}N_2O_5$	C, H, N	25
12	3-$OCH_2C_6H_5$	CH_3	Fumaric	EtOH	165-166	$C_{24}H_{26}N_2O_5$	C, H, N	12
13	2-Br-5-OH	CH_3	Tartaric	H_2O	218-220	$C_{17}H_{21}BrN_2O_7$	C, H, N	50
14	2-Cl-3-OH	CH_3	Tartaric	H_2O	196-198	$C_{17}H_{21}ClN_2O_7$	C, H, N, Cl	>200
15[b]	3,4-$(OH)_2$	CH_3	Tartaric	H_2O	206-208	$C_{17}H_{22}N_2O_8$	C, H, N	>200
16	3-OH-4-OCH_3	CH_3	Tartaric	H_2O-2-PrOH	203-205	$C_{18}H_{24}N_2O_8$	C, H, N	>200

[a]Reaction condns: heat 0.1 mole of aldehyde and 0.1 mole of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine in 0.22 mole of ethyl formate at 75° for 18 hr. [b]Reaction condns: heat 0.1 mole of aldehyde and 0.1 mole of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine in 150 ml of toluene under reflux in apparatus equipped with moisture collection trap. [c]See ref 1.

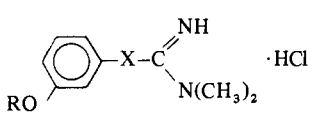
Table III



No.	X	R	*n*	Salt	Solvent: Reaction	Solvent: Recrystn	Mp, °C	Formula	Analyses	ED_{90} mg/kg
17	2-OH	H	2	Tartaric	H_2O	H_2O-EtOH	158-160	$C_{15}H_{20}N_2O_7$	C, H, N	>200
18	3-OH	H	2	Tartaric	H_2O-EtOH	MeOH	159-160	$C_{15}H_{20}N_2O_7$	H, N; C[a]	>200
19	4-OH	H	2	HCl	EtOH	2-PrOH	190-191	$C_{11}H_{15}ClN_2O$	C, H, N	>200
20	3-OH	H	3	Tartaric	H_2O-EtOH	H_2O	186-188	$C_{16}H_{22}N_2O_7$	C, H, N	200
21	3-OH	CH_3	3	HCl	H_2O-EtOH	EtOH	191-192	$C_{13}H_{19}ClN_2O$	C, H, N	25

[a]C: calcd, 52.9; found, 52.3.

Table IV

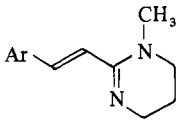


No.	R	X	Prep method	Recrystn solvent	Mp, °C	Formula	Analyses	ED_{90}, mg/kg
22	H	CH=CH	C	EtOH	233-234	$C_{11}H_{15}ClN_2O$	C, H, N	12
23	H	CH_2CH_2	B	EtOH	181-183	$C_{11}H_{17}ClN_2O$	C, H, N	50
24	CH_3	CH_2CH_2	C	MeCN	157-158	$C_{12}H_{19}ClN_2O$	C, H, N	>50

troscopy; the coupling constant between the vinyl protons ($J_{\alpha,\beta}$) is 16.0 cps which is consistent with a trans arrangement of H atoms across the double bond.[1] In contrast to the behavior of pyrantel, exposure of methanolic solutions of 7 to sunlight did not result in trans → cis isomerization. This is understandable since 7, unlike pyrantel, does not absorb light to any significant degree above 290 nm, and the sunlight spectrum has relatively few photons with wavelengths below 290 nm.

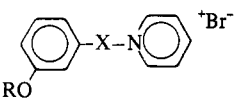
Biological Evaluation. Pinworm-free, CF#1 male mice were inoculated orally with 150-300 embryonated *T. muris* ova. A 230 mg/kg dose of cortisone acetate was adminis-

Table V. Activities of Some Other Tetrahydropyrimidines against *Trichuris muris*



No.	Ar	ED_{90}, mg/kg
25	2-Thienyl	>100
26	Ph	200
27	2-Furyl	100
28	*o*-Tolyl	>31
29	*m*-Tolyl	>200
30	*p*-Tolyl	>250
31	*m*-$O_2NC_6H_4$	100

Table VI. Activities of Some Pyridinium Salts against *Trichuris muris*



No.	R	X	ED_{90}, mg/kg
32	H	$CH(OH)CH_2$	200
33	H	CH=CH	8
34	C_6H_5CO	CH=CH	8
35	CH_3	CH=CH	50

tered sc 2 and 10 days postinfection to prevent the spontaneous elimination of worms which, as a result of acquired immunity, occurs 2 to 4 weeks postinfection. Test compounds, dissolved or suspended in 1% methylcellulose, were administered by gavage. Chemotherapeutic activity was noted as a per cent reduction in the average number of worms in a treated group relative to that of an untreated control group 30-35 days postinfection. Those compounds giving 100% reductions in worm burden were tested at successively lower doses until a dose giving a 90% reduction (ED_{90}) could be estimated. These results are recorded in Tables I-VI. Further details of these procedures are described elsewhere.[5]

Structure-Activity Relationships (SAR). Although **7** and its congeners have a different and narrower spectrum of activity than would be expected of active pyrantel analogs, there are striking similarities in the SAR of the 2 series even though *T. muris* is the target organism in the former case and *N. dubius* in the latter: (1) compounds with styryl side chains are more potent than the corresponding phenethyl congeners (compare **7** with **21**, **6** with **20**, and **22** with **23**); (2) an *N*-Me substituted compound is more potent than the corresponding unsubstituted compound (compare **7** with **6**, **10** with **9**, and **21** with **20**); (3) tetrahydropyrimidines are more potent than the corresponding imidazolines (compare **6** with **2**, and **20** with **18**); (4) noncyclic amidine analogs can be active (**22** and **23**); (5) 1-(2-arylvinyl)pyridinium analogs can be active (**33-35**).

A number of other tetrahydropyrimidines were active in the *T. muris* test system (see Table V). It is clear from these results that the *m*-OH substituent is not essential to whipworm activity *per se*, but it apparently makes a major contribution to potency. OH substituents (ortho and para) are apparently detrimental to activity. O-Alkylation of **7** results in a decrease in potency, but not loss of activity (see **10-12**). Whether these alkoxy derivatives are active in their own right or are merely prodrug forms of **7** has not been determined.

Experimental Section

Boiling points are uncorrected; melting points were determined on a Hoover capillary melting point apparatus (Arthur H. Thomas, Co., Philadelphia, Pa.) and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Method A. Condensation of an Aldehyde with a 2-Methyl Cyclic Amidine. 1,4,5,6-Tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine Hydrochloride (7). A soln of 12.2 g (0.10 mole) of 3-hydroxybenzaldehyde, 13.3 g (0.12 mole) of 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine, and 12.0 ml (0.20 mole) of HCO_2CH_3 was heated under reflux (bath temp 40–45°) for 18 hr. Upon cooling the volatile components of the reaction mixt were evapd under reduced pressure to furnish a gum. This was taken up in 100 ml of 2-PrOH and 11 ml of concd HCl. The resulting soln was evapd, and the residue was triturated under acetone until a cryst solid was obtained: yield, 17.8 g; mp 186–198°. The product was twice recrystd to furnish 2.6 g (10%) of analytically pure **7**: uv max (H_2O) 231 nm (ε 12,700), 274 nm (ε 20,100); see Table II.

Method A was generally useful for preparing compds in Tables I and II, but some variations were necessary. Certain aldehydes condensed more readily with 1,4,5,6-tetrahydro-1,2-dimethylpyrimidine than with 2-methyl-2-imidazoline. As a consequence more vigorous reaction condns were needed for prepg derivs of this latter compd (see Table I). A few other variations should be noted (see footnotes *a* and *b* in Table II).

Method B. Catalytic Hydrogenation. 1,4,5,6-Tetrahydro-2-(3-hydroxyphenethyl)-1-methylpyrimidine Hydrochloride (21). A mixt of 7.5 g (0.03 mole) of **7**, 2.0 g of 10% Pd/C, and 200 ml of EtOH was reduced in a Parr hydrogenation apparatus according to the procedure recommended by the manufacturer. The reaction mixt was filtered and the volatile components were evapd under reduced pressure. After triturating the residue under EtOH-Et_2O there was obtained 6.0 g of a cryst substance, mp 196°; mmp with **7** was 183–184°. One recrystn afforded the analytical sample: yield 2.6 g (35%); uv max (EtOH) 278 nm (ε 1820); see Table III.

The uv spectra of the other compds in Table III were similar to that of **21**, *i.e.*, consistent with the expected reduced products.

Method C. Pinner Synthesis. 3-Hydroxy-*N*,*N*-dimethylcinnamamidine Hydrochloride (22). A soln of 14.5 g (0.1 mole) of 3-hydroxycinnamonitrile, 150 ml of dry Et_2O, and 75 ml of MeOH (a large excess) was satd with dry HCl gas and was stored at 0–5° for 4 days. The cryst imidate ester·HCl was filtered and washed with Et_2O: yield, 16.0 g (75%). It was not characterized, but was used directly in the next step.

A soln of 15.0 g (0.33 mole) of Me_2NH in 125 ml of MeOH was chilled to −10 to −20°, and was treated portionwise with the entire amt of imidate ester·HCl prepared above. The soln was allowed to warm to room temp, and the volatile components were evapd under reduced pressure. The residual oil was triturated under Et_2O, and the Et_2O layer was discarded. The still oily residue crystd after being heated in MeCN. Recrystn of the product afforded **22**: yield, 6.6 g (29% based on starting nitrile); mp 233–234°. One further recrystn furnished the analytical sample, no change in mp was observed.

In the prepn of the imidate·HCl precursor to **24** only the theor amt of MeOH was required.

1,4,5,6-Tetrahydro-1-methyl-2-styrylpyrimidine dihydrogen citrate (26) was prepd by converting 90.1 g (0.26 mole) of the corresponding HPF_6 salt[1] to the free base with a mixt of Et_2O and 40% NaOH, and by treating the free base with an equimolar amt of citric acid: yield, 86.2 g (85%); mp 162–163°. A recrystn from MeOH–EtOH did not alter the mp. *Anal.* ($C_{19}H_{24}N_2O_7$) C, H, N.

1-(3-Benzoyloxystyryl)pyridinium bromide (34) was prepd by heating 9.5 g (0.032 mole) of 1-(3,β-dihydroxyphenethyl)pyridinium bromide[2] in 50 ml of BzCl at 200° for 16 hr. After standing for several days at room temp the reaction mixt was poured into 500 ml of H_2O and 2.0 g of an insol material (mp 139–141°) was filtered. The aq filtrate was evapd under reduced pressure to afford another 2.0 g of a material, mp 114–118°. The ir spectra of both crops indicated them to consist of the same crude material. After combining the crops and recrystg them from MeCN, analytically pure **34** was obtained: yield, 3.7 g (30%); mp 179–181°. *Anal.* ($C_{20}H_{16}BrNO_2$) C, H, N.

3-Methoxycinnamonitrile (36) was prepd by the condn of 161 g (1.2 moles) of 3-methoxybenzaldehyde and 95 g (1.1 moles) of cyanoacetic acid under the condns described by Patterson:[9] yield, 132.7 g (75%); bp 105–114° (0.5 mm); the nmr spectrum indicated the product was a mixt of cis and trans isomers, the latter in the greater abundance. *Anal.* ($C_{10}H_9NO$) C, H, N.

3-Methoxyhydrocinnamonitrile (37) was prepd from 32.0 g (0.2 mole) of 36 by method B: yield, 32.1 g (100%); bp 110–120° (0.5 mm). *Anal.* ($C_{10}H_{11}NO$) C, H, N.

Acknowledgments. The technical assistance of Messrs. R. W. Sumner, G. F. Smith, and J. Kivlin is gratefully acknowledged. Also we would like to thank Drs. L. H. Conover and J. E. Lynch for their advice and encouragement during the course of this work. Dr. J. M. Allison of Pfizer Ltd. Research Laboratories, Sandwich, U. K., kindly supplied compounds **8**, **10–16**, and **21** for evaluation against *T. muris*.

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Heterocyclic Steroids. 4.[1] Synthesis and Androgenic Activity of A-Ring Homosteroids†

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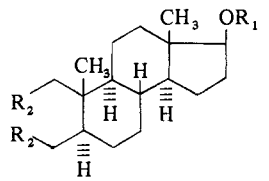
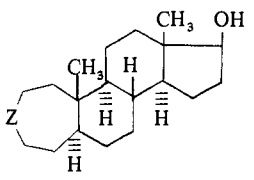
Received September 11, 1971

The synthesis of 3-oxa-, 3-thia-, 3-selena-, 3-tellura-*A*-homo-5α-androstan-17β-ol derivatives and 3,4-dithia-*A*-bishomo-5α-androstan-17β-ol by cyclization of appropriate seco compounds is described. All of the compounds except the tellurio derivative show both androgenic and myotrophic activity. The thia derivative is the most active; showing levator ani activity equivalent to testosterone but weaker seminal vesicle effects.

The results of our recent work on *A*-nor heterocyclic steroids[2-4] and 6-membered A-ring heterocyclic steroids[1,5] have prompted the present study in the preparation and activity of the corresponding *A*-homo compounds.

For the preparation of oxasteroid **6**, diester **1**[2] was reduced with LAH to give diol **2**, which on refluxing in PhMe containing *p*-TsOH gave the desired **6**. The other heterocyclic homosteroids were obtained by protecting the 17β-OH in **1** as the tetrahydropyranyl ether **3** and subsequent reduction with LAH to give diol **4**. Formation of the dimesylate **5** and cyclization in the presence of Na_2S, Na_2Se,[6] Na_2Te,[7] or Na_2S_2[8] and cleavage of protecting groups gave the desired **7**, **8**, **9**, and **10**, respectively.





1, R_2 = CO_2Me; R_1 = H
2, R_2 = CH_2OH; R_1 = H
3, R_2 = CO_2Me; R_1 = $-\overline{CH(CH_2)_4O}$;
4, R_2 = CH_2OH; R_1 = $-\overline{CH(CH_2)_4O}$;
5, R_2 = CH_2OMs; R_1 = $-\overline{CH(CH_2)_4O}$;

6, Z = O
7, Z = S
8, Z = Se
9, Z = Te
10, Z = SS

Results and Discussion

The data from the pharmacological testing‡ are displayed in Table I.

It can be seen that the oxa-, thia-, and selena-*A*-homo steroids (**6**, **7**, and **8**) are active compounds, whereas the tellurio derivative **9** is inactive. This is in contrast to the *A*-nor series in which the oxa derivative is inactive, whereas the tellurio derivative is active. The difference between the two series is probably a result of the change in size of the rings. In the androgenic indexes, as shown by the ventral prostate and seminal vesicle weights, the most active compound is the thia compound **7**, and both the oxa derivative **6** and the Se derivative **8** are less active. In myotrophic activity response, as shown by the levator ani test, the oxa compound **6** and the thia compound **7** are of similar activity with the Se compound being less active. The 8-membered A ring disulfide **10** is roughly comparable in activity to the oxa compound in all of the tests. The oxa and thia compounds **6** and **7** are equivalent in myotrophic activity to testosterone, whereas even the strongest androgen (**7**) is less active than testosterone in the ventral prostate test. In this connection, it is of interest that prior examinations of activity of carbo-

Table I. Androgenic-Myotrophic Assay

Compd (total dose), mg	Wt, mg[a] Ventral prostate	Seminal vesicle	Levator ani	Body wt, g Initial	Final
Castrate control	15.3 ± 0.23	10.4 ± 0.47	22.6 ± 3.04	55	87
Testosterone (0.3)	33.3 ± 2.66	13.7 ± 1.12	31.7 ± 1.16	54	96
p	<0.001	<0.05	<0.05		
Testosterone (3.0)	90.3 ± 6.19	77.9 ± 1.75	55.2 ± 1.82	54	97
p	<0.001	<0.001	<0.001		
6 (3.0) O	43.0 ± 2.40	23.8 ± 1.25	53.5 ± 1.49	54	91
p	<0.001	<0.001	<0.001		
7 (3.0) S	65.8 ± 1.44	32.2 ± 1.09	53.7 ± 1.02	58	95
p	<0.001	<0.001	<0.001		
8 (3.0) Se	40.05 ± 4.18	18.4 ± 1.43	42.1 ± 1.56	54	92
p	<0.001	<0.001	<0.001		
9 (3.0) Te	17.8 ± 0.01	11.1 ± 0.31	17.6 ± 0.80	54	76
p	<0.05	NS[b]	NS		
10 (3.0) SS	42.0 ± 5.92	23.4 ± 0.34	50.3 ± 1.35	54	95
p	<0.01	<0.001	<0.001		

[a] Mean ± S.E. at $p = 0.001$. [b] Not significant.

†This research was supported in part by a Public Health Service Grant (AM 05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

‡Pharmacological tests were performed at the Endocrine Laboratories, Madison, Wis. using essentially the method of Hershberger, *et al.*[9]